Development of the first selective proteolysis targeting chimera for the FK506-binding protein 51

Entwicklung des ersten selektiven ‚Proteolysis Targeting Chimeras' für das FK506-bindende Protein 51

TECHNISCHE UNIVERSITÄT DARMSTADT

Vom Fachbereich Chemie

der Technischen Universität Darmstadt

zur Erlangung des Grades

Doctor rerum naturalium (Dr. rer. nat.)

Dissertation von

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Darmstadt 2023

Tag der Einreichung: 16.März.2023

Tag der mündlichen Prüfung: 08.Mai.2023

Michael Walz: Entwicklung des ersten selektiven ‚Proteolysis Targeting Chimeras' für das FK506-bindende Protein 51
Darmstadt, Technische Universität Darmstadt,
Jahr der Veröffentlichung der Dissertation auf TUprints: 2023

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Acknowledgements

First of all, I would like to thank my family, who has always accompanied me on every step of my academic journey. First and foremost, I would like to thank my mother, for whose tremendous support I cannot find any words that could adequately describe my gratitude. A special thanks also belongs to my brother; the exchange about various modules during our studies and chemical research issues during our time as PhD students was of immense importance to me.

A major thanks also belongs to my professor, Felix Hausch, who allowed me to complete this dissertation. Your untiring commitment to research resulted in a laboratory that provided me with everything I needed for my thesis, whether it was constructive scientific discussions (with you and my colleagues as well), highly intelligent and kind colleagues, excellent laboratory equipment and also the one or other more expensive substance whose purchase would not have been permitted in every research group. You have always driven me to get the most out of my research and are an example of how much heart and soul one can invest in his work.

I am thankful for all the amazing people, coworkers, and friends I had the pleasure to meet during my time in the lab.
Fabian, Patrick, Thomas, Anna, Asat and Christian you shared the lab with me for my entire time as a PhD student and made my everyday life more enjoyable, I can't imagine the lab without you.
Steffen, you were the first person I met at the university and I couldn't have chosen a better person for this! Already in our early semesters we fantasized about working in the same lab and I am happy that we could actually realize this goal. With you, I have been privileged to meet one of the most warm-hearted people I have ever known. And I also thank you for always taking it with a smile when I express my affection for you in this (for many people not comprehensible) way.
Fabian, with no one else have I worked as "close" as I have with you and even though it is not always easy to share so little space, you have always made it easy for me. Thank you for everything you shared with me, be it professional things like synthesis ideas or private moments like at a certain event in Mannheim. On that note, I'd like to send you a "bleib gleich" and I'm happy to now be part of your armada of "Kumpeln".
Sabine, I am happy that I was able to get to know you so well during the one or other coffee break. I will miss not being able to just walk into the neighboring lab to talk to you anymore. Your Dorf-stories always were especially entertaining.... But I am sure that we will not loose touch with each other in the future. You can "calculate" with that. :P

Patrick, my barber of trust, and Robin, you one and only true Deutscher, you two have accompanied my scientific path even before we became PhD students and, moreover, you were the PhD students with whom I was allowed to work in immediate proximity for the longest time. There are countless great memories of the time with you, I'm sure I'll find one or the other on my hat and you can be sure I'll treasure them. Robin I send you a big hug and Patrick for all the times I was “allowed” to listen to your favorite artists G. M. and H. E you should always remember that Tinqi's favorite animal was the llama.

There are many more coworkers I would like to mention here. Anna you may not have been the doctoral student I deserved, but the one I needed. Moritz and Carlo let me just give you a quick KONTRA here. ~~Christian~~ Brudi, thank you for the beautiful musical moments and since no one else (even from Partick or Robin) in the lab continues the bloodline: Carry on Jürgens will and take over the lab. Thomas you were an excellent biochemical partner for this work and I hope that we can generate one or another paper from these and your data.

Johannes, Martha, Max, Min, Monika, Patryk, Oki, Sarah, Vanessa, Yuxin and also my former colleagues Andi, Christine, Jürgen, Michael, Stephanie, Tianqi and Tim thank you for being a part of this journey and for each of you having contributed to it in your own way.

A special thanks to all colleagues who contributed to this thesis through their work, be it synthesis or assays.

I would like to thank the students Horst, Brudi, Laura and Malte, which I supervised during my time as a PhD student, for their interest in the topic, their scientific contributions to it and the fact that each of you worked very independently. I wish you all the best for your own work and your future life.

I thank Reinhard Meusinger, Jörg Fohrer, and Christina Spanheimer for the many measurements of NMRs and Alexander Schießer, Christiane Rudolph, and Gül Sahinalp for the high-resolution masses. You were a great help in the characterization of my (unfortunately not always) desired substances.

Last but not least, I am thankful for all of my friends outside of chemistry. Be it through distractions by traveling or doing sports together, through long nights out, simple conversations or so much more, each one of you has had a small influence on the hundreds of pages that follow.

Table of content

1. Abstract

Because of its various potential applications, FKBP51 emerged as an interesting target protein for pharmacological research. In spite of many attempts, however, no conventional ligand with a sufficient pharmacological profile has yet been developed. Since the synthesis of such a ligand proved to be challenging and moreover it is still not exactly explored which domain is responsible for which function of the protein, the recently developed concept of PROTACs seemed to be an interesting possibility to investigate these problems.

Moreover, due to the recently clarified interactions of FKBP51 with GR by Baischew et al.[1], PROTACs prove to be a highly interesting target for the treatment of GR-mediated stress-related disorders.

In her doctoral thesis[2], Dr. Tianqi Mao was able to show that the degradation of FKBP51 by the use of a PROTAC is feasible in general. However, no PROTAC synthesized in the course of her work showed sufficient activity or selectivity. Therefore, the PROTAC library synthesized by Dr. Mao should be extended and screened for potential hits within the scope of this work. If possible, conclusions about structure-activity relationships should be drawn and then used for optimization of the PROTACs. The aim was to develop a highly active and selective PROTAC for FKBP51.

2. Introduction

2.1. FKBPs

FK506-binding proteins (FKBPs) belong to the immunophilin family. They occur in different phyla and exhibit catalytic activity for the isomerization of peptidyl-prolyl bonds in peptide and protein substrates, are highly conserved among species and possess various regulatory and chaperone-like functions, which are not always associated with their PPIase activity.[3–6]

To date, a total of 15 human FKBPs have been identified.[7] Among these, FKBP51 and FKBP12 are the best characterized members of this family. Various publications identified the homolog FKBP51 as a potential target for depression, obesity and chronic pain.[8–16] In contrast, the structurally close proteins FKBP12 and FKBP52 (a close Homolog of FKBP51) are considered off-targets, making it necessary for potential drugs to exhibit selectivity.[17]

2.2. FKBP51

FKBP51 is a protein consisting of three domains. The domain responsible for peptidyl-prolyl cis-trans isomerase activity (FK1 domain) is located at the N-terminus of the protein and is capable of binding the immunosuppressants FK506 and rapamycin. The FKBP-like domain (FK2 domain) has a similar structure to the FK1 domain. However, due to its lack of key residues, it does not exhibit binding to immunosuppressants and is catalytically inactive. The tetratricopeptide repeat domain (TPR domain) is located at the C-terminus of the protein and provides a binding site for Hsp90.[18–21]

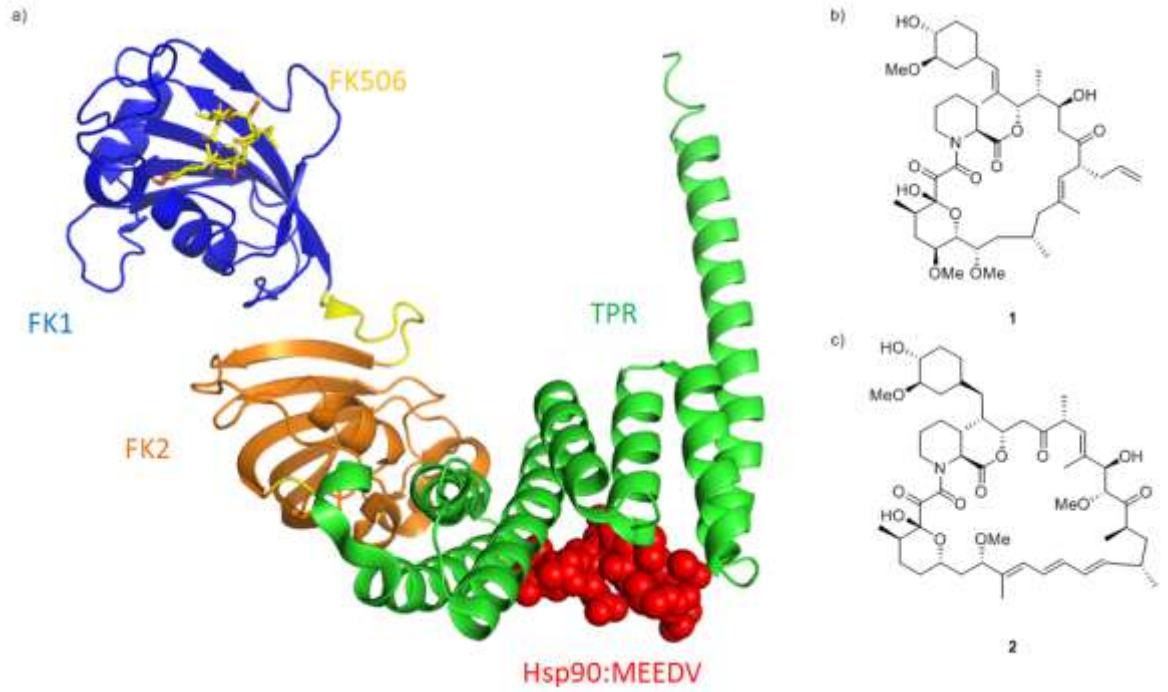


Figure 1: a) Depiction of the domains of FKBP51 with the TPR domain bound to the MEEDV motif of the Hsp90 and the FK1 domain bound to FK506 shown as sticks; adapted from Ref [22]; b) Structure of FK506; c) Structure of Rapamycin.

Hsp90 plays a central role in potein folding, stabilization, complex mediation and degradation, and exhibits hundreds of client proteins in this process. Therefore, it is involved in a variety of cellular pathways and processes. To date, nine TPR domain-containing proteins have been identified that can bind to Hsp90. All of these have a 20 amino acid sequence that appears to be required for recognition by Hsp90.[23,24] This results in a strong competition for association with Hsp90, which has been shown to be essential for the regulation of steroid receptor signaling. While it is clear that FKBP51 can associate with Hsp90, the involvement of Hsp90 as a mediating factor in the effects of FKBP51 often remains unclear due to the many pathways described for FKBP51.[23–26]

Discovery as well as motivation to study FKBP51 and other TPR domain proteins is related to the study of steroid hormone receptors (SHRs). FKBP51 and the glucocorticoid receptor (GR), which is part of the SHR family, were shown to form a negative feedback loop. Increased expression of FKBP51 resulted in the reduction of transcriptional activity of these receptors. Mass spectrometry studies[27] showed that FKBP51 stabilizes binding of cochaperone p23 in GR/Hsp90/Hsp70/ATP complexes, whereas FKBP52 leads to its release, preparing the complex for nuclear translocation. Thus, the reduction of GR reporter activity by FKBP51, could be associated with an attenuated translocation rate of GR to the nucleus.[28] Since it could be shown that the FD67/68DV mutant, which lacks PPIase activity on peptide substrates, retains GR inhibitory activity, it can be assumed that the PPIase activity of the FK1 domain is not required for this mechanism of action. However, amino acid 119 of the FK1 domain was found to determine the different activities of FKBP51 and FKBP52. While proline (FKBP52/FKBP51^{L119P}) supports receptor activation, leucine (FKBP51/FKBP52^{P119L}) inhibits it.[27,29,30]

Additional studies on interactions of FKBP51 with GR and other SHRs were published. In these studies, various interactions of FKBP51 with physiological and pathological signaling pathways were observed. However, the exact molecular mechanisms could not be fully understood.[31–35]

A recent study by Baischew et al. attempted to map the interaction interface of FKBP51 with GR. They were able to identify 46 crosslinks between FKBP51 and GR in complex. These interactions were not exclusively restricted to one domain of FKBP but included all three domains. Strikingly, the addition of ligands for FKBP51^{FK1} eliminated some interactions of the FK1 domain with GR, wheras the complex is still formed and the interactions of the FK2 and TPR domains were still detectable. Thus, these could be identified as mainly responsible for the formation of the complex, explaining the lack of effect of FKBP51^{FK1} ligands on GR-mediated depression.[1]

Several studies also showed an interaction of FKBP51 with Akt. The activity of Akt, which is dependent on the phosphorylation of S473, was reduced by the overexpression of FKBP51. It is assumed that the FK1 domain of FKBP51 recruits Akt whereas the TPR domain recruits PH domain and leucine-rich repeat protein phosphatases (PHLPP), which regulates the phosphorylation of S473. This may have a major impact on the various signalling pathways where Akt serves as a regulator. However, the exact

modes of actions of this interaction also are not completely understood and could not be confirmed in each study.[36–41]

FKBP51 has also been described as a regulator of the Nuclear Factor 'Kappa-Light-Chain-Enhancer' of Activated B-Cells (NF- kB) and thus as a potential drug candidate for NF-B-mediated inflammation and cancer. NF- kB belongs to a family of transcription factors which influences several cellular processes. Previous studies already addressed the elucidation of the interaction mechanism, which among others resulted in the identification of members of the IKK complex (inhibitor of nuclear factor kappa-B kinase subunits) as interaction partners. However, also in this case the exact roles of the FKBP domains could not be fully clarified and are controversially discussed within the scientific community.[42–49]

Various other interaction partners for FKBP51, like glomulin or ion channels, were identified and investigated. However, the full explanation of the mechanism of action always remained unclear. An overview of the identified interaction partners is shown in the following figure.[22]

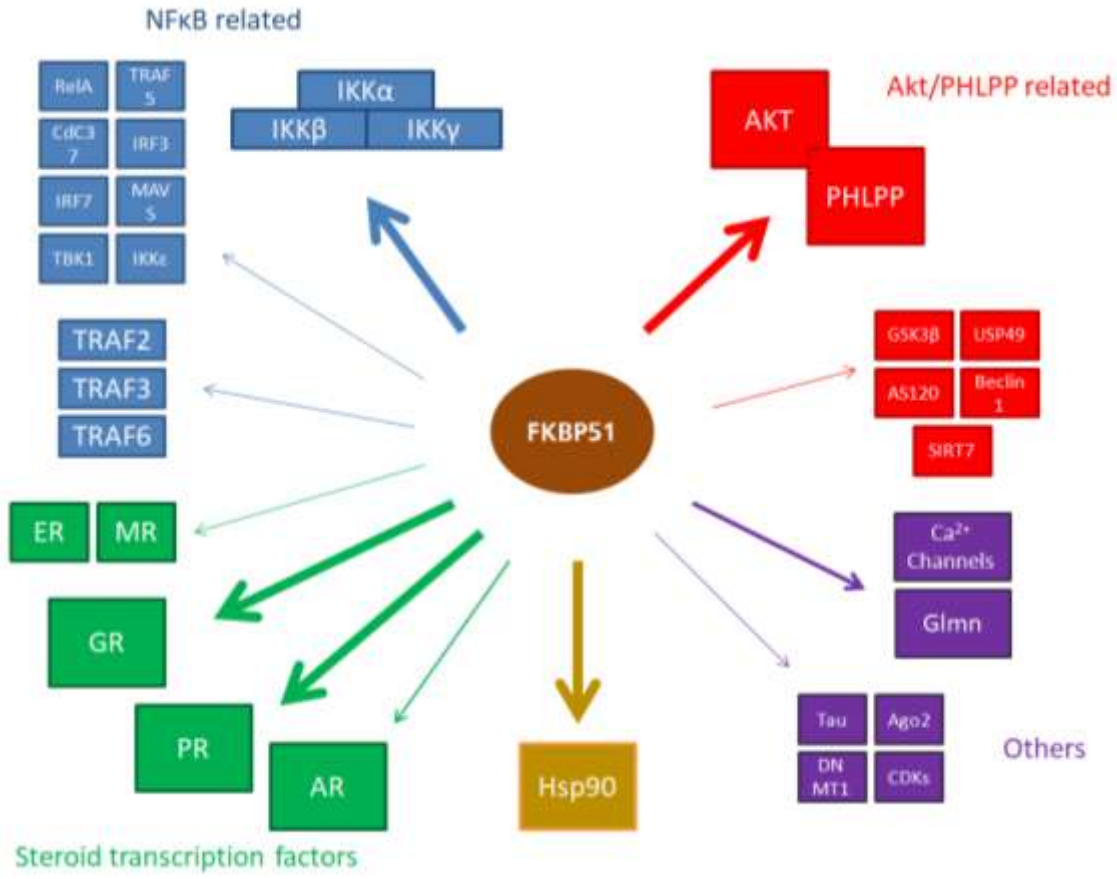


Figure 2: Overview of the interaction partners of FKBP51. More studied interactions have been indicated by thicker arrows; adapted from Ref [22].

2.2.1. Druggability of FKBPs

Due to their high sequence identity, the differentiation between FKBP51 and its counterpart FKBP52 by ligands proved to be problematic for a long time. In 2015, a study by Gaali et al. identified the first selective ligand for FKBP51. A ligand, which was actually designed for a bumb-and-hole study to show artificial selectivity between the wild-type proteins and their F67V mutants, surprisingly showed affinity for wild-type FKBP51. Examination of the co-crystal structure of this ligand with FKBP51 showed that binding was enabled by a conformational change of the protein in which Phe67, which was expected to prevent binding of the ligand to FKBP51, surprisingly stabilized an out conformation contacting lysine residues 58 and 60. The corresponding residues of FKBP52 (Thr58 and Trp60) did not allow this conformational change and therefore the binding of the ligand.[50–52]

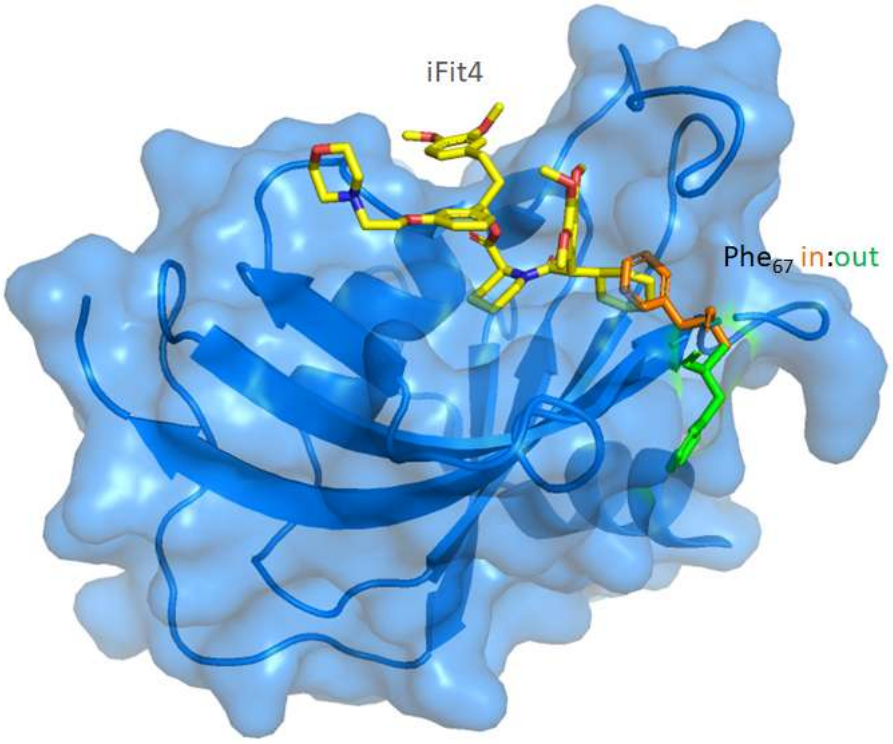


Figure 3: Binding of the selective ligand iFit4 to the FK1 domain (PDB-ID: 4tW7) of FKBP51 and the resulting conformational change from Phe67-in to Phe67-out; Phe67-in superimposed from PDB-ID: 5OBK; adapted from Ref [22].

Further ligand development led to the two best selective ligands for FKBP51 to date, SAFit1 and SAFit2. These were already shown to be an important tool for understanding the biological function of FKBP51 in recent years. However, since they only address the FK1 domain of FKBP51, for which domains have been discussed previously, their potential might be limited. In addition, the ligands were unsuitable as potential drugs due to their chemical and biological properties.[50,51]

In another approach, based on the cocrystal structure of FKBP-FK506 complexes and computaional design, another series of ligands was identified. The [4.3.1] bicycles are characterized by a bridging of the pipecolate which rigidifies the ligand. However, the structures obtained showed high affinities for numerous human FKBPs, including FKBP51 and its off-targets FKBP52 and FKBP12 and are thus considered pan-selective.[53,54]

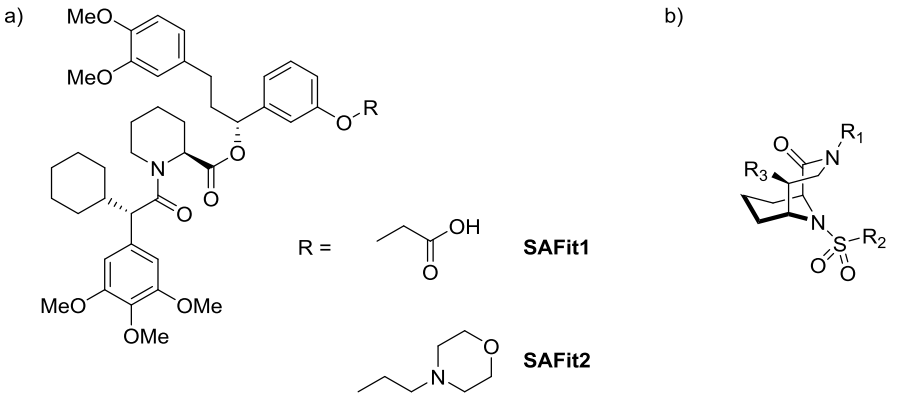


Figure 4: a) Structures of selective ligands SAFit1 and SAFit2; b) Basic structure of bicyclic ligands with variable positions $R_{1\text{-}3}$.

A potential approach to address selectivity issues, and most importantly, since these ligands were designed for the FK1 domain of FKBP51, to address each domain of the protein is the recently developed concept of targeted protein degradation (TPD). Using the ubiquitin proteasome system (UPS) complete degradation of the protein is achieved in a three-step process.[55]

2.3. Targeted protein degraders

2.3.1. The ubiquitin proteasome system

The UPS is essential for various biological processes such as cell cycle progression, signal transduction or the maintenance of genome integrity. In this process, a substrate is ubiquitinated with participation of several enzymes (Fig. 5). In the first step of this process, an enzyme (E1) activates ubiquitin in an ATP-dependent reaction and forms an acylamide acid mediator at the C-terminus of ubiquitin. This enables the transfer of ubiquitin to another enzyme E2. An E3 ligase then recognizes the target substrate for degradation and catalyzes the ubiquitin transfer from E2 to a lysine residue of the substrate. Ubiquitin itself has multiple lysine residues, allowing this process to be repeated multiple times. The resulting polyubiquitin chain can be recognized by the proteasome, resulting in degradation of the substrate and the recovery of ubiquitin.[56,57]

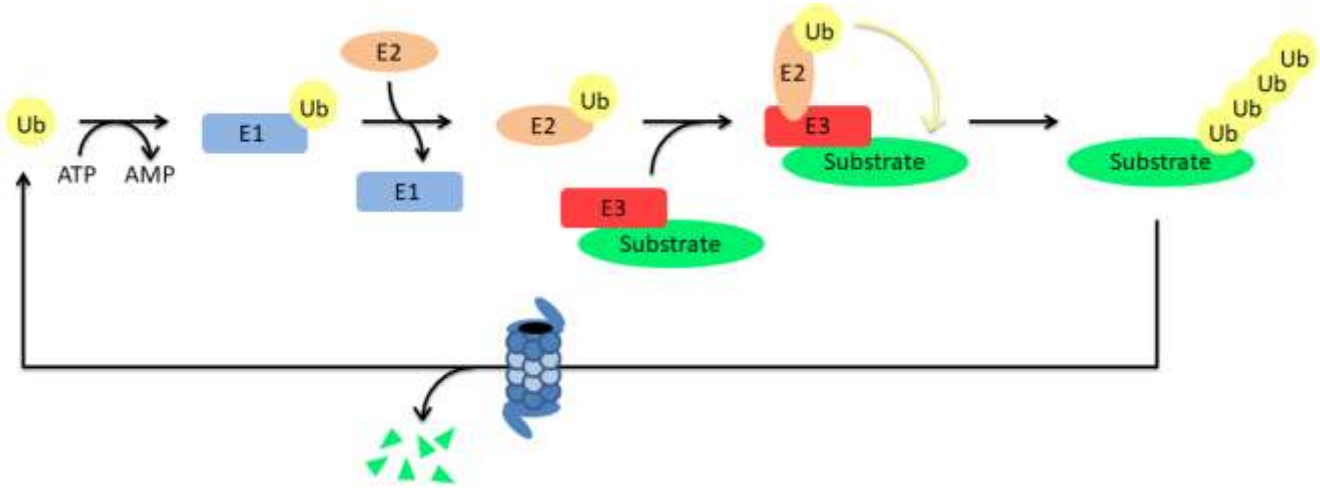


Figure 5: A Cycle of the ubiquitin-proteasome system.

In 2001, Crews et al. described a method to hijack this process by the use of heterobifunctional molecules called porteolysis targeting chimeras (PROTACs).[58]

2.3.2. Proteolysis targeting chimeras (PROTACs)

In principle, PROTACs consist of three connected building blocks: a ligand, which is responsible for the binding of the protein of interest (POI), a ligand that binds an E3 ligase and a linker that connects both ligands. Simultaneous binding of the POI and an E3 ligase creates proximity between the two proteins, and therefore enables ubiquitin to be transferred to the POI. This finally leads to the degradation of the POI (Fig. 6).[59–61]

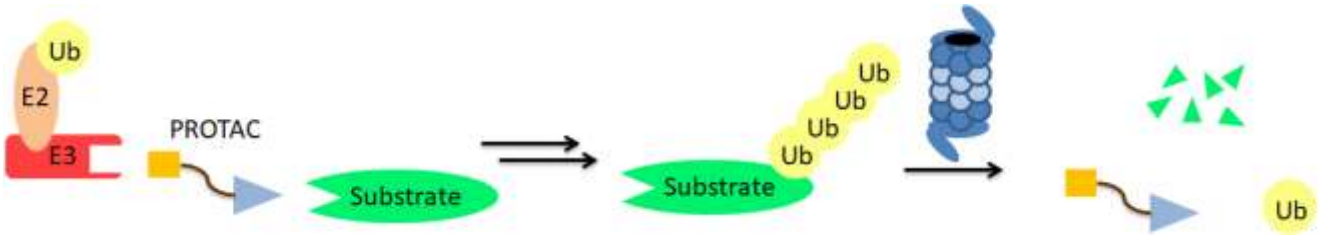


Figure 6: A PROTAC creating proximity between an E3 ligase and a target proteins resulting in its ubiquitination and degradation.

This process has three major advantages. First, as the PROTAC is not degradated with the POI, its catalytic mode of action enables the PROTAC to bind further substrates and lead to their proteolysis, which allows lower dosis compared to classical inhibition. Second, since they degrade the entire protein instead of inhibiting only one domain, they are capable of affecting protein functions that were previously considered undruggable. This ability may be of use for FKBP51, since in its interactions the

functions of the respective domains, as described before, remained unclear. In addition, PROTACs usually show higher selectivity than the ligands for the POI they are derived from. This is a result of their mechanism of action, in which protein-protein interactions are essential for the formation of the ternary complex.[62–64] One of the best known examples is the BRD4 selective PROTAC MZ1. It is based of the pan-BET selective bromodomain inhibitor JQ1, which was linked to a VHL ligand. For the PROTAC, as for the ligand itself, selective binding of BRD4 over its homologues BRD2 or BRD3 by ITC could not be detected. However, the PROTAC showed selectivity for the degradation of BRD4.[65]

In a study in 2017, Alessio Ciulli published the first ternary crystal structure of a PROTAC with the structure of MZ1 in complex with its POI and VHL. Surface mutagenesis swap and proximity binding assays supported his theory that the stability of the ternary complex is crucial for the selectivity of the PROTAC. Furthermore, based on this crystal structure, he was able to design a PROTAC (AT1) that exhibited excellent selectivity for the degradation of BRD4 over BRD2 and BRD3. Thus, it could be shown that the interactions between the proteins are crucial for degradation.[66]

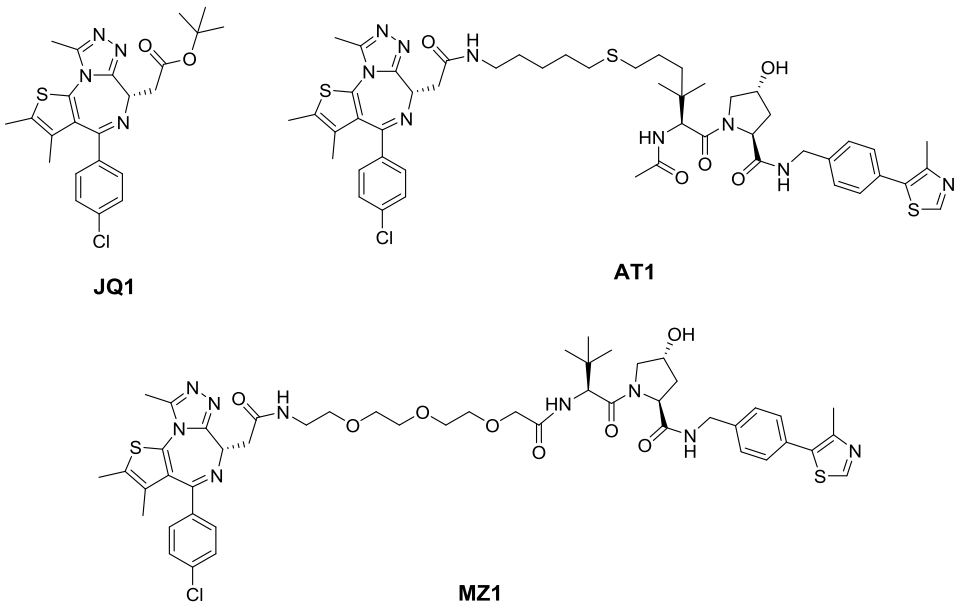


Figure 7: Structures of pan-BET selective bromodomain inhibitor JQ1 and its PROTACs MZ1 and AT1.

Since more than 600 E3 ligases are postulated for the human genome and the POI can also be varied, there are numerous possibilities for the synthesis of PROTACs. Despite this high number of possible E3 ligases, the number of ligases used for PROTACs is rather small. Cereblon (CRBN) and von Hippel-Lindau (VHL) based PROTACs have dominated the field to date. One of their characteristics is that specific binders are well-known, they are structurally and biophysically well characterized, and they have acceptable physicochemical properties. Although a few other ligands for E3 ligases have also been described (e.g. mouse double minute 2 (MDM2) or inhibitors of apoptosis proteins (IAPs)), the

progress of compounds based on these ligands has been rather slower, probably due to the greater complexity of the ligands. However, due to the steady increase of interest from academia and industry, the identification of additional E3 ligase ligands has been reported with increasing frequency in recent years.[57,67–69]

2.3.2.1. Linker design

Since the influence of the stability of the ternary complex on the degrader activity has been demonstrated, many attempts were made to improve this stability by varying the linker. Structure-activity relationships (SARs) first showed a clear correlation between the length and chemical composition of the linker and the properties of stiffness, hydrophobicity and solubility of PROTAC. However, these were shown to be very time-consuming and required a high synthetic effort.[70,71]

In order to rational optimize the linker several attempts were made based on structural biology and computational studies. These studies followed two basic principles: After identifying the protein-protein interactions, either the linker was evolved to further contribute to cooperativity through additional interactions, or the degrees of freedom of the linker were reduced so that the entropic loss due to binding of the PROTAC by both proteins was reduced. In this way, after identifying the stabilizing interactions of the PEG linker and VHL from the cocrystal structure of SMARCA2 and VHL in complex with P1, Farnaby et al. by introducing a phenyl moiety succeeded in establishing an additional stacking interaction and at the same time increasing the stiffness of the linker without losing the important PEG interactions. This resulted in the optimized SMARCA2/4 degrader ACBI1 (Fig. 8a).[72]

Another example is provided by a study by Ciulli et al. in which molecular dynamics simulations using the cocrystal structure of BRD4 and VHL in complex with the PROTAC MZ1 indicated that a macrocyclic linker could improve the efficiency of MZ1 by reducing the degrees of freedom of the PROTAC and simultaneously preorganizing BRD4 and VHL for the formation of a ternary complex. The resulting macrocyclic PROTAC exhibited lower binding affinity for BRD4 as well as VHL in the respective binary complex compared to MZ1, however, it showed comparable degradation potency, indicating a higher efficiency of ternary complex formation (Fig. 8b).[73]

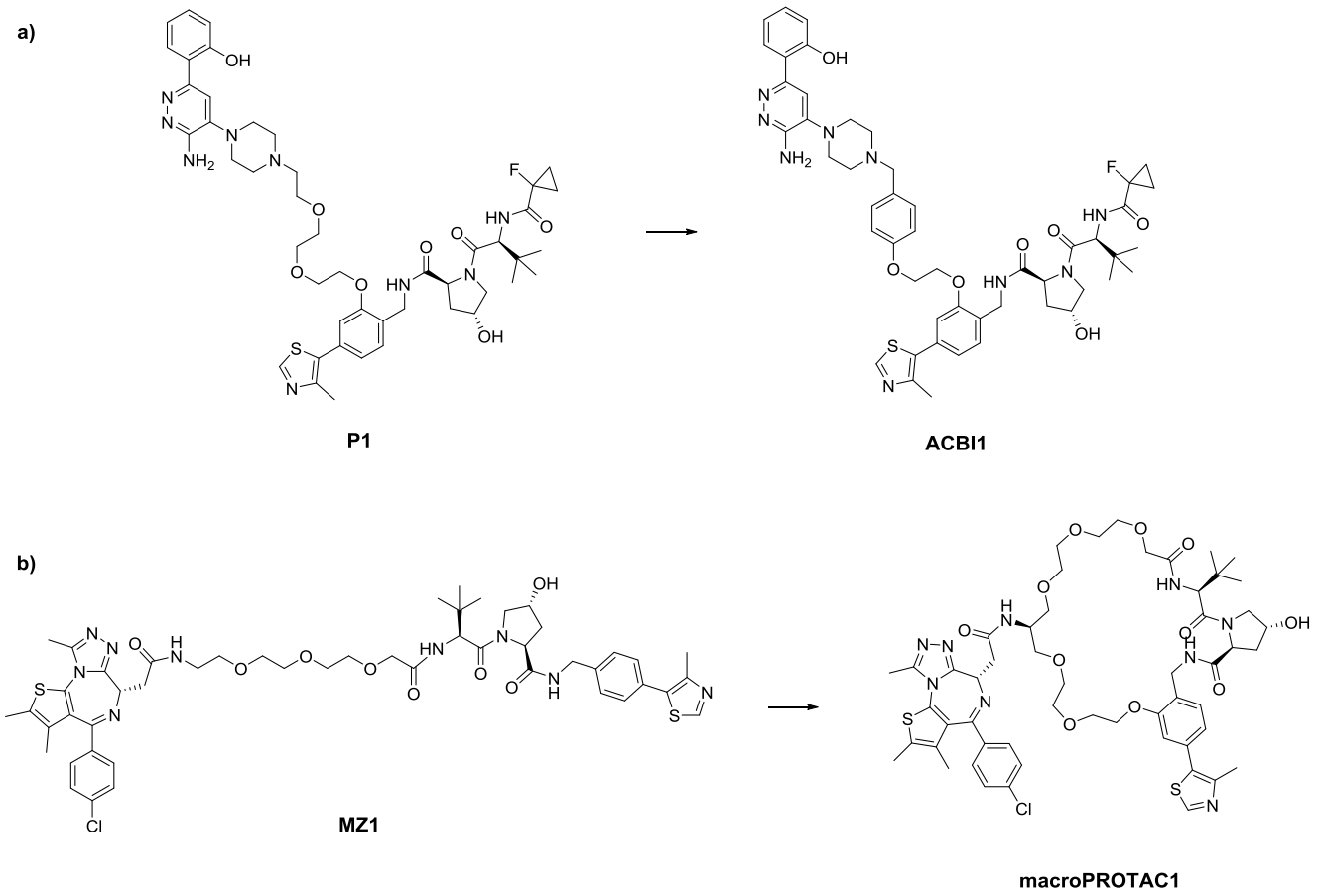


Figure 8: Exemplary rational linker development. a) Development of ACBI1 by establishing a additional stacking interaction and enhancement of stiffness; b) Development of macroPROTAC1 by limitation of the degree of freedom of MZ1.

While these studies on the rational optimization of PROTACs can be considered a great success, they all share the dependence on the prior isolation of a co-crystal structure of the ternary complex. Thus, two requirements must be fulfilled in order to apply these optimization methods: A PROTAC has to be synthesized which forms a stable ternary complex and this complex has to be crystallizable.

2.3.3. PROTACs for FKBP12

After the principle of PROTACs was first described in 2001 by the group of C.M. Crews, research on PROTACs was closely linked to the protein FKBP12. Thus, in 2004, Crews described the first cell-permeable PROTAC, which consisted of the FKBP ligand AP21998, the minimum recognition domain of VHL (ALAPYIP) and a poly-D-arginin tag to confer cell permeabilty, which showed activity towards $FKBP12^{F36V}$. Similarly, FKBP12 served as one of the first two in vivo examples of direct small molecule-triggered recruitment of target proteins to the proteasome.[74]

2017, in order to find new E3 ubiquitin ligases as PROTAC targets the group of C.M. Crews constructed a FKBP12^{F36V} binding PROTAC (dTAG13).[75] In a study by Nabet et al. in 2018, dTAG13 was tested together with its *meta*-variant (dTag51) for binding and degradation of FKBP12^{F36V} and FKBP12^{wt} in cells. Here, it has been shown that dTAG13 binds FKBP12^{F36V} and CRBN favorably, but has only weak activity towards FKBP12^{wt}. In contrast, the *meta*-variant dTag51 was able to degrade both FKBP12^{wt} and its mutant FKBP12^{F36V}. The study also tested the degradation of luciferase-coupled FKBP12 in vivo. Therefore human leukemia cells were injected into the bone marrow of mice and after administration of dTag a rapid and permanent decrease in bioluminescence was observed, which was reversible after withdrawal of the drug.[76]

Also, the first description of global knockdown of a protein by using PROTACs in large animal models was focused on FKBP12. In 2019, Sun et al. described knockdown of FKBP12 in nearly all organs except the brain by RC32, a PROTAC they developed, which they hypothesized was a result of RC32's inability to pass the blood-brain barrier. Moreover, they demonstrated the reversibility of this effect by determining the protein levels after withdrawal of medication. Mice, rats, bama pigs and rhesus monkeys were taken as test objects for this purpose.[77]

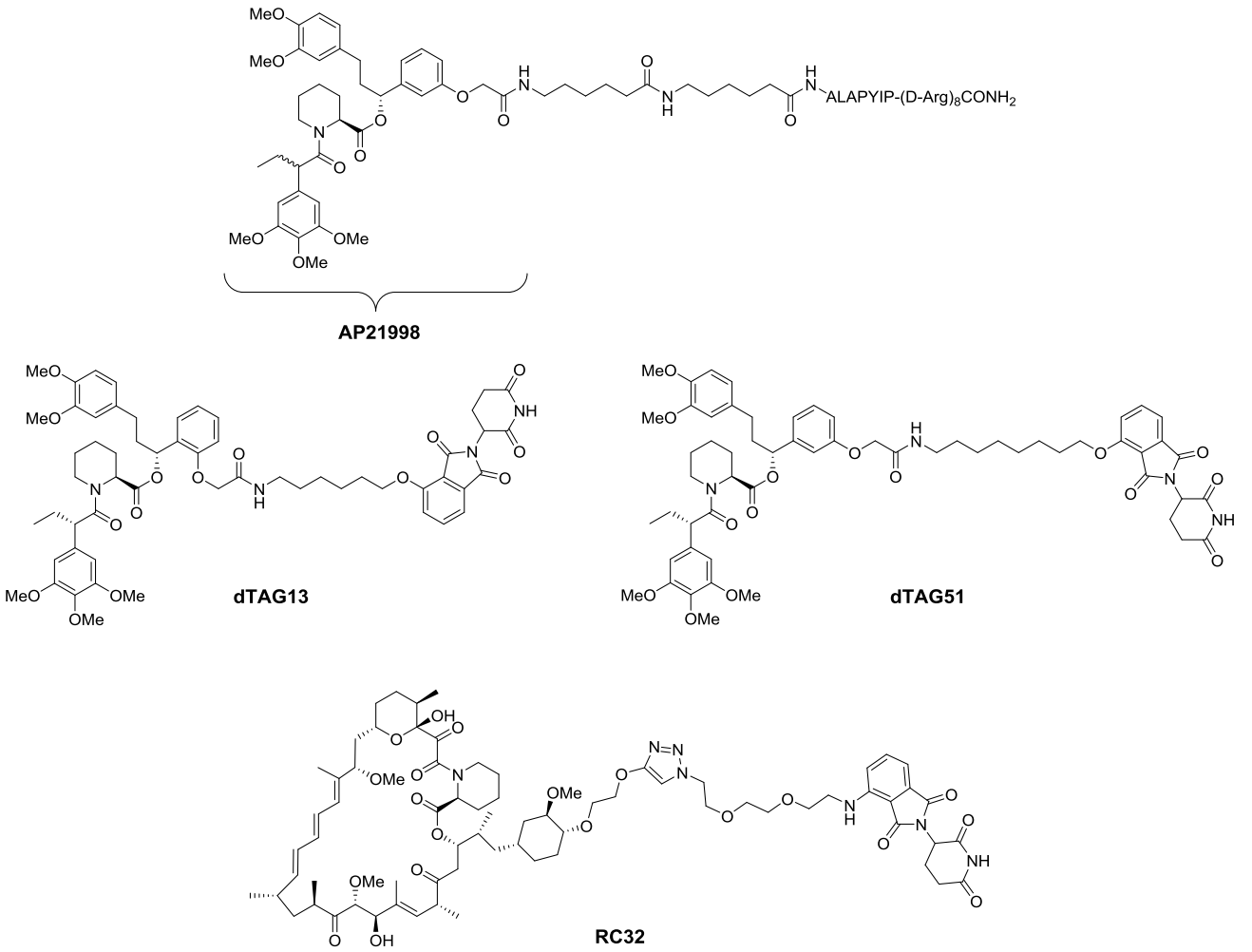


Figure 9: Structures of several FKBP12 PROTACs.

2.3.4. PROTACs for FKBP51

While due to the close linkage of studies on PROTACs with FKBP12 a couple of partially highly effective and selective PROTACs for FKBP12 have already been published, the state of research on FKBP51 shows a completely different picture with only one publication addressing this topic.
In her dissertation from 2020, Dr. Tianqi Mao described the synthesis of a PROTAC library based on the literature known and previously described lead structures of SAFit and [4.3.1] bicycles, respectively. In this work, 60 compounds were synthesized, characterized and tested for binding of FKBP51, FKBP52 or FKBP12 by FP-assay and degradation of FKBP51 by Western blots.[2]
MTQ202 was described as the only active PROTAC for FKBP51. It showed a K_i of 24 nM for FKBP51FK1 and 532 nM for FKBP12 and was able to degrade FKBP51 in both HEK and Hela cells. However, MTQ202 showed a rather low activity range between 125 nM and 1 μM, indicating moderate activity, as well as a rather strong hook effect (chapter 2.3.5.). Furthermore, no comment was made on the selectivity of the degradation, which indicates the requirement for further studies.[2]

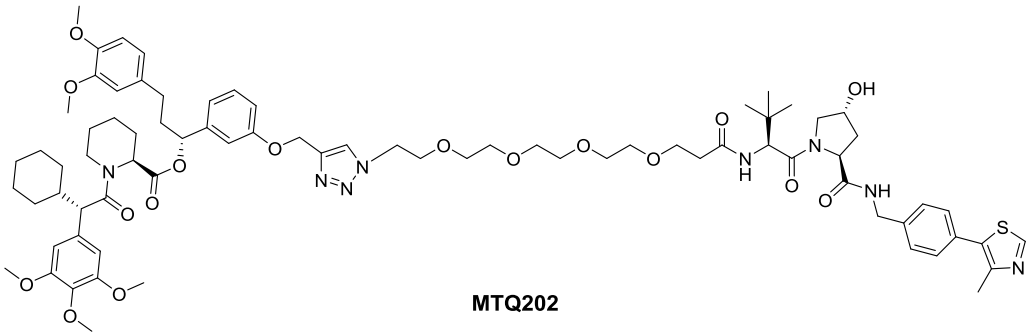


Figure 10: Structure of the first FKBP51 PROTAC.

2.3.5. Hook effect

The Hook effect basically refers to a reduction of activity in the presence of very high concentrations of an analyte in a three-component system (Fig. 11b). In this case, the formation of several binary complexes competes with the formation of the ternary complex and can be favored or discriminated depending on the dissociation constant (Fig. 11a). Therefore, a high cooperativity of PROTAC is desired, as this results in a stabilization of the ternary complex and thus a reduction of the Hook effect.[66,78]

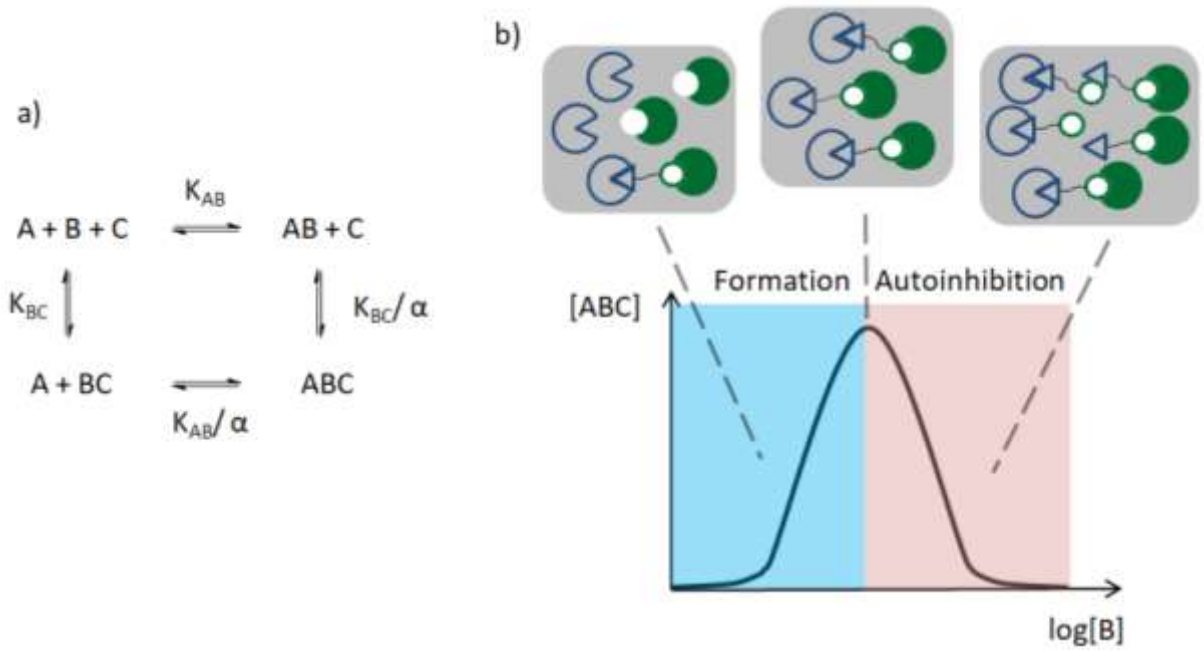


Figure 11: a) Thermodynamic equilibrium for the reversible formation of ternary complexes; b) Diagram of the concentration of the ternary complex ([ABC]) as a function of the total number of the bridging species ([B]), respectively the PROTAC.

3. Aim of the project

In this project a highly active and selective PROTAC for FKBP51 should be generated. For this purpose, the first PROTAC for FKBP51 described by Dr. Tianqi Mao[2] will be analyzed for selectivity and the library synthesized by her, which served as a basis for the development of MTQ202, should be extended.

The activity and selectivity data of the resulting library should then be used to generate potential structure-activity relationships. On the basis of the data obtained from the screening library, an optimization of the PROTACs should be performed.

The fundamental influencing factors of linker length and rotational freedom of the linkers should serve as starting points for this optimization. It is expected that the resulting compound will be a highly active and selective PROTAC for FKBP51.

4. Results and discussion

4.1. Design of a PROTAC library

Since there is no rational approach for the design of PROTACs by now, a library for screening should be created as a first step. For this purpose, the individual components were synthesized and then linked combinatorially. POI ligands based on the two established FKBP ligands were synthesized and coupled with the most common E3 ligase ligands. For VHL, two different ligands were used in order to generate different exit vectors and thus different possiblities for complex formation between the proteins. Linkers with functional groups that allow coupling to be realized in a straightforward manner were used for this purpose.

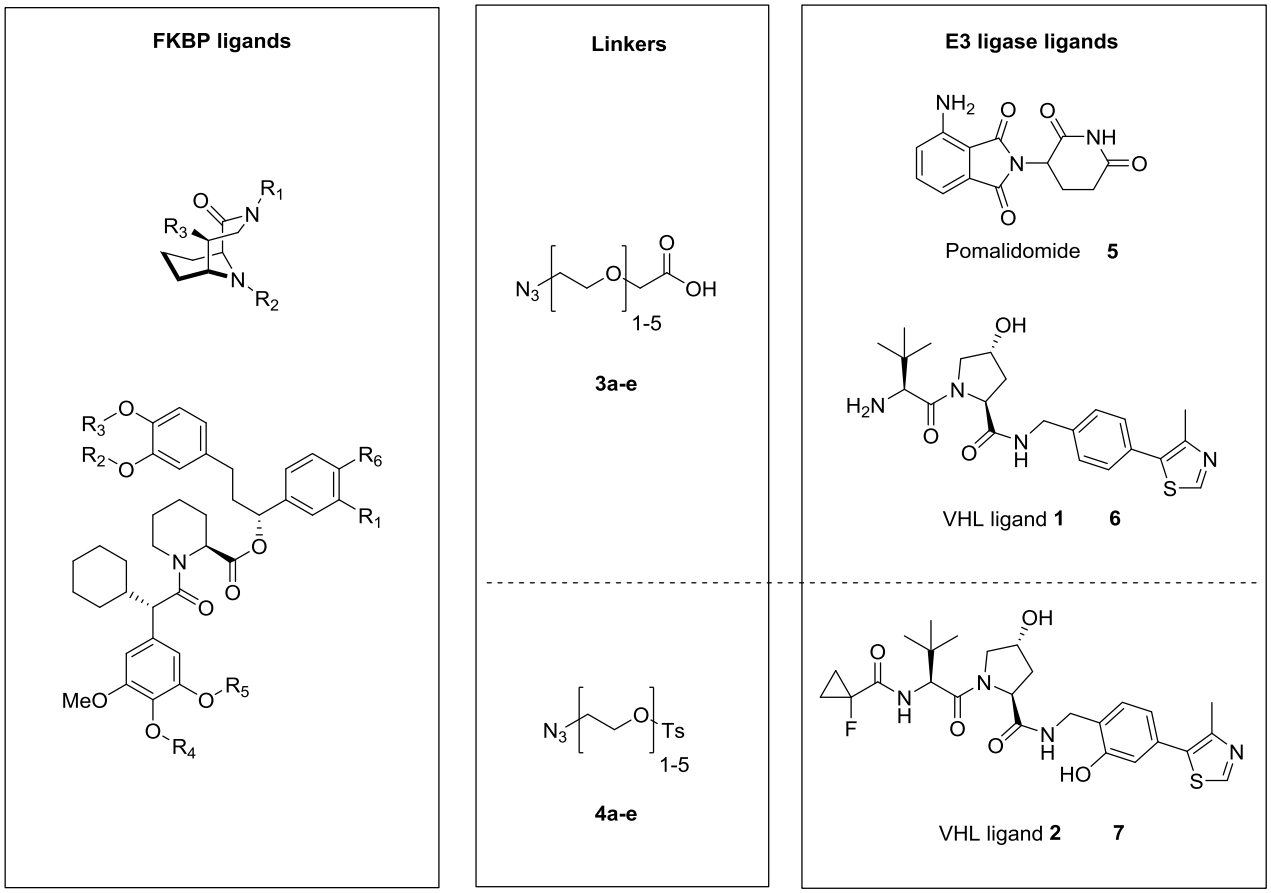
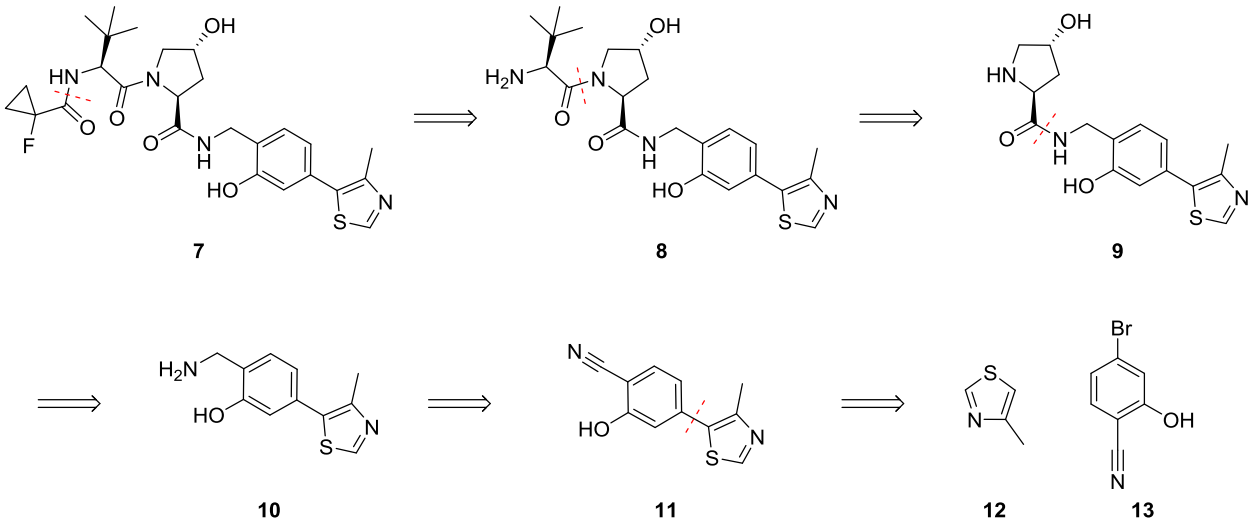


Figure 12: Overview of the building blocks to be synthesized; ligands **5** and **6** were coupled to linkers **3a-e** and ligand **7** to **4a-e**, which is indicated by separation with a dashed line.

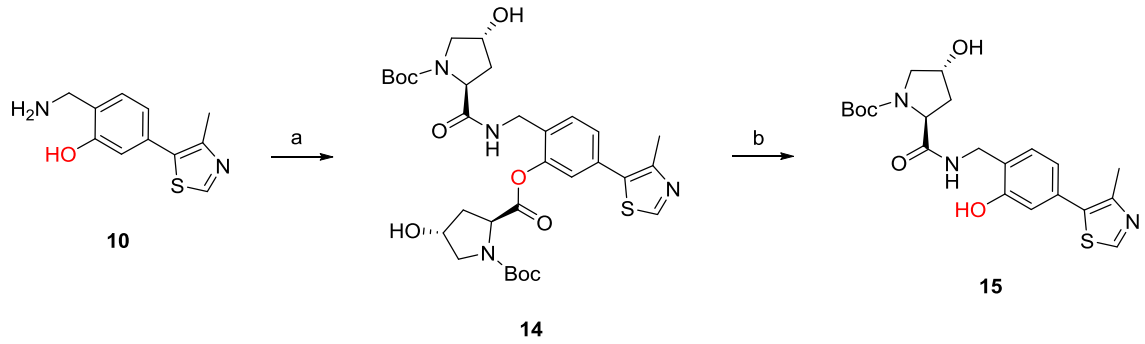
4.1.1. Synthesis of the E3 ligase ligands

Since pomalidomide (**5**) was commercially available and VHL-ligand **1** (**6** / L**1**) was already prepared in my masterthesis only VHL-ligand **2** (**7** / L**2**) with a different exit vector had to be synthesized. This should be prepared similar to L**1** (Scheme 1).



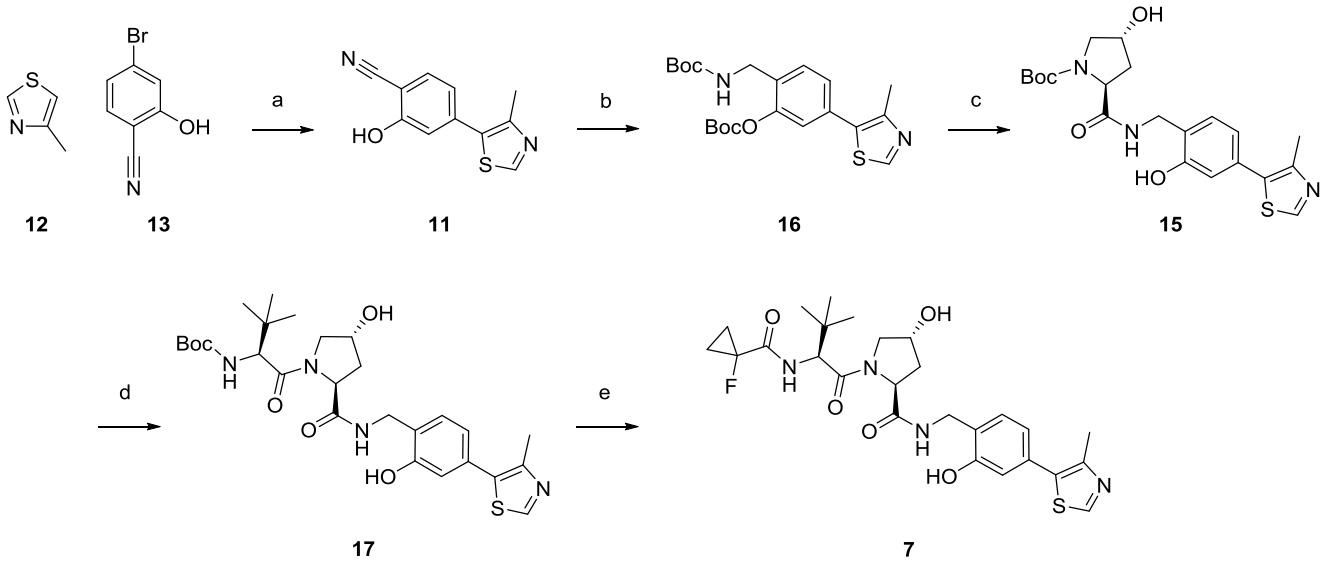
Scheme 1: Retrosynthesis of L**2**.

It soon became clear, that the additional phenolic hydroxy group (red in scheme 2) reacts similarly to the amino groups during the synthesis of the amide bonds. Here esters were formed, which subsequently had to be cleaved again.



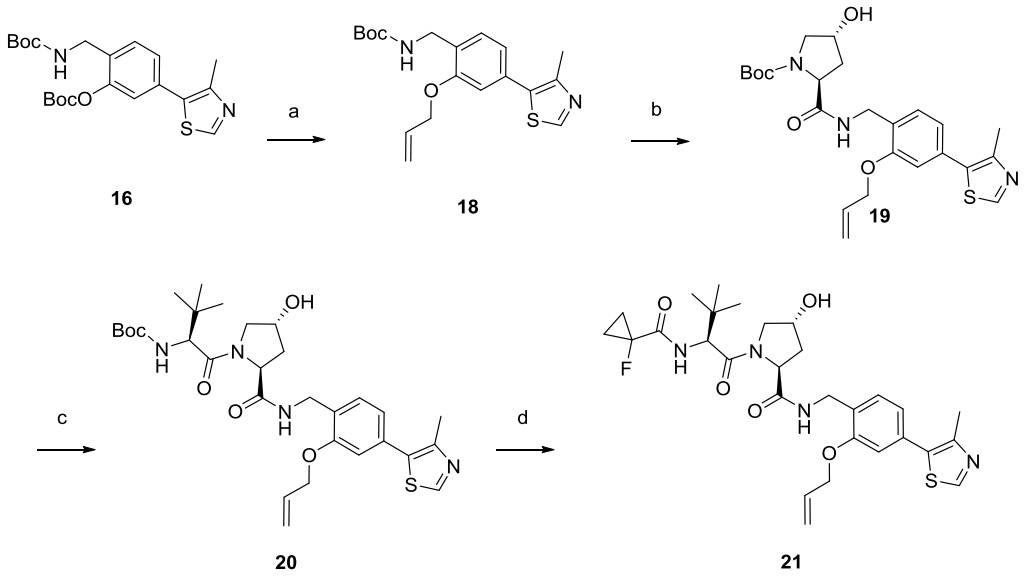
Scheme 2: Exemplary coupling step extended by ester cleavage with lithium hydroxide a) EDC, HOBT, DIPEA, *N*-Boc-*trans*-4-hydroxy-L-proline, DMF, 0 °C to rt, 3 d b) LiOH, THF/water (1:1), rt, overnight.

This way, according to the following scheme L**2** (**7**) was synthesized.



Scheme 3: Synthesis of VHL-ligand **2**. a) $Pd(OAc)_2$, KOAc, DMF, 120 °C, overnight, 72 %; b) $NaBH_4$, $CoCl_2$, Boc_2O, MeOH, 0 °C, 2 h, 51 %; c) 1) TFA, DCM, rt , 2 h; 2) EDC, HOBT, DIPEA, *N*-boc-4-hydroxy proline, DMF, 0 °C to rt, 3 d; 3) LiOH, THF/water (1:1), rt, overnight, 45 %; d) 1) TFA, DCM, rt , 2 h; 2) EDC, HOBT, DIPEA, *N*-boc-*tert*-leucin, DMF, 0 °C to rt, overnight; 3) LiOH, THF/water (1:1), rt, overnight, 87 %; e) 1) TFA, DCM, rt , 3 h; 2) HATU, TEA, 1-fluorocyclopropane carboxylic acid, DCM, rt, overnight; 3) LiOH, THF/water (1:1), rt, 3 h, 53 %.

The students Christian Brudy and Horst Wilhelm Schuchmann contributed to these experiments. However, due to the reactivity of the hydroxyl group, two equivalents of the respective amino acids had to be used in order to ensure a complete conversion. To avoid this, another attempt was made to synthesize the ligand. Here, the hydroxyl group was allyl-protected at the beginning of the synthesis.

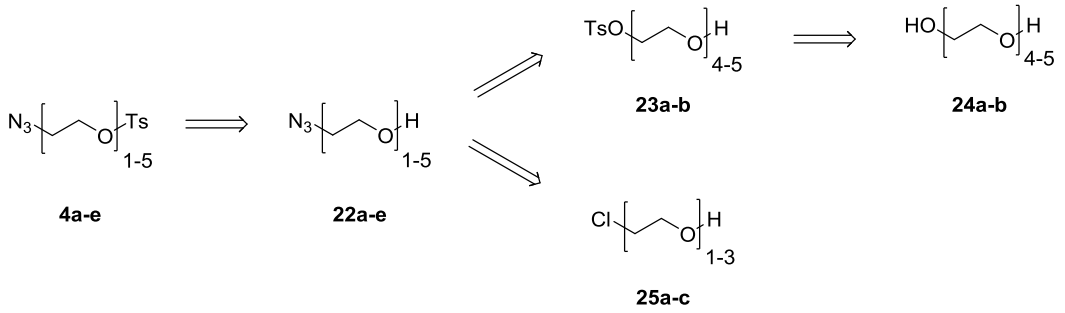


Scheme 4: Alternative synthesis of VHL-ligand **2**. a) 1) LiOH, THF/water/MeOH (1:1:1), rt, 5 d; 2) allyl bromide, K_2CO_3, acetone, 65 °C, 1 h, 90 %; b) 1) TFA, DCM, rt, 2 h; 2) EDC, HOBT, DIPEA, *N*-boc-4-hydroxy proline, DMF, 0 °C to rt, 3 h, 87 %; c) 1) TFA, DCM, rt , 2 h; 2) EDC, HOBT, DIPEA, *N*-boc-*tert*-leucin, DMF, 0 °C to rt, 2 d, 91 %; d) 1) TFA, DCM, rt , 2 h; 2) EDC, HOBT, DIPEA, 1-fluorocyclopropane carboxylic acid, DCM, 0 °C to rt, overnight, 50 %.

The student Malte Erbe contributed to these experiments. In this way, the quantities of amino acids used, as well as reaction steps were reduced. In addition, the ligand obtained can be bound to a solid phase before being deprotected, which could simplify further synthesis.

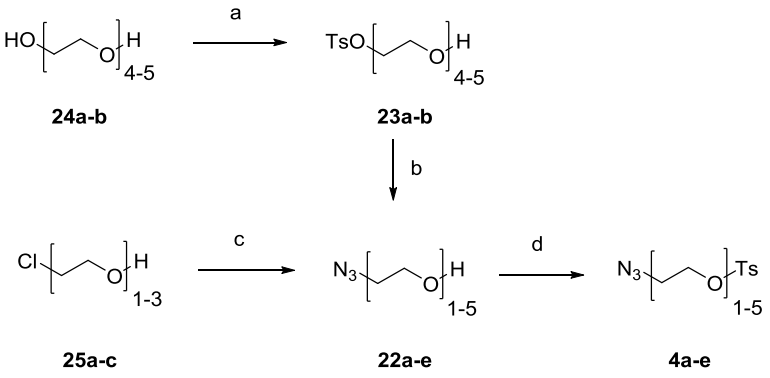
4.1.2. Synthesis of the linkers

Since linker building blocks having an azide-group on one and a carboxylic acid on the other side, were already prepared and linked to L**1** and pomalidomide in my master thesis, only the tosylated linkers had to be prepared and linked to L**2** according to the following scheme.



Scheme 5: Retrosynthesis of the tosylated linkers **4a-e**.

Since chlorinated ethylene glycol derivatives were commercially available for the linker lengths 1-3 at low prices, a synthesis step could be skipped here. In both cases, the nucleophilic substitution with sodium azide did not show any noticeable difference in yield. Only the linker length n = 1 gave a significantly lower yield, which can probably be explained by the volatility of the product.



Scheme 6: Synthesis of the toylated linkers **4a-e**. Yields are given in ascending linker length from 1 to 5. a) Ag_2O, KI, TsCl, DCM, 0 °C to rt, 1 h, 60 %, 51 %; b) NaN_3,DMF, rt, 2 - 3 d, 94 %, 97 %; c) NaN_3, NaOH, water; rt to 60 °C, 4 - 5 d, 65 %, 98 %, 97 %; d) TsCl, pyridine, DCM, 0 °C to rt, 2 - 4 d, 60 %, 82 %, 75 %, 88 %, 64 %.

The student Horst Wilhelm Schuchmann contributed to these experiments.

4.1.3. Design of bicyclic PROTACs

Considering that the bicyclic compounds synthesized in the Hausch group have high affinities for FKBP51, 52, and 12, they represent a good starting point for the synthesis of PROTACs for these proteins. Most of these compounds do not exhibit sufficient selectivity for exclusively one of these proteins. However, this was expected to not be a major problem because of the additional selectivity PROTACs intrinsicely possess through the need to form a terniary complex for protein degradation. In fact, quite the opposite is possible, as these compounds have the potential for PROTACs for each of these proteins.

Looking at the general structure of these bicycles, as well as the co-crystal structure of a bicycle binding to FKBP51FK1, it became clear that there are three obvious sites suitable for coupling to a linker-E3-ligase-ligand-complex (L-E3LL-complex) (Fig. 13a). For residue R_2 two exit vectors were identified (Fig. 13b), since its aromatic residue could be substituted in *meta* as well as in the *para*-position.

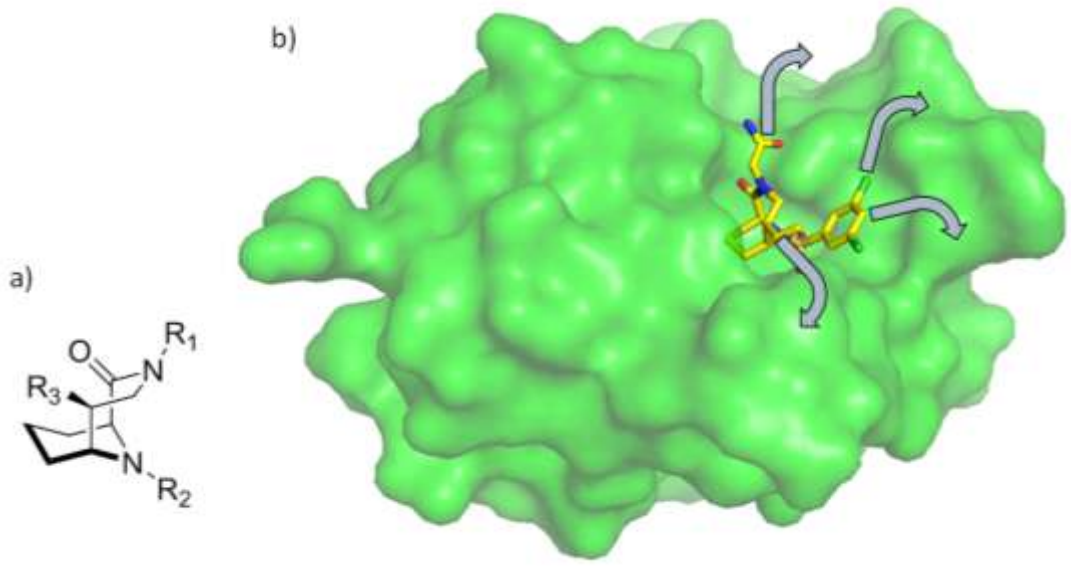
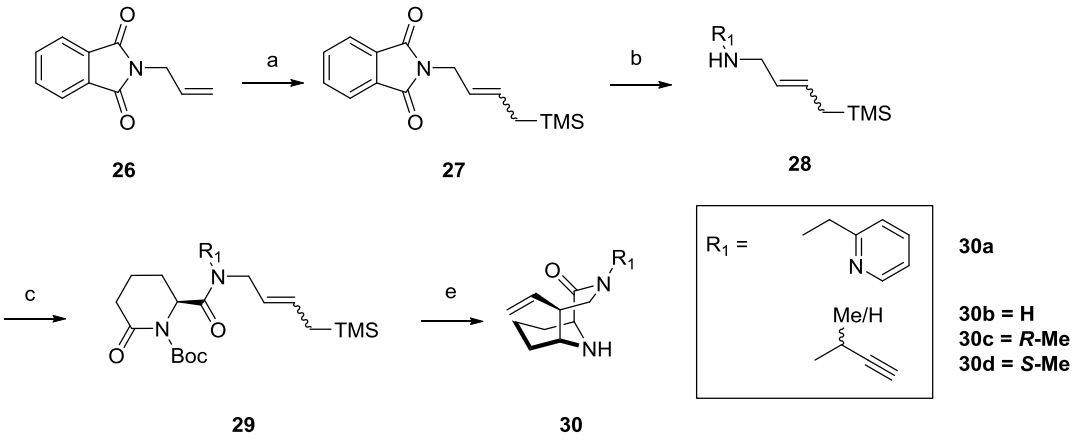


Figure 13: a) General structure of bicyclic compounds synthesized in the Hausch group. b) Co-crystal structure of a bicycle binding to FKBP51 (potential exit vectors are indicated by arrows); crystal isolated and measured by Dr. Christian Meyners (PDB-ID: unpublished by now).

4.1.3.1. Synthesis of the bicycles

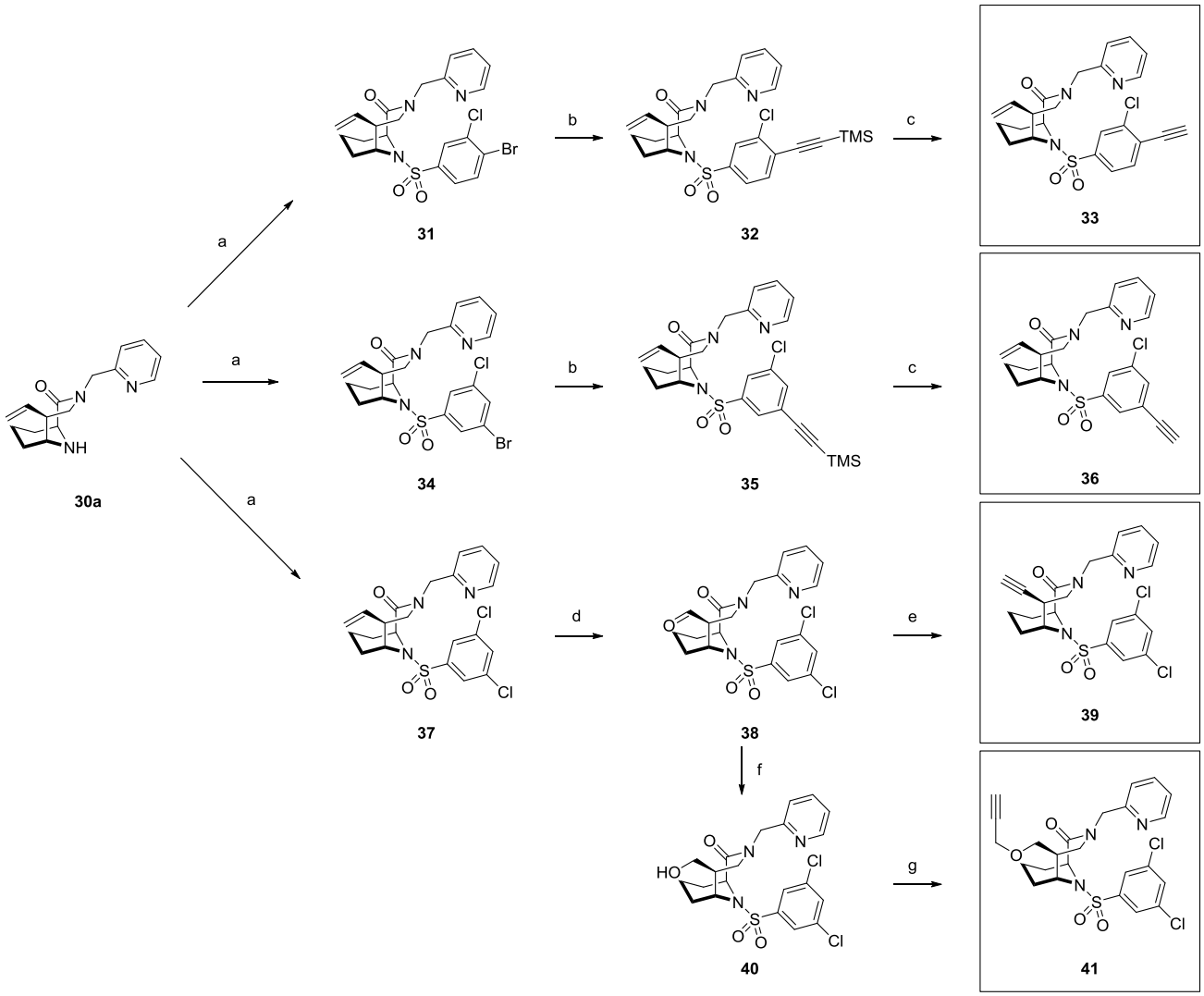
The bicyclic compounds were generally synthesized according to the following scheme. The bicycles with alkyne in R_1 position (**30b-d**) were already synthesized by the former PhD student Dr. Tianqi Mao and reproduced in my master thesis or by the student Horst Wilhelm Schuchmann, therefore yields and compound numbers in the following scheme refer to R_1 is pyridine. Thus, all further bicyclic alkynes could be prepared starting from the precursor **30a**.



26 **27** **28** **29** **30**

Scheme 7: Synthesis of bicyclic compounds; yields were given for R_1 = pyridine; a) allyl-TMS, Grubbs I, DCM, 60 °C, 4 h, 72 %; b) 1) hydrazine, MeOH, 80 °C, overnight; 2) picolinaldehyde, rt, overnight; 3) $NaBH_4$, rt, 3 d; 84 %; c) 1) (*S*)-6-oxopiperidine-2-carboxylic acid, HATU, DCM, rt, 3 d; 2) DIPEA, Boc_2O, DMAP, DCM, rt, overnight, 71 %; d) 1) DIBAL-H, THF, -78 °C, 30 min; 2) HF, DCM, - 78 °C to 0 °C, 3 h, 21 %.

Precursor **30a** was coupled with different sulfonyl chlorides in R_2 and subsequently R_3 was varied according to the following scheme.



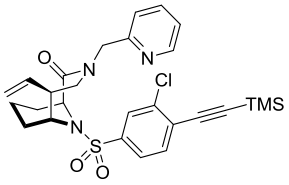
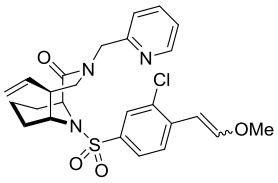
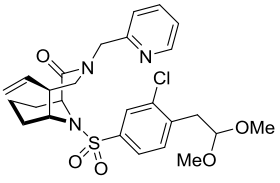
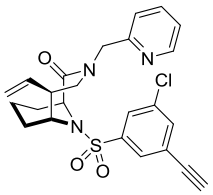
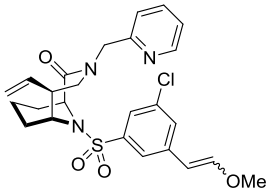
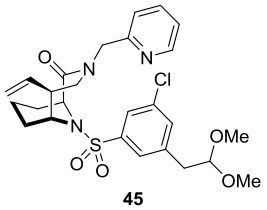
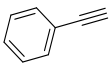
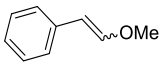
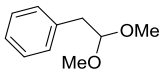
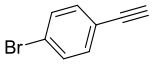
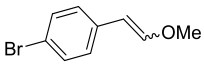
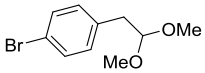
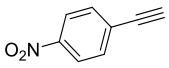
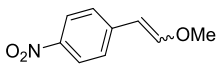
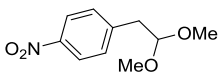
Scheme 8: Synthesis of bicyclic alkynes **33**, **36**, **39** and **41**; a) sulfonyl chloride, DIPEA, rt, 1 - 2 d, 45 - 62 %; b) ethynyltrimethylsilane, CuI, $Pd(PPh_3)_4$, TMEDA, 90 °C, 3 h, 70 - 84 %; c) K_2CO_3, MeOH, rt, 3 h, 38 - 57 %; d) 1) OsO_4, NMO, 2,6-lutidine, acetone/water (9:1), rt, overnight; 2) (diacetoxyiodo)benzene, rt, 4 h, 42 %; e) dimethyl (1-diazo-2-oxopropyl)¬phosphonate, K_2CO_3, MeOH, 0 °C to rt, overnight, 83 %; f) $NaBH_4$, EtOH, 0 °C to rt, 1 h, 56 %; g) propargyl bromide, NaH, Bu_4NI, 0 °C to rt, overnight, 56 %.

The low yields of TMS deprotection (c) can be explained by a side reaction that occurs reproducibly. In this reaction, methanol adds to the alkyne and the protected aldehyde **43** is formed. Further test reactions showed that the alkyne must be electron-poor for this to occur and $Pd(PPh_3)_4$ must be present in the reaction mixture. It can therefore be assumed that the TMS-protected alkynes used were not completely pure.

This assumption is underlined by the fact that in the case of resynthesis, in which the reactant was previously purified by preparative HPLC, this reaction did not occur, or occurred only after the addition of $Pd(PPh_3)_4$.

The fact that this reaction occurs preferentially with electron-poor alkynes is best seen directly from substrates **32** and **36**. While complete conversion occurs at the para position, the *meta* position, which is less influenced by the –M-effect of the sulfonyl, is clearly less reactive. This can also be seen in some model substrates, which are listed in the following table.

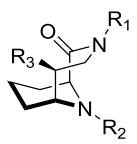
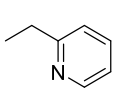
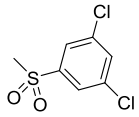
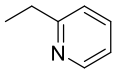
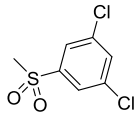
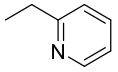
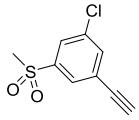
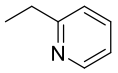
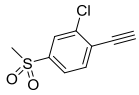
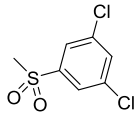
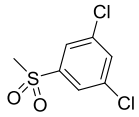
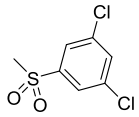
Table 1: Overview of the occuring side reaction, * = Conversion by LC-MS.

Educt	Product-1	Product-2	Conditions	Yield of P-1 and P-2 / %
 **32**	 **42**	 **43**	K_2CO_3, $Pd(PPh_3)_4$, MeOH, rt, 1 h	0 / 97
 **36**	 **44**	 **45**	K_2CO_3, $Pd(PPh_3)_4$, MeOH, 40 °C, 1 h	16* / 0* (84 % educt)
 **46**	 **47**	 **48**	K_2CO_3, $Pd(PPh_3)_4$, MeOH, rt to 70 °C, 1 d	0 / 0
 **49**	 **50**	 **51**	K_2CO_3, $Pd(PPh_3)_4$, MeOH, rt to 70 °C, 1 d	0 / 0
 **52**	 **53**	 **54**	K_2CO_3, $Pd(PPh_3)_4$, MeOH, rt to 50 °C, 6 h	0 / 27

This side reaction could be used for the synthesis of aldehydes. However, since the scope of application is rather small, the reaction was not investigated further.

A total of seven bicyclic alkynes for the conversion to PROTACs were synthesized. For a better overview, these are shown and numerated in the following table.

Table 2: Overview and numeration of the synthesized bicyclic alkynes; to facilitate reading, the general structure, with the variable residuals R_1 - R_3, is attached to the table.

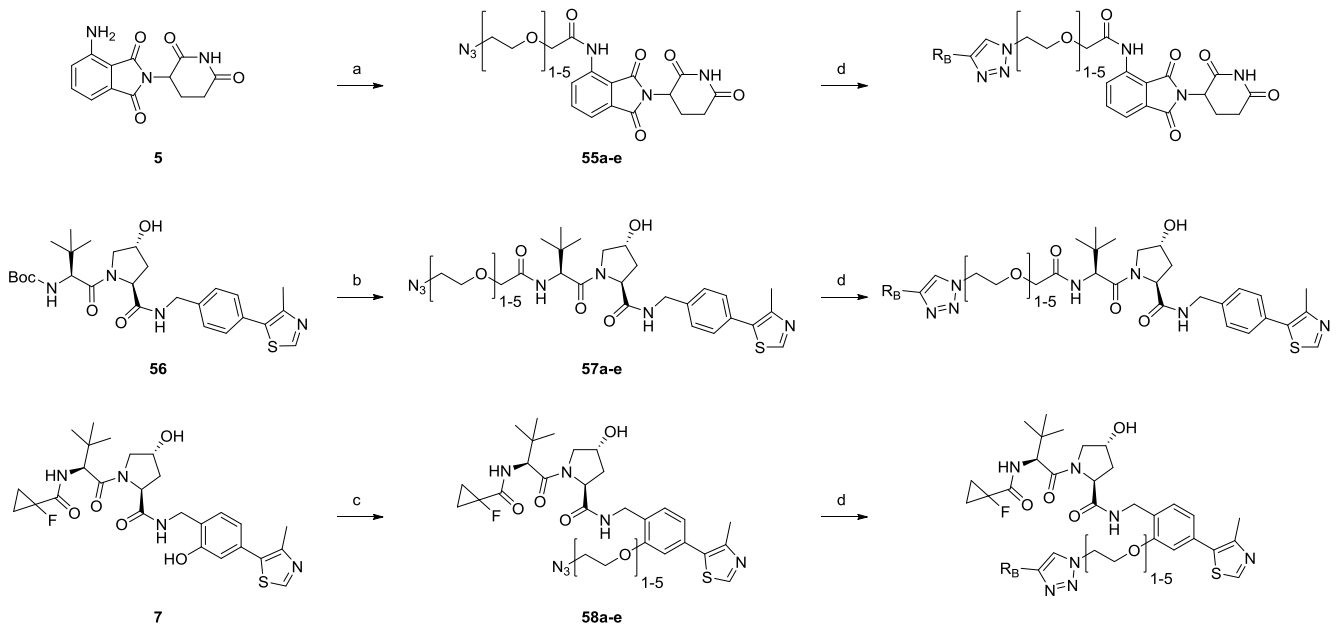
Gerneral structure	#	R1	R2	R3
	A1			
	A2			
	A3			
	A4			
	A5			
	A6			
	A7			

4.1.3.2. Synthesis of bicyclic PROTACs

While the amide bond formed between linker and L**1** could be synthesized via a simple HATU coupling, prior to the reaction with pomalidomide, the linker had to be activated by oxalylchlordie (Scheme 9). This can be explained by the lower reactivity of the aromatic amino group of pomalidomide compared to the aliphatic one of L**1**. These syntheses were already performed in my master thesis.

Tosylated linkers and L**2** were reacted in a nucleophilic substiution by the student Horst Wilhelm Schuchmann.

Subsequently, the L-E3LL-complexes were reacted with the bicyclic FKBP ligands via Click reaction.



Scheme 9: Synthesis of bicyclic PROTACs with R_B being the respective bicyclic compound; a) linker **3a-e**, $(COCl)_2$,, DCM, DMF, 0 °C to rt, 2 h then DMF, 0 °C to rt, overnight, 63 - 99 %; b) 1) TFA, DCM, rt, 90 min 2) linker **3a-e**, HATU, DIPEA, DCM, rt, overnight, 22 - 75 %; c) linker **4a-e**, K_2CO_3, DMF, rt, 1 - 3 d, 66 - 99 %; d) **A1-7**, sodium ascorbate, $CuSO_4$, *t*-BuOH, water, DMSO.

The combination of all building blocks leads to 105 possible PROTACs. 30 of these PROTACs were already synthesized by Dr. Tianqi Mao and described in her PhD thesis[2] (grey shaded in the following table). The PROTACs were tested for binding of FKBPs in a fluoreszenz polarisation assay by Wisely Oki Sugiarto. The following table shows an overview of the measured K_D-values of these PROTACs.

Table 3: Overview of the K_D-values (nM) of the synthesized bicyclic PROTACs (Pom = pomalidomide, numeration refers to the alkynes). PROTACs already synthesized and measured by Dr. Tianqi Mao are shaded in gray, PROTACs not synthesized in red, values greater than 1 µM are indicated as not detected (n.d.), values not measured are empty.

	FKBP	51FK1					52FK1					12				
	linker length	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Alkin #	E3 ligase															
A1	L1	1.2	11	8.0	4.1	3.5	2.2	16	12	6.9	6.4	0.1	0.1	0.1	0.1	0.1
	L2	26	21		33	7.7	26	23		30	15	0.5	0.5		0.7	0.2
	Pom	38	70	19	18	8.0	45	92	30	26	16	0.8	0.8	0.1	0.3	0.3
A2	L1	5.6	16	18	11	9.6	6.7	15	20	13	9.1	0.2	0.3	0.3	0.3	0.1
	L2	204	20	9.8	4.8	6.2	n.d.	25	36	9.1	11	114	0.2	1.4	0.1	0.1
	Pom	38	28	40	6.0	6.5	47	26	6.4	9.3	7.6	0.4	0.2	0.1	0.2	0.1
A3	L1	64	303	279	211	178	45	277	218	169	184	1.4	6.9	6.6	3.0	7.4
	L2	549	645	n.d.	n.d.	850	155	451	n.d.	n.d.	n.d.	22	22	42	59	36
	Pom	264	n.d.	n.d.	681	314	199	737	603	632	278	3.5	11	13	14	13
A4	L1	128	105	95	85	68	152	153	122	104	90	3.6	3.6	2.1	1.7	1.6
	L2	226	266	95	106	134	256	236	111	144	172	12	16	11	4.7	2.8
	Pom	107	268	63	102	118	173	297	102	168	158	4.8	9.4	4.0	3.9	3.3
A5	L1	80	8.8	20	31	18	115	11	26	55	29	4.7	0.1	0.6	1.4	1.6
	L2	115	157	122	144	384	319	441	280	154	n.d.	8.5	12	6.5	4.2	227
	Pom	8	25	17	28	12	1.9	43	16	30	60	0.2	2.1	2.4	1.5	0.7
A6	L1	5.3	0.9	1.2	1.1	1.9	6.3	0.2	2.9	2.2	1.7	0.6	0.1	0.2	0.1	0.2
	L2	6.1	7.0	27	35	32	7.3	14	64	31	103	0.1	0.1	25	0.1	1.4
	Pom	2.3	4.4	3.2	4.2	2.1	0.7	5.7	5.0	8.4	4.9	0.2	0.4	0.5	0.5	0.4
A7	L1	676	754	355	317	357	n.d.	n.d.	n.d.	772	609	95	131	95	67	54
	L2															
	Pom	506	387	590	357	537	n.d.	539	n.d.	817	783	84	62	108	91	158

For better illustration, these values are shown graphically for FKBP51, 52 and 12. For each protein a distinction was made between the different exit vectors. In addition, the linker length is shown by color and the E3-ligase by shape (Fig. 14-16).

Since a high ligand affinity is not essential for the activity of PROTACs, these values are less important for this project. However, they can be used as a data basis for projects with the aim to optimize the FKBP ligand.

The generally low K_D-values of the R_3 substituted PROTACs indicate that this site is particularly suitable for extensions. The R_1-(*S*)-Me derivatives also show great potential for this purpose, whereas dervatisation with larger residues in R_2 should be avoided.

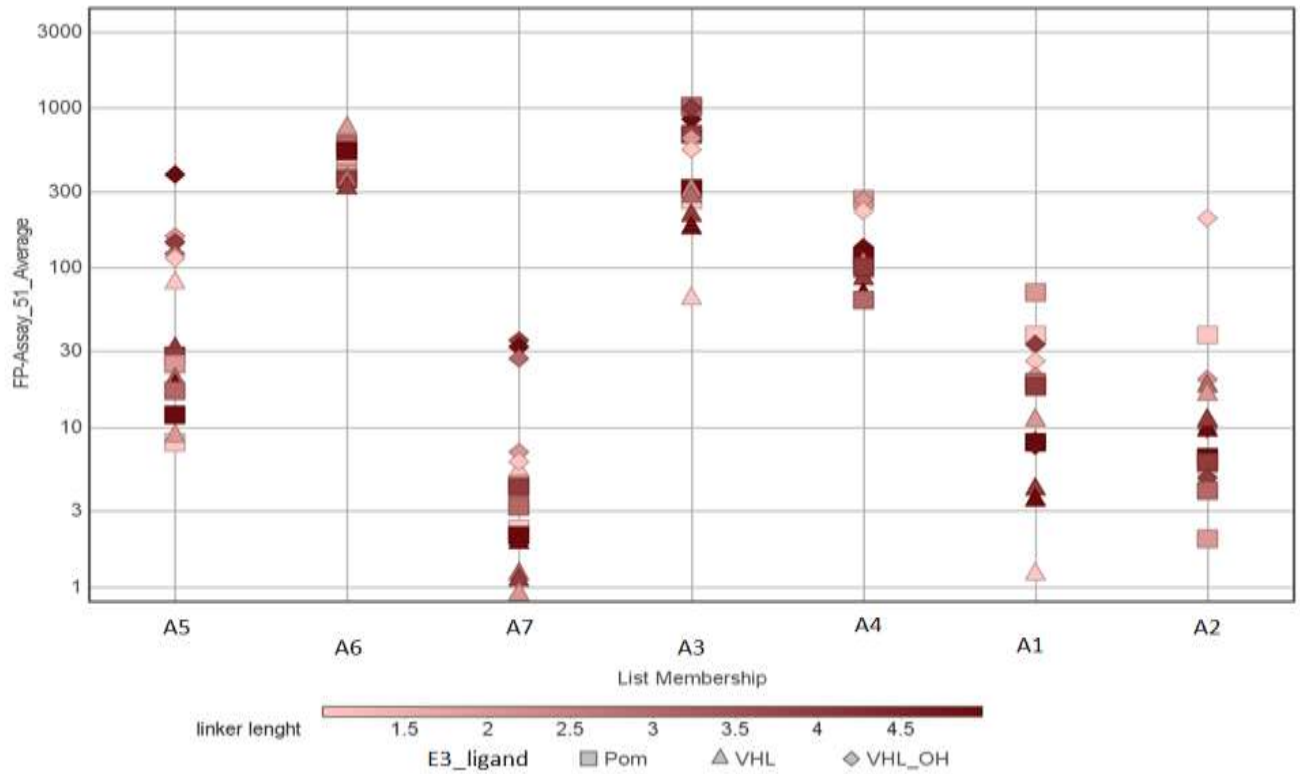


Figure 14: Graphical illustration of the K_D-values of bicyclic PROTACs for FKBP51FK1; linker length is illustrated by color; E3 ligase is illustrated by shape.

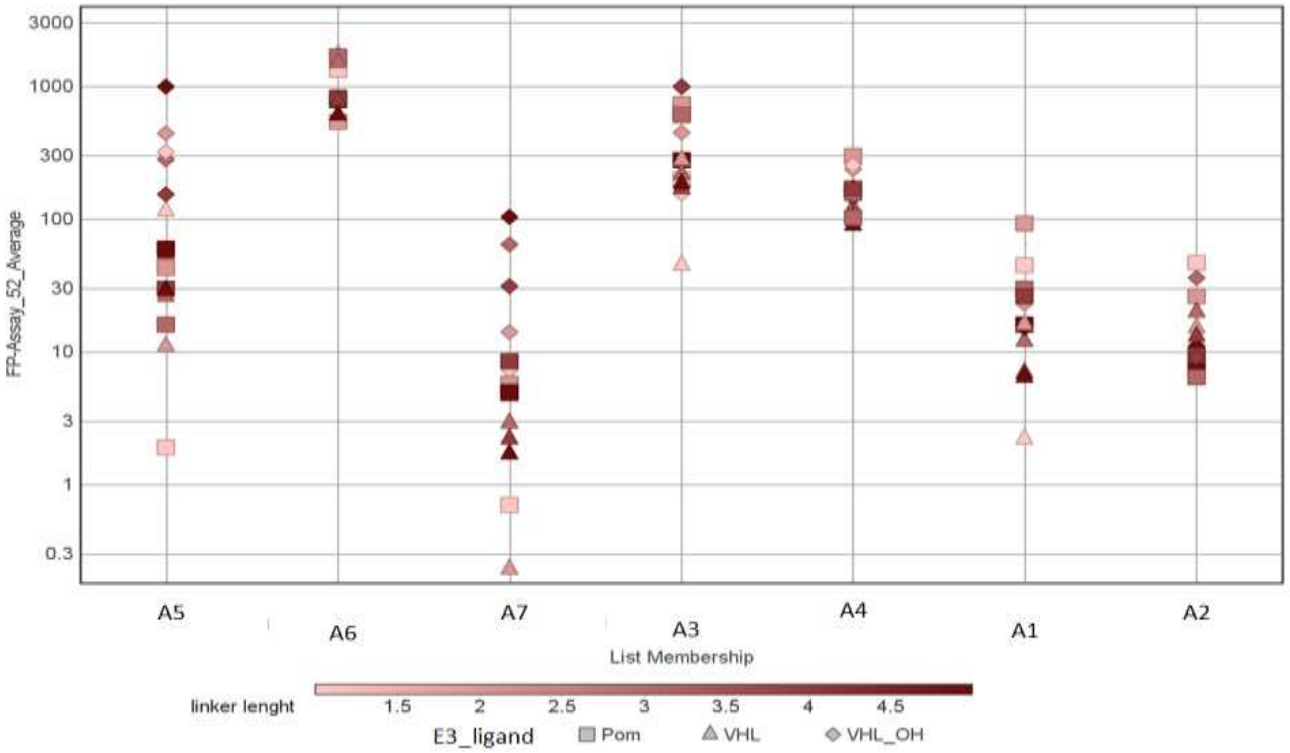


Figure 15: Graphical illustration of the K_D-values of bicyclic PROTACs for FKBP52FK1; linker length is illustrated by color; E3 ligase is illustrated by shape.

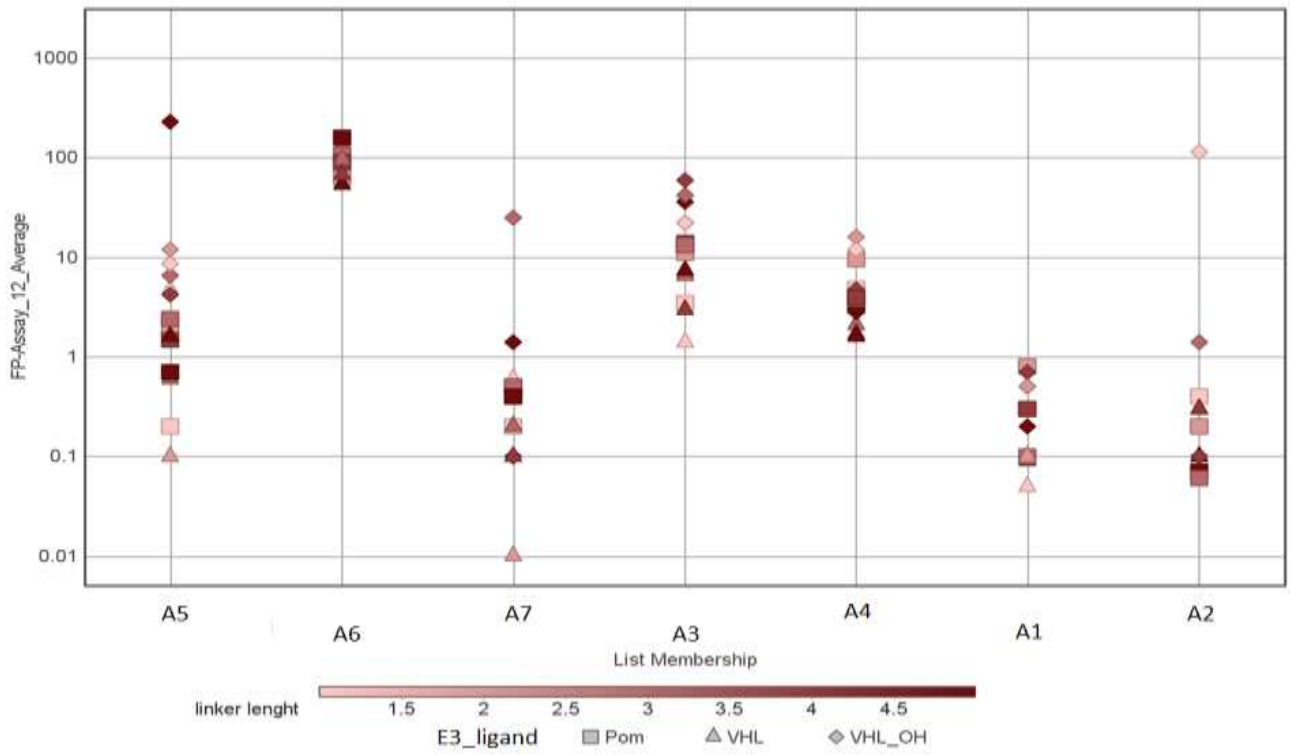


Figure 16: Graphical illustration of the K_D-values of bicyclic PROTACs for FKBP12; linker length is illustrated by color; E3 ligase is illustrated by shape.

4.1.4. Design of SAFit based PROTACs

SAFit1 and SAFit2, two compounds synthesized in the group of Prof. Dr. F. Hausch, show high selectivity for FKBP51 over FKBP52, as well as moderate binding to FKBP12. SAFit structures are generally built of three building blocks, which are referred to as the top, core and bottom group (highlighted in Fig. 17a). The different exit vectors of these compounds compared to the bicyclic compounds, in combination with their binding profile, also make them an interesting starting point for PROTACs for FKBP51 and potentially FKBP12.

The structure of the compound, in combination with the co-crystal structure of SAFit1 and FKBP51 suggests six potential exit vectors (Fig. 17a/c). Based on the fact, that the bottom group and the core group alone (Fig. 17b) still exhibits moderate binding to FKBP51 another option for the exit vector was explored (R_7).

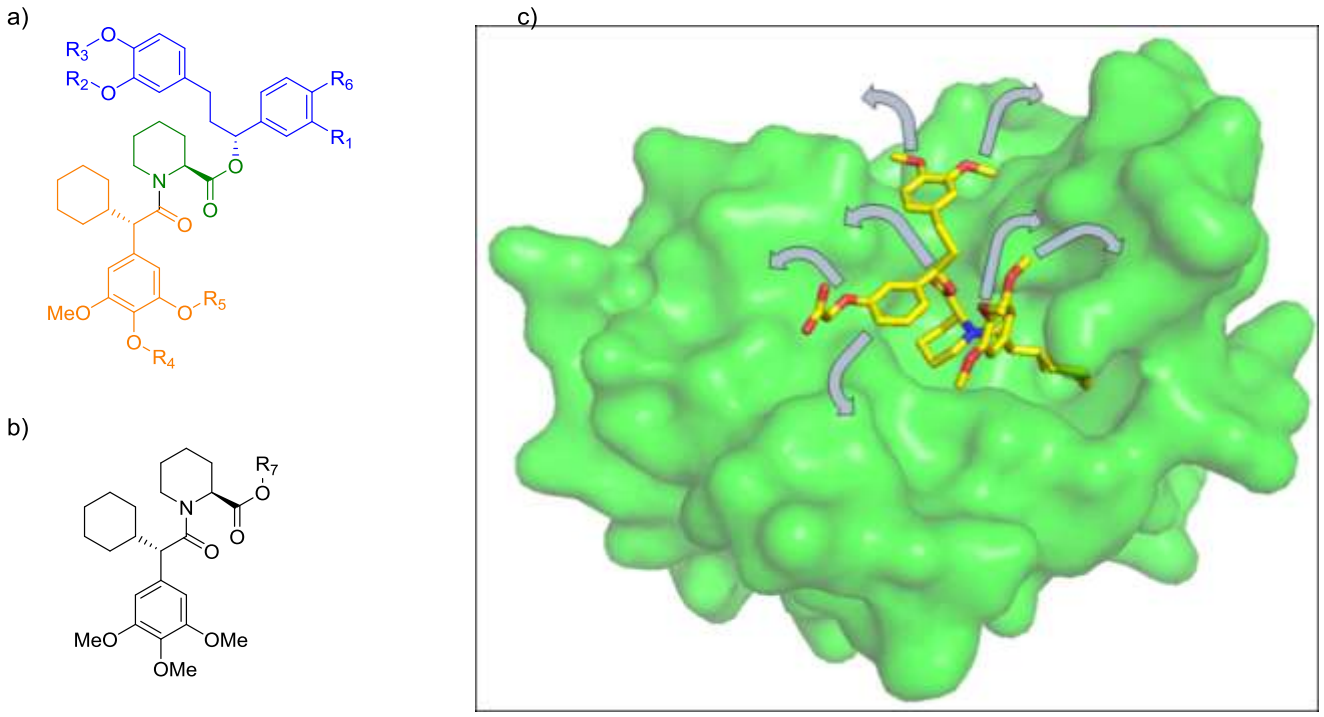
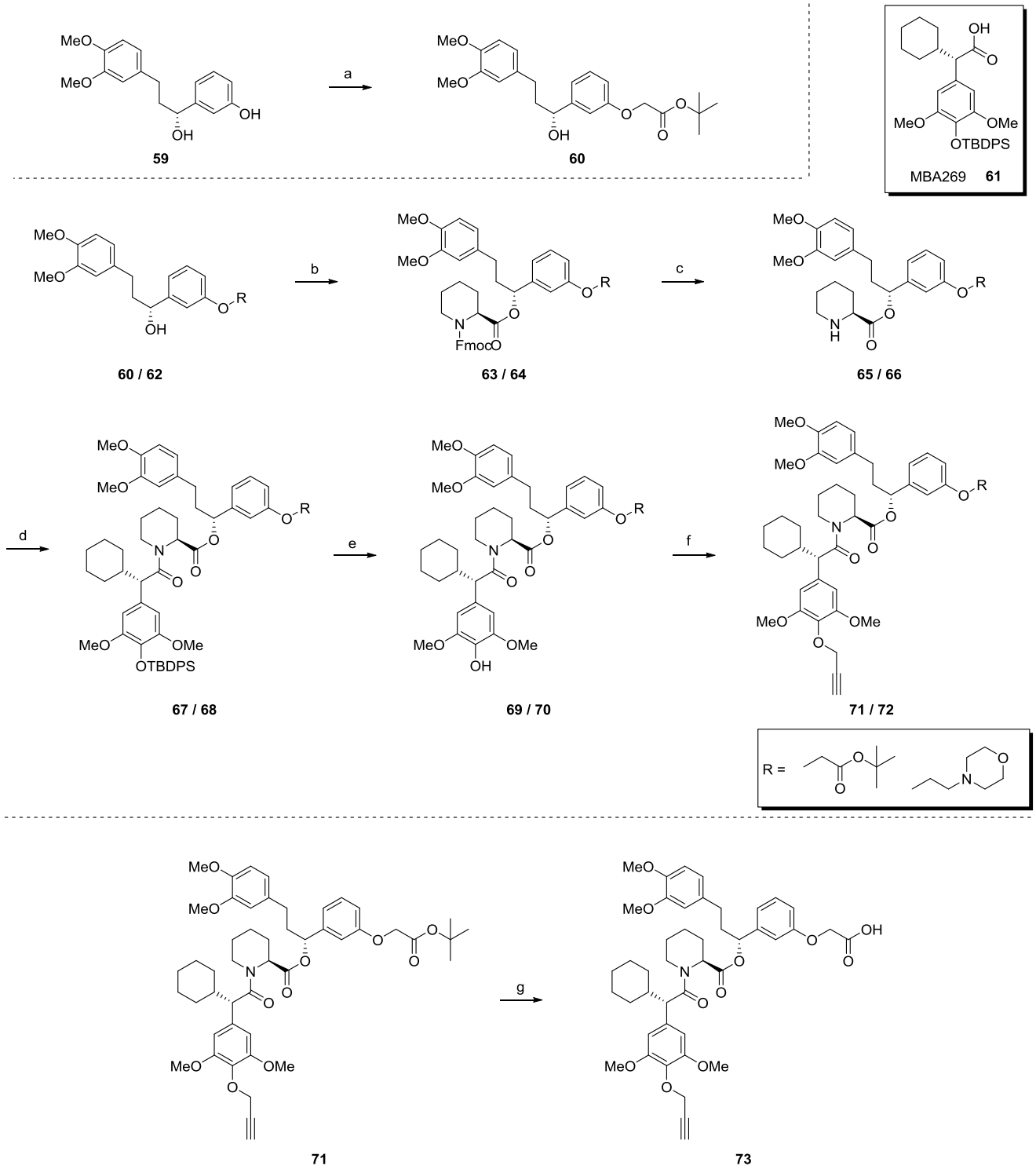


Figure 17: a) SAFit core-structure with potential alkyne adjustment points shown as $R_{1\text{-}6}$; top group highlighted blue, core group highlighted green and bottom group highlighted orange. b) Additional alkyne adjustment point directly on the bottom and core group. c) Co-crystal structure of SAFit1 binding to FKBP51 (potential exit vectors are indicated by arrows); crystal isolated and measured by Dr. Christian Meyners (PDB-ID: 8CCA).

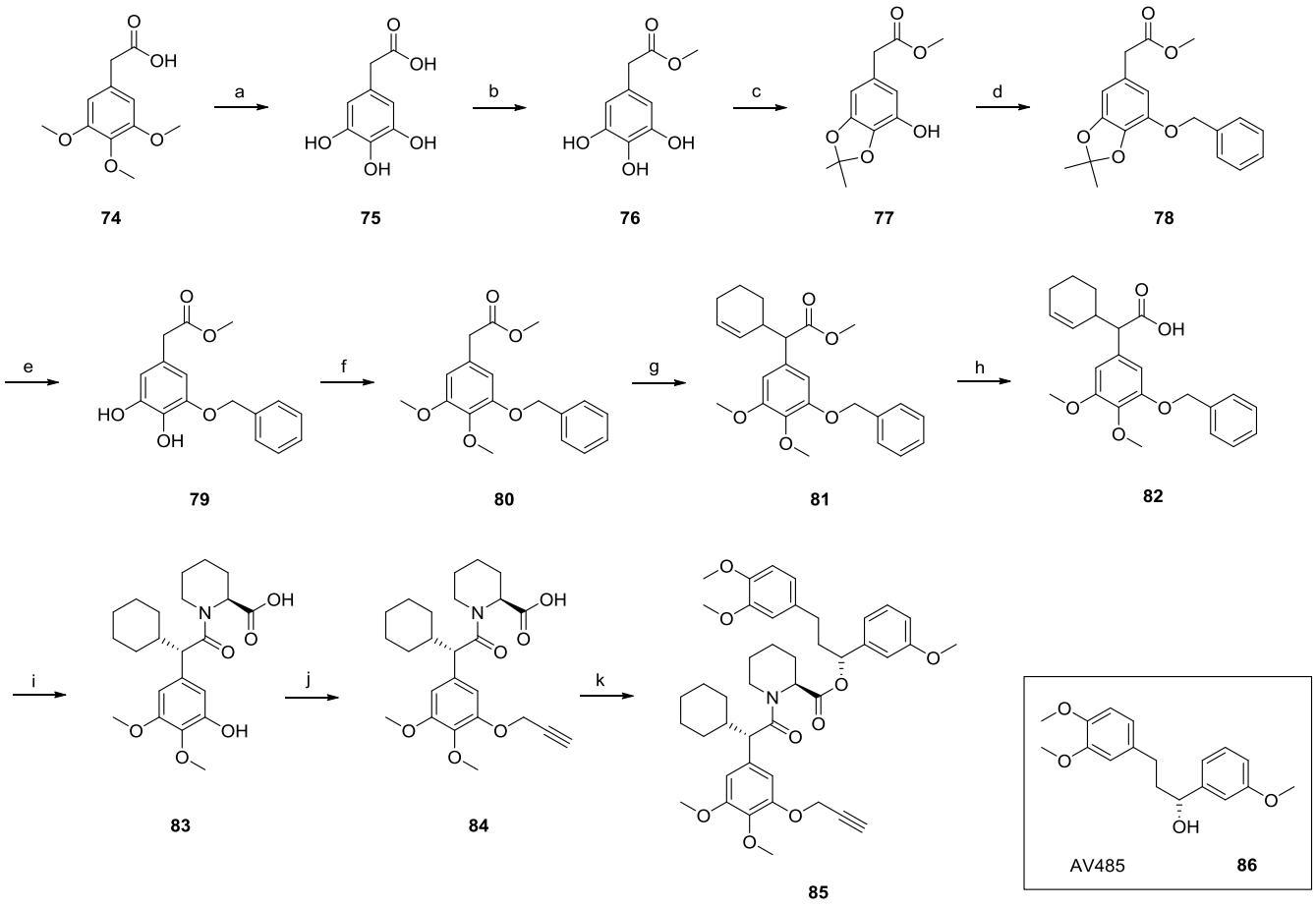
4.1.4.1. Synthesis of SAFit derivates

SAFit analogues with alkyne in position R_1, R_2 or R_3 were already synthesized by Dr. Tianqi Mao. For the synthesis of the analog with alkyne in R_4 position, top groups synthesized by Dr. Andreas Voll, as well as a bottom group synthesized by Dr. Michael Bauder were used. To investigate the influence of groups distant to the exit vector, two analogs (**73** and **74**) were prepared; corresponding to SAFit1 and SAFit2 (Scheme 10).



Scheme 10: Synthesis of R_4 substituted alkynes **72** and **73** starting from the top groups AV497 (**59**) and AV531 (**62**); structure of MBA269 (**61**) in the upper box. Yields and compound numbers are given first for the SAFit1 (carboxylic acid) and second for the SAFit2 (morpholine) analogs; a) *tert*-Butyl 2-bromoacetate, K_2CO_3, acetone, rt, overnight, 99 %; b) (*S*)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)piperidine-2-carboxylic acid, EDC, DMAP, DCM, 0 °C to rt, overnight, 98 %, 54 %; c) 4-methylpiperidine, DCM, rt, 3 h or overnight, 86 %, 76 %; d) MBA269 (**61**), HATU, DIPEA, DCM, DMF, 0 °C to rt, overnight or 2 d, 92 %, 97 %; e) TBAF, THF, 0 °C to rt, 5 h or overnight, 84 %, 60 %; f) 3-bromoprop-1-yne, K_2CO_3, acetone, rt, overnight or 3 d, crude, 53 %; g) TFA, DCM, rt, 1 h, 54 %.

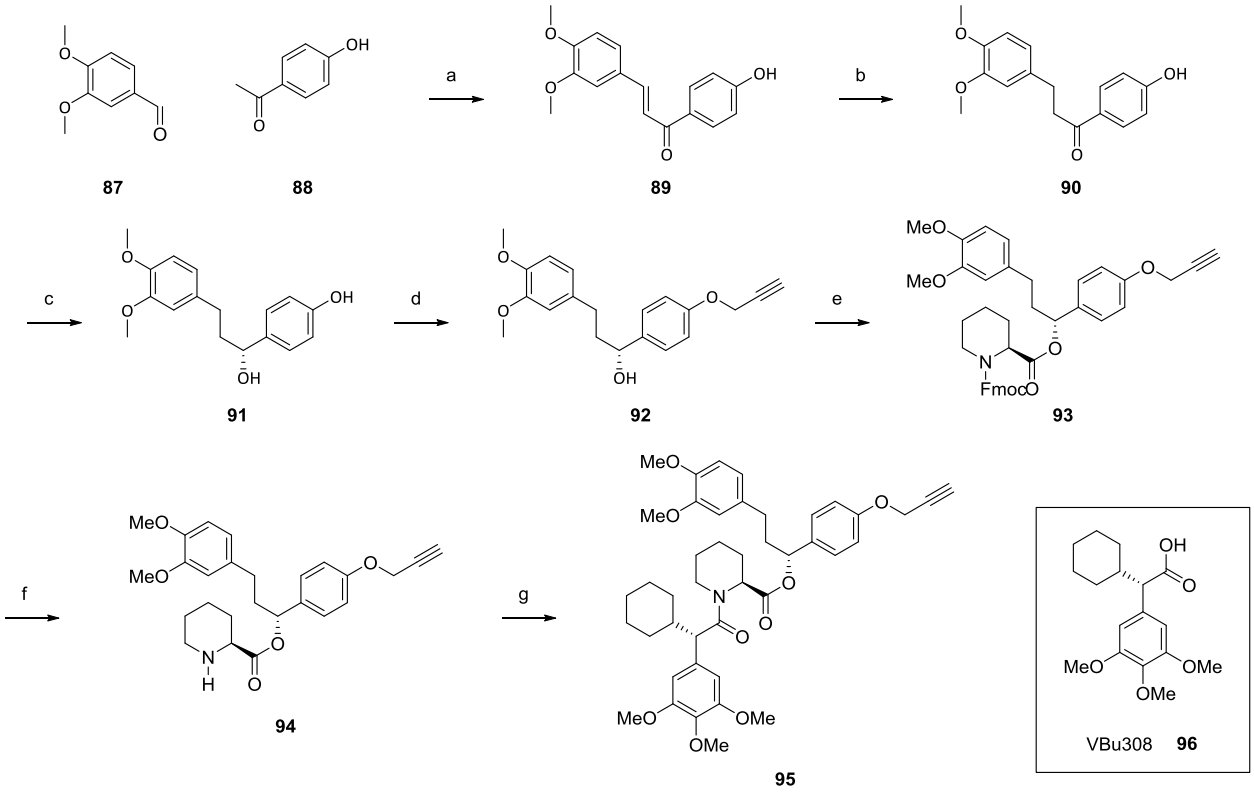
Since no suitable starting material was commercially available for the synthesis of the derivative with alkyne in the R_5 position, the para and one metha position were selectively protected in order to subsequently derivatize at the desired position (compound **77** to **78**). The addition of the (*S*)-piperidine-2-carboxylic acid and the separation of the diastereomers (step i) were performed by Moritz Spiske and will therefore be decribed in his dissertation. The top group added in the last step was provided by Dr. Andreas Voll.



Scheme 11: Synthesis of the R_5 substituted alkyne **85**. a) HBr, AcOH, 130 °C, overnight, crude; b) MeOH, H_2SO_4, 70 °C, 2 h, 99 %; c) 2,2-dimethoxypropane, p-TsOH, toluene, 115 °C, overnight, 99 %; d) benzyl bromide, K_2CO_3, acetone, 60 °C, overnight, 53 %; e) TFA, ACN, water, rt, 1 h, 99 %; f) MeI, K_2CO_3, DMF, 35 °C, overnight, 57 %; g) 3-bromo cyclohexene , lithium hexamethyldisilazide, THF, - 78 °C to - 40 °C, 3 h, 99 %; h) LiOH, THF, water, 80 °C, 5 d, 78 %; i) 1) $SOCl_2$, DCM, DMF, 0 °C, overnight; 2) (*S*)-piperidine-2-carboxylic acid, KOH, water, dioxan, 0 °C to room temperature, overnight; 3) H_2, Pd/C, THF, MeOH, rt, 2 h, separation of diastereomers, 16 %; j) 1) 3-bromoprop-1-yne, K_2CO_3, acetone, rt, overnight; 2) LiOH, THF/water (1:1), rt, 4 d, 77 %; k) AV485 (**86**), EDC, 4-pyrolidinopyridine, toluene, 0 °C to rt, 2 h, 52 %.

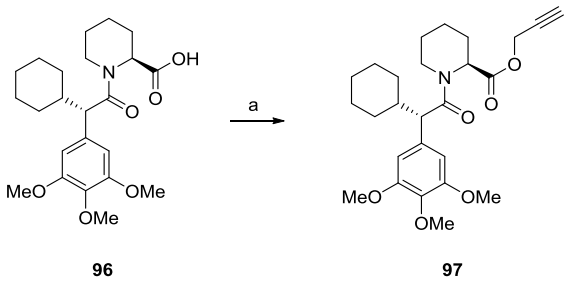
The student Laura Almena-Rodriguez contributed to these experiments.

Furthermore, a compound was synthesized in which the R_1-position was replaced by a hydrogen atom and the alkyne was placed in para position (R_6) instead.



Scheme 12: Synthesis of R_6-derivatized SAFit-based alkyne **95**; a) KOH, EtOH, water, 0 °C to rt, 2 d, 78 %; b) Zn, NH_4Cl, EtOH, water, 29 %; c) $RuCl_2$[(*S*)-dm-segphos®][(*S*)-daipen], H_2, KO*t*Bu, *i*-PrOH, rt, overnight, 64 %; d) 3-bromoprop-1-yne, K_2CO_3, acetone, rt, overnight, 79 %; e) (*S*)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)piperidine-2-carboxylic acid, EDC, DMAP, DCM, 0 °C to rt, overnight, 58 %; f) 4-methylpiperidine, DCM, rt, 3 h, 75 %; g) VBu308 (**96**), HATU, DIPEA, DCM, DMF, 0 °C to rt, overnight, 89 %.

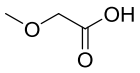
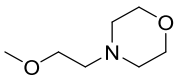
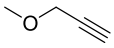
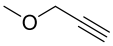
For the synthesis of the analog derivatized in R_7, bottom group (**96**) synthesized by Vanessa Buffa was reacted with propargyl bromide.



Scheme 13: Synthesis of the R_7 substituted alkyne **97**. a) 3-bromoprop-1-yne, DIPEA, ACN, rt, overnight, 95 %.

A total of eight SAFit-based alkynes for the conversion to PROTACs were synthesized. For a better overview, these are shown and numerated in the following table, along with the core structures, which are shown again for easier understanding (Fig. 18).

Table 4: Overview and numeration of the synthesized SAFit-based alkynes. Derivatization positions not included in the molecule are shaded in gray (numbering consecutively according to the bicyclic alkynes).

#	R_1	R_2	R_3	R_4	R_5	R_6	R_7
A8		Me	Me		Me	H	
A9		Me	Me		Me	H	
A10		Me	Me	Me	Me	H	
A11	OMe		Me	Me	Me	H	
A12	OMe	Me		Me	Me	H	
A13	OMe	Me	Me	Me		H	
A14	H	Me	Me	Me	Me		
A15				Me	Me		

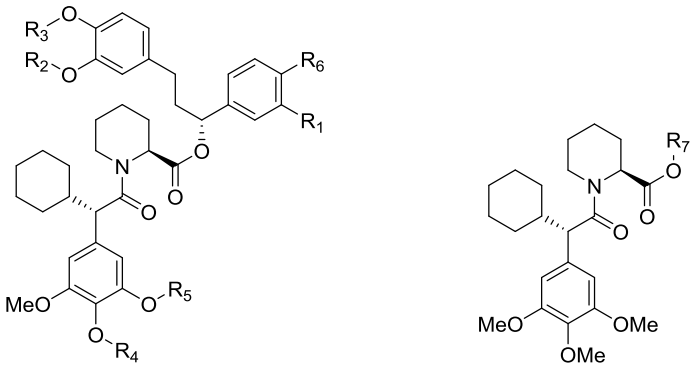


Figure 18: General structures of SAFit based alkynes, with the variable residuals R_1 - R_7.

4.1.4.2. Synthesis of SAFit based PROTACs

The alkynes synthesized in this way were reacted with the previously mentioned L-E3LL complexes identically to the bicyclic compounds (Chapter 4.1.3.2). The combination of all building blocks yields a total of 120 PROTACs, including 30 already synthesized by Dr. Tinqi Mao. The PROTACs were tested

for binding of FKBPs in an FP assay by Wisely Oki Sugiarto. The following table shows an overview of the measured K_D-values of these PROTACs.

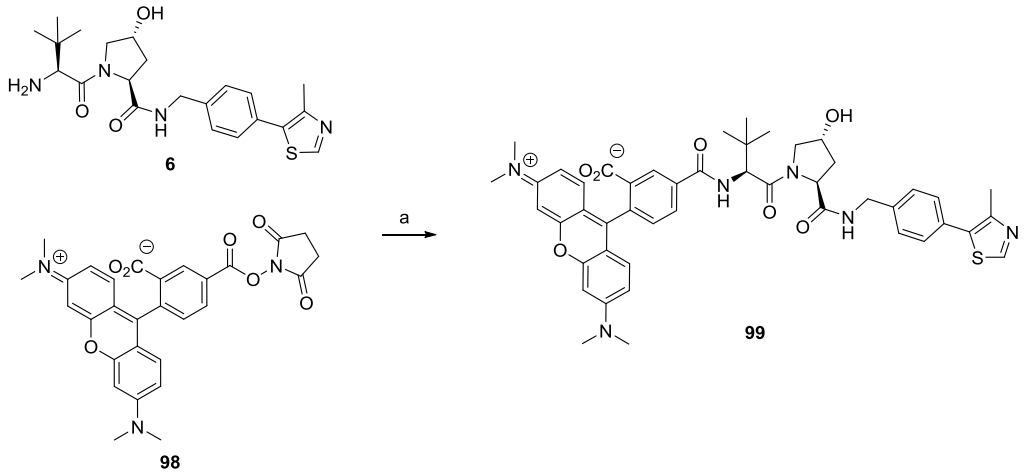
Table 5: Overview of the K_D-values (nM) of the synthesized SAFit-based PROTACs. PROTACs already synthesized and measured by Tianqi Mao are shaded in gray; values greater than 1 µM are indicated as not detected (n.d.) values not measured are empty.

	FKBP	**51FK1**					**52FK1**					**12**				
	linker length	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Alkin #	**E3 ligase**															
A8	L**1**	7.7	6.4	2.9	10	1.9	n.d.	n.d.	n.d.	n.d.	n.d.	43	19	28	50	24
	L**2**	457	314	269	191	176	n.d.	n.d.	n.d.	n.d.	n.d.	408	n.d.	901	174	n.d.
	Pom	1.8	8.4	1.1	0.9	1.8	n.d.	n.d.	n.d.	n.d.	n.d.	109	180	59	54	62
A9	L**1**	7.2	5.3	5.9	4.1	7.5	n.d.	n.d.	n.d.	n.d.	n.d.	26	20	20	13	23
	L**2**	157	115	14			n.d.	n.d.	n.d.			474	941	3.4		
	Pom	8.3	5.9	3.5	2.0	3.5	n.d.	n.d.	730	467	165	56	46	19	15	15
A10	L**1**	25	24	23	24	12	n.d.	n.d.	n.d.	n.d.	n.d.	408	677	436	532	814
	L**2**	82	110	93	104	118	n.d.	n.d.	n.d.	n.d.	n.d.	25	377	108	88	136
	Pom	19	16	22	18	5	n.d.	n.d.	n.d.	n.d.	n.d.	306	256	206	256	226
A11	L**1**	100	59	54	50	36	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	640	601	642	506
	L**2**	61	94	110	84	83	n.d.	n.d.	n.d.	n.d.	n.d.	35	160	177	80	228
	Pom	26	26	34	40	30	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	542	430	287	368
A12	L**1**	47	60	86	59	34	n.d.	n.d.	n.d.	n.d.	n.d.	409	584	410	368	455
	L**2**	70	75	104	87	98	n.d.	n.d.	n.d.	n.d.	n.d.	85	96	78	110	129
	Pom	22	21	18	24	25	n.d.	n.d.	n.d.	n.d.	n.d.	111	177	111	81	162
A13	L**1**	84	142	101	68	59	n.d.	n.d.	n.d.	n.d.	199	30	108	24	28	18
	L**2**	32	45	47	50	83	n.d.	n.d.	n.d.	n.d.	n.d.	20	100	97	42	228
	Pom	54	28	6.7	28	35	n.d.	n.d.	n.d.	n.d.	n.d.	84	70	15	35	48
A14	L**1**	62	40	45	60	59	n.d.	n.d.	n.d.	n.d.	n.d.	127	66	111	184	
	L**2**	68	108	117	172	144	n.d.	n.d.	n.d.	n.d.	n.d.	65	62	129	105	107
	Pom	40	44	18	20	31	n.d.	n.d.	n.d.	n.d.	n.d.	124	90	52	140	130
A15	L**1**	52	26	14	23	67	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	56	215	438	62
	L**2**	66	154	289	346	438	n.d.	n.d.	n.d.	n.d.	n.d.	71	434	n.d.	n.d.	n.d.
	Pom	272	309	401	503		n.d.	n.d.	n.d.	n.d.		n.d.	n.d.	n.d.	n.d.	

The SAFit analogs, as expected, show high selectivity for binding of FKBP51 over FKBP52 and mostly moderate binding of FKBP12. In rare cases, surprisingly low K_D-values were determined for the binding of FKBP12, which is suspected to be due to interactions of the E3LL with the protein surface. Since all synthesized ligands showed sufficient affinity for FKBP51 to be able to serve as PROTACs, cooperativities and activities were determined, which are discussed below.

4.1.5. Evaluation of cooperativity and degradation

The bicyclic and SAFit-like PROTACs containing a VHL ligand (L**1** or L**2**) were first analyzed in a one-point cooperativity assay developed and performed by Dr. Christian Meyners. For this purpose, I synthesized a tracer by the coupling of L**1** (**6**) with TAMRA (**98**). In the assay this tracer (1 nM) competes with the respective PROTAC (200 nM) or FKBP-PROTAC-complex (200 nM) in a fluorescence polarization assay for binding to the VHL-complex VCB (20 nM) (Fig. 19).



Scheme 14: Synthesis of Tracer **99** for the one-point cooperativity assay; a) TEA, DCM, DMF, rt, 4 d, 83 %.

The binding to VCB was determined and it was tested whether the binding affinity was enhanced or reduced by the addition of the respective FKBP. The two values are then divided and a one-point cooperative value (opc) is obtained (Equation 1).

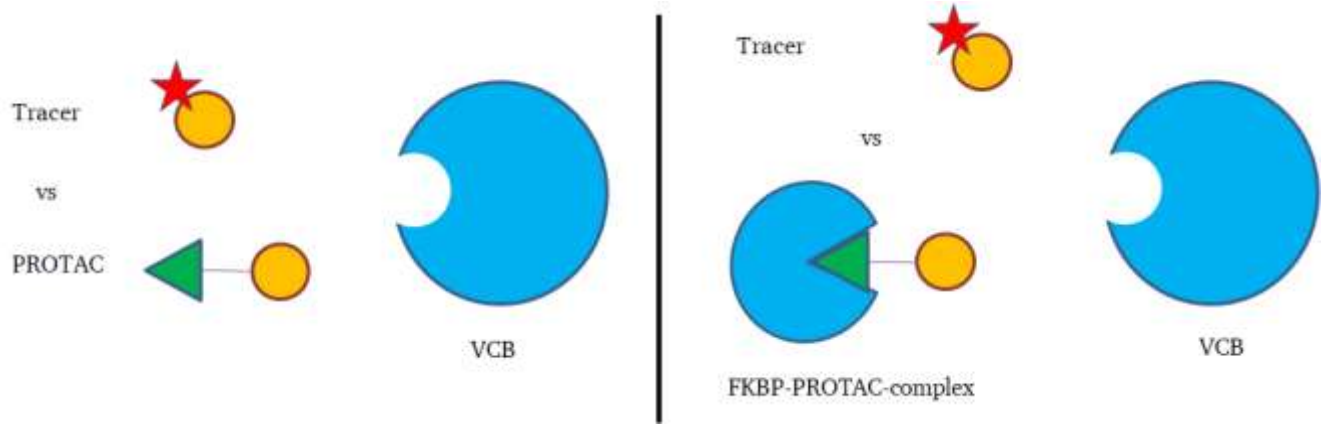


Figure 19: Setup of the one-point cooperativity assay; left: Binding of the PROTAC to VCB in competition with a tracer; right: Binding of the PROTAC-FKBP complex.

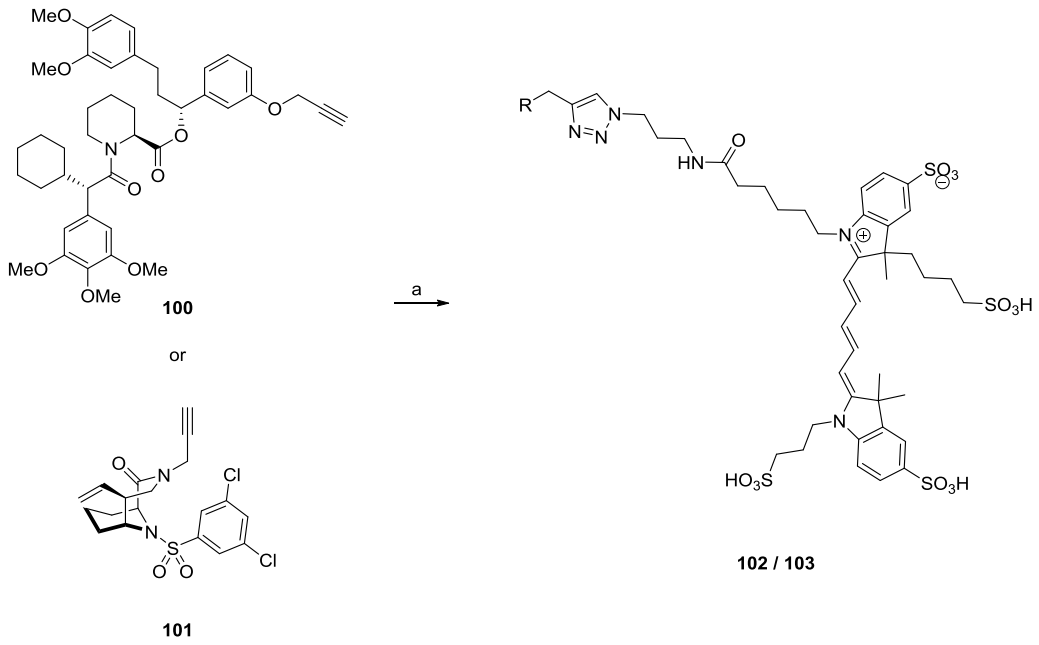
$$\text{opc} = \frac{\text{mP (PROTAC)}}{\text{mP (complex)}} \quad (1)$$

Although this does not allow any conclusions about the degradative properties of the PROTAC, it does provide a first indication of whether a possible ternary complex is stable. The cooperativity values calculated from the measured polarization values for the PROTACs with VHL-ligands are summarized in the following table. Due to a malfunction of the preperative HPLC and the resulting low yield, PROTAC (A3, L**1**, n=2) was exclusively analyzed by western-blots for the determination of the activity, therefore no one-point cooperative value was determined.

Table 6: Overview of the measured one-point cooperative values. PROTACs already synthesized and measured by Dr. Tianqi Mao are shaded in gray, PROTAC not tested is shaded in blue, PROTACs not synthesized are empty, PROTACs with negative values are shaded red and PROTACS with values greater than 4 are shaded green.

	FKBP	**51FK1**					**52FK1**					**12**				
	linker length	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Alkin #	**E3 ligase**															
A1	L1	0.7	1.0	1.0	0.9	1.2	0.8	1.0	1.4	1.4	1.1	0.8	1.1	1.0	1.5	1.5
	L2	1.0	1.0	1.5	1.2	0.6	0.9	1.1	2.8	1.7	0.7	0.9	1.0	1.3	1.4	0.9
A2	L1	0.7	0.9	0.6	0.3	0.8	1.8	1.0	0.7	0.4	1.0	1.0	1.2	1.7	0.6	1.2
	L2	1.2	1.0	1.0	0.8	0.7	0.9	0.9	1.0	1.0	0.8	0.9	0.9	1.3	1.2	1.0
A3	L1	1.1		0.5	1.0	0.9	1.0		0.5	1.1	1.0	1.0		0.7	1.6	1.0
	L2	0.7	0.9	1.0	1.3	0.8	0.7	0.9	1.0	1.2	0.8	0.9	1.1	1.5	2.6	1.0
A4	L1	1.1	0.9	1.0	0.9	0.7	1.0	1.0	1.0	0.9	0.8	1.2	1.4	1.2	1.1	0.8
	L2	0.9	1.1	1.0	1.0	1.1	1.1	1.1	1.1	1.3	1.4	0.8	1.6	1.3	0.9	1.0
A5	L1	0.5	0.8	0.8	0.9	1.2	1.0	0.8	0.9	1.0	1.4	12.3	1.0	6.3	2.3	2.0
	L2	0.9	1.0	1.0	1.0	1.1	1.0	1.1	1.1	1.1	1.3	1.0	1.7	2.1	2.6	2.1
A6	L1	0.7	0.9	0.8	0.9	0.4	1.1	1.0	0.9	0.9	0.4	3.4	0.9	3.6	1.4	2.4
	L2	1.0	1.0	1.0	1.1	1.0	1.0	1.1	1.1	1.2	1.4	1.0	1.4	1.8	1.8	1.9
A7	L1	1.0	1.2	1.0	1.0	1.0	1.4	1.3	1.2	1.1	0.9	2.1	1.5	1.4	1.4	1.0
	L2															
A8	L1	1.3	0.5	0.8	1.0	1.2	1.1	0.4	0.8	1.4	1.2	5.4	1.2	1.4	1.5	2.4
	L2	1.1	1.5	1.2	1.1	1.0	0.9	1.0	1.0	0.9	1.0	1.1	1.8	2.0	4.1	2.0
A9	L1	1.1	0.9	1.1	2.1	1.1	1.2	0.9	0.9	1.4	1.3	4.2	6.3	1.2	3.8	2.7
	L2	1.1	1.1	1.1	1.2	1.2	1.0	1.0	1.0	1.0	1.0	1.2	1.4	1.7	1.7	1.4
A10	L1	1.5	1.6	1.7	5.5	5.1	1.0	1.1	1.1	1.0	1.4	1.7	2.7	2.5	2.7	3.7
	L2	2.0	1.8	1.6	1.5	1.7	1.0	1.1	1.0	1.0	1.0	1.1	1.3	1.5	3.2	3.3
A11	L1	1.3	1.8	2.0	2.4	2.0	1.0	1.0	1.1	1.0	1.0	1.6	2.8	2.8	3.8	2.6
	L2	1.3	1.2	1.5	2.0	2.2	1.0	1.0	1.0	1.1	1.0	2.0	1.7	1.8	2.6	6.3
A12	L1	2.0	1.0	1.4	1.5	1.5	0.9	0.6	0.9	1.0	1.1	1.3	2.4	2.2	4.9	5.4
	L2	1.1	1.1	1.1	1.2	1.4	1.0	1.0	1.0	1.0	0.9	1.2	1.7	2.1	2.0	4.0
A13	L1	1.9	1.4	1.3	1.3	1.2	1.0	1.0	1.0	1.0	1.0	1.4	1.3	1.3	1.4	1.5
	L2	1.0	1.1	1.3	1.3	1.4	1.0	1.1	1.1	1.0	1.0	1.1	1.1	1.3	1.9	1.8
A14	L1	3.5	1.3	1.2	1.8	1.3	1.3	1.1	1.6	1.0	1.1	1.1	1.2	1.5	1.6	2.3
	L2	20.8	322	4.7	3.3	3.0	1.5	1.6	1.2	1.0	1.1	1.4	2.1	2.2	4.4	4.2
A15	L1	2.6	1.1	1.2	1.4	1.1	1.3	1.1	1.4	1.4	1.5	1.2	1.4	1.2	1.6	1.3
	L2	1.4	1.1	1.2	2.1	1.0	1.3	1.1	2.5	1.3	1.4	1.0	1.0	1.2	1.3	1.2

All PROTACs of the screening library were then tested in an HTRF assay developed and performed by Thomas Geiger (Fig. 20). In this assay, the FKBP concentration in the cell lysate was determined. Therefore Europium-tagged antibodies were bound to the TPR domain of the respective FKBP inducing an Alexa-Fluor-tagged tracer to emit at 665 nm if they are bound simultaneously. Pretreating the cells for 24 h with a PROTAC enables a reduction of the amount of FKBP in the cell lysate resulting in a reduction of the signal of Alexa-Fluor. This was tested at three different concentrations for each PROTAC. Two tracers were synthesized for this purpose (Scheme 15). A SAFit-based tracer (**102**) was used for the measurements of FKBP51 and a bicyclic tracer (**103**) for FKBP52.



Scheme 15: Synthesis of the tracers **102** and **103** for the HTRF assay; with R being the SAFit or bicyclic residue of **100** or **101**; the yield and numeration is given for the SAFit analog (**102**) first followed by the bicyclic analog (**103**); a) AF647-azide, $CuSO_4$, sodium ascorbate, DMSO, water, *t*-BuOH, rt, overnight, quant., 48 %.

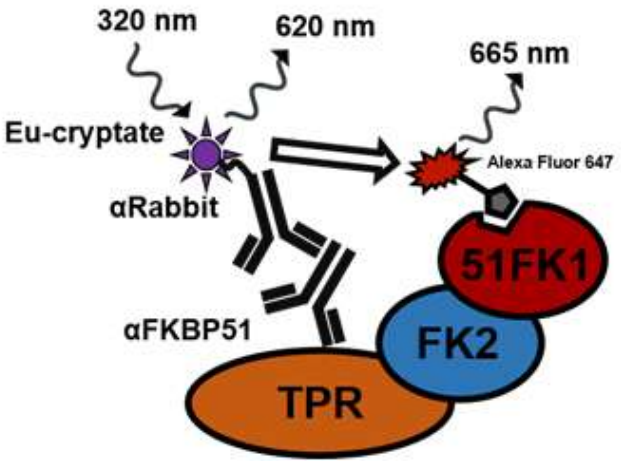


Figure 20: Mode of action of the HTRF assay; after irradiation with light of wavelength 320 nm europium emits light at 620 nm. If this happens in close proximity to the tracer, it gets stimulated to emit light at 665 nm; figure created by Thomas Geiger.

In addition, all PROTACs were measured in a fluorescent reporter assay developed and performed by Thomas Geiger. In this assay, cells were generated that stably express FKBP12-eGFP fusion proteins as well as mCherry. Upon treatment with a PROTAC the FKBP-eGFP fusion protein can be degraded while mCherry remains unaffected. This leads to a decrease of the eGFP/mCherry ratio (Fig. 21b).

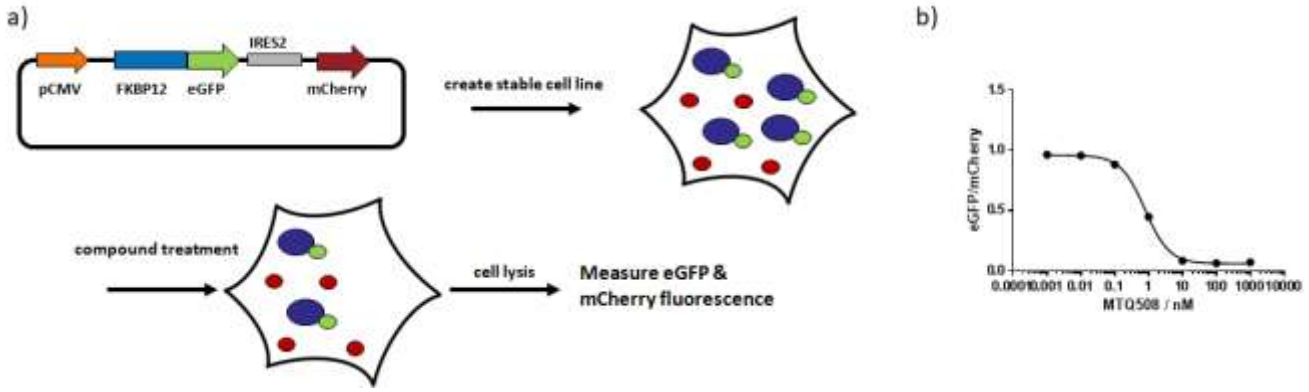


Figure 21: a) Mode of function of the reporter assay; figure created by Thomas Geiger b) Exemplary change of the fluorescence ratio with MTQ508 for FKBP12.

These data were compiled and the PROTACs were categorized into three classes based on their activity for better visualization (Table 7). PROTACs that led to a signal reduction of less than 20 % were classified as inactive (red), PROTACs that led to a signal reduction between 20 % and 60 % were classified as weakly active (yellow) and PROTACs that led to a signal reduction of more than 60 % were classified as active (green).

Analysis of these data showed, that degradation of FKBP12 could be achieved very frequently, whereas FKBP51 only exhibited a handful of active PROTACs. For FKBP52, not even a single potent degrader was identified.

Table 7: Preliminary overview of activities of the PROTAC library; FKBP51 and FKBP52 were measured in the HTRF assay and FKBP12 in the reporter assay; with red = not active, yellow = weakly active, green = active, blue = not tested and grey = not synthesized; full reports on the activity will be provided in the PhD thesis of Thomas Geiger.

	FKBP	51					52					12				
	Linker length	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Alkin	E3-Ligand															
A1	L1															
	L2															
	Pom															
A2	L1															
	L2															
	Pom															
A3	L1															
	L2															
	Pom															
A4	L1															
	L2															
	Pom															
A5	L1															
	L2															
	Pom															
A6	L1															
	L2															
	Pom															
A7	L1															
	L2															
	Pom															
A8	L1															
	L2															
	Pom															
A9	L1															
	L2															
	Pom															
A10	L1															
	L2															
	Pom															
A11	L1															
	L2															
	Pom															
A12	L1															
	L2															
	Pom															
A13	L1															
	L2															
	Pom															
A14	L1															
	L2															
	Pom															
A15	L1															
	L2															
	Pom															

The PROTACs active for FKBP51 at this point were then screened in Western blots performed by Thomas Geiger. Besides complete binding curves for the binding of the PROTAC as well as the PROTAC-FKBP-complex to VCB for the most promising ones (MWa421 and 422) were determined by Dr. Christian Meyners. Since the degrader synthesized by Dr. Tianqi Mao was only tested for degradation of FKBP51, it was retested in the course of this work to gain insights regarding its selectivity.

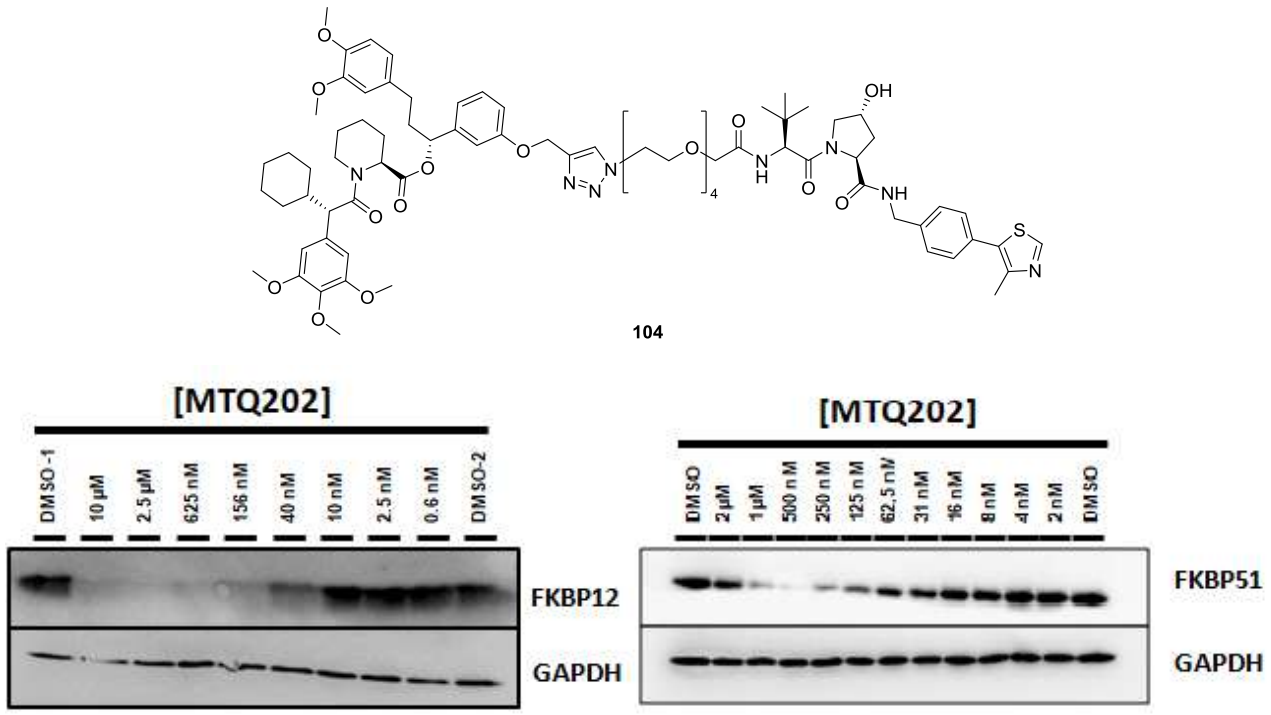


Figure 22: Structure and Western blots of MTQ202 (**104**, alkyne = **A10**; linker lenght = 4, L**1**).

As described in the thesis of Dr. Mao a degradation of FKBP51 by MTQ202 in the concentration range from 125 nM to 1 μM was observed. Besides, the selectivity profile of MTQ202 was worse than desired. The PROTAC showed degradation of FKBP12 above a concentration of 40 nM.

MWa282 (**106a**) and MWa283 (**106b**) also showed a poor degrader profile with a very weak degradation of FKBP51, wheras FKBP12 was degradated to a much greater extend (Fig. 23).

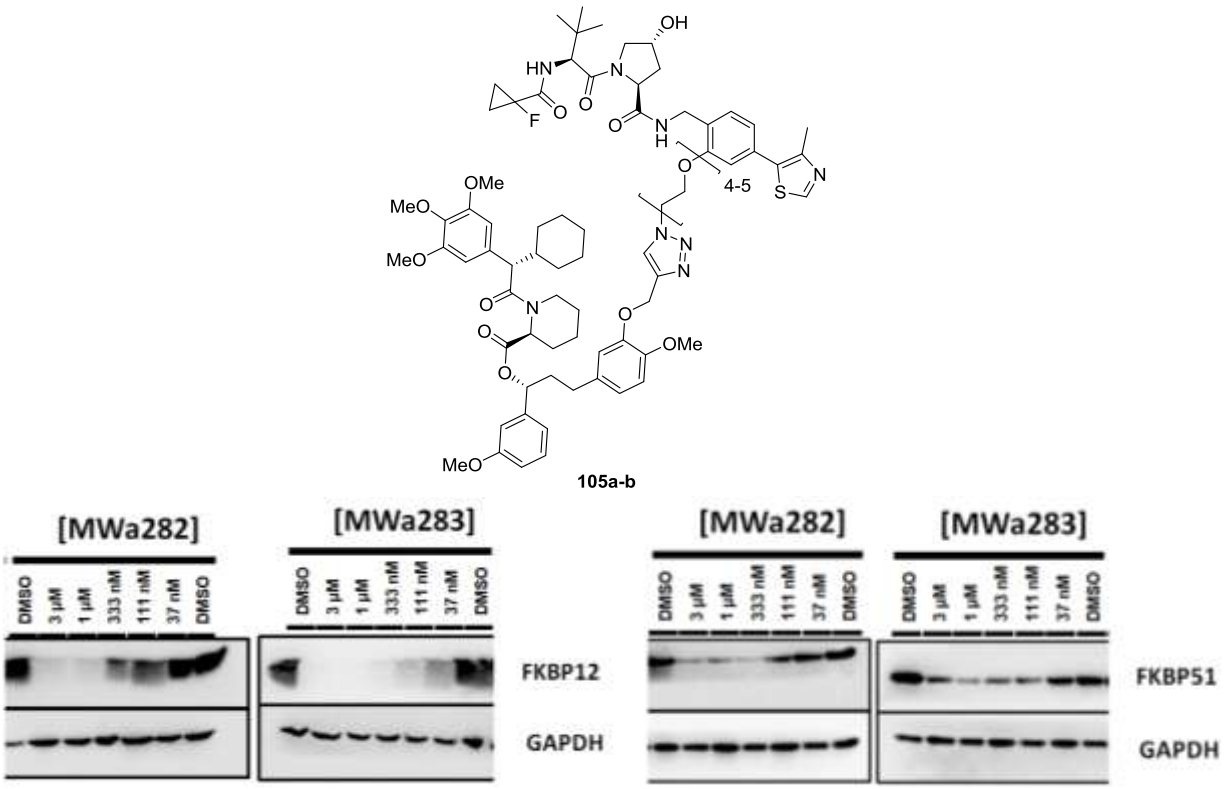


Figure 23: Structure and Western blots of MWa282 (**105a**, alkyne = **A11**; linker lenght = 4, L**2**) and MWa283 (**105b**, alkyne = **A11**; linker lenght = 5, L**2)**.

The very close analogs MWa287 (**106a**) and MWa288 (**106b**) showed a quite similar result, with a very weak degradation of FKBP51. However, while MWa288 also was a very strong degrader of FKBP12, MWa287 showed no activity for FKBP12 (Fig. 24).

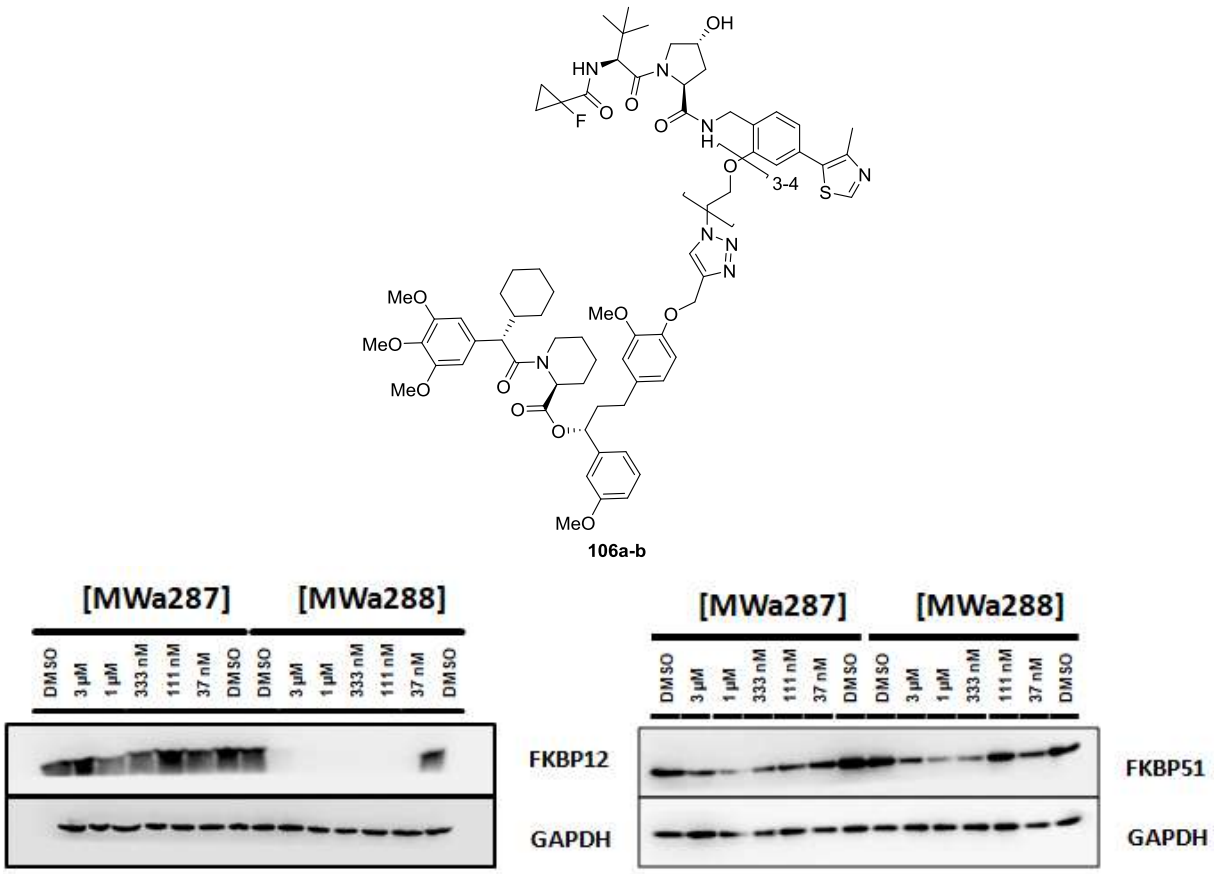


Figure 24: Structure and Western blots of MWa287 (**106a**, alkyne = **A12**; linker lenght = 3, L**2**) and MWa288 (**106b**, alkyne = **A12**; linker lenght = 4, L**2**).

The PROTACs MWa421 (**107a**) and MWa422 (**107b**) degraded FKBP51 above a concentration of approximately 10 - 40 nM and were thus the most potent degraders for this protein up to that time. A Hook-effect was not observable up to the highest tested concentration of 3 μM. Degradation of FKBP12, on the other hand, was only observed above 125 nM. Thus, these were the first PROTACs to exhibit low selectivity for FKBP51.

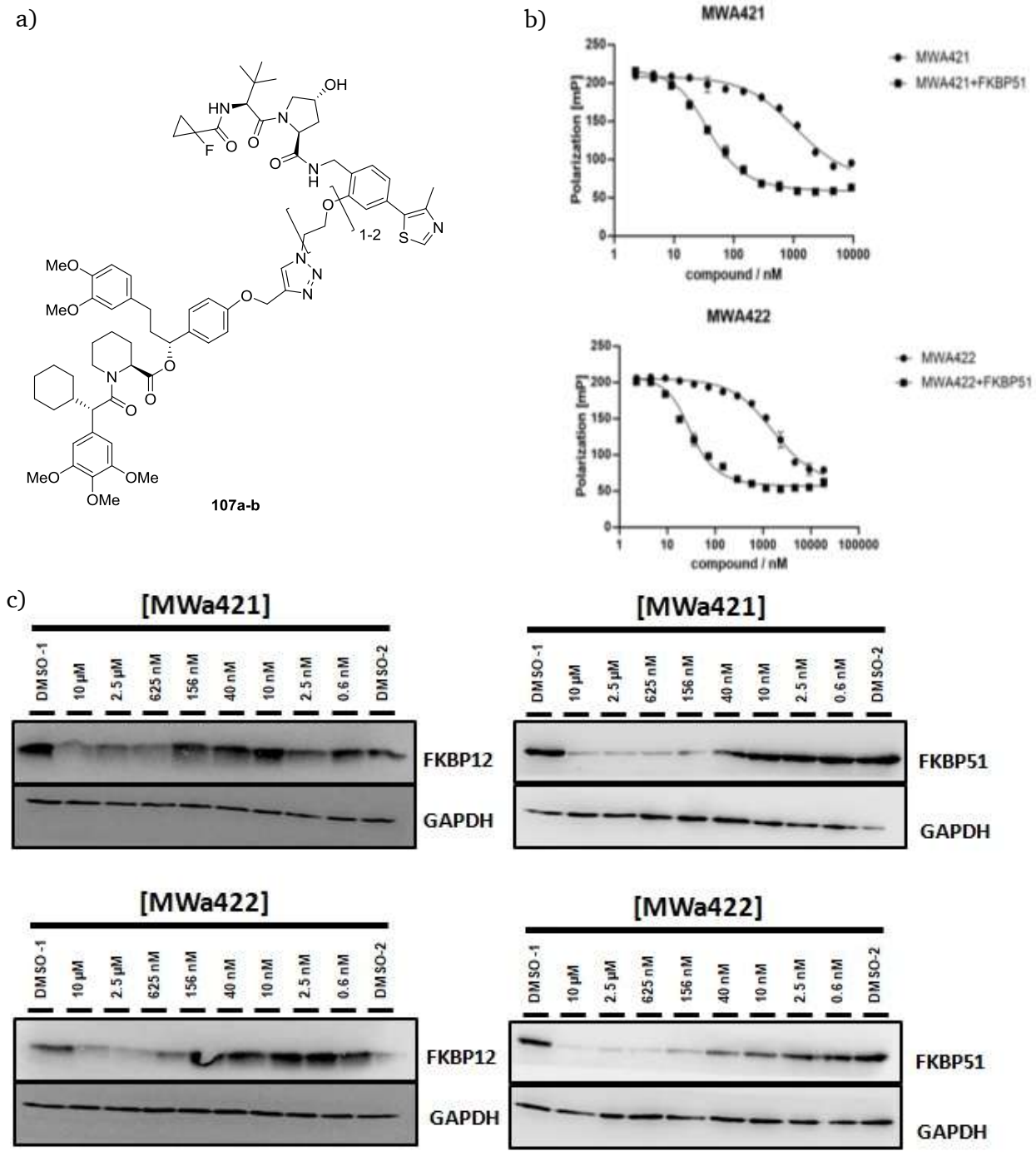


Figure 25: a) Structures; b) full binding curves and c) Western blot of MWa421 (**107a**, alkyne = **A14**; linker lenght = 1, L**2**) and MWa422 (**107b**, alkyne = **A14**; linker lenght = 2, L**2**).

To further investigate the cooperativity alpha values of the two PROTACs were calculated according to equation 2

$$\alpha = \frac{K_D^{binary}}{K_D^{ternary}} \tag{2}$$

This results in an alpha value of 48 for MWa421 and 106 for MWa422.

Since PROTACs MWa282, MWa283, MWa287 and MWa288 showed no, or very weak, degradation of FKBP51 and no selectivity against FKBP12 no further attempts were made to optimize them. MTQ202 showed moderate degradation of FKBP51 but also lacked selectivity over FKBP12. Only MWa421 and MWa422 showed moderate activity, as well as slight selectivity over FKBP12. MTQ202, MWa421 and MWa422 were therefore selected for further optimization steps.

4.2. Findings for FKBP12

Screening demonstrated that FKBP12 is much easier to degrade than FKBP51 or FKBP52. However, since there are already a couple of PROTACs published for this protein, the synthesis and detailed characterization of another PROTAC is not of high scientific interest. Nevertheless, the screening data was analysed in order to identify relationships between structure and activity. These should be used as potential approaches for the optimization of PROTACs for FKBP51.

4.2.1. Variation of the Chain length

As expected and already shown in various studies, a change in chain length showed a significant influence on the PROTACs activity. One example of such an effect was observed very clearly in the two PROTACs shown in the following figure.

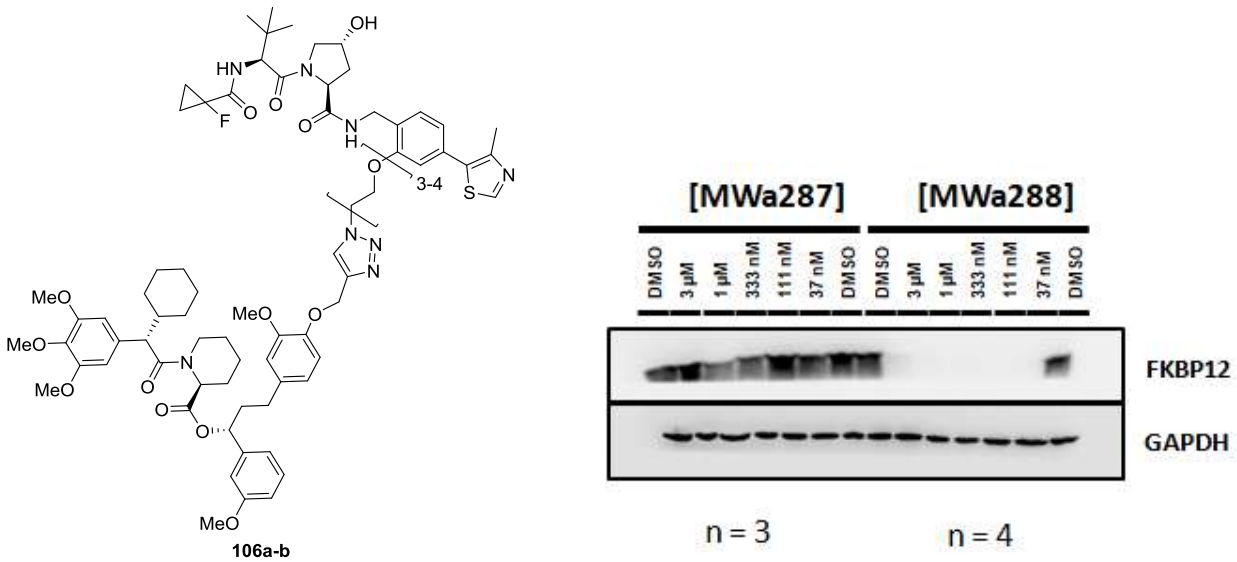


Figure 26: Influence of chain lengt on the PROTACs MWa287 (**106a**, alkyne = **A12**; linker lenght = 3, L**2**) and MWa288 (**106b**, alkyne = **A12**; linker lenght = 4, L**2**).

4.2.2. Variation of the POI-ligand

Another factor that was shown to have an influence on the activity of the PROTAC was the structure of the ligand for the POI. Even changes distant from the binding of the linker showed a distinct effect on degradation. This can probably be explained by changes in the interactions between the ligand and the proteins. PROTACs of alkynes **A8** and **A9**, for instance, show significant differences in their activity in some cases. This can best be seen in the example shown in the following figure, where the SAFit2 analog degradates FKBP12, wheras the SAFit1 analog showed no activity. However, this could also be a result of the different cell permeability of both compounds.

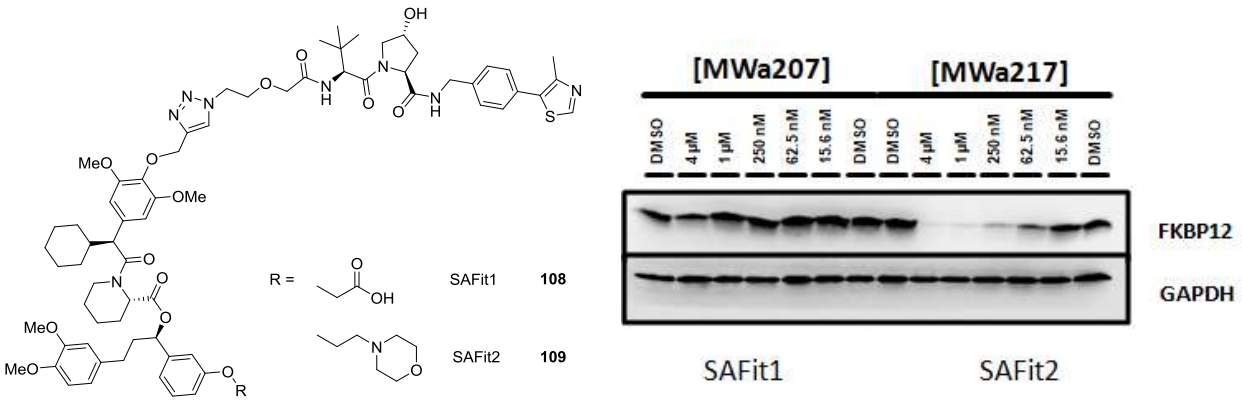


Figure 27: Influence of the structure of the ligand for the POI on the PROTACs MWa207 (**108**, alkyne = **A8**; linker lenght = 1, L**1**) and MWa217 (**109**, alkyne = **A9**; linker lenght = 1, L**1**).

4.3. Improvement of PROTACs for FKBP51

Since no co-crystal structure of FKBP51 and VHL in complex with a PROTAC could be obtained, the optimization of PROTACs could not follow a rational approach. Instead four approaches were made for systematical optimization.

First, since the exit vector of MTQ202 is a position which has already been varied in the research group of Prof. Dr. Felix Hausch, the variation of its binding type of the FKBP ligand to the linker is easily achievable. This way, new possible interactions between the linker and the two proteins could be generated or, because of the slightly different chain length, protein-protein interactions could be enhanced or, eventually, undesired ones with FKBP12 could be suppressed.

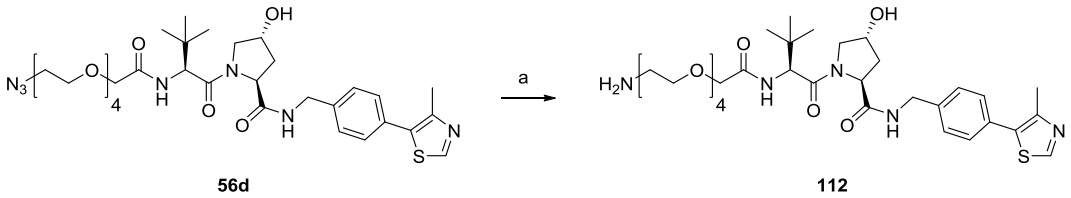
Second, by introducing side chains to the linker its rotation should be restricted. This should result in it being mainly in its active conformation of FKBP51 binding and discriminating the binding of FKBP12 as well.

Third, the linker length of MWa421 was slightly varied to cover the range in between MWa421 and MWa422.

Moreover, PROTACs were prepared, which differ slightly in the structure of the ligand for FKBP51.

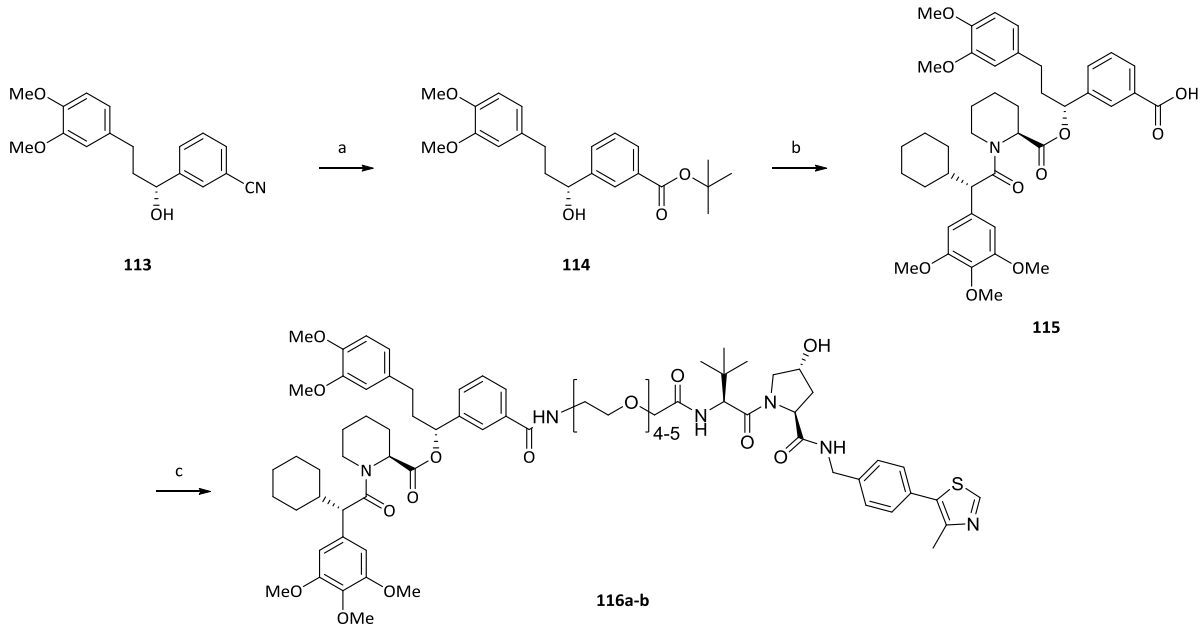
4.3.1. Improvement by different coupling type

Since amine-functionalized L-E3LL-complexes (with n = 3 or 5/Scheme 17 and 20) as well as carboxyl-functionalized L -E3LL-complexes (Scheme 18 and 19) were commercially available, only the structure shown in the following figure had to be synthesized. For this synthesis, the azide function was transformed by a Staudinger reaction.

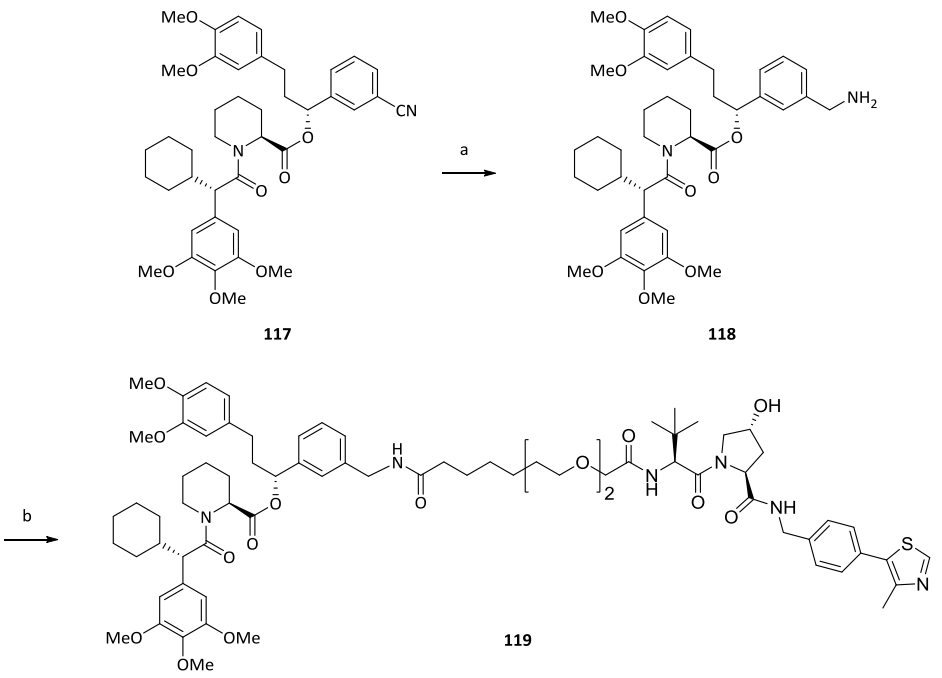


Scheme 16: Synthesis of amine- functionalized L-E3LL-complex **112**; a) PPh_3, THF, water, 40 °C, overnight, 73 %.

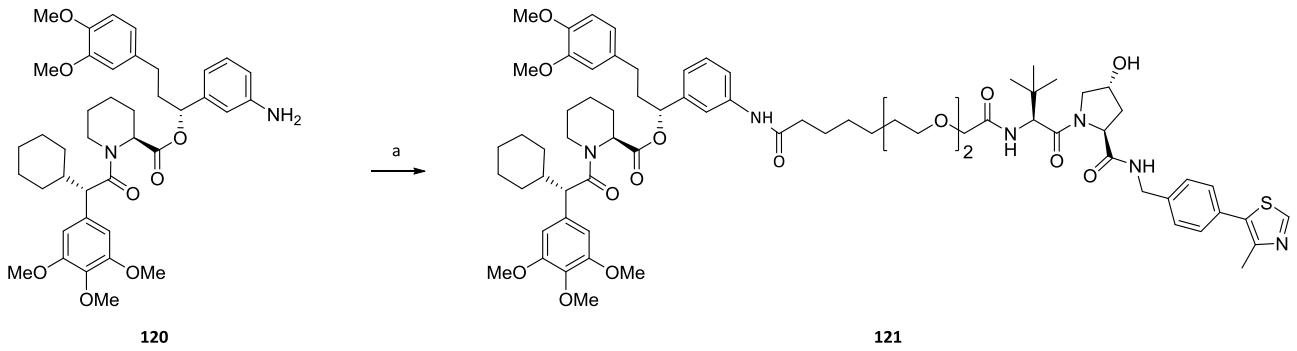
By using POI ligands, that were available in stock, eight compounds could be synthesized that have an amide bond instead of the triazole. These differ slightly in their chain length as well as in their chemical properties and should cover the chemical space quite well.



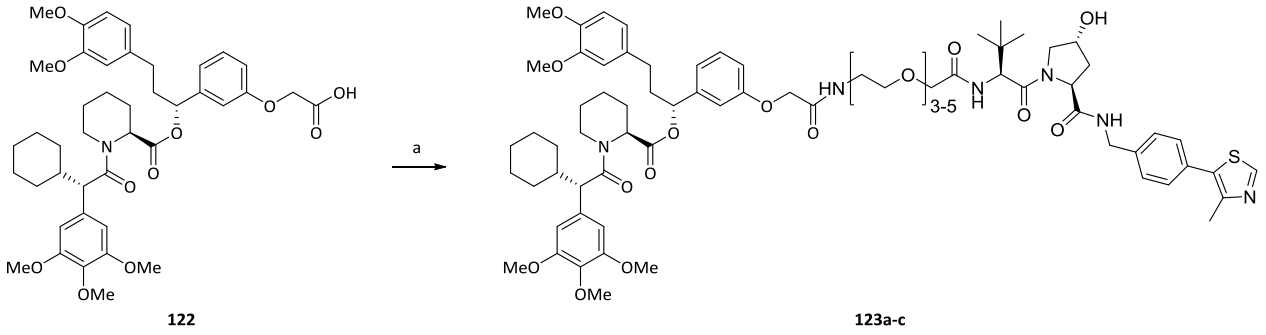
Scheme 17: Synthesis of PROTACs **116a-b** starting from AV532 (**113**); a) 1) NaOH, water, 115 °C, 2 h; 2) *t*-BuBr, acetonitrile, Ag_2O, rt, 1 h, 76 %; b) 1) VBu065 (**96**), 4-pyrolidinopyridine, EDC, 0 °C to rt, 2 h; 2) TFA, DCM, rt, 2 h, 48 %; c) L-E3LL, HATU, DIPEA, DCM, rt, 2 h, 43 - 46 %.



Scheme 18: Synthesis of PROTAC **119** starting from AV552 (**117**); a) BH_3·THF, THF, 60 °C, overnight; b) L-E3LL, HATU, DIPEA, DCM, rt, 2 h, 19 %.

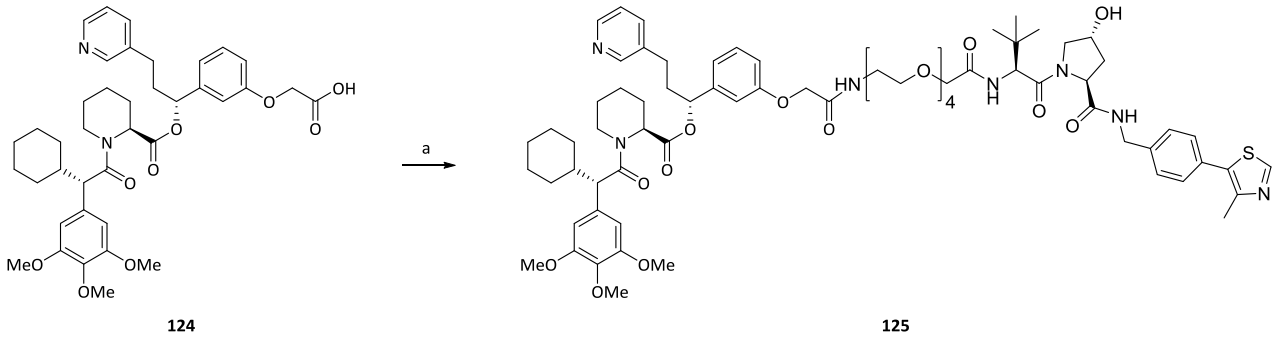


Scheme 19: Synthesis of PROTAC **121** starting from AV602 (**120**); a) L-E3LL, HATU, DIPEA, DCM, rt, 2 h, 56 %.



Scheme 20: Synthesis of PROTACs **123a-c** starting from THE10 (**122**); a) L-E3LL, HATU, DIPEA, DCM, rt, 2 h, 52 - 81 %.

In order to include the influence of a more distant group as well, an analog was synthesized, which contains a pyrdine ring.



Scheme 21: Synthesis of PROTAC **125** starting from AV736 (**124**); a) L-E3LL, HATU, DIPEA, DCM, rt, 2 h, 55 %.

The synthesized PROTACs were then tested in the one-point cooperativity assay by Dr. Christian Meyners (Table 8) as well as the reporter assay by Thomas Geiger.

Table 8: Overview of the measured one-point cooperative values. PROTACS with values greater than 4 are shaded green.

Structure #	Lab book ID	FKBP51	FKBP52	FKBP12
116a	MWa458	1.89	1.09	9.34
116b	MWa459	1.43	1.17	6.39
119	MWa472	2.00	1.03	11.79
121	MWa474	0.82	0.85	1.98
123a	MWa347	1.35	1.27	2.47
123b	MWa429	1.23	1.02	1.54
123c	MWa348	1.36	1.15	2.79
125	MWa431	1.19	0.99	1.03

Since none of these substances showed an improved cooperation with FKBP51 and in some cases even showed a strong increase in cooperation with FKBP12, it can be assumed that either the triazole interacts with at least one of the proteins and is essential for forming the ternary complex with FKBP51, or the amide bond exhibits negative cooperation.

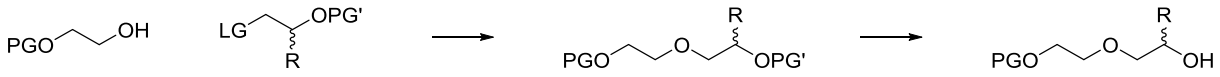
This observation was confirmed by the measurement of the activities of the PROTACs for FKBP51 (reports on the activity will be provided in the PhD thesis of Thomas Geiger). All PROTACs produced exhibited lower degradation of FKBP51 compared to the reference compound MTQ202. Thus, for further optimization, the triazole was again used for linkage.

4.3.2. Improvement by conformational restriction

Usually, for the optimization of a PROTAC by conformational restriction, a co-crystal structure of both proteins with the PROTAC is used to rationally substitute the linker. Since no such crystal structure could be obtained for FKBP51, the linkers should be methylated systematically. This should result in a restriction of rotational freedom and thus a preselection of the conformation and a reduction of entropic loss due to the binding of PROTAC to the proteins, leading to a stabilization of the binding and a more efficient degrader.
In the case of MWa421, four different linkers were synthesized and subsequently linked to the E3LL and the POI-ligand. The linker of MTQ202 exhibits 18 possible positions for the methyl-group.

4.3.2.1. Improvement of MTQ202

For the synthesis of the chiral linkers of the MTQ202 analogs, PEG units should be built up stepwise. This synthesis can be broken down to the following general concept.



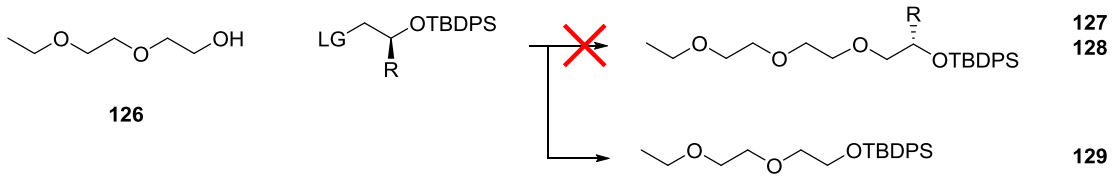
Scheme 22: General concept of linker elongation; R = H or Me.

There are many possible variations for this reaction. Starting with the choice of the protecting groups and the leaving group, over the choice of base and solvent up to further reaction additives, there is a multitude of possibilities, which is only limited by the restriction that it must be possible to selectively deprotect the two protecting groups for a step-by-step construction of the linker.

First silyl protecting groups as temporary protecting groups (PG') were tested. Silyl protecting groups were chosen because they can be deprotected with TBAF very easily and orthogonally to various other protecting groups. Various bases and solvents were tested, which are commonly used for these kind of reactions. However, the reactions showed either generally no conversion or a shift of the silyl protecting group to the free alcohol (Scheme 23).

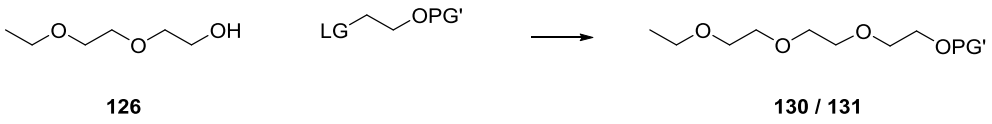
Table 9: Overview of reaction conditions tested with a silyl protection group and results of the corresponding reactions.

#	LG	B^-	T / °C	Solvent	Comment
1	Cl	KOtBu	rt	Dioxan	No conversion
2	Cl	DIPEA	rt	Dioxan	No conversion
3	Cl	LHMDS	rt	Dioxan	No conversion
4	Cl	KOtBu	rt	THF	Deprotection of TBDPS
5	Br	KOtBu	rt	THF	Deprotection of TBDPS
6	Br	-	80	ACN	No conversion
7	Br	DIPEA	80	ACN	No conversion
8	Br	DBU	90	DMF	No conversion
9	Br	LDA	rt	DMF	No conversion



Scheme 23: Shift of the silyl protecting group observed in some reactions. R = H (**127**) or Me (**128**), LG = Cl or Br.

Since the silyl protecting groups did not seem to be able to tolerate harsher conditions, further experiments were performed using benzylic temporary protecting groups.

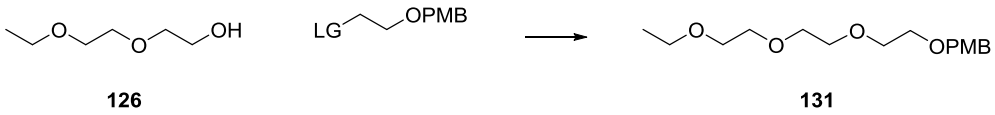


Scheme 24: Test reaction of elongation with a temporary benzylic protected substrate; PG' = Bn (**130**) or PMB (**131**).

Table 10: Overview of reaction conditions with benzylic temporary protecting groups and results of the corresponding reactions; eq. refers to the benzyl protected educt; conditions that were chosen for further experiments are shaded in green.

#	eq.	PG'	LG	Base	T / °C	Solvent	Comment
1	1	Bn	Br	NaH	rt	DMF	26 % yield
2	2	Bn	Br	NaH	rt	DMF	75 % yield
3	2	Bn	Br	KO*t*Bu	30	*t*BuOH	82 % yield
4	2	Bn	Br	KO*t*Bu	60	*t*BuOH	79 % yield
5	2	PMB	Br	NaH	rt	DMF	44 % yield
6	2	PMB	Br	KO*t*Bu	30 - 60	*t*BuOH	4 % conversion (by LC-MS)

Reaction conditions were found in which the reaction could be performed in good yields. However, since PMB can be deprotected much more mildly than benzyl and since DDQ offers an additional option of deprotection, an attempt was made to substitute the protecting group.
Contrary to expectations, the PMB protecting group showed significantly lower conversion than benzyl, therefore further reaction parameters were varied.



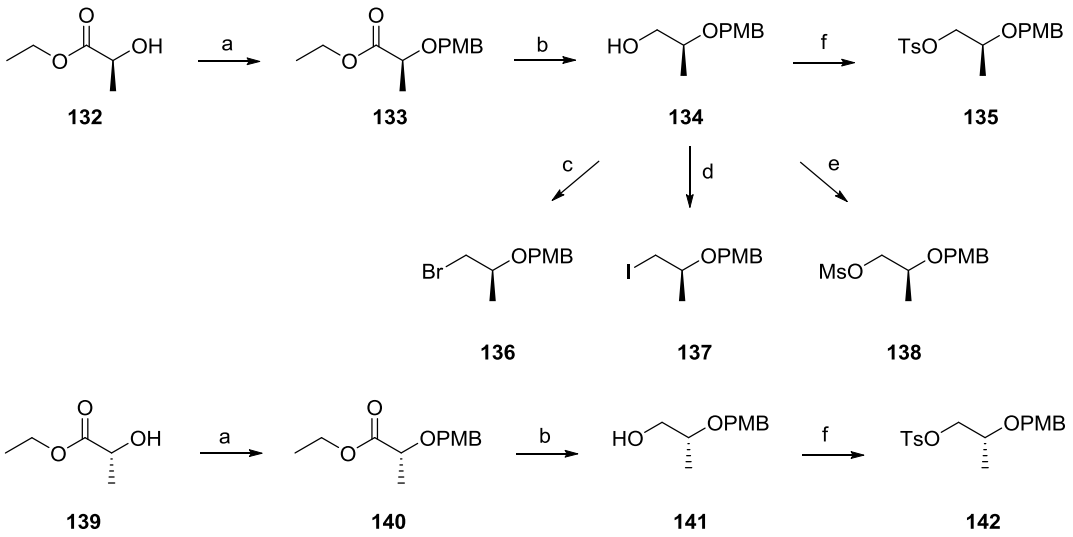
126 131

Scheme 25: Test reaction of elongation with a temporary PMB protected substrate.

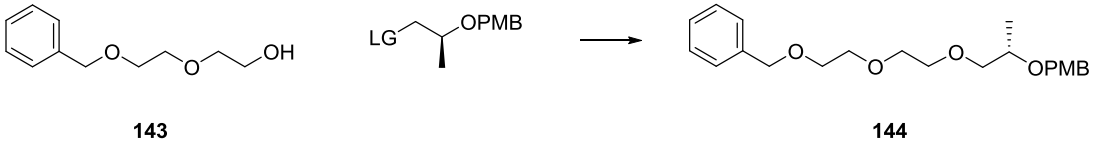
Table 11: Overview of reaction conditions with a PMB protection group and results of the corresponding reactions; eq. refers to the PMB protected educt; conditions that were chosen for further experiments are shaded in green.

#	eq.	PG'	LG	Base	T / °C	Solvent	Comment
1	2.5	PMB	Br	NaH	rt	DMF	54 % yield
2	2	PMB	Br	KO*t*Bu	70	*t*BuOH	85 % yield

This problem was solved by increasing the equivalents of PMB-protected reactant or the temperature. Chiral building blocks were to be connected in this way and were therefore synthesized according to the following scheme. However, the yield for the sterically hindered structure was observed to be significantly lower once more (reaction #1 of table 12), leading to another screening for optimization.



Scheme 26: Synthesis of chiral building blocks; the yields of the (*S*)-enantiomer are given first, followed by the (*R*)-enantiomer a) PMBCl, NaI, 2 h, 150 °C, 70 %, 35 %; b) LAH, 0 °C to rt, 2 h, quant., quant.; c) CBr_4, PPh_3, DCM, 0 °C to rt, 5 d, 50 %; d) I_2, PPh_3, imidazole, DCM, 0 °C to rt, overnight, 61 %; e) MsCl, TEA, DMAP, DCM, 0 °C to rt, overnight, quant.; f) TsCl, TEA, DMAP, DCM, 0 °C to rt, 2 h, quant., 73 %.



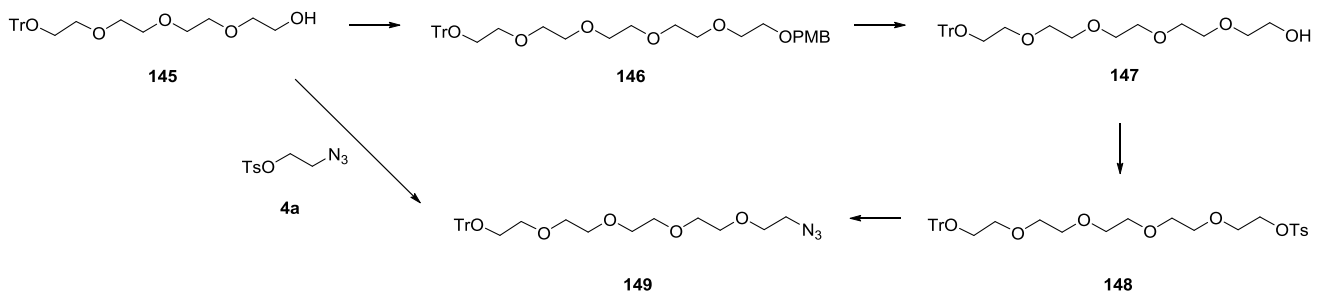
Scheme 27: Test reaction of elongation with a chiral PMB-protected substrate.

Table 12: Overview of reaction conditions with a chiral PMB protected substrate and results of the corresponding reaction; eq. refers to the PMB protected educt; conditions that were chosen for further experiments and linker synthesis are shaded in green.

#	eq.	LG	Base	T / °C	Solvent	Comment
1	2	Br	KO*t*Bu	70	*t*BuOH	10 % yield
2	2	I	KO*t*Bu	70	*t*BuOH	20 % yield
3	2	OMs	KO*t*Bu	70	*t*BuOH	60 % conversion (by LC-MS)
4	2	OTs	KO*t*Bu	70	*t*BuOH	50 % yield
5	2	OTs	KO*t*Bu	70	Benzol	No conversion
6	2	OTs	KO*t*Bu	70	DMF	No conversion
7	2	OTs	KO*t*Bu	70	Dimethyl glycol	79 % yield
8	2	OTs	KO*t*Bu	80	*t*BuOH	89 % yield

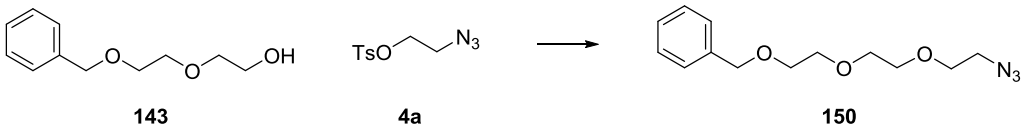
This way, it seemed possible to perform the linker elongation and to build up the linker step by step. A CTC resin was then tried to be used as permanent protective group. However, the surface of this collapsed when the necessary washing steps to get rid of potassium *tert*-butanolate were carried out. For this reason, trityl was chosen as the permanent protecting group for the further course of the synthesis.

To reduce the number of reaction steps, an attempt was made to carry out the reaction with an azide instead of the temporary protecting group (Scheme 28).



Scheme 28: Reduction of reaction steps by direct conversion with building blocks containing an azide.

Once again, the previously used conditions failed to achieve high conversion, hence further options for optimizing the reaction were screened.

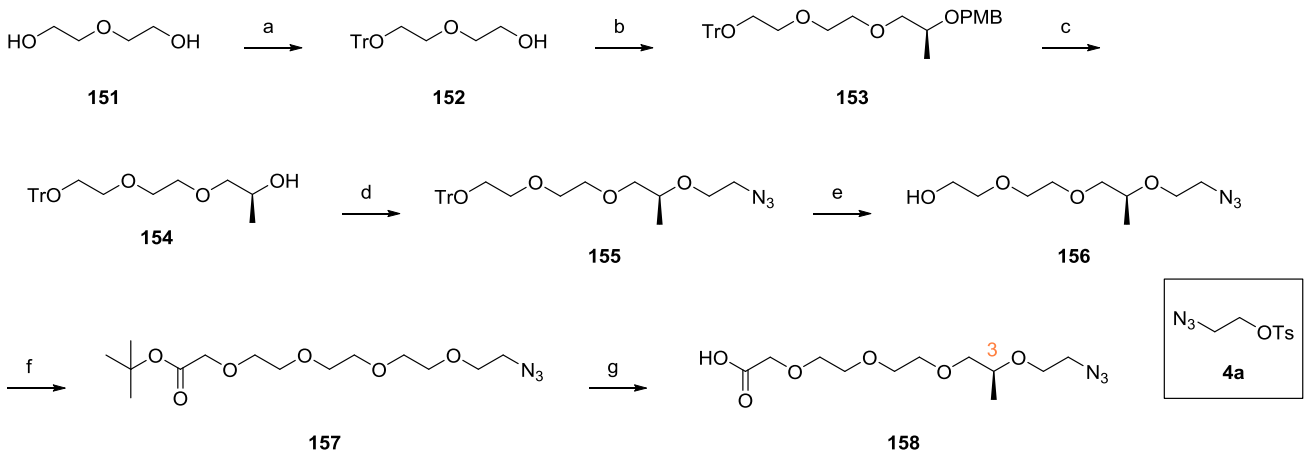


Scheme 29: Test reaction of elongation with an azide instead of a temporary protecting group.

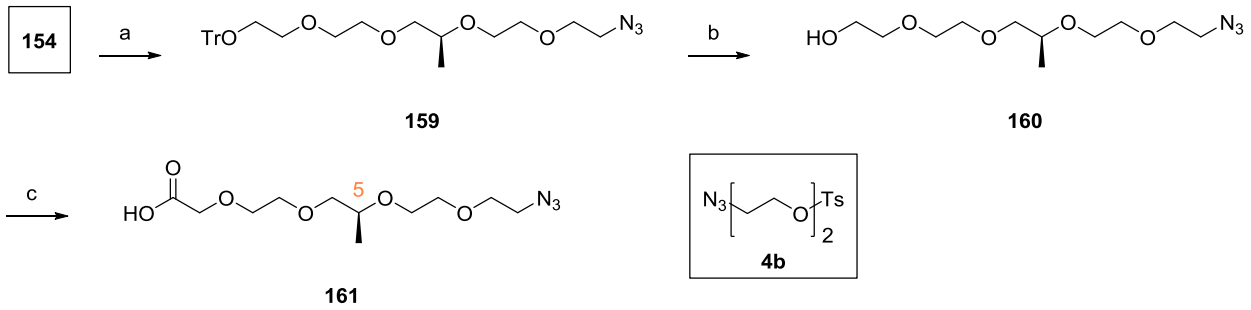
Table 13: Overview of reaction conditions with an azide and results of the corresponding reaction; eq. refers to the PMB protected educt; conversion was determined by LC-MS; conditions that were chosen for linker synthesis are shaded in green.

#	eq	Base	T / °C	Solvent	Additive	Comment
1	2	BuLi	80	THF		~ 10 % conversion
2	2	KO*t*Bu	80	*t*BuOH	$AlCl_3$	No conversion
3	2	KO*t*Bu	80	*t*BuOH	BBr_3	~ 5 % conversion
4	2	KO*t*Bu	80	*t*BuOH	Bu_4NI	~ 10 % conversion, decomposition of the azide
5	2	KO*t*Bu	30	*t*BuOH	[Bmim][BF_4]	~ 10 % conversion, decomposition of the azide
6	2	KO*t*Bu	80	*t*BuOH	NaI	~ 30 % conversion, decomposition of the azide
7	2	KO*t*Bu	rt	*t*BuOH	NaI	61 % yield
8	2	KO*t*Bu	30	*t*BuOH	NaI	~ 85 % conversion, lost on preperative HPLC due to instrument error
9	2	KO*t*Bu	40	*t*BuOH	NaI	~ 75 % conversion
10	2	KO*t*Bu	60	*t*BuOH	NaI	~ 30 % conversion, decomposition of the azide

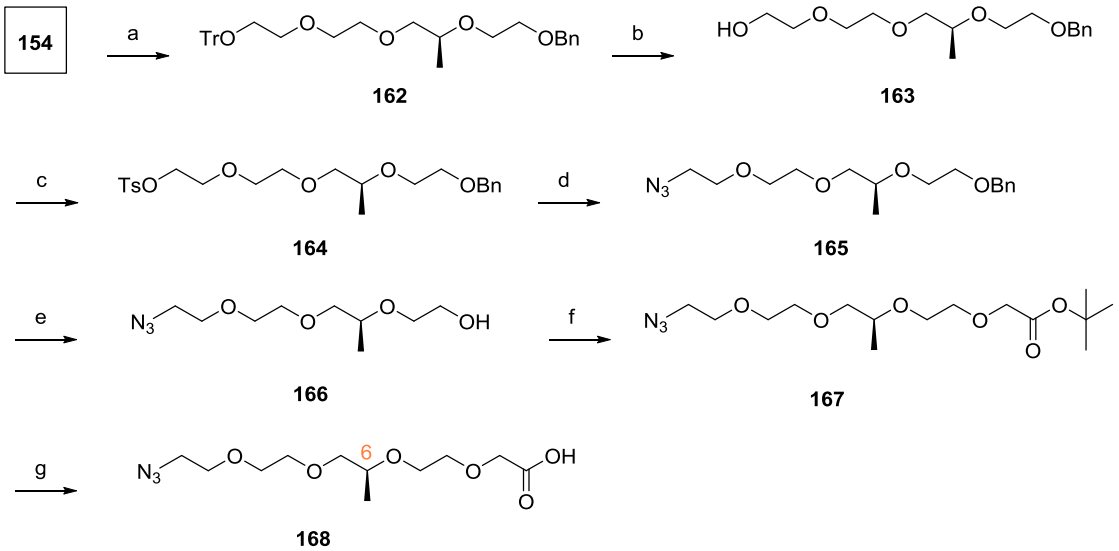
After all possible elongation steps were optimized, the synthesis of chiral linkers was performed according to the following schemes.



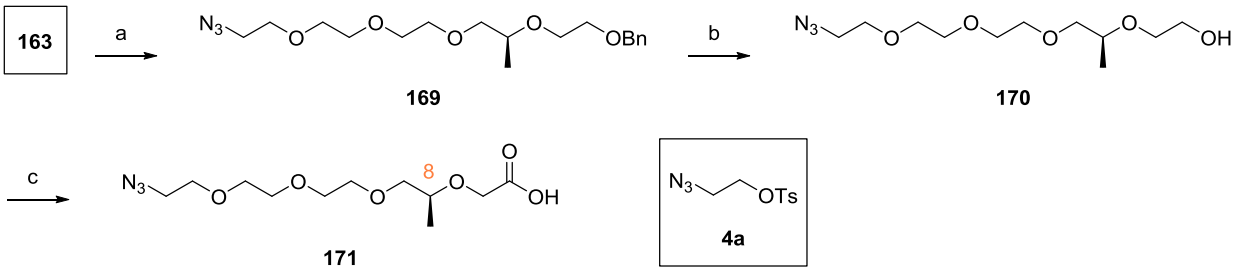
Scheme 30: Synthesis of the (3*S*)-methyl substituted linker **158** and intermediate **154**; a) TrCl, TEA, DMAP, 0 °C to rt, 4 h, 65 %; b) **135**,, KO*t*Bu, *t*BuOH, 80 °C, overnight, 93 %; c) DDQ, DCM, water, rt, 10 min, 82 %; d) **4a**, KO*t*Bu, NaI, *t*BuOH, 30 °C, 2 d, 98 %; e) TFA, DCM, rt, 2 h, 85 %; f) *tert*-Butyl 2-bromoacetate, KO*t*Bu, *t*BuOH, 30 °C, overnight, 47 %; g) LiOH, THF, water, rt, 6 h, 96 %.



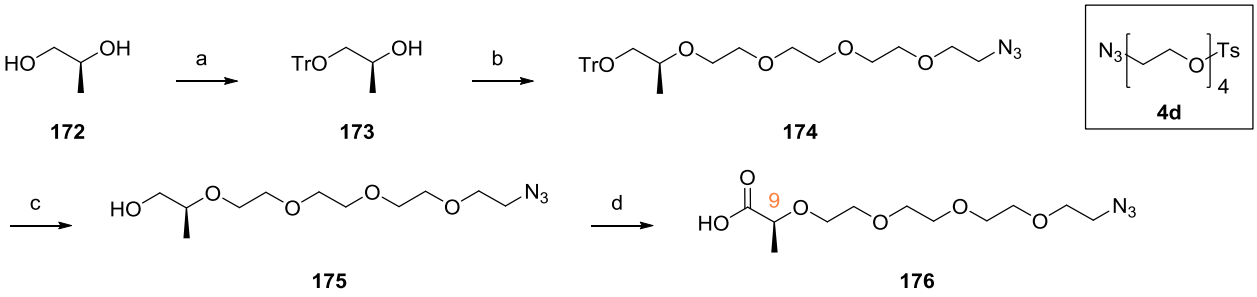
Scheme 31: Synthesis of the (5*S*)-methyl substituted linker **161** starting from intermediate **154**; a) **4b**, KO*t*Bu, NaI, *t*BuOH, 30 °C, 2 d, 50 %; b) TFA, DCM, rt, 2 h, 33 %; c) Jones reagent, acetone, 0 °C, 30 min, quant..



Scheme 32: Synthesis of the (6*S*)-methyl substituted linker **168** and intermediate **163** starting from intermediate **154**; a) 2-(Benzyloxy)ethyl 4-methylbenzenesulfonate, KO*t*Bu, NaI, *t*BuOH, 30 °C to 60 °C, 4 d, 99 %; b) TFA, DCM, rt, 3 h, 83 %; c) TsCl, TEA, DMAP, DCM, 0 °C to 30 °C, 2 d, 74 %; d) NaN_3, DMF, 70 °C, 3 h, 73 %; e) HCl(37 %), rt, overnight, quant.; f) *tert*-Butyl 2-bromoacetate, KO*t*Bu, *t*BuOH, 30 °C, overnight, 75 %; g) LiOH, THF, water, rt, overnight, quant..

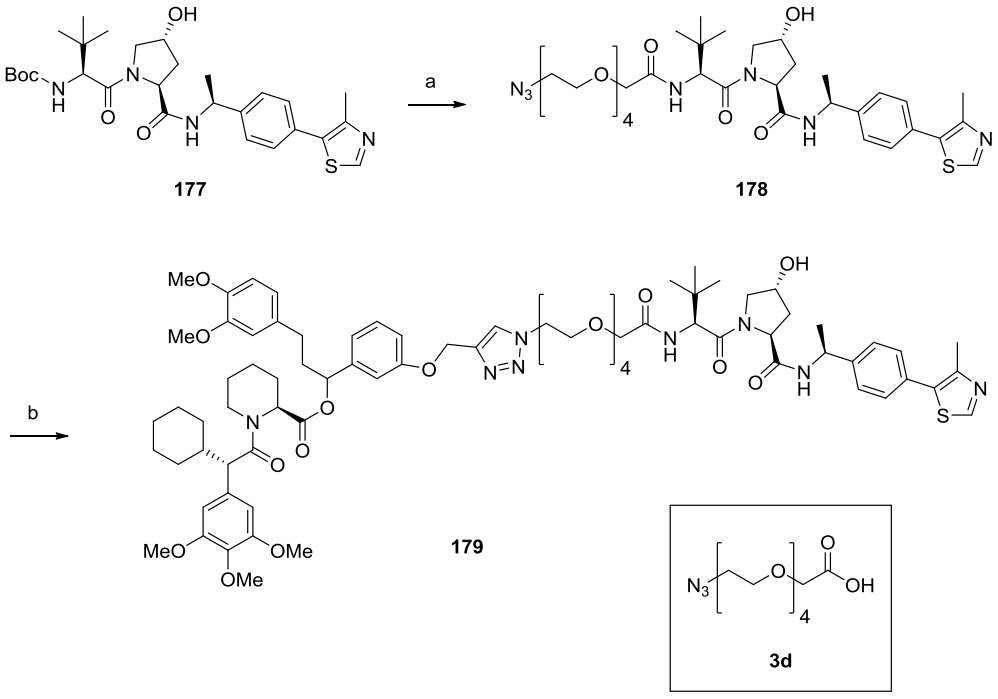


Scheme 33: Synthesis of the (8*S*)-methyl substituted linker **171** starting from intermediate **163**; a) **4a**, KO*t*Bu, NaI, *t*BuOH, 30 °C, overnight, 16 %; b) HCl(37 %), rt, 2 d, quant.; c) Jones reagent, acetone, 0 °C, 30 min, 95 %.



Scheme 34: Synthesis of the (9*S*)-methyl substituted linker **176**; a) TrCl, TEA, DCM 0 °C to rt, overnight, 74 %; b) **4d**, KO*t*Bu, NaI, *t*BuOH, 30 °C, overnight, 18 %; c) TFA, DCM, rt, 2 h, 35 %; d) Jones reagent, acetone, 0 °C, 30 min, 76 %.

Linkers were coupled to VHL and subsequently converted to PROTACs according to scheme 9 (chapter 4.1.3.2). In addition, a VHL methylated PROTAC was synthesized starting from the methylated VHL analog **177**, provided by Johannes Dreizler.



Scheme 35: Synthesis of the VHL-methylated analog **179**; a) 1) TFA, DCM, rt, 90 min; 2) **3d**, HATU, DIPEA, DCM, rt, overnight, 82 %; b) sodium ascorbate, $CuSO_4$, *t*BuOH, water, DMSO, rt, overnight, 68 %.

Cooperativity was determined by single-point-assay by Dr. Christian Meyners and Western blots were prepared by Thomas Geiger.

Table 14: Overview of the measured single-point cooperativity values of chiral MTQ202 analogs at 200 nM. PROTACS with values greater than 4 are shaded green.

Structure #	Lab book ID	Methyl attachment	FKBP51	FKBP52	FKBP12
158	MWa600	3*S*	1.66	1.01	1.06
161	MWa601	5*S*	3.42	1.00	2.17
168	MWa602	6*S*	3.70	1.03	1.79
171	MWa603	8*S*	5.59	1.00	1.95
176	MWa604	9*S*	2.24	0.97	1.20
179	MWa484	VHL	9.93	1.87	224.22

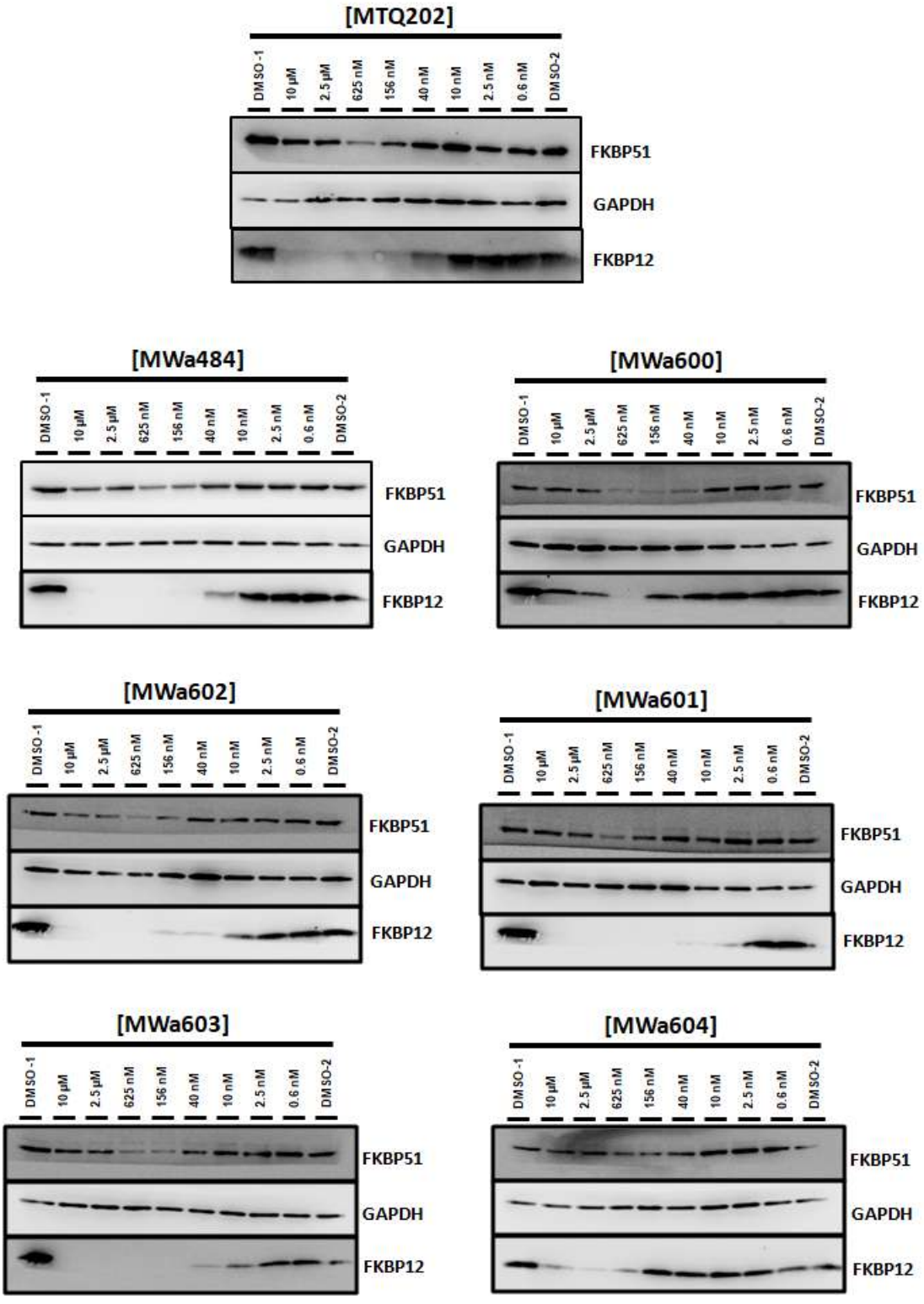


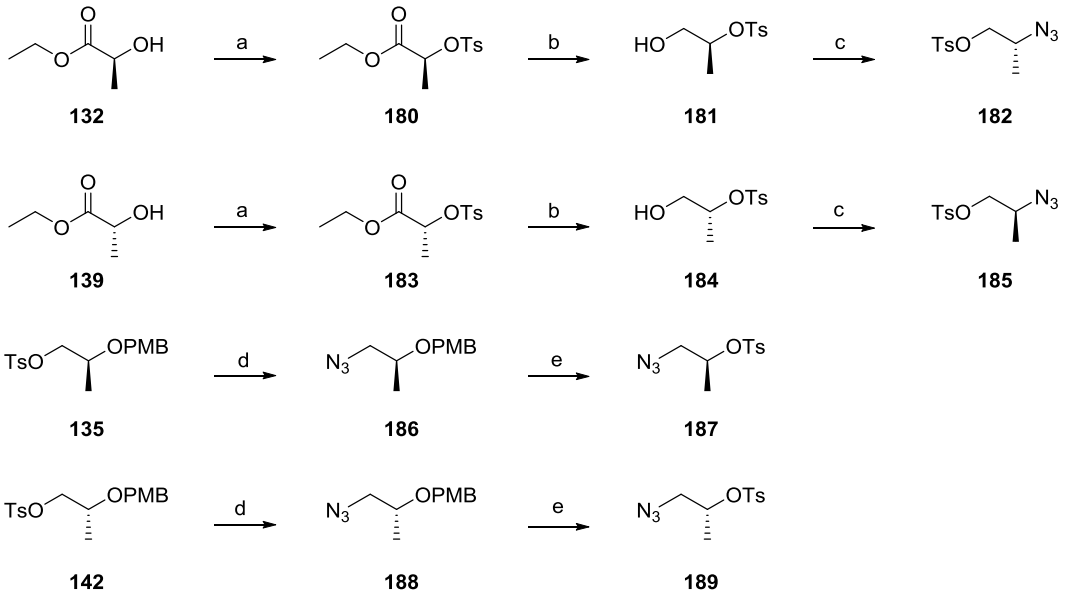
Figure 28: Western blots of chiral MTQ202 analogs in comparison with MTQ202.

Western blots clearly showed that the different methyl groups have significant influence on the activity and selectivity of the PROTAC, confirming the general approach for PROTAC optimization. However, only MWa600 showed an improved activity and selectivity profile. The remaining PROTACs show no

selectivity as well as low activity for FKBP51. Since the activity of the PROTACs generally was low, optimization was not pursued further and optimization of the more active PROTACs MWa421/MWa422 was pursued instead.

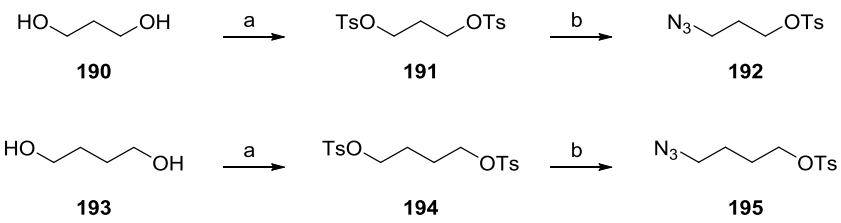
4.3.2.2. Improvement of MWa421 and MWa422

Here, the chiral linkers were first synthesized according to the following scheme.



Scheme 36: Synthesis of the chiral linkers for variation of MWa421; the yields of the upper reaction paths are given first, followed by the lower reaction paths; a) TsCl, TEA, DMAP, DCM, 0 °C to 30 °C, 2 h, 71 %., 50 %; b) $NaBH_4$, LiCl, THF, EtOH, -5 °C to rt, overnight, 68 %, 59 %; c) 1) NaN_3, DMF, 70 °C, overnight; 2) TsCl, TEA, DMAP, DCM, 0 °C to 30 °C, 3 h, 22 %, 20 %; d) NaN_3, DMF, 70 °C, overnight, 87 %, 82 %; e) 1) TFA, DCM, rt, 30 min; 2) TsCl, TEA, DMAP, DCM, 0 °C to 30 °C, overnight, 14 %, 34 %.

In addition, a C3 and a C4 linker were prepared to investigate the activity of PROTACs with linker lengths between the two active PROTACs.



Scheme 37: Synthesis of the propargyl **192** and butyl linkers **195**; yields are given for propargyl first, followed by butyl; a) TsCl, TEA, DMAP, DCM, 0 °C to rt, 2 h, 68 %, 62 %; b) NaN_3DMF, 70 °C, 18 h, 25 %, 9 %.

Linkers were coupled to VHL and subsequently converted to PROTACs according to scheme 9 (chapter 4.1.3.2). Cooperativity of the respective PROTACs was estimated by a single-point-assay performed by Dr. Christian Meyners (Table 15).

Table 15: Overview of the measured one-point cooperative values of MWa421 analogs. PROTACS with values greater than 4 or negative are shaded green.

Linker	Lab book ID	FKBP51	FKBP52	FKBP12
1*R*-Me	MWa554	20.01	1.39	1.43
1*S*-Me	MWa556	-17.35	2.50	3.78
2*R*-Me	MWa557	10.68	1.20	1.28
2*S*-Me	MWa555	19.67	1.23	1.46
propyl	MWa558	-25.14	1.66	1.83
butyl	MWa559	-9.59	2.08	2.73

Negative values were generated if the measured polarization of the FKBP-PROTAC complex is slightly below the baseline. Therefore, it can be assumed that these PROTACs also form a stable ternary complex. Thus, all PROTACs show good cooperativity for FKBP51 and were tested for activity by Western blot prepared by Thomas Geiger (Fig. 29).

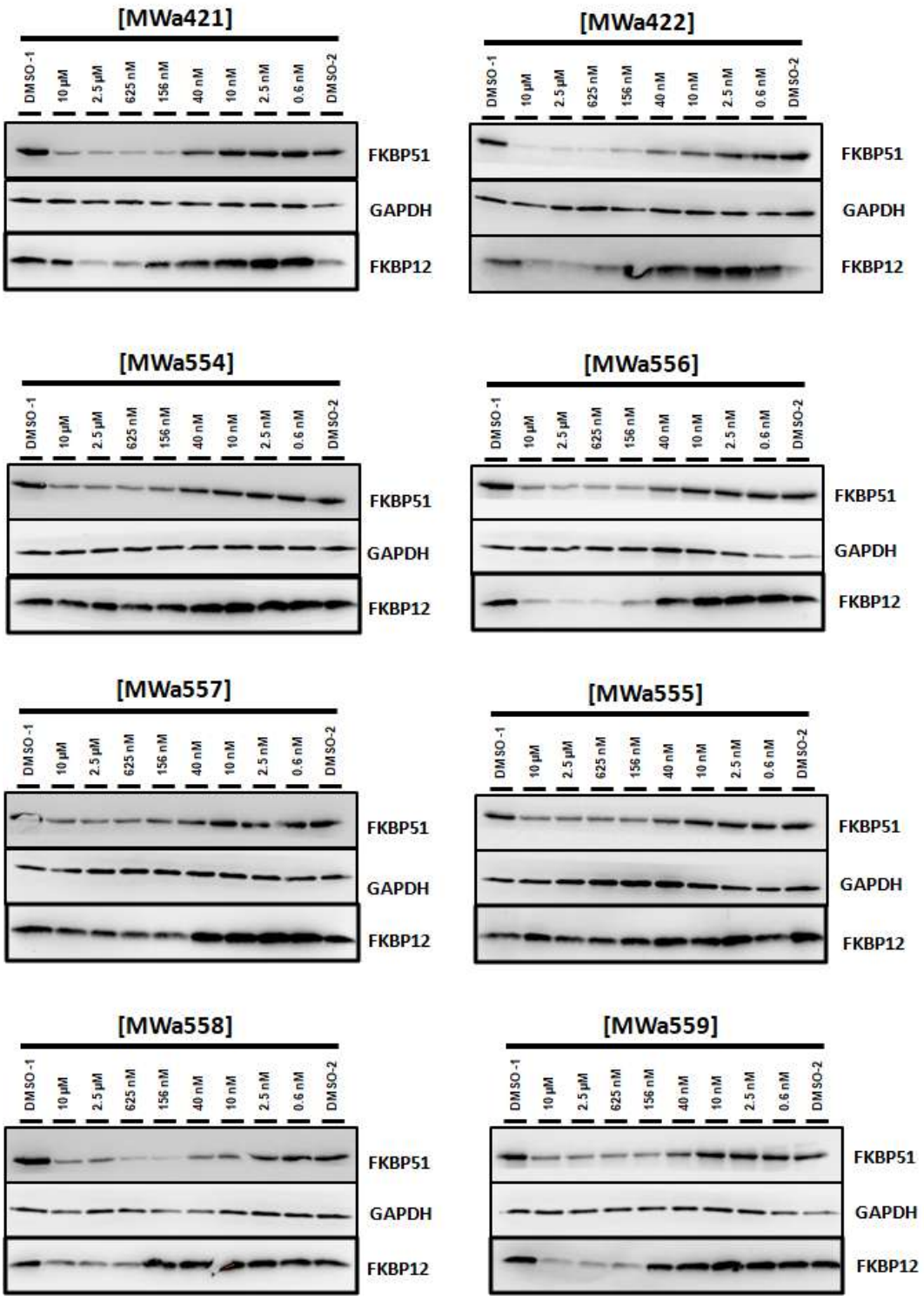


Figure 29: Western blots of MWa421 analogs in comparison with MWa421 and MWa422.

The PROTACs with methylated linkers showed compareable activity profiles as the two primer PROTACs, whereas MWa554 exhibited an increase in selectivity. However, PROTACs with modified chain length, especially propyl as linker was able to increase the activity slightly. Therfore methylated analogs of this PROTAC (MWa558) were subsequently also synthesized. The linker building blocks were prepared by Dr. Min Zheng and could be directly connected to L**2** and the SAFit-based alkyne.

Since previous screenings showed that the one-point cooperativity assay was not relevant for the activity and selectivity of PROTACs in the current scope any longer, the resulting PROTACs were tested directly by Western blots prepared by Thomas Geiger.

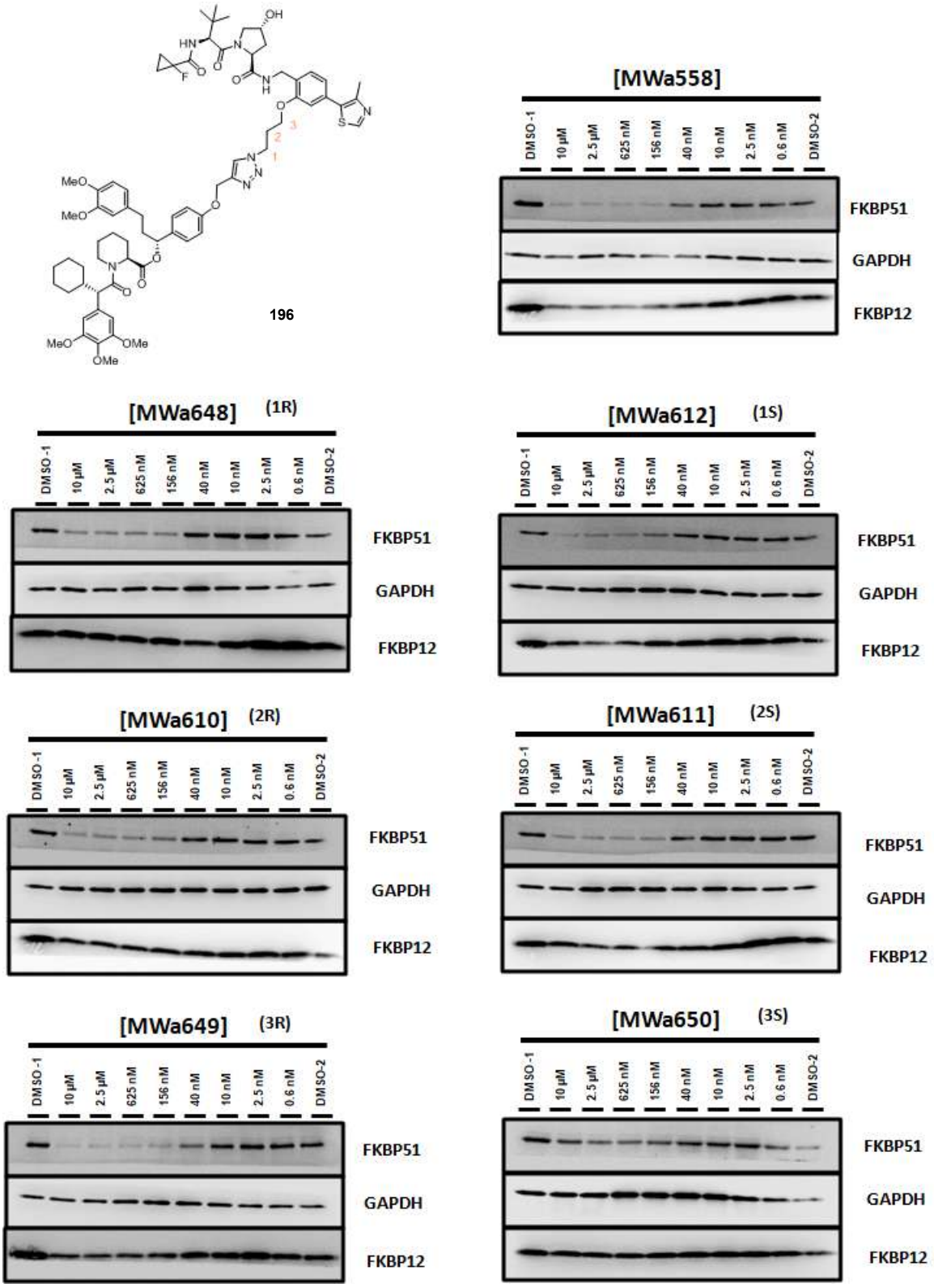


Figure 30: Structure of MWa558 (**196**) with methylation positions indicated and Western blots of MWa558 and its analogs; position and stereochemistry of the methyl group is indicated in the upper right corner.

Both 1-methyl substituted analogs show a slightly reduced activity for FKBP51 as well as FKBP12. The Western blots of the 2-methyl substituted PROTACs show no significant change in the degradation profile. 3-Methyl substituted PROTACs show highly different results depending on their stereocenter. The 3*S*-substituted PROTAC hardly degrades FKBP51, whereas the 3*R*-substituted PROTAC shows no obvious change of activity for FKBP51 and at the same time no degradation of FKBP12.
MWa649 therefore exhibits the properties desired at the beginning of the work and has to be highlighted as the best PROTAC for FKBP51 to date.

4.3.3. Improvement by variation of the POI-ligand

Since the variation of individual groups of the ligand for the POI achieved highly different results in previous experiments, additional analogs were synthesized which differ slightly in their SAFit structure. Since this can lead to different protein-protein interactions, the non-methylated propargyl linker was chosen for the synthesis of these PROTACs in order to avoid limitations in the flexibility of the linker.
Three analogs were selected for the variation of the bottom group, which are shown in the following figure.

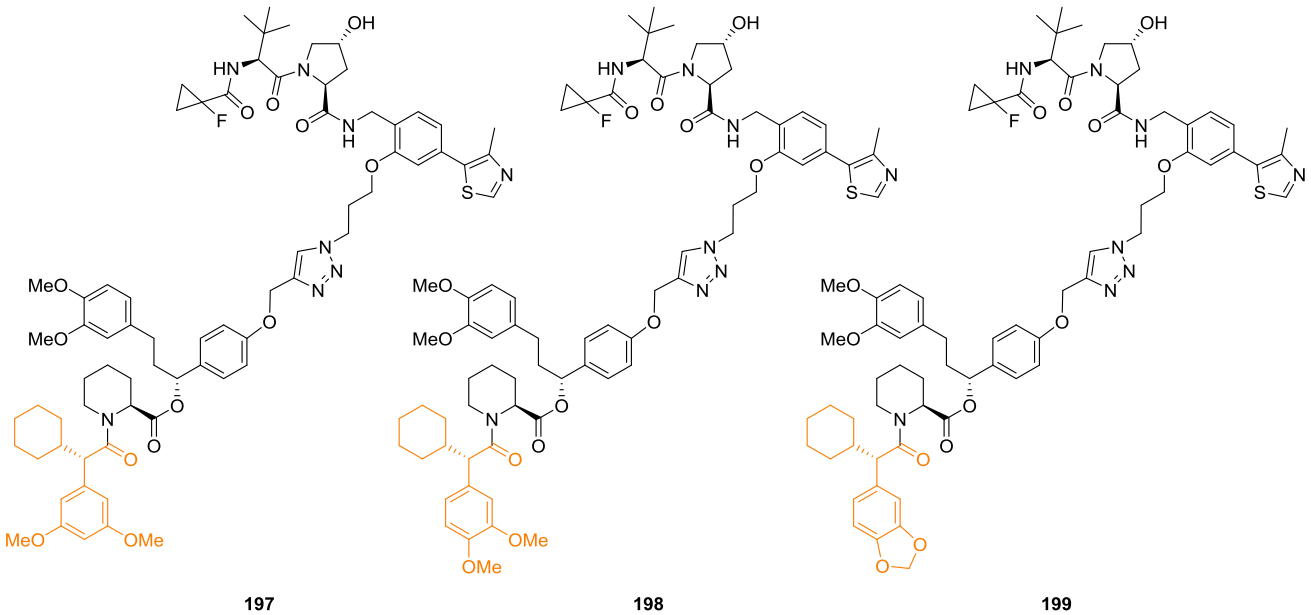
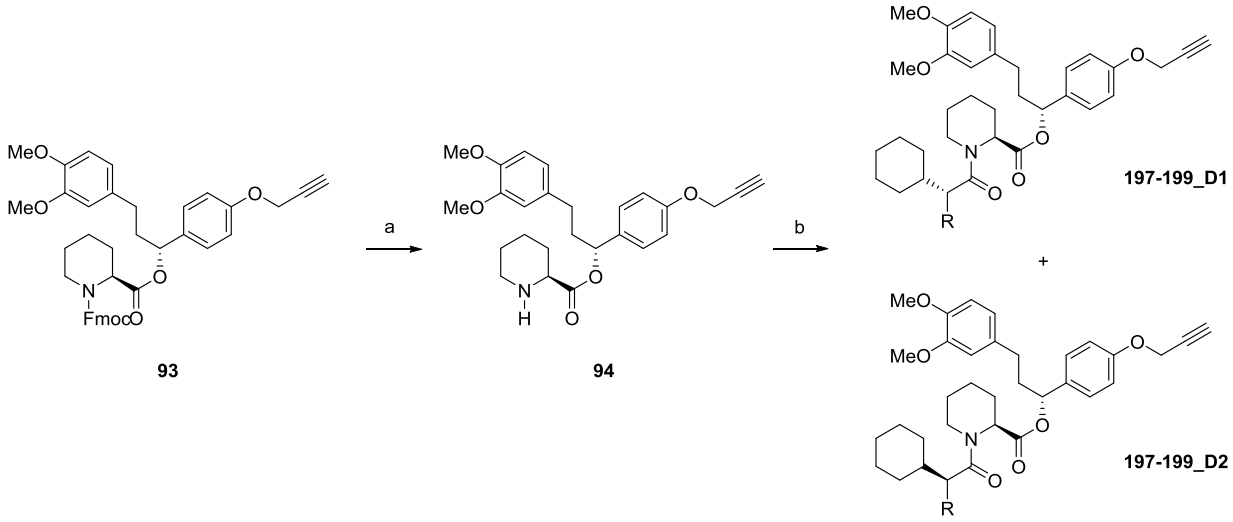


Figure 31: Target structures for variation of the bottom group (orange).

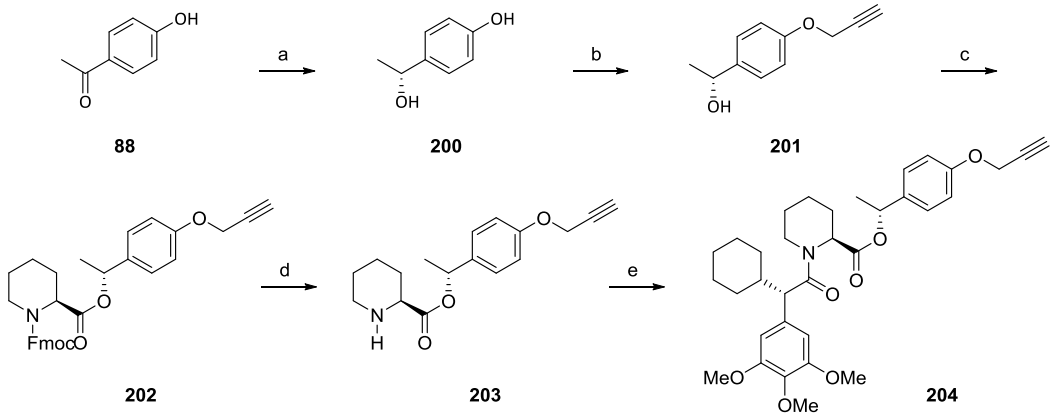
The bottom group (orange in Fig. 31) was varied according to the following scheme. The carboxylic acids used for this purpose were provided as a racemic mixture by Fabian Knaup.



Scheme 38: Synthesis of alkynes for variation of the bottom group; separation of diastereomers was performed at the stage of the final alkynes; yields are given in order for **197_D1** + **197_D2**, **198_D1** + **198_D2**, **199_D1** + **199_D2**; a) 4-methylpiperidine, DCM, rt, 3 h, 75 %; b) FKN735 / FKN029 or FKN224, HATU, DIPEA, DCM, DMF, 0 °C to rt, overnight, 31 % + 25 %, 25 % + 31 %, 32 % + 19 %.

Knowing the binding mode of SAFit only the D1-diastereomers should exhibit binding of FKBPs wheras the D2-diastereomes shoud be incapeable of binding. The diastereomers were therefore assigned accordingly to the FP assay data. The assignment of the diastereomers, however, was not done until the stage of PROTACs. Therefore both diastereomers were converted to PROTACs and then the stereocenter was assessed by FP assay prepared by Wisely Oki Sugiarto (Table 16).

In addition, another analog was synthesized in which a part of the top-group was removed. For this purpose, the ketone **88** was directly reduced without prior aldol condensation and then reacted following the regular synthesis of SAFit.



Scheme 39: Synthesis of a top-group varied SAFit analog **204**; a) $RuCl_2$[(*S*)-dm-segphos®][(*S*)-daipen], H_2, KO*t*Bu, *i*-PrOH, rt, 4 d, 46 %; b) 3-bromoprop-1-yne, K_2CO_3, acetone, rt, 4 d, 36 %; c) (*S*)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)piperidine-2-carboxylic acid, EDC, DMAP, DCM, 0 °C to rt, 2 h, 59 %; d) 4-methylpiperidine, DCM, rt, 2 h, quant.; e) VBu308, HATU, DIPEA, DCM, DMF, 0 °C to rt, overnight, 73 %.

Table 16: Overview of the K_D-values of the varied SAFit-based PROTACs and resulting assignment of the diastereomers; values greater than 2 µM are indicated as not detected (n.d.).

Structure #	Lab book ID	K_D (nM)			Diastereomer assignment
		FKBP51FK1	FKBP52FK1	FKBP12	
197	MWa660	n.d.	n.d.	n.d.	D2
197	MWa661	29	n.d.	n.d.	D1
198	MWa662	n.d.	n.d.	n.d.	D2
198	MWa663	15	n.d.	n.d.	D1
199	MWa664	n.d.	n.d.	n.d.	D2
199	MWa665	n.d.	n.d.	1749	D1
204	MWa666	236	n.d.	574	-

The compounds with the desired stereochemistry were then tested for activity in western blots by Thomas Geiger.

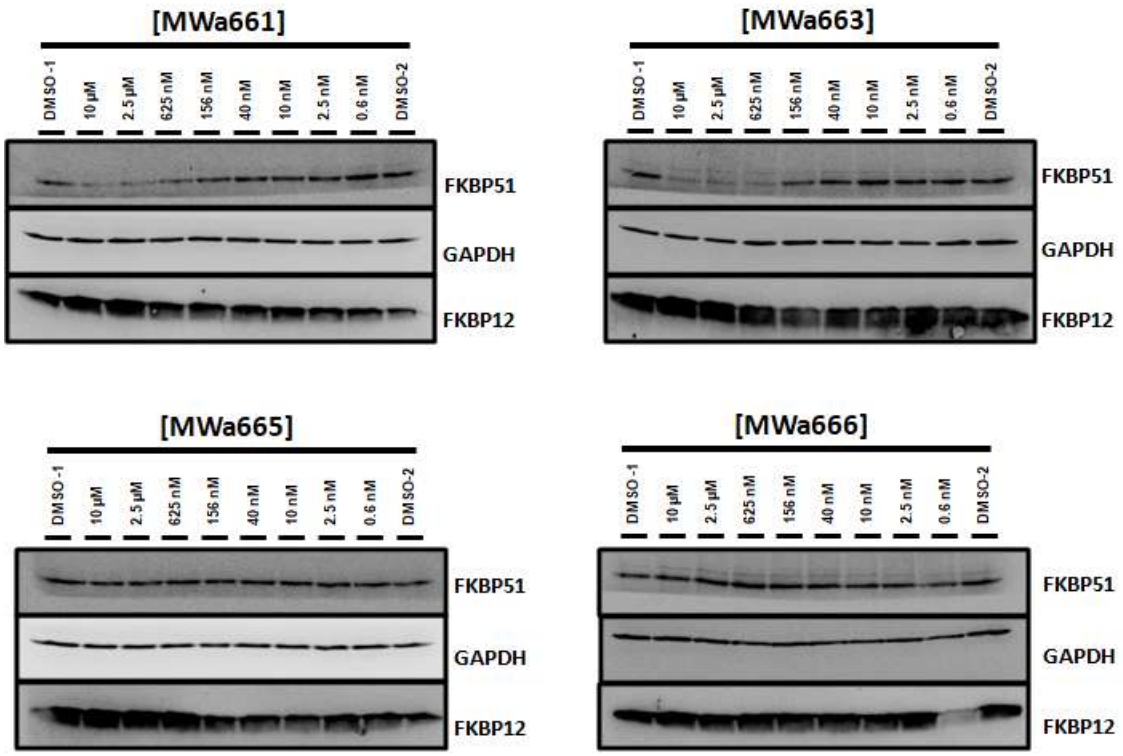
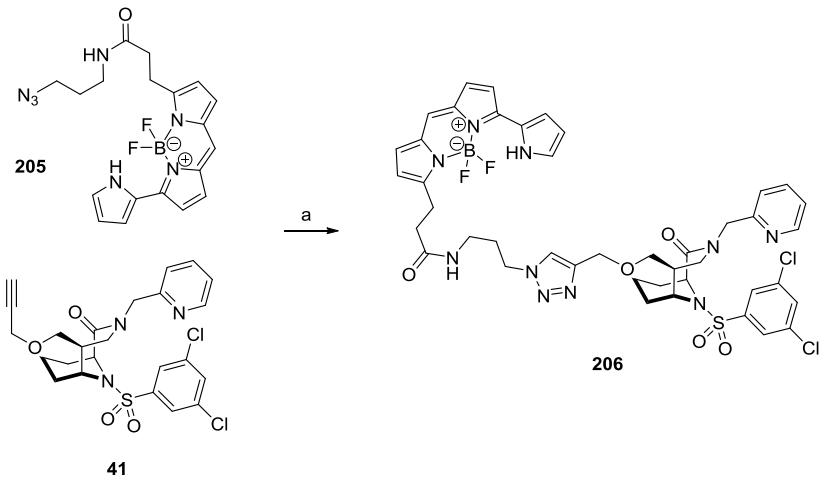


Figure 32: Western blots of SAFit variation for optimization of MWa558.

Western blots showed that MWa661 and MWa663 have reduced activity for FKBP51 but high selectivity towards FKBP12. MWa665 and MWa666 show no remaining activity at all. Therefore, the previously described MWa649 remained the PROTAC with the best activity and selectivity profile and has to be outlined as the final result of this thesis.

4.4. Synthesis of a tracer for a NanoBRET assay

Furthermore, to determine the IC_{50} values of highly interesting FKBP ligands of the research group, a NanoBRET assay tracer was synthesized (Scheme 40).



Scheme 40: Synthesis of a nanoBRET assay tracer **206;** a) $CuSO_4$, sodium ascorbate, DMSO, water, *t*-BuOH, rt, overnight, 59 %.

The main advantage of this method is that target protein occupancy is measured directly in the cell. Thus in comparison to the previously used FP-assay, a statement about the membrane permeability of the compound can be made. The assay was described in details in the publication of Gnatzy et al..[79]

5. Summary

In this work, the screening library of PROTACs for FKBPs was expanded from previously 60 PROTACs, of which only one had mild activity for FKBP51 and none showed selectivity for FKBP51 over FKBP12, to 220. The PROTACs were first tested for affinity towards different FKBPs. As expected, the bicyclic compounds showed high affinities for all tested FKBPs. The SAFit-based compounds showed selectivity for FKBP51, while still weakly binding FKBP12. Subsequently, the PROTACs were tested in a one-point cooperativity assay for the formation of a stable ternary complex. For the PROTACs that showed the best cooperativity for FKBP51, complete binding curves were measured and alpha values were determined. The PROTACs were then tested for degradation of FKBPs in HTRF- and reporter assays and by Western blots analysis for the resulting hits.

An initial approach to optimize one the previously reported mildly active PROTACs by varying the coupling type of the linker to the FKBP ligand, showed no increase in activity or selectivity.

For the optimization of PROTACs by systematic introduction of methyl groups and the resulting restriction of rotational freedom, a procedure was established for the stepwise construction of the linkers. The PROTACs synthesized in this way showed significant changes in activity and selectivity profiles compared to their lead compound, however, these could unpredictably be beneficial or unfavorable. Especially the results of the 3*S*-methyl-substituted PROTAC, which showed a significantly increased activity as well as selectivity, demonstrated the impact this approach can have for PROTACs that cannot be crystallized, impeding a rational optimization of the linker.

The optimization of the linker of MWa421 was achieved in two steps. In the first step, the degradation profile of the PROTAC was improved by extending the linker by another carbon atom. The introduction of a methyl group in the 3*R* position of the extended linker during the second optimization step resulted in the the highly selective PROTAC MWa649, which is the best PROTAC for FKBP51 at the current state of research.

A final attempt to optimize the PROTAC by variation of particular parts of the FKBP ligand could not achieve an increased activity and selecivity profile.

Overall, in the course of this work, the first selective PROTAC for FKBP51 was synthesized and characterized, which was also found to have a significant increase in activity compared to the only known FKBP51-PROTAC (MTQ202) prior to this work.

6. Zusammenfassung

Im Rahmen dieser Arbeit konnte die Screening-Bibliothek von PROTACs für FKBPs von bisher 60 PROTACs auf 220 erweitert werden. Die PROTACs wurden daraufhin zunächst auf Affinität gegenüber unterschiedlichen FKBPs getestet. Wie erwartet zeigten die bizyklischen Verbindungen hohe Affinitäten für sämtliche getesteten FKBPs während die SAFit basierten Verbindungen Selektivität für FKBP51 aufwiesen. Anschließend wurden die PROTACs in einem Einpunkt-Kooperativitätsassay auf die Bildung eines stabilen ternären Komplexes getestet. Für die PROTACs, welche die beste Kooperativität für FKBP51 zeigten wurden daraufhin vollständige Bindungskurven gemessen und daraus ein Alpha-Wert bestimmt. Anschließend wurde die PROTACs in HTRF- und Reportergen-Assays auf Degradation von FKBPs getestet und Western-Blots für die hieraus resultierenden Hits angefertigt.

Ein erster Ansatz zur Optimierung eines der aktivsten PROTACs, durch die Variation der Linkerbindungsstelle an den FKBP-Liganden, zeigte keinerlei Steigerung der Aktivität oder Selektivität.

Für die Optimierung der PROTACs durch systematische Einführung von Methyl-gruppen und damit einhergehender Einschränkung der Rotationsfreiheit wurde zunächst ein Verfahren für den schrittweisen Aufbau der Linker etabliert, welches darüber hinaus bereits in weiteren Projekten des Arbeitskreises Anwendung fand. Die so synthetisierten PROTACs zeigten deutliche Veränderungen des Aktivitäts- und Selektivitätsprofils im Vergleich zu deren Ausgangssubstanz. Vor allem die Ergebnisse des 3*S*-methyl-substituierten PROTACs, welcher eine erheblich gesteigerte Aktivität, sowie Selektivität aufweist, zeigten die Bedeutung die dieser Ansatz für PROTACs haben kann, welche nicht kristallisiert werden können, sodass eine rationale Optimierung des Linkers nicht möglich ist.

Die Optimierung des Linkers von MWa421 erfolgte in zwei Schritten. Im ersten Schritt konnte das Degradationsprofil des PROTACs durch die Verlängerung des Linkers um ein weiteres Kohlenstoffatom verbessert werden. Die Einführung einer Methyl-Gruppe in der 3*R*-Position des verlängerten Linkers während des zweiten Optimierungsschritts resultierte in dem hochselektiven PROTAC MWa649, dem besten PROTAC für FKBP51 nach aktuellem Stand der Forschung.

Ein letzter Versuch zur Optimierung des PROTACs durch Variation einzelner Teile des FKBP-Liganden konnte nicht den gewünschten Effekt erzielen.

Somit konnte im Verlauf dieser Arbeit der erste selektive PROTAC für FKBP51 synthetisiert und charakterisiert werden, welcher sich darüber hinaus durch eine deutliche Steigerung der Aktivität im Vergleich zu dem vor meiner Arbeit einzig bekannten FKBP51-PROTAC (MTQ202) auszeichnet.

7. Experimental part

General

In general reactions were performed in round bottom or three-neck flasks.

Reagents and solvents from commercial sources were used without further purification.

Nuclear Magnetic Resonance Spectroscopy

NMR spectroscopy was performed by the NMR department of TU Darmstadt. NMR spectra were recorded on a 300 MHz Avance II NMR spectrometer from Bruker BioSpin GmbH (^{1}H-NMR only), a 300 MHz Avance III NMR spectrometer from Bruker BioSpin GmbH (^{1}H-, ^{13}C-NMR), or a 500 MHz NMR spectrometer DRX 500 from Bruker BioSpin GmbH (^{1}H- and ^{13}C-NMR). NMR spectra were recorded at room temperature. Chemical shifts are given in parts per million. Coupling constants are given in hertz (Hz), peak multiplicities are given as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m).

Liquid Chromatography – Mass Spectrometry

LC was performed either with a Beckman Coulter System Gold 126 solvent module, Beckman Coulter System Gold 508 autosampler and Beckman Coulter System Gold 166 detector, with a YMC-Pack Pro C8 3 μm 120 Å, 100x4.6 mm column from YMC, or with an Agilent 1260 Infinity II system with a Poroshell 120 EC-C18 1.9 μm, 2.1 x 50 mm column from Agilent. Eluents were 0.1 % formic acid in water (Eluent A) and 0.1 % formic acid in acetonitrile (Eluent B), the used method was 5 % B to 100 % B in either 19 min or in 2 to 3 min, respectively. MS was recorded either with a Thermo Finnigan LCQ Deca XP Plus or an Agilent InfinityLab G6125B LC/MSD, respectively.

High Resolution Mass Spectrometry

HR-MS was performed by the mass spectrometry department of TU Darmstadt. Mass spectra were recorded on an Impact II, quadrupol-time-of-flight spectrometer from Bruker Daltonics.

Column chromatography

Column chromatography was performed with silica gel 60 (0.04-0.063 mm, 230-400 mesh) from Carl Roth GmbH.

Preparative HPLC

Preparative HPLC was performed on an Interchim Puriflash 5.250 system with a Luna 250 x 21.2 mm, 5 μm C18 column with 100 Å pore size. The gradient was varied from 5 % B to 100 % B at a flow rate of 30 mL/min. Solvent A was water with 0.1 % TFA and solvent B acetonitrile with 0.1 % TFA.

Flash column chromatography

Flash silica gel column chromatography was performed with a Biotage® Isolera One system with Biotage® Sfär Silica HC D columns. Cyclohexane, ethyl acetate, DCM and methanol were used as solvents.

Thin layer chromatography

TLC was performed on TLC Silica gel 60 F254 Aluminum sheets from Merck Millipore.

Fluorescence Polarization assay

FP-Assays were performed by Stephanie Merz, Patrick Purder or Wisely Oki Sugiarto. For most pipetting steps, a Beckman Coulter FXP Laboratory Automation Workstation was used. FKBP12, 51FK1 and 52FK1 were expressed and purified in house. The compound was diluted in a 1:2 serial dilution in DMSO, mixed in pseudo-duplicates with Protein and tracer in buffer (20 mM Hepes, pH 8, 0.002 % v/v Triton X-100, 150 mM NaCl) in a black, nonbinding 384-well plate and incubated in the dark for 30 min. Polarization was measured on a Tecan Spark at room temperature with an excitation wavelength of 535 nm and an emission wavelength of 595 nm. The competition curves were visualized using GraphPad Prism 6.0. K_D-values were calculated from the fitting according to KOZANY et al..[18]

General procedure A - Click reaction

Azides (1.0 eq.) and alkynes (1.0 eq.) were dissolved in *tert*-butanol, water and DMSO (1:1:10). The solution was degassed by argon. Copper(II) sulfate pentahydrate (1 M in water, 0.4 eq.) and (+)-sodium L-ascorbate (1 M in water, 0.4 eq.) were added. The solution was stirred for 18 h at room temperature. DCM was added and the mixture was washed with brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure.

General procedure B - Amide coupling

Amines (1.0 eq.), carboxylic acids (1.0 eq.) and HATU (1.3 eq.) were dissolved in DCM and the solution was degassed by argon. DIPEA (5.0 eq.) was added and the mixture was stirred for 2 h at room temperature. Brine was added to the solution and the mixture was extracted with DCM. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure.

General procedure C - Alcohol tosylation

Alcohols (1.0 eq.), triethylamine (3.0 eq.) and 4-dimethylaminopyridine (0.2 eq.) were dissolved in DCM and cooled to 0 °C. *p*-Toluenesulfonyl chloride (1.5 eq.) was added and the mixture stirred for 2 h at 0 °C to room temperature. Water was added and the mixture was extracted with DCM. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure.

General procedure D - Ether coupling

Alcohols (1.0 eq.) and potassium *tert*-butoxide (1.5 eq.) were dissolved in *tert*-butanol. Tosylates (2.0 eq.) were added and the mixture was stirred for 18 h at 80 °C. Additional potassium *tert*-butoxide (1.5 eq.) and tosylates (2.0 eq.) were added and the mixture was stirred for 24 h at 80 °C. The solvent was removed under reduced pressure.

General procedure E - Boc deprotection and amide coupling

Boc-protected amines (1.0 eq.) and TFA were stirred in DCM for 60 min at room temperature under argon. The solvent was removed under reduced pressure.

Carboxylic acids (1.0 eq.) in DCM were added to the deprotected amine. DIPEA (5.0 eq.) and HATU (1.3 eq.) were added and the mixture was stirred for 18 h at room temperature under argon. DCM was

added and the mixture was washed with Brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure.

General procedure F - Ether coupling

Alcohols (1.0 eq.), tosylates (2.0 eq), potassium *tert*-butoxide (1.5 eq.) and sodium iodide (0.5 eq.) were dissolved in *tert*-butanol. The mixture was stirred for 18 h at 30 °C. Additional potassium *tert*-butoxide (1.5 eq.) and sodium iodide (0.5 eq.) were added and the mixture was stirred for 24 h at 30 °C. The solvent was removed under reduced pressure. The crude product was dissolved in DCM and filtered. The solvent was removed under reduced pressure.

General procedure G - Jones oxidation

Alcohols (1.0 eq.) were dissolved in acetone and the mixture was cooled to 0 °C. Jones reagent (2 M, 4.0 eq.) was added and the mixture was stirred for 30 min at 0 °C. The reaction was quenched with *iso*-propanol. A pH value of 3 was set by the addition of sodium hydrogen carbonate (sat., aq). Water was added and the mixture was extracted with DCM. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure.

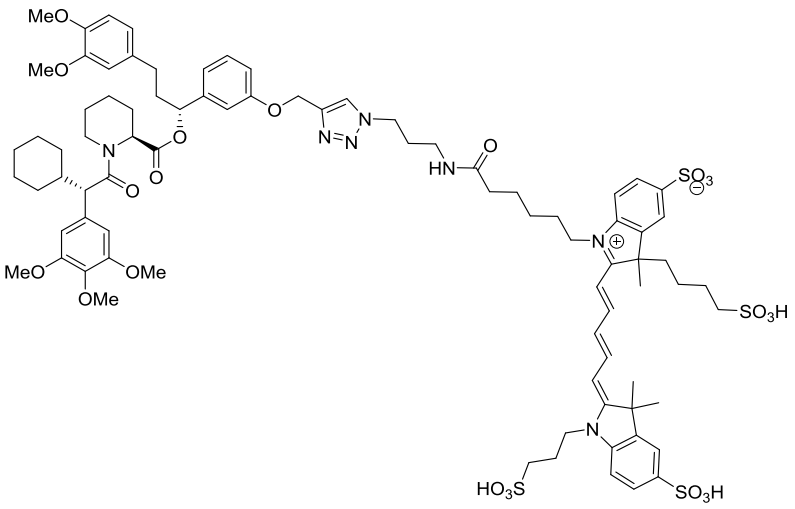
General procedure H - Ether coupling

(2*S*,4*R*)-1-((*S*)-2-(1-Fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(2-hydroxy-4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (HWS02, 1.0 eq.), tosylates (1.35 eq.) and potassium carbonate (2.7 eq.) were dissolved in DMF. The mixture was stirred for 18 h at 70 °C. The solvent was removed under reduced pressure.

General procedure I - Amide coupling

Carboxylic acids (1.0 eq.) and HATU (1.1 eq.) were dissolved in DCM and DMF. The mixture was cooled to 0 °C and DIPEA (3.0 eq.) was added. The mixture was stirred for 15 min at 0 °C. Amines (1.0 eq.) in DCM (2 mL) were added and the mixture was stirred for 18 h at 0 °C to room temperature. The solution was concentrated under reduced pressure.

1-(6-((3-(4-((3-((*R*)-1-(((*S*)-1-((*S*)-2-Cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)propyl)amino)-6-oxohexyl)-2-((1*E*,3*E*)-5-((*E*)-3,3-dimethyl-5-sulfo-1-(3-sulfopropyl)indolin-2-ylidene)penta-1,3-dien-1-yl)-3-methyl-3-(4-sulfobutyl)-3H-indol-1-ium-5-sulfonate



$C_{83}H_{107}N_7O_{22}S_4$, MW = 1683.04 g / mol

The product was synthesized from 1-(6-((3-azidopropyl)amino)-6-oxohexyl)-2-((1*E*,3*E*)-5-((*E*)-3,3-dimethyl-5-sulfo-1-(3-sulfopropyl)indolin-2-ylidene)penta-1,3-dien-1-yl)-3-methyl-3-(4-sulfobutyl)-3H-indol-1-ium-5-sulfonate (2.9 mg, 3.0 μmol, 1.0 eq.) and alkyne **A10** (2.2 mg, 3.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by chromatography (2 g SiO_2, DCM:MeOH = 20:1 → 2:1). The product was dried by lyophilisation.

To determine the purity absorption of a 5 μM solution at 647 nm and 650 nm was detected and compared to its theoretical values. This showed a purtiy of over 99 %.

Yield: 5.0 mg (quant., 3.0 μmol)

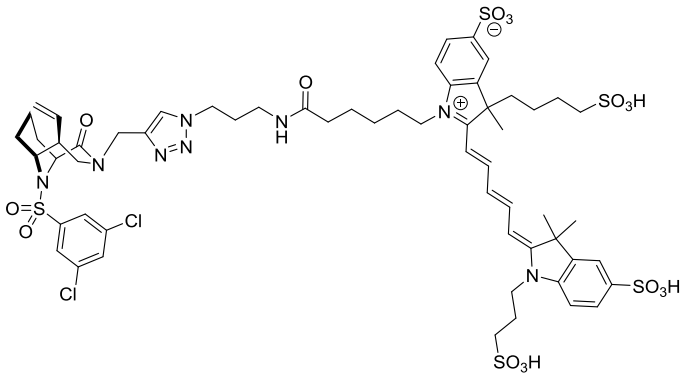
Appearance: blue solid.

TLC: R_f = 0.30 (DCM:MeOH = 2:1).

HRMS (ESI) m/z: $[M+2H]^{2+}$ calculated for $C_{83}H_{107}N_7O_{22}S_4$ = 841.82488; found = 841.82251.

Lab book number(s): MWa144.

1-(6-((3-(4-(((5*S*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-5-vinyl-3,10-diazabicyclo[4.3.1]decan-3-yl)methyl)-1H-1,2,3-triazol-1-yl)propyl)amino)-6-oxohexyl)-2-((1E,3E)-5-((E)-3,3-dimethyl-5-sulfo-1-(3-sulfopropyl)indolin-2-ylidene)penta-1,3-dien-1-yl)-3-methyl-3-(4-sulfobutyl)-3H-indol-1-ium-5-sulfonate



$C_{59}H_{74}Cl_2N_8O_{16}S_5$, MW = 1382.48 g / mol

The product was synthesized from 1-(6-((3-azidopropyl)amino)-6-oxohexyl)-2-((1*E*,3*E*)-5-((*E*)-3,3-dimethyl-5-sulfo-1-(3-sulfopropyl)indolin-2-ylidene)penta-1,3-dien-1-yl)-3-methyl-3-(4-sulfobutyl)-3H-indol-1-ium-5-sulfonate (2.9 mg, 3.0 μmol, 1.0 eq.) and alkyne **A5** (1.3 mg, 3.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by chromatography (2 g SiO_2, DCM:MeOH = 2:1). The product was dried by lyophilisation.

To determine the purity absorption of a 5 μM solution at 647 nm and 650 nm was detected and compared to its theoretical values. This showed a purtiy of over 99 %.

Yield: 2.0 mg (48 %, 1.4 μmol).

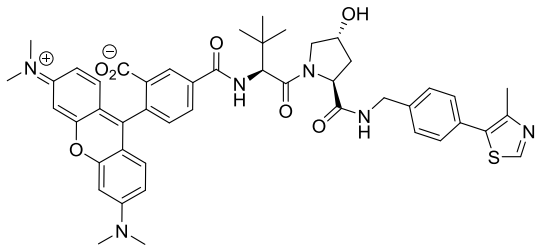
Appearance: blue solid.

TLC: R_f = 0.19 (DCM:MeOH = 2:1).

HRMS (ESI) m/z: $[M+2H]^{2+}$ calculated for $C_{59}H_{74}Cl_2N_8O_{16}S_5$ = 691.16745; found = 691.16817.

Lab book number(s): MWa146.

2-(6-(Dimethylamino)-3-(dimethyliminio)-3H-xanthen-9-yl)-5-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)carbamoyl)benzoate



$C_{47}H_{50}N_6O_7S$, MW = 843.01 g / mol

tert-Butyl *((S)*-1-((2*S,*4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (3.2 mg, 6.0 μmol, 1.0 eq.) and TFA (200 μL) were stirred in DCM (200 μL) for 90 min at room temperature. The mixture was concentrated under reduced pressure.

TLC: R_f = 0.11 (DCM:MeOH = 20:1, 1 % TEA).

To crude (2*S*,4*R*)-1-((*S*)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (2.6 mg, 6.0 μmol, 1.0 eq.), TEA (8.4 μL, 60.0 μmol, 10.0 eq.) and TAMRA-NHS (3.2 mg, 6.0 μmol, 1.0 eq.) in DCM:DMF (1:1, 400 μL) were added. The mixture was stirred for 90 h at room temperatue and concentrated under reduced pressure. The obtained product was purified by chromatography (2 g SiO_2, DCM:MeOH = 15:1 → 5:1). The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 4.2 mg (5.0 μmol, 83 %).

Appearance: pink solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 1.09 (m, 3H), 1.11 (m, 3H), 1.17 (d, *J* = 3.7 Hz, 9H), 1.25 – 1.37 (m, 6H), 2.14 (ddd, *J* = 13.2, 9.1, 4.4 Hz, 1H), 2.23 – 2.31 (m, 1H), 2.48 (s, 3H), 3.74 – 3.84 (m, 1H), 3.91 (dd, *J* = 11.0, 3.9 Hz, 1H), 4.03 (d, *J* = 11.2 Hz, 1H), 4.36 (d, *J* = 15.5 Hz, 1H), 4.54 – 4.61 (m, 2H), 4.64 (dd, *J* = 9.1, 7.5 Hz, 1H), 5.00 (s, 1H), 6.96 (d, *J* = 2.4 Hz, 2H), 7.04 (dd, *J* =

9.4, 2.6 Hz, 2H), 7.20 (dd, *J* = 9.5, 1.5 Hz, 2H), 7.40 – 7.52 (m, 5H), 8.16 (dd, *J* = 7.9, 1.6 Hz, 1H), 8.67 (s, 1H), 8.87 (s, 1H).

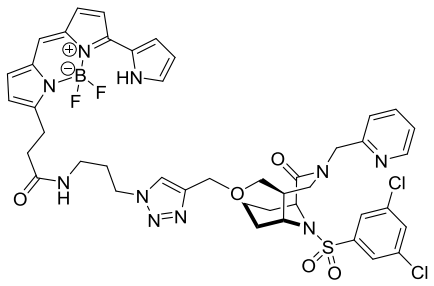
TLC: R_f = 0.22 (DCM:MeOH = 10:1).

HPLC: [30-50 % Solvent B, 20 min]: R_t = 10.8 min.
95 % purity (220 nm).

HRMS (ESI) m/z: $[M+2H]^{2+}$ calculated for $C_{47}H_{50}N_6O_7S$ = 843.35345; found = 843.35360.

Lab book number(s): MWa151.

***N*-(3-(4-((((1*S*,5*S*, 6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)methoxy)methyl)-1H-1,2,3-triazol-1-yl)propyl)-3-(5,5-difluoro-7-(1H-pyrrol-2-yl)-5H-5l4,6l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-3-yl)propanamide**



$C_{43}H_{45}BCl_2F_2N_{10}O_5S$, MW = 933.66 g / mol

The product was synthesized from *N*-(3-azidopropyl)-3-(5,5-difluoro-7-(1H-pyrrol-2-yl)-5H-5l4,6l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-3-yl)propanamide (5.0 mg, 12.2 μmol, 1.0 eq.) and alkyne **A2** (6.4 mg, 12.2 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 6.7 mg (59 %, 7.2 μmol).

Appearance: purple solid.

TLC: R_f = 0.15 (DCM:MeOH = 5:1)

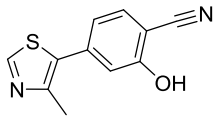
LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.1 min.

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{43}H_{45}BCl_2F_2N_{10}O_5S$ = 933.28135; found = 933.27969.

Lab book number(s): MWa462.

2-Hydroxy-4-(4-methylthiazol-5-yl)benzonitrile



$C_{11}H_8N_2OS$, MW = 216.26 g / mol

4-Bromo-2-hydroxybenzonitrile (12.5 g, 63.0 mmol, 1.0 eq.), palladium(II) acetate (140 mg, 0.63 mmol, 0.01eq.) and potassium acetate (12.4 g, 126.0 mmol, 2.0 eq.) were dissolved in DMF (500 mL, dry) under argon. 4-Methylthiazole (5.8 mL, 63.0 mmol, 1.0 eq.) was added and the mixture was stirred for 18 h at 120 °C. The mixture was allowed to cool to room temperature. Water (100 mL) and brine (250 mL) were added and the mixture was extracted with DCM (3 x 300 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 8.9 g (65 %, 40.9 mmol).

Appearance: yellow solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 2.86 (dd, *J* = 5.8, 3.6 Hz, 3H), 7.28 (ddt, *J* = 9.8, 5.9, 1.7 Hz, 1H), 7.45 (dt, *J* = 6.0, 1.7 Hz, 1H), 7.78 – 7.86 (m, 1H), 9.01 – 9.11 (m, 1H), 11.00 – 11.10 (m, 1H).

^{13}**C-NMR** (75 MHz, Chloroform-*d*): δ = 15.9, 98.5, 116.2, 116.4, 119.7, 130.1, 132.8, 137.4, 149.0, 150.9, 159.9.

TLC: R_f = 0.11 (CH:EA = 1:1).

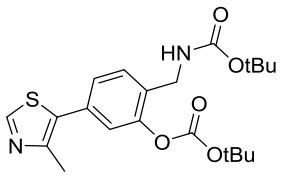
LC-MS: Mass (ESI), calculated = 217.0 $[M+H]^+$, found = 217.0.

[5-100 % Solvent B, 3.0 min]: R_t = 1.6 min.

> 99 % purity (220 nm).

Lab book number(s): MWa569.

tert-Butyl (2-((*tert*-butoxycarbonyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)carbamate



$C_{21}H_{28}N_2O_5S$, MW = 420.52 g / mol

2-Hydroxy-4-(4-methylthiazol-5-yl)benzonitrile (8.8 g, 40.7 mmol, 1.0 eq.), cobalt(II) chloride (5.3 g, 40.7 mmol, 1.0 eq.) and di-*tert*-butyl dicarbonate (53.3 g, 244.0 mmol, 6.0 eq.) were dissolved in MeOH (200 mL) and cooled to 0 °C. Sodium borohydride (7.7 g, 204.0 mmol, 5.0 eq.) was added slowly and the mixture was stirred for 2 h at 0 °C. The mixture was filtered over Celite, rinsed with MeOH and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 8.8 g (51 %, 20.9 mmol).

Appearance: yellow solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.45 (s, 9H), 1.57 (s, 9H), 2.53 (s, 3H), 4.22 – 4.35 (m, 2H), 7.22 – 7.24 (m, 1H), 7.30 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 1H), 8.68 (s, 1H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 16.1, 27.7, 28.4, 39.4, 60.4, 84.2, 122.9, 127.2, 130.0, 130.6, 130.7, 132.5, 133.5, 149.0, 150.6, 151.7, 151.9.

TLC: R_f = 0.11 (CH:EA = 1:1).

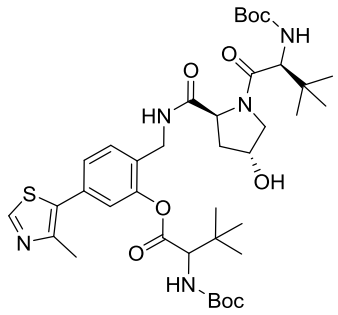
LC-MS: Mass (ESI), calculated = 421.2 $[M+H]^+$, found = 421.2.

[5-100 % Solvent B, 3.0 min]: R_t = 2.2 min.

66 % purity (220 nm).

Lab book number(s): MWa572.

2-(((2*S*,4*R*)-1-((*S*)-2-((*tert*-Butoxycarbonyl)amino)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenyl 2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoate



$C_{38}H_{57}N_5O_9S$, MW = 759.96 g / mol

tert-Butyl (*2S*,*4R*)-4-hydroxy-2-((2-hydroxy-4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carboxylate (6.5 g, 15.0 mmol, 1.0 eq.) was dissolved in DCM:TFA (1:1, 100 mL). The mixture was stirred for 2 h at room temperature. The solvent was removed under reduced pressure.
(*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoic acid (9.0 g 39.0 mmol, 2.6 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (7.5 g, 39.0 mmol, 2.6 eq.) and HOBT·H_2O (6.00 g, 39.0 mmol, 2.6 eq.) were dissolved in DMF (dry, 50 mL) under argon. The mixture was cooled to 0 °C and DIPEA (26.2 mL, 150.0 mmol, 10 .0 eq.) was added. The mixture was stirred for 30 min at 0 °C. Crude (2*S*,4*R*)-4-hydroxy-*N*-(2-hydroxy-4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (5.0 g 15.0 mmol, 1.0 eq.) was added and the mixture was stirred for 18 h at 0 °C to room temperature. Brine (300 mL) was added and the solution was extracted with DCM (3 x 300 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 6.6 g (58 %, 8.7 mmol).

Appearance: yellow solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.89 (s, 9H), 1.12 (s, 10H), 1.40 (d, *J* = 25.6 Hz, 20H), 2.10 (t, *J* = 11.1 Hz, 1H), 2.26 – 2.39 (m, 1H), 2.48 (s, 3H), 3.57 – 3.67 (m, 1H), 3.96 (d, *J* = 11.1 Hz, 1H), 4.28 (t, *J* = 10.6 Hz, 2H), 4.49 (d, *J* = 16.7 Hz, 2H), 5.33 (dd, *J* = 26.8, 9.1 Hz, 2H), 7.10 (s, 1H), 7.18 – 7.23 (m, 1H), 7.32 – 7.52 (m, 3H), 7.99 (s, 1H), 8.69 (s, 1H).

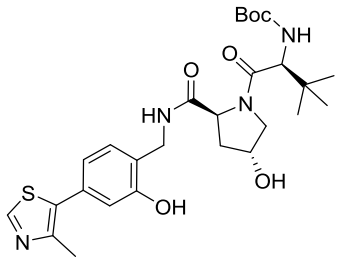
^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 15.9, 26.3, 26.8, 28.3, 31.5, 35.2, 36.6, 56.4, 58.5, 58.7, 62.5, 70.0, 80.0, 80.4, 110.2, 118.5, 122.6, 125.1, 126.7, 127.2, 128.3, 148.7, 150.9, 156.0, 162.7, 170.5, 171.2, 171.9.

TLC: R_f = 0.41 (EA).

LC-MS: Mass (ESI), calculated = 760.4 $[M+H]^+$, found = 760.4.
[5-100 % Solvent B, 3.0 min]: R_t = 2.2 min.
86 % purity (220 nm).

Lab book number(s): MWa578.

***tert*-Butyl ((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((2-hydroxy-4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate**



$C_{27}H_{38}N_4O_6S$, MW = 546.68 g / mol

tert-Butyl (2*S*,4*R*)-4-hydroxy-2-((2-hydroxy-4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carboxylate (CBR09, 8.1 g, 18.6 mmol, 1.0 eq.) and TFA (100 mL) were stirred in DCM (100 mL) for 60 min at room temperature under argon.

HOBT·H_2O (3.7 g, 24.2 mmol, 1.3 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.6 g, 24.2 mmol, 1.3 eq.) and (*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoic acid (5.6 g, 24.2 mmol, 1.3 eq.) were dissolved in DMF (dry, 75 mL) and cooled to 0 °C. DIPEA (16.2 mL, 93.0 mmol, 5.0 eq.) was added and the mixture was stirred for 30 min at 0 °C. Crude *tert*-butyl (2*S*,4*R*)-4-hydroxy-2-((2-hydroxy-4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carboxylate in DMF (dry, 50 mL) was added and the mixture was stirred for 16 h at 0 °C to room temperature. Additional HOBT·H_2O (1.9 g, 12.1 mmol, 0.65 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.3 g, 12.1 mmol, 0.65 eq.) and (*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoic acid (2.8 g, 12.1 mmol, 0.65 eq.) were dissolved in DMF (dry, 30 mL) and cooled to 0 °C. DIPEA (8.1 mL, 46.5 mmol, 2.5 eq.) was added. The mixture was stirred for 30 min at 0 °C and added to the reaction mixture. The mixture was stirred for 20 h at room temperature. Brine (200 mL) was added and the mixture was extracted with DCM (2 x 200 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by column chromatography (600 g SiO_2, EA).

Appearance: white foam.

TLC: R_f = 0.37 & 0.23 (EA).

The mixture of *tert*-butyl ((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((2-hydroxy-4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate and 2-(((2*S*,4*R*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoate was dissolved in THF:water (1:1, 150 mL). Lithium hydroxide (2.25 g, 93.8 mmol, 5.0 eq.) was added and the mixture was stirred for 16 h at room temperature. The mixture was concentrated under reduced pressure and extracted with EA (3 x 300 mL) and DCM (2 x 300 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by column chromatography (50 g SiO_2, EA).

Yield: 8.88 g (87 % o2s, 16.2 mmol).

Appearance: yellow solid.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 0.83 (s, 10H), 1.36 (s, 9H), 2.06 (dd, *J* = 13.3, 9.1 Hz, 1H), 2.37 – 2.45 (m, 1H), 2.48 (s, 3H), 3.58 (dd, *J* = 11.3, 3.8 Hz, 1H), 3.96 (d, *J* = 11.2 Hz, 1H), 4.12 (d, *J* = 7.4 Hz, 1H), 4.17 (dd, *J* = 14.7, 5.6 Hz, 1H), 4.41 (dd, *J* = 14.6, 7.3 Hz, 1H), 4.50 (s, 1H), 4.71 (t, *J* = 7.9 Hz, 1H), 5.27 (d, *J* = 9.1 Hz, 1H), 6.83 (dd, *J* = 7.7, 1.8 Hz, 1H), 6.93 (d, *J* = 1.8 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.97 – 8.13 (m, 1H), 8.64 (s, 1H), 9.12 (d, *J* = 164.1 Hz, 1H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 16.2, 26.3, 28.4, 35.2, 35.8, 40.0, 56.6, 58.2, 59.1, 70.1, 80.4, 118.2, 120.8, 124.2, 131.1, 131.8, 133.3, 148.4, 150.5, 155.9, 156.4, 172.5, 172.8.

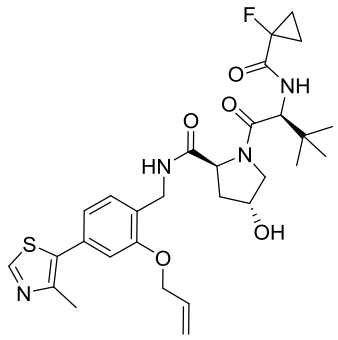
TLC: R_f = 0.23 (EA).

LC-MS: Mass (ESI), calculated = 547.3 $[M+H]^+$, found = 547.2.

HPLC: [0-100 % Solvent B, 20 min]: R_t = 11.2 min.
[20-70 % Solvent B, 20 min]: R_t = 10.1 min.
> 99 % purity (220 nm).

Lab book number(s): MWa156 + MWa159.

(2*S*,4*R*)-*N*-(2-(Allyloxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{29}H_{37}FN_4O_5S$, MW = 572.70 g / mol

tert-Butyl ((*S*)-1-((2*S*,4*R*)-2-((2-(allyloxy)-4-(4-methylthiazol-5-yl)benzyl)carbamoyl)-4-hydroxypyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (MME018, 13.6 g, 23.2 mmol, 1.0 eq.) was dissolved in DCM:TFA (1:1, 200 mL). The mixture was stirred for 2 h at room temperature. The solvent was removed under reduced pressure.

TLC: R_f = 0.04 (CH:EA = 1:2).

1-Fluorocyclopropane-1-carboxylic acid (3.1 g, 30.2 mmol, 1.3 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (5.8 g, 30.2 mmol, 1.3 eq.) and HOBT·H_2O (4.6 g, 30.2 mmol, 1.3 eq.) were dissolved in DMF (dry, 100 mL) under argon. The mixture was cooled to 0 °C and DIPEA (20.3 mL, 116 mmol, 5.0 eq.) was added. The mixture was stirred for 30 min at 0 °C. Crude (*2S,4R*)-*N*-(2-(allyloxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (11.3 g, 23.2 mmol, 1.0 eq.) was added and the mixture was stirred for 18 h at 0 °C to room temperature. Brine (300 mL) was added and the solution was extracted with DCM (3 x 300 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 6.60 g (50 %, 11.5 mmol).

Appearance: yellow foam.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 0.95 (s, 9H), 1.23 – 1.36 (m, 4H), 2.10 (t, *J* = 7.1 Hz, 1H), 2.50 (s, 4H), 3.65 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.95 (d, *J* = 11.2 Hz, 1H), 4.44 – 4.62 (m, 6H), 4.71 (t,

J = 7.8 Hz, 1H), 5.30 (dq, J = 10.5, 1.4 Hz, 1H), 5.42 (dq, J = 17.2, 1.5 Hz, 1H), 6.07 (ddt, J = 16.9, 10.4, 5.1 Hz, 1H), 6.86 (d, J = 1.7 Hz, 1H), 6.94 (dd, J = 7.7, 1.6 Hz, 1H), 7.09 (dd, J = 9.0, 3.7 Hz, 1H), 7.34 (d, J = 7.6 Hz, 2H), 8.68 (s, 1H).

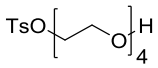
^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 13.6, 13.8, 16.1, 26.4, 35.7, 36.2, 38.8, 56.6, 57.5, 58.8, 69.0, 70.2, 79.8, 112.6, 117.8, 121.8, 126.6, 129.4, 132.0, 132.1, 133.0, 148.4, 150.5, 156.4, 170.1, 170.4, 170.8.

TLC: R_f = 0.11 (CH:EA = 1:2).
R_f = 0.28 (EA).

LC-MS: Mass (ESI), calculated = 573.3 $[M+H]^+$, found = 573.0.
[5-100 % Solvent B, 3.0 min]: R_t = 1.9 min.
87 % purity (220 nm).

Lab book number(s): MWa639.

2-(2-(2-(2-Hydroxyethoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate



$C_{15}H_{24}O_7S$, MW = 348.41 g / mol

2,2'-((Oxybis(ethane-2,1-diyl))bis(oxy))bis(ethan-1-ol) (3.5 g, 18.0 mmol, 1.0 eq.), *p*-toluenesulfonyl chloride (3.43 g, 18.0 mmol, 1.0 eq.), silver oxide (6.3 g, 27.0 mmol, 1.5 eq.) and potassium iodide (0.6 g, 3.6 mmol, 0.2 eq.) were stirred in DCM (20 mL) for 90 min at 0 °C. The solution was allowed to warm to room temperature. The solution was filtered through celite, rinsed with DCM and concentrated under reduced pressure. The obtained product was purified by column chromatography (300 g SiO_2, CH:EA = 1:1 → 1:4).

Yield: 3.70 g (60 %, 10.8 mmol).

Appearance: slightly yellow oil.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 2.43 (s, 3H), 2.53 (s, 1H), 3.56 – 3.65 (m, 10H), 3.65 – 3.70 (m, 4H), 4.13 – 4.16 (m, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.78 (d, *J* = 8.1 Hz, 2H).

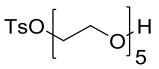
^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 21.7, 61.8, 68.8, 69.3, 70.4, 70.6, 70.7, 70.8, 72.6, 128.0, 129.9, 133.1, 144.9.

TLC: R_f = 0.48 (DCM:MeOH = 20:1).

LC-MS: Mass (ESI), calculated = 349.4 $[M+H]^+$, found = 349.4.

Lab book number(s): MWa114.

14-Hydroxy-3,6,9,12-tetraoxatetradecyl 4-methylbenzenesulfonate



$C_{17}H_{28}O_8S$, MW = 392.46 g / mol

3,6,9,12-Tetraoxatetradecane-1,14-diol (4.3 g, 18.0 mmol, 1.0 eq.), *p*-toluenesulfonyl chloride (3.4 g, 18.0 mmol, 1.0 eq.), silver oxide (6.3 g, 27.0 mmol, 1.5 eq.) and potassium iodide (0.6 g, 3.6 mmol, 0.2 eq.) were stirred in DCM (20 mL) for 1 h at 0 °C. The solution was allowed to warm to room temperature, filtered through celite, rinsed with DCM and concentrated under reduced pressure. The obtained product was purified by column chromatography (800 g SiO_2, CH:EA = 1:1 → 1:9).

Yield: 3.6 g (51 %, 9.2 mmol).

Appearance: slightly yellow oil.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 2.44 (s, 3H), 2.53 – 2.68 (m, 1H), 3.53 – 3.77 (m, 18H), 4.15 (t, *J* = 4.9 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.79 (d, *J* = 7.8 Hz, 2H).

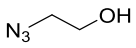
^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 21.8, 61.9, 68.8, 69.4, 70.5, 70.6, 70.7, 70.7, 70.9, 72.6, 128.1, 129.9, 133.2, 144.9.

TLC: R_f = 0.40 (DCM:MeOH = 20:1).

LC-MS: Mass (ESI), calculated = 393.5 $[M+H]^+$, found = 393.4.

Lab book number(s): MWa121.

2-Azidoethan-1-ol



$C_2H_5N_3O$, MW = 87.08 g / mol

2-Chloroethan-1-ol (1.0 g, 12.4 mmol, 1.0 eq.), sodium azide (1.2 g, 15.3 mmol, 1.23 eq.), and sodium hydroxide (0.05 g, 1.2 mmol, 0.1 eq.) were stirred in water (10 mL) for 72 h at room temperature. Additional sodium azide (1.0 eq.) and sodium hydroxide (0.15 eq.) were added and stirred for 22 h. Sodium thiosulfate (1.5 g) and brine (20 mL) were added and the solution was extracted with DCM (4 x 30 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure.

Yield: 0.7 g (65 %, 8.0 mmol).

Appearance: slightly yellow oil.

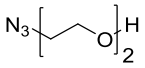
^{1}H-NMR: (300 MHz, Chloroform-*d*): δ = 2.25 (s, 1H), 3.38 – 3.47 (m, 2H), 3.72 – 3.80 (m, 2H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 53.6, 61.6.

TLC: R_f = 0.33 (DCM:MeOH = 50:1).

Lab book number(s): MWa111.

2-(2-Azidoethoxy)ethan-1-ol



$C_4H_9N_3O_2$, MW = 131.14 g / mol

2-(2-chloroethoxy)ethan-1-ol (1.5 g, 12.4 mmol, 1.0 eq.) and sodium azide (4.0 g, 62.0 mmol, 5.0 eq.) were stirred in water (10 mL) for 42 h at room temperature. Temperature has been increased to 60 °C for 72 h. Then sodium thiosulfate (1.5 g) and brine (50 mL) were added and the solution was extracted with DCM (3 x 80 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure.

Yield: 1.6 g (98 %, 12.2 mmol).

Appearance: slightly yellow oil.

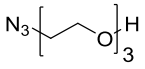
^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 2.59 (d, *J* = 3.7 Hz, 1H), 3.36 (t, *J* = 5.0 Hz, 2H), 3.56 (dd, *J* = 5.3, 3.8 Hz, 2H), 3.64 (t, *J* = 5.0 Hz, 2H), 3.67 – 3.74 (m, 2H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 50.7, 61.7, 70.0, 72.5.

TLC: R_f = 0.53 (CH:EA = 1:2).

Lab book number(s): MWa115.

2-(2-(2-Azidoethoxy)ethoxy)ethan-1-ol



$C_6H_{13}N_3O_3$, MW = 175.19 g / mol

2-(2-(2-Chloroethoxy)ethoxy)ethan-1-ol (2.1 g, 12.4 mmol, 1.0 eq.) and sodium azide (1.2 g, 15.3 mmol, 1.23 eq.) were stirred in water (10 mL) for 65 h at room temperature. Additional sodium azide (1.0 eq.) and sodium hydroxide (0.15 eq.) were added and stirred for 24 h. Temperature has

been increased to 40 °C for 24 h and afterwards to 60 °C for 48 h. Then sodium thiosulfate (1.5 g) and brine (50 mL) were added and the solution was extracted with DCM (3 x 80 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure.

Yield: 2.1 g (97 %, 12.0 mmol).

Appearance: slightly yellow oil.

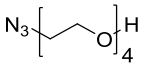
^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 2.48 – 2.67 (m, 1H), 3.29 – 3.42 (m, 2H), 3.51 – 3.75 (m, 10H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 50.7, 61.7, 70.0, 70.4, 70.7, 72.6.

TLC: R_f = 0.53 (CH:EA = 1:2).

Lab book number(s): MWa113.

2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethan-1-ol



$C_8H_{17}N_3O_4$, MW = 219.24 g / mol

2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (3.7 g, 10.8 mmol, 1.0 eq.) and sodium azide (1.4 g, 21.6 mmol, 2.0 eq.) were stirred in DMF (80 mL) for 40 h at room temperature. The solution was diluted with Brine (100 mL) and extracted with DCM (3 x 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by column chromatography (200 g SiO_2, DCM:MeOH = 20:1).

Yield: 2.2 g (94 %, 10.1 mmol).

Appearance: slightly yellow oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 2.74 (s, 1H), 3.33 (t, *J* = 5.1 Hz, 2H), 3.53 – 3.57 (m, 2H), 3.58 – 3.65 (m, 10H), 3.65 – 3.68 (m, 2H).

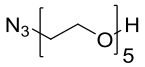
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 50.7, 61.7, 70.0, 70.4, 70.6, 70.7, 70.7, 72.5.

TLC: R_f = 0.30 (DCM:MeOH = 20:1).

LC-MS: Mass (ESI), calculated = 220.2 $[M+H]^+$, found = 220.2.

Lab book number(s): MWa118.

14-Azido-3,6,9,12-tetraoxatetradecan-1-ol



$C_{10}H_{21}N_3O_5$, MW = 263.29 g / mol

14-Hydroxy-3,6,9,12-tetraoxatetradecyl 4-methylbenzenesulfonate (3.6 g, 9.2 mmol, 1.0 eq.) and sodium azide (1.2 g, 18.4 mmol, 2.0 eq.) were stirred in DMF (70 mL) for 70 h at room temperature. The solution was diluted with brine (300 mL) and extracted with DCM (3 x 300 mL). The combined organic phases were dried over MgSO4 and concentrated under reduced pressure. The obtained product was purified by column chromatography (600 g SiO2, DCM:MeOH = 20:1).

Yield: 2.3 g (97 %, 8.9 mmol).

Appearance: slightly yellow oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 2.75 (s, 1H), 3.30 – 3.42 (m, 2H), 3.53 – 3.76 (m, 18H).

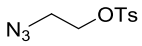
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 50.7, 61.8, 70.1, 70.4, 70.6, 70.7, 70.7, 72.6.

TLC: R_f = 0.24 (DCM:MeOH = 20:1).

LC-MS: Mass (ESI), calculated = 264.2 $[M+H]^+$, found = 264.2.
Mass (ESI), calculated = 281.2 $[M+NH_4]^+$, found = 281.1.

Lab book number(s): MWa124.

2-Azidoethyl 4-methylbenzenesulfonate



$C_9H_{11}N_3O_3S$, MW = 241.27 g / mol

Ethane-1,2-diyl bis(4-methylbenzenesulfonate) (25 g, 68 mmol, 1.0 eq.) and sodium azide (4.4 g, 68 mmol, 1.0 eq.) were dissolved in DMF (300 mL). The mixture was stirred for 18 h at 70 °C. The solvent was removed under reduced pressure. The crude product was dissolved in DCM (200 mL) and filtered through Celite. The solvent was removed under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 2.7 g (17 %, 11 mmol).

Appearance: colorless oil.

^{1}**H-NMR** (500 MHz, Chloroform-*d*): δ = 2.47 (s, 3H), 3.49 (t, *J* = 5.1 Hz, 2H), 4.17 (t, *J* = 5.1 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.77 – 7.87 (m, 2H).

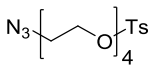
^{13}**C-NMR** (126 MHz, Chloroform-*d*): δ = 21.6, 49.6, 68.1, 127.9, 130.0, 132.6, 145.3.

TLC: R_f = 0.08 (CH:EA = 5:1).

LC-MS: Mass (ESI), calculated = 264.1 $[M+Na]^+$, found = 264.0.
[5-100 % Solvent B, 3.0 min]: R_t = 1.9 min.
> 99 % purity (220 nm).

Lab book number(s): MWa583.

2-(2-(2-(2-Azidoethoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate



$C_{15}H_{23}N_3O_6S$, MW = 373.42 g / mol

2-(2-(2-(2-Azidoethoxy)ethoxy)ethoxy)ethan-1-ol (100 mg, 456 μmol, 1.0 eq.) and 4-toluenesulfonyl chloride (130 mg, 684 μmol, 1.5 eq.) in DCM (0.5 mL) were cooled to 0 °C. Pyridine (74 μL, 912 μmol, 2.0 eq.) was added and the mixture was stirred for 1 h at 0 °C, followed by 70 h at room temperature. The mixture was concentrated under reduced pressure. The obtained crude product was purified by column chromatography (20 g SiO_2, DCM).

Yield: 150 mg (88 %, 402 μmol).

Appearance: yellow oil.

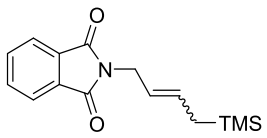
^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 2.42 (s, 3H), 3.35 (t, *J* = 4.9 Hz, 2H), 3.54 – 3.67 (m, 12H), 4.13 (t, *J* = 4.9 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 7.9 Hz, 2H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 21.7, 50.7, 68.7, 69.3, 70.1, 70.6, 70.7, 70.8, 128.0, 129.9, 133.1, 144.9.

TLC: R_f = 0.50 (CH:EA = 9:1).
R_f = 0.60 (CH:DCM = 1:1)

Lab book number(s): MWa128.

2-(4-(Trimethylsilyl)but-2-en-1-yl)isoindoline-1,3-dione



$C_{15}H_{19}NO_2Si$, MW = 273.41 g / mol

2-Allylisoindoline-1,3-dione (30.0 g, 160.0 mmol, 1.0 eq.), allyltrimethylsilane (255 mL, 1600 mmol, 10.0 eq.) and Grubbs I (11.9 g, 14.4 mmol, 0.1 eq.) were dissolved in DCM (1 L) and heated to 60 °C for 4 h under argon. Tris(hydroxymethyl)phosphine (1 M in *i*-PrOH, 160 mL, 135.0 mmol, 1.0 eq.) was added to the solution and the reaction mixture was stirred for 16 h. After cooling to room temperature, the solution was diluted with brine (1 L) and extracted with DCM (3 x 300 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained oil was purified by column chromatography (1000 g SiO_2, CH:EA = 9:1).

Yield: 31.5 g (72 %, 115.2 mmol).

Appearance: white solid.

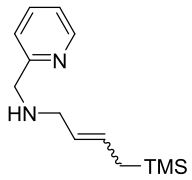
^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.00 (d, *J* = 22.7 Hz, 9H), 1.39 – 1.48 (m, 2H), 4.18 – 4.33 (m, 2H), 5.27 – 5.47 (m, 1H), 5.56 – 5.87 (m, 1H), 7.66 – 7.73 (m, 2H), 7.80 – 7.87 (m, 2H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ = -1.9, 19.1, 22.9, 34.9, 40.0, 120.7, 121.5, 123.3, 130.9, 132.4, 132.5, 133.9, 168.1.

TLC: R_f = 0.43 (CH:EA = 5:1).

Lab book number(s): MWa110.

***N*-(Pyridin-2-ylmethyl)-4-(trimethylsilyl)but-2-en-1-amine**



$C_{13}H_{22}N_2Si$, MW = 234.42 g / mol

2-(4-(Trimethylsilyl)but-2-en-1-yl)isoindoline-1,3-dione (31.5 g, 115.2 mmol, 1.0 eq.) and hydrazine (35 %, 20.6 mL, 230.4 mmol, 2.0 eq.) were dissolved in methanol (600 mL) and stirred for 20 h at 80 °C. 1 N NaOH (200 mL) was added. The solution was diluted with water (800 mL) and extracted with DCM (2 x 400 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The product was used in the next step without further purification.

TLC: R_f = 0.20 (DCM:MeOH = 20:1, 1 % TEA).

Crude 4-(trimethylsilyl)but-2-en-1-amine (16.5 g, 115.2 mmol, 1.0 eq.) and picolinaldehyde (12 mL, 126.7 mmol, 1.1 eq.) were dissolved in ethanol (600 mL) and the solution was stirred for 2 h at room temperature. Additional picolinaldehyde (5 mL, 46.1 mmol, 0.4 eq.) was added and the solution was stirred for 18 h at room temperature. Sodium borohydride (8.7 g, 230.4 mmol, 2.0 eq.) was added portion-wise. The solution was stirred for 72 h at room temperature. The mixture was quenched with water (200 mL) and filtered through Celite. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by column chromatography (1000 g SiO_2, EA, 3 % TEA).

Yield: 22.8 g (84 % o2s, 97.3 mmol).

Appearance: yellow oil.

TLC: R_f = 0.32 (EA, 3 % TEA).

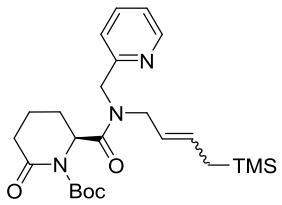
^{1}H-NMR (300 MHz, Chloroform-*d*): δ = -0.07 (d, *J* = 3.2 Hz, 9H), 1.35 – 1.44 (m, 2H), 2.14 (s, 1H), 3.12 – 3.26 (m, 2H), 3.83 (d, *J* = 7.8 Hz, 2H), 5.26 – 5.45 (m, 1H), 5.40 – 5.61 (m, 1H), 7.08 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 7.21 – 7.25 (m, 1H), 7.56 (td, *J* = 7.7, 1.8 Hz, 1H), 8.48 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ = -1.8, 19.0, 22.8, 46.0, 51.8, 54.5, 54.9, 121.9, 122.4, 126.7, 129.5, 136.5, 149.4, 160.0.

LC-MS: Mass (ESI), calculated = 235.2 $[M+H]^+$, found = 235.6
[5-100 % Solvent B, 3.0 min]: R_t = 1.6 min.
98 % purity (220 nm).

Lab book number(s): MWa116 + MWa117 / MWa633 + MWa634.

tert-Butyl (*S*)-2-oxo-6-((pyridin-2-ylmethyl)(4-(trimethylsilyl)but-2-en-1-yl)carbamoyl)piperidine-1-carboxylate



$C_{24}H_{37}N_3O_4Si$, MW = 459.66 g / mol

(*S*)-6-oxopiperidine-2-carboxylic acid (15.3 g, 107.0 mmol, 1.1 eq.) and HATU (40.7 g, 107.0 mmol, 1.1 eq.) were dissolved in DCM (700 mL). DIPEA (34.0 mL, 194.6 mmol, 2.0 eq.) was added and the mixture was stirred for 5 min at room temperature. N-(Pyridin-2-ylmethyl)-4-(trimethylsilyl)but-2-en-1-amine (22.8 g, 97.3 mmol, 1.0 eq.) was added and the mixture was stirred for 3 h at room temperature. Additional (*S*)-6-oxopiperidine-2-carboxylic acid (0.2 eq.), HATU (0.05 eq.) and DIPEA (0.4 eq.) were added and the mixture was stirred for 72 h at room temperature. The solution was extracted with brine (300 mL + 200 mL). The aqueous solution was counter washed with DCM (300 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure.

TLC: R_f = 0.15 (EA, 3 % TEA)
LC-MS: Mass (ESI), calculated = 360.5 $[M+H]^+$, found = 360.7

(*S*)-6-Oxo-*N*-(pyridin-2-ylmethyl)-*N*-(4-(trimethylsilyl)but-2-en-1-yl)piperidine-2-carboxamide (34.9 g, 97.3 mmol, 1.0 eq.), DIPEA (82.7 mL, 486.5 mmol, 5.0 eq.) and di-*tert*-butyl dicarbonate (84.9 g,

389.2 mmol, 4.0 eq.) and were dissolved in DCM (100 mL). 4-Dimethylaminopyridine (11.9 g, 97.3 mmol, 1.0 eq) in DCM (200 mL) was added and the solution was stirred for 20 h at room temperature. DCM (400 mL) was added and the solution was extracted with Water (2 x 100 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by chromatography (1200 g SiO_2, CH:EA = 1:1 → EA).

Yield: 31.6 g (68.5 mmol, 71 %) over 2 steps.

Appearance: yellow solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = -0.14 – 0.02 (m, 9H), 1.37 – 1.50 (m, 11H), 1.60 – 1.75 (m, 1H), 1.77 – 1.95 (m, 2H), 1.98 (dt, *J* = 5.2, 1.9 Hz, 1H), 2.27 – 2.50 (m, 1H), 2.50 – 2.61 (m, 1H), 3.80 – 4.18 (m, 2H), 4.42 – 4.61 (m, 1H), 4.67 – 4.84 (m, 1H), 4.93 – 5.10 (m, 1H), 5.15 – 5.38 (m, 1H), 5.45 – 5.70 (m, 1H), 7.06 – 7.21 (m, 1H), 7.23 – 7.40 (m, 1H), 7.50 – 7.73 (m, 1H), 8.41 – 8.55 (m, 1H).

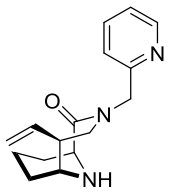
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = -1.8, -1.7, 18.3, 22.9, 23.0, 25.8, 26.0, 34.5, 34.6, 48.6, 50.2, 50.7, 51.7, 55.7, 55.9, 83.1, 121.6, 122.2, 122.2, 122.7, 132.0, 132.2, 136.7, 137.0, 149.1, 149.7, 153.6, 157.5, 171.3, 171.4.

TLC: R_f = 0.127 (CH:EA = 1:1)
0.20 (EA).

LC-MS: Mass (ESI), calculated = 460.3 $[M+H]^+$, found = 460.3.

Lab book number(s): MWa122 + MWa123 / MWa642 + MWa645.

(1*S*,5*S*, 6*R*)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



$C_{16}H_{21}N_3O$, MW = 271.36 g / mol

tert-Butyl (*S*)-2-oxo-6-((pyridin-2-ylmethyl)(4-(trimethylsilyl)but-2-en-1-yl)carbamoyl) piperidine-1-carboxylate (3.1 g, 6.74 mmol, 1.0 eq.) was dissolved in THF (dry, 150 mL) under argon. The mixture was cooled to -78 °C and DIBAL (1 M in DCM, 7.4 mL, 7.42 mmol, 1.1 eq.) was added over 30 min. Sodium sulfate hexahydrate was added to quench the reaction. The mixture was filtered over celite and concentrated under reduced pressure

TLC: R_f = 0.50 (DCM:MeOH = 20:1).

Crude *tert*-butyl (6*S*)-2-hydroxy-6-((pyridin-2-ylmethyl)(4-(trimethylsilyl)but-2-en-1-yl)carbamoyl)piperidine-1-carboxylate (3.1 g, 6.74 mmol, 1.0 eq.) was dissolved in DCM (250 mL) and cooled to -78 °C. Hydrofluoric acid (70 % in pyridine, 19 mL, 674 mmol, 100 eq.) was added. The mixture was allowed to warm to 0 °C and was stirred for 2 h. The reaction was quenched by addition of sodium hydroxide (10 M, 150 mL) and calcium carbonate (150 g in 400 mL water). The mixture was filtered and the filtrate was extracted with DCM (5 x 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 624 mg (35 % o2s, 2.30 mmol).

Appearance: orange solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.42 – 1.50 (m, 1H), 1.54 – 1.70 (m, 4H), 2.26 (dt, *J* = 9.6, 3.3 Hz, 1H), 2.51 – 2.74 (m, 2H), 2.79 (dd, *J* = 7.5, 2.9 Hz, 1H), 3.05 (dd, *J* = 13.8, 1.9 Hz, 1H), 3.80 (d, *J* = 3.9 Hz, 1H), 4.01 (dd, *J* = 13.9, 10.8 Hz, 1H), 4.67 (d, *J* = 14.9 Hz, 1H), 4.80 (s, 1H), 4.83 – 4.92 (m, 2H), 5.54 (ddd, *J* = 16.7, 10.3, 8.3 Hz, 1H), 7.13 (dd, *J* = 7.5, 5.0 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.61 (td, *J* = 7.7, 1.8 Hz, 1H), 8.44 – 8.52 (m, 1H).

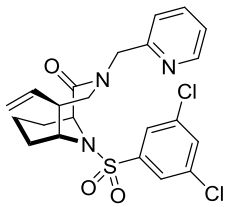
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 16.9, 28.1, 29.4, 49.5, 51.3, 52.6, 55.9, 57.8, 115.1, 122.3, 136.7, 139.1, 149.1, 157.8, 174.9.

TLC: R_f = 0.16 (EA, 5 % MeOH, 3 % TEA).

LC-MS: Mass (ESI), calculated = 272.2 $[M+H]^+$, found = 272.2.
[5-100 % Solvent B, 3.0 min]: R_t = 1.1 min.
74 % purity (220 nm).

Lab book number(s): MWa139 + MWa140 / MWa165 + MWa166 / MWa651 + MWa652.

(1*S*,5*S*, 6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



$C_{22}H_{23}Cl_2N_3O_3S$, MW = 480.40 g / mol

(5*S*)-3-(Pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one (500 mg, 1.84 mmol, 1.0 eq.), 3,5-dichlorobenzenesulfonyl chloride (589 mg, 2.40 mmol, 1.3 eq.) and DIPEA (0.63 mL, 3.69 mmol, 2.0 eq.) were dissolved in acetonitrile (dry, 50 mL) and stirred for 18 h at room temperature under argon. Additional 3,5-dichlorobenzenesulfonyl chloride (0.2 eq.) and DIPEA (0.3 eq.) were added and the mixture was stirred for 24 h. Brine (100 mL) was added and the mixture was extracted with DCM (2 x 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by column chromatography (50 g SiO2, CH:EA = 1:1)

Yield: 400 mg (0.83 mmol, 45 %).

Appearance: white foam.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.14 – 1.41 (m, 2H), 1.46 – 1.67 (m, 3H), 2.31 (dt, *J* = 14.1, 2.4 Hz, 1H), 2.63 – 2.78 (m, 1H), 3.11 (dd, *J* = 14.3, 2.0 Hz, 1H), 3.95 – 4.07 (m, 2H), 4.68 – 4.79 (m, 2H), 4.86 (d, *J* = 15.2 Hz, 1H), 4.93 – 5.08 (m, 2H), 5.70 (ddd, *J* = 16.9, 10.2, 8.7 Hz, 1H), 7.18 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 7.31 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.55 (t, *J* = 1.8 Hz, 1H), 7.66 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.70 (d, *J* = 1.8 Hz, 2H), 8.52 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 15.7, 26.6, 27.7, 49.2, 52.2, 55.1, 56.4, 57.1, 117.0, 122.2, 122.6, 125.0, 132.8, 136.5, 137.0, 137.3, 144.2, 149.3, 157.1, 170.5.

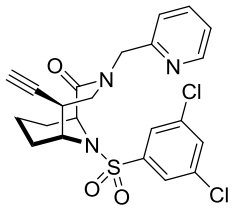
TLC: R_f = 0.26 (CH:EA = 1:1).

LC-MS: Mass (ESI), calculated = 480.1 $[M+H]^+$, found = 480.8.

HPLC: [0-100 % Solvent B, 20 min]: R_t = 13.3 min.
[40-70 % Solvent B, 20 min]: R_t = 6.7 min.
97 % purity (220 nm).

Lab book number(s): MWa145.

(1*S*,5*S*, 6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-5-ethynyl-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



$C_{22}H_{21}Cl_2N_3O_3S$, MW = 478.39 g / mol

(5*S*)-10-((3,5-Dichlorophenyl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1] decan-2- one (400 mg, 830 μmol, 1.0 eq.), 2,6-lutidine (178 mg, 1660 μmol, 2.0 eq.) and NMO (146 mg, 1250 μmol, 1.5 eq.) were dissolved in acetone:water (20 mL, 9:1). Osmium tetroxide (2.5 % in *t*-BuOH, 212 μL, 17 μmol, 0.02 eq.) was added and the mixture was stirred for 4 h at room temperature. Additional osmium tetroxide (2.5 % in *t*-BuOH, 0.02 eq.) was added and the mixture was

stirred for 18 h at room temperature. (Diacetoxyiodo)benzene (535 mg, 1660 mmol, 2.0 eq.) was added and the solution was stirred for 4 h at room temperature. The reaction was quenched by the addition of a sodium thiosulfate solution (sat., aq, 50 mL). The solution was extracted with EA (3 x 30 mL). The organic phase was washed with copper(II) sulfate (sat., aq, 50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by chromatography (50 g SiO_2, EA).

Yield: 169 mg.
TLC: R_f = 0.25 (EA).
LC-MS: Mass (ESI), calculated = 482.1 $[M+H]^+$, found 482.7.

(5*S*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1] decane-5-carbaldehyde (169 mg, 350 μmol, 1.0 eq.), was dissolved in methanol (dry, 15 mL). The mixture was cooled to 0 °C and dimethyl (1-diazo-2-oxopropyl) phosphonate (1.7 mL, 700 μmol, 2.0 eq.) was added. Potassium carbonate (97 mg, 700 μmol, 2.0 eq.) was added and the mixture was stirred for 18 h at room temperature. Water (70 mL) was added and the solution was extracted with DCM (3 x 30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by chromatography (20 g SiO_2, CH:EA = 1:1).

Yield: 138 mg (35 % o2s, 288 μmol).

Appearance: white solid

TLC: R_f = 0.35 (CH:EA = 1:1).

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 1.15 – 1.33 (m, 1H), 1.34 – 1.51 (m, 1H), 1.55 (ddd, *J* = 13.5, 7.9, 4.5 Hz, 2H), 1.69 (d, *J* = 14.0 Hz, 1H), 2.20 – 2.32 (m, 2H), 3.14 – 3.25 (m, 1H), 3.36 (dd, *J* = 14.4, 1.9 Hz, 1H), 4.08 (dd, *J* = 10.8, 3.7 Hz, 1H), 4.37 (td, *J* = 5.1, 2.5 Hz, 1H), 4.64 (d, *J* = 15.4 Hz, 1H), 4.73 (dt, *J* = 6.1, 1.9 Hz, 1H), 4.91 (d, *J* = 15.4 Hz, 1H), 7.18 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 7.25 (dt, *J* = 7.6, 1.1 Hz, 1H), 7.56 (t, *J* = 1.9 Hz, 1H), 7.65 (td, *J* = 7.7, 1.8 Hz, 1H), 7.71 (d, *J* = 1.9 Hz, 2H), 8.52 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H).

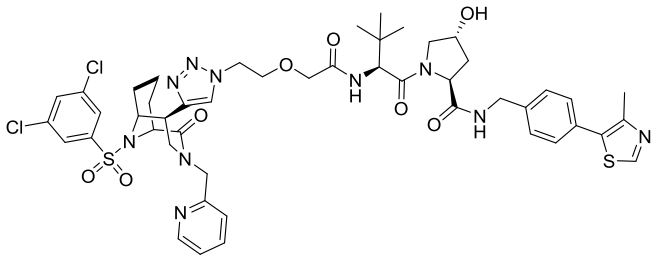
^{13}**C-NMR** (126 MHz, Chloroform-*d*): δ = 15.3, 27.3, 27.7, 36.2, 51.9, 56.1, 56.4, 56.8, 72.2, 82.6, 122.0, 122.6, 125.1, 132.9, 136.5, 137.0, 143.9, 149.5, 156.6, 170.2.

LC-MS: Mass (ESI), calculated = 478.1 $[M+H]^+$, found = 478.8.

HPLC: [0-100 % Solvent B, 20 min]: R_t = 12.9 min.
98 % purity (220 nm).

Lab book number(s): MWa150 + MWa152.

(2*S*,4*R*)-1-((2*S*)-2-(2-(2-(4-((1*S*,5*R*, 6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)-1H-1,2,3-triazol-1-yl)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{48}H_{56}Cl_2N_{10}O_8S_2$, MW = 1036.06 g / mol

The product was synthesized from azide **57a** (8.4 mg, 15.0 μmol, 1.0 eq.) and alkyne **A1** (7.2 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by chromatography (3 g SiO_2, DCM:MeOH = 30:1 → 20:1). The product was dried by lyophilisation.

Yield: 9.0 mg (58 %, 8.7 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.97 (s, 9H), 1.26 -1.38 (m, 3H), 1.59 (m, 1H), 1.78(m, 2H), 2.19 (m, 3H), 2.45 (m, 3H), 3.64 - 3.95 (m, 9H), 4.46 - 4.79 (m, 11H), 7.04 (m, 2H), 7.34 (m, 6H), 7.54 (m, 2H), 7.69 (m, 3H).

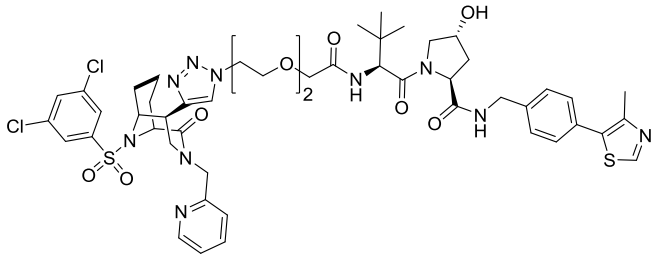
TLC: R_f = 0.08 (DCM:MeOH = 10:1).

HPLC: [0-100 % Solvent B, 20 min]: R_t = 12.1 min.
[20-80 % Solvent B, 20 min]: R_t = 10.2 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{48}H_{56}Cl_2N_{10}O_8S_2$ = 1035.31738; found = 1035.31674.

Lab book number(s): MWa093.

(2*S*,4*R*)-1-((2*S*)-2-(2-(2-(2-(4-((1*S*,5*R*, 6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{50}H_{60}Cl_2N_{10}O_9S_2$, MW = 1080.11 g / mol

The product was synthesized from azide **57b** (9.0 mg, 15.0 μmol, 1.0 eq.) and and alkyne **A1** (7.2 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by chromatography (3 g SiO_2, DCM:MeOH = 30:1 → 20:1). The product was dried by lyophilisation.

Yield: 6.5 mg (40 %, 6.0 μmol).

Appearance: white solid.

^{1}**H-NMR** (500 MHz, Chloroform-*d*): δ = 0.96 (s, 9H), 1.18 – 1.45 (m, 3H), 1.56 (d, *J* = 14.5 Hz, 1H), 1.75 (dd, *J* = 34.8, 14.1 Hz, 2H), 2.15 – 2.34 (m, 2H), 2.46 (ddd, *J* = 13.1, 8.4, 4.7 Hz, 1H), 2.51 (s, 3H), 3.38 (d, *J* = 14.4 Hz, 1H), 3.51 – 3.73 (m, 7H), 3.78 – 3.96 (m, 4H), 4.03 (d, *J* = 11.3 Hz, 1H), 4.35 (dd, *J* = 14.9, 5.6 Hz, 1H), 4.45 (dt, *J* = 8.9, 4.1 Hz, 2H), 4.55 (dd, *J* = 9.3, 6.1 Hz, 4H), 4.69 (t, *J* = 8.0 Hz, 1H), 4.72 – 4.76 (m, 1H), 4.82 – 4.90 (m, 2H), 7.26 (d, *J* = 5.6 Hz, 3H), 7.34 (d, *J* = 1.0 Hz, 4H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 1.3 Hz, 1H), 7.66 – 7.70 (m, 2H), 7.72 (s, 1H), 7.77 (t, *J* = 7.9 Hz, 1H), 8.49 (d, *J* = 5.0 Hz, 1H), 8.67 (s, 1H).

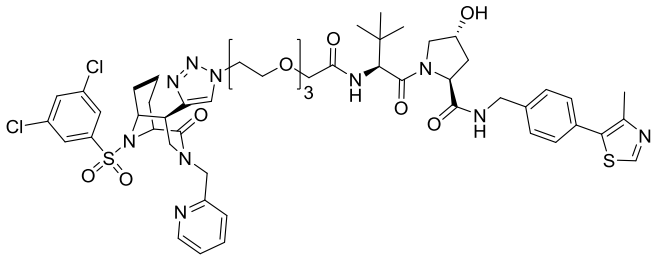
TLC: R_f = 0.08 (DCM:MeOH = 10:1).

HPLC: [0-100 % Solvent B, 20 min]: R_t = 12.3 min.
[30-60 % Solvent B, 20 min]: R_t = 11.0 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{50}H_{60}Cl_2N_{10}O_9S_2$ = 1079.34360; found = 1079.34353.

Lab book number(s): MWa094.

(2*S*,4*R*)-1-((2*S*)-2-(*tert*-butyl)-14-(4-((1*S*,5*R*, 6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)-1H-1,2,3-triazol-1-yl)-4-oxo-6,9,12-trioxa-3-azatetradecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{52}H_{64}Cl_2N_{10}O_{10}S_2$, MW = 1124.16 g / mol

The product was synthesized from azide **57c** (9.7 mg, 15.0 μmol, 1.0 eq.) and alkyne **A1** (7.2 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by chromatography (3 g SiO_2, DCM:MeOH = 30:1 → 20:1). The product was dried by lyophilisation.

Yield: 12.0 mg (71 %, 10.7 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.96 (s, 9H), 1.25 - 1.40 (m, 3H), 1.53 - 1.59 (m, 1H), 1.73 - 1.76 (m, 2H), 2.31 - 2.34 (m, 3H), 2.48 - 2.51 (m, 3H), 3.33 - 3.36 (m, 1H), 3.61 - 3.64 (m, 10H), 3.83 - 3.87 (t, 2H), 3.98 - 4.07 (m, 3H), 4.26 - 4.38 (m, 2H), 4.44 - 4.56 (m, 6H), 4.66 - 4.83 (m, 4H), 7.19 - 7.26 (m, 2H), 7.31 - 7.41 (m, 6H), 7.55 - 7.56 (t, 1H), 7.70 - 7.71 (m, 4H), 8.50 - 8.67 (m, 2H).

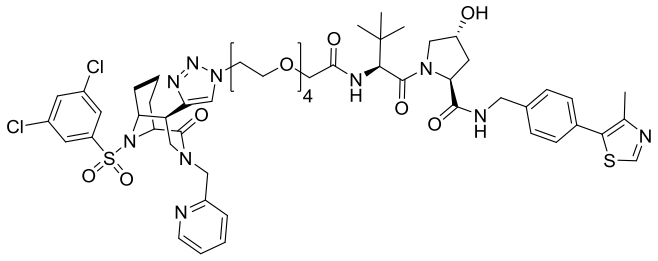
TLC: R_f = 0.08 (DCM:MeOH = 10:1).

HPLC: [0-100 % Solvent B, 20 min]: R_t = 12.4 min.
[30-100 % Solvent B, 20 min]: R_t = 7.8 min.
96 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{52}H_{64}Cl_2N_{10}O_{10}S_2$ = 1123.36981; found = 1123.37016.

Lab book number(s): MWa095.

(2*S*,4*R*)-1-((2*S*)-2-(*tert*-Butyl)-17-(4-((1*S*,5*R*, 6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)-1H-1,2,3-triazol-1-yl)-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{54}H_{68}Cl_2N_{10}O_{11}S_2$, MW = 1168.22 g / mol

The product was synthesized from azide **57d** (10.3 mg, 15.0 μmol, 1.0 eq.) and alkyne **A1** (7.2 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by chromatography (3 g SiO_2, DCM:MeOH = 30:1 → 20:1). The product was dried by lyophilisation.

Yield: 12.0 mg (69 %, 10.3 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 0.89 (s, 9H), 1.19 - 1.33 (m, 3H), 1.52 (m, 1H), 1.72 (m, 2H), 2.07 - 2.11 (m, 3H), 2.44 - 2.48 (m, 3H), 3.31 (m, 1H), 3.54 - 3.57 (m, 14H), 3.82 (s, 2H), 3.93 - 4.02 (m, 3H), 4.27 - 4.33 (m, 2H), 4.46 (m, 6H), 4.74 (m, 4H), 7.19 (m, 2H), 7.28 (m, 6H), 7.49 (m, 1H), 7.65 - 7.72 (m, 4H).

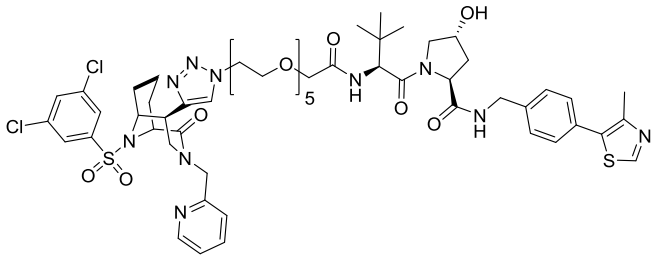
TLC: R_f = 0.08 (DCM:MeOH = 10:1).

HPLC: [0-100 % Solvent B, 20 min]: R_t = 12.4 min.
[30-60 % Solvent B, 20 min]: R_t = 11.3 min.
96 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{54}H_{68}Cl_2N_{10}O_{11}S_2$ = 1189.37797; found = 1189.37857.

Lab book number(s): MWa096.

(2*S*,4*R*)-1-((2*S*)-2-(*tert*-Butyl)-20-(4-((1*S*,5*R*, 6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)-1H-1,2,3-triazol-1-yl)-4-oxo-6,9,12,15,18-pentaoxa-3-azaicosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{56}H_{72}Cl_2N_{10}O_{12}S_2$, MW = 1212.27 g / mol

The product was synthesized from azide **57e** (11.0 mg, 15.0 μmol, 1.0 eq.) and alkyne **A1** (7.2 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by chromatography (3 g SiO_2, DCM:MeOH = 30:1 → 20:1). The product was dried by lyophilisation.

Yield: 10.4 mg (57 %, 8.6 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.89 (s, 9H), 1.18 - 1.33 (m, 3H), 1.53 (m, 1H), 1.68 (m, 2H), 2.04 - 2.07 (m, 2H), 2.30 (m, 1H), 2.43 - 2.47 (m, 2H), 3.29 (m, 1H), 3.53 - 3.59 (m, 18H), 3.81 (m, 2H), 3.88 - 3.97 (m, 2H), 4.00 - 4.02 (d, 1H), 4.23 (m, 1H), 4.28 - 4.31 (m, 1H), 4.37 (m, 1H), 4.46 (m, 5H), 4.66 – 4.73 (m, 4H), 7.20 (m, 2H), 7.29 (m, 6H), 7.50 (m, 1H), 7.65 (m, 4H).

TLC: R_f = 0.08 (DCM:MeOH = 10:1).

HPLC: [0-100 % Solvent B, 20 min]: R_t = 12.3 min.

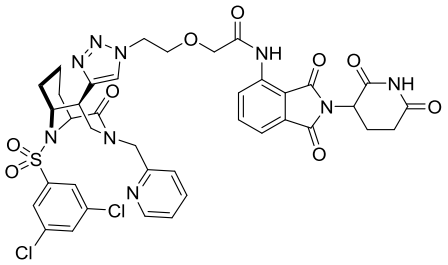
[20-80 % Solvent B, 20 min]: R_t = 11.4min.

> 99 % purity.

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{56}H_{72}Cl_2N_{10}O_{12}S_2$ = 1211.42224; found = 1211.42163.

Lab book number(s): MWa097.

2-(2-(4-((1*S*,5*R*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)-1H-1,2,3-triazol-1-yl)ethoxy)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)acetamide



$C_{39}H_{37}Cl_2N_9O_9S$, MW = 878.74 g / mol

The product was synthesized from azide **55a** (6.0 mg, 15.0 μmol, 1.0 eq.) and alkyne **A1** (7.2 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by chromatography (3 g SiO_2, DCM:MeOH = 30:1 → 20:1). The product was dried by lyophilisation.

Yield: 10.0 mg (76 %, 11.4 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 1.30 (d, *J* = 26.2 Hz, 3H), 1.56 (s, 1H), 1.60 – 1.79 (m, 2H), 2.00 (s, 1H), 2.16 (d, *J* = 7.8 Hz, 1H), 2.35 (s, 1H), 2.61 (s, 2H), 2.82 (dd, *J* = 24.3, 12.1 Hz, 3H), 3.97 (d, *J* = 29.8 Hz, 2H), 4.14 (t, *J* = 7.8 Hz, 2H), 4.19 – 4.39 (m, 1H), 4.77 (s, 3H), 4.97 – 5.42 (m, 2H), 7.46 – 7.86 (m, 8H), 8.84 (dd, *J* = 8.4, 5.0 Hz, 1H), 10.64 (d, *J* = 24.5 Hz, 2H).

TLC: R_f = 0.28 (DCM:MeOH = 20:1).

HPLC: [0-100 % Solvent B, 20 min]: R_t = 12.1 min.

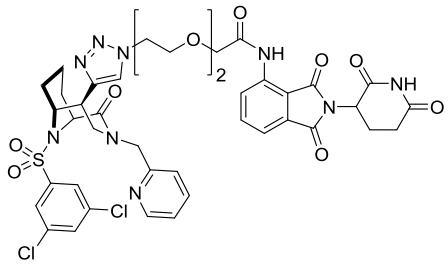
[30-60 % Solvent B, 20 min]: R_t = 9.9 & 10.1 min (diastereromers).

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{39}H_{37}Cl_2N_9O_9S$ = 878.18848; found = 878.18695.

Lab book number(s): MWa098.

2-(2-(2-(4-((1*S*,5*R*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)acetamide



$C_{41}H_{41}Cl_2N_9O_{10}S$, MW = 922.79 g / mol

The product was synthesized from azide **55b** (6.7 mg, 15.0 μmol, 1.0 eq.) and alkyne **A1** (7.2 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by chromatography (3 g SiO_2, DCM:MeOH = 30:1 → 20:1). The product was dried by lyophilisation.

Yield: 12.5 mg (91 %, 13.5 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 1.25 (s, 2H), 1.38 (s, 1H), 1.56 (s, 1H), 1.73 (s, 2H), 2.00 (d, *J* = 0.9 Hz, 1H), 2.15 (s, 1H), 2.34 (s, 1H), 2.61 (d, *J* = 0.9 Hz, 2H), 2.77 (d, *J* = 14.4 Hz, 2H), 2.89 (s, 1H), 3.79 (d, *J* = 5.6 Hz, 4H), 3.98 (t, *J* = 5.4 Hz, 2H), 4.16 (d, *J* = 5.2 Hz, 2H), 4.42 (s, 1H), 4.56 (s, 2H), 4.76 (s, 1H), 4.97 (dd, *J* = 18.8, 12.4 Hz, 2H), 7.52 – 7.82 (m, 8H), 8.85 (t, *J* = 8.5 Hz, 1H), 9.50 (s, 1H), 9.77 (s, 1H), 10.45 (d, *J* = 18.1 Hz, 2H).

TLC: R_f = 0.29 (DCM:MeOH = 20:1).

HPLC: [0-100 % Solvent B, 20 min]: R_t = 12.4 min.

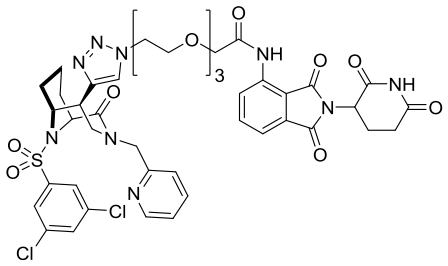
[30-60 % Solvent B, 20 min]: R_t = 10.7 & 10.8 min (diastereomers).

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{41}H_{41}Cl_2N_9O_{10}S$ = 922.21469; found = 922.21361.

Lab book number(s): MWa099.

2-(2-(2-(2-(4-((1*S*,5*R*,6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)acetamide



$C_{43}H_{45}Cl_2N_9O_{11}S$, MW = 966.85 g / mol

The product was synthesized from azide **55c** (7.3 mg, 15.0 μmol, 1.0 eq.) and alkyne **A1** (7.2 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by chromatography (3 g SiO_2, DCM:MeOH = 30:1 → 20:1). The product was dried by lyophilisation.

Yield: 13.0 mg (90 %, 13.4 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 1.16 – 1.44 (m, 3H), 1.53 – 1.63 (m, 1H), 1.77 (d, *J* = 9.2 Hz, 2H), 2.00 (s, 1H), 2.15 (s, 1H), 2.38 (s, 1H), 2.61 (s, 2H), 2.82 (s, 3H), 3.64 (d, *J* = 6.2 Hz, 4H), 3.78 (s, 4H), 3.84 – 3.90 (m, 2H), 4.19 (s, 2H), 4.46 (d, *J* = 23.9 Hz, 3H), 4.85 (dd, *J* = 40.8, 7.4 Hz, 3H), 7.45 – 7.96 (m, 8H), 8.84 (d, *J* = 8.4 Hz, 1H), 9.19 (d, *J* = 16.7 Hz, 1H), 10.44 (d, *J* = 3.3 Hz, 1H).

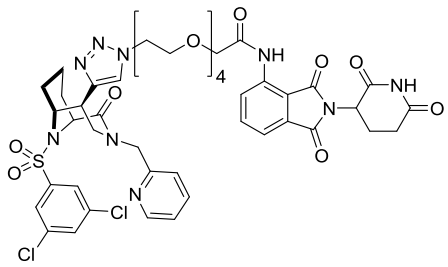
TLC: R_f = 0.25 (DCM:MeOH = 20:1).

HPLC: [0-100 % Solvent B, 20 min]: R_t = 12.6 min.
[30-60 % Solvent B, 20 min]: R_t = 11.1 min.
97 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{43}H_{45}Cl_2N_9O_{11}S$ = 966.24091; found = 966.23813.

Lab book number(s): MWa100.

14-(4-((1*S*,5*R*,6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)-1H-1,2,3-triazol-1-yl)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-3,6,9,12-tetraoxatetradecanamide



$C_{45}H_{49}Cl_2N_9O_{12}S$, MW = 1010.90 g / mol

The product was synthesized from azide **55d** (8.0 mg, 15.0 μmol, 1.0 eq.) and alkyne **A1** (7.2 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by chromatography (3 g SiO_2, DCM:MeOH = 30:1 → 20:1). The product was dried by lyophilisation.

Yield: 9.0 mg (59 %, 8.9 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 1.21 – 1.45 (m, 3H), 1.59 (s, 1H), 1.76 (s, 3H), 2.14 (d, *J* = 8.0 Hz, 1H), 2.28 – 2.45 (m, 1H), 2.61 (s, 2H), 2.80 (dq, *J* = 22.0, 12.2, 11.1 Hz, 3H), 3.62 (d, *J* = 4.4 Hz, 6H), 3.67 (d, *J* = 4.5 Hz, 2H), 3.79 (s, 4H), 3.89 (s, 2H), 4.18 (s, 2H), 4.48 (d, *J* = 27.6 Hz, 3H), 4.88 (d, *J* = 47.5 Hz, 3H), 7.49 – 7.84 (m, 8H), 8.84 (d, *J* = 8.4 Hz, 1H), 9.11 (d, *J* = 17.4 Hz, 1H), 10.49 (s, 1H).

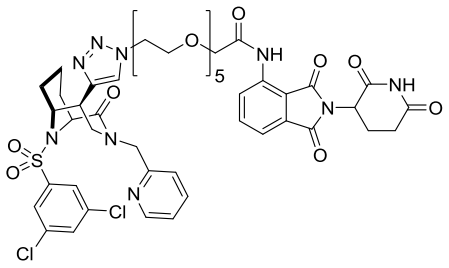
TLC: R_f = 0.22 (DCM:MeOH = 20:1).

HPLC: [0-100 % Solvent B, 20 min]: R_t = 12.6 min.
[20-80 % Solvent B, 20 min]: R_t = 11.5 min.
96 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{45}H_{49}Cl_2N_9O_{12}S$ = 1010.26712; found = 1010.26580.

Lab book number(s): MWa101.

17-(4-((1*S*,5*R*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)-1H-1,2,3-triazol-1-yl)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-3,6,9,12,15-pentaoxaheptadecanamide



$C_{47}H_{53}Cl_2N_9O_{13}S$, MW = 1054.95 g / mol

The product was synthesized from azide **55e** (8.6 mg, 15.0 μmol, 1.0 eq.) and alkyne **A1** (7.2 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by chromatography (3 g SiO_2, DCM:MeOH = 30:1 → 20:1). The product was dried by lyophilisation.

Yield: 15.0 mg (95 %, 14.2 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 1.20 – 1.47 (m, 3H), 1.58 (s, 1H), 1.66 – 1.89 (m, 3H), 2.12 – 2.21 (m, 1H), 2.38 (s, 1H), 2.61 (s, 2H), 2.82 (dt, *J* = 36.1, 11.5 Hz, 3H), 3.61 (t, *J* = 6.8 Hz, 10H), 3.68 (t, *J* = 5.2 Hz, 2H), 3.79 (s, 4H), 3.88 (d, *J* = 4.9 Hz, 2H), 4.18 (d, *J* = 3.6 Hz, 2H), 4.47 (d, *J* = 40.0 Hz, 3H), 4.82 (s, 2H), 4.99 (s, 1H), 7.52 – 7.84 (m, 8H), 8.84 (d, *J* = 8.4 Hz, 1H), 9.15 (s, 1H), 10.48 (s, 1H).

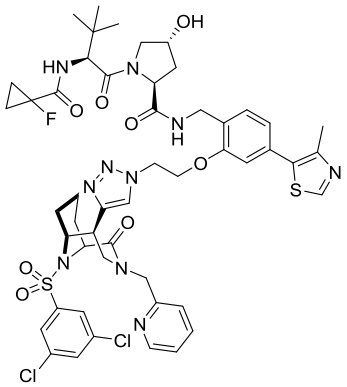
TLC: R_f = 0.21 (DCM:MeOH = 20:1).

HPLC: [0-100 % Solvent B, 20 min]: R_t = 12.8 min.
[20-80 % Solvent B, 20 min]: R_t = 11.7 min.
97 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{47}H_{53}Cl_2N_9O_{13}S$ = 1054.29334; found = 1054.29483.

Lab book number(s): MWa102.

(2*S*,4*R*)-*N*-(2-(2-(4-((1*S*,5*R*,6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)-1H-1,2,3-triazol-1-yl)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{50}H_{57}Cl_2FN_{10}O_8S_2$, MW = 1080.09 g / mol

The product was synthesized from azide **58a** (6.0 mg, 10.0 μmol, 1.0 eq.) and alkyne **A1** (4.8 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.2 mg (94 %, 9.4 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.96 (s, 9H), 1.26 (dd, *J* = 9.9, 7.0 Hz, 5H), 1.46 (d, *J* = 13.1 Hz, 1H), 1.60 (s, 2H), 1.79 (d, *J* = 12.8 Hz, 1H), 2.14 – 2.36 (m, 3H), 2.53 (s, 3H), 3.53 – 3.76 (m, 3H), 3.94 (d, *J* = 11.1 Hz, 1H), 4.26 – 4.52 (m, 6H), 4.56 (d, *J* = 8.6 Hz, 2H), 4.72 (t, *J* = 8.0 Hz,

2H), 4.77 – 4.96 (m, 3H), 5.33 – 5.56 (m, 2H), 6.81 (d, J = 1.7 Hz, 1H), 6.98 (dd, J = 7.6, 1.6 Hz, 1H), 6.99 – 7.10 (m, 1H), 7.40 (dd, J = 12.9, 8.0 Hz, 2H), 7.58 (t, J = 1.8 Hz, 1H), 7.70 (d, J = 1.8 Hz, 3H), 7.87 (d, J = 8.1 Hz, 1H), 7.96 (s, 1H), 8.26 (t, J = 7.0 Hz, 1H), 8.76 (d, J = 4.7 Hz, 1H), 8.95 (s, 1H).

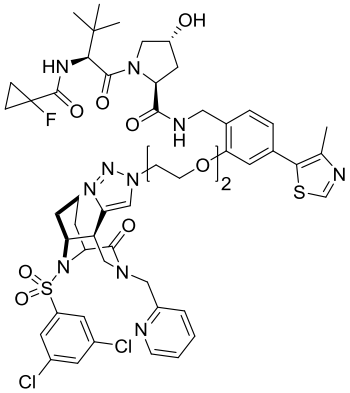
TLC: R_f = 0.11 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 0.7 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{50}H_{57}Cl_2FN_{10}O_8S_2$ = 1079.32361; found = 1079.32534.

Lab book number(s): MWa235.

(2*S*,4*R*)-*N*-(2-(2-(2-(4-((1*S*,5*R*,6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{52}H_{61}Cl_2FN_{10}O_9S_2$, MW = 1124.14 g / mol

The product was synthesized from azide **58b** (6.5 mg, 10.0 μmol, 1.0 eq.) and alkyne **A1** (4.8 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.0 mg (44 %, 4.4 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.92 (s, 9H), 1.05 – 1.29 (m, 6H), 1.55 (s, 2H), 1.70 (d, *J* = 12.9 Hz, 1H), 2.05 – 2.31 (m, 3H), 2.46 (s, 3H), 3.42 (d, *J* = 12.3 Hz, 1H), 3.62 (d, *J* = 8.4 Hz, 2H), 3.76 – 4.01 (m, 6H), 4.11 (dd, *J* = 9.2, 5.6 Hz, 2H), 4.37 – 4.42 (m, 4H), 4.43 – 4.45 (m, 2H), 4.43 – 4.53 (m, 2H), 4.53 – 4.62 (m, 1H), 4.63 (d, *J* = 5.5 Hz, 1H), 4.83 (d, *J* = 16.6 Hz, 1H), 5.30 (d, *J* = 16.3 Hz, 1H), 6.79 (d, *J* = 1.9 Hz, 1H), 6.88 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.91 – 7.01 (m, 1H), 7.24 – 7.35 (m, 2H), 7.49 (t, *J* = 1.8 Hz, 1H), 7.57 (d, *J* = 1.8 Hz, 2H), 7.64 (t, *J* = 6.6 Hz, 1H), 7.72 – 7.86 (m, 2H), 8.21 (t, *J* = 7.8 Hz, 1H), 8.67 (s, 1H), 8.94 (s, 1H).

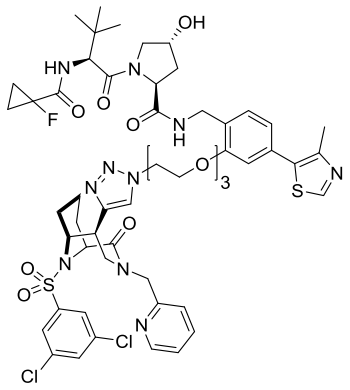
TLC: R_f = 0.11 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 0.9 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{52}H_{61}Cl_2FN_{10}O_9S_2$ = 1123.34983; found = 1123.35172.

Lab book number(s): MWa236.

(2*S*,4*R*)-*N*-(2-(2-(2-(2-(4-((1*S*,5*R*, 6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{54}H_{65}Cl_2FN_{10}O_{10}S_2$, MW = 1168.19 g / mol

The product was synthesized from azide **58c** (6.9 mg, 10.0 μmol, 1.0 eq.) and alkyne **A1** (4.8 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 4.5 mg (39 %, 3.9 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.91 (d, *J* = 5.2 Hz, 9H), 1.07 – 1.31 (m, 6H), 1.56 (s, 2H), 1.71 (d, *J* = 13.1 Hz, 1H), 2.17 (d, *J* = 14.2 Hz, 3H), 2.49 (s, 3H), 3.42 (d, *J* = 14.1 Hz, 1H), 3.54 – 3.70 (m, 6H), 3.76 – 3.96 (m, 5H), 4.04 – 4.22 (m, 3H), 4.42 – 4.44 (m, 4H), 4.57 – 4.69 (m, 3H), 4.87 (d, *J* = 14.9 Hz, 1H), 5.28 (d, *J* = 16.0 Hz, 1H), 6.82 (s, 1H), 6.87 – 6.92 (m, 1H), 7.00 (d, *J* = 5.4 Hz, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.40 – 7.51 (m, 1H), 7.51 (t, *J* = 1.8 Hz, 1H), 7.60 (d, *J* = 1.8 Hz, 2H), 7.66 (dd, *J* = 7.2, 4.1 Hz, 1H), 7.72 – 7.88 (m, 2H), 8.22 (t, *J* = 7.7 Hz, 1H), 8.69 (s, 1H), 9.02 (s, 1H).

TLC: R_f = 0.10 (DCM:MeOH = 10:1).

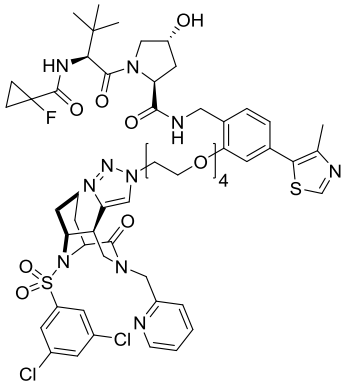
LC-MS: [30-100 % Solvent B, 2.7 min]: R_t = 1.6 min.

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{54}H_{65}Cl_2FN_{10}O_{10}S_2$= 1167.37604; found = 1167.37653.

Lab book number(s): MWa237.

(2*S*,4*R*)-*N*-(2-(2-(2-(2-(2-(4-((1*S*,5*R*,6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{56}H_{69}Cl_2FN_{10}O_{11}S_2$, MW = 1212.25 g / mol

The product was synthesized from azide **58d** (7.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A1** (4.8 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 4.3 mg (35 %, 3.5 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.91 (s, 9H), 1.10 – 1.29 (m, 6H), 1.55 (s, 2H), 1.69 (s, 1H), 2.09 – 2.33 (m, 3H), 2.49 (s, 3H), 3.52 – 3.69 (m, 10H), 3.77 – 3.96 (m, 8H), 4.05 – 4.21 (m, 3H), 4.35 – 4.54 (m, 6H), 4.56 – 4.71 (m, 2H), 4.82 (s, 1H), 5.29 (s, 1H), 6.83 (s, 1H), 6.90 (d, *J* = 7.9 Hz, 1H), 6.99 (s, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 17.9 Hz, 2H), 7.62 (d, *J* = 1.9 Hz, 3H), 7.82 (d, *J* = 6.1 Hz, 1H), 8.20 (d, *J* = 7.4 Hz, 1H), 8.70 (s, 1H), 9.00 (s, 1H).

TLC: R_f = 0.10 (DCM:MeOH = 10:1).

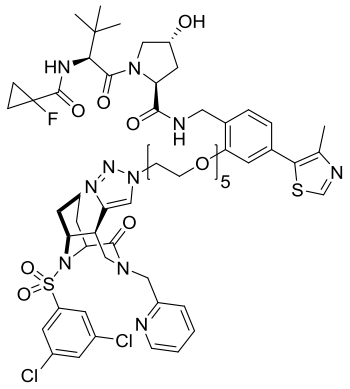
LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 1.1 min.

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{56}H_{69}Cl_2FN_{10}O_{11}S_2$ = 1211.40226; found = 1211.40402.

Lab book number(s): MWa238.

(2*S*,4*R*)-*N*-(2-((14-(4-((1*S*,5*R*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)-1H-1,2,3-triazol-1-yl)-3,6,9,12-tetraoxatetradecyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{58}H_{73}Cl_2FN_{10}O_{12}S_2$, MW = 1256.30 g / mol

The product was synthesized from azide **58e** (7.8 mg, 10.0 μmol, 1.0 eq.) and alkyne **A1** (4.8 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 7.2 mg (57 %, 5.7 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 0.92 (s, 9H), 1.12 – 1.37 (m, 6H), 1.55 (s, 2H), 1.69 (s, 1H), 2.08 – 2.33 (m, 3H), 2.50 (d, *J* = 3.1 Hz, 3H), 3.25 – 3.74 (m, 15H), 3.74 – 4.00 (m, 5H), 4.04 – 4.22 (m, 2H), 4.24 – 4.50 (m, 8H), 4.50 – 4.64 (m, 2H), 4.62 – 4.71 (m, 2H), 5.27 – 5.42 (m, 1H), 6.83 (s,

1H), 6.89 (d, J = 7.4 Hz, 1H), 6.97 – 7.10 (m, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.44 – 7.57 (m, 2H), 7.57 – 7.75 (m, 3H), 7.85 (d, J = 7.2 Hz, 1H), 8.24 (d, J = 7.0 Hz, 1H), 8.69 (s, 1H), 9.09 (s, 1H).

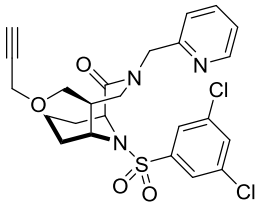
TLC: R_f = 0.10 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 2.7 min]: R_t = 1.6 min.
[50-100 % Solvent B, 2.7 min]: R_t = 1.0 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{58}H_{73}Cl_2FN_{10}O_{12}S_2$= 1255.42847; found = 1255.43025.

Lab book number(s): MWa239.

(1*S*,5*S*, 6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-5-((prop-2-yn-1-yloxy)methyl)-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



$C_{24}H_{25}Cl_2N_3O_3S$, MW = 522.44 g / mol

(1*S*, 5*S*, 6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-5-(hydroxymethyl)-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-2-one (48 mg, 99.1 μmol, 1.0 eq.) was dissolved in DMF (dry, 5 mL) at 0 °C. Sodium hydride (7.1 mg, 297 μmol, 3.0 eq.) was added and the mixture was stirred for 30 min at 0 °C. 3-Bromoprop-1-yne (47 mg, 396 μmol, 4.0 eq.) and tetrabutylammonium iodide (1.8 mg, 5.0 μmol, 0.05 eq.) were added and the mixture was was stirred for 18 h at 0 °C to room temperature. Ammonium chloride (sat., aq, 30 mL) was added and the mixture was extracted with EA (3 x 30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by column chromatography (25 g SiO_2, CH:EA = 1:1).

Yield: 29 mg (56 %, 54.9 μmol).

Appearance: white foam.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.30 (tdd, *J* = 13.3, 6.2, 4.1 Hz, 1H), 1.44 (ddt, *J* = 14.3, 9.5, 4.7 Hz, 71H), 1.50 – 1.66 (m, 3H), 2.33 (d, *J* = 15.0 Hz, 1H), 2.35 – 2.43 (m, 1H), 2.44 (t, *J* = 2.4 Hz, 1H), 3.24 (dd, *J* = 14.3, 1.9 Hz, 1H), 3.40 (d, *J* = 6.5 Hz, 2H), 3.76 (dd, *J* = 14.3, 10.7 Hz, 1H), 3.94 – 4.00 (m, 1H), 4.09 (d, *J* = 2.4 Hz, 2H), 4.79 (d, *J* = 8.5 Hz, 2H), 4.83 (d, *J* = 15.3 Hz, 1H), 7.20 (dd, *J* = 7.1, 5.2 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.56 (t, *J* = 1.8 Hz, 1H), 7.68 (td, *J* = 7.7, 1.7 Hz, 1H), 7.71 (d, *J* = 1.9 Hz, 2H), 8.53 (d, *J* = 4.9 Hz, 1H).

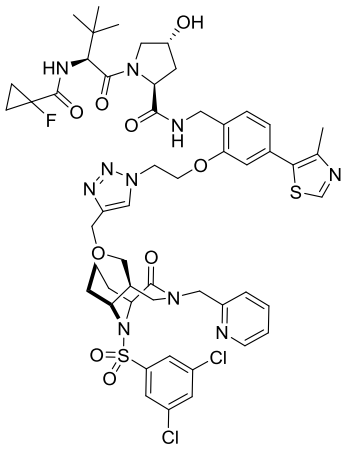
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 15.7, 28.2, 28.3, 44.5, 49.7, 52.9, 56.3, 57.2, 58.5, 70.5, 75.2, 79.3, 122.2, 122.6, 125.2, 132.8, 136.4, 137.3, 144.2, 149.2, 157.0, 170.5.

TLC: R_f = 0.53 (EA).

LC-MS: Mass (ESI), calculated = 522.1 $[M+H]^+$, found = 522.6.

Lab book number(s): MWa160.

(2*S*,4*R*)-*N*-(2-(2-(4-((((1*S*,5*S*, 6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)methoxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{52}H_{61}Cl_2FN_{10}O_9S_2$, MW = 1124.14 g / mol

The product was synthesized from azide **58a** (4.8 mg, 8.0 μmol, 1.0 eq.) and alkyne **A2** (4.2 mg, 8.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.0 mg (56 %, 4.4 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.83 (s, 1H), 0.98 (s, 9H), 1.20 – 1.37 (m, 6H), 1.46 – 1.65 (m, 4H), 2.25 (d, J = 10.8 Hz, 3H), 2.37 (s, 1H), 2.52 (s, 3H), 3.44 (s, 3H), 3.69 (s, 1H), 3.96 (s, 3H), 4.43 (d, J = 5.9 Hz, 3H), 4.52 (d, J = 10.4 Hz, 2H), 4.58 (d, J = 7.7 Hz, 2H), 4.66 – 4.80 (m, 3H), 4.86 (d, J = 19.2 Hz, 2H), 5.43 (d, J = 16.3 Hz, 1H), 6.81 (s, 1H), 6.97 (dd, J = 7.6, 1.3 Hz, 1H), 7.01 – 7.07 (m, 1H), 7.35 (d, J = 7.9 Hz, 2H), 7.57 (t, J = 1.8 Hz, 1H), 7.67 (d, J = 1.8 Hz, 3H), 7.79 (d, J = 7.3 Hz, 1H), 8.03 (s, 1H), 8.23 (t, J = 7.7 Hz, 1H), 8.68 (s, 1H), 8.89 (s, 1H).

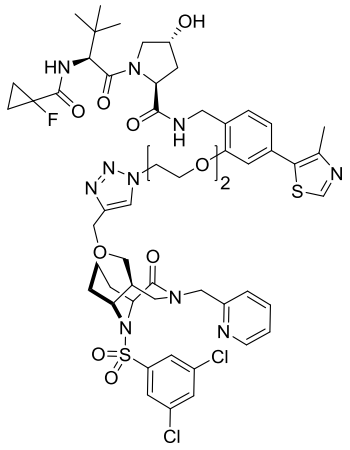
TLC: R_f = 0.08 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 2.7 min]: R_t = 1.5 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{52}H_{61}Cl_2FN_{10}O_9S_2$ = 1123.34983; found = 1123.35134.

Lab book number(s): MWa242.

(2*S*,4*R*)-*N*-(2-(2-(2-(4-((((1*S*,5*S*, 6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)methoxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{54}H_{65}Cl_2FN_{10}O_{10}S_2$, MW = 1168.19 g / mol

The product was synthesized from azide **58b** (5.2 mg, 8.0 μmol, 1.0 eq.) and alkyne **A2** (4.2 mg, 8.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.0 mg (54 %, 4.3 μmol).

Appearance: white solid.

^{1}**H-NMR** (500 MHz, Chloroform-*d*): δ = 0.71 – 0.83 (m, 1H), 0.90 (s, 9H), 1.13 – 1.29 (m, 6H), 1.31 – 1.38 (m, 1H), 1.48 (d, *J* = 15.1 Hz, 3H), 2.10 (s, 1H), 2.17 (d, *J* = 13.9 Hz, 1H), 2.27 (d, *J* = 35.0 Hz, 2H), 2.47 (s, 3H), 3.31 (d, *J* = 18.4 Hz, 3H), 3.75 – 3.88 (m, 5H), 3.88 – 4.03 (m, 3H), 4.03 – 4.15 (m, 2H), 4.38 (t, *J* = 5.9 Hz, 2H), 4.42 – 4.51 (m, 3H), 4.54 (dd, *J* = 10.3, 5.9 Hz, 3H), 4.62 (d, *J* = 5.5 Hz, 1H), 4.76 (d, *J* = 15.0 Hz, 1H), 5.25 (d, *J* = 15.8 Hz, 1H), 6.78 (s, 1H), 6.90 (d, *J* = 7.1

Hz, 1H), 6.98 (d, *J* = 4.3 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.50 (t, *J* = 1.8 Hz, 1H), 7.60 (d, *J* = 1.9 Hz, 3H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.75 (s, 1H), 8.13 (t, *J* = 7.5 Hz, 1H), 8.61 (s, 1H), 8.83 (s, 1H).

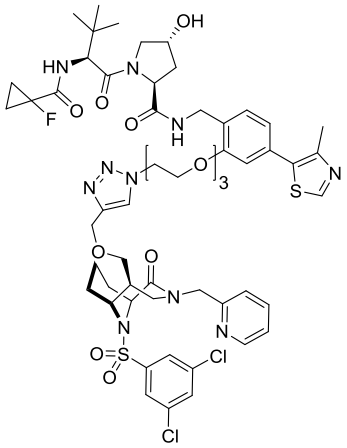
TLC: R_f = 0.08 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 2.7 min]: R_t = 1.5 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{54}H_{65}Cl_2FN_{10}O_{10}S_2$ = 1167.37604; found = 1167.37735.

Lab book number(s): MWa243.

(2*S*,4*R*)-*N*-(2-(2-(2-(2-(4-((((1*S*,5*S*, 6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)methoxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{56}H_{69}Cl_2FN_{10}O_{11}S_2$, MW = 1212.25 g / mol

The product was synthesized from azide **58c** (5.5 mg, 8.0 μmol, 1.0 eq.) and alkyne **A2** (4.2 mg, 8.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.3 mg (55 %, 4.4 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.84 (s, 1H), 0.98 (s, 9H), 1.16 – 1.62 (m, 10H), 2.13 – 2.33 (m, 4H), 2.55 (s, 3H), 3.36 (d, *J* = 13.6 Hz, 3H), 3.60 – 3.77 (m, 5H), 3.79 – 4.04 (m, 7H), 4.15 – 4.26 (m, 2H), 4.43 – 4.61 (m, 7H), 4.70 (s, 2H), 4.89 (d, *J* = 16.0 Hz, 1H), 5.22 (d, *J* = 15.5 Hz, 1H), 6.93 (d, *J* = 7.3 Hz, 1H), 6.95 – 7.09 (m, 2H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.50 (s, 1H), 7.54 – 7.68 (m, 2H), 7.69 (d, *J* = 1.8 Hz, 2H), 7.73 (d, *J* = 9.3 Hz, 1H), 7.81 (s, 1H), 8.14 (t, *J* = 7.7 Hz, 1H), 8.63 (s, 1H), 8.86 (s, 1H).

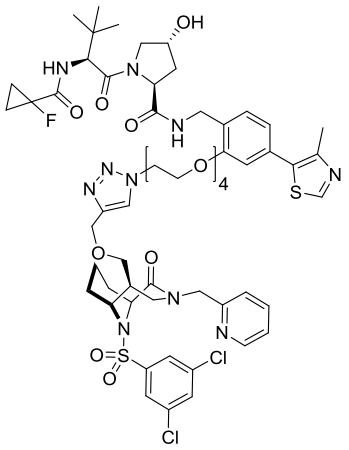
TLC: R_f = 0.07 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 2.7 min]: R_t = 1.6 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{56}H_{69}Cl_2FN_{10}O_{11}S_2$= 1211.40226; found = 1211.40424.

Lab book number(s): MWa244.

(2*S*,4*R*)-*N*-(2-(2-(2-(2-(2-(4-((((1*S*,5*S*, 6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)methoxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{58}H_{73}Cl_2FN_{10}O_{12}S_2$, MW = 1256.30 g / mol

The product was synthesized from azide **58d** (5.9 mg, 8.0 μmol, 1.0 eq.) and alkyne **A2** (4.2 mg, 8.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 1.8 mg (18 %, 1.4 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.71 – 0.85 (m, 1H), 0.90 (s, 9H), 1.09 – 1.30 (m, 6H), 1.35 (s, 1H), 1.47 (s, 3H), 2.10 (s, 1H), 2.19 (d, *J* = 15.6 Hz, 1H), 2.28 (s, 2H), 2.46 (s, 3H), 3.20 – 3.39 (m, 3H), 3.53 (s, 4H), 3.61 (d, *J* = 24.6 Hz, 5H), 3.72 – 3.95 (m, 7H), 4.14 (s, 2H), 4.35 – 4.51 (m, 7H), 4.58 – 4.67 (m, 2H), 4.75 (d, *J* = 18.5 Hz, 1H), 5.18 (d, *J* = 16.7 Hz, 1H), 6.84 (s, 1H), 6.90 (d, *J* = 7.9 Hz, 1H), 6.91 – 7.01 (m, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.36 (s, 1H), 7.50 (t, *J* = 1.7 Hz, 2H), 7.61 (d, *J* = 1.8 Hz, 2H), 8.04 (s, 1H), 8.59 (s, 1H), 8.75 (s, 1H).

TLC: R_f = 0.07 (DCM:MeOH = 10:1).

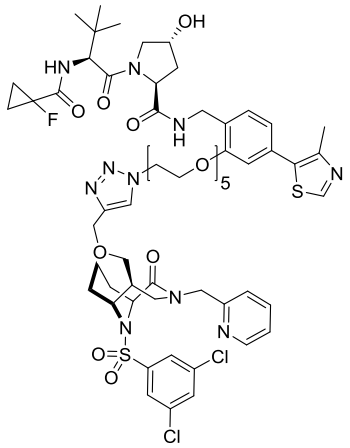
LC-MS: [30-100 % Solvent B, 2.7 min]: R_t = 1.6 min.

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{58}H_{73}Cl_2FN_{10}O_{12}S_2$= 1255.42847; found = 1255.43060.

Lab book number(s): MWa245.

(2*S*,4*R*)-*N*-(2-((14-(4-((((1*S*,5*S*, 6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)methoxy)methyl)-1H-1,2,3-triazol-1-yl)-3,6,9,12-tetraoxatetradecyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{60}H_{77}Cl_2FN_{10}O_{13}S_2$, MW = 1300.35 g / mol

The product was synthesized from azide **58e** (6.2 mg, 8.0 μmol, 1.0 eq.) and alkyne **A2** (4.2 mg, 8.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.2 mg (50 %, 4.0 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 0.70 – 0.87 (m, 1H), 0.90 (s, 9H), 1.21 (dd, *J* = 22.1, 8.0 Hz, 6H), 1.35 (s, 1H), 1.47 (s, 3H), 2.10 (s, 1H), 2.13 – 2.34 (m, 3H), 2.47 (s, 3H), 3.23 – 3.42 (m, 3H), 3.52 (d, *J* = 6.9 Hz, 8H), 3.57 – 3.73 (m, 5H), 3.76 – 3.96 (m, 7H), 4.13 (s, 2H), 4.36 – 4.53 (m, 7H), 4.55 – 4.68 (m, 2H), 4.75 (d, *J* = 16.7 Hz, 1H), 5.23 (d, *J* = 14.4 Hz, 1H), 6.83 (s, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 6.97 (s, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.36 (s, 1H), 7.48 – 7.57 (m, 2H), 7.61 (d, *J* = 1.9 Hz, 2H), 7.65 – 7.77 (m, 2H), 8.08 (s, 1H), 8.61 (s, 1H), 8.78 (s, 1H).

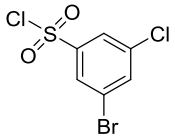
TLC: R_f = 0.07 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 2.7 min]: R_t = 1.6 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{58}H_{73}Cl_2FN_{10}O_{12}S_2$= 1255.42847; found = 1255.43060.

Lab book number(s): MWa246.

3-Bromo-5-chlorobenzenesulfonyl chloride



$C_6H_3BrCl_2O_2S$, MW = 289.95 g / mol

3-Bromo-5-chloroaniline (1.79 g, 8.67 mmol, 1.0 eq.) was dissolved in acetonitrinle (150 mL) and cooled to 0 °C. Hydrocloric acid (37 %, aq, 3 mL), followed by sodium nitrite (0.72 g, 10.4 mmol, 1.2 eq.) and water (5 mL) were added and the mixture was stirred for 15 min at 0 °C. Thionyl chloride (56.5 mL, 780 mmol, 90 eq.) in water was added and the mixture was stirred for 20 min at 0 °C. Copper(II) chloride dihydrate (0.74 g, 4.33 mmol, 0.5 eq.) in water (5 mL) was added and the mixture was stirred for 3 h at 0 °C. The aqueous solution was extracted with wit EA (3 x 300 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by column chromatography (100 g SiO_2, CH:EA = 9:1).

Yield: 1.57 g (63 %, 5.41 mmol).

Appearance: brown oil.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 7.87 (t, *J* = 1.8 Hz, 1H), 7.96 (t, *J* = 1.8 Hz, 1H), 8.06 (t, *J* = 1.7 Hz, 1H).

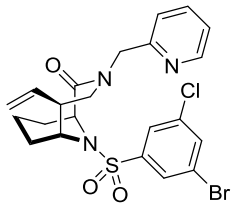
^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 124.1, 125.9, 128.2, 136.9, 138.1, 146.3.

TLC: R_f = 0.25 (CH).

HPLC: [0-100 % Solvent B, 20 min]: R_t = 16.7 min.
82 % purity (220 nm).

Lab book number(s): MWa155.

(1*S*, 5*S*, 6*R*)-10-((3-Bromo-5-chlorophenyl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



$C_{22}H_{23}ClBrN_3O_3S$, MW = 524.86 g / mol

(1*S*, 5*S*, 6*R*)-3-(Pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one (750 mg, 2.76 mmol, 1.0 eq.), 3-bromo-5-chlorobenzenesulfonyl chloride (1041 mg, 3.59 mmol, 1.3 eq.) and DIPEA (0.94 mL, 5.53 mmol, 2.0 eq.) were dissolved in acetonitrile (dry, 75 mL) and stirred for 18 h at room temperature under argon. Brine (100 mL) was added and the mixture was extracted with DCM (2 x 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by column chromatography (100 g SiO_2, CH:EA = 1:1)

Yield: 710 mg (1.35 mmol, 49 %).

Appearance: white foam.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 1.14 – 1.38 (m, 4H), 1.44 – 1.69 (m, 3H), 2.23 – 2.35 (m, 1H), 2.69 (dd, *J* = 9.0, 2.2 Hz, 1H), 3.09 (dd, *J* = 14.2, 2.0 Hz, 1H), 3.94 – 4.04 (m, 2H), 4.66 – 4.76 (m, 2H), 4.85 (d, *J* = 15.1 Hz, 1H), 4.92 – 5.05 (m, 2H), 5.69 (ddd, *J* = 17.0, 10.2, 8.7 Hz, 1H), 7.17 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 7.27 – 7.31 (m, 1H), 7.65 (td, *J* = 7.7, 1.8 Hz, 1H), 7.69 (t, *J* = 1.8 Hz, 1H), 7.73 (t, *J* = 1.7 Hz, 1H), 7.83 (t, *J* = 1.6 Hz, 1H), 8.50 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H).

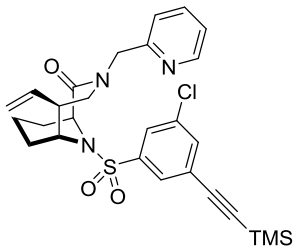
TLC: R_f = 0.57 (EA).

LC-MS: Mass (ESI), calculated = 526.0 $[M+H]^+$, found = 526.5.

HPLC: [0-100 % Solvent B, 20 min]: R_t = 13.6 min.
> 99 % purity (220 nm).

Lab book number(s): MWa157.

(1*S*, 5*S*, 6*R*)-10-((3-Chloro-5-((trimethylsilyl)ethynyl)phenyl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



$C_{27}H_{32}ClN_3O_3SSi$, MW = 542.17 g / mol

(1*S*, 5*S*, 6*R*)-10-((3-Bromo-5-chlorophenyl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo [4.3.1]decan-2-one (710 mg, 1.35 mmol, 1.0 eq.), copper(I) iodide (129 mg, 0.68 mmol, 0.5 eq.) and palladium-tetrakis(triphenylphosphine) (786 mg, 0.68 mmol, 0.5 eq.) were dissolved in TMEDA (350 mL) under argon. Ethynyltrimethylsilane (1.88 mL, 13.5 mmol, 10.0 eq.) was added and the mixture was stirred for 3 h at 90 °C. Brine (2 L) was added and the mixture was extracted with DCM (4 x 1 L). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by column chromatography (150 g SiO_2, CH:EA = 2:1 → 1:1)

Yield: 510 mg (0.94 mmol, 70 %).

Appearance: white foam.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 0.25 (d, *J* = 2.0 Hz, 9H), 1.16 – 1.35 (m, 5H), 2.24 – 2.33 (m, 1H), 2.63 – 2.73 (m, 1H), 3.09 (dd, *J* = 14.2, 2.1 Hz, 1H), 3.97 – 4.04 (m, 2H), 4.70 – 4.77 (m, 2H), 4.84 (dd, *J* = 15.3, 1.7 Hz, 1H), 4.93 – 4.99 (m, 1H), 5.02 (dt, *J* = 9.9, 1.6 Hz, 1H), 5.63 – 5.76 (m, 1H), 7.17 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 7.30 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.56 – 7.61 (m, 1H),

7.66 (td, *J* = 7.7, 1.8 Hz, 1H), 7.67 – 7.73 (m, 1H), 7.73 – 7.78 (m, 1H), 8.51 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ = -0.2, 15.7, 26.5, 27.6, 49.2, 52.2, 54.9, 56.3, 57.0, 99.2, 101.4, 116.9, 122.1, 122.5, 126.2, 126.5, 128.0, 135.5, 135.6, 137.0, 137.4, 143.2, 149.3, 157.1, 170.6.

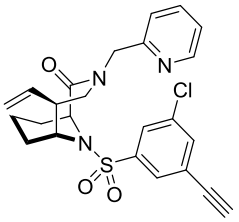
TLC: R_f = 0.50 (CH:EA = 1:2).

LC-MS: Mass (ESI), calculated = 542.2 $[M+H]^+$, found = 542.9.

HPLC: [60-90 % Solvent B, 20 min]: R_t = 5.9 min.
94 % purity (220 nm).

Lab book number(s): MWa158.

(*1S, 5S, 6R*)-10-((3-chloro-5-ethynylphenyl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



$C_{24}H_{24}ClN_3O_3S$, MW = 469.98 g / mol

(*1S, 5S, 6R*)-10-((3-Chloro-5-((trimethylsilyl)ethynyl)phenyl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one (510 mg, 0.94 mmol, 1.0 eq.) and potassium carbonate (130 mg, 0.94 mmol, 1.0 eq) were dissolved in methanol (dry, 100 mL) and the mixture was stirred for 3 h at room temperature. The mixture was concentrated under reduced pressure and the obtained product was purified by column chromatography (40 g SiO_2, CH:EA = 1:1).

Yield: 170 mg (38 %, 0.36 mmol).

Appearance: white solid.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.18 – 1.32 (m, 2H), 1.47 – 1.54 (m, 2H), 1.59 (tt, *J* = 11.3, 3.0 Hz, 1H), 2.25 – 2.34 (m, 1H), 2.70 (td, *J* = 9.0, 6.8 Hz, 1H), 3.11 (dd, *J* = 14.2, 2.0 Hz, 1H), 3.25 (s, 1H), 3.97 – 4.06 (m, 2H), 4.71 – 4.79 (m, 2H), 4.86 (d, *J* = 15.2 Hz, 1H), 4.98 (dt, *J* = 17.0, 1.1 Hz, 1H), 5.04 (dd, *J* = 10.1, 1.3 Hz, 1H), 5.71 (ddd, *J* = 17.0, 10.1, 8.8 Hz, 1H), 7.16 – 7.22 (m, 1H), 7.31 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.64 (t, *J* = 1.7 Hz, 1H), 7.68 (td, *J* = 7.7, 1.8 Hz, 1H), 7.78 (t, *J* = 1.8 Hz, 1H), 7.81 (t, *J* = 1.5 Hz, 1H), 8.52 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 15.7, 26.5, 27.7, 49.2, 52.2, 55.0, 56.4, 57.0, 80.5, 81.2, 116.9, 122.2, 122.6, 125.5, 126.8, 128.2, 135.7, 135.9, 137.0, 137.4, 143.4, 149.4, 157.1, 170.6.

TLC: R_f = 0.26 (CH:EA = 1:1).

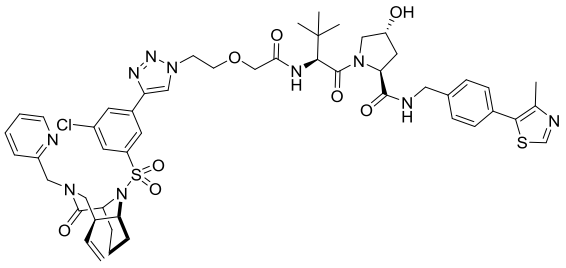
LC-MS: Mass (ESI), calculated = 470.1 [M+H]$^{1+}$, found = 470.8.

HPLC: [0-100 % Solvent B, 20 min]: R_t = 13.0 min.
[20-70 % Solvent B, 20 min]: R_t = 12.8 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{24}H_{24}ClN_3O_3S$ = 470.12997; found = 470.13016.

Lab book number(s): MWa164.

(2*S*,4*R*)-1-((2*S*)-2-(2-(2-(4-(3-Chloro-5-(((*1S*, *5S*, *6R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{50}H_{59}ClN_{10}O_8S_2$, MW = 1027.65 g / mol

The product was synthesized from azide **57a** (8.4 mg, 15.0 μmol, 1.0 eq.) and alkyne **A3** (7.0 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 14.9 mg (97 %, 14.5 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.92 (s, 10H), 1.18 – 1.67 (m, 6H), 2.18 (d, J = 11.6 Hz, 2H), 2.37 – 2.52 (m, 1H), 2.55 (s, 3H), 2.79 (d, J = 8.2 Hz, 1H), 3.14 (d, J = 13.5 Hz, 1H), 3.66 (d, J = 8.7 Hz, 1H), 4.07 (d, J = 18.6 Hz, 7H), 4.36 (dd, J = 15.2, 5.1 Hz, 2H), 4.47 – 4.83 (m, 8H), 5.07 – 5.20 (m, 2H), 5.59 (d, J = 16.7 Hz, 1H), 5.74 (dt, J = 17.9, 9.2 Hz, 1H), 7.09 (d, J = 8.6 Hz, 1H), 7.33 (d, J = 18.4 Hz, 6H), 7.65 – 7.83 (m, 3H), 8.04 – 8.17 (m, 3H), 8.23 (t, J = 7.7 Hz, 1H), 8.79 (d, J = 4.9 Hz, 1H), 9.12 (s, 1H).

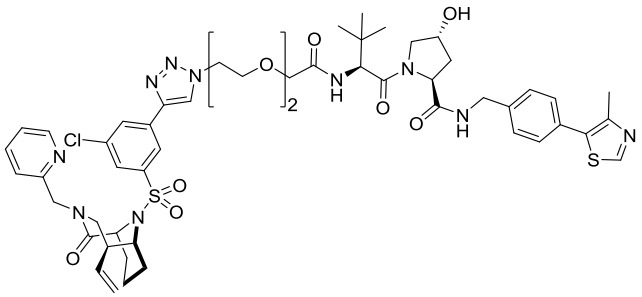
TLC: R_f = 0.11 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 0.7 min
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+2H]^{2+}$ calculated for $C_{50}H_{59}ClN_{10}O_8S_2$= 514.18964; found = 514.19004.

Lab book number(s): MWa201.

(2*S*,4*R*)-1-((2*S*)-2-(2-(2-(2-(4-(3-chloro-5-(((*1S*, *5S*, *6R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{52}H_{63}ClN_{10}O_9S_2$, MW = 1071.71 g / mol

The product was synthesized from azide **57b** (9.0 mg, 15.0 μmol, 1.0 eq.) and alkyne **A3** (7.0 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 15.8 mg (98 %, 14.7 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.99 (s, 7H), 1.23 – 1.37 (m, 1H), 1.35 – 1.47 (m, 1H), 1.52 – 1.62 (m, 3H), 2.18 (t, *J* = 11.3 Hz, 2H), 2.41 (dq, *J* = 13.1, 4.4 Hz, 1H), 2.55 (s, 3H), 2.77 (d, *J* = 8.7 Hz, 1H), 3.14 (d, *J* = 13.1 Hz, 1H), 3.66 (ddt, *J* = 16.6, 11.7, 5.8 Hz, 3H), 3.85 – 3.93 (m, 0H), 3.93 – 4.16 (m, 3H), 4.33 (dd, *J* = 15.2, 5.6 Hz, 1H), 4.48 – 4.76 (m, 6H), 5.08 – 5.18 (m, 2H), 5.59 (d, *J* = 16.4 Hz, 1H), 5.74 (ddd, *J* = 17.3, 10.0, 8.7 Hz, 1H), 7.16 – 7.22 (m, 1H), 7.26 – 7.32 (m, 2H), 7.29 – 7.36 (m, 2H), 7.41 (d, *J* = 8.8 Hz, 1H), 7.68 (t, *J* = 1.8 Hz, 1H), 7.70 – 7.75 (m, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 8.09 (t, *J* = 1.6 Hz, 1H), 8.14 (t, *J* = 1.7 Hz, 1H), 8.27 – 8.33 (m, 2H), 8.78 (d, *J* = 5.2 Hz, 1H), 9.09 (s, 1H).

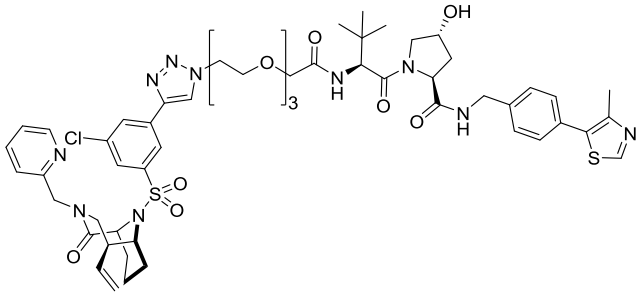
TLC: R_f = 0.11 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 0.7 min
94 % purity (220 nm).

HRMS (ESI) m/z: $[M+2H]^{2+}$ calculated for $C_{52}H_{63}ClN_{10}O_9S_2$ = 536.20275; found = 536.20290.

Lab book number(s): MWa197.

(2*S*,4*R*)-1-((2*S*)-2-(*tert*-Butyl)-14-(4-(3-chloro-5-(((*1S*, *5S*, *6R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)-4-oxo-6,9,12-trioxa-3-azatetradecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{54}H_{67}ClN_{10}O_{10}S_2$, MW = 1115.76 g / mol

The product was synthesized from azide **57c** (9.7 mg, 15.0 μmol, 1.0 eq.) and alkyne **A3** (7.0 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 12.5 mg (75 %, 11.2 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.96 (s, 8H), 1.27 (d, *J* = 7.8 Hz, 1H), 1.36 – 1.52 (m, 1H), 1.59 (d, *J* = 14.3 Hz, 2H), 2.18 (d, *J* = 9.8 Hz, 2H), 2.37 – 2.53 (m, 1H), 2.54 (s, 3H), 2.78 (dd, *J* = 17.8, 9.6 Hz, 1H), 3.13 (d, *J* = 14.1 Hz, 1H), 3.64 (s, 8H), 3.87 – 4.19 (m, 7H), 4.36 (dd, *J* = 15.4, 5.2 Hz, 1H), 4.48 – 4.79 (m, 7H), 5.07 – 5.17 (m, 2H), 5.55 (d, *J* = 16.5 Hz, 1H), 5.75 (dt, *J* = 18.0, 9.2 Hz, 1H), 7.24 (s, 1H), 7.34 (d, *J* = 9.0 Hz, 5H), 7.58 – 7.69 (m, 1H), 7.74 (d, *J* = 11.2 Hz, 2H), 8.04 – 8.12 (m, 1H), 8.14 (s, 1H), 8.21 (d, *J* = 12.8 Hz, 2H), 8.77 (d, *J* = 4.6 Hz, 1H), 8.96 (s, 1H).

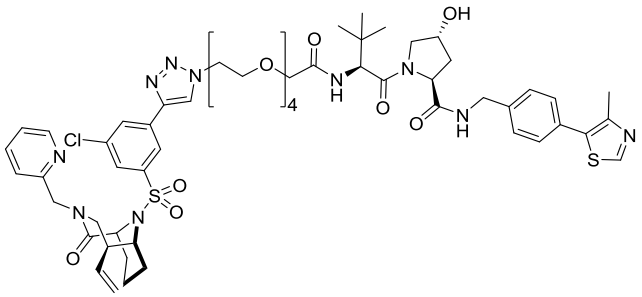
TLC: R_f = 0.10 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 0.7 min
93 % purity (220 nm).

HRMS (ESI) m/z: $[M+2H]^{2+}$ calculated for $C_{54}H_{67}ClN_{10}O_{10}S_2$ = 558.21586; found = 558.21627.

Lab book number(s): MWa198.

(2*S*,4*R*)-1-((2*S*)-2-(*tert*-Butyl)-17-(4-(3-chloro-5-(((*1S*, *5S*, *6R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{56}H_{71}ClN_{10}O_{11}S_2$, MW = 1159.81 g / mol

The product was synthesized from azide **57d** (10.3 mg, 15.0 μmol, 1.0 eq.) and alkyne **A3** (7.0 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 16.8 mg (97 %, 14.5 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.96 (s, 8H), 1.29 (dd, *J* = 15.5, 7.2 Hz, 1H), 1.38 – 1.52 (m, 1H), 1.58 (q, *J* = 11.1, 8.3 Hz, 3H), 2.20 (dd, *J* = 16.5, 11.1 Hz, 2H), 2.41 (td, *J* = 8.9, 4.4 Hz, 1H), 2.55 (s, 3H), 2.81 (q, *J* = 7.2, 6.8 Hz, 1H), 3.14 (d, *J* = 12.9 Hz, 1H), 3.64 (s, 11H), 3.87 – 4.20 (m, 6H), 4.38 (dd, *J* = 15.2, 5.4 Hz, 1H), 4.46 – 4.80 (m, 5H), 5.10 – 5.21 (m, 2H), 5.64 (d, *J* = 16.7 Hz, 1H), 5.75 (ddd, *J* = 17.2, 9.9, 8.6 Hz, 1H), 8.07 (t, *J* = 1.7 Hz, 1H), 8.17 (t, *J* = 1.6 Hz, 1H), 8.24 (s, 1H), 8.23 – 8.34 (m, 1H), 8.80 (d, *J* = 5.1 Hz, 1H), 9.12 (s, 1H).

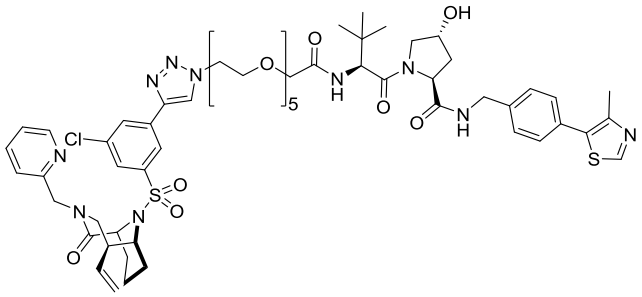
TLC: R_f = 0.10 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 0.7 min
97 % purity (220 nm).

HRMS (ESI) m/z: $[M+2H]^{2+}$ calculated for $C_{56}H_{71}ClN_{10}O_{11}S_2$ = 580.22896; found = 580.22869.

Lab book number(s): MWa199.

(2*S*,4*R*)-1-((2*S*)-2-(*tert*-Butyl)-20-(4-(3-chloro-5-(((*1S*, *5S*, *6R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)-4-oxo-6,9,12,15,18-pentaoxa-3-azaicosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{58}H_{75}ClN_{10}O_{12}S_2$, MW = 1203.87 g / mol

The product was synthesized from azide **57e** (11.0 mg, 15.0 μmol, 1.0 eq.) and alkyne **A3** (7.0 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 15.1 mg (83 %, 12.5 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 0.96 (s, 9H), 1.20 – 1.36 (m, 1H), 1.38 – 1.52 (m, 1H), 1.60 (d, *J* = 16.0 Hz, 3H), 2.19 (d, *J* = 13.3 Hz, 2H), 2.36 – 2.52 (m, 1H), 2.55 (s, 3H), 2.80 (d, *J* = 7.7 Hz, 1H), 3.14 (d, *J* = 13.9 Hz, 1H), 3.54 – 3.75 (m, 16H), 3.88 – 4.20 (m, 7H), 4.37 (dd, *J* = 15.1, 4.3 Hz, 1H), 4.46 – 4.83 (m, 8H), 5.07 – 5.23 (m, 2H), 5.64 (d, *J* = 17.3 Hz, 1H), 5.76 (dt, *J* = 17.6, 9.2 Hz, 1H), 7.39 (dt, *J* = 21.6, 7.2 Hz, 6H), 7.70 (d, *J* = 16.3 Hz, 2H), 7.79 (d, *J* = 7.6 Hz, 1H), 8.08 (s, 1H), 8.23 (dd, *J* = 18.9, 10.3 Hz, 3H), 8.79 (s, 1H), 9.06 (s, 1H).

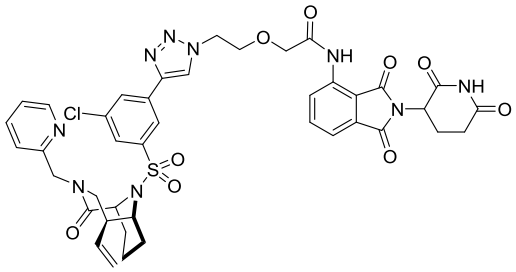
TLC: R_f = 0.10 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 0.7 min
97 % purity (220 nm).

HRMS (ESI) m/z: $[M+2H]^{2+}$ calculated for $C_{58}H_{75}ClN_{10}O_{12}S_2$ = 602.24207; found = 602.24277.

Lab book number(s): MWa200.

(2*S*,4*R*)-2-(2-(4-(3-Chloro-5-(((*1S*, *5S*, *6R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)ethoxy)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)acetamide



$C_{41}H_{40}ClN_9O_9S$, MW = 870.34 g / mol

The product was synthesized from azide **55a** (6.0 mg, 15.0 μmol, 1.0 eq.) and alkyne **A3** (7.0 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 8.8 mg (68 %, 10.1 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.24 (d, J = 8.3 Hz, 4H), 1.49 (s, 4H), 2.16 (d, J = 9.2 Hz, 3H), 2.57 – 2.91 (m, 3H), 3.06 (d, J = 14.1 Hz, 1H), 3.87 – 4.19 (m, 6H), 4.66 – 4.86 (m, 4H), 4.89 – 5.13 (m, 4H), 5.66 (dt, J = 18.4, 9.9 Hz, 1H), 7.32 – 7.51 (m, 2H), 7.56 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 12.2 Hz, 2H), 7.88 (q, J = 7.6 Hz, 1H), 8.09 (d, J = 8.7 Hz, 2H), 8.28 (s, 1H), 8.60 (s, 1H), 8.79 (d, J = 8.0 Hz, 1H), 10.42 (d, J = 5.5 Hz, 1H).

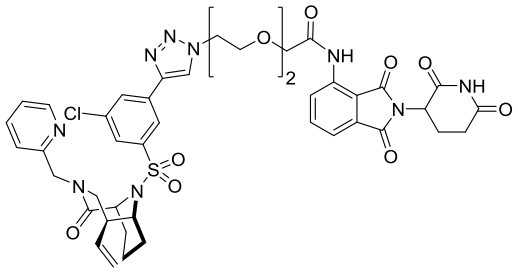
TLC: R_f = 0.28 (DCM:MeOH = 20:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 0.6 min
96 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{41}H_{40}ClN_9O_9S$ = 870.24310; found = 870.24396.

Lab book number(s): MWa202.

(2*S*,4*R*)- 2-(2-(2-(4-(3-Chloro-5-(((*1S*, *5S*, *6R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)acetamide



$C_{43}H_{44}ClN_9O_{10}S$, MW =914.39 g / mol

The product was synthesized from azide **55b** (6.7 mg, 15.0 μmol, 1.0 eq.) and alkyne **A3** (7.0 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.1 mg (74 %, 11.0 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 1.15 – 1.34 (m, 2H), 1.43 – 1.55 (m, 3H), 2.17 (td, *J* = 9.3, 8.7, 3.4 Hz, 2H), 2.59 – 2.89 (m, 5H), 3.34 (p, *J* = 1.7 Hz, 1H), 3.77 (dq, *J* = 4.6, 2.7, 2.2 Hz, 4H), 3.91 – 4.07 (m, 4H), 4.12 (d, *J* = 1.4 Hz, 2H), 4.53 – 4.59 (m, 2H), 4.62 – 4.74 (m, 2H), 4.83 – 5.03 (m, 4H), 5.67 (ddd, *J* = 17.0, 10.2, 8.7 Hz, 1H), 7.27 – 7.31 (m, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.50 (dd, *J* = 7.3, 0.9 Hz, 1H), 7.59 (t, *J* = 1.8 Hz, 1H), 7.64 (tt, *J* = 8.0, 1.1 Hz, 1H), 7.79 (td, *J* = 7.7, 1.6 Hz, 1H), 7.89 – 7.95 (m, 1H), 7.98 – 8.03 (m, 1H), 8.14 (s, 1H), 8.51 (d, *J* = 4.9 Hz, 1H), 8.69 (dt, *J* = 8.5, 0.9 Hz, 1H), 10.29 (s, 1H).

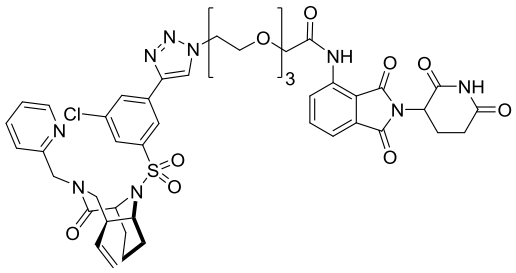
TLC: R_f = 0.26 (DCM:MeOH = 20:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 0.6 min
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{43}H_{44}ClN_9O_{10}S$ =914.26931; found = 914.27007.

Lab book number(s): MWa203.

(2*S*,4*R*)-2-(2-(2-(2-(4-(3-Chloro-5-(((*1S*, *5S*, *6R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)acetamide



$C_{45}H_{48}ClN_9O_{11}S$, MW = 958.44 g / mol

The product was synthesized from azide **55c** (7.3 mg, 15.0 μmol, 1.0 eq.) and alkyne **A3** (7.0 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.7 mg (75 %, 11.2 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.21 – 1.33 (m, 3H), 1.49 (d, J = 4.7 Hz, 3H), 2.08 – 2.26 (m, 2H), 2.63 – 2.90 (m, 2H), 3.07 (d, J = 14.1 Hz, 1H), 3.58 – 3.67 (m, 5H), 3.76 (d, J = 4.7 Hz, 4H), 3.84 – 3.92 (m, 2H), 3.95 – 4.11 (m, 2H), 4.15 (s, 2H), 4.53 (d, J = 5.0 Hz, 2H), 4.75 (s, 2H), 4.86 – 5.09 (m, 4H), 5.69 (dt, J = 18.2, 9.1 Hz, 1H), 7.32 (t, J = 6.1 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.48 – 7.58 (m, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.82 (t, J = 7.6 Hz, 1H), 8.03 – 8.14 (m, 2H), 8.20 (s, 1H), 8.55 (s, 1H), 8.77 (d, J = 9.1 Hz, 1H), 9.56 (s, 1H), 10.38 (s, 1H).

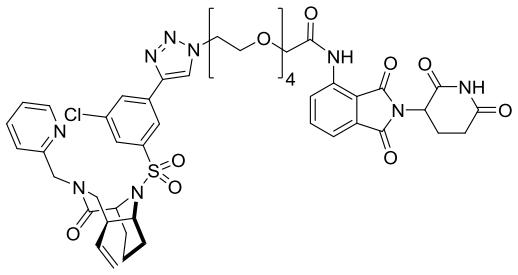
TLC: R_f = 0.25 (DCM:MeOH = 20:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 0.7 min
98 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{45}H_{48}ClN_9O_{11}S$ = 958.29553; found = 958.29647.

Lab book number(s): MWa204.

(2*S*,4*R*)-14-(4-(3-Chloro-5-(((*1S*, *5S*, *6R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-3,6,9,12-tetraoxatetradecanamide



$C_{47}H_{52}ClN_9O_{12}S$, MW = 1002.49 g / mol

The product was synthesized from azide **55d** (8.0 mg, 15.0 μmol, 1.0 eq.) and alkyne **A3** (7.0 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 9.0 mg (60 %, 9.0 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 1.15 – 1.39 (m, 2H), 1.43 – 1.57 (m, 3H), 2.07 – 2.24 (m, 2H), 2.58 – 2.83 (m, 4H), 3.05 (d, *J* = 14.0 Hz, 1H), 3.53 – 3.68 (m, 10H), 3.67 – 3.78 (m, 4H), 3.83 – 3.94 (m, 2H), 3.95 – 4.10 (m, 2H), 4.12 (s, 2H), 4.56 (t, *J* = 4.9 Hz, 3H), 4.64 – 4.81 (m, 2H), 4.84 – 5.08 (m, 4H), 5.68 (ddd, *J* = 17.0, 10.1, 8.8 Hz, 1H), 7.29 (d, *J* = 6.1 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.52 (ddd, *J* = 7.3, 1.4, 0.8 Hz, 1H), 7.63 – 7.74 (m, 2H), 7.78 (td, *J* = 7.7, 1.7 Hz, 1H), 8.05 (t,

J = 1.7 Hz, 1H), 8.09 – 8.16 (m, 1H), 8.21 – 8.25 (m, 1H), 8.52 (d, J = 4.8 Hz, 1H), 8.76 (dd, J = 8.5, 0.9 Hz, 1H), 9.69 (s, 1H), 10.40 (s, 1H).

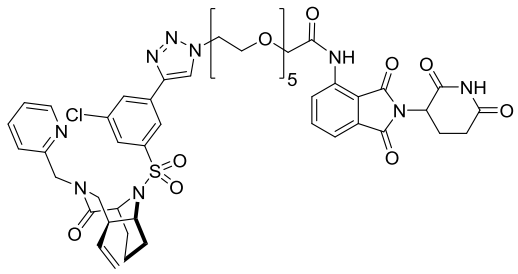
TLC: R_f = 0.24 (DCM:MeOH = 20:1).

LC-MS: [30-100 % Solvent B, 2.2 min]: R_t = 1.5 min
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{47}H_{52}ClN_9O_{12}S$ = 1002.32174; found = 1002.32255.

Lab book number(s): MWa205.

(2*S*,4*R*)-17-(4-(3-Chloro-5-(((*1S*, *5S*, *6R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-3,6,9,12,15-pentaoxaheptadecanamide



$C_{49}H_{56}ClN_9O_{13}S$, MW = 1046.55 g / mol

The product was synthesized from azide **55e** (8.6 mg, 15.0 μmol, 1.0 eq.) and alkyne **A3** (7.0 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 13.4 mg (85 %, 12.8 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.16 – 1.40 (m, 2H), 1.43 – 1.62 (m, 3H), 2.05 – 2.24 (m, 2H), 2.58 – 2.88 (m, 3H), 3.05 (d, J = 14.2 Hz, 1H), 3.29 – 3.36 (m, 1H), 3.54 – 3.75 (m, 17H), 3.87 (t, J = 4.9 Hz, 2H), 3.97 – 4.16 (m, 4H), 4.54 (d, J = 5.0 Hz, 2H), 4.69 (d, J = 15.7 Hz, 2H), 4.83 –

5.07 (m, 4H), 5.56 – 5.79 (m, 1H), 7.32 (t, *J* = 6.0 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.62 – 7.70 (m, 2H), 7.83 (t, *J* = 7.7 Hz, 1H), 8.01 – 8.05 (m, 1H), 8.10 – 8.15 (m, 1H), 8.20 – 8.25 (m, 1H), 8.51 – 8.57 (m, 1H), 8.75 (d, *J* = 8.4 Hz, 1H), 9.79 (s, 1H), 10.41 (s, 1H).

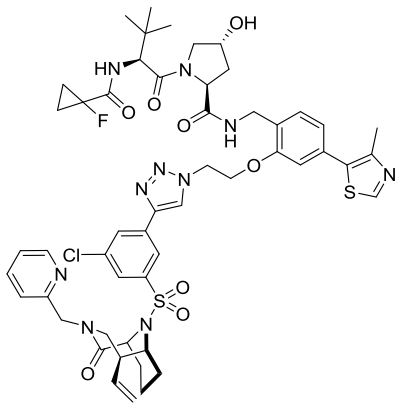
TLC: R_f = 0.24 (DCM:MeOH = 20:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 0.8 min
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{50}H_{59}ClN_{10}O_8S_2$=1046.34796; found = 1046.34976.

Lab book number(s): MWa206.

(2*S*,4*R*)-*N*-(2-(2-(4-(3-Chloro-5-(((*1S*, *5S*, *6R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{52}H_{60}ClFN_{10}O_8S_2$, MW = 1071.68 g / mol

The product was synthesized from azide **58a** (6.0 mg, 10.0 μmol, 1.0 eq.) and alkyne **A3** (4.7 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 6.5 mg (61 %, 6.1 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.94 (s, 9H), 1.16 – 1.65 (m, 5H), 2.09 (d, *J* = 13.1 Hz, 1H), 2.25 (d, *J* = 8.0 Hz, 2H), 2.52 (s, 3H), 2.82 (q, *J* = 8.3 Hz, 1H), 3.14 (d, *J* = 12.9 Hz, 1H), 3.65 (dd, *J* = 11.2, 3.2 Hz, 1H), 3.92 (d, *J* = 11.4 Hz, 1H), 4.03 – 4.25 (m, 3H), 4.35 – 4.72 (m, 5H), 4.78 (d, *J* = 6.0 Hz, 1H), 4.85 – 5.06 (m, 1H), 5.09 – 5.23 (m, 2H), 5.65 – 5.85 (m, 2H), 6.78 (d, *J* = 1.7 Hz, 1H), 6.99 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.07 (dd, *J* = 8.7, 3.4 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.42 – 7.52 (m, 1H), 7.66 – 7.71 (m, 1H), 7.73 (t, *J* = 1.8 Hz, 1H), 7.79 (dd, *J* = 7.0, 5.6 Hz, 1H), 8.21 (dt, *J* = 12.4, 1.7 Hz, 2H), 8.25 – 8.38 (m, 1H), 8.45 (s, 1H), 8.75 (d, *J* = 5.3 Hz, 1H), 9.04 (s, 1H).

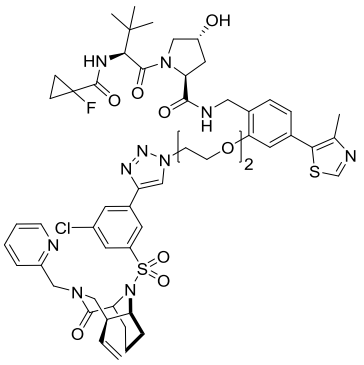
TLC: R_f = 0.12 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 1.2 min
98 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{52}H_{60}ClFN_{10}O_8S_2$ = 1071.37823; found = 1071.37582.

Lab book number(s): MWa228.

(2*S*,4*R*)-*N*-(2-(2-(2-(4-(3-Chloro-5-(((*1S*, *5S*, *6R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{54}H_{64}ClFN_{10}O_9S_2$, MW = 1115.74 g / mol

The product was synthesized from azide **58b** (6.5 mg, 10.0 μmol, 1.0 eq.) and alkyne **A3** (4.7 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.0 mg (45 %, 4.5 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 0.98 (s, 10H), 1.14 – 1.37 (m, 3H), 1.36 – 1.49 (m, 0H), 1.46 – 1.70 (m, 4H), 2.13 – 2.21 (m, 2H), 2.38 (ddd, *J* = 13.1, 8.5, 4.4 Hz, 1H), 2.53 (s, 3H), 2.79 (q, *J* = 9.0 Hz, 1H), 3.14 (dd, *J* = 14.1, 2.1 Hz, 1H), 3.66 (dd, *J* = 11.0, 3.6 Hz, 1H), 3.90 (dt, *J* = 5.2, 3.2 Hz, 2H), 4.02 (d, *J* = 11.2 Hz, 1H), 4.05 – 4.18 (m, 3H), 4.45 (dd, *J* = 6.0, 2.4 Hz, 2H), 4.50 – 4.56 (m, 2H), 4.61 – 4.68 (m, 4H), 4.74 (d, *J* = 6.5 Hz, 1H), 5.07 – 5.19 (m, 2H), 5.62 (d, *J* = 16.4 Hz, 1H), 5.75 (ddd, *J* = 16.9, 10.3, 8.7 Hz, 1H), 6.80 (d, *J* = 1.7 Hz, 1H), 6.95 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.03 – 7.07 (m, 1H), 7.35 (dd, *J* = 15.7, 6.9 Hz, 2H), 7.66 – 7.71 (m, 2H), 7.77 (d, *J* = 7.6 Hz, 1H), 8.05 (t, *J* = 1.7 Hz, 1H), 8.10 (t, *J* = 1.6 Hz, 1H), 8.14 (s, 1H), 8.26 (td, *J* = 7.8, 1.6 Hz, 1H), 8.78 (dt, *J* = 5.5, 1.3 Hz, 1H), 8.99 (s, 1H).

TLC: R_f = 0.10 (DCM:MeOH = 10:1).

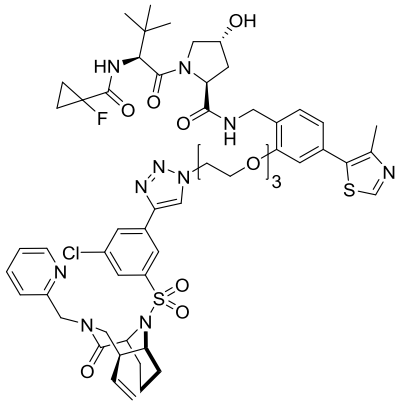
LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 1.0 min

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{54}H_{64}ClFN_{10}O_9S_2$ = 1115.40445; found = 1115.40269.

Lab book number(s): MWa229.

(2*S*,4*R*)-*N*-(2-(2-(2-(2-(4-(3-Chloro-5-(((*1S*, *5S*, *6R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{56}H_{68}ClFN_{10}O_{10}S_2$, MW = 1159.79 g / mol

The product was synthesized from azide **58c** (6.9 mg, 10.0 μmol, 1.0 eq.) and alkyne **A3** (4.7 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 3.8 mg (33 %, 3.3 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.01 (s, 8H), 1.16 – 1.68 (m, 6H), 1.99 – 2.29 (m, 3H), 2.47 (s, 2H), 2.82 – 2.96 (m, 1H), 3.13 – 3.33 (m, 2H), 3.64 – 3.78 (m, 3H), 3.76 – 3.87 (m, 3H), 3.95 (t, *J* = 4.9 Hz, 2H), 4.05 – 4.24 (m, 1H), 4.36 (d, *J* = 6.5 Hz, 1H), 4.48 (s, 1H), 4.56 – 4.71 (m, 3H), 4.69 – 4.82 (m, 3H), 5.04 – 5.22 (m, 4H), 5.72 – 5.91 (m, 1H), 6.93 – 7.04 (m, 2H), 7.42 (d, *J* = 7.7 Hz,

1H), 7.49 (d, *J* = 5.9 Hz, 1H), 7.69 – 7.84 (m, 2H), 8.07 – 8.15 (m, 1H), 8.21 – 8.35 (m, 2H), 8.61 (s, 1H), 8.68 (s, 1H), 8.95 (s, 1H).

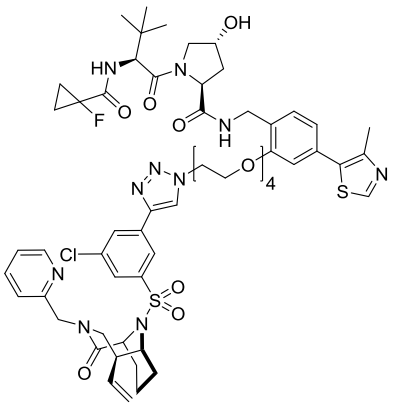
TLC: R_f = 0.10 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 1.1 min
95 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{56}H_{68}ClFN_{10}O_{10}S_2$ = 1159.43066; found = 1159.43165.

Lab book number(s): MWa230.

(2*S*,4*R*)-*N*-(2-(2-(2-(2-(2-(4-(3-Chloro-5-(((*1S*, *5S*, *6R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{58}H_{72}ClFN_{10}O_{11}S_2$, MW = 1203.84 g / mol

The product was synthesized from azide **58d** (7.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A3** (4.7 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.0 mg (42 %, 4.2 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.02 (s, 7H), 1.20 – 1.69 (m, 7H), 2.01 – 2.29 (m, 3H), 2.48 (s, 2H), 2.90 (q, *J* = 8.2 Hz, 1H), 3.19 – 3.31 (m, 2H), 3.56 – 3.73 (m, 8H), 3.81 (d, *J* = 6.3 Hz, 4H), 3.91 (t, *J* = 4.9 Hz, 2H), 4.06 – 4.23 (m, 4H), 4.38 (d, *J* = 10.9 Hz, 2H), 4.48 (s, 1H), 4.56 – 4.67 (m, 3H), 4.69 – 4.83 (m, 3H), 5.04 – 5.30 (m, 4H), 5.70 – 5.91 (m, 1H), 6.91 – 7.04 (m, 2H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 9.5 Hz, 1H), 7.75 (dd, *J* = 7.6, 4.6 Hz, 2H), 7.84 (t, *J* = 1.8 Hz, 1H), 8.14 (t, *J* = 1.7 Hz, 1H), 8.23 – 8.38 (m, 2H), 8.62 (s, 1H), 8.64 – 8.73 (m, 1H), 8.96 (s, 1H).

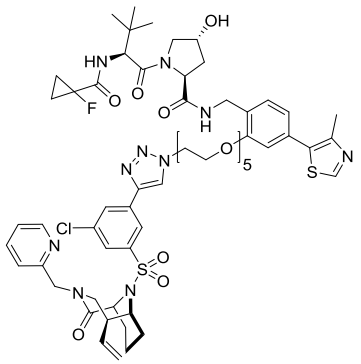
TLC: R_f = 0.09 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 1.1 min
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{58}H_{72}ClFN_{10}O_{11}S_2$ = 1203.45688; found = 1203.45299.

Lab book number(s): MWa231.

(2*S*,4*R*)-*N*-(2-((14-(4-(3-Chloro-5-(((*1S*, *5S*, *6R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)-3,6,9,12-tetraoxatetradecyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{60}H_{76}ClFN_{10}O_{12}S_2$, MW = 1247.89 g / mol

The product was synthesized from azide **58e** (7.8 mg, 10.0 μmol, 1.0 eq.) and alkyne **A3** (4.7 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 6.1 mg (49 %, 4.9 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.02 (s, 10H), 1.18 – 1.71 (m, 10H), 1.97 – 2.30 (m, 3H), 2.49 (s, 3H), 2.91 (q, *J* = 9.1, 8.5 Hz, 1H), 3.20 – 3.32 (m, 2H), 3.48 – 3.71 (m, 12H), 3.77 – 3.85 (m, 3H), 3.92 (t, *J* = 5.0 Hz, 2H), 4.09 – 4.24 (m, 4H), 4.40 (d, *J* = 11.6 Hz, 2H), 4.48 (d, *J* = 3.9 Hz, 1H), 4.56 – 4.65 (m, 4H), 4.75 (dd, *J* = 16.4, 3.1 Hz, 3H), 5.06 – 5.24 (m, 3H), 5.72 – 5.94 (m, 1H), 7.00 (d, *J* = 6.9 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.46 – 7.56 (m, 1H), 7.78 (d, *J* = 7.9 Hz, 2H), 7.85 (t, *J* = 1.8 Hz, 1H), 8.16 (t, *J* = 1.7 Hz, 1H), 8.29 (t, *J* = 1.6 Hz, 1H), 8.35 (t, *J* = 7.8 Hz, 1H), 8.63 (s, 1H), 8.71 (s, 1H), 8.97 (s, 1H).

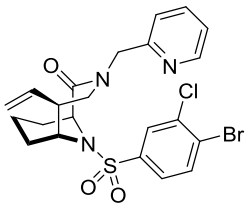
TLC: R_f = 0.08 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 1.2 min
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{60}H_{76}ClFN_{10}O_{12}S_2$ = 1247.48309; found = 1247.47983.

Lab book number(s): MWa232.

(1*S*, 5*S*, 6*R*)-10-((4-Bromo-3-chlorophenyl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



$C_{22}H_{23}ClBrN_3O_3S$, MW = 524.86 g / mol

(1*S*, 5*S*, 6*R*)-3-(Pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one (750 mg, 2.76 mmol, 1.0 eq.), 4-bromo-3-chlorobenzenesulfonyl chloride (1042 mg, 3.59 mmol, 1.3 eq.) and DIPEA (0.94 mL, 5.53 mmol, 2.0 eq.) were dissolved in acetonitrile (dry, 75 mL) and stirred for 18 h at room temperature under argon. Brine (100 mL) was added and the mixture was extracted with DCM (2 x

100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by column chromatography (100 g SiO_2, CH:EA = 1:1)

Yield: 904 mg (62 %, 1.72 mmol).

Appearance: white foam.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.15 – 1.39 (m, 2H), 1.44 – 1.69 (m, 3H), 2.29 (dq, *J* = 13.4, 2.7 Hz, 1H), 2.62 – 2.77 (m, 1H), 3.10 (dd, *J* = 14.2, 2.0 Hz, 1H), 3.95 – 4.07 (m, 2H), 4.71 – 4.78 (m, 2H), 4.84 (d, *J* = 15.2 Hz, 1H), 4.93 – 5.06 (m, 2H), 5.62 – 5.78 (m, 1H), 7.18 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 7.30 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.55 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.67 (td, *J* = 7.7, 1.8 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 2.2 Hz, 1H), 8.52 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H).

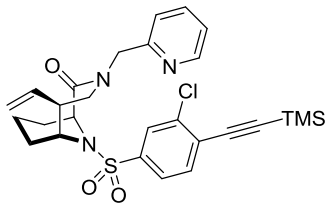
^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 15.5, 26.4, 27.5, 49.0, 52.1, 54.8, 56.2, 56.9, 116.8, 122.0, 122.4, 125.5, 127.8, 128.2, 134.7, 136.0, 136.9, 137.3, 141.8, 149.2, 157.0, 170.4.

TLC: R_f = 0.55 (EA).

LC-MS: Mass (ESI), calculated = 526.0 $[M+H]^+$, found = 526.3.

Lab book number(s): MWa169 / MWa194.

(1*S*, 5*S*, 6*R*)-10-((3-Chloro-4-((trimethylsilyl)ethynyl)phenyl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



$C_{27}H_{32}ClN_3O_3SSi$, MW = 542.17 g / mol

(1*S*, 5*S*, 6*R*)-10-((4-Bromo-3-chlorophenyl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo [4.3.1]decan-2-one (702 mg, 1.34 mmol, 1.0 eq.), copper(I) iodide (128 mg, 0.67 mmol, 0.5 eq.) and palladium-tetrakis(triphenylphosphine) (774 mg, 0.67 mmol, 0.5 eq.) were dissolved in TMEDA (100mL) under argon. Ethynyltrimethylsilane (1.86 mL, 13.4 mmol, 10.0 eq.) was added and the mixture was stirred at 90 °C for 3 h. Brine (100 mL) was added and the mixture was extracted with DCM (2 x 100 mL). The combined organic phases were dried over MgSO4 and concentrated under reduced pressure. The obtained product was purified by column chromatography (150 g SiO2, CH:EA = 2:1 → 1:1)

Yield: 607 mg (1.12 mmol, 84 %).

Appearance: slightly brown foam.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 0.27 (s, 9H), 1.13 – 1.32 (m, 3H), 1.43 – 1.51 (m, 2H), 2.25 (d, *J* = 13.5 Hz, 1H), 2.59 – 2.74 (m, 1H), 3.07 (dd, *J* = 14.1, 2.0 Hz, 1H), 3.90 – 4.06 (m, 2H), 4.74 (d, *J* = 3.9 Hz, 2H), 4.80 (s, 1H), 4.91 – 5.07 (m, 2H), 5.59 – 5.77 (m, 1H), 7.17 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.54 – 7.71 (m, 3H), 7.84 (d, *J* = 1.6 Hz, 1H), 8.50 (dt, *J* = 4.9, 1.2 Hz, 1H).

^{13}**C-NMR** (75 MHz, Chloroform-*d*): δ = -0.2, 15.7, 26.4, 27.5, 49.1, 52.1, 54.8, 56.3, 57.0, 99.7, 105.1, 116.8, 122.1, 122.5, 124.3, 127.2, 127.5, 134.3, 137.0, 137.4, 137.4, 141.8, 149.3, 157.1, 170.6.

TLC: R_f = 0.50 (CH:EA = 1:2).

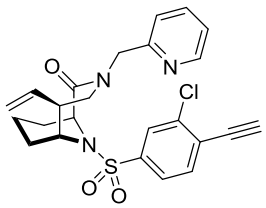
LC-MS: Mass (ESI), calculated = 542.2 $[M+H]^+$, found = 542.8.

[5-100 % Solvent B, 20 min]: R_t = 15.1 min.

93 % purity (220 nm).

Lab book number(s): MWa171 / MWa195.

(1*S*, 5*S*, 6*R*)-10-((3-Chloro-4-ethynylphenyl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



$C_{24}H_{24}ClN_3O_3S$, MW = 469.98 g / mol

(1*S*, 5*S*, 6*R*)-10-((3-Chloro-4-((trimethylsilyl)ethynyl)phenyl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one (130 mg, 240 μmol, 1.0 eq.) and potassium carbonate (33 mg, 240 μmol, 1.0 eq) were dissolved in methanol (dry, 13 mL) and the mixture was stirred for 3 h at room temperature. Water (30 mL) was added and the mixture was extracted with EA (3 x 30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 64 mg (57 %, 136 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 1.16 – 1.44 (m, 2H), 1.51 – 1.64 (m, 3H), 2.24 (d, *J* = 12.9 Hz, 1H), 2.77 (q, *J* = 8.3 Hz, 1H), 3.13 (d, *J* = 14.2 Hz, 1H), 3.59 (s, 1H), 4.07 (dd, *J* = 9.6, 3.8 Hz, 2H), 4.59 – 4.78 (m, 2H), 5.07 – 5.22 (m, 2H), 5.54 (d, *J* = 16.4 Hz, 1H), 5.75 (dt, *J* = 18.2, 9.4 Hz, 1H), 7.56 – 7.77 (m, 4H), 7.87 (s, 1H), 8.16 (t, *J* = 7.8 Hz, 1H), 8.78 (d, *J* = 5.4 Hz, 1H).

^{13}**C-NMR** (75 MHz, Chloroform-*d*): δ = 15.5, 26.5, 27.4, 49.2, 53.1, 53.5, 54.9, 56.9, 78.9, 86.5, 117.7, 124.4, 124.5, 126.9, 127.3, 134.9, 136.5, 137.8, 142.1, 143.1, 144.2, 154.7, 171.7.

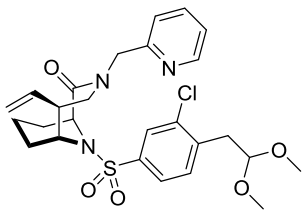
TLC: R_f = 0.40 (CH:EA = 1:2).

LC-MS: Mass (ESI), calculated = 470.1 $[M+H]^+$, found = 470.1.
[50-100 % Solvent B, 2.7 min]: R_t = 1.0 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{24}H_{24}ClN_3O_3S$ = 470.12997; found = 470.12999.

Lab book number(s): MWa233.

(1*S*, 5*S*, 6*R*)-10-((3-Chloro-4-(2,2-dimethoxyethyl)phenyl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



$C_{26}H_{32}ClN_3O_5S$, MW = 534.07 g / mol

(1*S*, 5*S*, 6*R*)-10-((3-Chloro-4-((trimethylsilyl)ethynyl)phenyl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one (14 mg, 26 μmol, 1.0 eq.) and potassium carbonate (11 mg, 78 μmol, 3.0 eq) were dissolved in methanol (dry, 4 mL) and the mixture was stirred for 1 h at room temperature. TMEDA (20 μL, 13 mmol, 0.5 eq.) was added and mixture was stirred for 1 h at room temperature. Palladium-tetrakis(triphenylphosphine) (1.0 mg, 0.9 μmol, 0.03 eq.) was added and mixture was stirred for 1 h at room temperature. The mixture was concentrated under reduced pressure. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 13.5 mg (97 %, 25.3 μmol).

Appearance: white solid.

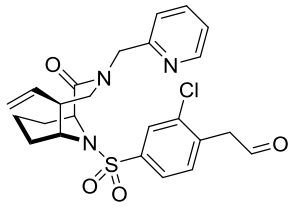
^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.12 – 1.68 (m, 4H), 2.25 (d, *J* = 13.1 Hz, 1H), 2.66 (q, *J* = 8.6 Hz, 1H), 3.06 (dd, *J* = 15.3, 3.8 Hz, 3H), 3.32 (s, 6H), 3.94 – 4.08 (m, 2H), 4.57 (t, *J* = 5.6 Hz, 1H), 4.67 – 4.77 (m, 2H), 4.83 (d, *J* = 15.2 Hz, 1H), 4.90 – 5.05 (m, 2H), 5.68 (ddd, *J* = 16.9, 10.2, 8.7 Hz, 1H), 7.12 – 7.19 (m, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.58 – 7.69 (m, 2H), 7.80 (d, *J* = 2.0 Hz, 1H), 8.49 (d, *J* = 4.3 Hz, 1H).

TLC: R_f = 0.35 (CH:EA = 1:2).

LC-MS: Mass (ESI), calculated = 534.2 $[M+H]^+$, found = 534.2.
[50-100 % Solvent B, 2.7 min]: R_t = 1.0 min.
> 99 % purity (220 nm).

Lab book number(s): MWa177 / MWa234.

2-(2-chloro-4-(((1*S*, 5*S*, 6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)acetaldehyde



$C_{24}H_{26}ClN_3O_4S$, MW = 488.00 g / mol

(1*S*, 5*S*, 6*R*)-10-((3-Chloro-4-(2,2-dimethoxyethyl)phenyl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one (245 mg, 465 μmol, 1.0 eq.) and hydrochloric acid (37 % (aq), 2.5 mL, 465 μmol, 1.0 eq.) were stirred for 3 h at room temperature. Sodium hydrogen carbonate (sat., aq, 50 mL) was added and the mixture was extracted with DCM (2 x 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure.

Yield: 220 mg (97 %, 451 μmol).

Appearance: yellow oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.19 – 1.38 (m, 3H), 2.29 (d, *J* = 13.4 Hz, 1H), 2.66 – 2.75 (m, 1H), 3.10 (dd, *J* = 14.2, 1.9 Hz, 1H), 3.95 (d, *J* = 1.4 Hz, 2H), 3.98 – 4.09 (m, 2H), 4.76 (d, *J* =

15.1 Hz, 2H), 4.85 (d, *J* = 15.1 Hz, 1H), 4.95 – 5.06 (m, 2H), 5.72 (ddd, *J* = 17.0, 10.2, 8.8 Hz, 1H), 7.19 (dd, *J* = 6.9, 5.4 Hz, 1H), 7.33 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.64 – 7.74 (m, 2H), 7.90 (d, *J* = 1.9 Hz, 1H), 8.53 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 9.79 (t, *J* = 1.4 Hz, 1H).

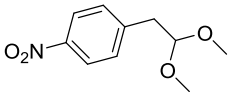
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 15.6, 26.4, 27.5, 48.0, 49.1, 52.1, 54.7, 56.2, 56.9, 116.7, 122.1, 122.4, 125.1, 127.7, 132.6, 135.7, 135.9, 137.0, 137.3, 142.2, 149.1, 157.0, 170.6, 196.1.

TLC: R_f = 0.55 (DCM:MeOH = 10:1).

LC-MS: Mass (ESI), calculated = 488.1 $[M+H]^+$, found = 488.8.
[50-100 % Solvent B, 2.7 min]: R_t = 1.0 min.
96 % purity (220 nm).

Lab book number(s): MWa178 / MWa265.

1-(2,2-Dimethoxyethyl)-4-nitrobenzene



$C_{10}H_{13}NO_4$, MW = 211.22 g / mol

1-ethynyl-4-nitrobenzene (100 mg, 680 μmol, 1.0 eq.) and potassium carbonate (282 mg, 2.04 mmol, 3.0 eq) were dissolved in methanol (dry, 50 mL). Palladium-tetrakis(triphenylphosphine) (39 mg, 34 μmol, 0.05 eq.) was added and mixture was stirred for 1 h at room temperature followed by 6 h at 50 °C. The mixture was concentrated under reduced pressure. The obtained product was purified by column chromatography (CH:EA = 5:1).

Yield: 39.0 mg (27 %, 185 μmol).

Appearance: yellow oil.

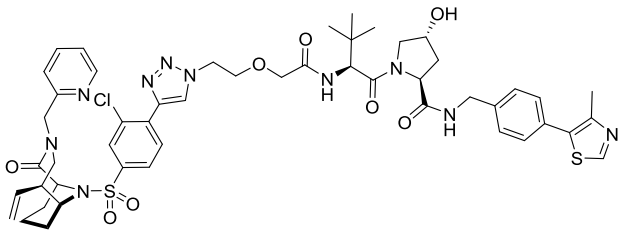
^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 2.94 (d, *J* = 5.4 Hz, 2H), 3.28 (s, 6H), 4.47 (t, *J* = 5.5 Hz, 1H), 7.29 – 7.37 (m, 2H), 8.04 – 8.12 (m, 2H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 39.7, 53.8, 104.6, 123.6, 130.5, 144.9, 146.9.

TLC: R_f = 0.40 (CH:EA = 3:1).

Lab book number(s): MWa413.

(2*S*,4*R*)-1-((*S*)-2-(2-(2-(4-(2-Chloro-4-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{50}H_{59}ClN_{10}O_8S_2$, MW = 1027.65 g / mol

The product was synthesized from azide **57a** (3.9 mg, 7.0 μmol, 1.0 eq.) and alkyne **A4** (3.3 mg, 7.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 6.4 mg (89 %, 6.2 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.89 (s, 9H), 1.15 – 1.38 (m, 2H), 1.50 (d, *J* = 11.5 Hz, 3H), 2.05 – 2.33 (m, 3H), 2.45 (s, 3H), 2.60 – 2.75 (m, 1H), 3.07 (d, *J* = 9.9 Hz, 1H), 3.34 (p, *J* = 1.6 Hz, 1H), 3.61 (dd, *J* = 11.2, 3.6 Hz, 1H), 3.81 – 4.12 (m, 7H), 4.29 – 4.59 (m, 5H), 4.63 – 4.76 (m, 4H), 4.95 – 5.12 (m, 3H), 5.61 – 5.78 (m, 1H), 7.13 – 7.20 (m, 1H), 7.28 – 7.58 (m, 7H), 7.73 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.84 – 7.95 (m, 2H), 8.37 (d, *J* = 8.4 Hz, 1H), 8.45 (s, 1H), 8.71 (s, 2H).

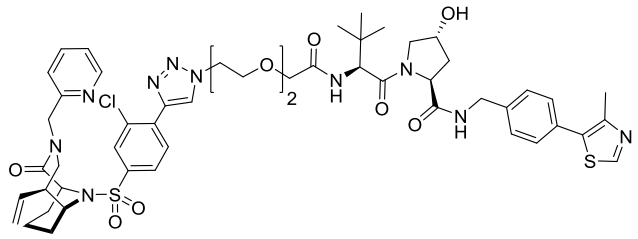
TLC: R_f = 0.11 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.7 min]: R_t = 1.8 min.
96 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{50}H_{59}ClN_{10}O_8S_2$ = 1027.37201; found = 1027.37209.

Lab book number(s): MWa250.

(2*S*,4*R*)-1-((2*S*)-2-(2-(2-(2-(4-(2-Chloro-4-(((*1S*, *5S*, *6R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{52}H_{63}ClN_{10}O_9S_2$, MW = 1071.71 g / mol

The product was synthesized from azide **57b** (4.2 mg, 7.0 μmol, 1.0 eq.) and alkyne **A4** (3.3 mg, 7.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 6.8 mg (91 %, 6.3 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.94 (s, 9H), 1.25 – 1.43 (m, 2H), 1.55 (d, *J* = 13.6 Hz, 3H), 2.21 (d, *J* = 14.0 Hz, 1H), 2.35 – 2.44 (m, 2H), 2.49 (s, 3H), 2.74 (q, *J* = 8.8 Hz, 1H), 3.11 (dd, *J* = 14.3, 2.0 Hz, 1H), 3.59 – 3.70 (m, 6H), 3.89 – 4.11 (m, 7H), 4.33 (dd, *J* = 15.1, 4.3 Hz, 1H), 4.48 – 4.75 (m, 8H), 5.05 – 5.08 (m, 1H), 5.10 (s, 1H), 5.32 (d, *J* = 16.1 Hz, 1H), 5.73 (ddd, *J* = 16.7, 10.4, 8.6 Hz, 1H), 7.33 (s, 4H), 7.50 (t, *J* = 6.5 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.75 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.92 (d, *J* = 1.9 Hz, 1H), 8.04 (td, *J* = 7.8, 1.5 Hz, 1H), 8.41 (d, *J* = 8.3 Hz, 1H), 8.47 (s, 1H), 8.69 (d, *J* = 5.3 Hz, 1H), 8.75 (s, 1H).

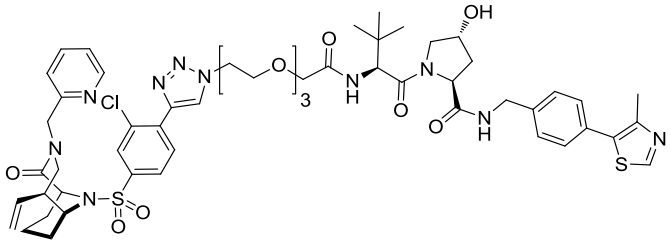
TLC: R_f = 0.10 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.7 min]: R_t = 1.8 min.
97 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{52}H_{63}ClN_{10}O_9S_2$= 1071.39822; found = 1071.39822.

Lab book number(s): MWa251.

(2*S*,4*R*)-1-((*S*)-2-(*tert*-Butyl)-14-(4-(2-chloro-4-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)-4-oxo-6,9,12-trioxa-3-azatetradecan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{54}H_{67}ClN_{10}O_{10}S_2$, MW = 1115.75 g / mol

The product was synthesized from azide **57c** (4.5 mg, 7.0 μmol, 1.0 eq.) and alkyne **A4** (3.3 mg, 7.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC for three times. The product was dried by lyophilisation.

Yield: 2.2 mg (28 %, 2.0 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.95 (s, 9H), 1.22 – 1.41 (m, 2H), 1.52 (d, *J* = 11.5 Hz, 3H), 2.10 – 2.21 (m, 2H), 2.33 (d, *J* = 4.1 Hz, 1H), 2.48 (s, 3H), 2.70 (q, *J* = 8.8 Hz, 1H), 3.09 (d, *J* = 14.1 Hz, 1H), 3.39 (p, *J* = 1.6 Hz, 1H), 3.62 (d, *J* = 4.1 Hz, 9H), 3.84 – 4.14 (m, 7H), 4.34 (d, *J* = 15.2 Hz, 1H), 4.42 – 4.66 (m, 6H), 4.71 (d, *J* = 15.6 Hz, 2H), 4.97 – 5.15 (m, 3H), 5.63 – 5.79 (m, 1H), 7.32 (s, 5H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.76 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.87 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.92 (d, *J* = 1.9 Hz, 1H), 8.39 (d, *J* = 8.4 Hz, 1H), 8.46 (s, 1H), 8.59 (d, *J* = 5.2 Hz, 1H), 8.69 (s, 1H).

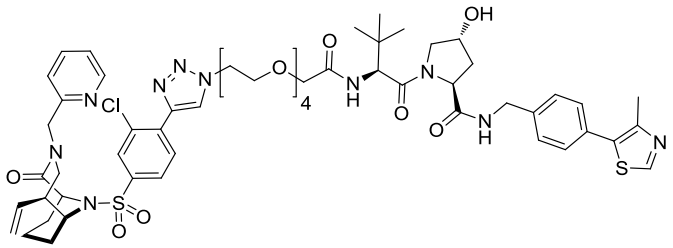
TLC: R_f = 0.10 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.7 min]: R_t = 1.8 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{54}H_{67}ClN_{10}O_{10}S_2$ = 1115.42443; found = 1115.42399.

Lab book number(s): MWa252.

(2*S*,4*R*)-1-((2*S*)-2-(*tert*-Butyl)-17-(4-(2-chloro-4-(((*1S*, *5S*, *6R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{56}H_{71}ClN_{10}O_{11}S_2$, MW = 1159.81 g / mol

The product was synthesized from azide **57d** (4.8 mg, 7.0 μmol, 1.0 eq.) and alkyne **A4** (3.3 mg, 7.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 4.7 mg (58 %, 4.1 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 0.94 (s, 9H), 1.18 – 1.38 (m, 2H), 1.51 (d, *J* = 11.1 Hz, 3H), 2.10 – 2.34 (m, 3H), 2.46 (s, 3H), 2.62 – 2.78 (m, 1H), 3.08 (d, *J* = 13.6 Hz, 1H), 3.35 (p, *J* = 1.6 Hz, 1H), 3.53 – 3.66 (m, 13H), 3.83 – 4.10 (m, 7H), 4.34 (d, *J* = 15.2 Hz, 1H), 4.42 – 4.76 (m, 8H), 4.98 – 5.09 (m, 2H), 5.17 (d, *J* = 16.0 Hz, 1H), 5.70 (ddd, *J* = 16.8, 10.4, 8.7 Hz, 1H), 7.32 (s, 4H), 7.39 – 7.45 (m, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.75 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.90 (d, *J* = 1.9 Hz, 1H), 7.95 (td, *J* = 7.8, 1.7 Hz, 1H), 8.38 (d, *J* = 8.3 Hz, 1H), 8.46 (s, 1H), 8.61 (d, *J* = 5.2 Hz, 1H), 8.70 (s, 1H).

TLC: R_f = 0.09 (DCM:MeOH = 10:1).

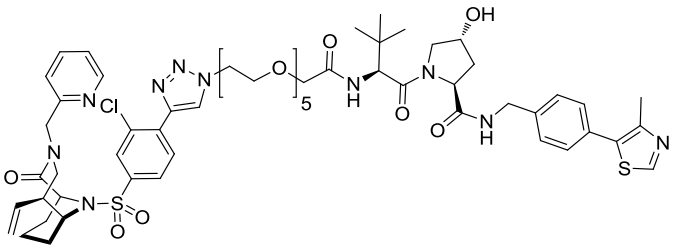
LC-MS: [5-100 % Solvent B, 2.7 min]: R_t = 1.8 min.

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{56}H_{71}ClN_{10}O_{11}S_2$ = 1159.45065; found = 1159.44975.

Lab book number(s): MWa253.

(2*S*,4*R*)-1-((*S*)-2-(*tert*-Butyl)-20-(4-(2-chloro-4-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)-4-oxo-6,9,12,15,18-pentaoxa-3-azaicosan-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{58}H_{75}ClN_{10}O_{12}S_2$, MW = 1203.86 g / mol

The product was synthesized from azide **57e** (5.1 mg, 7.0 μmol, 1.0 eq.) and alkyne **A4** (3.3 mg, 7.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 4.9 mg (58 %, 4.1 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 0.94 (s, 9H), 1.21 – 1.42 (m, 2H), 1.45 – 1.57 (m, 3H), 2.11 – 2.37 (m, 3H), 2.47 (s, 3H), 2.76 (s, 1H), 3.08 (d, *J* = 14.1 Hz, 1H), 3.36 (p, *J* = 1.6 Hz, 1H), 3.51 – 3.71 (m, 17H), 3.84 – 4.12 (m, 7H), 4.34 (d, *J* = 15.2 Hz, 1H), 4.42 – 4.78 (m, 8H), 4.97 – 5.16 (m, 3H), 5.70 (ddd, *J* = 16.9, 10.3, 8.7 Hz, 1H), 7.29 – 7.39 (m, 5H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.75 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.85 – 7.93 (m, 2H), 8.39 (d, *J* = 8.3 Hz, 1H), 8.47 (s, 1H), 8.55 – 8.60 (m, 1H), 8.68 (s, 1H).

TLC: R_f = 0.09 (DCM:MeOH = 10:1).

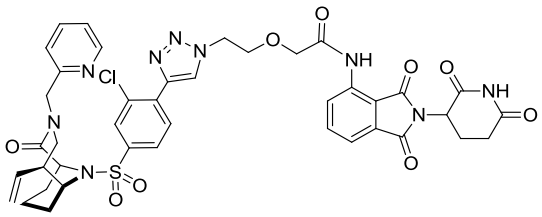
LC-MS: [5-100 % Solvent B, 2.7 min]: R_t = 1.8 min.

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{58}H_{75}ClN_{10}O_{12}S_2$ = 1203.47686; found = 1203.47595.

Lab book number(s): MWa254.

2-(2-(4-(2-Chloro-4-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)ethoxy)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)acetamide



$C_{41}H_{40}ClN_9O_9S$, MW = 870.33 g / mol

The product was synthesized from azide **55a** (2.8 mg, 7.0 μmol, 1.0 eq.) and alkyne **A4** (3.3 mg, 7.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 4.9 mg (80 %, 5.6 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.25 – 1.50 (m, 2H), 1.51 – 1.63 (m, 3H), 2.06 – 2.18 (m, 2H), 2.72 – 2.98 (m, 4H), 3.13 (d, *J* = 14.0 Hz, 1H), 4.04 – 4.20 (m, 6H), 4.66 (d, *J* = 16.5 Hz, 2H), 4.83 – 4.98 (m, 3H), 5.07 – 5.17 (m, 2H), 5.53 (dd, *J* = 16.4, 4.4 Hz, 1H), 5.66 – 5.83 (m, 1H), 7.56 – 7.64 (m, 2H), 7.70 – 7.80 (m, 3H), 7.88 (dd, *J* = 6.1, 1.9 Hz, 1H), 8.12 – 8.20 (m, 1H), 8.38 – 8.51 (m, 2H), 8.67 (s, 1H), 8.71 – 8.81 (m, 1H), 8.85 (ddd, *J* = 8.4, 2.8, 0.8 Hz, 1H), 10.45 (d, *J* = 2.6 Hz, 1H).

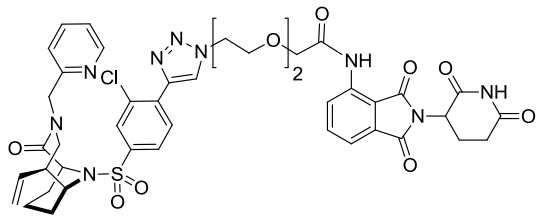
TLC: R_f = 0.22 (DCM:MeOH = 20:1).

LC-MS: [5-100 % Solvent B, 2.7 min]: R_t = 1.3 min.
97 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{41}H_{40}ClN_9O_9S$ = 870.24310; found = 870.24374.

Lab book number(s): MWa255.

2-(2-(2-(4-(2-Chloro-4-(((*1S*, *5S*, *6R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)acetamide



$C_{43}H_{44}ClN_9O_{10}S$, MW = 914.38 g / mol

The product was synthesized from azide **55b** (3.1 mg, 7.0 μmol, 1.0 eq.) and alkyne **A4** (3.3 mg, 7.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.4 mg (84 %, 5.9 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.24 – 1.35 (m, 1H), 1.37 – 1.44 (m, 1H), 1.59 (d, *J* = 18.6 Hz, 3H), 2.17 – 2.28 (m, 2H), 2.71 – 2.84 (m, 3H), 2.90 – 2.96 (m, 1H), 3.14 (dd, *J* = 14.1, 2.0 Hz, 1H), 3.80 (td, *J* = 5.7, 5.2, 2.7 Hz, 4H), 3.97 – 4.18 (m, 6H), 4.61 – 4.72 (m, 4H), 4.94 (ddd, *J* = 12.7, 5.5, 2.1 Hz, 1H), 5.10 – 5.18 (m, 2H), 5.62 (dd, *J* = 16.5, 3.4 Hz, 1H), 5.76 (ddd, *J* = 16.9, 10.2, 8.7 Hz, 1H), 7.53 – 7.56 (m, 1H), 7.62 – 7.70 (m, 3H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.82 (dd, *J* = 3.9, 1.9 Hz, 1H), 8.20 – 8.26 (m, 1H), 8.31 – 8.39 (m, 2H), 8.52 (d, *J* = 1.5 Hz, 1H), 8.74 (d, *J* = 8.4 Hz, 1H), 8.80 (dd, *J* = 5.7, 1.6 Hz, 1H), 10.35 (d, *J* = 3.0 Hz, 1H).

TLC: R_f = 0.20 (DCM:MeOH = 20:1).

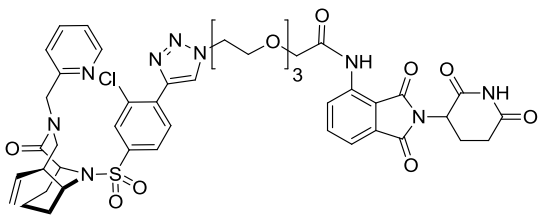
LC-MS: [5-100 % Solvent B, 2.7 min]: R_t = 1.3 min.

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{43}H_{44}ClN_9O_{10}S$ = 914.26931; found = 914.26943.

Lab book number(s): MWa256.

2-(2-(2-(2-(4-(2-Chloro-4-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)acetamide



$C_{45}H_{48}ClN_9O_{11}S$, MW = 958.43 g / mol

The product was synthesized from azide **55c** (3.4 mg, 7.0 μmol, 1.0 eq.) and alkyne **A4** (3.3 mg, 7.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 6.5 mg (97 %, 6.8 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.13 – 1.42 (m, 2H), 1.44 – 1.58 (m, 3H), 2.04 – 2.20 (m, 2H), 2.65 – 2.89 (m, 4H), 3.07 (d, *J* = 13.6 Hz, 1H), 3.59 (s, 4H), 3.71 (dddd, *J* = 8.5, 7.0, 3.8, 1.7 Hz, 4H), 3.87 (t, *J* = 4.9 Hz, 2H), 4.00 – 4.10 (m, 2H), 4.13 (d, *J* = 0.9 Hz, 2H), 4.52 – 4.63 (m, 3H), 4.67 (d, *J* = 6.1 Hz, 1H), 4.85 – 4.95 (m, 1H), 5.03 – 5.13 (m, 2H), 5.54 – 5.77 (m, 2H), 7.51 (dt, *J* = 7.3, 1.0 Hz, 1H), 7.58 – 7.70 (m, 3H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 1.8 Hz, 1H), 8.19 (tt, *J* = 7.9, 1.6 Hz, 1H), 8.34 – 8.46 (m, 3H), 8.72 – 8.79 (m, 2H), 10.35 (s, 1H).

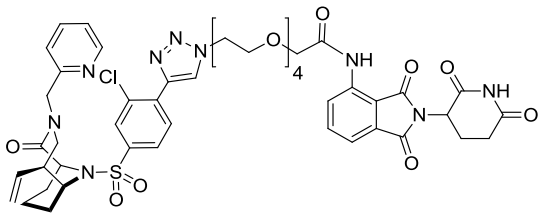
TLC: R_f = 0.19 (DCM:MeOH = 20:1).

LC-MS: [5-100 % Solvent B, 2.7 min]: R_t = 1.4 min.
95 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{45}H_{48}ClN_9O_{11}S$ = 958.29553; found = 958.29545.

Lab book number(s): MWa257.

14-(4-(2-Chloro-4-(((*1S*, *5S*, *6R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-3,6,9,12-tetraoxatetradecan-1-amide



$C_{47}H_{52}ClN_9O_{12}S$, MW = 1002.49 g / mol

The product was synthesized from azide **55d** (3.7 mg, 7.0 μmol, 1.0 eq.) and alkyne **A4** (3.3 mg, 7.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC for two times. The product was dried by lyophilisation.

Yield: 2.2 mg (31 %, 2.2 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.11 – 1.44 (m, 2H), 1.44 – 1.59 (m, 3H), 2.02 – 2.18 (m, 2H), 2.66 – 2.89 (m, 4H), 3.07 (d, *J* = 14.0 Hz, 1H), 3.46 – 3.79 (m, 12H), 3.89 (t, *J* = 5.0 Hz, 2H), 3.99 – 4.17 (m, 4H), 4.57 (dt, *J* = 12.4, 4.0 Hz, 3H), 4.67 (d, *J* = 6.0 Hz, 1H), 4.89 (ddd, *J* = 9.9, 5.6, 2.5 Hz, 1H), 5.05 (s, 1H), 5.10 (d, *J* = 6.3 Hz, 1H), 5.58 (d, *J* = 16.6 Hz, 1H), 5.63 – 5.77 (m, 1H), 7.49 – 7.54 (m, 1H), 7.55 – 7.76 (m, 4H), 7.85 (d, *J* = 1.9 Hz, 1H), 8.18 (td, *J* = 7.9, 1.6 Hz, 1H), 8.38 (d, *J* = 8.4 Hz, 1H), 8.43 (d, *J* = 0.7 Hz, 1H), 8.56 (s, 1H), 8.76 (t, *J* = 8.1 Hz, 2H), 10.40 (s, 1H).

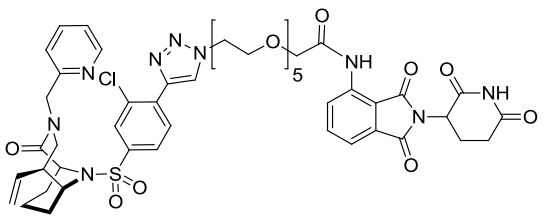
TLC: R_f = 0.19 (DCM:MeOH = 20:1).

LC-MS: [5-100 % Solvent B, 2.7 min]: R_t = 1.4 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{47}H_{52}ClN_9O_{12}S$ = 1002.32174; found = 1002.32214.

Lab book number(s): MWa258.

17-(4-(2-Chloro-4-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-3,6,9,12,15-pentaoxaheptadecan-1-amide



$C_{49}H_{56}ClN_9O_{13}S$, MW = 1046.54 g / mol

The product was synthesized from azide **55e** (4.0 mg, 7.0 μmol, 1.0 eq.) and alkyne **A4** (3.3 mg, 7.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 7.1 mg (97 %, 6.8 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.24 – 1.47 (m, 2H), 1.50 – 1.65 (m, 3H), 2.10 – 2.27 (m, 2H), 2.69 – 2.92 (m, 4H), 3.14 (d, *J* = 14.1 Hz, 1H), 3.56 – 3.73 (m, 12H), 3.74 – 3.85 (m, 4H), 3.90 – 3.97 (m, 2H), 4.15 (dd, *J* = 19.8, 2.2 Hz, 4H), 4.63 (dd, *J* = 10.8, 5.8 Hz, 3H), 4.73 (d, *J* = 6.1 Hz, 1H), 4.91 – 5.01 (m, 1H), 5.12 (s, 1H), 5.17 (d, *J* = 7.2 Hz, 1H), 5.67 (d, *J* = 16.7 Hz, 1H), 5.76 (ddd, *J* = 17.2, 10.3, 8.8 Hz, 1H), 7.57 (d, *J* = 7.3 Hz, 1H), 7.63 – 7.84 (m, 4H), 7.92 (d, *J* = 1.8 Hz, 1H), 8.22 – 8.34 (m, 1H), 8.38 – 8.51 (m, 2H), 8.74 – 8.88 (m, 3H), 10.47 (s, 1H).

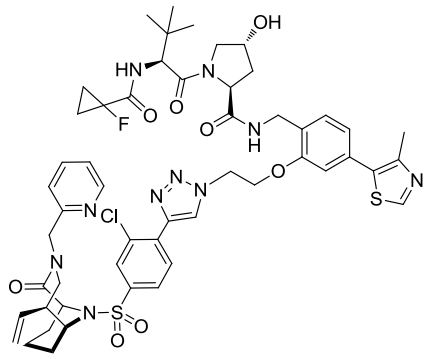
TLC: R_f = 0.18 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.7 min]: R_t = 1.4 min.
95 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{49}H_{56}ClN_9O_{13}S$ = 1046.34796; found = 1046.34806.

Lab book number(s): MWa259.

(2*S*,4*R*)-*N*-(2-(2-(4-(2-Chloro-4-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropanecarboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{52}H_{60}ClFN_{10}O_8S_2$, MW = 1071.68 g / mol

The product was synthesized from azide **58a** (4.2 mg, 7.0 μmol, 1.0 eq.) and alkyne **A4** (3.3 mg, 7.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 2.2 mg (29 %, 2.1 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.93 (s, 9H), 1.17 – 1.38 (m, 6H), 1.51 – 1.66 (m, 3H), 2.14 – 2.27 (m, 2H), 2.40 (ddd, *J* = 12.9, 8.2, 4.4 Hz, 1H), 2.52 (s, 3H), 2.79 (q, *J* = 8.8 Hz, 1H), 3.13 (d, *J* = 14.0 Hz, 1H), 3.64 (dd, *J* = 11.3, 3.5 Hz, 1H), 3.98 – 4.20 (m, 4H), 4.36 – 4.57 (m, 6H), 4.64 (d, *J* = 16.6 Hz, 1H), 4.69 – 4.81 (m, 2H), 4.94 – 5.05 (m, 2H), 5.12 (s, 1H), 5.16 (d, *J* = 5.8 Hz, 1H), 5.63 (d, *J* = 16.6 Hz, 1H), 5.66 – 5.85 (m, 1H), 6.81 (d, *J* = 1.6 Hz, 1H), 6.99 (dd, *J* = 7.7, 1.6 Hz, 2H), 7.27 – 7.41 (m, 2H), 7.64 – 7.70 (m, 1H), 7.74 – 7.80 (m, 2H), 7.92 (d, *J* = 1.9 Hz, 1H), 8.24 (td, *J* = 7.9, 1.6 Hz, 1H), 8.45 (d, *J* = 8.3 Hz, 1H), 8.67 (s, 1H), 8.80 (d, *J* = 5.5 Hz, 1H), 8.92 (s, 1H).

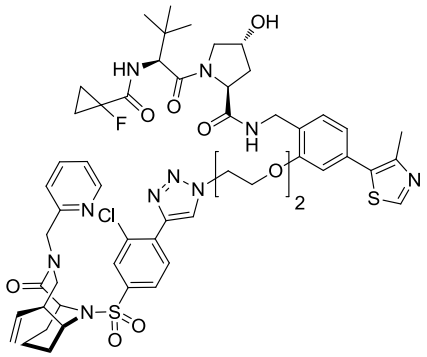
TLC: R_f = 0.10 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.7 min]: R_t = 1.5 min.
97 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{52}H_{60}ClFN_{10}O_8S_2$ = 1071.37823; found = 1071.37928.

Lab book number(s): MWa260.

(2*S*,4*R*)-*N*-(2-(2-(2-(4-(2-Chloro-4-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropanecarboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{54}H_{64}ClFN_{10}O_9S_2$, MW = 1115.73 g / mol

The product was synthesized from azide **58b** (4.5 mg, 7.0 μmol, 1.0 eq.) and alkyne **A4** (3.3 mg, 7.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.1 mg (65 %, 4.6 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.97 (s, 9H), 1.19 – 1.37 (m, 6H), 1.52 – 1.67 (m, 3H), 2.17 (dd, *J* = 22.6, 10.7 Hz, 2H), 2.40 (ddd, *J* = 13.0, 8.3, 4.4 Hz, 1H), 2.54 (s, 3H), 2.81 (q, *J* = 9.1 Hz, 1H), 3.15 (d, *J* = 14.1 Hz, 1H), 3.66 (dd, *J* = 11.3, 3.6 Hz, 1H), 3.91 (s, 2H), 3.97 – 4.24 (m, 8H), 4.30 – 4.58 (m, 5H), 4.65 – 4.73 (m, 5H), 5.13 (s, 1H), 5.17 (d, *J* = 7.2 Hz, 1H), 5.62 – 5.86 (m, 2H), 6.80 (d, *J* = 1.6 Hz, 1H), 6.94 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.07 (dd, *J* = 8.7, 3.7 Hz, 1H), 7.30 (t, *J* =

6.3 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.68 – 7.78 (m, 2H), 7.82 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 1.9 Hz, 1H), 8.29 (dd, J = 7.9, 1.6 Hz, 1H), 8.39 (d, J = 8.4 Hz, 1H), 8.46 (s, 1H), 8.78 – 8.85 (m, 1H), 9.07 (s, 1H).

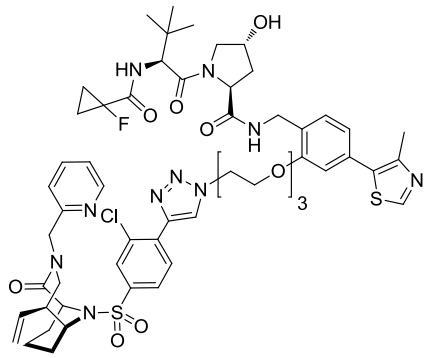
TLC: R_f = 0.10 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.7 min]: R_t = 1.5 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{54}H_{64}ClFN_{10}O_9S_2$ = 1115.40445; found = 1115.40662.

Lab book number(s): MWa261.

(2*S*,4*R*)-*N*-(2-(2-(2-(2-(4-(2-Chloro-4-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropanecarboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{56}H_{68}ClFN_{10}O_{10}S_2$, MW = 1159.78 g / mol

The product was synthesized from azide **58c** (4.8 mg, 7.0 μmol, 1.0 eq.) and alkyne **A4** (3.3 mg, 7.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.3 mg (65 %, 4.6 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.97 (s, 9H), 1.28 (dddd, *J* = 29.0, 13.0, 9.8, 6.1 Hz, 5H), 1.37 – 1.46 (m, 1H), 1.56 (dd, *J* = 14.6, 7.0 Hz, 3H), 2.11 – 2.23 (m, 2H), 2.33 (ddd, *J* = 13.0, 8.3, 4.5 Hz, 1H), 2.55 (s, 3H), 2.80 (q, *J* = 8.8 Hz, 1H), 3.14 (dd, *J* = 14.2, 2.0 Hz, 1H), 3.66 (dt, *J* = 11.5, 3.3 Hz, 3H), 3.71 (dd, *J* = 5.4, 2.8 Hz, 2H), 3.80 – 3.91 (m, 2H), 3.92 – 3.96 (m, 2H), 3.99 – 4.16 (m, 5H), 4.18 (ddd, *J* = 9.3, 5.5, 3.5 Hz, 1H), 4.44 (dd, *J* = 6.1, 3.6 Hz, 2H), 4.54 (d, *J* = 9.1 Hz, 2H), 4.60 – 4.73 (m, 5H), 5.11 – 5.19 (m, 2H), 5.63 (d, *J* = 16.6 Hz, 1H), 5.76 (ddd, *J* = 17.0, 10.1, 8.6 Hz, 1H), 6.85 (d, *J* = 1.6 Hz, 1H), 6.96 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.06 (dd, *J* = 8.6, 3.5 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.66 – 7.71 (m, 1H), 7.74 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 1.9 Hz, 1H), 8.26 (td, *J* = 7.9, 1.7 Hz, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 8.49 (s, 1H), 8.78 – 8.82 (m, 1H), 9.02 (s, 1H).

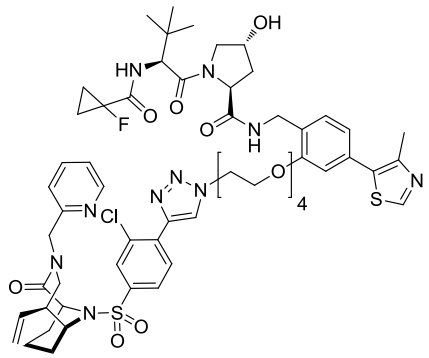
TLC: R_f = 0.09 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.7 min]: R_t = 1.5 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{56}H_{68}ClFN_{10}O_{10}S_2$ = 1159.43066; found = 1159.43337.

Lab book number(s): MWa262.

(2*S*,4*R*)-*N*-(2-(2-(2-(2-(2-(4-(2-Chloro-4-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropanecarboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{58}H_{72}ClFN_{10}O_{11}S_2$, MW = 1203.83 g / mol

The product was synthesized from azide **58d** (5.1 mg, 7.0 μmol, 1.0 eq.) and alkyne **A4** (3.3 mg, 7.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.9 mg (70 %, 4.9 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.97 (s, 9H), 1.19 – 1.39 (m, 5H), 1.50 – 1.66 (m, 3H), 2.17 (t, *J* = 9.9 Hz, 2H), 2.30 (ddd, *J* = 13.0, 8.5, 4.3 Hz, 1H), 2.80 (q, *J* = 8.7 Hz, 1H), 3.14 (d, *J* = 14.1 Hz, 1H), 3.57 – 3.74 (m, 10H), 3.86 (dt, *J* = 5.5, 3.7 Hz, 2H), 3.92 (t, *J* = 5.0 Hz, 2H), 4.00 (d, *J* = 11.4 Hz, 1H), 4.06 – 4.24 (m, 4H), 4.32 – 4.59 (m, 2H), 4.57 – 4.74 (m, 5H), 5.62 – 5.71 (m, 1H), 5.72 – 5.84 (m, 1H), 6.86 (d, *J* = 1.6 Hz, 1H), 6.96 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.09 (dd, *J* = 8.8, 3.6 Hz, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 6.1 Hz, 1H), 7.67 – 7.78 (m, 2H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.91 (d, *J* = 1.9 Hz, 1H), 8.29 (td, *J* = 7.9, 1.6 Hz, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 8.48 (s, 1H), 8.81 (d, *J* = 5.3 Hz, 1H), 9.08 (s, 1H).

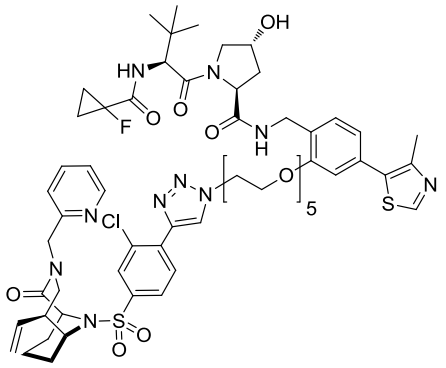
TLC: R_f = 0.09 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.7 min]: R_t = 1.5 min.
96 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{58}H_{72}ClFN_{10}O_{11}S_2$ = 1203.45688; found = 1203.45942.

Lab book number(s): MWa263.

(2*S*,4*R*)-*N*-(2-((14-(4-(2-Chloro-4-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)-1H-1,2,3-triazol-1-yl)-3,6,9,12-tetraoxatetradecyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropanecarboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{60}H_{76}ClFN_{10}O_{12}S_2$, MW = 1247.89 g / mol

The product was synthesized from azide **58e** (5.4 mg, 7.0 μmol, 1.0 eq.) and alkyne **A4** (3.3 mg, 7.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 6.9 mg (79 %, 5.5 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 0.97 (s, 10H), 1.19 – 1.41 (m, 6H), 1.50 – 1.66 (m, 3H), 2.15 – 2.34 (m, 3H), 2.55 (s, 3H), 2.80 (q, *J* = 8.6 Hz, 1H), 3.14 (d, *J* = 14.2 Hz, 1H), 3.51 – 3.69 (m, 11H), 3.71 (td, *J* = 7.0, 6.3, 3.9 Hz, 2H), 3.81 – 3.96 (m, 4H), 3.99 (d, *J* = 11.5 Hz, 1H), 4.12 – 4.25 (m, 1H), 4.44 – 4.57 (m, 4H), 4.58 – 4.68 (m, 4H), 4.71 (d, *J* = 6.0 Hz, 1H), 5.12 (s, 1H), 5.13 – 5.19 (m, 1H), 5.66 (d, *J* = 16.7 Hz, 1H), 5.76 (ddd, *J* = 17.1, 10.1, 8.6 Hz, 1H), 6.87 (d, *J* = 1.6 Hz, 1H), 6.95 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.09 (dd, *J* = 8.8, 3.7 Hz, 1H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 6.0 Hz, 1H), 7.67 – 7.73 (m, 1H), 7.76 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.91 (d, *J*

= 1.9 Hz, 1H), 8.28 (td, *J* = 7.9, 1.6 Hz, 1H), 8.43 (d, *J* = 8.3 Hz, 1H), 8.49 (s, 1H), 8.77 – 8.84 (m, 1H), 9.06 (s, 1H).

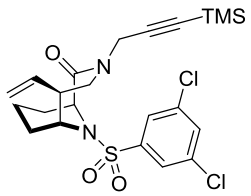
TLC: R_f = 0.09 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.7 min]: R_t = 1.5 min.
98 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{60}H_{76}ClFN_{10}O_{12}S_2$ = 1247.48309; found = 1247.48621.

Lab book number(s): MWa264.

(*1S*, *5S*, *6R*)-10-((3,5-Dichlorophenyl)sulfonyl)-3-(3-(trimethylsilyl)prop-2-yn-1-yl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



$C_{22}H_{28}Cl_2N_2O_3SSi$, MW = 499.52 g / mol

(5*S*)-3-(3-(Trimethylsilyl)prop-2-yn-1-yl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one (1.00 g, 3.44 mmol, 1.0 eq.), 3,5-dichlorobenzenesulfonyl chloride (1.10 g, 4.48 mmol, 1.3 eq.) and DIPEA (1.17 mL, 6.88 mmol, 2.0 eq.) were dissolved in acetonitrile (dry, 100 mL) and stirred for 18 h at room temperature under argon. Brine (300 mL) was added and the mixture was extracted with DCM (3 x 300 mL). The combined organic phases were dried over MgSO4 and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 989 mg (1.98 mmol, 58 %).

Appearance: white foam.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.17 (d, *J* = 0.8 Hz, 9H), 1.05 – 1.42 (m, 3H), 1.54 (dt, *J* = 10.5, 3.1 Hz, 3H), 2.29 (d, *J* = 13.5 Hz, 1H), 2.71 (tt, *J* = 8.9, 4.3 Hz, 1H), 3.28 (dd, *J* = 14.3, 2.0

Hz, 1H), 3.80 (d, *J* = 17.4 Hz, 1H), 3.93 – 4.06 (m, 2H), 4.72 (dt, *J* = 6.1, 1.9 Hz, 1H), 4.83 (d, *J* = 17.4 Hz, 1H), 5.11 – 5.21 (m, 2H), 5.76 – 5.90 (m, 1H), 7.58 (q, *J* = 1.9, 1.3 Hz, 1H), 7.70 (d, *J* = 1.9 Hz, 2H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ = -0.1, 15.5, 26.4, 27.8, 40.1, 49.7, 50.4, 55.1, 57.0, 88.9, 100.4, 117.1, 125.0, 132.8, 136.5, 137.2, 144.1, 169.8.

TLC: R_f = 0.68 (CH:EA = 3:1).

LC-MS: Mass (ESI), calculated = 499.1 $[M+H]^+$, found = 499.0.

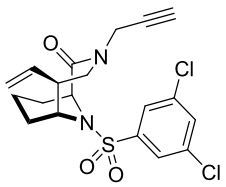
[5-100 % Solvent B, 3.0 min]: R_t = 2.6 min.

[30-100 % Solvent B, 2.6 min]: R_t = 2.1 min.

95 % purity (220 nm).

Lab book number(s): MWa303 / MWa613.

(*1S, 5S, 6R*)-10-((3,5-Dichlorophenyl)sulfonyl)-3-(prop-2-yn-1-yl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



$C_{19}H_{20}Cl_2N_2O_3S$, MW = 427.34 g / mol

(5*S*)-10-((3,5-Dichlorophenyl)sulfonyl)-3-(3-(trimethylsilyl)prop-2-yn-1-yl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one (192 mg, 384 μmol, 1.0 eq.) and potassium carbonate (53 mg, 384 μmol, 1.0 eq) were dissolved in methanol (dry, 20 mL) and the mixture was stirred for 3 h at room temperature. The mixture was concentrated under reduced pressure and the obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 127 mg (77 %, 297 μmol).

Appearance: white solid.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.12 – 1.39 (m, 2H), 1.47 – 1.65 (m, 3H), 2.19 – 2.35 (m, 2H), 2.72 (tdd, *J* = 10.7, 7.7, 1.8 Hz, 1H), 3.21 (dd, *J* = 14.3, 2.0 Hz, 1H), 3.92 (dd, *J* = 17.2, 2.5 Hz, 1H), 4.61 – 4.75 (m, 2H), 5.11 – 5.23 (m, 2H), 5.82 (ddd, *J* = 16.8, 10.1, 8.7 Hz, 1H), 7.57 (q, *J* = 1.8, 1.4 Hz, 1H), 7.68 – 7.72 (m, 2H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 15.42, 26.22, 27.53, 39.31, 49.30, 50.86, 54.93, 56.87, 71.74, 78.56, 117.15, 124.90, 132.75, 136.37, 137.06, 144.00, 169.93.

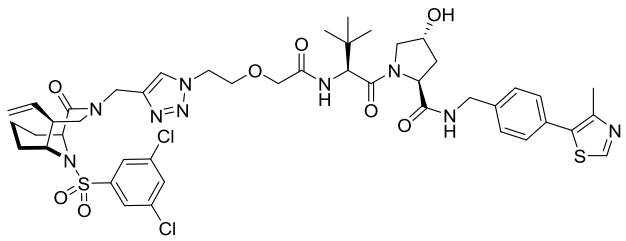
TLC: R_f = 0.41 (CH:EA = 3:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.3 min.
[30-100 % Solvent B, 2.6 min]: R_t = 1.9 min.
98 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{19}H_{20}Cl_2N_2O_3S$ = 427.06445; found = 427.06441.

Lab book number(s): MWa304 / MWa620.

(2*S*,4*R*)-1-((2*S*)-2-(2-(2-(4-(((*1S*, *5S*, *6R*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-5-vinyl-3,10-diazabicyclo[4.3.1]decan-3-yl)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{45}H_{55}Cl_2N_9O_8S_2$, MW = 985.01 g / mol

The product was synthesized from azide **57a** (223 mg, 400 μmol, 1.0 eq.) and alkyne **A5** (171 mg, 400 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 299 mg (76 %, 304 μmol).

Appearance: white solid.

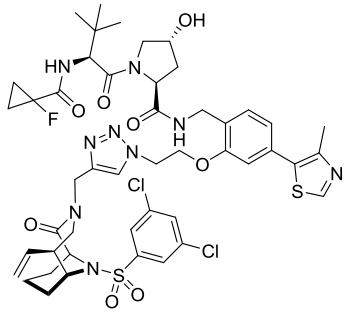
TLC: R_f = 0.12 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.1 min.
[50-100 % Solvent B, 3.0 min]: R_t = 1.3 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{45}H_{55}Cl_2N_9O_8S_2$= 984.30648; found = 984. 30667.

Lab book number(s): MWa412 / MWa624.

(2*S*,4*R*)-*N*-(2-(2-(4-(((1*S*,5*S*,6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-5-vinyl-3,10-diazabicyclo[4.3.1]decan-3-yl)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{47}H_{56}Cl_2FN_9O_8S_2$, MW = 1029.04 g / mol

The product was synthesized from azide **58a** (6.0 mg, 10.0 μmol, 1.0 eq.) and alkyne **A5** (4.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 9.6 mg (93 %, 9.3 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.89 (s, 9H), 1.04 – 1.47 (m, 9H), 2.04 – 2.14 (m, 2H), 2.25 (ddd, *J* = 13.0, 8.4, 4.3 Hz, 1H), 2.43 (s, 3H), 2.56 (q, *J* = 8.8 Hz, 1H), 3.13 – 3.23 (m, 1H), 3.59 (dd, *J* = 11.2, 3.6 Hz, 1H), 3.80 – 4.01 (m, 3H), 4.28 – 4.88 (m, 12H), 4.93 – 5.05 (m, 2H), 5.56 – 5.74 (m, 1H), 6.72 (d, *J* = 1.6 Hz, 1H), 6.90 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.01 (dd, *J* = 8.9, 3.5 Hz, 1H), 7.25 – 7.34 (m, 2H), 7.48 (t, *J* = 1.8 Hz, 1H), 7.58 (d, *J* = 1.9 Hz, 2H), 7.81 (s, 1H), 8.74 (s, 1H).

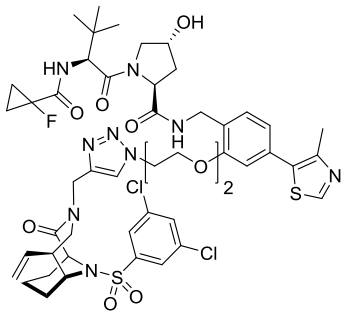
TLC: R_f = 0.14 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 2.6 min]: R_t = 1.8 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{47}H_{56}Cl_2FN_9O_8S_2$= 1028.31271; found = 1028.30930.

Lab book number(s): MWa307.

(2*S*,4*R*)-*N*-(2-(2-(2-(4-(((1*S*,5*S*,6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-5-vinyl-3,10-diazabicyclo[4.3.1]decan-3-yl)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{49}H_{60}Cl_2FN_9O_9S_2$, MW = 1073.09 g / mol

The product was synthesized from azide **58b** (6.5 mg, 10.0 μmol, 1.0 eq.) and alkyne **A5** (4.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 9.6 mg (90 %, 9.0 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.00 (s, 9H), 1.13 – 1.39 (m, 5H), 1.38 – 1.55 (m, 3H), 2.10 – 2.20 (m, 2H), 2.37 (ddd, *J* = 13.2, 8.7, 4.3 Hz, 1H), 2.52 (s, 3H), 2.57 – 2.68 (m, 1H), 3.29 – 3.33 (m, 4H), 3.70 (dd, *J* = 11.1, 3.6 Hz, 1H), 3.80 – 4.08 (m, 7H), 4.11 – 4.19 (m, 2H), 4.40 – 4.66 (m, 9H), 4.79 (d, *J* = 14.9 Hz, 1H), 5.00 – 5.14 (m, 2H), 5.72 (ddd, *J* = 16.7, 10.6, 8.7 Hz, 1H), 6.83 (d, *J* = 1.6 Hz, 1H), 6.92 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.08 (dd, *J* = 8.8, 3.5 Hz, 1H), 7.36 (d, *J* = 7.7 Hz, 1H), 7.43 (t, *J* = 6.0 Hz, 1H), 7.53 (t, *J* = 1.8 Hz, 1H), 7.58 (d, *J* = 1.8 Hz, 2H), 7.76 (s, 1H), 8.87 (s, 1H).

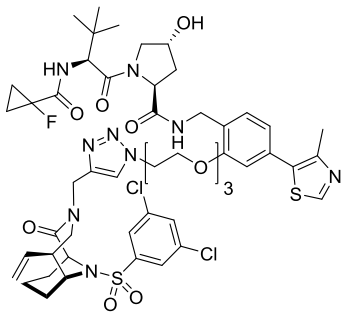
TLC: R_f = 0.13 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 2.6 min]: R_t = 1.9 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{49}H_{60}Cl_2FN_9O_9S_2$= 1072.33893; found = 1072.33752.

Lab book number(s): MWa308.

(2*S*,4*R*)-*N*-(2-(2-(2-(2-(4-(((1*S*,5*S*,6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-5-vinyl-3,10-diazabicyclo[4.3.1]decan-3-yl)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{51}H_{64}Cl_2FN_9O_{10}S_2$, MW = 1117.14 g / mol

The product was synthesized from azide **58c** (6.9 mg, 10.0 μmol, 1.0 eq.) and alkyne **A5** (4.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 11.0 mg (98 %, 9.8 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.99 (s, 9H), 1.24 (dddd, *J* = 16.9, 14.4, 11.4, 7.0 Hz, 7H), 1.43 – 1.57 (m, 3H), 2.20 (dd, *J* = 11.4, 8.0 Hz, 3H), 2.55 (s, 3H), 2.58 – 2.72 (m, 1H), 3.31 (d, *J* = 14.2 Hz, 1H), 3.52 – 3.86 (m, 6H), 3.95 (tdd, *J* = 15.3, 7.9, 3.6 Hz, 6H), 4.09 – 4.31 (m, 1H), 4.44 – 4.80 (m, 10H), 5.03 – 5.09 (m, 1H), 5.11 (s, 1H), 5.65 – 5.84 (m, 1H), 6.90 (d, *J* = 1.7 Hz, 1H), 6.97 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.07 (dd, *J* = 9.0, 3.6 Hz, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 6.0 Hz, 1H), 7.56 (t, *J* = 1.8 Hz, 1H), 7.67 (d, *J* = 1.9 Hz, 2H), 7.77 (s, 1H), 8.98 (s, 1H).

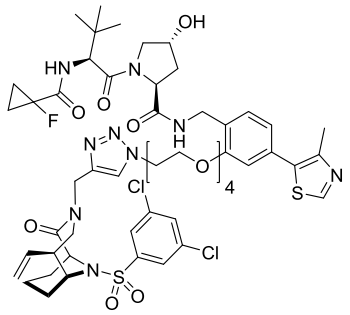
TLC: R_f = 0.12 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 2.6 min]: R_t = 1.9 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{51}H_{64}Cl_2FN_9O_{10}S_2$= 1116.36514; found = 1116.36245.

Lab book number(s): MWa309.

(2*S*,4*R*)-*N*-(2-(2-(2-(2-(2-(4-(((1*S*,5*S*,6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-5-vinyl-3,10-diazabicyclo[4.3.1]decan-3-yl)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{53}H_{68}Cl_2FN_9O_{11}S_2$, MW = 1161.20 g / mol

The product was synthesized from azide **58d** (7.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A5** (4.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 11.5 mg (99 %, 9.9 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.90 (s, 9H), 1.08 – 1.29 (m, 3H), 1.42 (d, *J* = 11.2 Hz, 3H), 2.06 – 2.28 (m, 3H), 2.47 (s, 3H), 2.49 – 2.60 (m, 1H), 3.22 (d, *J* = 14.2 Hz, 1H), 3.44 – 3.73 (m, 10H), 3.72 – 4.00 (m, 5H), 4.14 (d, *J* = 7.6 Hz, 2H), 4.35 – 4.65 (m, 10H), 4.94 – 5.07 (m, 2H), 5.66 (ddd, *J* = 16.6, 10.5, 8.6 Hz, 1H), 6.82 (d, *J* = 1.6 Hz, 1H), 6.89 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.01 (dd, *J* = 9.0, 3.5 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.43 (t, *J* = 6.0 Hz, 1H), 7.48 (t, *J* = 1.8 Hz, 1H), 7.60 (d, *J* = 1.8 Hz, 2H), 7.67 (s, 1H), 8.87 (s, 1H).

TLC: R_f = 0.12 (DCM:MeOH = 10:1).

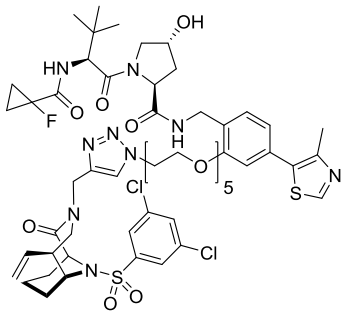
LC-MS: [30-100 % Solvent B, 2.6 min]: R_t = 1.9 min.

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{53}H_{68}Cl_2FN_9O_{11}S_2$= 1160.39136; found = 1160.38912.

Lab book number(s): MWa310.

(2*S*,4*R*)-*N*-(2-((14-(4-(((1*S*,5*S*,6*R*)-10-((3,5-Dichlorophenyl)sulfonyl)-2-oxo-5-vinyl-3,10-diazabicyclo[4.3.1]decan-3-yl)methyl)-1H-1,2,3-triazol-1-yl)-3,6,9,12-tetraoxatetradecyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{55}H_{72}Cl_2FN_9O_{12}S_2$, MW = 1205.25 g / mol

The product was synthesized from azide **58e** (7.8 mg, 10.0 μmol, 1.0 eq.) and alkyne **A5** (4.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.0 mg (82 %, 8.2 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.90 (s, 9H), 1.07 – 1.32 (m, 7H), 1.33 – 1.47 (m, 3H), 2.04 – 2.29 (m, 3H), 2.47 (s, 3H), 2.51 – 2.60 (m, 1H), 3.15 – 3.29 (m, 1H), 3.46 – 3.73 (m, 12H), 3.70 – 4.00 (m, 8H), 4.03 – 4.22 (m, 2H), 4.35 – 4.69 (m, 10H), 4.95 – 5.07 (m, 2H), 5.66 (ddd, *J* = 16.7, 10.4, 8.6 Hz, 1H), 6.82 (d, *J* = 1.6 Hz, 1H), 6.89 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.01 (dd, *J* = 8.9, 3.6 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 6.1 Hz, 1H), 7.48 (t, *J* = 1.8 Hz, 1H), 7.60 (d, *J* = 1.8 Hz, 2H), 7.67 (s, 1H), 8.89 (s, 1H).

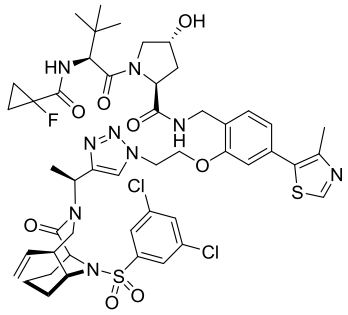
TLC: R_f = 0.12 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 2.6 min]: R_t = 1.9 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{55}H_{72}Cl_2FN_9O_{12}S_2$= 1204.41757; found = 1204.41453.

Lab book number(s): MWa311.

(2*S*,4*R*)-*N*-(2-(2-(4-((*S*)-1-((1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-2-oxo-5-vinyl-3,10-diazabicyclo[4.3.1]decan-3-yl)ethyl)-1H-1,2,3-triazol-1-yl)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{48}H_{58}Cl_2FN_9O_8S_2$, MW = 1043.07 g / mol

The product was synthesized from azide **58a** (6.0 mg, 10.0 μmol, 1.0 eq.) and alkyne **A6** (4.4 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 7.2 mg (69 %, 6.9 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.87 (s, 9H), 1.07 – 1.34 (m, 6H), 1.38 – 1.57 (m, 7H), 2.05 – 2.24 (m, 2H), 2.28 (ddd, *J* = 13.3, 8.8, 4.4 Hz, 1H), 2.44 (s, 3H), 3.03 (d, *J* = 14.7 Hz, 1H), 3.42 (dd, *J* = 14.8, 10.7 Hz, 1H), 3.60 (dd, *J* = 11.2, 3.6 Hz, 1H), 3.84 – 3.96 (m, 2H), 4.23 – 4.67 (m, 9H), 4.82 (dtd, *J* = 14.9, 10.2, 4.7 Hz, 2H), 4.98 – 5.10 (m, 2H), 5.57 – 5.72 (m, 1H), 6.03 (q, *J* = 6.9 Hz, 1H), 6.74 (d, *J* = 1.6 Hz, 1H), 6.90 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.01 (dd, *J* = 9.1, 3.5 Hz, 1H), 7.23 (t, *J* = 5.9 Hz, 1H), 7.30 (d, *J* = 7.7 Hz, 1H), 7.49 (t, *J* = 1.8 Hz, 1H), 7.57 (d, *J* = 1.9 Hz, 2H), 7.80 (s, 1H), 8.79 (s, 1H).

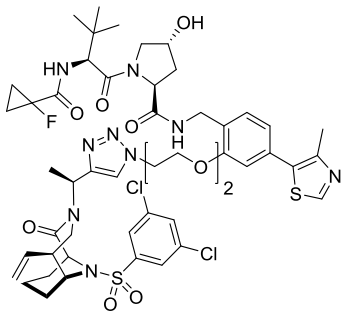
TLC: R_f = 0.15 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.2 min]: R_t = 1.3 min.
97 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{48}H_{58}Cl_2FN_9O_8S_2$= 1042.3284; found = 1042.3305.

Lab book number(s): MWa295.

(2*S*,4*R*)-*N*-(2-(2-(2-(4-((*S*)-1-((1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-2-oxo-5-vinyl-3,10-diazabicyclo[4.3.1]decan-3-yl)ethyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{50}H_{62}Cl_2FN_9O_9S_2$, MW = 1087.12 g / mol

The product was synthesized from azide **58b** (6.5 mg, 10.0 μmol, 1.0 eq.) and alkyne **A6** (4.4 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 7.0 mg (64 %, 6.4 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.93 (s, 9H), 1.06 – 1.29 (m, 7H), 1.41 – 1.55 (m, 6H), 2.03 – 2.10 (m, 1H), 2.16 (d, *J* = 13.6 Hz, 1H), 2.28 (ddd, *J* = 13.2, 8.7, 4.3 Hz, 1H), 2.43 (d, *J* = 1.2 Hz, 3H), 2.98 (d, *J* = 14.7 Hz, 1H), 3.35 (dd, *J* = 14.8, 10.7 Hz, 1H), 3.62 (dd, *J* = 11.4, 3.7 Hz, 1H),

3.70 – 3.85 (m, 2H), 3.84 – 4.02 (m, 4H), 4.08 (t, J = 4.4 Hz, 2H), 4.46 (dddd, J = 52.5, 27.4, 13.4, 6.7 Hz, 7H), 4.94 – 5.11 (m, 2H), 5.63 (dt, J = 16.6, 9.5 Hz, 1H), 5.97 (q, J = 6.9 Hz, 1H), 6.76 (d, J = 1.6 Hz, 1H), 6.80 (dd, J = 7.5, 1.5 Hz, 1H), 6.95 – 7.03 (m, 1H), 7.27 (d, J = 7.7 Hz, 1H), 7.33 (t, J = 6.0 Hz, 1H), 7.40 – 7.50 (m, 3H), 7.59 (s, 1H), 8.86 (s, 1H).

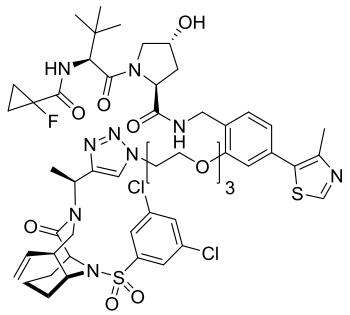
TLC: R_f = 0.14 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.2 min]: R_t = 1.3 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{50}H_{62}Cl_2FN_9O_9S_2$= 1086.3546; found = 1086.3564.

Lab book number(s): MWa296.

(2*S*,4*R*)-*N*-(2-(2-(2-(2-(4-((*S*)-1-((1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-2-oxo-5-vinyl-3,10-diazabicyclo[4.3.1]decan-3-yl)ethyl)-1H-1,2,3-triazol-1-yl)ethoxy) ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{52}H_{66}Cl_2FN_9O_{10}S_2$, MW = 1131.17 g / mol

The product was synthesized from azide **58c** (6.9 mg, 10.0 μmol, 1.0 eq.) and alkyne **A6** (4.4 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 7.0 mg (64 %, 6.4 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.91 (s, 9H), 1.06 – 1.30 (m, 7H), 1.49 (dd, *J* = 16.0, 9.4 Hz, 6H), 2.04 – 2.26 (m, 3H), 2.47 (s, 3H), 3.02 (d, *J* = 14.6 Hz, 1H), 3.39 (dd, *J* = 14.8, 10.7 Hz, 1H), 3.48 – 3.70 (m, 5H), 3.69 – 3.97 (m, 5H), 4.00 – 4.24 (m, 2H), 4.30 – 4.65 (m, 9H), 4.98 – 5.09 (m, 2H), 5.65 (dt, *J* = 17.0, 9.4 Hz, 1H), 6.01 (q, *J* = 6.9 Hz, 1H), 6.82 (d, *J* = 1.6 Hz, 1H), 6.88 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.01 (dd, *J* = 9.0, 3.6 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 6.1 Hz, 1H), 7.48 (t, *J* = 1.8 Hz, 1H), 7.53 – 7.62 (m, 3H), 8.84 (s, 1H).

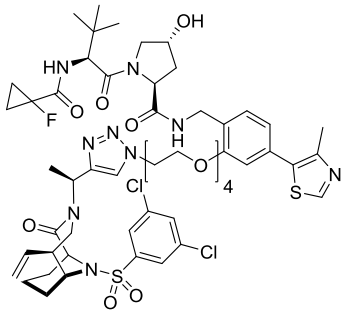
TLC: R_f = 0.14 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.2 min]: R_t = 1.4 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{52}H_{66}Cl_2FN_9O_{10}S_2$= 1130.3808; found = 1130.3822.

Lab book number(s): MWa297.

(2*S*,4*R*)-*N*-(2-(2-(2-(2-(2-(4-((*S*)-1-((1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-2-oxo-5-vinyl-3,10-diazabicyclo[4.3.1]decan-3-yl)ethyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{54}H_{70}Cl_2FN_9O_{11}S_2$, MW = 1175.22 g / mol

The product was synthesized from azide **58d** (7.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A6** (4.4 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 8.5 mg (72 %, 7.2 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.90 (s, 9H), 1.07 – 1.30 (m, 7H), 1.42 – 1.57 (m, 6H), 2.02 – 2.16 (m, 1H), 2.15 – 2.29 (m, 2H), 2.47 (s, 3H), 2.99 (d, *J* = 14.7 Hz, 1H), 3.29 – 3.43 (m, 1H), 3.46 – 3.72 (m, 9H), 3.74 – 3.97 (m, 6H), 4.05 – 4.19 (m, *J* = 4.5 Hz, 2H), 4.34 – 4.69 (m, 9H), 4.95 – 5.11 (m, 2H), 5.55 – 5.74 (m, 1H), 6.02 (q, *J* = 6.9 Hz, 1H), 6.81 (d, *J* = 1.6 Hz, 1H), 6.88 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.02 (dd, *J* = 8.9, 3.6 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 6.0 Hz, 1H), 7.48 (t, *J* = 1.8 Hz, 1H), 7.55 – 7.62 (m, 3H), 8.90 (s, 1H).

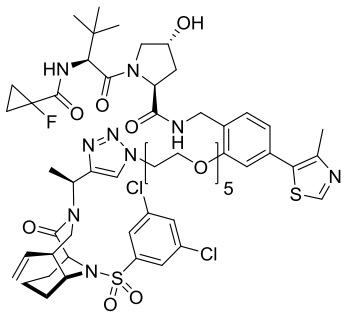
TLC: R_f = 0.13 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.2 min]: R_t = 1.4 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{54}H_{70}Cl_2FN_9O_{11}S_2$= 1174.4070; found = 1174.4089.

Lab book number(s): MWa298.

(2*S*,4*R*)-*N*-(2-((14-(4-((*S*)-1-((1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-2-oxo-5-vinyl-3,10-diazabicyclo[4.3.1]decan-3-yl)ethyl)-1H-1,2,3-triazol-1-yl)-3,6,9,12-tetraoxatetradecyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{56}H_{74}Cl_2FN_9O_{12}S_2$, MW = 1219.28 g / mol

The product was synthesized from azide **58e** (7.8 mg, 10.0 μmol, 1.0 eq.) and alkyne **A6** (4.4 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 7.6 mg (62 %, 6.2 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.89 (s, 9H), 1.07 – 1.31 (m, 7H), 1.41 – 1.58 (m, 6H), 2.10 (s, 1H), 2.15 – 2.30 (m, 2H), 2.47 (s, 3H), 2.98 (d, J = 14.6 Hz, 1H), 3.40 (dd, J = 14.8, 10.7 Hz, 1H), 3.48 – 3.73 (m, 13H), 3.74 – 3.95 (m, 6H), 4.13 (q, J = 5.0 Hz, 2H), 4.32 – 4.68 (m, 9H), 4.96 – 5.10 (m, 2H), 5.55 – 5.73 (m, 1H), 6.03 (q, J = 6.9 Hz, 1H), 6.82 (d, J = 1.6 Hz, 1H), 6.89 (dd, J = 7.7, 1.6 Hz, 1H), 7.03 (dd, J = 8.9, 3.6 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 7.42 (t, J = 6.0 Hz, 1H), 7.49 (t, J = 1.8 Hz, 1H), 7.55 – 7.62 (m, 3H), 8.86 (s, 1H).

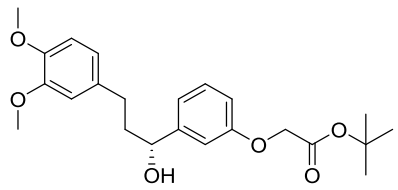
TLC: R_f = 0.13 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.2 min]: R_t = 1.4 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{56}H_{74}Cl_2FN_9O_{12}S_2$= 1218.4332; found = 1218.4350.

Lab book number(s): MWa299

***tert*-Butyl (*R*)-2-(3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenoxy)acetate**



$C_{23}H_{30}O_6$, MW = 402.49 g / mol

(*R*)-3-(3-(3,4-Dimethoxyphenyl)-1-hydroxypropyl)phenol (AV497, 500 mg, 1.73 mmol, 1.0 eq.) and potassium carbonate (2.4 g, 17.3 mmol, 10.0 eq.) were mixed in acetone (10 mL). *tert*-Butyl 2-bromoacetate (405 mg, 2.08 mmol, 1.2 eq.) was added and the mixture was stirred for 18 h at room temperature. The solution was concentrated under reduced pressure. Water (50 mL) and DCM (50 mL) was added. The organic phase was separated, dried over MgSO4 and concentrated under reduced pressure.

Yield: 690 mg (99 %, 1.71 mmol).

Appearance: slightly yellow oil.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.41 (s, 9H), 1.81 – 2.13 (m, 3H), 2.45 – 2.70 (m, 2H), 3.78 (d, *J* = 2.0 Hz, 6H), 4.44 (s, 2H), 4.58 (t, *J* = 6.6 Hz, 1H), 6.60 – 6.67 (m, 2H), 6.68 – 6.77 (m, 2H), 6.82 – 6.93 (m, 2H), 7.13 – 7.22 (m, 1H).

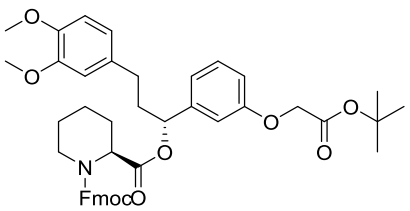
^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 28.0, 31.6, 40.6, 55.8, 55.9, 65.7, 73.7, 82.3, 111.3, 111.8, 112.2, 113.6, 119.1, 120.2, 129.5, 134.3, 146.5, 147.2, 148.9, 158.1, 168.0.

TLC: R_f = 0.50 (CH:EA = 1:1).

LC-MS: Mass (ESI), calculated = 420.2 $[M+NH_4]^+$, found = 420.4.

Lab book number(s): MWa125.

1-((9H-Fluoren-9-yl)methyl) 2-((*R*)-1-(3-(2-(*tert*-butoxy)-2-oxoethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl) (*S*)-piperidine-1,2-dicarboxylate



$C_{44}H_{49}NO_9$, MW = 735.87 g / mol

(*S*)-1-(((9H-Fluoren-9-yl)methoxy)carbonyl)piperidine-2-carboxylic acid (580 mg, 1.65 mmol, 1.0 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (380 mg, 1.98 mmol, 1.2 eq.) and 4-dimethylaminopyridine (61 mg, 0.50 mmol, 0.3 eq.) were cooled to 0 °C under Argon. DCM (dry, 5 mL) was added and the mixture was stirred for 30 min. *tert*-Butyl (*R*)-2-(3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenoxy)acetate (665 mg, 1.65 mmol, 1.0 eq.) in DCM (dry, 10 mL) was added and the mixture was stirred for 15 min at 0 °C followed by 18 h at room temperature. The solution was diluted with brine (100 mL) and extracted with DCM (3 x 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by column chromatography (50 g SiO_2, CH:EA = 3:1).

Yield: 1.20 g (98 %, 1.63 mmol).

Appearance: white foam.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 1.47 (s, 9H), 1.60 – 1.83 (m, 4H), 2.04 (q, *J* = 8.2, 7.2 Hz, 1H), 2.13 – 2.38 (m, 2H), 2.41 – 2.65 (m, 2H), 2.91 – 3.23 (m, 1H), 3.82 (d, *J* = 7.1 Hz, 6H), 4.02 – 4.57 (m, 6H), 4.77 – 5.10 (m, 1H), 5.76 (s, 1H), 6.61 (d, *J* = 12.6 Hz, 2H), 6.76 (dd, *J* = 13.2, 5.5 Hz, 2H), 6.90 (d, *J* = 2.3 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 7.34 (dddd, *J* = 51.5, 25.3, 14.7, 7.6 Hz, 6H), 7.59 (t, *J* = 6.9 Hz, 1H), 7.74 (dd, *J* = 15.3, 7.5 Hz, 2H).

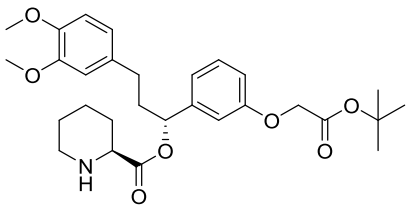
^{13}**C-NMR** (75 MHz, Chloroform-*d*): δ = 20.8, 20.9, 24.7, 24.9, 26.9, 27.2, 28.1, 31.2, 38.1, 42.0, 42.1, 47.3, 55.9, 56.0, 65.8, 65.9, 67.9, 76.3, 82.4, 111.5, 111.8, 113.4, 113.5, 114.1, 119.8, 120.1, 120.2, 125.2, 127.2, 127.8, 129.8, 133.5, 133.6, 141.4, 144.0, 147.4, 149.0, 158.2, 168.0, 171.0.

TLC: R_f = 0.35 (CH:EA = 3:1).

LC-MS: Mass (ESI), calculated = 753.3 $[M+NH_4]^+$, found = 753.7.

Lab book number(s): MWa127.

(*R*)-1-(3-(2-(*tert*-Butoxy)-2-oxoethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl (*S*)-piperidine-2-carboxylate



$C_{29}H_{39}NO_7$, MW = 513.63 g / mol

1-((9H-Fluoren-9-yl)methyl) 2-((*R*)-1-(3-(2-(*tert*-butoxy)-2-oxoethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl) (*S*)-piperidine-1,2-dicarboxylate (1.20 g, 1.63 mmol, 1.0 eq.) and 4-methylpiperidine (789 μL, 6.68 mmol, 4.1 eq) were dissolved in DCM (7.1 mL) and the mixture was stirred for 18 h at room temperature. The solution was diluted with DCM (50 mL) and washed with NH_4Cl (sat., aq, 3 x 20 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by column chromatography (50 g SiO_2, DCM:MeOH 100:1, 1 % TEA).

Yield: 724 mg (86 %, 1.41 mmol).

Appearance: colorless oil.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 1.52 (s, 9H), 1.76 – 1.90 (m, 3H), 2.00 – 2.16 (m, 2H), 2.20 – 2.36 (m, 1H), 2.48 – 2.76 (m, 3H), 3.11 (dt, *J* = 11.8, 3.6 Hz, 1H), 3.41 (dd, *J* = 9.7, 3.2 Hz, 1H), 3.51 (s, 1H), 3.89 (d, *J* = 2.7 Hz, 6H), 4.54 (s, 2H), 5.81 (dd, *J* = 7.9, 5.7 Hz, 1H), 6.67 – 6.74 (m, 2H), 6.79 – 6.87 (m, 2H), 6.93 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.98 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.28 – 7.32 (m, 1H).

^{13}**C-NMR** (75 MHz, Chloroform-*d*): δ = 24.3, 25.9, 28.2, 29.4, 31.5, 38.1, 45.8, 56.0, 56.1, 58.9, 65.9, 75.6, 82.5, 111.5, 111.9, 113.3, 114.0, 119.9, 120.3, 129.7, 133.8, 142.1, 147.5, 149.1, 158.2, 168.0, 172.9.

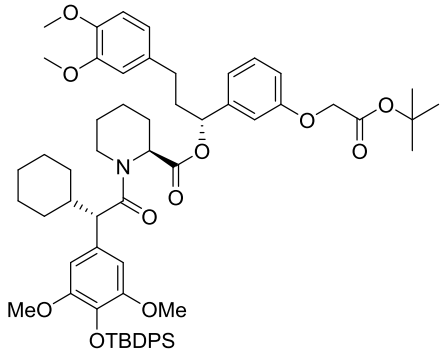
TLC: R_f = 0.50 (EA, 3 % TEA).

R_f = 0.17 (DCM:MeOH = 50:1, 1 % TEA).

LC-MS: Mass (ESI), calculated = 514.3 $[M+H]^+$, found = 514.4.

Lab book number(s): MWa131.

(*R*)-1-(3-(2-(*tert*-Butoxy)-2-oxoethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl (*S*)-1-((*S*)-2-(4-((*tert*-butyldiphenylsilyl)oxy)-3,5-dimethoxyphenyl)-2-cyclohexylacetyl)piperidine-2-carboxylate



$C_{61}H_{77}NO_{11}Si$, MW = 1028.37 g / mol

(*S*)-2-(4-((*tert*-Butyldiphenylsilyl)oxy)-3,5-dimethoxyphenyl)-2-cyclohexylacetic acid (MBA269, 362 mg, 0.68 mmol, 1.0 eq.) and HATU (176 mg, 0.75 mmol, 1.1 eq.) were dissolved in DCM (2 mL) and DMF (3mL). The mixture was cooled to 0 °C and DIPEA (356 μL, 2.04 mmol, 3.0 eq.) were added. The mixture was stirred for 15 min at 0 °C. (*R*)-1-(3-(2-(*tert*-Butoxy)-2-oxoethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl (*S*)-piperidine-2-carboxylate (350 mg, 0.68 mmol, 1.0 eq.) in DCM (4 mL) was added and the mixture was stirred for 18 h at room temperature. Additional HATU (1.1 eq.) and DIPEA (3.0 eq.) were added and the mixture was stirred for 5 h at room temperature. The solution was concentrated under reduced pressure and the obtained product was purified by column chromatography (40 g SiO_2, CH:EA 3:1).

Yield: 643 mg (92 %, 0.63 mmol).

Appearance: white foam.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.47 – 0.76 (m, 1H), 0.87 (t, *J* = 11.0 Hz, 1H), 1.06 – 1.15 (m, 14H), 1.19 – 1.35 (m, 3H), 1.48 (d, *J* = 1.9 Hz, 9H), 1.53 – 1.71 (m, 7H), 1.79 – 2.11 (m, 5H), 2.18 – 2.34 (m, 1H), 2.36 – 2.62 (m, 2H), 3.27 (s, 3H), 3.43 (d, *J* = 10.7 Hz, 3H), 3.79 – 3.89 (m, 6H), 4.50 (d, *J* = 1.8 Hz, 2H), 5.55 – 5.82 (m, 1H), 6.24 (d, *J* = 18.2 Hz, 2H), 6.47 – 7.01 (m, 6H), 7.08 – 7.45 (m, 10H), 7.60 – 7.73 (m, 5H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 20.2, 21.2, 25.6, 26.1, 26.3, 26.4, 26.4, 26.7, 27.1, 28.2, 30.6, 31.1, 33.0, 38.2, 41.4, 43.7, 55.3, 55.6, 55.8, 56.1, 65.8, 65.9, 75.7, 82.4, 105.7, 111.5, 111.8, 113.4, 113.9, 119.5, 120.4, 120.8, 127.0, 129.1, 129.2, 129.8, 130.5, 133.3, 133.8, 134.4, 135.4, 142.0, 147.4, 149.1, 151.0, 158.0, 168.1, 170.5, 172.6.

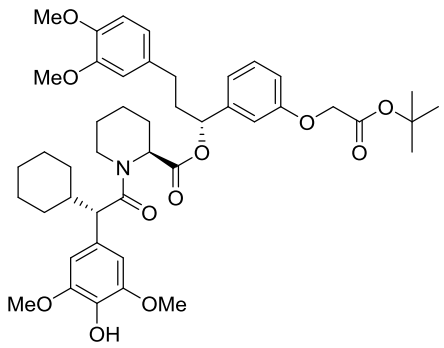
TLC: R_f = 0.78 (CH:EA = 1:1).
R_f = 0.35 (CH:EA = 3:1).

LC-MS: Mass (ESI), calculated = 1050.5 $[M+H]^+$, found = 1050.6.

HPLC: [80-100 % Solvent B, 20 min]: R_t = 19.7 min.
75 % purity (220 nm).

Lab book number(s): MWa132.

(*R*)-1-(3-(2-(*tert*-Butoxy)-2-oxoethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(4-hydroxy-3,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{45}H_{59}NO_{11}$, MW = 789.96 g / mol

(*R*)-1-(3-(2-(*tert*-Butoxy)-2-oxoethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl (*S*)-1-((*S*)-2-(4-((*tert*-butyldiphenylsilyl)oxy)-3,5-dimethoxyphenyl)-2-cyclohexylacetyl) piperidine-2-carboxylate (643 mg, 0.63 mmol, 1.0 eq.) was dissolved in THF (dry, 11 mL) and cooled to 0 °C under argon. TBAF (1 M in THF, 0.6 mL) was added and the mixture was stirred for 5 h at 0 °C to room temperature. The reaction was quenched with water (15 mL) and the mixture was extracted with DCM (3 x 40 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by column chromatography (50 g SiO_2, CH:EA = 2:1).

Yield: 420 mg (84 %, 0.53 mmol).

Appearance: white foam.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 1.47 (s, 9H), 1.56 – 1.70 (m, 10H), 1.76 – 1.98 (m, 4H), 2.03 (s, 2H), 2.25 – 2.31 (m, 1H), 2.32 – 2.48 (m, 2H), 2.49 – 2.63 (m, 1H), 2.75 (td, *J* = 13.4, 3.0 Hz, 1H), 3.31 – 3.37 (m, 1H), 3.67 (d, *J* = 9.2 Hz, 1H), 3.82 – 3.88 (m, 12H), 4.48 (s, 2H), 5.45 (d, *J* = 3.5 Hz, 2H), 5.58 (dd, *J* = 7.9, 5.7 Hz, 1H), 6.47 (s, 2H), 6.58 – 6.70 (m, 3H), 6.69 – 6.86 (m, 3H), 7.10 (t, *J* = 7.9 Hz, 1H).

^{13}**C-NMR** (75 MHz, Chloroform-*d*): δ = 21.1, 25.7, 26.4, 26.7, 26.9, 28.2, 30.8, 31.1, 33.0, 38.1, 41.4, 43.7, 52.2, 55.0, 56.0, 56.4, 56.7, 60.5, 65.8, 75.7, 82.4, 105.7, 111.4, 112.0, 113.4, 113.7, 119.5, 120.4, 129.1, 129.7, 133.7, 133.8, 141.9, 147.1, 147.4, 149.0, 158.0, 168.1, 170.7, 172.6.

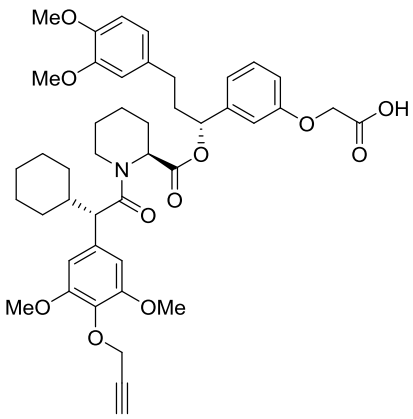
TLC: R_f = 0.42 (CH:EA = 2:1).

LC-MS: Mass (ESI), calculated = 790.4 $[M+H]^+$, found = 790.4.

HPLC: [0-100 % Solvent B, 20 min]: R_t = 19.8 min.
[70-100 % Solvent B, 20 min]: R_t = 7.1 min.
81 % purity (220 nm).

Lab book number(s): MWa134.

2-(3-((*R*)-1-(((*S*)-1-((*S*)-2-Cyclohexyl-2-(3,5-dimethoxy-4-(prop-2-yn-1-yloxy)phenyl) acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid



$C_{44}H_{53}NO_{11}$, MW = 771.90 g / mol

(*R*)-1-(3-(2-(*tert*-Butoxy)-2-oxoethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(4-hydroxy-3,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate (420 mg, 0.53 mmol, 1.0 eq.), 3-bromoprop-1-yne (76 mg, 0.64 mmol, 1.2 eq.) and potassium carbonate (732 mg, 5.30 mmol, 10.0 eq.) were stirred in acetone (5 mL) for 64 h at room temperature. The solution was filtered and concentrated under reduced pressure.

Appearance: colorless oil.
TLC: R_f = 0.23 (CH:EA = 3:1).
LC-MS: Mass (ESI), calculated = 828.4 $[M+H]^+$, found = 828.5.

To crude (*R*)-1-(3-(2-(*tert*-butoxy)-2-oxoethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,5-dimethoxy-4-(prop-2-yn-1-yloxy)phenyl)acetyl)piperidine-2-carboxylate in DCM

(12 mL) TFA (5 mL) was added and the mixture was stirred for 1 h at room temperature. The solution was diluted with NH_4Cl (sat., aq, 20 mL) and extracted with DCM (3 x 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by column chromatography (50 g SiO_2, CH:EA = 2:1, 1 % HCOOH)

Yield: 220 mg (54 % o2s, 0.29 mmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 1.05 – 1.17 (m, 2H), 1.30 – 1.53 (m, 2H), 1.55 – 2.00 (m, 10H), 2.02 – 2.15 (m, 2H), 2.32 (d, *J* = 12.7 Hz, 1H), 2.44 – 2.66 (m, 2H), 2.86 (td, *J* = 13.4, 3.0 Hz, 1H), 3.35 (d, *J* = 9.3 Hz, 1H), 3.61 (s, 5H), 3.85 (d, *J* = 3.4 Hz, 9H), 4.03 – 4.17 (m, 1H), 4.63 (dd, *J* = 10.5, 3.6 Hz, 4H), 5.41 – 5.56 (m, 2H), 6.34 (s, 2H), 6.66 (dd, *J* = 9.2, 2.3 Hz, 4H), 6.74 – 6.84 (m, 2H), 7.16 (t, *J* = 7.8 Hz, 1H), 8.02 (s, 1H).

^{13}**C-NMR** (75 MHz, Chloroform-*d*): δ = 21.0, 25.5, 26.3, 26.7, 27.3, 30.8, 31.5, 33.0, 38.3, 41.2, 43.7, 52.5, 55.4, 56.1, 56.2, 56.6, 60.1, 65.6, 74.9, 76.3, 79.7, 106.0, 110.2, 111.5, 111.9, 115.3, 119.7, 120.4, 129.7, 133.5, 133.6, 134.7, 142.5, 147.5, 149.1, 153.3, 158.0, 170.1, 171.4, 173.2.

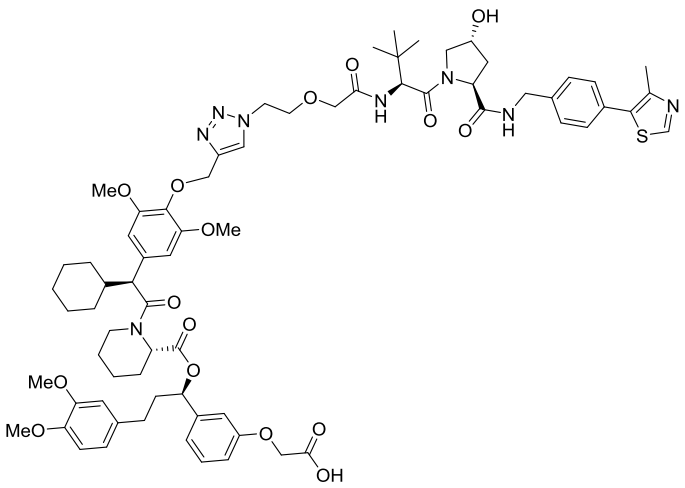
TLC: R_f = 0.40 (CH:EA = 1:1, 1 % HCOOH).

HPLC: [0-100 % Solvent B, 20 min]: R_t = 18.1 min.
[50-100 % Solvent B, 20 min]: R_t = 10.7 min.
96 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{44}H_{53}NO_{11}$ = 772.36914; found = 772.36891.

Lab book number(s): MWa136 + MWa138.

2-(3-((*R*)-1-(((*S*)-1-((*S*)-2-Cyclohexyl-2-(4-((1-(2-(2-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid



$C_{70}H_{88}N_8O_{16}S$, MW = 1329.57 g / mol

The product was synthesized from azide **57a** (8.4 mg, 15.0 μmol, 1.0 eq.) and alkyne **A8** (11.6 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 14.5 mg (73 %, 10.9 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.74 (d, *J* = 8.7 Hz, 1H), 0.96 (s, 10H), 1.05 – 1.18 (m, 2H), 1.22 – 1.37 (m, 4H), 1.56 – 1.80 (m, 4H), 1.85 (d, *J* = 13.1 Hz, 1H), 1.87 – 2.20 (m, 4H), 2.19 – 2.40 (m, 2H), 2.41 – 2.52 (m, 1H), 2.53 (s, 3H), 2.54 – 2.66 (m, 1H), 2.79 – 2.97 (m, 1H), 3.38 (d, *J* = 9.7 Hz, 1H), 3.53 (s, 6H), 3.62 – 3.81 (m, 4H), 3.83 (d, *J* = 1.3 Hz, 7H), 3.86 – 4.19 (m, 4H), 4.30 (dd, *J* = 15.3, 5.2 Hz, 1H), 4.47 (s, 3H), 4.53 – 4.70 (m, 4H), 5.07 (s, 2H), 5.39 – 5.52 (m, 2H), 6.33 (s, 2H), 6.58 (s, 1H), 6.65 (dt, *J* = 4.0, 1.9 Hz, 2H), 6.68 – 6.82 (m, 3H), 7.14 (t, *J* = 7.9 Hz, 1H), 7.31 – 7.37 (m, 3H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.53 (t, *J* = 5.9 Hz, 1H), 7.81 (s, 1H), 9.19 (s, 1H).

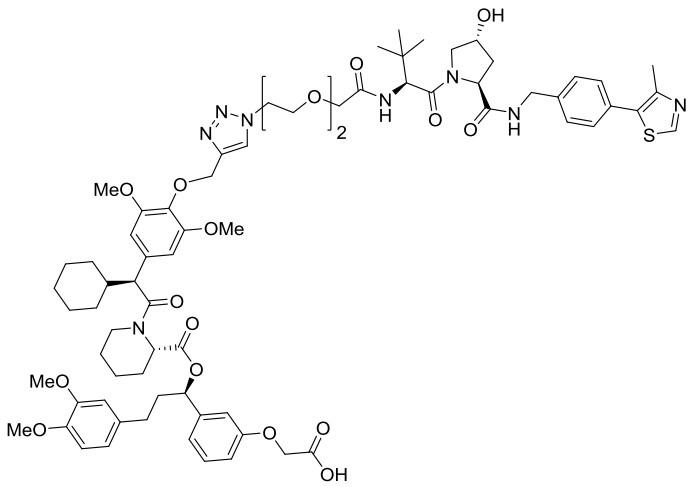
TLC: R_f = 0.11 (DCM:MeOH = 10:1, 1 % HCOOH).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 1.9 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+2H]^{2+}$ calculated for $C_{70}H_{88}N_8O_{16}S$ =665.30923; found = 665.30995.

Lab book number(s): MWa207.

2-(3-((*R*)-1-(((*S*)-1-((*S*)-2-Cyclohexyl-2-(4-((1-(2-(2-(2-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid



$C_{72}H_{92}N_8O_{17}S$, MW = 1373.63 g / mol

The product was synthesized from azide **57b** (9.0 mg, 15.0 μmol, 1.0 eq.) and alkyne **A8** (11.6 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 14.0 mg (68 %, 10.2 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.76 (d, *J* = 9.6 Hz, 1H), 1.04 (s, 10H), 1.10 – 1.18 (m, 2H), 1.31 (d, *J* = 11.1 Hz, 4H), 1.59 – 2.19 (m, 12H), 2.35 (d, *J* = 13.5 Hz, 1H), 2.46 – 2.68 (m, 5H), 2.98 (d, *J* = 10.0 Hz, 1H), 3.41 (d, *J* = 9.6 Hz, 1H), 3.55 (s, 5H), 3.57 – 3.81 (m, 8H), 3.85 (d, *J* = 2.7 Hz,

9H), 3.87 – 4.00 (m, 4H), 4.09 – 4.22 (m, 2H), 4.42 (td, *J* = 14.4, 13.8, 8.3 Hz, 4H), 4.66 (d, *J* = 27.3 Hz, 4H), 5.05 (d, *J* = 5.9 Hz, 2H), 5.48 (d, *J* = 4.1 Hz, 2H), 6.39 (d, *J* = 13.2 Hz, 2H), 6.63 – 6.68 (m, 5H), 6.75 – 6.83 (m, 4H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 1.7 Hz, 4H), 7.63 (t, *J* = 6.0 Hz, 1H), 7.71 (d, *J* = 9.7 Hz, 1H), 8.46 (s, 1H), 9.20 (s, 1H).

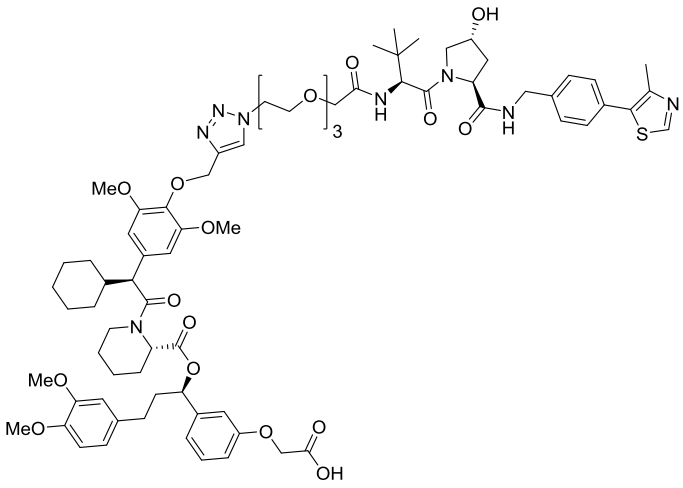
TLC: R_f = 0.11 (DCM:MeOH = 10:1, 1 % HCOOH).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 1.9 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+2H]^{2+}$ calculated for $C_{72}H_{92}N_8O_{17}S$ =687.32233; found = 687.32312.

Lab book number(s): MWa208.

2-(3-((*R*)-1-(((*S*)-1-((*S*)-2-Cyclohexyl-2-(4-((1-((*S*)-13-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-14,14-dimethyl-11-oxo-3,6,9-trioxa-12-azapentadecyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid



$C_{74}H_{96}N_8O_{18}S$, MW = 1417.68 g / mol

The product was synthesized from azide **57c** (9.7 mg, 15.0 μmol, 1.0 eq.) and alkyne **A8** (11.6 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 11.7 mg (55 %, 8.3 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.74 (d, *J* = 12.1 Hz, 1H), 0.98 (d, *J* = 1.9 Hz, 10H), 1.13 (q, *J* = 9.3, 8.7 Hz, 2H), 1.24 – 1.35 (m, 5H), 1.52 – 1.77 (m, 6H), 1.88 (d, *J* = 11.3 Hz, 2H), 1.95 – 2.13 (m, 3H), 2.23 – 2.36 (m, 2H), 2.47 (t, *J* = 7.2 Hz, 1H), 2.52 (s, 3H), 2.52 – 2.62 (m, 1H), 2.81 – 2.88 (m, 1H), 3.37 (d, *J* = 9.8 Hz, 1H), 3.58 (d, *J* = 1.4 Hz, 6H), 3.58 – 3.66 (m, 6H), 3.78 (s, 1H), 3.83 (s, 4H), 3.84 (d, *J* = 1.4 Hz, 6H), 3.85 (d, *J* = 2.2 Hz, 1H), 3.95 – 4.03 (m, 3H), 4.31 (dd, *J* = 15.1, 5.5 Hz, 1H), 4.39 (s, 1H), 4.42 – 4.52 (m, 2H), 4.55 (dd, *J* = 15.6, 7.0 Hz, 2H), 4.58 – 4.62 (m, 3H), 5.02 (s, 2H), 5.47 (d, *J* = 4.7 Hz, 1H), 5.51 (dd, *J* = 8.4, 4.9 Hz, 1H), 6.39 (d, *J* = 1.4 Hz, 2H), 6.60 – 6.68 (m, 4H), 6.72 – 6.79 (m, 2H), 7.13 (t, *J* = 8.0 Hz, 1H), 7.33 (s, 3H), 7.38 (d, *J* = 9.0 Hz, 1H), 7.42 – 7.46 (m, 1H), 7.90 (s, 1H), 8.83 (s, 1H).

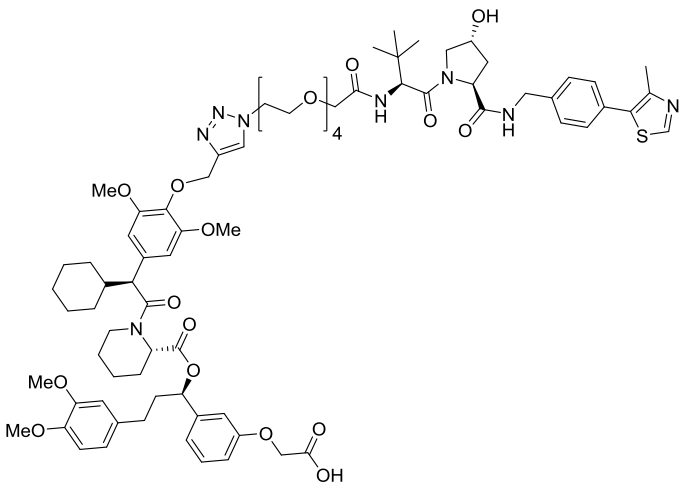
TLC: R_f = 0.11 (DCM:MeOH = 10:1, 1 % HCOOH).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 2.0 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+2H]^{2+}$ calculated for $C_{74}H_{96}N_8O_{18}S$ = 709.33544; found = 709.33577.

Lab book number(s): MWa209.

2-(3-((*R*)-1-(((*S*)-1-((*S*)-2-Cyclohexyl-2-(4-((1-((*S*)-16-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-17,17-dimethyl-14-oxo-3,6,9,12-tetraoxa-15-azaoctadecyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid



$C_{76}H_{100}N_8O_{19}S$, MW = 1461.73 g / mol

The product was synthesized from azide **57d** (10.3 mg, 15.0 μmol, 1.0 eq.) and alkyne **A8** (11.6 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 21.4 mg (98 %, 14.6 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.75 (d, *J* = 11.5 Hz, 1H), 0.99 (s, 8H), 1.13 (s, 2H), 1.23 – 1.35 (m, 4H), 1.55 – 1.80 (m, 6H), 1.80 – 1.95 (m, 2H), 1.94 – 2.13 (m, 2H), 2.18 – 2.26 (m, 1H), 2.33 (d, *J* = 10.3 Hz, 1H), 2.39 – 2.56 (m, 1H), 2.56 (s, 3H), 2.57 (s, 1H), 2.83 – 2.98 (m, 1H), 3.40 (d, *J* = 9.7 Hz, 1H), 3.51 – 3.70 (m, 18H), 3.78 (s, 1H), 3.83 (s, 6H), 3.82 – 3.91 (m, 2H), 4.04 (s, 3H), 4.34 (dd, *J* = 15.5, 5.3 Hz, 1H), 4.46 – 4.67 (m, 9H), 5.05 (s, 2H), 5.46 (d, *J* = 4.6 Hz, 1H), 5.51 (dd, *J* = 8.5, 5.0 Hz, 1H), 6.39 (s, 2H), 6.55 – 6.70 (m, 4H), 6.71 – 6.82 (m, 2H), 7.13 (t, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.48 (t, *J* = 8.1 Hz, 2H), 7.97 (s, 1H), 9.29 (s, 1H).

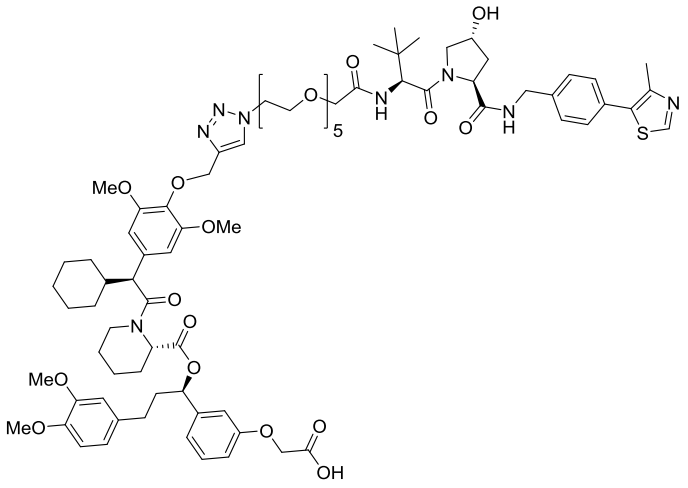
TLC: R_f = 0.10 (DCM:MeOH = 10:1, 1 % HCOOH).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 2.0 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+2H]^{2+}$ calculated for $C_{76}H_{100}N_8O_{19}S$ = 731.34855; found = 731.34905.

Lab book number(s): MWa210.

2-(3-((*R*)-1-(((*S*)-1-((*S*)-2-Cyclohexyl-2-(4-((1-((*S*)-19-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-20,20-dimethyl-17-oxo-3,6,9,12,15-pentaoxa-18-azahenicosyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid



$C_{78}H_{104}N_8O_{20}S$, MW = 1505.79 g / mol

The product was synthesized from azide **57e** (11.0 mg, 15.0 μmol, 1.0 eq.) and alkyne **A8** (11.6 mg, 15.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 18.3 mg (81 %, 12.2 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.75 (d, *J* = 11.8 Hz, 1H), 0.99 (s, 10H), 1.13 (s, 2H), 1.20 – 1.39 (m, 4H), 1.52 – 1.78 (m, 6H), 1.78 – 1.96 (m, 2H), 1.93 – 2.14 (m, 3H), 2.14 – 2.27 (m, 1H),

2.32 (d, J = 9.5 Hz, 2H), 2.43 – 2.53 (m, 1H), 2.56 (d, J = 2.7 Hz, 4H), 2.81 – 2.98 (m, 1H), 3.39 (d, J = 9.5 Hz, 1H), 3.55 – 3.73 (m, 23H), 3.79 (s, 1H), 3.83 (s, 6H), 3.82 – 3.90 (m, 3H), 4.05 (d, J = 3.0 Hz, 4H), 4.35 (dd, J = 15.4, 5.0 Hz, 1H), 4.46 – 4.74 (m, 9H), 5.06 (s, 2H), 5.43 – 5.55 (m, 2H), 6.39 (s, 2H), 6.62 – 6.67 (m, 5H), 6.75 (t, J = 7.6 Hz, 2H), 7.13 (t, J = 8.0 Hz, 1H), 7.29 – 7.52 (m, 6H), 7.93 (s, 9H), 9.24 (s, 1H).

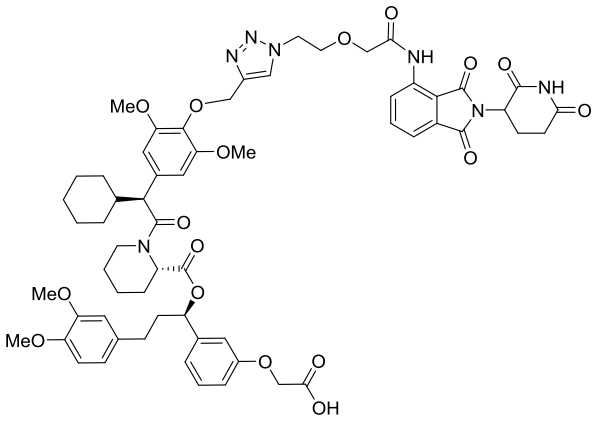
TLC: R_f = 0.10 (DCM:MeOH = 10:1, 1 % HCOOH).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 2.0 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+2H]^{2+}$ calculated for $C_{78}H_{104}N_8O_{20}S$ =753.36166; found = 753.36246.

Lab book number(s): MWa211.

2-(3-((1*R*)-1-(((2*S*)-1-((2*S*)-2-Cyclohexyl-2-(4-((1-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid



$C_{61}H_{69}N_7O_{17}$, MW = 1172.26 g / mol

The product was synthesized from azide **55a** (4.0 mg, 10.0 μmol, 1.0 eq.) and alkyne **A8** (7.7 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 7.0 mg (60 %, 6.0 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.66 – 0.77 (m, 1H), 0.90 (d, *J* = 9.8 Hz, 1H), 1.03 – 1.37 (m, 5H), 1.51 – 2.15 (m, 6H), 2.34 (d, *J* = 12.5 Hz, 1H), 2.42 – 2.78 (m, 2H), 2.94 (q, *J* = 11.6, 10.9 Hz, 1H), 3.36 (d, *J* = 9.5 Hz, 1H), 3.48 (d, *J* = 7.1 Hz, 5H), 3.73 (t, *J* = 3.8 Hz, 1H), 3.79 – 3.89 (m, 6H), 4.11 – 4.20 (m, 2H), 4.59 – 4.79 (m, 4H), 4.86 – 5.22 (m, 3H), 5.40 – 5.57 (m, 2H), 6.26 – 6.44 (m, 2H), 6.59 – 7.00 (m, 4H), 7.15 (td, *J* = 7.9, 3.4 Hz, 1H), 7.57 (dd, *J* = 7.4, 0.8 Hz, 1H), 7.72 (td, *J* = 8.6, 8.1, 1.7 Hz, 1H), 8.25 (d, *J* = 5.5 Hz, 1H), 8.65 (d, *J* = 13.8 Hz, 1H), 8.78 – 8.88 (m, 1H), 10.45 (d, *J* = 5.5 Hz, 1H).

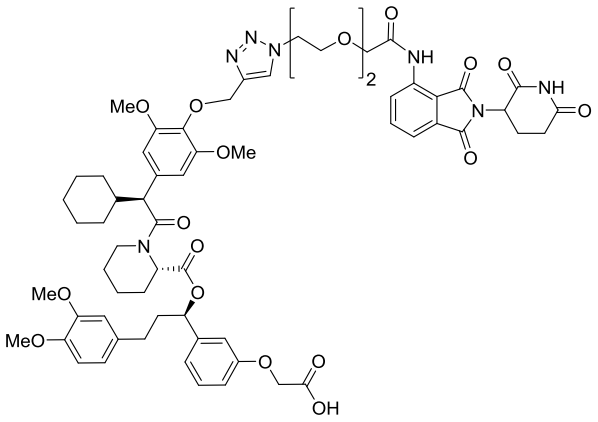
TLC: R_f = 0.22 (DCM:MeOH = 20:1, 1 % HCOOH).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 1.9 min
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{61}H_{69}N_7O_{17}$ = 1172.48227; found = 1172.48239.

Lab book number(s): MWa212.

2-(3-((1*R*)-1-(((2*S*)-1-((2*S*)-2-Cyclohexyl-2-(4-((1-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid



$C_{63}H_{73}N_7O_{18}$, MW = 1216.26 g / mol

The product was synthesized from azide **55b** (4.4 mg, 10.0 μmol, 1.0 eq.) and alkyne **A8** (7.7 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 1.4 mg (12 %, 1.2 μmol).

Appearance: white solid.

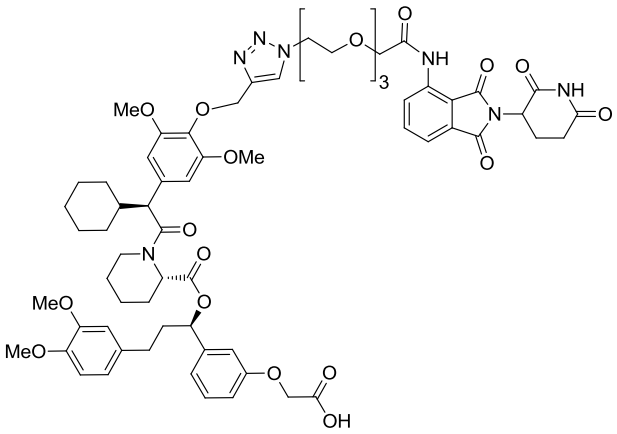
TLC: R_f = 0.20 (DCM:MeOH = 20:1, 1 % HCOOH).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 1.9 min
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{63}H_{73}N_7O_{18}$ = 1216.50848; found = 1216.50858.

Lab book number(s): MWa213.

2-(3-((1*R*)-1-(((2*S*)-1-((2*S*)-2-Cyclohexyl-2-(4-((1-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid



$C_{65}H_{77}N_7O_{19}$, MW = 1260.34 g / mol

The product was synthesized from azide **55c** (4.9 mg, 10.0 μmol, 1.0 eq.) and alkyne **A8** (7.7 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 6.2 mg (49 %, 4.9 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.73 (d, *J* = 12.0 Hz, 1H), 0.86 – 0.95 (m, 1H), 1.06 – 1.18 (m, 3H), 1.22 – 1.37 (m, 4H), 1.70 (dd, *J* = 31.8, 14.8 Hz, 7H), 1.82 – 1.96 (m, 1H), 1.97 – 2.19 (m, 1H), 2.33 (d, *J* = 13.2 Hz, 1H), 2.48 (dt, *J* = 14.0, 8.0 Hz, 1H), 2.58 (ddd, *J* = 14.5, 9.4, 5.4 Hz, 1H), 2.70 – 2.80 (m, 2H), 2.83 – 2.90 (m, 2H), 3.37 (d, *J* = 9.8 Hz, 1H), 3.57 (s, 5H), 3.58 – 3.64 (m, 2H), 3.65 – 3.68 (m, 2H), 3.76 (t, *J* = 2.8 Hz, 2H), 3.78 – 3.81 (m, 2H), 3.84 (d, *J* = 3.1 Hz, 5H), 3.86 (d, *J* = 1.6 Hz, 1H), 4.21 (d, *J* = 10.2 Hz, 2H), 4.50 (t, *J* = 5.8 Hz, 2H), 4.62 – 4.66 (m, 2H), 4.91 – 4.99 (m, 1H), 5.08 (d, *J* = 2.4 Hz, 2H), 5.44 – 5.53 (m, 2H), 6.61 (d, *J* = 2.4 Hz, 1H), 6.64 – 6.70 (m, 3H), 6.74 – 6.82 (m, 2H), 7.12 – 7.18 (m, 1H), 7.57 (dt, *J* = 7.3, 0.8 Hz, 1H), 7.70 (ddd, *J* = 9.0, 7.3, 1.8 Hz, 1H), 7.93 (d, *J* = 3.5 Hz, 1H), 8.65 (s, 1H), 8.82 (dq, *J* = 8.5, 0.9 Hz, 1H), 10.46 (s, 1H).

TLC: R_f = 0.19 (DCM:MeOH = 20:1, 1 % HCOOH).

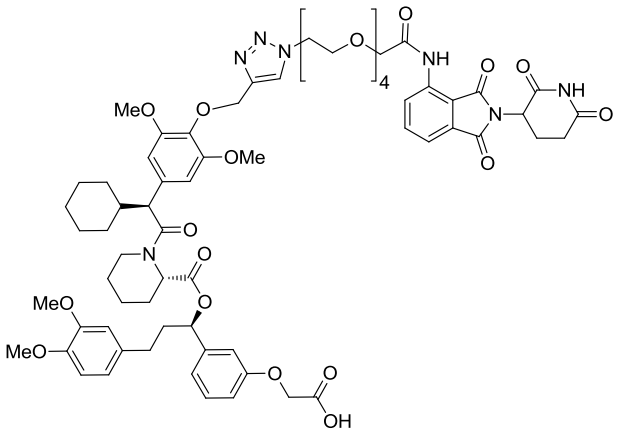
LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 2.0 min

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{65}H_{77}N_7O_{19}$ = 1260.53470; found = 1260.53456.

Lab book number(s): MWa214.

2-(3-((1*R*)-1-(((2*S*)-1-((2*S*)-2-Cyclohexyl-2-(4-((1-(14-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-14-oxo-3,6,9,12-tetraoxatetradecyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid



$C_{67}H_{81}N_7O_{20}$, MW = 1304.39 g / mol

The product was synthesized from azide **55d** (5.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A8** (7.7 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 7.1 mg (55 %, 5.5 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 0.68 – 0.80 (m, 1H), 0.82 – 0.96 (m, 1H), 1.08 – 1.37 (m, 7H), 1.60 – 1.77 (m, 6H), 1.96 (dd, *J* = 49.6, 9.5 Hz, 3H), 2.32 (d, *J* = 13.9 Hz, 1H), 2.40 – 2.65 (m, 2H), 2.67 – 2.95 (m, 3H), 3.37 (d, *J* = 9.4 Hz, 1H), 3.59 (d, *J* = 8.2 Hz, 10H), 3.63 – 3.75 (m, 4H),

3.79 (s, 3H), 3.84 (d, J = 1.5 Hz, 7H), 3.86 (d, J = 1.0 Hz, 1H), 4.15 (d, J = 23.1 Hz, 2H), 4.45 – 4.68 (m, 4H), 4.89 – 5.14 (m, 3H), 5.50 (d, J = 9.4 Hz, 2H), 6.37 (d, J = 11.7 Hz, 2H), 6.58 – 6.71 (m, 4H), 6.78 (dt, J = 8.7, 5.0 Hz, 2H), 7.15 (t, J = 7.7 Hz, 1H), 7.57 (d, J = 7.1 Hz, 1H), 7.71 (t, J = 7.9 Hz, 1H), 7.89 (s, 1H), 8.65 (s, 1H), 8.83 (d, J = 8.3 Hz, 1H), 10.48 (s, 1H).

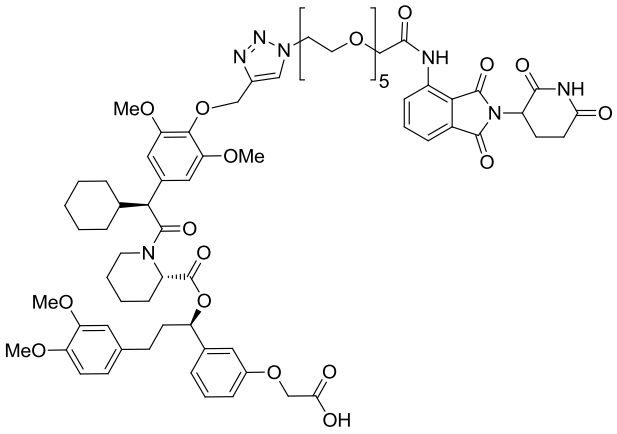
TLC: R_f = 0.18 (DCM:MeOH = 20:1, 1 % HCOOH).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 2.0 min
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{67}H_{81}N_7O_{20}$ = 1304.56091; found = 1304.56107.

Lab book number(s): MWa215.

2-(3-((1*R*)-1-(((2*S*)-1-((2*S*)-2-Cyclohexyl-2-(4-((1-(17-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-17-oxo-3,6,9,12,15-pentaoxaheptadecyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid



$C_{69}H_{85}N_7O_{21}$, MW = 1348.45 g / mol

The product was synthesized from azide **55e** (5.8 mg, 10.0 μmol, 1.0 eq.) and alkyne **A8** (7.7 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 8.9 mg (66 %, 6.6 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.65 – 0.81 (m, 1H), 0.82 – 1.00 (m, 1H), 1.07 – 1.38 (m, 7H), 1.65 (d, *J* = 10.3 Hz, 6H), 1.81 – 2.21 (m, 4H), 2.32 (d, *J* = 13.4 Hz, 1H), 2.39 – 2.64 (m, 2H), 2.69 – 2.94 (m, 4H), 3.37 (d, *J* = 9.8 Hz, 1H), 3.55 – 3.74 (m, 18H), 3.79 (s, 5H), 3.84 (s, 5H), 3.86 (d, *J* = 1.1 Hz, 1H), 4.20 (s, 2H), 4.46 – 4.72 (m, 4H), 4.97 (d, *J* = 11.4 Hz, 1H), 5.15 (d, *J* = 31.6 Hz, 2H), 5.42 – 5.57 (m, 2H), 6.58 – 6.74 (m, 4H), 6.72 – 6.85 (m, 2H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.52 – 7.64 (m, 1H), 7.65 – 7.78 (m, 1H), 7.92 (s, 1H), 8.76 (s, 1H), 8.83 (d, *J* = 8.4 Hz, 1H), 10.48 (s, 1H).

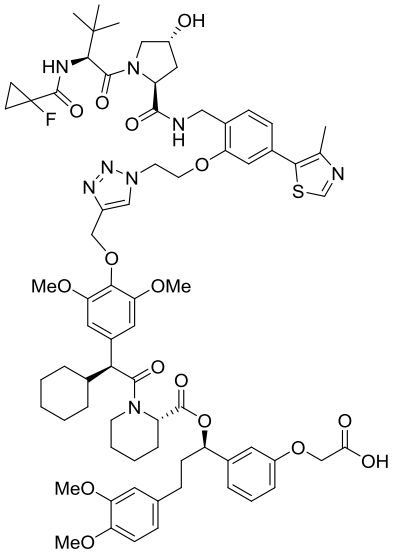
TLC: R_f = 0.18 (DCM:MeOH = 20:1, 1 % HCOOH).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 2.0 min
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{69}H_{85}N_7O_{21}$ = 1348.58713; found = 1348.58628.

Lab book number(s): MWa216

2-(3-((*R*)-1-(((*S*)-1-((*S*)-2-Cyclohexyl-2-(4-((1-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid



$C_{72}H_{89}FN_8O_{16}S$, MW = 1373.60 g / mol

The product was synthesized from azide **58a** (6.0 mg, 10.0 μmol, 1.0 eq.) and alkyne **A8** (7.7 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.2 mg (74 %, 7.4 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.91 (d, *J* = 6.5 Hz, 9H), 0.97 – 1.31 (m, 11H), 1.50 – 1.75 (m, 6H), 1.75 – 1.89 (m, 0H), 1.93 – 2.16 (m, 2H), 2.26 (d, *J* = 12.7 Hz, 1H), 2.46 (s, 5H), 2.82 (t, *J* = 12.6 Hz, 1H), 3.32 (d, *J* = 9.7 Hz, 1H), 3.50 (s, 5H), 3.56 – 3.65 (m, 1H), 3.68 – 3.80 (m, 7H), 3.81 – 3.96 (m, 2H), 4.25 (t, *J* = 3.5 Hz, 1H), 4.31 – 4.41 (m, 3H), 4.54 (d, *J* = 9.2 Hz, 3H), 4.58 – 4.86 (m, 3H), 4.97 (s, 2H), 5.41 (dd, *J* = 8.4, 5.0 Hz, 2H), 6.31 (s, 2H), 6.50 – 6.77 (m, 7H), 6.90 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.08 (t, *J* = 7.9 Hz, 1H), 7.14 (dd, *J* = 9.1, 3.3 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 6.1 Hz, 1H), 7.75 (s, 1H), 8.98 (s, 1H).

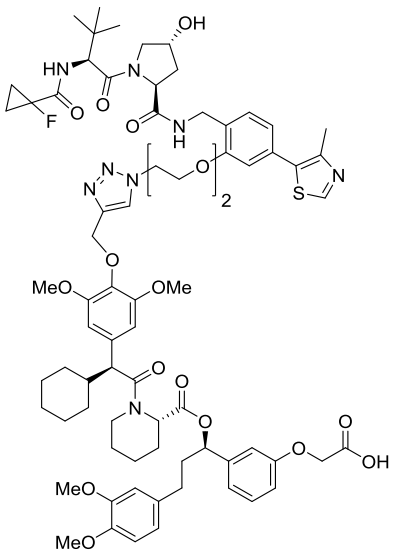
TLC: R_f = 0.12 (DCM:MeOH = 10:1, 1 % HCOOH).

LC-MS: [50-100 % Solvent B, 2.2 min]: R_t = 1.5 min.
96 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{72}H_{89}FN_8O_{16}S$ = 1373.61740; found = 1373.61759.

Lab book number(s): MWa290.

2-(3-((*R*)-1-(((*S*)-1-((*S*)-2-Cyclohexyl-2-(4-((1-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid



$C_{74}H_{93}FN_8O_{17}S$, MW = 1417.66 g / mol

The product was synthesized from azide **58b** (6.5 mg, 10.0 μmol, 1.0 eq.) and alkyne **A8** (7.7 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 11.9 mg (84 %, 8.4 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.90 (d, *J* = 2.2 Hz, 9H), 0.99 – 1.31 (m, 11H), 1.44 – 1.67 (m, 6H), 1.71 – 1.85 (m, 2H), 2.01 – 2.30 (m, 2H), 2.29 – 2.39 (m, 1H), 2.39 – 2.53 (m, 3H), 2.77 (t, *J* = 13.3 Hz, 1H), 3.27 – 3.36 (m, 1H), 3.55 (d, *J* = 1.2 Hz, 4H), 3.60 (dd, *J* = 11.2, 3.6 Hz, 1H), 3.69 – 3.71 (m, 1H), 3.73 – 3.85 (m, 6H), 3.85 – 3.97 (m, 1H), 3.99 – 4.12 (m, 1H), 4.27 – 4.66 (m, 10H), 4.96 (d, *J* = 39.7 Hz, 2H), 5.35 (d, *J* = 5.5 Hz, 1H), 5.46 (dd, *J* = 8.4, 5.2 Hz, 1H), 6.34 (d, *J* = 5.7 Hz, 2H), 6.50 – 6.94 (m, 8H), 7.05 (dd, *J* = 9.0, 6.9 Hz, 1H), 7.16 (dd, *J* = 9.5, 3.4 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.77 (d, *J* = 27.3 Hz, 1H), 8.64 – 8.72 (m, 1H).

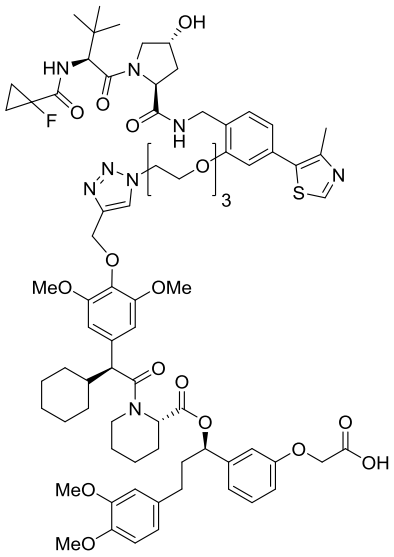
TLC: R_f = 0.12 (DCM:MeOH = 10:1, 1 % HCOOH).

LC-MS: [50-100 % Solvent B, 2.2 min]: R_t = 1.5 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{74}H_{93}FN_8O_{17}S$ = 1417.64362; found = 1417.64346.

Lab book number(s): MWa291.

2-(3-((*R*)-1-(((*S*)-1-((*S*)-2-Cyclohexyl-2-(4-((1-(2-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid



$C_{76}H_{97}FN_8O_{18}S$, MW = 1461.71 g / mol

The product was synthesized from azide **58c** (6.9 mg, 10.0 μmol, 1.0 eq.) and alkyne **A8** (7.7 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 12.2 mg (84 %, 8.4 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.91 (s, 9H), 0.98 – 1.33 (m, 11H), 1.38 – 1.68 (m, 7H), 1.68 – 1.85 (m, 2H), 2.08 (dd, *J* = 8.2, 3.1 Hz, 2H), 2.13 – 2.55 (m, 7H), 2.74 (t, *J* = 13.0 Hz, 1H), 3.32 (d, *J* = 9.9 Hz, 1H), 3.48 – 3.71 (m, 11H), 3.71 (s, 3H), 3.73 – 3.95 (m, 7H), 4.09 (hept, *J* = 5.1 Hz, 2H), 4.27 – 4.69 (m, 11H), 4.97 (d, *J* = 20.6 Hz, 2H), 5.34 (d, *J* = 5.3 Hz, 1H), 5.45 (t, *J* = 6.8 Hz, 1H), 6.35 (d, *J* = 11.5 Hz, 2H), 6.43 – 6.75 (m, 6H), 6.76 – 6.94 (m, 3H), 7.04 (t, *J* = 7.9 Hz, 1H), 7.15 – 7.26 (m, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 15.5 Hz, 1H), 8.63 (s, 1H).

TLC: R_f = 0.11 (DCM:MeOH = 10:1, 1 % HCOOH).

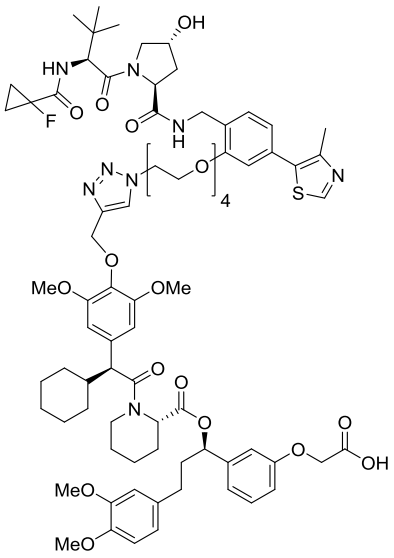
LC-MS: [50-100 % Solvent B, 2.2 min]: R_t = 1.5 min.

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{76}H_{97}FN_8O_{18}S$ = 1461.66983; found = 1461.66976.

Lab book number(s): MWa292.

2-(3-((*R*)-1-(((*S*)-1-((*S*)-2-Cyclohexyl-2-(4-((1-(2-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)ethoxy) ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid



$C_{78}H_{101}FN_8O_{19}S$, MW = 1505.76 g / mol

The product was synthesized from azide **58d** (7.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A8** (7.7 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.9 mg (73 %, 7.3 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.92 (s, 9H), 0.95 – 1.34 (m, 11H), 1.44 – 1.70 (m, 7H), 1.69 – 1.84 (m, 2H), 2.10 (dd, *J* = 8.4, 3.1 Hz, 2H), 2.16 – 2.27 (m, 1H), 2.42 (s, 4H), 2.75 (t, *J* = 13.0 Hz, 1H), 3.33 (d, *J* = 9.9 Hz, 1H), 3.47 – 3.71 (m, 14H), 3.68 – 3.81 (m, 10H), 4.09 (q, *J* = 4.2 Hz, 2H), 4.26 – 4.74 (m, 11H), 4.99 (d, *J* = 21.5 Hz, 2H), 5.35 (d, *J* = 5.2 Hz, 1H), 5.46 (dd, *J* = 8.1, 5.4 Hz, 1H), 6.37 (d, *J* = 11.9 Hz, 2H), 6.43 – 6.77 (m, 6H), 6.77 – 6.97 (m, 3H), 7.06 (t, *J* = 7.9 Hz, 1H), 7.17 – 7.26 (m, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 15.8 Hz, 1H), 8.66 (s, 1H).

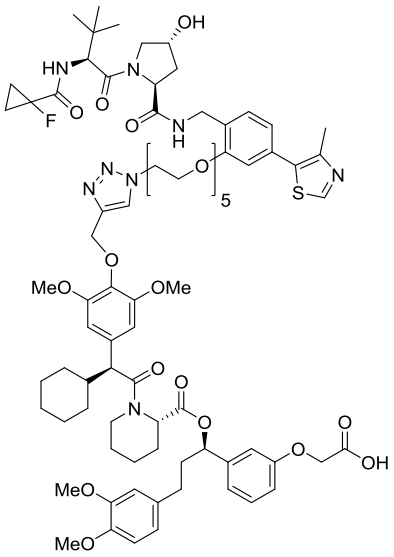
TLC: R_f = 0.10 (DCM:MeOH = 10:1, 1 % HCOOH).

LC-MS: [50-100 % Solvent B, 2.2 min]: R_t = 1.5 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{78}H_{101}FN_8O_{19}S$ = 1505.69605; found = 1505.69640.

Lab book number(s): MWa293.

2-(3-((*R*)-1-(((*S*)-1-((*S*)-2-Cyclohexyl-2-(4-((1-(14-(2-(((2*S*,4*R*)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)-3,6,9,12-tetraoxatetradecyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid



$C_{80}H_{105}FN_8O_{20}S$, MW = 1549.81 g / mol

The product was synthesized from azide **58e** (7.8 mg, 10.0 μmol, 1.0 eq.) and alkyne **A8** (7.7 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 14.8 mg (95 %, 9.5 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.85 (s, 9H), 0.91 – 1.28 (m, 11H), 1.49 (ddt, *J* = 22.3, 14.3, 8.7 Hz, 7H), 1.63 – 1.76 (m, 2H), 2.03 (dd, *J* = 8.2, 3.4 Hz, 2H), 2.08 – 2.21 (m, 1H), 2.35 (s, 6H), 2.68 (t, *J* = 13.0 Hz, 1H), 3.29 (d, *J* = 9.8 Hz, 1H), 3.43 – 3.61 (m, 14H), 3.62 – 3.86 (m, 13H), 3.95 – 4.17 (m, 2H), 4.19 – 4.68 (m, 11H), 4.92 (d, *J* = 20.2 Hz, 2H), 5.28 (d, *J* = 5.2 Hz, 1H), 5.40 (dd, *J* = 8.2, 5.4 Hz, 1H), 6.32 (d, *J* = 15.7 Hz, 2H), 6.33 – 6.71 (m, 6H), 6.72 – 6.87 (m, 3H), 6.99 (t, *J* = 7.9 Hz, 1H), 7.17 (dd, *J* = 8.9, 4.1 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.76 (d, *J* = 17.4 Hz, 1H), 8.59 (s, 1H).

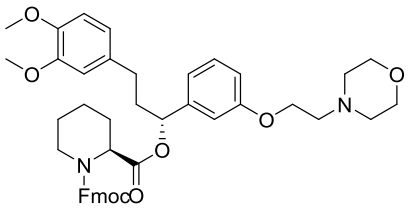
TLC: R_f = 0.10 (DCM:MeOH = 10:1, 1 % HCOOH).

LC-MS: [50-100 % Solvent B, 2.2 min]: R_t = 1.5 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{80}H_{105}FN_8O_{20}S$ = 1549.72226; found = 1549.72245.

Lab book number(s): MWa294.

1-((9H-Fluoren-9-yl)methyl) 2-((*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl) (*S*)-piperidine-1,2-dicarboxylate



C44H50N2O8, MW = 734.89 g / mol

(*S*)-1-(((9H-Fluoren-9-yl)methoxy)carbonyl)piperidine-2-carboxylic acid (350 mg, 1.00 mmol, 1.0 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (230 mg, 1.20 mmol, 1.2 eq.) and 4-dimethylaminopyridine (37 mg, 0.3 mmol, 0.3 eq.) were cooled to 0 °C under Argon. DCM (dry, 5 mL) was added and the mixture was stirred for 30 min. (*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propan-1-ol (AV531, 400 mg, 1.00 mmol, 1.0 eq.) in DCM (dry, 5 mL) was added and the mixture was stirred for 15 min at 0 °C followed by 18 h at room temperature. The solution was diluted with brine (100 mL) and extracted with DCM (3 x 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by column chromatography (50 g SiO_2, CH:EA = 3:1 → 1:5).

Yield: 396 mg (54 %, 0.54 mmol).

Appearance: white foam.

TLC: R_f = 0.14 (CH:EA = 1:1).

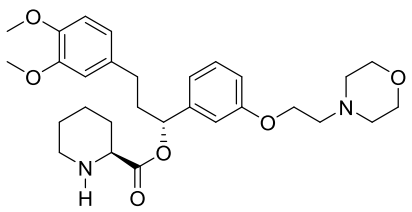
LC-MS: Mass (ESI), calculated = 735.4 $[M+H]^+$, found = 735.6.

[0-100 % Solvent B, 20 min]: R_t = 10.1 min.

95 % purity (220 nm).

Lab book number(s): MWa126.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-piperidine-2-carboxylate



$C_{29}H_{40}N_2O_6$, MW = 512.65 g / mol

1-((9H-Fluoren-9-yl)methyl) 2-((*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy) phenyl)propyl) (*S*)-piperidine-1,2-dicarboxylate (396 mg, 0.54 mmol, 1.0 eq.) and 4-methylpiperidine (260 μL, 2.21 mmol, 4.1 eq) were dissolved in DCM (2.4 mL) and the mixture was stirred for 3 h at room temperature. The solution was diluted with DCM (50 mL) and washed with NH_4Cl (sat., aq, 3 x 20 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by column chromatography (20 g SiO_2, EA → DCM:MeOH 10:1, 3 % TEA).

Yield: 210 mg (76 %, 0.41 mmol).

Appearance: yellow oil.

TLC: R_f = 0.10 (EA).

R_f = 0.66 (DCM:MeOH = 10:1, 3 % TEA).

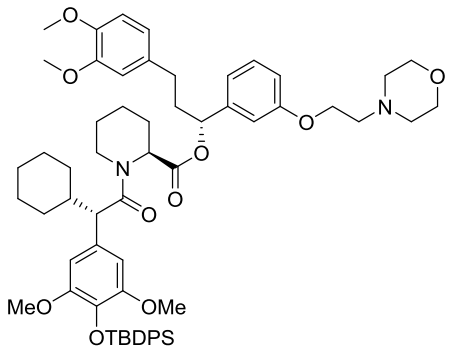
LC-MS: Mass (ESI), calculated = 513.3 $[M+H]^+$, found = 513.2.

[5-100 % Solvent B, 2.6 min]: R_t = 1.0 min.

85 % purity (220 nm).

Lab book number(s): MWa129 / MWa357.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-1-((*S*)-2-(4-((*tert*-butyldiphenylsilyl)oxy)-3,5-dimethoxyphenyl)-2-cyclohexylacetyl)piperidine-2-carboxylate



$C_{61}H_{78}N_2O_{10}Si$, MW = 1027.38 g / mol

(*S*)-2-(4-((*tert*-Butyldiphenylsilyl)oxy)-3,5-dimethoxyphenyl)-2-cyclohexylacetic acid (MBA269, 218 mg, 0.41 mmol, 1.0 eq.) and HATU (106 mg, 0.45 mmol, 1.1 eq.) were dissolved in DCM (1 mL) and DMF (2mL). The mixture was cooled to 0 °C and DIPEA (215 μL, 1.23 mmol, 3.0 eq.) were added. The mixture was stirred for 15 min at 0 °C. (*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-piperidine-2-carboxylate (210 mg, 0.41 mmol, 1.0 eq.) in DCM (3 mL) was added and the mixture was stirred for 18 h at room temperature. Additional HATU (0.5 eq.) and DIPEA (1.5 eq.) were added and the mixture was stirred for 24 h at room temperature. The solution was concentrated under reduced pressure and the obtained product was purified by column chromatography (40 g SiO_2, CH:EA 1:1).

Yield: 410 mg (97 %, 0.40 mmol).

Appearance: orange solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.79 – 1.07 (m, 1H), 1.13 – 1.28 (m, 1H), 1.36 (d, *J* = 11.6 Hz, 9H), 1.47 – 1.63 (m, 4H), 1.74 – 2.02 (m, 5H), 2.04 – 2.40 (m, 5H), 2.55 (d, *J* = 13.4 Hz, 1H), 2.71 (ddd, *J* = 22.7, 11.2, 6.0 Hz, 1H), 3.02 – 3.09 (m, 3H), 3.15 (s, 12H), 3.56 (d, *J* = 3.1 Hz, 2H), 3.58 – 3.70 (m, 2H), 3.71 (s, 1H), 4.01 – 4.19 (m, 8H), 4.24 – 4.53 (m, 3H), 5.58 – 5.91 (m, 1H), 6.50 – 6.79 (m, 2H), 6.84 – 7.32 (m, 5H), 7.40 – 7.66 (m, 6H), 7.82 – 8.06 (m, 4H), 8.24 (s, 2H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 20.5, 21.5, 26.8, 27.1, 30.9, 31.7, 33.3, 37.0, 38.5, 38.8, 41.9, 44.4, 53.0, 54.2, 55.6, 55.8, 56.3, 56.3, 57.9, 61.9, 65.0, 66.5, 76.6, 106.2, 112.4, 112.8, 113.4, 114.6,

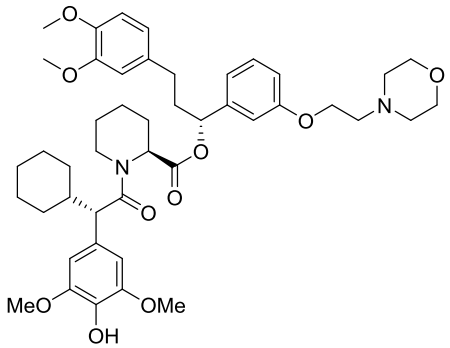
119.7, 121.2, 127.5, 129.6, 129.7, 130.4, 131.0, 133.9, 134.5, 134.9, 135.8, 135.9, 142.5, 147.8, 149.4, 151.6, 158.9, 171.3, 174.0.

TLC: R_f = 0.15 (CH:EA = 1:1).

LC-MS: Mass (ESI), calculated = 1027.5 [M+H]+, found = 1027.6.
[5-100 % Solvent B, 2.6 min]: R_t = 1.9 min.
91 % purity (220 nm).

Lab book number(s): MWa130 / MWa358.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(4-hydroxy-3,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{45}H_{60}N_2O_{10}$, MW = 788.98 g / mol

((*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-1-((*S*)-2-(4-((*tert*-butyldiphenylsilyl)oxy)-3,5-dimethoxyphenyl)-2-cyclohexylacetyl)piperidine-2-carboxylate (365 mg, 355 μmol, 1.0 eq.) was dissolved in THF (dry, 7 mL) and cooled to 0 °C under argon. TBAF (1 M in THF, 355 μL) was added and the mixture was stirred for 5 h at 0 °C to room temperature. The reaction was quenched with water (10 mL) and the mixture was extracted with DCM (2 x 40 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by column chromatography (25 g SiO_2, EA:MeOH = 20:1).

Yield: 197 mg (70 %, 250 μmol).

Appearance: white foam.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.53 – 0.95 (m, 2H), 1.29 (dd, *J* = 15.3, 5.6 Hz, 3H), 1.62 (t, *J* = 16.3 Hz, 5H), 1.80 – 2.12 (m, 4H), 2.29 (d, *J* = 13.6 Hz, 1H), 2.37 – 2.68 (m, 6H), 2.72 – 2.98 (m, 9H), 3.31 (d, *J* = 9.8 Hz, 1H), 3.73 (d, *J* = 20.9 Hz, 8H), 3.85 (d, *J* = 4.3 Hz, 7H), 4.07 (dt, *J* = 20.2, 6.0 Hz, 2H), 5.25 – 5.50 (m, 1H), 5.55 – 5.85 (m, 1H), 6.45 (d, *J* = 9.9 Hz, 2H), 6.52 (d, *J* = 5.0 Hz, 1H), 6.65 (d, *J* = 7.7 Hz, 2H), 6.69 – 7.00 (m, 2H), 7.10 (t, *J* = 8.0 Hz, 1H), 7.26 (s, 1H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 21.1, 25.7, 26.4, 26.8, 26.9, 30.8, 31.3, 33.0, 38.0, 38.7, 41.4, 43.7, 52.2, 54.2, 55.2, 56.1, 56.4, 57.9, 65.1, 66.8, 75.8, 105.9, 111.5, 112.1, 113.1, 113.6, 119.3, 120.5, 128.8, 129.5, 129.9, 133.8, 134.2, 141.9, 147.5, 149.0, 158.8, 170.9, 172.5.

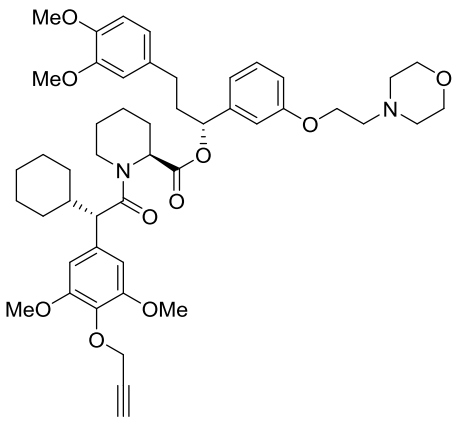
TLC: R_f = 0.18 (EA).
R_f = 0.42 (EA:MeOH = 10:1).

LC-MS: Mass (ESI), calculated = 789.4 $[M+H]^+$, found = 789.7.

HPLC: [30-100 % Solvent B, 25 min]: R_t = 11.0 min.
96 % purity (220 nm).

Lab book number(s): MWa133 / MWa360.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,5-dimethoxy-4-(prop-2-yn-1-yloxy)phenyl)acetyl)piperidine-2-carboxylate



$C_{48}H_{62}N_2O_{10}$, MW = 827.03 g / mol

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(4-hydroxy-3,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate (190 mg, 240 μmol, 1.0 eq.), 3-bromoprop-1-yne (34.5 mg, 290 μmol, 1.2 eq.) and potassium carbonate (332 mg, 2.40 mmol, 10.0 eq.) were stirred in acetone (3 mL) for 18 h at room temperature. Additional 3-bromoprop-1-yne (0.3 eq.) and potassium carbonate (1 eq.) were added and the mixture was stirred for 24 h at room temperature. The solution was filtered and concentrated under reduced pressure. The obtained product was purified by column chromatography (20 g SiO_2, CH:EA = 1:1 → EA).

Yield: 105 mg (53 %, 127 μmol).

Appearance: white foam.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 1.13 (ddd, *J* = 20.9, 10.3, 6.0 Hz, 2H), 1.19 – 1.36 (m, 3H), 1.51 – 1.71 (m, 5H), 1.96 – 2.13 (m, 4H), 2.25 – 2.30 (m, 1H), 2.57 (dq, *J* = 4.9, 2.4 Hz, 6H), 2.76 – 2.80 (m, 9H), 3.37 (d, *J* = 9.8 Hz, 1H), 3.72 (t, *J* = 4.7 Hz, 5H), 3.81 – 3.86 (m, 12H), 4.03 – 4.10 (m, 2H), 4.60 (d, *J* = 2.4 Hz, 2H), 5.42 – 5.49 (m, 1H), 5.54 (dd, *J* = 8.2, 5.5 Hz, 1H), 6.48 (s, 2H), 6.60 – 6.70 (m, 4H), 6.73 – 6.78 (m, 2H), 7.09 (t, *J* = 8.0 Hz, 1H).

^{13}**C-NMR** (75 MHz, Chloroform-*d*): δ = 20.0, 24.5, 25.2, 25.6, 25.8, 29.6, 30.0, 31.8, 37.0, 37.6, 40.4, 42.6, 51.0, 53.1, 54.0, 54.9, 55.1, 56.6, 59.0, 64.7, 65.9, 73.7, 74.6, 78.6, 104.8, 110.3, 110.8, 112.0, 112.7, 117.5, 119.3, 128.5, 132.5, 133.3, 133.6, 140.8, 146.3, 147.8, 152.2, 157.6, 169.5, 171.3.

TLC: R_f = 0.38 (EA).

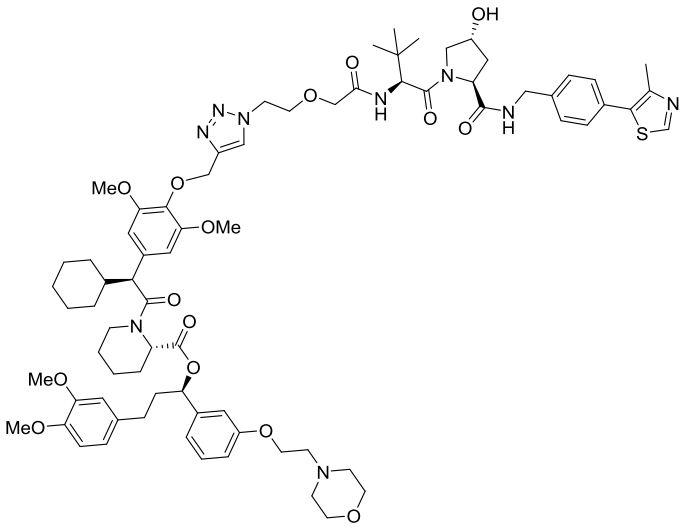
LC-MS: Mass (ESI), calculated = 827.4 $[M+H]^+$, found = 827.7.

HPLC: [0-100 % Solvent B, 20 min]: R_t = 16.1 min.
[40-70 % Solvent B, 20 min]: R_t = 13.9 min.
96 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{48}H_{62}N_2O_{10}$ = 827.44772; found = 827.44770.

Lab book number(s): MWa135 / MWa362.

2-(3-((*R*)-1-(((*S*)-1-((*S*)-2-Cyclohexyl-2-(4-((1-(2-(2-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid



$C_{74}H_{97}N_9O_{15}S$, MW = 1329.57 g / mol

The product was synthesized from azide **57a** (3.3 mg, 6.0 μmol, 1.0 eq.) and alkyne **A9** (5.0 mg, 6.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 4.8 mg (58 %, 3.5 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.62 – 0.76 (m, 1H), 0.81 (s, 2H), 0.90 (s, 8H), 0.99 – 1.12 (m, 2H), 1.11 – 1.28 (m, 4H), 1.32 – 1.45 (m, 1H), 1.47 – 1.72 (m, 6H), 1.71 – 2.17 (m, 6H), 2.20 – 2.31 (m, 2H), 2.48 (s, 5H), 2.73 (t, J = 12.2 Hz, 1H), 2.93 – 3.14 (m, 1H), 3.33 (d, J = 10.1 Hz, 1H), 3.49 – 3.66 (m, 8H), 3.70 (s, 1H), 3.75 – 3.80 (m, 9H), 3.79 – 4.01 (m, 8H), 4.09 – 4.33 (m, 4H), 4.35 – 4.74 (m, 8H), 4.99 (s, 2H), 5.37 (d, J = 4.6 Hz, 1H), 5.49 (dd, J = 8.4, 5.2 Hz, 1H), 6.36 (d, J = 4.5 Hz, 2H), 6.47 – 6.75 (m, 6H), 7.09 (t, J = 8.0 Hz, 1H), 7.30 (q, J = 8.4 Hz, 4H), 7.41 (s, 2H), 7.75 (s, 1H), 9.12 (d, J = 4.2 Hz, 1H).

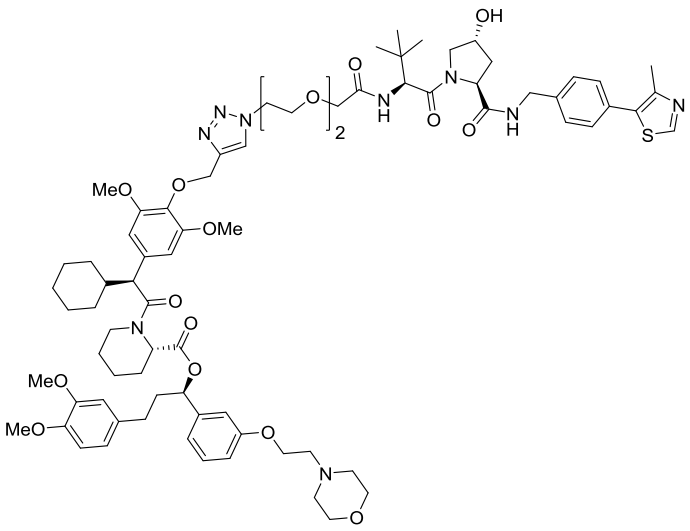
TLC: R_f = 0.08 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 1.0 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+2H]^{2+}$ calculated for $C_{74}H_{97}N_9O_{15}S$ = 692.84852; found = 692.84859.

Lab book number(s): MWa217.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(4-((1-(2-(2-(2-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{76}H_{101}N_9O_{16}S$, MW = 1428.75 g / mol

The product was synthesized from azide **57b** (3.6 mg, 6.0 μmol, 1.0 eq.) and alkyne **A9** (5.0 mg, 6.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 6.6 mg (77 %, 4.6 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 0.70 (d, *J* = 12.1 Hz, 1H), 0.81 – 0.90 (m, 2H), 0.90 – 1.00 (m, 9H), 1.07 (s, 2H), 1.21 (d, *J* = 27.6 Hz, 2H), 1.40 (d, *J* = 12.8 Hz, 1H), 1.52 – 1.72 (m, 6H), 1.81 (dd, *J* = 35.1, 10.2 Hz, 3H), 1.91 – 2.09 (m, 1H), 2.25 (d, *J* = 13.1 Hz, 1H), 2.40 (d, *J* = 12.1 Hz, 1H), 2.49 (d, *J* = 1.4 Hz, 4H), 2.78 (t, *J* = 11.9 Hz, 1H), 3.03 (d, *J* = 10.6 Hz, 1H), 3.34 (d, *J* = 9.9 Hz, 1H), 3.46 – 3.66 (m, 12H), 3.72 (d, *J* = 1.7 Hz, 1H), 3.75 – 3.80 (m, 6H), 3.80 – 3.98 (m, 6H), 3.99 – 4.14 (m, 2H), 4.15 – 4.24 (m, 2H), 4.24 – 4.29 (m, 1H), 4.29 – 4.48 (m, 5H), 4.50 – 4.60 (m, 2H), 5.37 (d, *J* = 4.4 Hz, 1H), 5.46 (dd, *J* = 7.6, 4.1 Hz, 1H), 6.33 – 6.39 (m, 2H), 6.53 – 6.76 (m, 6H), 7.08 (dt, *J* = 16.2, 8.2 Hz, 1H), 7.18 – 7.26 (m, 4H), 7.45 (t, *J* = 5.2 Hz, 1H), 7.47 – 7.56 (m, 1H), 8.28 (d, *J* = 18.0 Hz, 1H), 9.05 (d, *J* = 2.0 Hz, 1H).

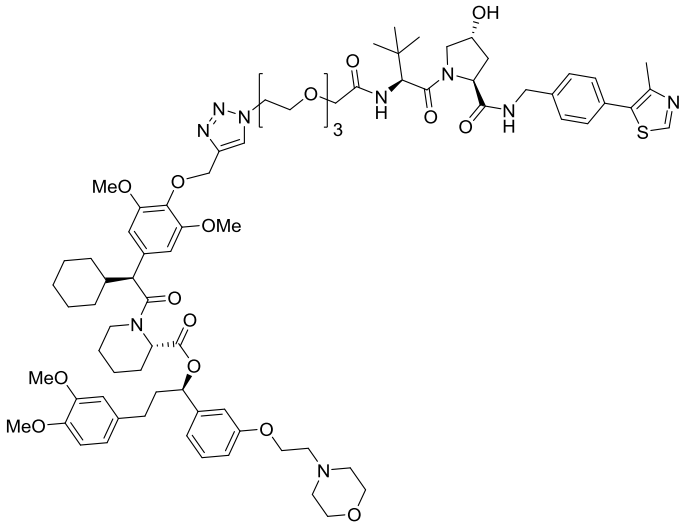
TLC: R_f = 0.07 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 1.0 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+2H]^{2+}$ calculated for $C_{76}H_{101}N_9O_{16}S$ = 714.86163; found = 714.86206.

Lab book number(s): MWa218.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(4-((1-((*S*)-13-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-14,14-dimethyl-11-oxo-3,6,9-trioxa-12-azapentadecyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{78}H_{105}N_9O_{17}S$, MW = 1472.80 g / mol

The product was synthesized from azide **57c** (3.9 mg, 6.0 μmol, 1.0 eq.) and alkyne **A9** (5.0 mg, 6.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.8 mg (66 %, 3.9 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.69 (d, *J* = 9.8 Hz, 1H), 0.75 – 0.90 (m, 1H), 0.92 (d, *J* = 2.9 Hz, 9H), 1.07 (dd, *J* = 12.9, 9.1 Hz, 2H), 1.13 – 1.28 (m, 4H), 1.31 – 1.44 (m, 1H), 1.58 (d, *J* = 11.2 Hz, 6H), 1.72 – 2.16 (m, 6H), 2.18 – 2.30 (m, 2H), 2.32 – 2.50 (m, 2H), 2.49 (d, *J* = 1.2 Hz, 3H), 2.70 (t, *J* = 11.9 Hz, 1H), 2.93 – 3.13 (m, 1H), 3.32 (d, *J* = 9.9 Hz, 1H), 3.59 (q, *J* = 9.2, 7.8 Hz, 11H), 3.72 (s, 1H), 3.78 (d, *J* = 6.8 Hz, 6H), 3.79 – 4.02 (m, 8H), 4.19 (dd, *J* = 19.9, 7.4 Hz, 4H), 4.36 – 4.66 (m, 7H), 5.02 (d, *J* = 30.9 Hz, 2H), 5.38 (d, *J* = 4.1 Hz, 1H), 5.51 (dd, *J* = 8.5, 5.3 Hz, 1H), 6.39 (d, *J* = 3.5 Hz, 2H), 6.44 – 6.79 (m, 6H), 7.08 (t, *J* = 7.9 Hz, 1H), 7.22 – 7.36 (m, 4H), 7.41 (t, *J* = 6.0 Hz, 1H), 7.87 (s, 1H), 9.04 (s, 1H).

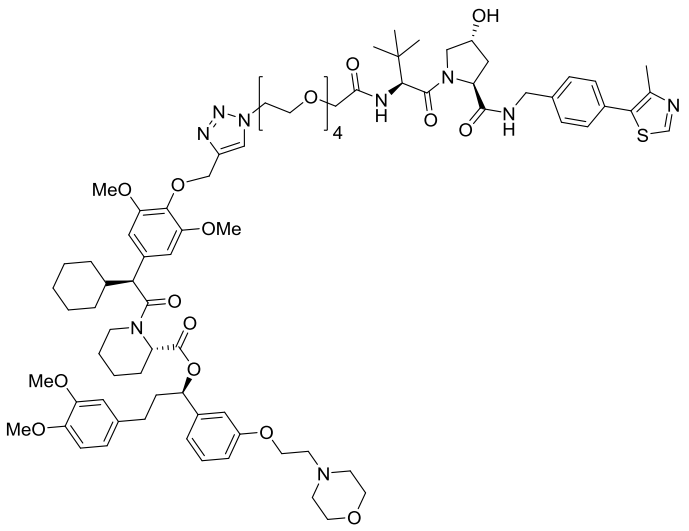
TLC: R_f = 0.07 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 1.0 min.
98 % purity (220 nm).

HRMS (ESI) m/z: $[M+2H]^{2+}$ calculated for $C_{78}H_{105}N_9O_{17}S$ = 736.87473; found = 736.87515.

Lab book number(s): MWa219.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(4-((1-((*S*)-16-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-17,17-dimethyl-14-oxo-3,6,9,12-tetraoxa-15-azaoctadecyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{80}H_{109}N_9O_{18}S$, MW = 1516.86 g / mol

The product was synthesized from azide **57d** (4.1 mg, 6.0 μmol, 1.0 eq.) and alkyne **A9** (5.0 mg, 6.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 6.4 mg (70 %, 4.2 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.75 (m, 1H), 0.72 – 0.86 (m, 1H), 0.88 – 0.96 (m, 9H), 0.99 – 1.28 (m, 6H), 1.38 (d, *J* = 14.8 Hz, 0H), 1.45 – 1.71 (m, 6H), 1.71 – 2.17 (m, 3H), 2.17 – 2.31 (m, 2H), 2.31 – 2.56 (m, 5H), 2.71 (t, *J* = 12.7 Hz, 1H), 2.93 – 3.10 (m, 1H), 3.33 (dd, *J* = 10.2, 5.5 Hz, 1H), 3.46 – 3.64 (m, 19H), 3.73 (s, 1H), 3.78 (d, *J* = 5.7 Hz, 6H), 3.80 – 4.04 (m, 5H), 4.09 – 4.27 (m, 4H), 4.27 – 4.72 (m, 8H), 4.97 (s, 2H), 5.39 (s, 1H), 5.47 – 5.57 (m, 1H), 6.37 (d, *J* = 18.2 Hz, 2H), 6.44 – 6.77 (m, 6H), 7.00 – 7.15 (m, 1H), 7.21 – 7.39 (m, 4H), 7.46 (s, 1H), 7.87 (s, 1H), 8.97 (s, 1H).

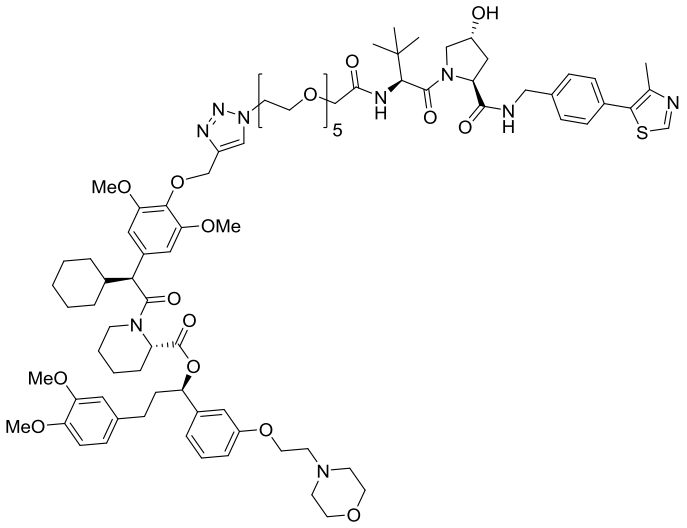
TLC: R_f = 0.06 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 1.0 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+2H]^{2+}$ calculated for $C_{80}H_{109}N_9O_{18}S$ = 758.88784; found = 758.88805.

Lab book number(s): MWa220.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(4-((1-((*S*)-19-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-20,20-dimethyl-17-oxo-3,6,9,12,15-pentaoxa-18-azahenicosyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{82}H_{113}N_9O_{19}S$, MW = 1560.91 g / mol

The product was synthesized from azide **57e** (3.3 mg, 6.0 μmol, 1.0 eq.) and alkyne **A9** (5.0 mg, 6.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 6.2 mg (66 %, 4.0 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.64 – 0.74 (m, 1H), 0.71 – 0.83 (m, 2H), 0.91 (s, 11H), 1.03 – 1.27 (m, 6H), 1.29 – 1.44 (m, 1H), 1.44 – 1.70 (m, 6H), 1.70 – 2.18 (m, 6H), 2.13 – 2.31 (m, 1H), 2.30 – 2.54 (m, 5H), 2.69 (t, *J* = 12.8 Hz, 1H), 2.94 – 3.16 (m, 1H), 3.32 (d, *J* = 9.8 Hz, 1H), 3.56 (d, *J* = 13.3 Hz, 38H), 3.73 (s, 1H), 3.78 (d, *J* = 6.0 Hz, 6H), 3.80 – 4.04 (m, 8H), 4.26 (dd, *J* = 40.1, 5.2 Hz, 4H), 4.47 (s, 8H), 4.98 (s, 2H), 5.38 (s, 1H), 5.44 – 5.57 (m, 1H), 6.38 (d, *J* = 14.5 Hz, 2H), 6.45 – 6.82 (m, 6H), 7.08 (t, *J* = 7.8 Hz, 1H), 7.24 – 7.38 (m, 5H), 7.81 (s, 1H), 9.00 (s, 1H).

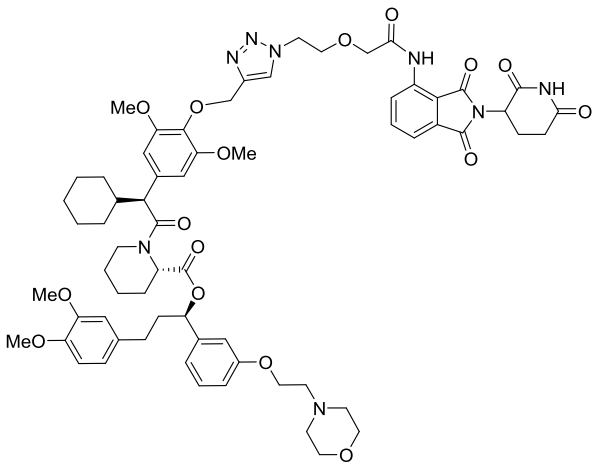
TLC: R_f = 0.06 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 1.0 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+2H]^{2+}$ calculated for $C_{82}H_{113}N_9O_{19}S$ = 780.90095; found = 780.90105.

Lab book number(s): MWa221.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (2*S*)-1-((2*S*)-2-cyclohexyl-2-(4-((1-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{65}H_{78}N_8O_{16}$, MW = 1227.38 g / mol

The product was synthesized from azide **55a** (2.4 mg, 6.0 μmol, 1.0 eq.) and alkyne **A9** (5.0 mg, 6.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 3.9 mg (53 %, 3.2 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.62 – 0.89 (m, 2H), 0.96 – 1.31 (m, 7H), 1.46 – 1.66 (m, 6H), 1.72 – 2.05 (m, 6H), 2.24 (d, *J* = 13.8 Hz, 1H), 2.31 – 2.42 (m, 1H), 2.48 – 2.70 (m, 4H), 2.67 – 2.83 (m, 2H), 2.91 – 3.10 (m, 2H), 3.29 (d, *J* = 9.4 Hz, 1H), 3.37 – 3.55 (m, 7H), 3.55 – 3.65 (m, 1H), 3.69 (s, 1H), 3.78 (d, *J* = 7.4 Hz, 6H), 3.92 (s, 5H), 4.05 – 4.12 (m, 3H), 4.11 – 4.31 (m, 2H), 4.69 (s, 3H), 4.77 – 5.14 (m, 3H), 5.37 (s, 1H), 5.50 (s, 1H), 6.30 – 6.43 (m, 2H), 6.52 – 6.87 (m, 6H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.61 – 7.70 (m, 1H), 8.14 (s, 1H), 8.60 – 8.84 (m, 2H), 10.42 (s, 1H).

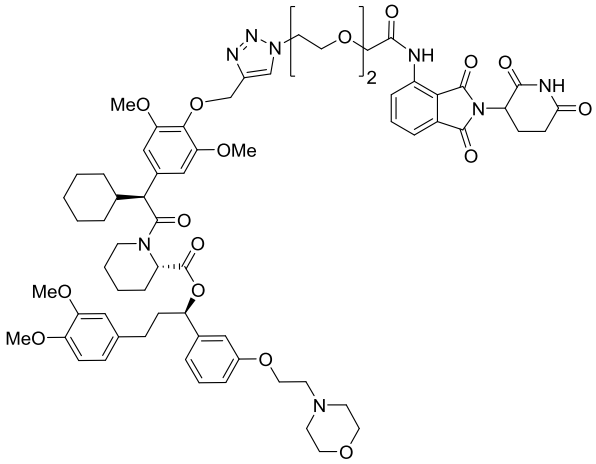
TLC: R_f = 0.19 (DCM:MeOH = 20:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 0.9 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{80}H_{109}N_9O_{18}S$ = 1227.56085; found = 1227.55794.

Lab book number(s): MWa223.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (2*S*)-1-((2*S*)-2-cyclohexyl-2-(4-((1-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{67}H_{82}N_8O_{17}$, MW = 1271.43 g / mol

The product was synthesized from azide **55b** (2.7 mg, 6.0 μmol, 1.0 eq.) and alkyne **A9** (5.0 mg, 6.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 3.7 mg (49 %, 2.9 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.67 (d, *J* = 10.4 Hz, 1H), 0.83 (q, *J* = 12.0, 11.4 Hz, 1H), 1.01 – 1.29 (m, 7H), 1.36 – 1.46 (m, 1H), 1.62 (d, *J* = 24.1 Hz, 6H), 1.80 (dd, *J* = 24.4, 9.3 Hz, 2H), 1.98 (q, *J* = 11.2, 7.7 Hz, 2H), 2.11 (q, *J* = 5.1 Hz, 1H), 2.25 (d, *J* = 12.5 Hz, 1H), 2.32 – 2.43 (m, 1H), 2.42 – 2.74 (m, 2H), 2.74 – 2.88 (m, 2H), 3.03 (dt, *J* = 15.3, 7.4 Hz, 1H), 3.30 (d, *J* = 13.9 Hz, 1H), 3.45 (d, *J* = 1.8 Hz, 1H), 3.54 (dd, *J* = 4.7, 3.2 Hz, 5H), 3.70 (d, *J* = 1.3 Hz, 1H), 3.73 – 3.75 (m, 3H), 3.76 – 3.80 (m, 5H), 3.84 – 3.98 (m, 1H), 4.11 (d, *J* = 1.6 Hz, 2H), 4.16 – 4.22 (m, 2H), 4.53 (t, *J* = 4.7 Hz, 2H), 4.65 – 4.93 (m, 3H), 5.39 (s, 1H), 5.46 – 5.53 (m, 1H), 6.30 (dd, *J* = 7.5, 4.8 Hz, 2H), 6.50 – 6.82 (m, 6H), 7.02 – 7.10 (m, 1H), 7.26 – 7.61 (m, 2H), 7.94 (d, *J* = 6.3 Hz, 1H), 8.53 – 8.76 (m, 1H), 10.38 (s, 1H).

TLC: R_f = 0.19 (DCM:MeOH = 10:1).

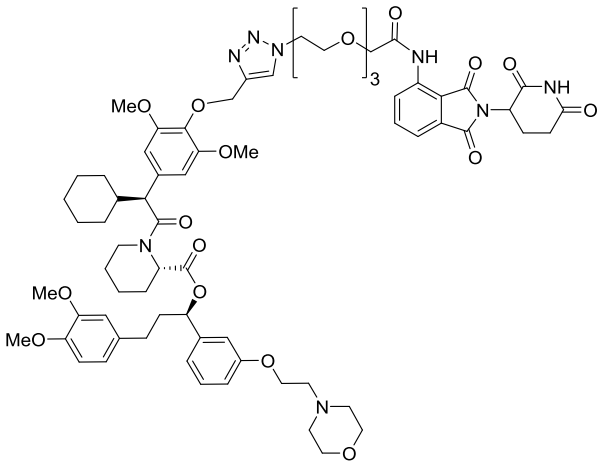
LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 1.0 min.

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{67}H_{82}N_8O_{17}$ = 1271.58707; found = 1271.58356.

Lab book number(s): MWa224.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (2*S*)-1-((2*S*)-2-cyclohexyl-2-(4-((1-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{69}H_{86}N_8O_{18}$, MW = 1315.49 g / mol

The product was synthesized from azide **55c** (2.9 mg, 6.0 μmol, 1.0 eq.) and alkyne **A9** (5.0 mg, 6.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 4.2 mg (53 %, 3.2 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.69 (d, *J* = 10.5 Hz, 1H), 0.83 (d, *J* = 12.7 Hz, 1H), 0.98 – 1.28 (m, 9H), 1.37 (d, *J* = 13.0 Hz, 0H), 1.48 – 1.70 (m, 6H), 1.79 (d, *J* = 8.6 Hz, 2H), 1.86 – 2.13 (m, 2H), 2.24 (d, *J* = 12.8 Hz, 1H), 2.30 – 2.57 (m, 2H), 2.59 – 2.84 (m, 4H), 3.00 (s, 2H), 3.31 (d, *J*

= 9.5 Hz, 1H), 3.45 (s, 3H), 3.60 (d, *J* = 11.2 Hz, 9H), 3.72 (d, *J* = 2.5 Hz, 4H), 3.77 (d, *J* = 1.4 Hz, 6H), 3.78 – 3.97 (m, 7H), 4.13 (d, *J* = 6.5 Hz, 2H), 4.20 (s, 3H), 4.37 – 4.50 (m, 2H), 5.39 (d, *J* = 3.9 Hz, 1H), 5.44 – 5.56 (m, 1H), 6.32 – 6.41 (m, 2H), 6.46 – 6.80 (m, 6H), 7.07 (d, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 6.1 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.82 (s, 1H), 8.54 (s, 1H), 8.76 (d, *J* = 8.4 Hz, 1H), 10.36 (s, 1H).

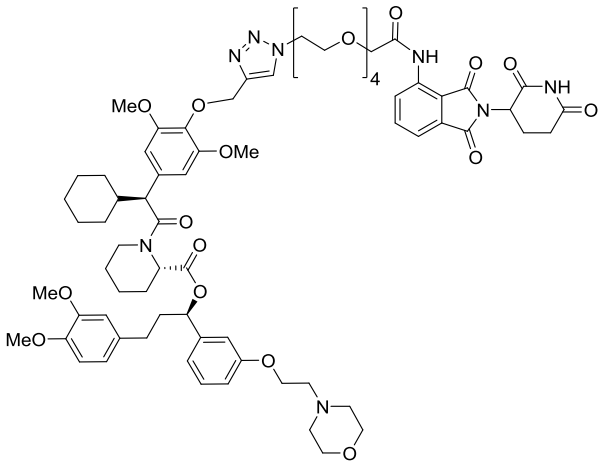
TLC: R_f = 0.18 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 1.0 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{69}H_{86}N_8O_{18}$ = 1315.61328; found = 1315.61925.

Lab book number(s): MWa225.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (2*S*)-1-((2*S*)-2-cyclohexyl-2-(4-((1-(14-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-14-oxo-3,6,9,12-tetraoxatetradecyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{71}H_{90}N_8O_{19}$, MW = 1359.54 g / mol

The product was synthesized from azide **55d** (3.2 mg, 6.0 μmol, 1.0 eq.) and alkyne **A9** (5.0 mg, 6.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 4.1 mg (50 %, 3.0 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.76 (d, *J* = 11.0 Hz, 0H), 0.89 (t, *J* = 10.0 Hz, 1H), 1.07 – 1.36 (m, 7H), 1.43 (d, *J* = 13.6 Hz, 0H), 1.66 (s, 7H), 1.80 – 1.94 (m, 2H), 1.93 – 2.21 (m, 3H), 2.30 (d, *J* = 12.7 Hz, 1H), 2.38 – 2.61 (m, 3H), 2.81 (d, *J* = 27.0 Hz, 4H), 3.08 (s, 1H), 3.38 (d, *J* = 9.4 Hz, 1H), 3.50 (s, 1H), 3.58 – 3.72 (m, 18H), 3.80 (d, *J* = 4.5 Hz, 3H), 3.83 – 3.88 (m, 5H), 3.86 – 4.04 (m, 7H), 4.17 (d, *J* = 10.6 Hz, 2H), 4.22 – 4.37 (m, 2H), 4.54 (s, 2H), 4.90 – 5.18 (m, 3H), 5.46 (s, 1H), 5.58 (s, 1H), 6.40 – 6.50 (m, 2H), 6.49 – 6.85 (m, 6H), 7.14 (q, *J* = 15.4, 7.3 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.72 (t, *J* = 7.8 Hz, 1H), 7.83 (s, 1H), 8.76 (s, 1H), 8.84 (d, *J* = 8.3 Hz, 1H), 10.48 (s, 1H).

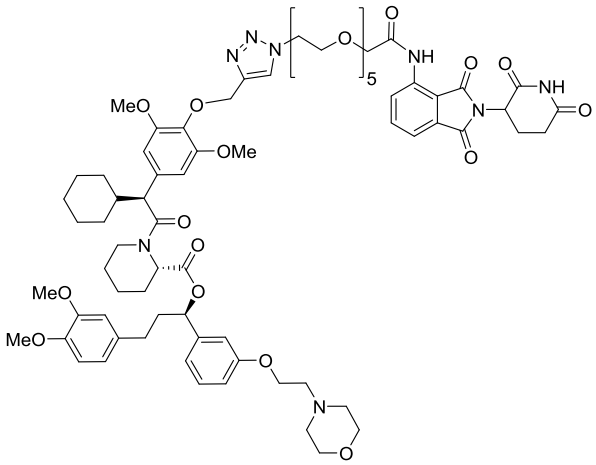
TLC: R_f = 0.18 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 1.1 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{71}H_{90}N_8O_{19}$ = 1359.63950; found = 1359.63559.

Lab book number(s): MWa226.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (2*S*)-1-((2*S*)-2-cyclohexyl-2-(4-((1-(17-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-17-oxo-3,6,9,12,15-pentaoxaheptadecyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{73}H_{94}N_8O_{20}$, MW = 1403.59 g / mol

The product was synthesized from azide **55e** (2.3 mg, 4.0 μmol, 1.0 eq.) and alkyne **A9** (3.3 mg, 4.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 3.4 mg (61 %, 2.4 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.69 (d, *J* = 12.1 Hz, 1H), 0.82 (t, *J* = 9.4 Hz, 1H), 0.99 – 1.28 (m, 7H), 1.27 – 1.41 (m, 0H), 1.49 – 1.71 (m, 6H), 1.74 – 1.87 (m, 2H), 1.90 – 2.13 (m, 3H), 2.23 (d, *J* = 14.1 Hz, 1H), 2.33 – 2.56 (m, 0H), 2.59 – 2.86 (m, 4H), 3.02 (s, 1H), 3.30 (d, *J* = 9.9 Hz, 1H), 3.36 – 3.67 (m, 18H), 3.73 (s, 4H), 3.74 – 3.86 (m, 7H), 3.91 (s, 4H), 4.12 (s, 2H), 4.22 (s, 2H), 4.40 – 4.50 (m, 2H), 4.94 (d, *J* = 27.0 Hz, 3H), 5.39 (d, *J* = 3.7 Hz, 1H), 5.50 (s, 1H), 6.37 (d, *J* = 17.7 Hz, 2H), 6.45 – 6.76 (m, 6H), 7.00 – 7.12 (m, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.59 – 7.71 (m, 1H), 7.74 (s, 1H), 8.73 – 8.87 (m, 2H), 10.42 (s, 1H).

TLC: R_f = 0.17 (DCM:MeOH = 10:1).

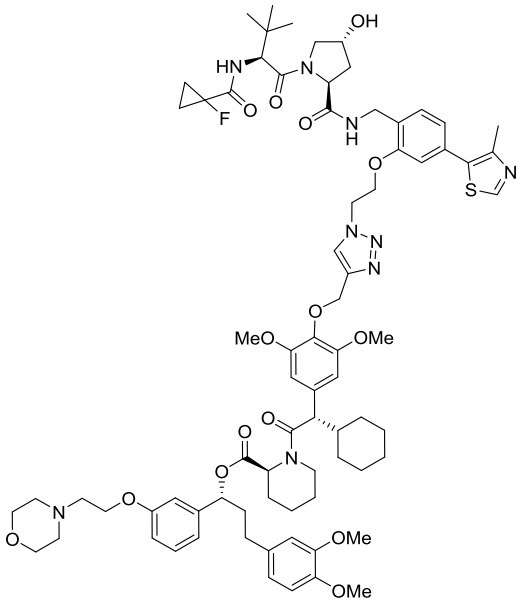
LC-MS: [50-100 % Solvent B, 2.7 min]: R_t = 1.1 min.

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{73}H_{94}N_8O_{20}$ = 1403.66571; found = 1403.67120.

Lab book number(s): MWa227.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(4-((1-(2-(2-(((2*S*,4*R*)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{76}H_{98}FN_9O_{15}S$, MW = 1428.73 g / mol

The product was synthesized from azide **58a** (6.0 mg, 10.0 μmol, 1.0 eq.) and alkyne **A9** (8.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 11.3 mg (79 %, 7.9 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.67 – 0.77 (m, 1H), 0.92 (s, 10H), 0.96 – 1.34 (m, 12H), 1.33 – 1.47 (m, 1H), 1.49 – 1.72 (m, 6H), 1.76 – 1.87 (m, 2H), 1.89 – 2.32 (m, 6H), 2.47 (s, 4H), 2.52 – 2.60 (m, 1H), 2.72 (t, *J* = 13.0 Hz, 1H), 3.05 (d, *J* = 12.6 Hz, 1H), 3.34 (d, *J* = 9.8 Hz, 1H), 3.45 (s, 2H), 3.61 (s, 5H), 3.69 (d, *J* = 6.5 Hz, 1H), 3.74 – 3.85 (m, 8H), 3.86 – 4.02 (m, 5H), 4.21 – 4.49 (m, 7H), 4.58 (d, *J* = 9.0 Hz, 1H), 4.66 – 4.91 (m, 4H), 4.92 – 5.15 (m, 2H), 5.41 (d, *J* = 5.3 Hz, 1H), 5.51 (t, *J* = 6.9 Hz, 1H), 6.40 (d, *J* = 11.9 Hz, 2H), 6.53 – 6.85 (m, 7H), 6.95 (d, *J* = 7.7 Hz, 1H), 7.01 – 7.15 (m, 2H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 6.1 Hz, 1H), 7.92 (d, *J* = 17.6 Hz, 1H), 8.67 (s, 1H).

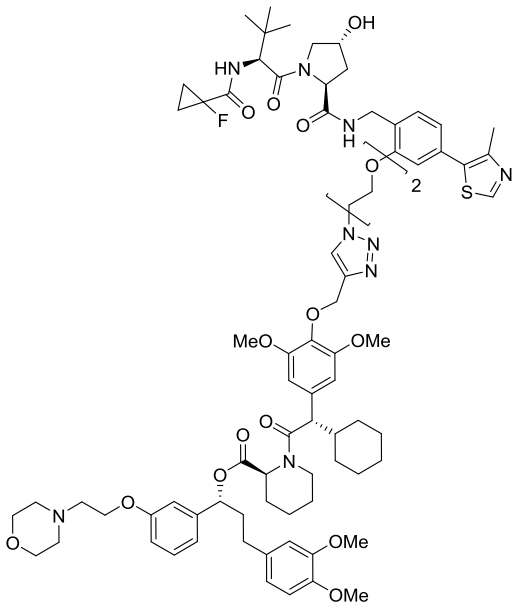
TLC: R_f = 0.08 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 1.7 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{76}H_{98}FN_9O_{15}S$ = 1428.69599; found = 1428.70331.

Lab book number(s): MWa364.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(4-((1-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{78}H_{102}FN_9O_{16}S$, MW = 1472.78 g / mol

The product was synthesized from azide **58b** (6.5 mg, 10.0 μmol, 1.0 eq.) and alkyne **A9** (8.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 9.5 mg (65 %, 6.5 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 0.68 (d, *J* = 11.8 Hz, 1H), 0.79 – 0.91 (m, 11H), 0.97 – 1.10 (m, 3H), 1.10 – 1.29 (m, 9H), 1.35 (dd, *J* = 14.0, 4.7 Hz, 1H), 1.56 (q, *J* = 15.2, 12.3 Hz, 6H), 1.78 (q, *J* = 5.7 Hz, 2H), 1.84 – 2.06 (m, 3H), 2.16 – 2.28 (m, 2H), 2.30 – 2.40 (m, 1H), 2.42 (d, *J* = 2.8 Hz, 4H), 2.48 – 2.54 (m, 1H), 2.59 – 2.71 (m, 1H), 3.00 – 3.09 (m, 0H), 3.29 (d, *J* = 9.8 Hz, 1H), 3.39 (tt, *J* = 9.7, 5.2 Hz, 2H), 3.55 (s, 5H), 3.59 (dd, *J* = 10.8, 4.2 Hz, 1H), 3.66 – 3.82 (m, 10H), 3.81 – 3.96 (m, 7H), 4.06 (dtd, *J* = 14.4, 11.1, 10.6, 5.9 Hz, 2H), 4.15 – 4.46 (m, 6H), 4.47 (p, *J* = 6.1, 5.4 Hz, 2H), 4.51 – 4.59 (m, 2H), 4.87 – 5.04 (m, 2H), 5.35 (d, *J* = 5.4 Hz, 1H), 5.47 (dd, *J* =

8.6, 5.2 Hz, 1H), 6.32 – 6.41 (m, 2H), 6.45 – 6.74 (m, 6H), 6.76 – 6.79 (m, 2H), 6.86 – 6.91 (m, 1H), 6.98 – 7.09 (m, 2H), 7.27 (s, 2H), 7.74 (d, J = 20.3 Hz, 1H), 8.60 (s, 1H).

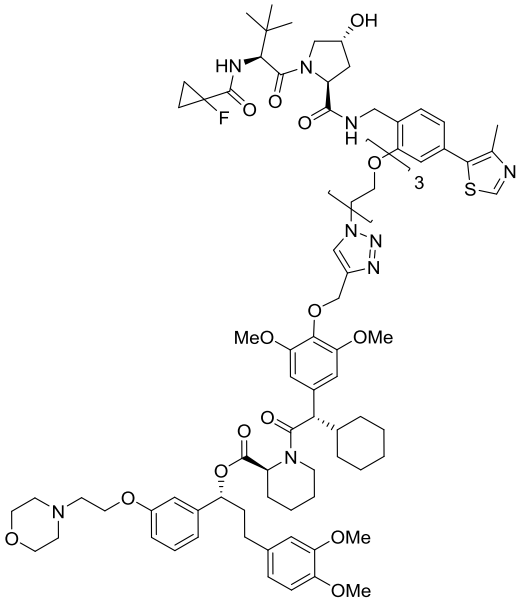
TLC: R_f = 0.08 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 1.7 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{78}H_{102}FN_9O_{16}S$ = 1472.72220; found = 1472.72922.

Lab book number(s): MWa365.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(4-((1-(2-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{80}H_{106}FN_9O_{17}S$, MW = 1516.83 g / mol

The product was synthesized from azide **58c** (6.9 mg, 10.0 μmol, 1.0 eq.) and alkyne **A9** (8.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 8.0 mg (53 %, 5.3 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.60 – 0.80 (m, 1H), 0.88 (s, 10H), 0.97 – 1.40 (m, 13H), 1.40 – 1.68 (m, 6H), 1.70 – 1.84 (m, 2H), 1.83 – 2.10 (m, 3H), 2.10 – 2.26 (m, 3H), 2.30 – 2.42 (m, 1H), 2.42 (s, 3H), 2.50 (p, *J* = 1.9 Hz, 1H), 2.58 – 2.70 (m, 1H), 2.99 – 3.10 (m, 6H), 3.24 – 3.35 (m, 1H), 3.39 (dd, *J* = 7.5, 4.3 Hz, 2H), 3.57 (s, 6H), 3.57 – 3.67 (m, 2H), 3.68 – 3.82 (m, 12H), 3.81 – 3.99 (m, 5H), 3.98 – 4.18 (m, 2H), 4.19 – 4.48 (m, 8H), 4.51 – 4.61 (m, 2H), 4.91 – 5.04 (m, 2H), 5.35 (d, *J* = 5.2 Hz, 1H), 5.46 (dd, *J* = 8.5, 5.1 Hz, 1H), 6.36 (d, *J* = 15.4 Hz, 2H), 6.42 – 6.76 (m, 6H), 6.79 (d, *J* = 7.1 Hz, 1H), 6.85 – 6.90 (m, 1H), 6.97 – 7.10 (m, 2H), 7.25 – 7.41 (m, 2H), 7.76 (d, *J* = 12.3 Hz, 1H), 8.62 (s, 1H).

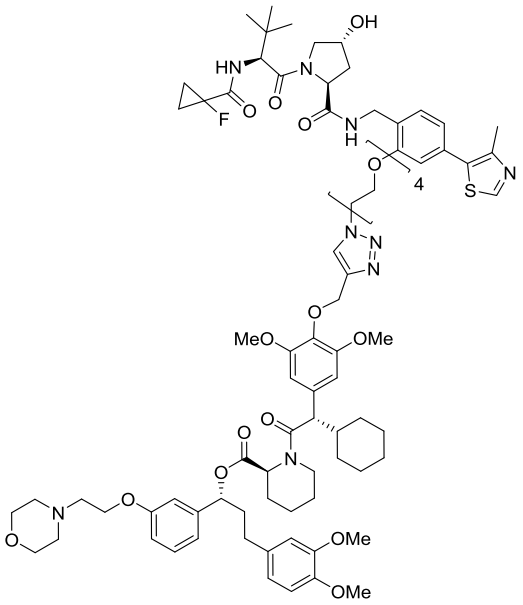
TLC: R_f = 0.08 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 1.7 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{80}H_{106}FN_9O_{17}S$ = 1516.74842; found = 1516.75723.

Lab book number(s): MWa366.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(4-((1-(2-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{82}H_{110}FN_9O_{18}S$, MW = 1560.89 g / mol

The product was synthesized from azide **58d** (7.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A9** (8.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 7.8 mg (50 %, 5.0 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.62 – 0.72 (m, 1H), 0.74 – 0.85 (m, 1H), 0.90 (s, 11H), 0.96 – 1.42 (m, 13H), 1.47 – 1.69 (m, 6H), 1.78 (d, *J* = 11.4 Hz, 2H), 1.93 (s, 75H), 2.03 – 2.27 (m, 3H), 2.47 (s, 5H), 2.69 (dd, *J* = 12.9, 10.3 Hz, 1H), 2.99 – 3.13 (m, 1H), 3.30 (d, *J* = 9.7 Hz, 1H), 3.37 – 3.48 (m, 2H), 3.55 (d, *J* = 15.2 Hz, 10H), 3.57 – 3.68 (m, 3H), 3.70 – 3.83 (m, 8H), 3.83 – 3.99 (m, 5H), 4.04 – 4.27 (m, 4H), 4.30 – 4.66 (m, 8H), 5.01 (d, *J* = 31.0 Hz, 2H), 5.37 (d, *J* = 5.1 Hz, 1H), 5.49 (d, *J* = 8.0 Hz, 1H), 6.29 – 6.43 (m, 2H), 6.45 – 6.78 (m, 6H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.88 (d,

J = 7.7 Hz, 1H), 6.94 – 7.11 (m, 2H), 7.31 (d, J = 7.7 Hz, 1H), 7.39 (s, 1H), 7.81 (d, J = 13.2 Hz, 1H), 8.90 (s, 1H).

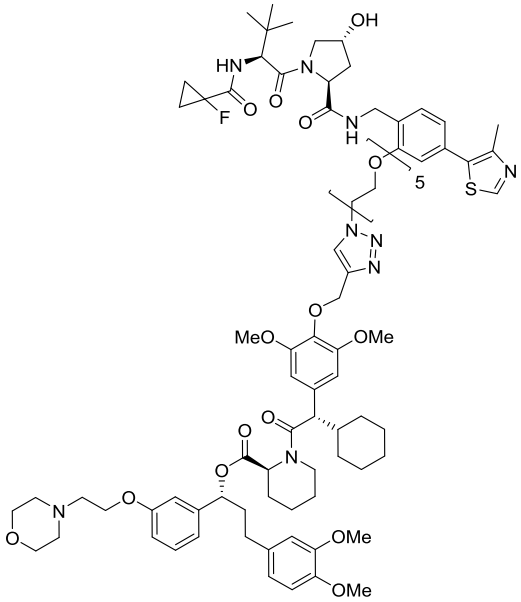
TLC: R_f = 0.07 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 1.7 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+2H]^{2+}$ calculated for $C_{82}H_{110}FN_9O_{18}S$ = 780.89095; found = 780.89167.

Lab book number(s): MWa367.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(4-((1-(14-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)-3,6,9,12-tetraoxatetradecyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{84}H_{114}FN_9O_{19}S$, MW = 1604.94 g / mol

The product was synthesized from azide **58e** (7.8 mg, 10.0 μmol, 1.0 eq.) and alkyne **A9** (8.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.1 mg (63 %, 6.3 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.70 (ddd, *J* = 21.9, 10.1, 5.3 Hz, 1H), 0.80 – 1.03 (m, 7H), 1.03 – 1.41 (m, 8H), 1.52 – 1.70 (m, 4H), 1.77 – 1.87 (m, 1H), 1.97 (dd, *J* = 3.8, 2.1 Hz, 57H), 2.16 – 2.34 (m, 1H), 2.48 (s, 3H), 2.70 (s, 0H), 3.00 – 3.11 (m, 0H), 3.34 (d, *J* = 9.4 Hz, 1H), 3.39 – 3.51 (m, 2H), 3.51 – 3.72 (m, 10H), 3.75 – 3.89 (m, 8H), 3.91 – 4.01 (m, 6H), 4.06 – 4.33 (m, 4H), 4.35 – 4.66 (m, 8H), 4.96 – 5.13 (m, 2H), 5.37 – 5.45 (m, 1H), 5.47 – 5.57 (m, 1H), 6.33 – 6.49 (m, 2H), 6.50 – 6.77 (m, 5H), 6.79 – 7.00 (m, 3H), 7.00 – 7.16 (m, 2H), 7.28 – 7.41 (m, 2H), 7.79 (s, 1H), 8.68 (s, 1H).

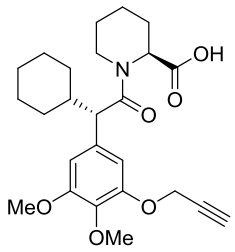
TLC: R_f = 0.07 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 1.7 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+2H]^{2+}$ calculated for $C_{84}H_{114}FN_9O_{19}S$ = 802.90406; found = 802.90462.

Lab book number(s): MWa368.

(*S*)-1-((*S*)-2-Cyclohexyl-2-(3,4-dimethoxy-5-(prop-2-yn-1-yloxy)phenyl)acetyl) piperidine-2-carboxylic acid



$C_{25}H_{33}NO_6$, MW = 443.54 g / mol

(*S*)-1-((*S*)-2-Cyclohexyl-2-(3-hydroxy-4,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylic acid (214 mg, 0.53 mmol, 1.0 eq.), 3-bromoprop-1-yne (151 mg, 1.27 mmol, 2.4 eq.) and potassium carbonate (729 mg, 5.28 mmol, 10.0 eq.) were stirred in acetone (5 mL) for 18 h at room temperature. The solution was filtered and concentrated under reduced pressure.

Appearance: colorless oil.
TLC: R_f = 0.33 (CH:EA = 3:1).

To crude prop-2-yn-1-yl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4-dimethoxy-5-(prop-2-yn-1-yloxy)phenyl)acetyl)piperidine-2-carboxylate (254 mg, 0.53 mmol, 1.0 eq.) in THF:water (1:1, 10 mL) lithium hydroxide (127 mg, 5.3 mmol, 10 eq.) was added and the mixture was stirred for 4 d at 70 °C. The solution was diluted with hydrochloric acid (1 M, aq, 50 mL) and extracted with DCM (3 x 30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 180 mg (77 % o2s, 0.41 mmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.63 – 1.75 (m, 14H), 1.76 – 1.93 (m, 1H), 2.13 (dd, *J* = 61.4, 12.2 Hz, 2H), 2.45 (dt, *J* = 8.7, 2.4 Hz, 1H), 2.80 (dt, *J* = 84.2, 12.8 Hz, 1H), 3.25 (dd, *J* = 71.7, 9.7 Hz, 1H), 3.69 – 3.85 (m, 6H), 3.92 (d, *J* = 13.9 Hz, 1H), 4.71 (dd, *J* = 9.4, 2.6 Hz, 2H), 5.32 (q, *J* = 2.4 Hz, 1H), 6.42 – 6.60 (m, 2H), 10.69 (s, 2H).

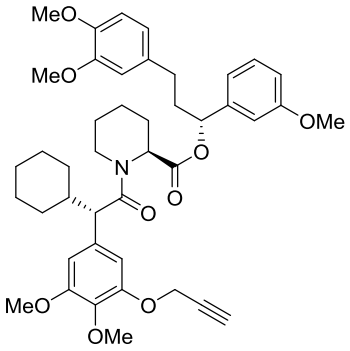
^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 20.9, 25.3, 26.1, 26.2, 26.2, 26.5, 26.6, 30.7, 32.8, 41.1, 43.9, 55.2, 56.1, 57.0, 61.0, 75.6, 78.7, 106.4, 108.8, 132.8, 137.8, 150.6, 153.3, 173.8, 176.0.

TLC: R_f = 0.30 (CH:EA = 1:1, 1 % HCOOH).

LC-MS: Mass (ESI), calculated = 444.2 $[M+H]^+$, found = 444.2.
[5-100 % Solvent B, 2.6 min]: R_t = 2.0 min.
> 99 % purity (220 nm).

Lab book number(s): MWa363 + MWa369.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-methoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4-dimethoxy-5-(prop-2-yn-1-yloxy)phenyl)acetyl)piperidine-2-carboxylate



$C_{43}H_{53}NO_9$, MW = 727.90 g / mol

(*S*)-1-((*S*)-2-Cyclohexyl-2-(3,4-dimethoxy-5-(prop-2-yn-1-yloxy)phenyl)acetyl)piperidine-2-carboxylic acid (78 mg, 175 μmmol, 1.0 eq.) and 4-pyrolidinopyridine (104 mg, 700 μmol, 4.0 eq.) were weighted in a flask and flooded with argon. (*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-methoxyphenyl)propan-1-ol (AV485, 53 mg, 175 μmol, 1.0eq.) and toluene (dry, 15 mL) were added and the mixture was cooled to 0 °C. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (37 mg, 193 μmol, 1.1 eq.) was added and the mixture was stirred for 2 h at 0 °C to room temperature. The solution was diluted with hydrochloric acid (1 M, aq, 10 mL) and brine (40 mL) and extracted with DCM (2 x 40 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 66 mg (52 %, 91 μmol).

Appearance: white solid.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 0.50 – 0.80 (m, 1H), 0.82 – 1.02 (m, 1H), 1.04 – 1.74 (m, 8H), 1.76 – 2.19 (m, 4H), 2.24 – 2.50 (m, 3H), 2.59 (qdd, *J* = 20.3, 9.0, 5.8 Hz, 1H), 2.75 – 2.99 (m, 1H), 3.40 (d, *J* = 9.8 Hz, 1H), 3.65 – 3.88 (m, 15H), 3.95 – 4.03 (m, 1H), 4.63 – 4.78 (m, 2H), 5.40 – 5.49 (m, 1H), 5.53 – 5.59 (m, 1H), 6.39 – 6.53 (m, 1H), 6.55 – 6.71 (m, 4H), 6.73 – 6.81 (m, 2H), 6.84 – 6.97 (m, 1H), 7.22 (dt, *J* = 83.9, 7.9 Hz, 1H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 20.9, 25.6, 26.1, 26.2, 26.6, 26.8, 30.7, 31.1, 32.8, 38.0, 41.3, 44.0, 52.5, 55.0, 55.3, 55.9, 56.1, 57.1, 61.0, 75.6, 76.0, 78.8, 106.4, 109.0, 111.5, 111.9, 112.5, 113.2, 118.5, 120.4, 129.8, 133.1, 133.5, 138.0, 141.7, 147.4, 148.9, 150.8, 153.6, 159.6, 170.3, 173.0.

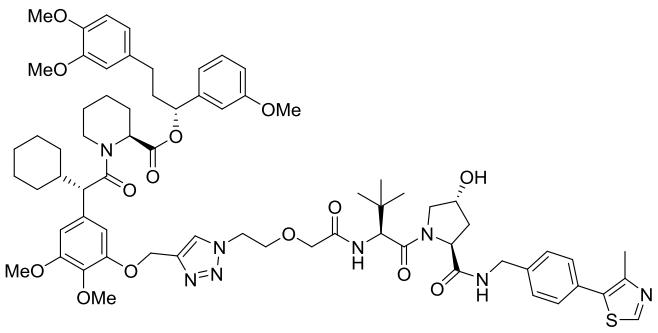
TLC: R_f = 0.31 (CH:EA = 2:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.3 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{43}H_{53}NO_9$ = 728.37931; found = 728.37947.

Lab book number(s): MWa370.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-methoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3-((1-(2-(2-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-4,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{69}H_{88}N_8O_{14}S$, MW = 1285.57 g / mol

The product was synthesized from azide **57a** (2.2 mg, 4.0 μmol, 1.0 eq.) and alkyne **A13** (2.9 mg, 4.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 3.5 mg (69 %, 2.7 μmol).

Appearance: white solid.

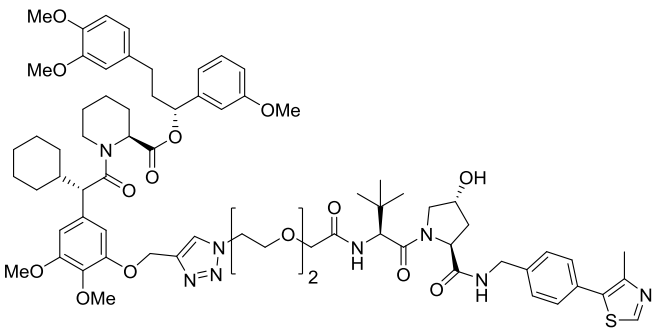
TLC: R_f = 0.16 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 2.6 min]: R_t = 1.9 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{69}H_{88}N_8O_{14}S$ = 1285.62135; found = 1285.62040.

Lab book number(s): MWa375.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-methoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3-((1-(2-(2-(2-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-4,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{71}H_{92}N_8O_{15}S$, MW = 1329.62 g / mol

The product was synthesized from azide **57b** (2.4 mg, 4.0 μmol, 1.0 eq.) and alkyne **A13** (2.9 mg, 4.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.0 mg (94 %, 3.8 μmol).

Appearance: white solid.

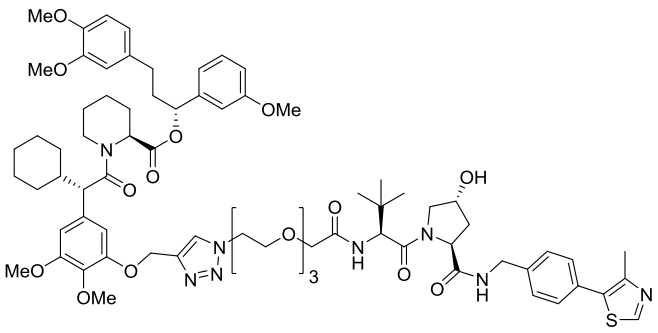
TLC: R_f = 0.16 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 2.6 min]: R_t = 1.9 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{71}H_{92}N_8O_{15}S$ = 1329.64756; found = 1329.64704.

Lab book number(s): MWa376.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-methoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3-((1-((*S*)-13-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-14,14-dimethyl-11-oxo-3,6,9-trioxa-12-azapentadecyl)-1H-1,2,3-triazol-4-yl)methoxy)-4,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{73}H_{96}N_8O_{16}S$, MW = 1373.67 g / mol

The product was synthesized from azide **57c** (2.6 mg, 4.0 μmol, 1.0 eq.) and alkyne **A13** (2.9 mg, 4.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 3.5 mg (64 %, 2.5 μmol).

Appearance: white solid.

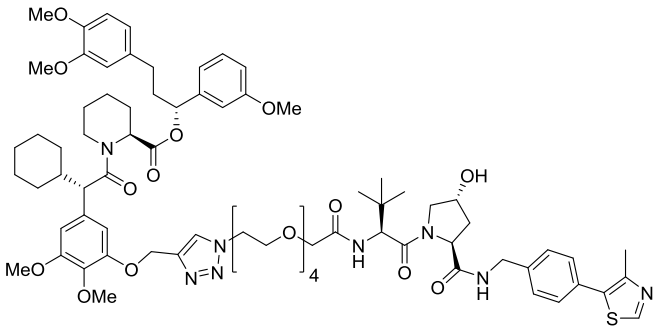
TLC: R_f = 0.15 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 2.6 min]: R_t = 1.9 min.
98 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{73}H_{96}N_8O_{16}S$ = 1373.67378; found = 1373.67526.

Lab book number(s): MWa377.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-methoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3-((1-((*S*)-16-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-17,17-dimethyl-14-oxo-3,6,9,12-tetraoxa-15-azaoctadecyl)-1H-1,2,3-triazol-4-yl)methoxy)-4,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{75}H_{100}N_8O_{17}S$, MW = 1417.72 g / mol

The product was synthesized from azide **57d** (2.8 mg, 4.0 μmol, 1.0 eq.) and alkyne **A13** (2.9 mg, 4.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 4.1 mg (72 %, 2.9 μmol).

Appearance: white solid.

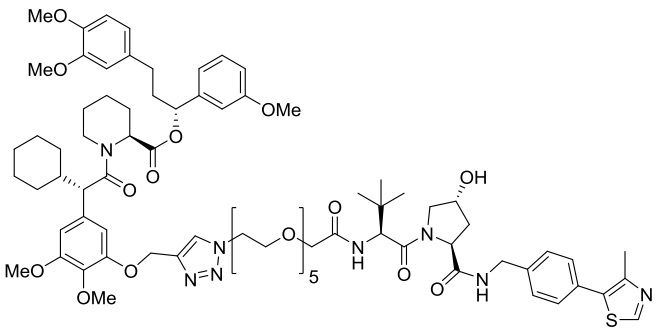
TLC: R_f = 0.14 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 2.6 min]: R_t = 1.9 min.
98 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{75}H_{100}N_8O_{17}S$ = 1417.69999; found = 1417.70019.

Lab book number(s): MWa378.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-methoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3-((1-((*S*)-19-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-20,20-dimethyl-17-oxo-3,6,9,12,15-pentaoxa-18-azahenicosyl)-1H-1,2,3-triazol-4-yl)methoxy)-4,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{77}H_{104}N_8O_{18}S$, MW = 1461.78 g / mol

The product was synthesized from azide **57e** (2.9 mg, 4.0 μmol, 1.0 eq.) and alkyne **A13** (2.9 mg, 4.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 4.7 mg (81 %, 3.2 μmol).

Appearance: white solid.

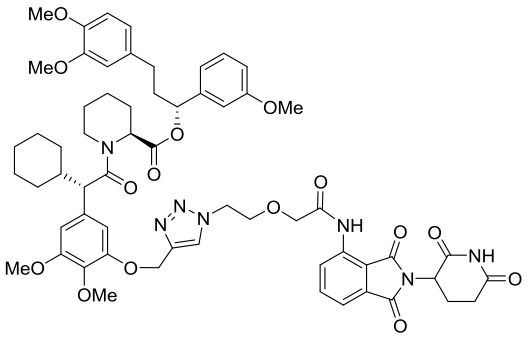
TLC: R_f = 0.14 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 2.6 min]: R_t = 1.9 min.
95 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{77}H_{104}N_8O_{18}S$ = 1461.72621; found = 1461.72623.

Lab book number(s): MWa379.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-methoxyphenyl)propyl (2*S*)-1-((2*S*)-2-cyclohexyl-2-(3-((1-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-4,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{60}H_{69}N_7O_{15}$, MW = 1128.25 g / mol

The product was synthesized from azide **55a** (1.6 mg, 4.0 μmol, 1.0 eq.) and alkyne **A13** (2.9 mg, 4.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 2.9 mg (64 %, 2.6 μmol).

Appearance: white solid.

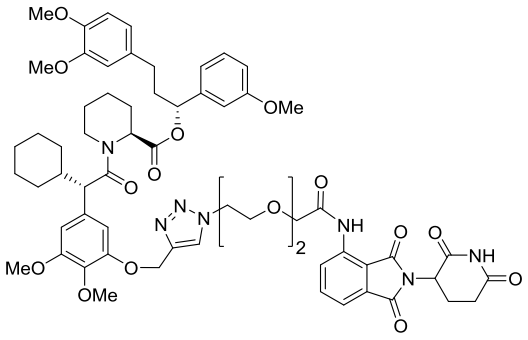
TLC: R_f = 0.30 (DCM:MeOH = 20:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.2 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.6 min.
97 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{60}H_{69}N_7O_{15}$= 1128.49244; found = 1128.49277.

Lab book number(s): MWa385.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-methoxyphenyl)propyl (2*S*)-1-((2*S*)-2-cyclohexyl-2-(3-((1-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-4,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{62}H_{73}N_7O_{16}$, MW = 1172.30 g / mol

The product was synthesized from azide **55b** (1.8 mg, 4.0 μmol, 1.0 eq.) and alkyne **A13** (2.9 mg, 4.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 4.6 mg (98 %, 3.9 μmol).

Appearance: white solid.

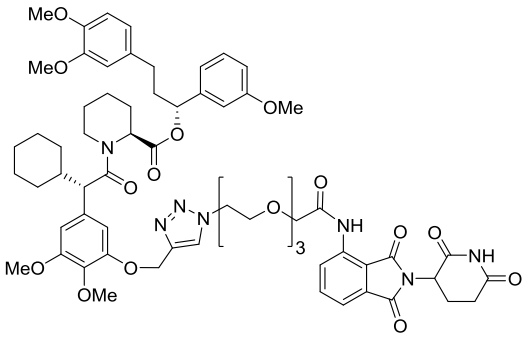
TLC: R_f = 0.28 (DCM:MeOH = 20:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.2 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.7 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{62}H_{73}N_7O_{16}$= 1172.51866; found = 1172.51918.

Lab book number(s): MWa386.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-methoxyphenyl)propyl (2*S*)-1-((2*S*)-2-cyclohexyl-2-(3-((1-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-4,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{64}H_{77}N_7O_{17}$, MW = 1216.35 g / mol

The product was synthesized from azide **55c** (2.0 mg, 4.0 μmol, 1.0 eq.) and alkyne **A13** (2.9 mg, 4.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 4.8 mg (98 %, 3.9 μmol).

Appearance: white solid.

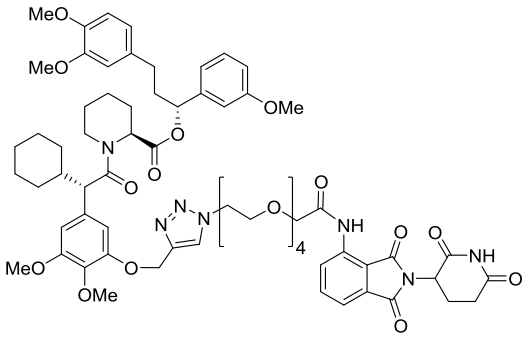
TLC: R_f = 0.27 (DCM:MeOH = 20:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.2 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.6 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{64}H_{77}N_7O_{17}$= 1216.54487; found = 1216.54524.

Lab book number(s): MWa387.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-methoxyphenyl)propyl (2*S*)-1-((2*S*)-2-cyclohexyl-2-(3-((1-(2-((8-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethoxy)octyl)oxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-4,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{66}H_{81}N_7O_{18}$, MW = 1260.41 g / mol

The product was synthesized from azide **55d** (2.1 mg, 4.0 μmol, 1.0 eq.) and alkyne **A13** (2.9 mg, 4.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 4.1 mg (82 %, 3.3 μmol).

Appearance: white solid.

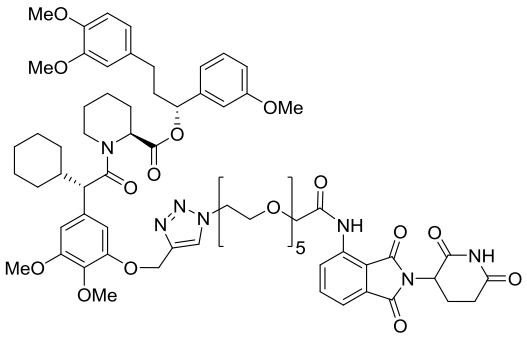
TLC: R_f = 0.26 (DCM:MeOH = 20:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.2 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.6 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{66}H_{81}N_7O_{18}$= 1260.57109; found = 1260.57124.

Lab book number(s): MWa388.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-methoxyphenyl)propyl (2*S*)-1-((2*S*)-2-cyclohexyl-2-(3-((1-(17-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-17-oxo-3,6,9,12,15-pentaoxaheptadecyl)-1H-1,2,3-triazol-4-yl)methoxy)-4,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{68}H_{85}N_7O_{19}$, MW = 1304.46 g / mol

The product was synthesized from azide **55e** (2.3 mg, 4.0 μmol, 1.0 eq.) and alkyne **A13** (2.9 mg, 4.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 4.8 mg (92 %, 3.7 μmol).

Appearance: white solid.

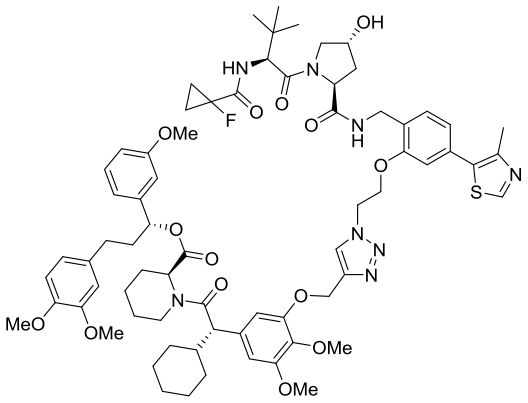
TLC: R_f = 0.26 (DCM:MeOH = 20:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.2 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.6 min.
98 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{68}H_{85}N_7O_{19}$= 1304.59730; found = 1304.59795.

Lab book number(s): MWa389.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-methoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3-((1-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-4,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{71}H_{89}FN_8O_{14}S$, MW = 1329.59 g / mol

The product was synthesized from azide **58a** (2.4 mg, 4.0 μmol, 1.0 eq.) and alkyne **A13** (2.9 mg, 4.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 4.9 mg (92 %, 3.7 μmol).

Appearance: white solid.

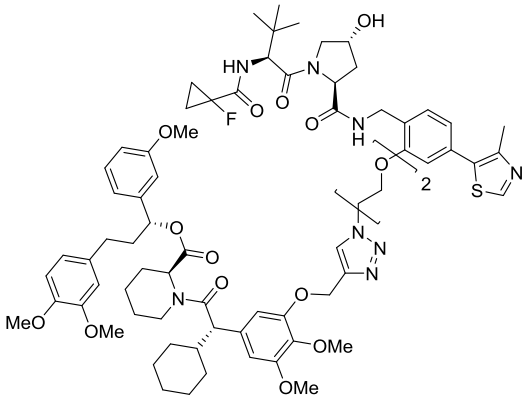
TLC: R_f = 0.13 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.6 min]: R_t = 1.8 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{71}H_{89}FN_8O_{14}S$ = 1329.62758; found = 1329.62804.

Lab book number(s): MWa380.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-methoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3-((1-(2-(2-(((2*S*,4*R*)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-4,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{73}H_{93}FN_8O_{15}S$, MW = 1373.65 g / mol

The product was synthesized from azide **58b** (2.6 mg, 4.0 μmol, 1.0 eq.) and alkyne **A13** (2.9 mg, 4.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 4.7 mg (85 %, 3.4 μmol).

Appearance: white solid.

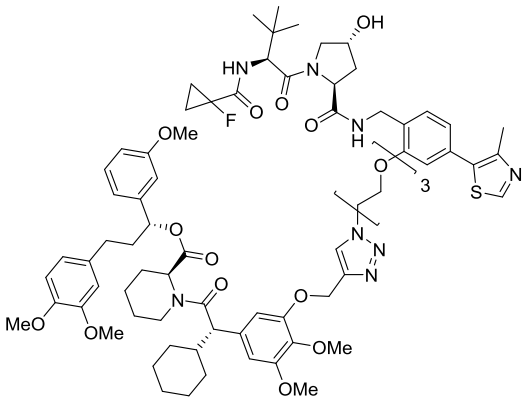
TLC: R_f = 0.12 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.6 min]: R_t = 1.8 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{73}H_{93}FN_8O_{15}S$ = 1373.65379; found = 1373.65448.

Lab book number(s): MWa381.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-methoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3-((1-(2-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-4,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate (382)



$C_{75}H_{97}FN_8O_{16}S$, MW = 1417.70 g / mol

The product was synthesized from azide **58c** (2.8 mg, 4.0 μmol, 1.0 eq.) and alkyne **A13** (2.9 mg, 4.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.0 mg (88 %, 3.5 μmol).

Appearance: white solid.

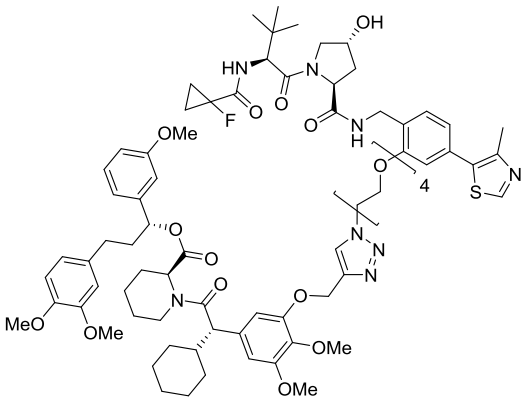
TLC: R_f = 0.12 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.6 min]: R_t = 1.8 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{75}H_{97}FN_8O_{16}S$ = 1417.68000; found = 1417.67944.

Lab book number(s): MWa382.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-methoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3-((1-(2-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-4,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{77}H_{101}FN_8O_{17}S$, MW = 1461.75 g / mol

The product was synthesized from azide **58d** (2.9 mg, 4.0 μmol, 1.0 eq.) and alkyne **A13** (2.9 mg, 4.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.1 mg (88 %, 3.5 μmol).

Appearance: white solid.

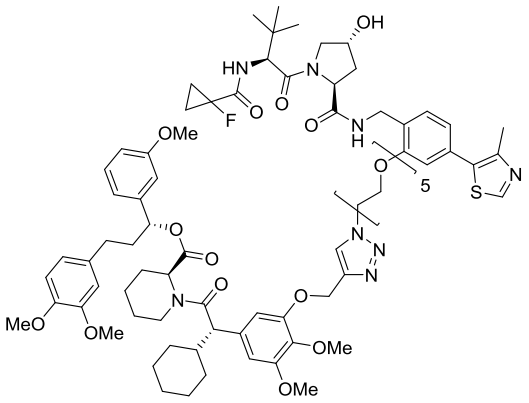
TLC: R_f = 0.11 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.6 min]: R_t = 1.8 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{77}H_{101}FN_8O_{17}S$ = 1461.70622; found = 1461.70634.

Lab book number(s): MWa383.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-methoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3-((1-(14-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)-3,6,9,12-tetraoxatetradecyl)-1H-1,2,3-triazol-4-yl)methoxy)-4,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{79}H_{105}FN_8O_{18}S$, MW = 1505.81 g / mol

The product was synthesized from azide **58e** (3.1 mg, 4.0 μmol, 1.0 eq.) and alkyne **A13** (2.9 mg, 4.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 4.8 mg (80 %, 3.2 μmol).

Appearance: white solid.

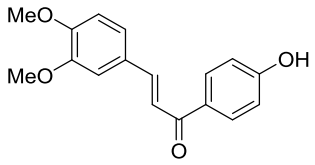
TLC: R_f = 0.11 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.6 min]: R_t = 1.8 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{79}H_{105}FN_8O_{18}S$ = 1505.73243; found = 1505.73201.

Lab book number(s): MWa384.

(*E*)-3-(3,4-Dimethoxyphenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one



$C_{17}H_{16}O_4$, MW = 284.31 g / mol

3,4-Dimethoxybenzaldehyde (6.65 g, 40.0 mmol, 1.0 eq.) and 1-(4-hydroxyphenyl)ethanone (5.45 g, 40.0 mmol, 1.0 eq.) were dissolved in EtOH (100 mL). The mixture was cooled to 0 °C and potassium hydroxide (8.98 g, 160 mmol, 4.0 eq.) in water (30 mL) was slowly added. The mixture was stirred for 18 h at 0 °C to room temperature. Additional potassium hydroxide (9.0 g 160 mmol, 4.0 eq.) was added and the mixture was stirred for 24 h at room temperature. The solvent was removed under reduced pressure. Ice (100 mL) was added and a pH value of 5-6 was set by the addition of hydrochloric acid. The mixture was extracted with DCM (3 x 200 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by recrystallization in methanol.

Yield: 8.9 g (78 %, 31.3 mmol).

Appearance: yellow solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 3.74 (d, *J* = 1.5 Hz, 3H), 3.80 (d, *J* = 1.6 Hz, 3H), 6.82 – 6.89 (m, 2H), 6.93 (d, *J* = 8.3 Hz, 1H), 7.28 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.46 (d, *J* = 2.2 Hz, 1H), 7.59 (d, *J* = 15.4 Hz, 1H), 7.74 (d, *J* = 15.5 Hz, 1H), 8.00 – 8.05 (m, 2H), 10.31 (s, 1H).

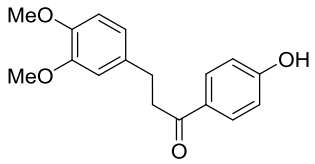
^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 55.6, 55.7, 110.6, 111.5, 115.3, 119.7, 123.6, 127.8, 129.4, 131.1, 143.2, 149.0, 151.0, 162.0, 187.1.

TLC: R_f = 0.38 (CH:EA = 1:1)

LC-MS: Mass (ESI), calculated = 285.1 $[M+H]^+$, found = 285.2.
[5-100 % Solvent B, 3.0 min]: R_t = 1.7 min.
> 99 % purity (220 nm).

Lab book number(s): MWa581 / MWa587 / MWa625 / MWa667.

3-(3,4-Dimethoxyphenyl)-1-(4-hydroxyphenyl)propan-1-one



$C_{17}H_{16}O_4$, MW = 284.31 g / mol

(*E*)-3-(3,4-Dimethoxyphenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (6.55 g, 23.0 mmol, 1.0 eq.) and ammonium chloride (123 g, 2.30 mol, 100 eq.) were dissolved in ethanol:water (2:1, 900 mL). Zn powder (4.5 g, 69.0 mmol, 3.0 eq) was slowly added over 1 h. After complete addition ethanol was removed under reduced pressure. The mixture was extracted with DCM (3 x 300 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 1.89 g (29 %, 6.60 mmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 2.87 (dd, *J* = 8.4, 6.8 Hz, 2H), 3.04 – 3.14 (m, 2H), 3.73 (d, *J* = 3.9 Hz, 6H), 6.66 (dd, *J* = 2.8, 1.7 Hz, 3H), 6.73 – 6.79 (m, 2H), 7.71 – 7.77 (m, 2H), 9.46 (s, 1H).

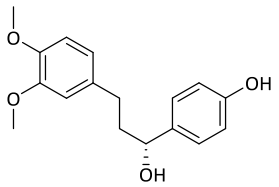
^{13}C-NMR (74 MHz, Chloroform-*d*): δ = 30.0, 40.0, 55.7, 55.9, 111.4, 111.9, 115.4, 120.2, 128.7, 130.4, 130.7, 134.1, 147.2, 148.8, 162.1, 197.9.

TLC: R_f = 0.28 (CH:EA = 2:1)

LC-MS: Mass (ESI), calculated = 287.1 $[M+H]^+$, found = 287.2.
[5-100 % Solvent B, 3.0 min]: R_t = 1.7 min.
96 % purity (220 nm).

Lab book number(s): MWa584 / MWa591 / MWa627 / MWa668.

(*R*)-4-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenol



$C_{17}H_{20}O_4$, MW = 288.34 g / mol

3-(3,4-Dimethoxyphenyl)-1-(4-hydroxyphenyl)propan-1-one (410 mg, 1.43 mmol, 1.0 eq.) was dissolved in *iso*-propanole (20 mL) and degassed by argon. $RuCl_2$[(S)-dm-segphos®][(*S*)-daipen] (36 mg, 0.03 mmol, 0.02 eq.) was added and the mixture was sparged with H_2. Potassium *tert*-butoxide (481 mg, 4.29 mmol, 3.0 eq.) was added and the mixture was stirred for 18 h at room temperature. The mixture was concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 266 mg (64 %, 0.92 mmol).

Appearance: white solid.

^{1}**H-NMR** (500 MHz, Chloroform-*d*): δ = 1.93 – 2.19 (m, 2H), 2.55 – 2.71 (m, 2H), 3.83 – 3.91 (m, 6H), 4.63 (dd, *J* = 7.8, 5.5 Hz, 1H), 6.69 – 6.74 (m, 2H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.80 – 6.84 (m, 1H), 7.21 – 7.24 (m, 2H), 7.26 (d, *J* = 0.8 Hz, 1H).

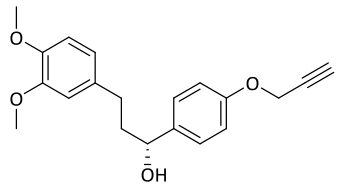
^{13}**C-NMR** (126 MHz, Chloroform-*d*): δ = 136.9, 134.6, 127.6, 120.4, 115.5, 112.0, 111.5, 73.7, 56.1, 56.0, 40.6, 31.9.

TLC: R_f = 0.21 (CH:EA = 1:1).
R_f = 0.41 (DCM:MeOH = 20:1).

LC-MS: Mass (ESI), calculated = 289.1 $[M+H]^+$, found = 271.2.
[5-100 % Solvent B, 2.6 min]: R_t = 1.6 min.
88 % purity (220 nm).

Lab book number(s): MWa373 / MWa628 / MWa669.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-(prop-2-yn-1-yloxy)phenyl)propan-1-ol



$C_{20}H_{22}O_4$, MW = 326.39 g / mol

(*R*)-4-(3-(3,4-Dimethoxyphenyl)-1-hydroxypropyl)phenol (1.38 g, 4.79 mmol, 1.0 eq.), 3-bromoprop-1-yne (684 mg, 5.75 mmol, 1.2 eq.) and potassium carbonate (6.62 g, 47.9 mmol, 10.0 eq.) were stirred in acetone (50 mL) for 18 h at room temperature. The solution was filtered and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 1.23 g (79 %, 3.89 mmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 1.91 – 2.19 (m, 3H), 2.52 (t, *J* = 2.4 Hz, 1H), 2.64 (tdt, *J* = 13.9, 9.1, 6.7 Hz, 2H), 3.84 (d, *J* = 1.3 Hz, 6H), 4.62 (dd, *J* = 7.7, 5.5 Hz, 1H), 4.67 (d, *J* = 2.4 Hz, 2H), 6.68 – 6.81 (m, 3H), 6.92 – 6.98 (m, 2H), 7.24 – 7.31 (m, 2H).

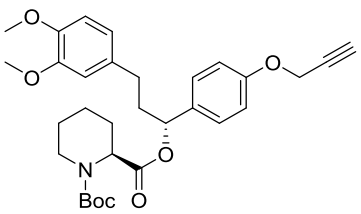
^{13}**C-NMR** (75 MHz, Chloroform-*d*): δ = 31.7, 40.5, 55.8, 55.9, 55.9, 73.4, 75.6, 78.6, 111.4, 111.9, 114.9, 120.2, 127.2, 134.4, 137.7, 147.2, 148.9, 157.0.

TLC: R_f = 0.45 (CH:EA = 1:1).

LC-MS: Mass (ESI), calculated = 349.2 $[M+Na]^+$, found = 349.2.
[5-100 % Solvent B, 3.0 min]: R_t = 1.9 min.
[30-100 % Solvent B, 2.6 min]: R_t = 1.3 min.
> 99 % purity (220 nm).

Lab book number(s): MWa352 / MWa374 / MWa632 / MWa670.

1-(*tert*-Butyl) 2-((*R*)-3-(3,4-dimethoxyphenyl)-1-(4-(prop-2-yn-1-yloxy)phenyl)propyl) (*S*)-piperidine-1,2-dicarboxylate



$C_{31}H_{39}NO_7$, MW = 537.65 g / mol

(*S*)-1-(*tert*-Butoxycarbonyl)piperidine-2-carboxylic acid (54 mg, 236 μmmol, 1.0 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (54 mg, 283 μmol, 1.2 eq.) and 4-dimethylaminopyridine (9.0 mg, 71 μmol, 0.3 eq.) were dissolved in DCM (dry, 1mL) under argon and cooled to 0 °C. (*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-(prop-2-yn-1-yloxy)phenyl)propan-1-ol (77 mg, 236 μmol, 1.0 eq.) was added and the mixture was stirred for 18 h at 0 °C to room temperature. The solvent was removed under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 99 mg (78 %, 184 μmol).

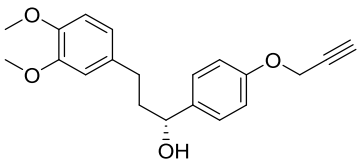
Appearance: white solid.

TLC: R_f = 0.31 (CH:EA = 2:1).

LC-MS: Mass (ESI), calculated = 560.3 $[M+Na]^+$, found = 560.2.
[5-100 % Solvent B, 2.6 min]: R_t = 2.4 min.
> 99 % purity (220 nm).

Lab book number(s): MWa608.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-(prop-2-yn-1-yloxy)phenyl)propan-1-ol



$C_{20}H_{22}O_4$, MW = 326.39 g / mol

1-(*tert*-Butyl) 2-((*R*)-3-(3,4-dimethoxyphenyl)-1-(4-(prop-2-yn-1-yloxy)phenyl)propyl) (*S*)-piperidine-1,2-dicarboxylate (100 mg, 186 μmol, 1.0 eq.) and lithium hydroxide (45 mg, 1860 μmol, 10.0 eq.) were dissolved in THF:water:MeOH (1:1:1, 9 mL). The mixture was stirred for 18 h at room temperature. Sodium hydrogen carbonate (sat., aq, 20 mL) was added and the mixture was extracted with DCM (3 x 30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 50 mg (82 %, 153 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.91 – 2.19 (m, 3H), 2.52 (t, *J* = 2.4 Hz, 1H), 2.64 (tdt, *J* = 13.9, 9.1, 6.7 Hz, 2H), 3.84 (d, *J* = 1.3 Hz, 6H), 4.62 (dd, *J* = 7.7, 5.5 Hz, 1H), 4.67 (d, *J* = 2.4 Hz, 2H), 6.68 – 6.81 (m, 3H), 6.92 – 6.98 (m, 2H), 7.24 – 7.31 (m, 2H).

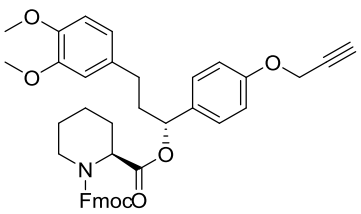
^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 31.7, 40.5, 55.8, 55.9, 55.9, 73.4, 75.6, 78.6, 111.4, 111.9, 114.9, 120.2, 127.2, 134.4, 137.7, 147.2, 148.9, 157.0.

TLC: R_f = 0.45 (CH:EA = 1:1).

LC-MS: Mass (ESI), calculated = 349.2 $[M+H]^+$, found = 349.0.
[5-100 % Solvent B, 3.0 min]: R_t = 1.9 min.
95 % purity (220 nm).

Lab book number(s): MWa619 / MWa637.

1-((9H-Fluoren-9-yl)methyl) 2-((*R*)-3-(3,4-dimethoxyphenyl)-1-(4-(prop-2-yn-1-yloxy)phenyl)propyl) (*S*)-piperidine-1,2-dicarboxylate



$C_{41}H_{41}NO_7$, MW = 659.78 g / mol

(*S*)-1-(((9H-Fluoren-9-yl)methoxy)carbonyl)piperidine-2-carboxylic acid (21 mg, 61 μmol, 1.0 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (14 mg, 74 μmol, 1.2 eq.) and 4-dimethylaminopyridine (2.2 mg, 18 μmol, 0.3 eq.) were cooled to 0 °C under argon. DCM (dry, 1 mL) was added. (*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-(prop-2-yn-1-yloxy)phenyl)propan-1-ol (20 mg, 61 μmol, 1.0 eq.) was added and the mixture was stirred for 15 min at 0 °C followed by 18 h at room temperature. The solution was concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 23 mg (58 %, 35 μmol).

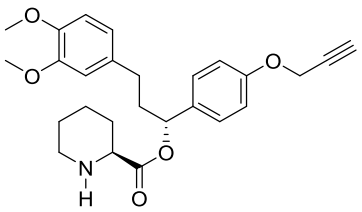
Appearance: white foam.

TLC: R_f = 0.65 (CH:EA = 1:1).

LC-MS: Mass (ESI), calculated = 682.3 $[M+Na]^+$, found = 682.0.
[5-100 % Solvent B, 3.0 min]: R_t = 2.6 min.
99 % purity (220 nm).

Lab book number(s): MWa638 / MWa644.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-(prop-2-yn-1-yloxy)phenyl)propyl (*S*)-piperidine-2-carboxylate



$C_{26}H_{31}NO_5$, MW = 437.54 g / mol

1-((9H-Fluoren-9-yl)methyl) 2-((*R*)-3-(3,4-dimethoxyphenyl)-1-(4-(prop-2-yn-1-yloxy)phenyl)propyl) (*S*)-piperidine-1,2-dicarboxylate (60 mg, 91 μmol, 1.0 eq.) and 4-methylpiperidine (44 μL, 373 μmol, 4.1 eq) were dissolved in DCM (400 μL) and the mixture was stirred for 3 h at room temperature. The obtained product was purified by by flash chromatography.

Yield: 30 mg (75 %, 69 μmol).

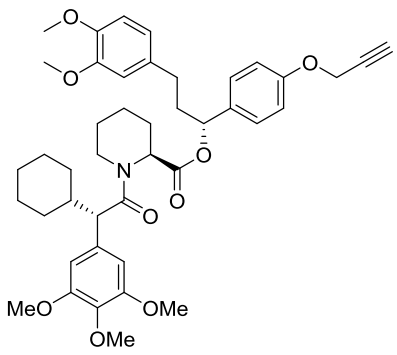
Appearance: yellow oil.

TLC: R_f = 0.26 (CH:EA = 1:1, 3 % TEA).

LC-MS: Mass (ESI), calculated = 438.2 $[M+H]^+$, found = 438.0.
[5-100 % Solvent B, 3.0 min]: R_t = 1.6 min.
99 % purity (220 nm).

Lab book number(s): MWa640 / MWa646 / MWa656.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-(prop-2-yn-1-yloxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{43}H_{53}NO_9$, MW = 727.90 g / mol

(*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylic acid (VBu308, 32 mg, 105 μmol, 1.0 eq.) and HATU (27 mg, 116 μmol, 1.1 eq.) were dissolved in DCM (1.2 mL) and DMF (1.8mL). The mixture was cooled to 0 °C and DIPEA (55 μL, 315 μmol, 3.0 eq.) was added. The mixture was stirred for 15 min at 0 °C. (*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-(prop-2-yn-1-yloxy)phenyl)propyl (*S*)-piperidine-2-carboxylate (46 mg, 105 μmol, 1.0 eq.) in DCM (3 mL) was added and the mixture was stirred for 18 h at 0 °C to room temperature. The solution was concentrated under reduced pressure and the obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 68 mg (89 %, 93 μmol).

Appearance: white solid.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 0.70 – 0.81 (m, 1H), 0.89 (qd, *J* = 12.5, 3.3 Hz, 1H), 1.07 – 1.47 (m, 6H), 1.51 – 2.17 (m, 10H), 2.25 – 2.69 (m, 5H), 3.38 (d, *J* = 10.0 Hz, 1H), 3.72 – 3.88 (m, 17H), 3.96 (d, *J* = 14.7 Hz, 1H), 4.68 (dd, *J* = 18.2, 2.4 Hz, 2H), 5.48 (d, *J* = 5.4 Hz, 1H), 5.59 (dd, *J* = 7.7, 6.3 Hz, 1H), 6.47 (d, *J* = 62.9 Hz, 2H), 6.59 – 6.70 (m, 2H), 6.73 – 6.82 (m, 4H), 6.96 – 7.02 (m, 0H), 7.29 – 7.36 (m, 1H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 20.8, 25.6, 26.0, 26.1, 26.5, 30.6, 31.0, 32.7, 37.7, 41.2, 43.9, 52.2, 55.0, 55.7, 55.8, 55.9, 56.1, 56.3, 60.8, 75.5, 105.7, 111.3, 111.8, 114.6, 120.2, 127.8, 133.0, 133.4, 137.0, 147.3, 148.8, 153.2, 157.2, 170.2, 172.6.

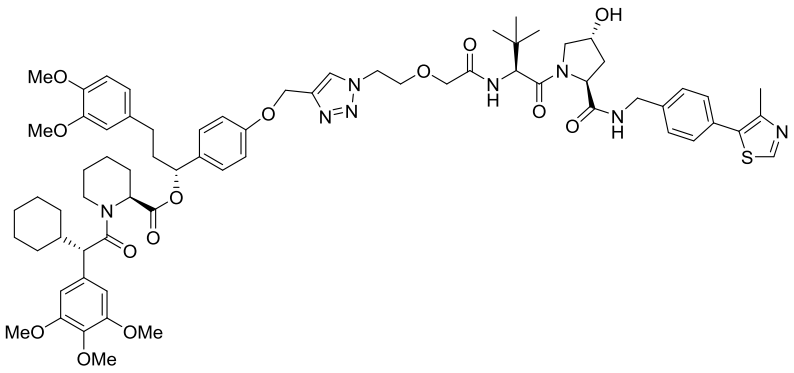
TLC: R_f = 0.31 (CH:EA = 2:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.5 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.9 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{43}H_{53}NO_9$ = 728.37931; found = 728.38039.

Lab book number(s): MWa406 / MWa641 / MWa647.

3-(3,4-Dimethoxyphenyl)-1-(4-((1-(2-(2-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{69}H_{88}N_8O_{14}S$, MW = 1285.57 g / mol

The product was synthesized from azide **57a** (5.6 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 9.0 mg (70 %, 7.0 μmol).

Appearance: white solid.

TLC: R_f = 0.16 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.1 min.

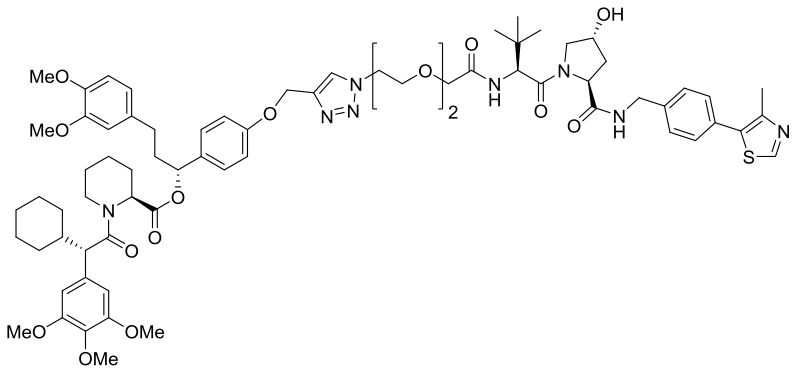
[50-100 % Solvent B, 2.6 min]: R_t = 1.5 min.

98 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{69}H_{88}N_8O_{14}S$ = 1285.62135; found = 1285.62228.

Lab book number(s): MWa407.

3-(3,4-Dimethoxyphenyl)-1-(4-((1-(2-(2-(2-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{71}H_{92}N_8O_{15}S$, MW = 1329.62 g / mol

The product was synthesized from azide **57b** (6.0 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.1 mg (76 %, 7.6 μmol).

Appearance: white solid.

TLC: R_f = 0.16 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.1 min.

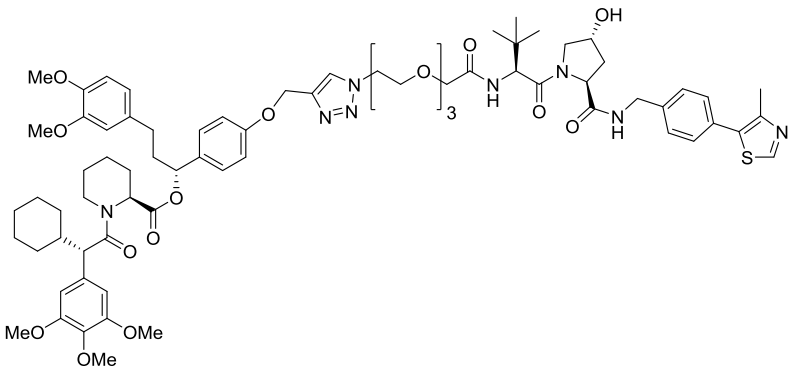
[50-100 % Solvent B, 2.6 min]: R_t = 1.5 min.

97 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{71}H_{92}N_8O_{15}S$ = 1329.64756; found = 1329.64684.

Lab book number(s): MWa408.

3-(3,4-Dimethoxyphenyl)-1-(4-((1-((*S*)-13-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-14,14-dimethyl-11-oxo-3,6,9-trioxa-12-azapentadecyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{73}H_{96}N_8O_{16}S$, MW = 1373.67 g / mol

The product was synthesized from azide **57c** (6.5 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 9.7 mg (71 %, 7.1 μmol).

Appearance: white solid.

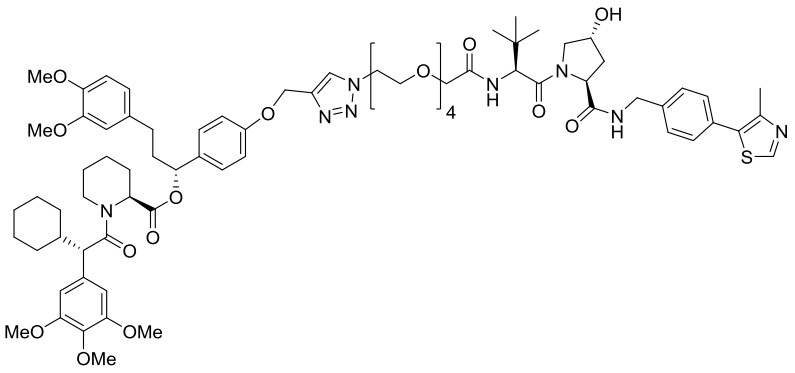
TLC: R_f = 0.15 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.1 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.5 min.
96 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{73}H_{96}N_8O_{16}S$ = 1373.67378; found = 1373.67298.

Lab book number(s): MWa409.

3-(3,4-Dimethoxyphenyl)-1-(4-((1-((*S*)-16-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-17,17-dimethyl-14-oxo-3,6,9,12-tetraoxa-15-azaoctadecyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{75}H_{100}N_8O_{17}S$, MW = 1417.72 g / mol

The product was synthesized from azide **57d** (6.9 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.0 mg (71 %, 7.1 μmol).

Appearance: white solid.

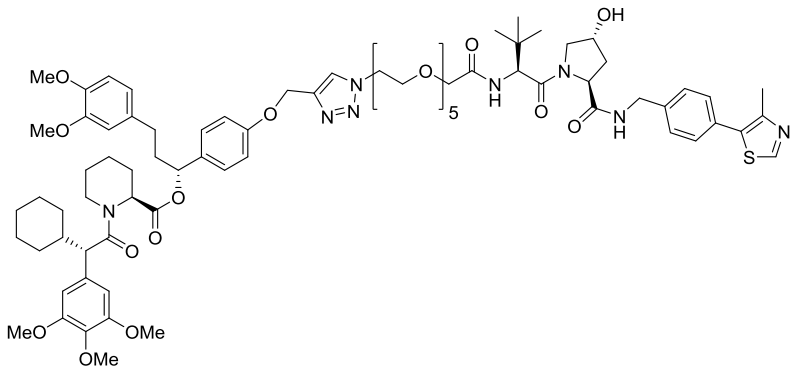
TLC: R_f = 0.15 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.1 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.5 min.
97 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{75}H_{100}N_8O_{17}S$ = 1417.69999; found = 1417.69950.

Lab book number(s): MWa410.

3-(3,4-Dimethoxyphenyl)-1-(4-((1-((*S*)-19-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-20,20-dimethyl-17-oxo-3,6,9,12,15-pentaoxa-18-azahenicosyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{77}H_{104}N_8O_{18}S$, MW = 1461.78 g / mol

The product was synthesized from azide **57e** (7.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 9.8 mg (67 %, 6.7 μmol).

Appearance: white solid.

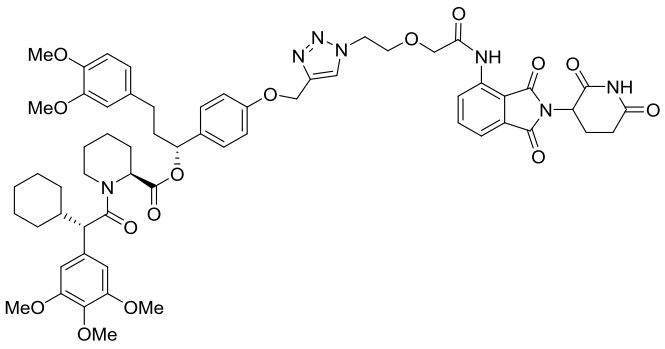
TLC: R_f = 0.14 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.1 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.5 min.
94 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{77}H_{104}N_8O_{18}S$ = 1461.72621; found = 1461.72587.

Lab book number(s): MWa411.

3-(3,4-Dimethoxyphenyl)-1-(4-((1-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{60}H_{69}N_7O_{15}$, MW = 1128.25 g / mol

The product was synthesized from azide **55a** (4.0 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.2 mg (46 %, 4.6 μmol).

Appearance: white solid.

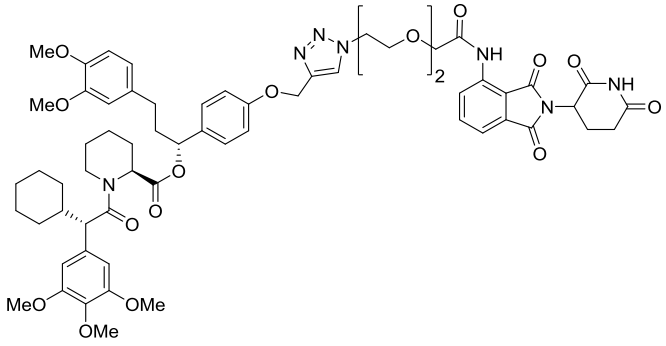
TLC: R_f = 0.30 (DCM:MeOH = 20:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.1 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.5 min.
98 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{60}H_{69}N_7O_{15}$= 1128.49244; found = 1128.49311.

Lab book number(s): MWa416.

3-(3,4-Dimethoxyphenyl)-1-(4-((1-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{62}H_{73}N_7O_{16}$, MW = 1172.30 g / mol

The product was synthesized from azide **55b** (4.4 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 9.1 mg (78 %, 7.8 μmol).

Appearance: white solid.

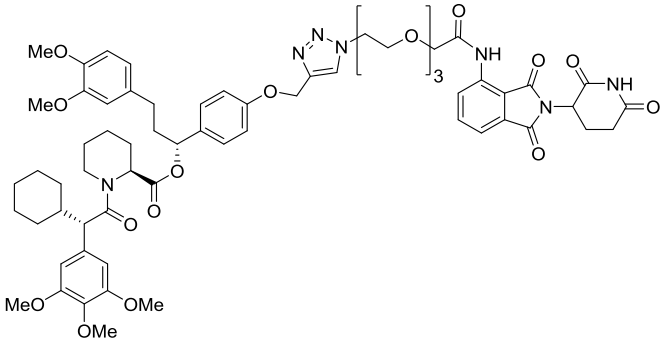
TLC: R_f = 0.28 (DCM:MeOH = 20:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.1 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.5 min.
98 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{62}H_{73}N_7O_{16}$= 1172.51866; found = 1172.51949.

Lab book number(s): MWa417.

3-(3,4-Dimethoxyphenyl)-1-(4-((1-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{64}H_{77}N_7O_{17}$, MW = 1216.35 g / mol

The product was synthesized from azide **55c** (4.9 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.6 mg (87 %, 8.7 μmol).

Appearance: white solid.

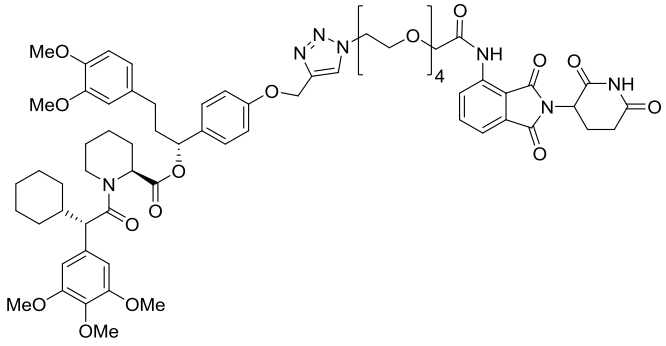
TLC: R_f = 0.27 (DCM:MeOH = 20:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.1 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.5 min.
97 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{64}H_{77}N_7O_{17}$= 1216.54487; found = 1216.54567.

Lab book number(s): MWa418.

3-(3,4-Dimethoxyphenyl)-1-(4-((1-(14-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-14-oxo-3,6,9,12-tetraoxatetradecyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{66}H_{81}N_7O_{18}$, MW = 1260.41 g / mol

The product was synthesized from azide **55d** (5.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 8.1 mg (64 %, 6.4 μmol).

Appearance: white solid.

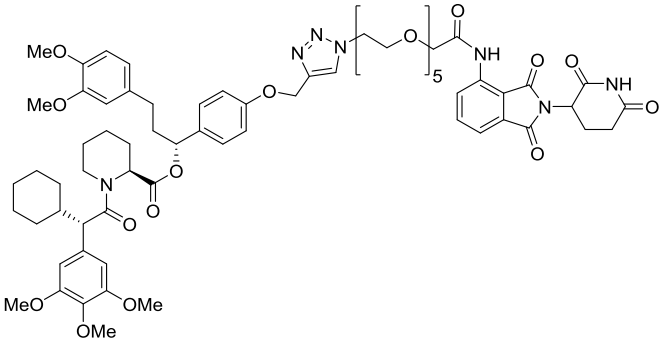
TLC: R_f = 0.26 (DCM:MeOH = 20:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.1 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.5 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{66}H_{81}N_7O_{18}$= 1260.57109; found = 1260.57244.

Lab book number(s): MWa419.

3-(3,4-Dimethoxyphenyl)-1-(4-((1-(17-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-17-oxo-3,6,9,12,15-pentaoxaheptadecyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{68}H_{85}N_7O_{19}$, MW = 1304.46 g / mol

The product was synthesized from azide **55e** (5.8 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 11.2 mg (86 %, 8.6 μmol).

Appearance: white solid.

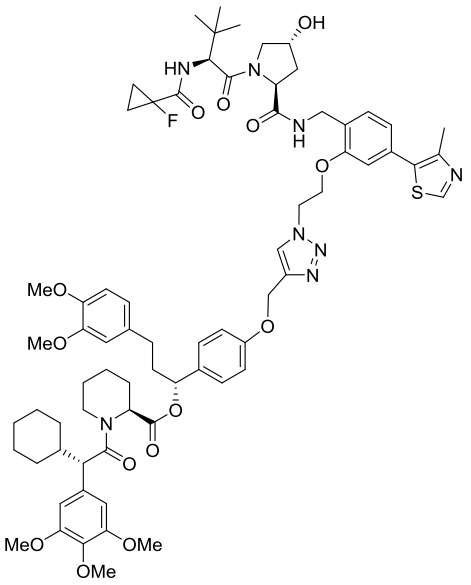
TLC: R_f = 0.25 (DCM:MeOH = 20:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.1 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.5 min.
98 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{68}H_{85}N_7O_{19}$= 1304.59730; found = 1304.59794.

Lab book number(s): MWa420.

3-(3,4-Dimethoxyphenyl)-1-(4-((1-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{71}H_{89}FN_8O_{14}S$, MW = 1329.59 g / mol

The product was synthesized from azide **58a** (6.0 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 11.1 mg (83 %, 8.3 μmol).

Appearance: white solid.

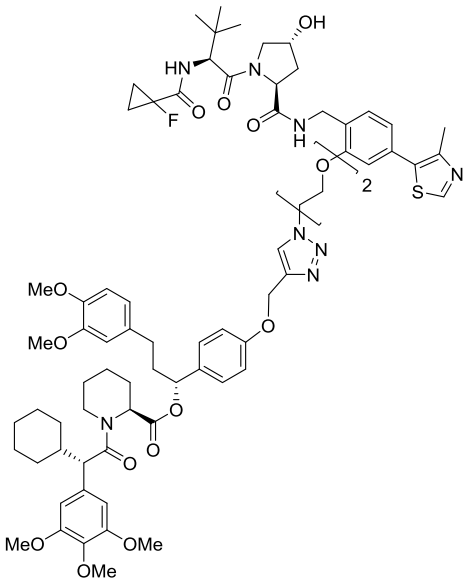
TLC: R_f = 0.13 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.1 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.6 min.
98 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{71}H_{89}FN_8O_{14}S$ = 1329.6309; found = 1329.6296.

Lab book number(s): MWa421.

3-(3,4-Dimethoxyphenyl)-1-(4-((1-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{73}H_{93}FN_8O_{15}S$, MW = 1373.65 g / mol

The product was synthesized from azide **58b** (6.5 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 11.7 mg (85 %, 8.5 μmol).

Appearance: white solid.

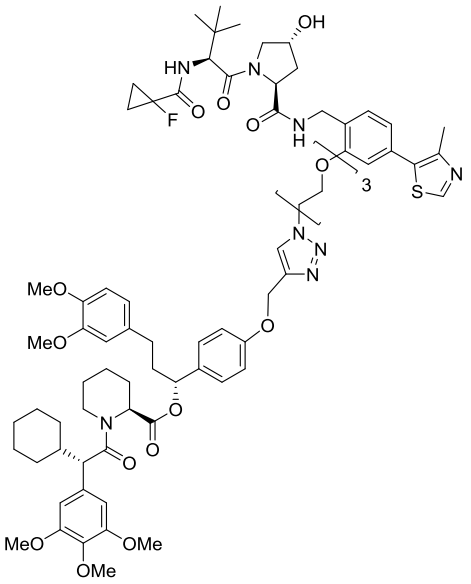
TLC: R_f = 0.12 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.1 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.6 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{73}H_{93}FN_8O_{15}S$ = 1373.6538; found = 1373.6532.

Lab book number(s): MWa422.

3-(3,4-Dimethoxyphenyl)-1-(4-((1-(2-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (423)



$C_{75}H_{97}FN_8O_{16}S$, MW = 1417.70 g / mol

The product was synthesized from azide **58c** (6.9 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 13.0 mg (92 %, 9.2 μmol).

Appearance: white solid.

TLC: R_f = 0.12 (DCM:MeOH = 10:1).

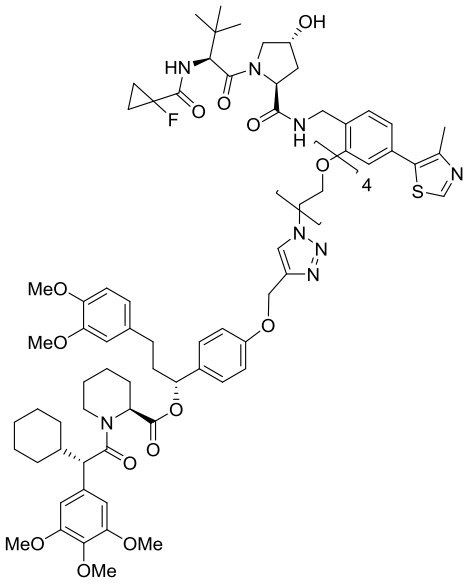
LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.1 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.6 min.

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{75}H_{97}FN_8O_{16}S$ = 1417.6800; found = 1417.6798.

Lab book number(s): MWa423.

3-(3,4-Dimethoxyphenyl)-1-(4-((1-(2-(2-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{77}H_{101}FN_8O_{17}S$, MW = 1461.75 g / mol

The product was synthesized from azide **58d** (7.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 12.8 mg (88 %, 8.8 μmol).

Appearance: white solid.

TLC: R_f = 0.11 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.1 min.

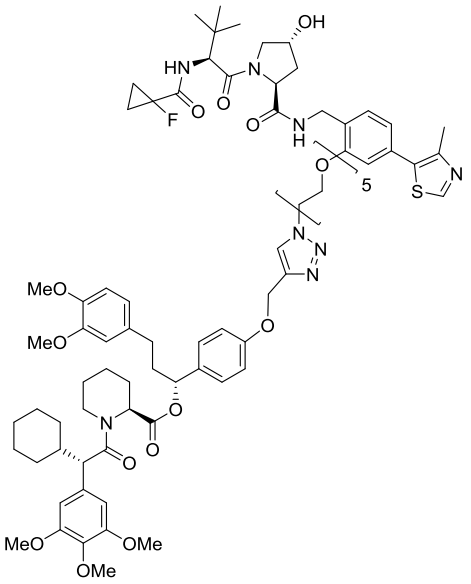
[50-100 % Solvent B, 2.6 min]: R_t = 1.6 min.

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{77}H_{101}FN_8O_{17}S$ = 1461.7062; found = 1461.7065.

Lab book number(s): MWa424.

3-(3,4-Dimethoxyphenyl)-1-(4-((1-(14-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)-3,6,9,12-tetraoxatetradecyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{79}H_{105}FN_8O_{18}S$, MW = 1505.81 g / mol

The product was synthesized from azide **58e** (7.8 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 13.3 mg (88 %, 8.8 μmol).

Appearance: white solid.

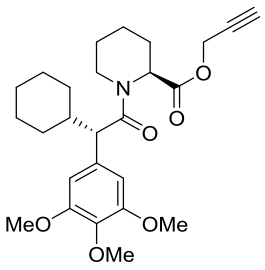
TLC: R_f = 0.11 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.1 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.6 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+2H]^{2+}$ calculated for $C_{79}H_{105}FN_8O_{18}S$ = 753.3699; found = 753.3701.

Lab book number(s): MWa425.

Prop-2-yn-1-yl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{26}H_{35}NO_6$, MW = 457.57 g / mol

(*S*)-1-((*S*)-2-Cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylic acid (VBu065, 250 g, 596 μmol, 1.0 eq.), 3-bromoprop-1-yne (213 mg, 1788 μmol, 3.0 eq.) and DIPEA (507 μL, 2980 μmol, 5.0 eq.) were stirred in acetonitrile (dry, 6 mL) for 18 h at room temperature. The solution was concentrated under reduced pressure. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 259 mg (95 %, 566 μmol).

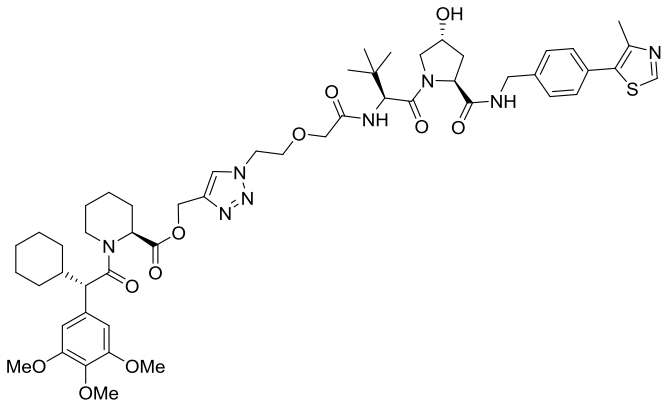
Appearance: white solid.

TLC: R_f = 0.50 (CH:EA = 1:1).

LC-MS: Mass (ESI), calculated = 458.3 $[M+H]^+$, found = 458.2.
[5-100 % Solvent B, 2.6 min]: R_t = 2.1 min.
[30-100 % Solvent B, 2.6 min]: R_t = 1.8 min.
95 % purity (220 nm).

Lab book number(s): MWa390.

(1-(2-(2-(((*S*)-1-((2*S*,4*R*)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{52}H_{70}N_8O_{11}S$, MW = 1015.24 g / mol

The product was synthesized from azide **57a** (5.6 mg, 10.0 μmol, 1.0 eq.) and alkyne **A15** (4.6 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 7.7 mg (75 %, 7.5 μmol).

Appearance: white solid.

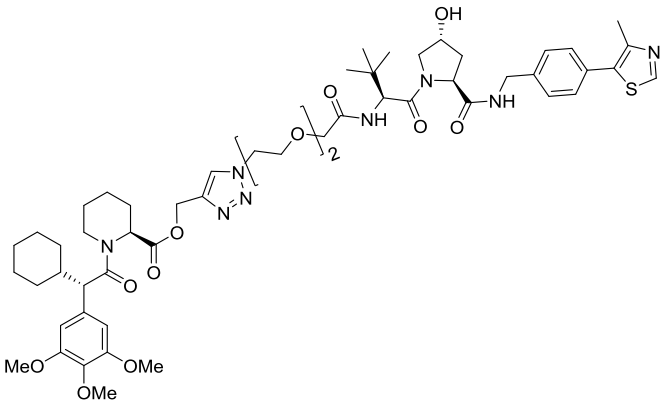
TLC: R_f = 0.18 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.0 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.1 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{52}H_{70}N_8O_{11}S$ = 1015.49575; found = 1015.49512.

Lab book number(s): MWa391.

(1-(2-(2-(2-(((*S*)-1-((2*S*,4*R*)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{54}H_{74}N_8O_{12}S$, MW = 1059.29 g / mol

The product was synthesized from azide **57b** (6.0 mg, 10.0 μmol, 1.0 eq.) and alkyne **A15** (4.6 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 8.0 mg (75 %, 7.5 μmol).

Appearance: white solid.

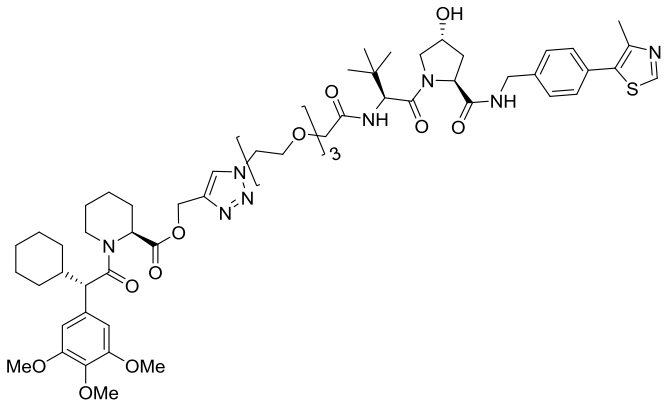
TLC: R_f = 0.18 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.0 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.1 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{54}H_{74}N_8O_{12}S$ = 1059.52197; found = 1059.52209.

Lab book number(s): MWa392.

(1-((*S*)-13-((2*S*,4*R*)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-14,14-dimethyl-11-oxo-3,6,9-trioxa-12-azapentadecyl)-1H-1,2,3-triazol-4-yl)methyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{56}H_{78}N_8O_{13}S$, MW = 1103.34 g / mol

The product was synthesized from azide **57c** (6.5 mg, 10.0 μmol, 1.0 eq.) and alkyne **A15** (4.6 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 7.9 mg (72 %, 7.2 μmol).

Appearance: white solid.

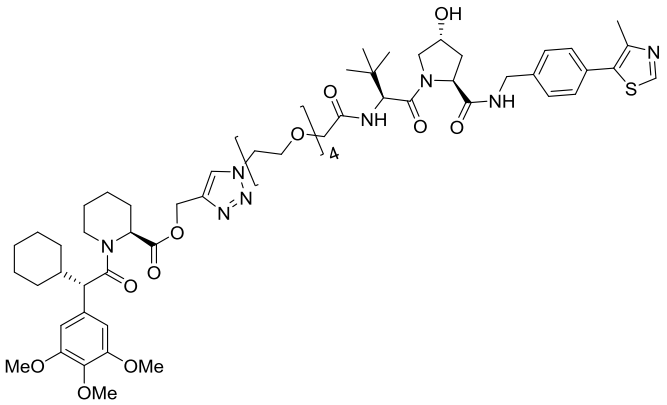
TLC: R_f = 0.17 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.0 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.1 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{56}H_{78}N_8O_{13}S$ = 1103.54818; found = 1103.54811.

Lab book number(s): MWa393.

(1-((*S*)-16-((2*S*,4*R*)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-17,17-dimethyl-14-oxo-3,6,9,12-tetraoxa-15-azaoctadecyl)-1H-1,2,3-triazol-4-yl)methyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{58}H_{82}N_8O_{14}S$, MW = 1147.40 g / mol

The product was synthesized from azide **57d** (6.9 mg, 10.0 μmol, 1.0 eq.) and alkyne **A15** (4.6 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 8.7 mg (76 %, 7.6 μmol).

Appearance: white solid.

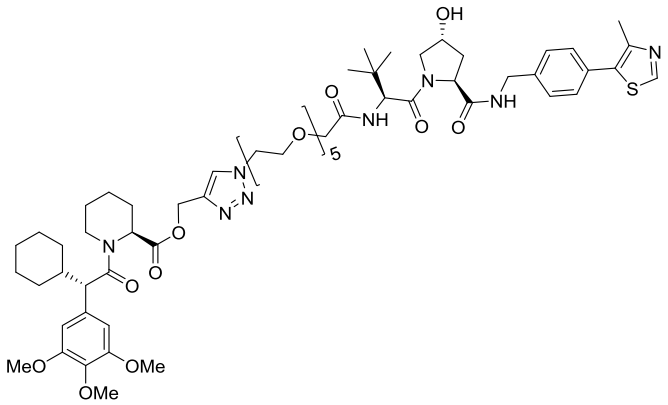
TLC: R_f = 0.16 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.0 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.1 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{58}H_{82}N_8O_{14}S$ = 1147.57440; found = 1147.57469.

Lab book number(s): MWa394.

(1-((*S*)-19-((2*S*,4*R*)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-20,20-dimethyl-17-oxo-3,6,9,12,15-pentaoxa-18-azahenicosyl)-1H-1,2,3-triazol-4-yl)methyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{60}H_{86}N_8O_{15}S$, MW = 1191.45 g / mol

The product was synthesized from azide **57e** (7.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A15** (4.6 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 7.7 mg (65 %, 6.5 μmol).

Appearance: white solid.

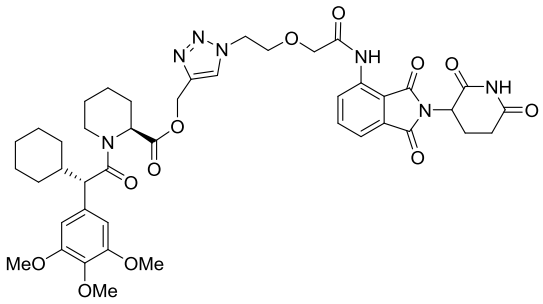
TLC: R_f = 0.16 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.0 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.2 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{60}H_{86}N_8O_{15}S$ = 1191.60061; found = 1191.60022.

Lab book number(s): MWa395.

(1-(2-(2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{43}H_{51}N_7O_{12}$, MW = 857.92 g / mol

The product was synthesized from azide **55a** (4.0 mg, 10.0 μmol, 1.0 eq.) and alkyne **A15** (4.6 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.1 mg (59 %, 5.9 μmol).

Appearance: white solid.

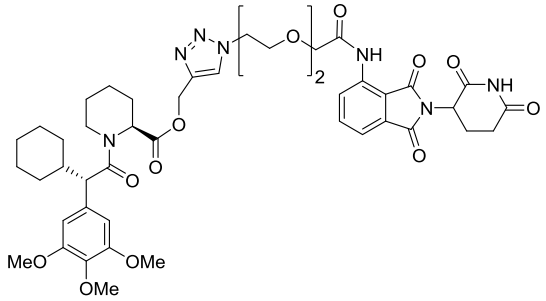
TLC: R_f = 0.34 (DCM:MeOH = 20:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.0 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.0 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{43}H_{51}N_7O_{12}$= 858.36685; found = 858.36666.

Lab book number(s): MWa401.

(1-(2-(2-(2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{45}H_{55}N_7O_{13}$, MW = 901.97 g / mol

The product was synthesized from azide **55b** (4.4 mg, 10.0 μmol, 1.0 eq.) and alkyne **A15** (4.6 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.2 mg (58 %, 5.8 μmol).

Appearance: white solid.

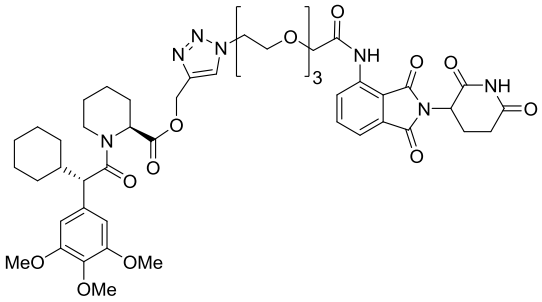
TLC: R_f = 0.32 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.0 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.0 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{45}H_{55}N_7O_{13}$= 902.39306; found = 902.39298.

Lab book number(s): MWa402.

(1-(2-(2-(2-(2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{47}H_{59}N_7O_{14}$, MW = 946.02 g / mol

The product was synthesized from azide **55c** (4.9 mg, 10.0 μmol, 1.0 eq.) and alkyne **A15** (4.6 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 8.9 mg (94 %, 9.4 μmol).

Appearance: white solid.

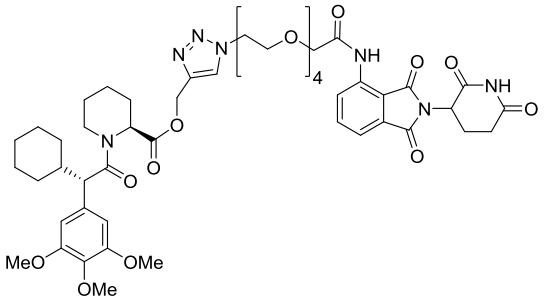
TLC: R_f = 0.30 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.0 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.1 min.
98 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{47}H_{59}N_7O_{14}$= 946.41928; found = 946.41926.

Lab book number(s): MWa403.

(1-(14-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-14-oxo-3,6,9,12-tetraoxatetradecyl)-1H-1,2,3-triazol-4-yl)methyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{49}H_{63}N_7O_{15}$, MW = 990.08 g / mol

The product was synthesized from azide **55d** (5.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A15** (4.6 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.0 mg (51 %, 5.1 μmol).

Appearance: white solid.

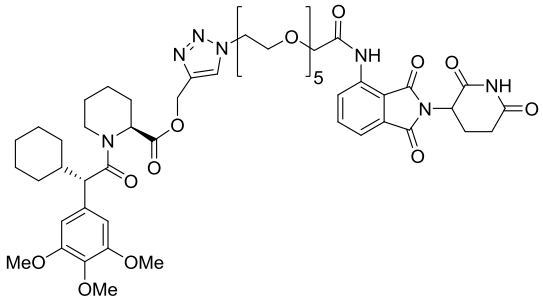
TLC: R_f = 0.29 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.0 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.1 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{49}H_{63}N_7O_{15}$= 990.44549; found = 990.44627.

Lab book number(s): MWa404.

(1-(17-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-17-oxo-3,6,9,12,15-pentaoxaheptadecyl)-1H-1,2,3-triazol-4-yl)methyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{51}H_{67}N_7O_{16}$, MW = 1034.13 g / mol

The product was synthesized from azide **55e** (5.8 mg, 10.0 μmol, 1.0 eq.) and alkyne **A15** (4.6 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 9.4 mg (91 %, 9.1 μmol).

Appearance: white solid.

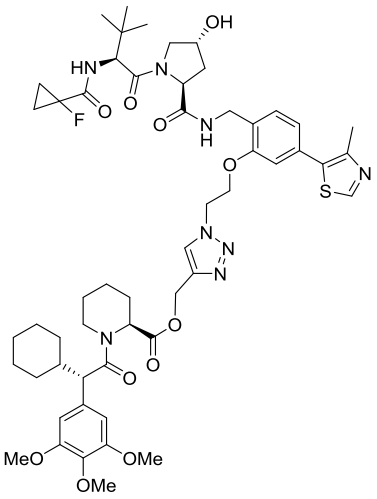
TLC: R_f = 0.28 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.0 min.
[50-100 % Solvent B, 2.6 min]: R_t = 1.0 min.
98 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{49}H_{63}N_7O_{15}$= 1034.47171; found = 1034.47225.

Lab book number(s): MWa405.

(1-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{54}H_{71}FN_8O_{11}S$, MW = 1059.27 g / mol

The product was synthesized from azide **58a** (6.0 mg, 10.0 μmol, 1.0 eq.) and alkyne **A15** (4.6 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 9.1 mg (86 %, 8.6 μmol).

Appearance: white solid.

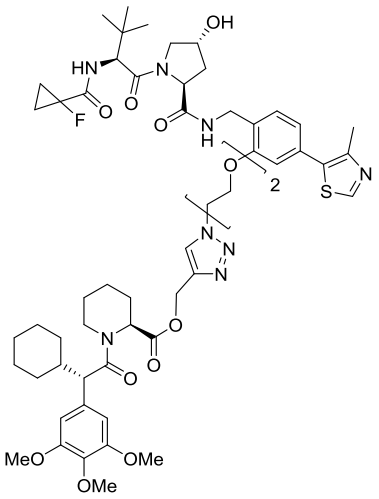
TLC: R_f = 0.16 (DCM:MeOH = 20:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.0 min.
[30-100 % Solvent B, 2.6 min]: R_t = 1.8 min.
98 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{54}H_{71}FN_8O_{11}S$ = 1059.50198; found = 1059.50206.

Lab book number(s): MWa396.

(1-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-Fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{56}H_{75}FN_8O_{12}S$, MW = 1103.32 g / mol

The product was synthesized from azide **58b** (6.5 mg, 10.0 μmol, 1.0 eq.) and alkyne **A15** (4.6 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 9.4 mg (85 %, 8.5 μmol).

Appearance: white solid.

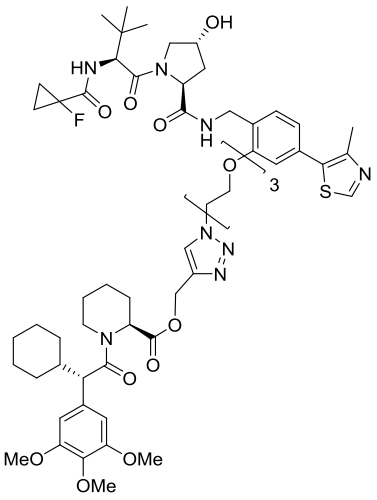
TLC: R_f = 0.15 (DCM:MeOH = 20:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.0 min.
[30-100 % Solvent B, 2.6 min]: R_t = 1.8 min.
98 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{56}H_{75}FN_8O_{12}S$ = 1103.52820; found = 1103.52878.

Lab book number(s): MWa397.

(1-(2-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-Fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{58}H_{79}FN_8O_{13}S$, MW = 1147.37 g / mol

The product was synthesized from azide **58c** (6.9 mg, 10.0 μmol, 1.0 eq.) and alkyne **A15** (4.6 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.3 mg (90 %, 9.0 μmol).

Appearance: white solid.

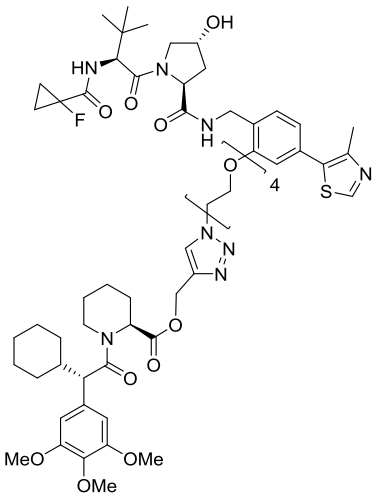
TLC: R_f = 0.15 (DCM:MeOH = 20:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.0 min.
[30-100 % Solvent B, 2.6 min]: R_t = 1.8 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{58}H_{79}FN_8O_{13}S$ = 1147.55441; found = 1147.55490.

Lab book number(s): MWa398.

(1-(2-(2-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-Fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{60}H_{83}FN_8O_{14}S$, MW = 1191.42 g / mol

The product was synthesized from azide **58d** (7.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A15** (4.6 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.5 mg (88 %, 8.8 μmol).

Appearance: white solid.

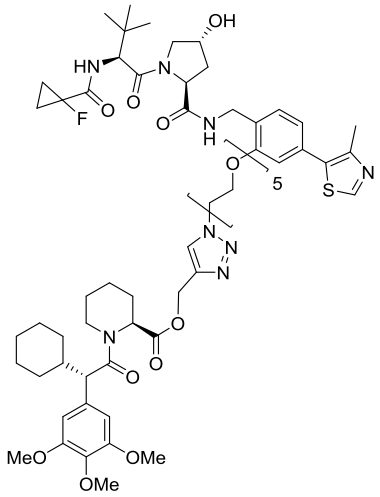
TLC: R_f = 0.14 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.0 min.
[30-100 % Solvent B, 2.6 min]: R_t = 1.8 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{60}H_{83}FN_8O_{14}S$ = 1191.58063; found = 1191.58131.

Lab book number(s): MWa399.

(1-(14-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-Fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)-3,6,9,12-tetraoxatetradecyl)-1H-1,2,3-triazol-4-yl)methyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{62}H_{87}FN_8O_{15}S$, MW = 1235.48 g / mol

The product was synthesized from azide **58e** (7.8 mg, 10.0 μmol, 1.0 eq.) and alkyne **A15** (4.6 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 11.9 mg (96 %, 9.6 μmol).

Appearance: white solid.

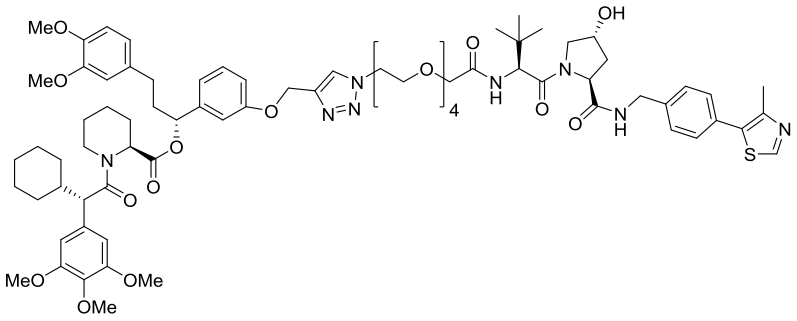
TLC: R_f = 0.14 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.0 min.
[30-100 % Solvent B, 2.6 min]: R_t = 1.8 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{62}H_{87}FN_8O_{15}S$ = 1235.60684; found = 1235.60729.

Lab book number(s): MWa400.

3-(3,4-dimethoxyphenyl)-1-(4-((1-((*S*)-16-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-17,17-dimethyl-14-oxo-3,6,9,12-tetraoxa-15-azaoctadecyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{75}H_{100}N_8O_{17}S$, MW = 1417.72 g / mol

The product was synthesized from azide **57d** (172 mg, 250 μmol, 1.0 eq.) and alkyne **A10** (182 mg, 250 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 249 mg (70 %, 176 μmol).

Appearance: white solid.

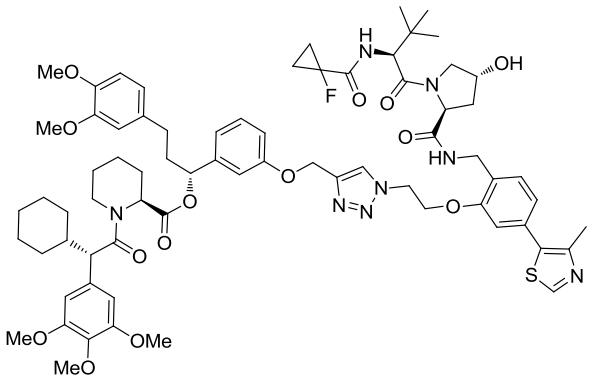
TLC: R_f = 0.15 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 10.5 min]: R_t = 8.2 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{75}H_{100}N_8O_{17}S$ = 1417.69999; found = 1417.70034.

Lab book number(s): MWa538.

(*S*)-(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-((1-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropanecarboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{71}H_{89}FN_8O_{14}S$, MW = 1329.57 g / mol

The product was synthesized from azide **58a** (4.2 mg, 7.0 μmol, 1.0 eq.) and alkyne **A10** (5.1 mg, 7.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 6.7 mg (72 %, 5.0 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ =0.68 – 0.79 (m, 1H), 0.94 (s, 10H), 1.08 – 1.19 (m, 2H), 1.18 – 1.37 (m, 7H), 1.55 – 1.75 (m, 6H), 1.85 (dt, *J* = 7.5, 3.4 Hz, 2H), 2.14 – 2.34 (m, 3H), 2.31 – 2.53 (m, 1H), 2.47 – 2.66 (m, 4H), 2.79 (t, *J* = 12.9 Hz, 1H), 3.39 (d, *J* = 9.8 Hz, 1H), 3.62 – 3.71 (m, 6H), 3.76 (s, 3H), 3.80 – 3.86 (m, 10H), 3.90 – 4.06 (m, 3H), 4.27 – 4.59 (m, 7H), 4.70 (t, *J* = 8.5 Hz, 1H), 4.85 – 4.94 (m, 2H), 5.11 – 5.22 (m, 2H), 5.44 (d, *J* = 5.0 Hz, 1H), 5.53 (dd, *J* = 8.1, 5.6 Hz, 1H), 6.44 – 6.50 (m, 2H), 6.60 – 6.70 (m, 2H), 6.73 – 6.86 (m, 4H), 6.94 – 7.04 (m, 2H), 7.06 – 7.15 (m, 2H), 7.37 – 7.44 (m, 2H), 7.91 – 8.02 (m, 1H), 9.10 (s, 1H).

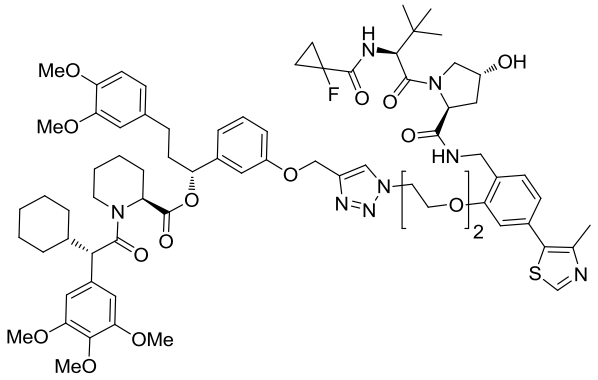
TLC: R_f = 0.18 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.7 min]: R_t = 1.5 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{71}H_{89}FN_8O_{14}S$ = 1329.62758; found = 1329.62725.

Lab book number(s): MWa267.

(*S*)-(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-((1-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropanecarboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{73}H_{93}FN_8O_{15}S$, MW = 1373.63 g / mol

The product was synthesized from azide **58b** (4.5 mg, 7.0 μmol, 1.0 eq.) and alkyne **A10** (5.1 mg, 7.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 7.2 mg (75 %, 5.2 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.68 – 0.80 (m, 1H), 0.84 – 0.95 (m, 1H), 0.97 (s, 9H), 1.08 – 1.19 (m, 2H), 1.18 – 1.36 (m, 7H), 1.49 – 1.74 (m, 6H), 1.77 – 1.93 (m, 2H), 2.08 – 2.20 (m, 1H), 2.19 – 2.52 (m, 4H), 2.43 – 2.64 (m, 4H), 2.72 – 2.87 (m, 1H), 3.39 (d, *J* = 9.9 Hz, 1H), 3.59 – 3.72 (m, 6H), 3.72 – 3.80 (m, 3H), 3.78 – 3.88 (m, 10H), 3.94 – 4.08 (m, 4H), 4.12 (dd, *J* = 5.9, 3.2 Hz, 2H), 4.32 – 4.79 (m, 9H), 5.11 (d, *J* = 16.3 Hz, 2H), 5.44 (d, *J* = 5.2 Hz, 1H), 5.54 (dd, *J* = 8.0, 5.6

Hz, 1H), 6.43 – 6.49 (m, 2H), 6.58 – 6.69 (m, 2H), 6.66 – 6.87 (m, 4H), 6.89 – 7.02 (m, 2H), 7.04 – 7.17 (m, 2H), 7.28 – 7.35 (m, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 9.3 Hz, 1H), 9.07 (s, 1H).

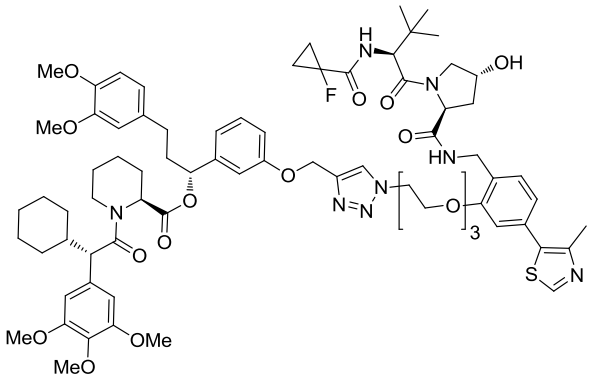
TLC: R_f = 0.18 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.7 min]: R_t = 1.5 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{73}H_{93}FN_8O_{15}S$ = 1373.65379; found = 1373.65357.

Lab book number(s): MWa268.

(*S*)-(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-((1-(2-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropanecarboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{75}H_{97}FN_8O_{16}S$, MW = 1417.68 g / mol

The product was synthesized from azide **58c** (4.8 mg, 7.0 μmol, 1.0 eq.) and alkyne **A10** (5.1 mg, 7.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 6.6 mg (67 %, 4.7 μmol).

Appearance: white solid.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 0.70 – 0.80 (m, 1H), 0.86 – 0.93 (m, 1H), 0.98 (s, 8H), 1.13 (dd, *J* = 19.2, 9.9 Hz, 2H), 1.22 – 1.36 (m, 7H), 1.55 (d, *J* = 11.8 Hz, 1H), 1.60 – 1.72 (m, 2H), 1.77 – 1.90 (m, 2H), 2.10 – 2.21 (m, 1H), 2.20 – 2.32 (m, 2H), 2.31 – 2.41 (m, 1H), 2.46 (ddd, *J* = 14.4, 9.3, 5.4 Hz, 1H), 2.50 – 2.62 (m, 4H), 2.80 (t, *J* = 13.5 Hz, 1H), 3.39 (d, *J* = 9.8 Hz, 1H), 3.60 – 3.68 (m, 2H), 3.67 – 3.70 (m, 7H), 3.73 – 3.79 (m, 2H), 3.81 (s, 1H), 3.82 – 3.83 (m, 12H), 3.88 – 3.93 (m, 4H), 3.95 – 4.06 (m, 2H), 4.11 – 4.23 (m, 2H), 4.41 – 4.58 (m, 7H), 4.65 (q, *J* = 8.6 Hz, 1H), 5.14 (d, *J* = 24.6 Hz, 2H), 5.45 (d, *J* = 5.4 Hz, 1H), 5.54 (dd, *J* = 8.1, 5.6 Hz, 1H), 6.44 – 6.50 (m, 2H), 6.60 – 6.70 (m, 2H), 6.71 – 6.73 (m, 1H), 6.74 – 6.77 (m, 1H), 6.80 (dt, *J* = 8.0, 2.6 Hz, 1H), 6.87 (dd, *J* = 6.6, 1.7 Hz, 1H), 6.91 – 7.00 (m, 2H), 7.05 – 7.13 (m, 2H), 7.40 (dd, *J* = 7.7, 2.5 Hz, 1H), 7.45 (t, *J* = 5.8 Hz, 1H), 7.82 (d, *J* = 14.8 Hz, 1H), 9.10 (d, *J* = 4.5 Hz, 1H).

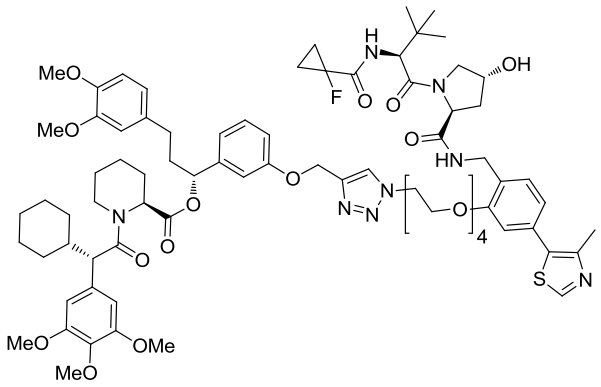
TLC: R_f = 0.17 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.7 min]: R_t = 1.5 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{75}H_{97}FN_8O_{16}S$ = 1417.68000; found = 1417.67861.

Lab book number(s): MWa269.

(*S*)-(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-((1-(2-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropanecarboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{77}H_{101}FN_8O_{17}S$, MW = 1461.73 g / mol

The product was synthesized from azide **58d** (5.1 mg, 7.0 μmol, 1.0 eq.) and alkyne **A10** (5.1 mg, 7.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 7.2 mg (71 %, 4.9 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.69 – 0.81 (m, 1H), 0.84 – 0.95 (m, 1H), 0.97 (s, 8H), 1.10 – 1.18 (m, 3H), 1.29 (td, *J* = 10.6, 9.4, 6.4 Hz, 7H), 1.49 – 1.75 (m, 6H), 1.76 – 1.92 (m, 2H), 2.02 – 2.08 (m, 1H), 2.19 – 2.49 (m, 4H), 2.47 – 2.64 (m, 4H), 2.78 (t, *J* = 13.0 Hz, 1H), 3.39 (d, *J* = 9.9 Hz, 1H), 3.58 (s, 4H), 3.58 – 3.69 (m, 2H), 3.66 – 3.76 (m, 7H), 3.75 (s, 2H), 3.78 – 3.88 (m, 8H), 3.88 – 3.97 (m, 1H), 3.99 (t, *J* = 5.4 Hz, 1H), 4.18 (q, *J* = 5.5 Hz, 2H), 4.38 – 4.79 (m, 8H), 5.15 (d, *J* = 12.5 Hz, 2H), 5.45 (d, *J* = 5.1 Hz, 1H), 5.55 (dd, *J* = 8.0, 5.6 Hz, 1H), 6.46 (d, *J* = 10.4 Hz, 2H), 6.57 – 6.69 (m, 2H), 6.66 – 6.90 (m, 4H), 6.91 – 7.02 (m, 2H), 7.04 – 7.17 (m, 2H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.49 (t, *J* = 6.1 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 9.09 (s, 1H).

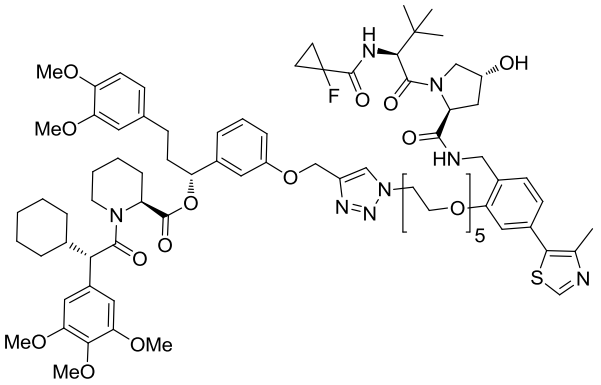
TLC: R_f = 0.16 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.7 min]: R_t = 1.5 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{77}H_{101}FN_8O_{17}S$ = 1461.70622; found = 1461.70535.

Lab book number(s): MWa270.

(*S*)-(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-((1-(14-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropanecarboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)-3,6,9,12-tetraoxatetradecyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{79}H_{105}FN_8O_{15}S$, MW = 1505.79 g / mol

The product was synthesized from azide **58e** (5.4 mg, 7.0 μmol, 1.0 eq.) and alkyne **A10** (5.1 mg, 7.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 8.0 mg (76 %, 5.3 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 0.69 – 0.81 (m, 1H), 0.84 – 0.95 (m, 1H), 0.97 (s, 9H), 1.09 – 1.17 (m, 3H), 1.20 – 1.37 (m, 7H), 1.51 – 1.74 (m, 6H), 1.80 – 1.91 (m, 1H), 2.02 – 2.12 (m, 1H), 2.21 – 2.48 (m, 2H), 2.49 – 2.66 (m, 4H), 2.78 (t, *J* = 12.9 Hz, 1H), 3.39 (d, *J* = 9.9 Hz, 1H), 3.53 – 3.62 (m, 8H), 3.66 (d, *J* = 3.7 Hz, 1H), 3.69 (s, 5H), 3.76 (s, 3H), 3.78 – 3.94 (m, 11H), 4.00 (d, *J* = 11.1 Hz, 1H), 4.19 (d, *J* = 5.1 Hz, 1H), 4.44 – 4.77 (m, 8H), 5.16 (d, *J* = 13.1 Hz, 2H), 5.46 (d, *J* =

5.2 Hz, 1H), 5.55 (dd, *J* = 8.0, 5.6 Hz, 1H), 6.46 (d, *J* = 13.2 Hz, 2H), 6.60 – 6.71 (m, 2H), 6.72 – 6.90 (m, 4H), 6.93 – 7.01 (m, 2H), 7.05 – 7.17 (m, 2H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.50 – 7.56 (m, 1H), 7.83 (d, *J* = 6.4 Hz, 1H), 9.12 (s, 1H).

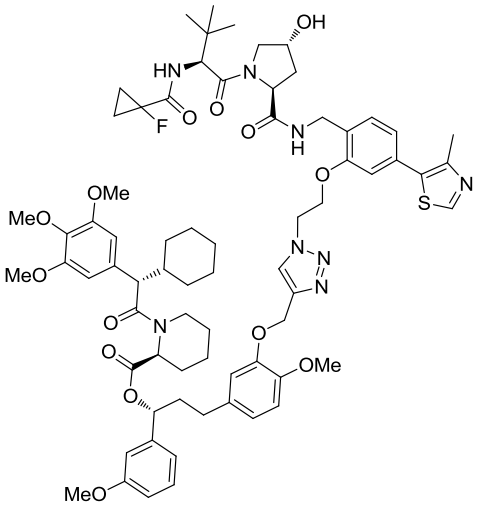
TLC: R_f = 0.16 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.7 min]: R_t = 1.5 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{79}H_{105}FN_8O_{15}S$ = 1505.73243; found = 1505.73167.

Lab book number(s): MWa271.

(*R*)-3-(3-((1-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-Fluorocyclopropanecarboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-4-methoxyphenyl)-1-(3-methoxyphenyl)propyl 1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{71}H_{89}FN_8O_{14}S$, MW = 1329.57 g / mol

The product was synthesized from azide **58a** (6.0 mg, 10.0 μmol, 1.0 eq.) and alkyne **A11** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 11.3 mg (85 %, 8.5 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.89 (s, 9H), 0.97 – 1.32 (m, 11H), 1.46 – 1.63 (m, 6H), 1.65 – 1.90 (m, 3H), 1.94 – 2.08 (m, 1H), 2.07 – 2.38 (m, 5H), 2.48 (s, 3H), 2.70 (t, *J* = 13.1 Hz, 1H), 3.33 (d, *J* = 9.9 Hz, 1H), 3.63 (s, 5H), 3.66 (s, 5H), 3.71 – 3.74 (m, 4H), 3.76 (s, 2H), 3.93 (d, *J* = 11.3 Hz, 2H), 4.22 – 4.53 (m, 7H), 4.62 – 4.93 (m, 4H), 5.14 (d, *J* = 3.7 Hz, 2H), 5.35 – 5.47 (m, 2H), 6.27 (d, *J* = 7.8 Hz, 1H), 6.43 (s, 2H), 6.48 – 6.51 (m, 1H), 6.60 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.63 – 6.74 (m, 4H), 6.88 – 6.94 (m, 1H), 6.96 – 7.11 (m, 2H), 7.34 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.45 (t, *J* = 6.3 Hz, 1H), 7.87 (d, *J* = 12.0 Hz, 1H), 9.12 (d, *J* = 6.2 Hz, 1H).

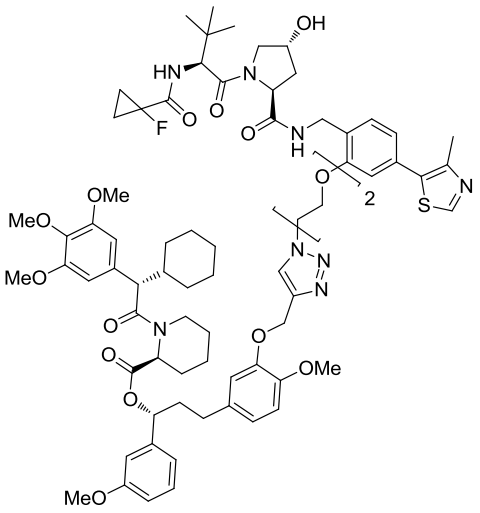
TLC: R_f = 0.13 (DCM:MeOH = 10:1).

LC-MS: [60-100 % Solvent B, 2.7 min]: R_t = 1.0 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{71}H_{89}FN_8O_{14}S$ = 1329.62758; found = 1329.62524.

Lab book number(s): MWa279.

(*R*)-3-(3-((1-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-Fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-4-methoxyphenyl)-1-(3-methoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{73}H_{73}FN_8O_{15}S$, MW = 1373.65 g / mol

The product was synthesized from azide **58b** (6.5 mg, 10.0 μmol, 1.0 eq.) and alkyne **A11** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 12.4 mg (91 %, 9.1 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.91 (s, 9H), 1.01 – 1.37 (m, 7H), 1.43 – 1.90 (m, 9H), 1.92 – 2.38 (m, 6H), 2.48 (s, 3H), 2.70 (t, *J* = 12.6 Hz, 1H), 3.32 (d, *J* = 9.9 Hz, 1H), 3.64 (s, 5H), 3.67 (d, *J* = 1.0 Hz, 5H), 3.72 (d, *J* = 7.7 Hz, 4H), 3.72 – 4.15 (m, 10H), 4.24 – 4.59 (m, 8H), 5.07 – 5.14 (m, 2H), 5.35 – 5.47 (m, 2H), 6.28 – 6.32 (m, 1H), 6.38 (d, *J* = 22.3 Hz, 2H), 6.50 – 6.53 (m, 1H), 6.59 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.60 – 6.74 (m, 3H), 6.75 (d, *J* = 1.8 Hz, 1H), 6.89 (dt, *J* = 7.7, 1.5 Hz, 1H), 6.97 – 7.11 (m, 2H), 7.31 – 7.39 (m, 2H), 7.79 (d, *J* = 2.5 Hz, 1H), 9.08 (d, *J* = 5.5 Hz, 1H).

TLC: R_f = 0. 12 (DCM:MeOH = 10:1).

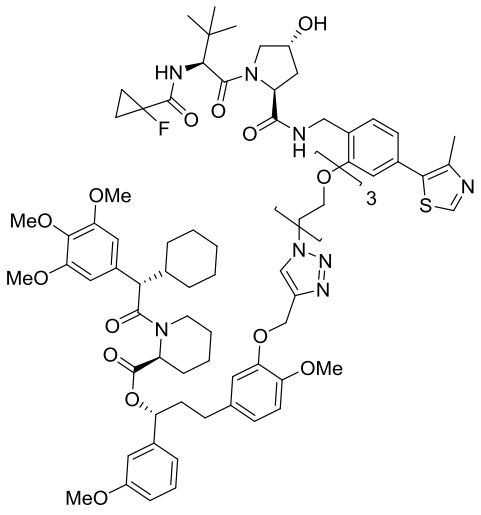
LC-MS: [60-100 % Solvent B, 2.7 min]: R_t = 1.0 min.

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{73}H_{73}FN_8O_{15}S$ = 1373.65379; found = 1373.65473.

Lab book number(s): MWa280.

(*R*)-3-(3-((1-(2-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-Fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-4-methoxyphenyl)-1-(3-methoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{75}H_{97}FN_8O_{16}S$, MW = 1417.70 g / mol

The product was synthesized from azide **58c** (6.9 mg, 10.0 μmol, 1.0 eq.) and alkyne **A11** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 13.0 mg (92 %, 9.2 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 0.91 (s, 9H), 1.00 – 1.36 (m, 9H), 1.43 – 1.90 (m, 9H), 1.91 – 2.39 (m, 6H), 2.48 (s, 3H), 2.63 – 2.77 (m, 1H), 3.32 (d, J = 9.9 Hz, 1H), 3.51 – 3.67 (m, 9H), 3.67 (s, 4H), 3.70 – 3.74 (m, 3H), 3.72 – 3.84 (m, 4H), 3.92 (t, J = 11.5 Hz, 1H), 3.99 – 4.19 (m, 2H), 4.34 – 4.64 (m, 8H), 5.12 (d, J = 4.8 Hz, 2H), 5.33 – 5.53 (m, 2H), 6.31 (d, J = 7.7 Hz, 1H), 6.38 (d,

J = 21.2 Hz, 2H), 6.50 – 6.54 (m, 1H), 6.59 (dd, J = 8.2, 1.9 Hz, 1H), 6.64 – 6.74 (m, 3H), 6.79 – 6.81 (m, 1H), 6.88 (dt, J = 7.8, 1.4 Hz, 1H), 6.98 – 7.07 (m, 2H), 7.31 – 7.36 (m, 1H), 7.35 – 7.49 (m, 1H), 7.80 (d, J = 2.1 Hz, 1H), 9.08 (d, J = 5.8 Hz, 1H).

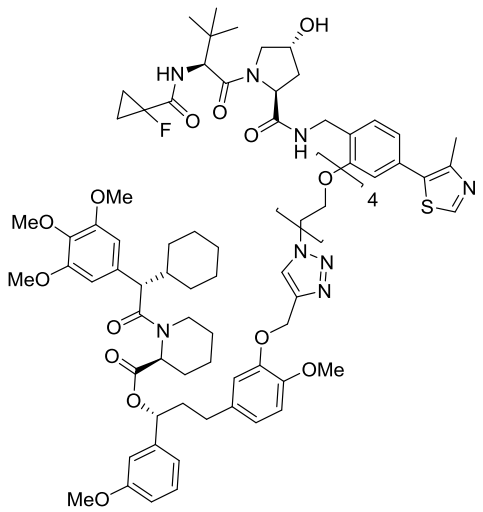
TLC: R_f = 0.12 (DCM:MeOH = 10:1).

LC-MS: [60-100 % Solvent B, 2.7 min]: R_t = 1.0 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{75}H_{97}FN_8O_{16}S$ = 1417.68000; found = 1417.67842.

Lab book number(s): MWa281.

(*R*)-3-(3-((1-(2-(2-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-Fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-4-methoxyphenyl)-1-(3-methoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{77}H_{101}FN_8O_{17}S$, MW = 1461.75 g / mol

The product was synthesized from azide **58d** (7.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A11** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 13.7 mg (94 %, 9.4 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.90 (s, 9H), 0.99 – 1.37 (m, 11H), 1.43 – 1.89 (m, 9H), 1.94 – 2.40 (m, 6H), 2.49 (s, 3H), 2.63 – 2.79 (m, 1H), 3.32 (d, J = 9.9 Hz, 1H), 3.50 (d, J = 2.2 Hz, 4H), 3.57 (td, J = 5.4, 3.0 Hz, 2H), 3.64 (s, 6H), 3.67 (d, J = 0.9 Hz, 4H), 3.71 – 3.74 (m, 4H), 3.72 – 3.85 (m, 6H), 3.91 (t, J = 10.2 Hz, 2H), 4.10 (d, J = 4.9 Hz, 2H), 4.34 – 4.60 (m, 8H), 5.14 (d, J = 5.4 Hz, 2H), 5.36 – 5.52 (m, 2H), 6.28 – 6.34 (m, 1H), 6.38 (d, J = 20.6 Hz, 2H), 6.50 – 6.54 (m, 1H), 6.60 (dd, J = 8.2, 1.9 Hz, 1H), 6.63 – 6.73 (m, 3H), 6.80 (t, J = 1.8 Hz, 1H), 6.88 (dt, J = 7.7, 1.3 Hz, 1H), 6.99 – 7.08 (m, 2H), 7.33 (d, J = 7.7 Hz, 1H), 7.46 (t, J = 6.3 Hz, 1H), 7.79 (d, J = 1.3 Hz, 1H), 9.09 (d, J = 4.2 Hz, 1H).

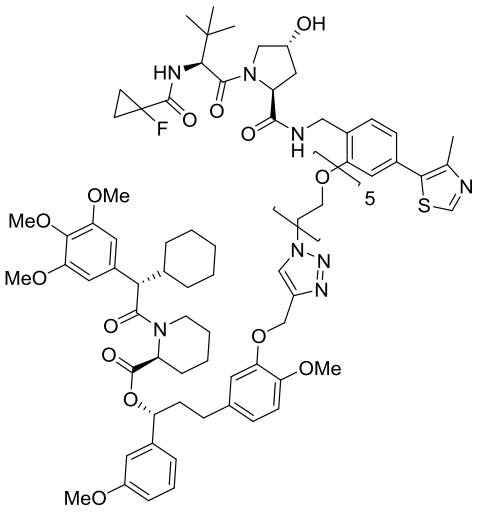
TLC: R_f = 0.11 (DCM:MeOH = 10:1).

LC-MS: [60-100 % Solvent B, 2.7 min]: R_t = 1.0 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{77}H_{101}FN_8O_{17}S$ = 1461.70622; found = 1461.70402.

Lab book number(s): MWa282.

(*R*)-3-(3-((1-(14-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-Fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)-3,6,9,12-tetraoxatetradecyl)-1H-1,2,3-triazol-4-yl)methoxy)-4-methoxyphenyl)-1-(3-methoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{79}H_{105}FN_8O_{18}S$, MW = 1505.81 g / mol

The product was synthesized from azide **58e** (7.8 mg, 10.0 μmol, 1.0 eq.) and alkyne **A11** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 13.3 mg (89 %, 8.9 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.88 (s, 9H), 0.98 – 1.40 (m, 11H), 1.42 – 1.92 (m, 9H), 1.89 – 2.11 (m, 2H), 2.09 – 2.42 (m, 4H), 2.48 (s, 3H), 2.63 – 2.79 (m, 1H), 3.31 (d, *J* = 9.9 Hz, 1H), 3.45 – 3.58 (m, 7H), 3.56 – 3.61 (m, 1H), 3.64 (s, 5H), 3.68 (s, 5H), 3.72 – 3.75 (m, 3H), 3.75 – 3.83 (m, 4H), 3.80 – 3.96 (m, 2H), 4.12 (dt, *J* = 5.4, 3.7 Hz, 2H), 4.31 – 4.63 (m, 8H), 5.15 (d, *J* = 5.8 Hz, 2H), 5.35 – 5.50 (m, 2H), 6.30 – 6.43 (m, 3H), 6.51 – 6.55 (m, 1H), 6.60 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.64 – 6.72 (m, 3H), 6.81 (d, *J* = 1.6 Hz, 1H), 6.88 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.99 – 7.09 (m, 2H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.42 – 7.49 (m, 1H), 7.78 (d, *J* = 2.4 Hz, 1H), 9.00 (d, *J* = 3.1 Hz, 1H).

TLC: R_f = 0.11 (DCM:MeOH = 10:1).

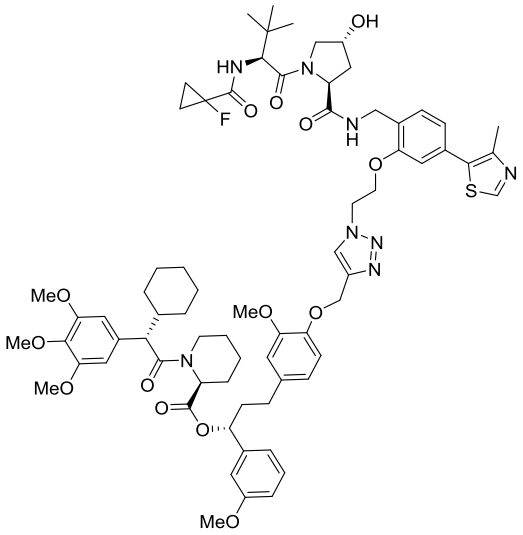
LC-MS: [60-100 % Solvent B, 2.7 min]: R_t = 1.0 min.

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{79}H_{105}FN_8O_{18}S$ = 1505.73243; found = 1505.73207.

Lab book number(s): MWa283.

(*R*)-3-(4-((1-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-Fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxyphenyl)-1-(3-methoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{71}H_{89}FN_8O_{14}S$, MW = 1329.59 g / mol

The product was synthesized from azide **58a** (6.0 mg, 10.0 μmol, 1.0 eq.) and alkyne **A12** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.6 mg (80 %, 8.0 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 0.95 (s, 9H), 1.05 – 1.49 (m, 11H), 1.50 – 1.75 (m, 6H), 1.73 – 1.99 (m, 3H), 2.01 – 2.46 (m, 6H), 2.54 (s, 3H), 2.77 (t, *J* = 12.9 Hz, 1H), 3.39 (d, *J* = 9.9 Hz, 1H),

3.71 (s, 5H), 3.74 (s, 5H), 3.80 – 3.82 (m, 3H), 3.83 (d, J = 1.6 Hz, 2H), 3.99 (dd, J = 16.6, 5.0 Hz, 2H), 4.29 – 4.61 (m, 6H), 4.67 – 4.98 (m, 3H), 5.21 (s, 2H), 5.46 (d, J = 5.3 Hz, 1H), 5.52 (t, J = 6.9 Hz, 1H), 6.34 – 6.53 (m, 3H), 6.54 – 6.67 (m, 2H), 6.72 – 6.80 (m, 2H), 6.82 – 7.03 (m, 3H), 7.04 – 7.16 (m, 2H), 7.35 – 7.49 (m, 2H), 7.95 (d, J = 4.1 Hz, 1H), 9.08 (s, 1H).

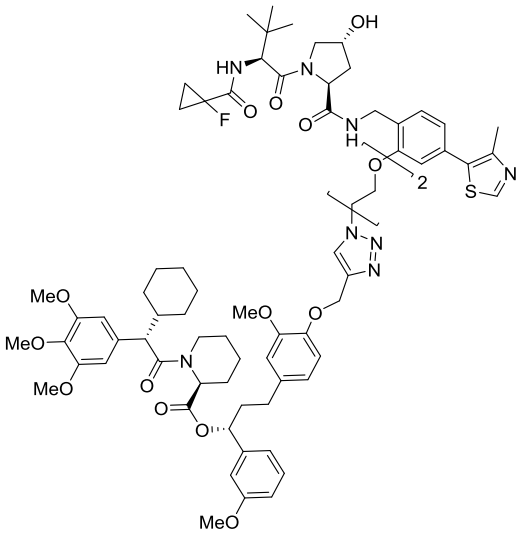
TLC: R_f = 0.13 (DCM:MeOH = 10:1).

LC-MS: [60-100 % Solvent B, 2.7 min]: R_t = 0.9 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{71}H_{89}FN_8O_{14}S$ = 1329.6276; found = 1329.6291.

Lab book number(s): MWa285.

(*R*)-3-(4-((1-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-Fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxyphenyl)-1-(3-methoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{73}H_{93}FN_8O_{15}S$, MW = 1373.65 g / mol

The product was synthesized from azide **58b** (6.5 mg, 10.0 μmol, 1.0 eq.) and alkyne **A12** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 11.3 mg (82 %, 8.2 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.98 (s, 9H), 1.08 – 1.38 (m, 6H), 1.52 – 1.72 (m, 6H), 1.73 – 1.96 (m, 3H), 2.04 – 2.20 (m, 2H), 2.20 – 2.48 (m, 4H), 2.54 (d, J = 1.0 Hz, 3H), 2.73 – 2.83 (m, 1H), 3.39 (d, J = 9.9 Hz, 1H), 3.65 – 3.70 (m, 1H), 3.71 (s, 5H), 3.74 (d, J = 1.4 Hz, 5H), 3.77 – 3.81 (m, 4H), 3.82 – 3.88 (m, 4H), 3.94 – 4.20 (m, 5H), 4.35 – 4.68 (m, 8H), 5.11 – 5.19 (m, 2H), 5.45 (d, J = 5.5 Hz, 1H), 5.52 (dd, J = 7.9, 5.9 Hz, 1H), 6.35 – 6.40 (m, 1H), 6.40 – 6.52 (m, 2H), 6.58 – 6.63 (m, 2H), 6.74 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 6.82 – 6.84 (m, 1H), 6.87 (d, J = 8.2 Hz, 1H), 6.87 – 6.96 (m, 1H), 6.97 (dd, J = 7.7, 1.5 Hz, 1H), 7.06 – 7.14 (m, 2H), 7.38 – 7.44 (m, 2H), 7.84 (s, 1H), 9.08 (d, J = 9.2 Hz, 1H).

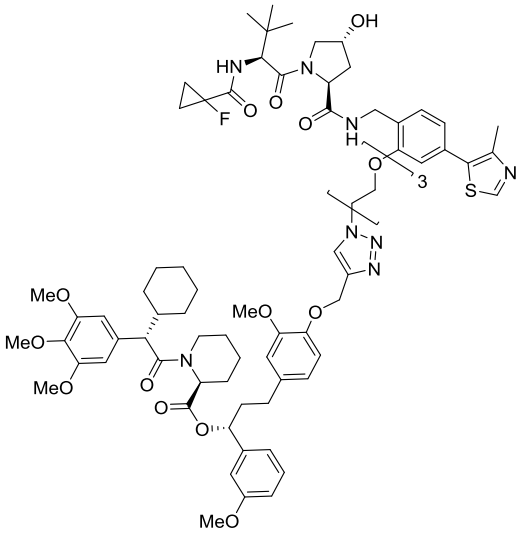
TLC: R_f = 0.12 (DCM:MeOH = 10:1).

LC-MS: [60-100 % Solvent B, 2.7 min]: R_t = 1.0 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{73}H_{93}FN_8O_{15}S$ = 1373.65379; found = 1373.65102.

Lab book number(s): MWa286.

(*R*)-3-(4-((1-(2-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-Fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxyphenyl)-1-(3-methoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{75}H_{97}FN_8O_{16}S$, MW = 1417.70 g / mol

The product was synthesized from azide **58c** (6.9 mg, 10.0 μmol, 1.0 eq.) and alkyne **A12** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.0 mg (70 %, 7.0 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 0.97 (s, 9H), 1.02 – 1.43 (m, 5H), 1.50 – 1.73 (m, 6H), 1.74 – 1.98 (m, 3H), 2.03 – 2.51 (m, 6H), 2.54 (d, *J* = 1.0 Hz, 3H), 2.69 – 2.85 (m, 1H), 3.38 (d, *J* = 9.9 Hz, 1H), 3.56 – 3.74 (m, 10H), 3.75 (s, 5H), 3.80 (d, *J* = 2.6 Hz, 4H), 3.82 – 3.84 (m, 30H), 3.88 – 4.04 (m, 3H), 4.06 – 4.27 (m, 1H), 4.42 – 4.76 (m, 8H), 5.18 (s, 2H), 5.46 (d, *J* = 5.2 Hz, 1H), 5.53 (dd, *J* = 7.9, 5.8 Hz, 1H), 6.38 (d, *J* = 7.8 Hz, 1H), 6.45 (d, *J* = 25.0 Hz, 2H), 6.60 (q, *J* = 2.1 Hz, 2H), 6.71 – 6.77 (m, 1H), 6.84 – 6.90 (m, 2H), 6.87 – 7.00 (m, 2H), 7.10 (t, *J* = 7.9 Hz, 2H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.46 (t, *J* = 6.1 Hz, 1H), 7.85 (s, 1H), 9.05 (d, *J* = 5.1 Hz, 1H).

TLC: R_f = 0.12 (DCM:MeOH = 10:1).

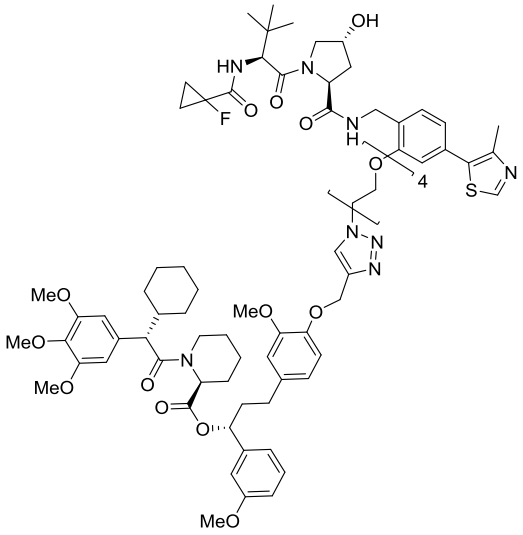
LC-MS: [60-100 % Solvent B, 2.2 min]: R_t = 1.0 min.

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{75}H_{97}FN_8O_{16}S$ = 1417.68000; found = 1417.67846.

Lab book number(s): MWa287.

(*R*)-3-(4-((1-(2-(2-(2-(2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-Fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)ethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxyphenyl)-1-(3-methoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{77}H_{101}FN_8O_{17}S$, MW = 1461.75 g / mol

The product was synthesized from azide **58d** (7.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A12** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 12.2 mg (84 %, 8.4 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.97 (s, 9H), 1.07 – 1.39 (m, 7H), 1.49 – 1.75 (m, 6H), 1.79 – 1.97 (m, 2H), 2.00 – 2.47 (m, 4H), 2.54 (s, 3H), 2.76 (dd, *J* = 14.0, 11.1 Hz, 1H), 3.38 (d, *J* = 9.9 Hz, 1H), 3.57 (d, *J* = 2.0 Hz, 4H), 3.59 – 3.66 (m, 1H), 3.70 (s, 6H), 3.74 (s, 5H), 3.81 (d, *J* = 2.6 Hz, 4H), 3.83 (d, *J* = 2.3 Hz, 2H), 3.88 – 4.02 (m, 3H), 4.08 – 4.26 (m, 2H), 4.40 – 4.75 (m, 8H), 5.19 (d, *J* = 1.8 Hz, 2H), 5.46 (d, *J* = 5.2 Hz, 1H), 5.53 (dd, *J* = 7.9, 5.8 Hz, 1H), 6.36 – 6.51 (m, 3H), 6.56 – 6.63 (m, 2H), 6.74 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 6.81 – 7.00 (m, 4H), 7.04 – 7.14 (m, 2H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 5.9 Hz, 1H), 7.84 (s, 1H), 9.03 (d, *J* = 3.7 Hz, 1H).

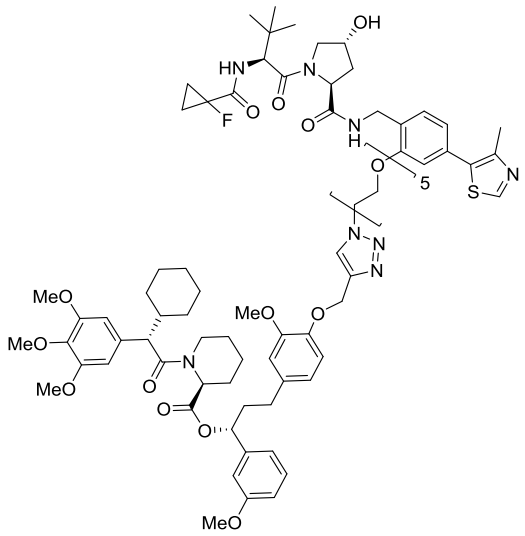
TLC: R_f = 0.11 (DCM:MeOH = 10:1).

LC-MS: [60-100 % Solvent B, 2.2 min]: R_t = 1.0 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{77}H_{101}FN_8O_{17}S$ = 1461.7062; found = 1461.7084.

Lab book number(s): MWa288.

(*R*)-3-(4-((1-(14-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-Fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)-3,6,9,12-tetraoxatetradecyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxyphenyl)-1-(3-methoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{79}H_{105}FN_8O_{18}S$, MW = 1505.81 g / mol

The product was synthesized from azide **58e** (7.8 mg, 10.0 μmol, 1.0 eq.) and alkyne **A12** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.1 mg (67 %, 6.7 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.97 (s, 9H), 1.07 – 1.42 (m, 5H), 1.59 (tt, *J* = 14.9, 6.1 Hz, 6H), 1.74 – 1.99 (m, 3H), 2.01 – 2.49 (m, 6H), 2.56 (s, 3H), 2.71 – 2.84 (m, 1H), 3.39 (d, *J* = 10.0 Hz, 1H), 3.51 – 3.62 (m, 8H), 3.59 – 3.71 (m, 2H), 3.71 (s, 6H), 3.75 (d, *J* = 0.8 Hz, 5H), 3.81 (d, *J* = 2.9 Hz, 4H), 3.79 – 3.93 (m, 6H), 3.91 – 4.08 (m, 2H), 4.18 (dq, *J* = 14.2, 5.5, 4.9 Hz, 2H), 4.42 – 4.68 (m, 6H), 5.20 (d, *J* = 2.0 Hz, 2H), 5.46 (d, *J* = 5.3 Hz, 1H), 5.54 (dd, *J* = 7.9, 5.8 Hz, 1H), 6.33 – 6.53 (m, 3H), 6.61 (dt, *J* = 4.3, 2.1 Hz, 2H), 6.72 – 6.80 (m, 1H), 6.82 – 6.99 (m, 4H), 7.10 (t, *J* = 7.9 Hz, 2H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.59 (t, *J* = 5.8 Hz, 1H), 7.86 (s, 1H), 9.14 (d, *J* = 3.3 Hz, 1H).

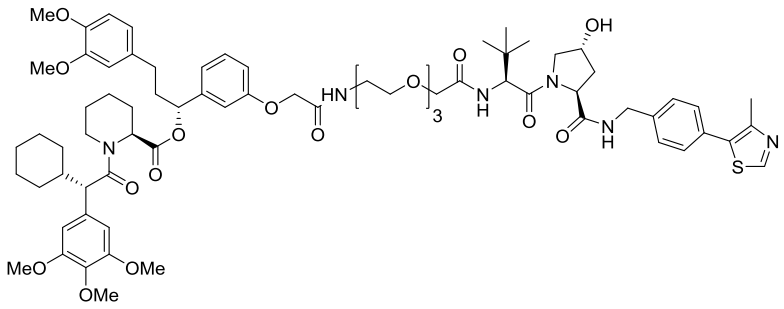
TLC: R_f = 0.11 (DCM:MeOH = 10:1).

LC-MS: [60-100 % Solvent B, 2.2 min]: R_t = 0.9 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{79}H_{105}FN_8O_{18}S$ = 1505.7324; found = 1505.7366.

Lab book number(s): MWa289.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(((*S*)-16-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-17,17-dimethyl-2,14-dioxo-6,9,12-trioxa-3,15-diazaoctadecyl)oxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{72}H_{96}N_6O_{17}S$, MW = 1349.65 g / mol

The product was synthesized from (2*S*,4*R*)-1-((*S*)-14-amino-2-(*tert*-butyl)-4-oxo-6,9,12-trioxa-3-azatetradecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride (4.6 mg, 7.0 μmol, 1.0 eq.) and carboxylic acid **122** (THE10, 5.2 mg, 7.0 μmol, 1.0 eq.) according to general procedure B. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 7.6 mg (81 %, 5.7 μmol).

Appearance: white solid.

^{1}**H-NMR** (500 MHz, Chloroform-*d*): δ = 0.99 (s, 9H), 1.13 (dt, *J* = 10.2, 6.4 Hz, 2H), 1.20 – 1.38 (m, 4H), 1.37 – 1.50 (m, 1H), 1.52 – 1.75 (m, 6H), 1.80 – 2.13 (m, 4H), 2.25 (dd, *J* = 33.5, 11.0 Hz, 2H), 2.32 – 2.45 (m, 2H), 2.48 (td, *J* = 9.1, 4.6 Hz, 1H), 2.56 (s, 3H), 2.76 (t, *J* = 13.1 Hz, 1H), 3.39 (d, *J*

= 9.9 Hz, 1H), 3.48 – 3.78 (m, 19H), 3.84 (q, *J* = 3.7, 3.0 Hz, 8H), 3.94 – 4.18 (m, 4H), 4.31 – 4.81 (m, 8H), 5.46 (d, *J* = 5.4 Hz, 1H), 5.56 (dd, *J* = 8.2, 5.4 Hz, 1H), 6.49 (d, *J* = 9.8 Hz, 2H), 6.58 – 6.66 (m, 3H), 6.70 – 6.82 (m, 2H), 7.12 (t, *J* = 7.9 Hz, 1H), 7.29 – 7.50 (m, 7H), 9.19 (s, 1H).

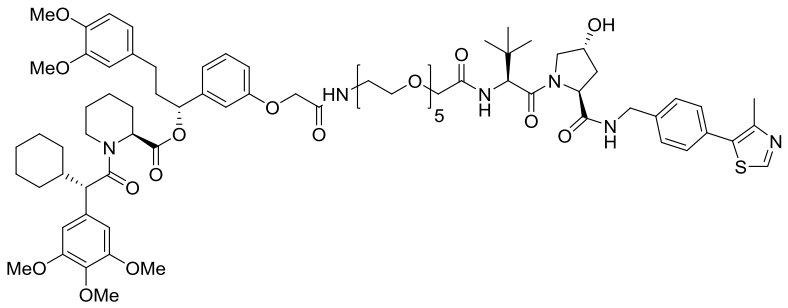
TLC: R_f = 0.08 (DCM:MeOH = 10:1).

LC-MS: [50-100 % Solvent B, 2.6 min]: R_t = 1.6 min.
95 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{72}H_{96}N_6O_{17}S$ = 1349.6625; found = 1349.6629.

Lab book number(s): MWa347.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(((*S*)-22-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-23,23-dimethyl-2,20-dioxo-6,9,12,15,18-pentaoxa-3,21-diazatetracosyl)oxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{76}H_{104}N_6O_{19}S$, MW = 1437.75 g / mol

The product was synthesized from (2*S*,4*R*)-1-((*S*)-20-amino-2-(*tert*-butyl)-4-oxo-6,9,12,15,18-pentaoxa-3-azaicosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride (5.2 mg, 7.0 μmol, 1.0 eq.) and carboxylic acid **122** (THE10, 5.2 mg, 7.0 μmol, 1.0 eq.) according to general procedure B. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 7.2 mg (71 %, 5.0 μmol).

Appearance: white solid.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 0.97 (s, 9H), 1.15 (dt, *J* = 20.1, 6.7 Hz, 2H), 1.22 – 1.36 (m, 4H), 1.37 – 1.49 (m, 1H), 1.53 – 1.74 (m, 6H), 1.77 – 2.13 (m, 4H), 2.15 – 2.23 (m, 1H), 2.29 (d, *J* = 13.2 Hz, 1H), 2.33 – 2.53 (m, 2H), 2.55 (s, 3H), 2.70 – 2.81 (m, 1H), 3.39 (d, *J* = 9.9 Hz, 1H), 3.46 – 3.73 (m, 27H), 3.76 (s, 2H), 3.81 – 3.87 (m, 8H), 3.92 – 4.13 (m, 4H), 4.33 – 4.79 (m, 8H), 5.47 (d, *J* = 5.3 Hz, 1H), 5.57 (dd, *J* = 8.2, 5.4 Hz, 1H), 6.40 – 6.51 (m, 3H), 6.60 – 6.70 (m, 3H), 6.72 – 6.81 (m, 2H), 7.13 (t, *J* = 7.9 Hz, 1H), 7.28 – 7.46 (m, 6H), 9.06 (s, 1H).

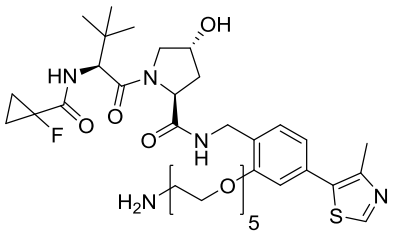
TLC: R_f = 0.07 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 2.6 min]: R_t = 2.0 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{76}H_{104}N_6O_{19}S$ = 1437.71497; found = 1437.71493.

Lab book number(s): MWa348.

(2*S*,4*R*)-*N*-(2-((14-Amino-3,6,9,12-tetraoxatetradecyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{36}H_{54}FN_5O_9S$, MW = 751.91 g / mol

Azide **58e** (7.8 mg, 10.0 μmol, 1.0 eq.) and triphenylphosphine (2.9 mg, 11.0 μmol, 1.1 eq.) were dissolved in THF (1 mL) and water (0.3 μL, 15 μmol, 1.5 eq.) and stirred for 18 h at 40 °C. The mixture was concentrated under reduced pressure. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.5 mg (73 %, 7.3 μmol).

Appearance: white solid.

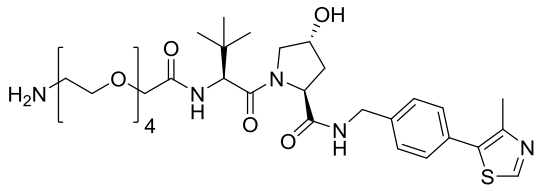
^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.01 (s, 9H), 1.14 – 1.37 (m, 6H), 2.13 – 2.27 (m, 2H), 2.54 (s, 3H), 3.56 – 3.81 (m, 16H), 3.94 (d, *J* = 12.4 Hz, 3H), 4.13 – 4.28 (m, 2H), 4.37 – 4.56 (m, 4H), 4.63 (t, *J* = 8.2 Hz, 1H), 6.90 (s, 1H), 6.98 (d, *J* = 7.7 Hz, 1H), 7.01 – 7.08 (m, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.60 – 7.71 (m, 1H), 7.90 (s, 2H), 8.96 (s, 1H).

TLC: R_f = 0.11 (DCM:MeOH = 20:1, 1 % TEA).

LC-MS: Mass (ESI), calculated = 752.4 $[M+H]^+$, found = 752.4.
[5-100 % Solvent B, 2.6 min]: R_t = 1.5 min.
97 % purity (220 nm).

Lab book number(s): MWa371.

(2*S*,4*R*)-1-((*S*)-17-Amino-2-(*tert*-butyl)-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{32}H_{49}N_5O_8S$, MW = 663.83 g / mol

Azide **57d** (50 mg, 72.5 μmol, 1.0 eq.) and triphenylphosphine (21 mg, 80.0 μmol, 1.1 eq.) were dissolved in THF (7 mL) and water (2.0 μL, 109 μmol, 1.5 eq.) and stirred for 18 h at 40 °C. The mixture was concentrated under reduced pressure. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 31.0 mg (65 %, 46.7 μmol).

Appearance: white solid.

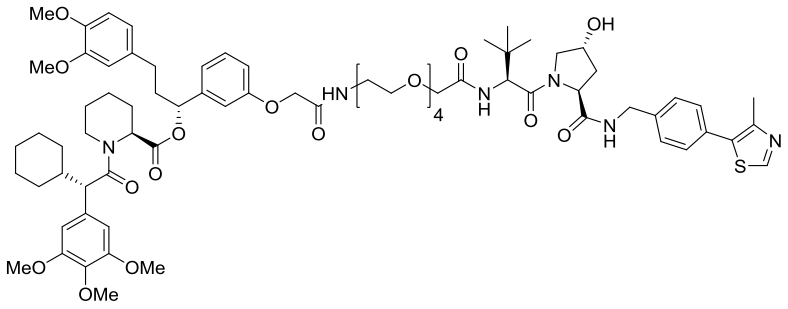
^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.86 (s, 9H), 2.08 – 2.21 (m, 1H), 2.49 (d, *J* = 3.8 Hz, 4H), 2.97 (t, *J* = 5.0 Hz, 2H), 3.40 – 3.64 (m, 16H), 3.85 (d, *J* = 48.0 Hz, 3H), 4.27 – 4.49 (m, 5H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 9.90 (s, 1H).

TLC: R_f = 0.10 (DCM:MeOH = 20:1, 1 % TEA).

LC-MS: Mass (ESI), calculated = 663.4 $[M+H]^+$, found = 664.2.
[5-100 % Solvent B, 2.6 min]: R_t = 1.4 min.
94 % purity (220 nm).

Lab book number(s): MWa426.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(((*S*)-19-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-20,20-dimethyl-2,17-dioxo-6,9,12,15-tetraoxa-3,18-diazahenicosyl)oxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{74}H_{100}N_6O_{18}S$, MW = 1393.70 g / mol

The product was synthesized from amine **112** (4.6 mg, 7.0 μmol, 1.0 eq.) and carboxylic acid **122** (THE10, 5.2 mg, 7.0 μmol, 1.0 eq.) according to general procedure B. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.1 mg (52 %, 3.6 μmol).

Appearance: white solid.

TLC: R_f = 0.07 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.1 min.

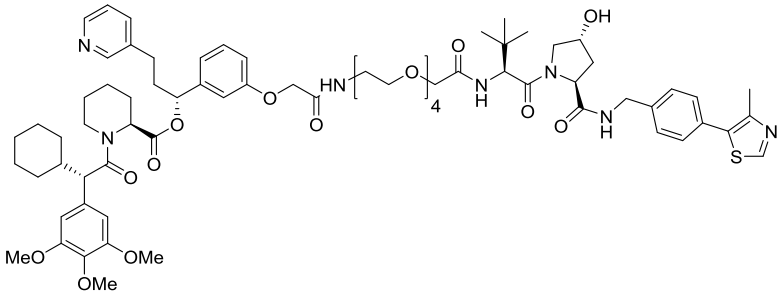
[30-100 % Solvent B, 2.6 min]: R_t = 1.8 min.

97 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{74}H_{100}N_6O_{18}S$ = 1393.68876; found = 1393.69030.

Lab book number(s): MWa429.

(*R*)-1-(3-(((*S*)-19-((2*S*,4*R*)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-20,20-dimethyl-2,17-dioxo-6,9,12,15-tetraoxa-3,18-diazahenicosyl)oxy)phenyl)-3-(pyridin-3-yl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{71}H_{95}N_7O_{16}S$, MW = 1334.63 g / mol

The product was synthesized from amine **112** (6.7 mg, 10.0 μmol, 1.0 eq.) and carboxylic acid **124** (AV739, 7.0 mg, 10.0 μmol, 1.0 eq.) according to general procedure B. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 7.3 mg (55 %, 5.5 μmol).

Appearance: white solid.

TLC: R_f = 0.08 (DCM:MeOH = 10:1).

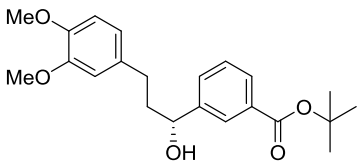
LC-MS: [30-100 % Solvent B, 2.6 min]: R_t = 1.4 min.

95 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{71}H_{95}N_7O_{16}S$ = 1334.66288; found = 1334.66370.

Lab book number(s): MWa431.

***tert*-Butyl (*R*)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)benzoate**



$C_{22}H_{28}O_5$, MW = 372.46 g / mol

(*R*)-3-(3-(3,4-Dimethoxyphenyl)-1-hydroxypropyl)benzonitrile (AV532, 10 mg, 34 μmol, 1.0 eq.) and potassium hydroxide (94 mg, 1682 μmol, 50.0 eq.) were dissolved in water (2 mL) and stirred for 2 h at 115 °C. Hydrochloric acid (1 M, aq, 20 mL) was added and the mixture was extracted with DCM (3 x 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure.

TLC: R_f = 0.32 (CH:EA = 1:1, 1 % HCOOH).

Crude (*R*)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)benzoic acid (11 mg, 34 μmol, 2.5 eq.) was dissolved in acetonitrile (1 mL) and water (50 μL). *tert*-Butly bromide (16 μL, 136 μmol, 4.0 eq.) and silver oxide (16 mg, 68 μmol, 2.0 eq.) were added and the solution was stirred for 1 h at room temperature. The mixture was filtered and the crude product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 9.7 mg (76 % o2s, 26 μmol).

Appearance: white solid.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.28 (s, 5H), 1.41 (d, *J* = 8.8 Hz, 2H), 1.81 (s, 1H), 1.90 – 2.16 (m, 3H), 2.60 (dddd, *J* = 23.5, 21.4, 11.6, 6.4 Hz, 2H), 3.73 – 3.82 (m, 6H), 4.72 (td, *J* = 8.7, 8.2, 4.9 Hz, 1H), 6.63 – 6.74 (m, 3H), 7.42 (dt, *J* = 24.2, 7.7 Hz, 1H), 7.49 – 7.61 (m, 1H), 7.79 – 8.05 (m, 2H).

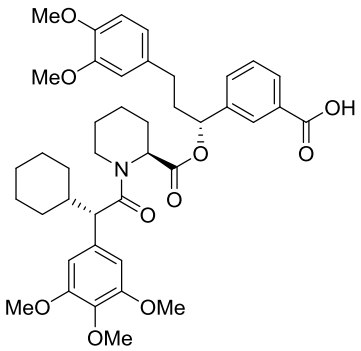
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 28.4, 28.6, 31.6, 40.7, 55.8, 56.0, 73.1, 73.4, 111.4, 111.8, 120.2, 127.7, 128.8, 129.4, 129.5, 131.3, 134.0, 145.1, 147.3, 148.9, 170.8.

TLC: R_f = 0.61 (CH:EA = 1:1, 1 % HCOOH).

LC-MS: Mass (ESI), calculated = 373.2 $[M+H]^+$, found = 414.2.
[30-100 % Solvent B, 2.6 min]: R_t = 1.3 min.
99 % purity (220 nm).

Lab book number(s): MWa427 + MWa428.

3-((*R*)-1-(((*S*)-1-((*S*)-2-Cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)benzoic acid



$C_{41}H_{51}NO_{10}$, MW = 717.86 g / mol

(*S*)-1-((*S*)-2-Cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylic acid (VBu065, 10.9 mg, 26 μmmol, 1.0 eq.) and 4-pyrolidinopyridine (15.4 mg, 104 μmol, 4.0 eq.) were weighted in a flask and flooded with argon. t*ert*-Butyl (*R*)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)benzoate (9.7 mg, 26 μmol, 1.0 eq.) and toluene (dry, 3 mL) were added and the mixture was cooled to 0 °C. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (5.6 mg, 29 μmol, 1.1 eq.) was added and the mixture was stirred for 2 h at 0 °C to room temperature. Hydrochloric acid (1 M, aq, 10 mL) and brine (40 mL) were added and the mixture was extracted with DCM (2 x 40 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure.

To crude (*R*)-1-(3-(*tert*-butoxycarbonyl)phenyl)-3-(3,4-dimethoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (20.1 mg, 26 μmol, 1.0 eq.) DCM (1.2 mL) and TFA (0.5 mL) were added and the mixture was stirred for 2 h at room temperature.

The mixture was concentrated under reduced pressure. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 9.0 mg (48 % o2s, 12.5 μmol).

Appearance: white solid.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 0.68 – 1.00 (m, 2H), 1.06 – 1.39 (m, 6H), 1.51 – 1.73 (m, 5H), 1.80 – 2.15 (m, 4H), 2.23 – 2.67 (m, 3H), 2.74 – 2.84 (m, 1H), 3.40 (d, *J* = 9.9 Hz, 1H), 3.66 – 3.92 (m, 14H), 3.99 (d, *J* = 13.6 Hz, 1H), 5.46 – 5.50 (m, 1H), 5.66 (dd, *J* = 8.2, 5.6 Hz, 1H), 6.46 (d, *J* = 31.8 Hz, 2H), 6.59 – 6.71 (m, 2H), 6.79 (dd, *J* = 15.9, 8.0 Hz, 1H), 7.04 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.89 (t, *J* = 1.7 Hz, 1H), 7.96 (dt, *J* = 7.7, 1.4 Hz, 1H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ =21.0, 25.6, 26.2, 26.3, 26.7, 26.8, 30.8, 31.1, 32.9, 38.1, 41.4, 44.0, 52.4, 55.2, 56.0, 56.1, 56.2, 56.5, 60.9, 75.4, 106.0, 111.5, 111.9, 120.4, 128.2, 129.0, 129.5, 129.9, 131.6, 133.2, 133.5, 137.1, 141.0, 147.5, 149.1, 153.3, 153.5, 170.2, 170.5, 173.0.

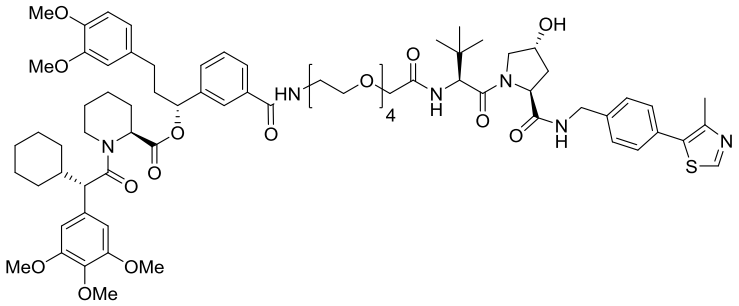
TLC: R_f = 0.24 (CH:EA = 1:1, 1 % HCOOH).

LC-MS: [30-100 % Solvent B, 2.6 min]: R_t = 1.9 min.
95 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{41}H_{51}NO_{10}$= 718.35857; found = 718.35847.

Lab book number(s): MWa432 + MWa433.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(((*S*)-16-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-17,17-dimethyl-14-oxo-3,6,9,12-tetraoxa-15-azaoctadecyl)carbamoyl)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{73}H_{98}N_6O_{17}S$, MW = 1363.67 g / mol

The product was synthesized from amine **112** (2.0 mg, 3.0 μmol, 1.0 eq.) and carboxylic acid **115** (2.2 mg, 3.0 μmol, 1.0 eq.) according to general procedure B. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 1.9 mg (46 %, 1.4 μmol).

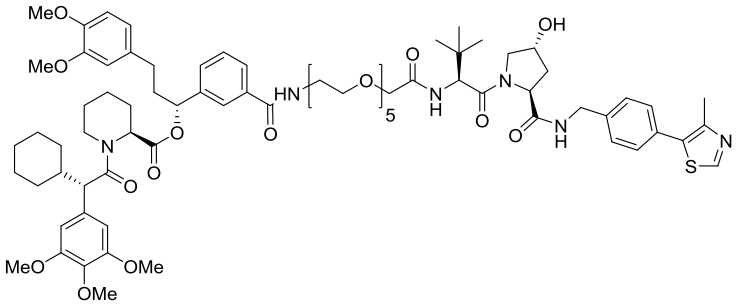
Appearance: white solid.

TLC: R_f = 0.07 (DCM:MeOH = 10:1).

LC-MS: Mass (ESI), calculated = 1363.7 $[M+H]^+$, found = 1363.6.
[5-100 % Solvent B, 3.0 min]: R_t = 2.4 min.
> 99 % purity (220 nm).

Lab book number(s): MWa458.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(((*S*)-19-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-20,20-dimethyl-17-oxo-3,6,9,12,15-pentaoxa-18-azahenicosyl)carbamoyl)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{75}H_{102}N_6O_{18}S$, MW = 1407.73.67 g / mol

The product was synthesized from (2*S*,4*R*)-1-((*S*)-20-amino-2-(*tert*-butyl)-4-oxo-6,9,12,15,18-pentaoxa-3-azaicosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride (2.2 mg, 3.0 μmol, 1.0 eq.) and carboxylic acid **115** (2.2 mg, 3.0 μmol, 1.0 eq.) according to general procedure B. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 1.8 mg (43 %, 1.3 μmol).

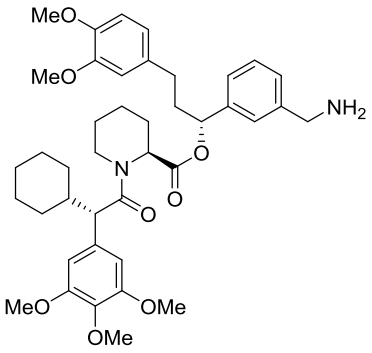
Appearance: white solid.

TLC: R_f = 0.07 (DCM:MeOH = 10:1).

LC-MS: Mass (ESI), calculated = 1407.7 $[M+H]^+$, found = 1407.8.
[5-100 % Solvent B, 3.0 min]: R_t = 2.4 min.
> 99 % purity (220 nm).

Lab book number(s): MWa459.

(*R*)-1-(3-(Aminomethyl)phenyl)-3-(3,4-dimethoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{41}H_{54}N_2O_8$, MW = 702.89 g / mol

(*R*)-1-(3-Cyanophenyl)-3-(3,4-dimethoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV552, 10 mg, 14.3 μmol, 1.0 eq.) was dissolved in THF (dry, 2 mL) under argon. BH_3-THF (1 M in THF, 71.5 μL, 71.5 μmol, 5.0 eq.) was added and the mixture was stirred for 18 h at 60 °C. Sodium hydrogen carbonate (sat., aq, 20 mL) was added and the mixture was extracted with DCM (3 x 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by column chromatography (3 g SiO_2, DCM:MeOH = 20:1, 1 % TEA).

Yield: 10 mg (quant. 14.3 μmol).

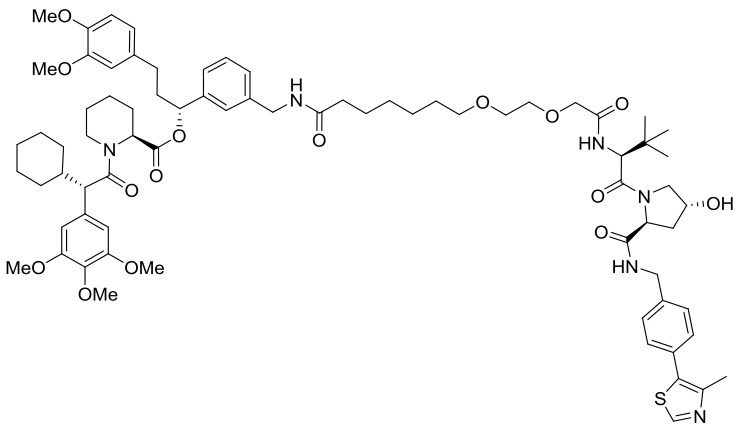
Appearance: yellow oil.

TLC: R_f = 0.19 (DCM:MeOH = 20:1, 1 % TEA).

LC-MS: Mass (ESI), calculated = 703.4 $[M+H]^+$, found = 703.4.
[5-100 % Solvent B, 2.6 min]: R_t = 1.6 min.
80 % purity (220 nm).

Lab book number(s): MWa355.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-((*S*)-17-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-18,18-dimethyl-3,15-dioxo-10,13-dioxa-2,16-diazanonadecyl)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{74}H_{100}N_6O_{15}S$, MW = 1345.70 g / mol

The product was synthesized from amine **118** (10 mg, 14.3 μmol, 1.0 eq.) and 7-(2-(2-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)ethoxy)heptanoic acid (9.5 mg, 14.3 μmol, 1.0 eq.) according to general procedure B. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 3.7 mg (19 %, 2.7 μmol).

Appearance: white solid.

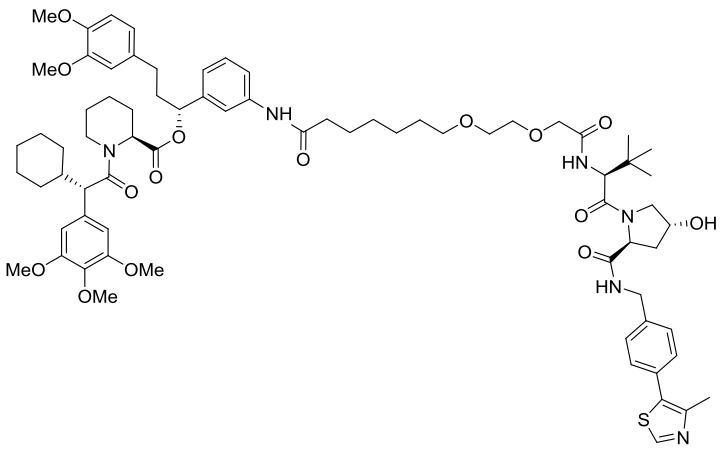
TLC: R_f = 0.10 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 3.0 min]: R_t = 2.4 min.
[70-100 % Solvent B, 3.0 min]: R_t = 2.4 min.
96 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{74}H_{100}N_6O_{15}S$ = 1345.70401; found = 1345.70401.

Lab book number(s): MWa472.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(3-(7-(2-(2-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)ethoxy)heptanamido)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{73}H_{98}N_6O_{15}S$, MW = 1331.67 g / mol

The product was synthesized from (*R*)-1-(3-aminophenyl)-3-(3,4-dimethoxyphenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV602, 0.8 mg, 1.2 μmol, 1.0 eq.) and 7-(2-(2-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl) pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)ethoxy)heptanoic acid (0.8 mg, 1.2 μmol, 1.0 eq.) according to general procedure B. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 0.9 mg (56 %, 0.7 μmol).

Appearance: white solid.

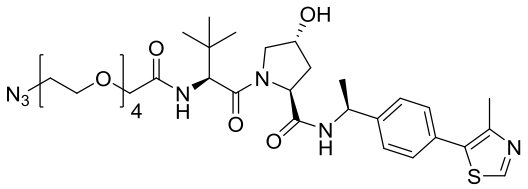
TLC: R_f = 0.10 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.4 min.
[50-100 % Solvent B, 10.5 min]: R_t = 8.6 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{73}H_{98}N_6O_{15}S$ = 1331.68836; found = 1331.68914.

Lab book number(s): MWa474.

(2*S*,4*R*)-1-((*S*)-17-Azido-2-(*tert*-butyl)-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



$C_{33}H_{49}N_7O_8S$, MW = 703.86 g / mol

The product was synthesized from *tert*-butyl ((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (JKD100, 50 mg, 91.8 μmol, 1.0 eq.) and 14-azido-3,6,9,12-tetraoxatetradecan-1-oic acid (26 mg, 91.8 μmol, 1.0 eq. according to general procedure E. The obtained product was purified by flash chromatography.

Yield: 53 mg (82 % o2s, 75.4 μmol).

Appearance: white solid.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 0.99 – 1.09 (m, 9H), 1.50 (d, J = 6.7 Hz, 3H), 2.07 (p, J = 6.1 Hz, 1H), 2.37 – 2.48 (m, 1H), 2.49 – 2.56 (m, 3H), 3.38 (p, J = 4.6 Hz, 2H), 3.67 (q, J = 7.7, 6.3 Hz, 16H), 3.95 – 4.08 (m, 3H), 4.46 – 4.64 (m, 2H), 4.72 (d, J = 7.4 Hz, 1H), 5.08 (q, J = 7.1 Hz, 1H), 5.28 – 5.33 (m, 2H), 7.38 (q, J = 7.7 Hz, 5H), 7.58 (d, J = 6.7 Hz, 1H), 8.65 – 8.71 (m, 1H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 16.1, 22.3, 26.5, 35.3, 35.8, 48.8, 50.6, 53.5, 56.7, 57.1, 58.6, 70.0, 70.0, 70.3, 70.4, 70.6, 70.6, 70.6, 70.6, 71.1, 126.4, 129.5, 130.7, 131.6, 143.3, 148.4, 150.3, 169.9, 170.4, 171.3.

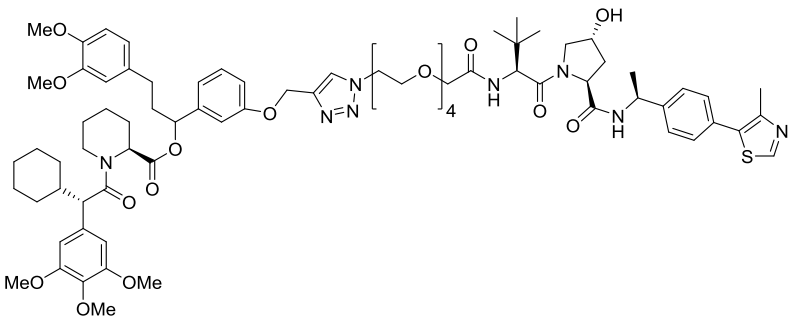
TLC: R_f (intermediate) = 0.55 (DCM:MeOH = 10:1, 3 % TEA).
R_f = 0.34 (DCM:MeOH = 10:1, 3 % TEA).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 1.8 min.
95 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{33}H_{49}N_7O_8S$ = 704.34361; found = 704.34307.

Lab book number(s): MWa479.

3-(3,4-Dimethoxyphenyl)-1-(4-((1-((*S*)-16-((2*S*,4*R*)-4-hydroxy-2-(((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidine-1-carbonyl)-17,17-dimethyl-14-oxo-3,6,9,12-tetraoxa-15-azaoctadecyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{76}H_{102}N_8O_{17}S$, MW = 1431.75 g / mol

The product was synthesized from azide **178** (7.0 mg, 10.0 μmol, 1.0 eq.) and alkyne **A10** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 9.7 mg (68 %, 6.8 μmol).

Appearance: white solid.

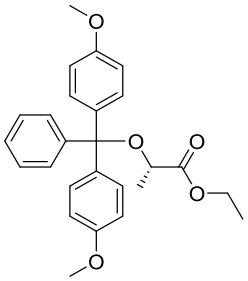
TLC: R_f = 0.11 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 2.6 min]: R_t = 2.4 min.
[50-100 % Solvent B, 2.6 min]: R_t = 2.4 min.
98 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{76}H_{102}N_8O_{17}S$ = 1431.71564; found = 1431.71684.

Lab book number(s): MWa484.

Ethyl (*S*)-2-(bis(4-methoxyphenyl)(phenyl)methoxy)propanoate



$C_{26}H_{28}O_5$, MW = 420.51 g / mol

4,4'-(Chloro(phenyl)methylene)bis(methoxybenzene) (3.30 g, 10.0 mmol, 1.0 eq.) and ethyl (*S*)-2-hydroxypropanoate (11.8 g, 100 mmol, 10.0 eq.) were dissolved in pyridine (20 mL). The mixture was stirred for 16 h at room temperature. Sodium hydrogen carbonate (aq, sat., 20 mL) was added and the solution was extracted by EA (300 mL). The organic phase was counter washed with brine (3 x 30 mL) dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by column chromatography (400 g SiO_2, CH:EA = 9:1 → 5:1).

Yield: 4.12 g (98 %, 9.8 mmol).

Appearance: yellow oil.

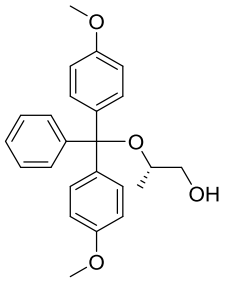
^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.04 (t, *J* = 7.1 Hz, 3H), 1.34 (d, *J* = 6.8 Hz, 3H), 3.69 (q, *J* = 7.2 Hz, 2H), 3.76 (s, 6H), 4.15 (q, *J* = 6.6 Hz, 1H), 6.79 (dd, *J* = 8.8, 3.0 Hz, 4H), 7.13 – 7.29 (m, 3H), 7.35 (d, *J* = 8.7 Hz, 4H), 7.47 (d, *J* = 7.6 Hz, 2H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 14.0, 20.2, 27.0, 55.3, 60.3, 69.6, 113.1, 127.0, 127.8, 128.6, 129.2, 130.6, 130.6, 136.2, 136.4, 145.1, 158.7, 158.7, 173.8.

TLC: R_f = 0.30 (CH:EA = 5:1).

Lab book number(s): MWa186.

(2*S*)-2-((4-Ethylphenyl)(4-methoxyphenyl)(phenyl)methoxy)propan-1-ol



$C_{24}H_{26}O_4$, MW = 378.47 g / mol

Ethyl (S)-2-(bis(4-methoxyphenyl)(phenyl)methoxy)propanoate (4.10 g, 9.8 mmol, 1.0 eq.) was dissolved in THF (50 mL, dry) under argon. The mixture was cooled to 0 °C and LAH in THF (1 M, 11.8 mL, 1.2 eq.) was added slowly. The mixture was allowed to warm to room temperature and was stirred for 2 h. The solution was filtered and rinsed with DEE. The organic phase was washed with Brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The obtained oil was purified by column chromatography (400 g SiO_2, CH:EA = 5:1).

Yield: 3.47 g (94 %, 9.2 mmol).

Appearance: yellow oil.

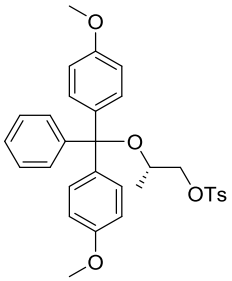
^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.12 – 1.21 (m, 3H), 2.99 – 3.11 (m, 1H), 3.14 – 3.26 (m, 1H), 3.81 – 3.84 (m, 6H), 3.87 – 4.04 (m, 1H), 6.85 – 6.88 (m, 4H), 7.17 – 7.40 (m, 9H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 19.1, 55.3, 67.2, 69.0, 86.2, 113.2, 126.9, 127.9, 128.3, 130.2, 136.2, 145.0, 158.6.

TLC: R_f = 0.34 (CH:EA = 3:1).

Lab book number(s): MWa190.

(*S*)-2-(Bis(4-methoxyphenyl)(phenyl)methoxy)propyl 4-methylbenzenesulfonate



$C_{31}H_{32}O_6S$, MW = 532.65 g / mol

The product was synthesized from (*S*)-2-(bis(4-methoxyphenyl)(phenyl)methoxy)propan-1-ol (3.40 g, 9.0 mmol, 1.0 eq.) according to general procedure C. The obtained product was purified by column chromatography (400 g SiO_2, CH:EA = 4:1 → 2:1).

Yield: 2.68 g (56 %, 5.0 mmol).

Appearance: slightly pink foam.

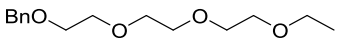
^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.17 (d, *J* = 6.5 Hz, 2H), 2.41 (s, 3H), 2.93 (dd, *J* = 10.6, 3.4 Hz, 1H), 3.04 (dd, *J* = 10.7, 6.2 Hz, 1H), 3.74 (s, 6H), 4.68 (ddt, *J* = 8.9, 6.0, 2.6 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 4H), 7.14 (dd, *J* = 9.0, 2.7 Hz, 4H), 7.18 – 7.25 (m, 3H), 7.27 (d, *J* = 4.4 Hz, 4H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 8.3 Hz, 2H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 17.5, 21.0, 55.0, 65.5, 78.9, 85.4, 113.1, 126.6, 127.4, 127.5, 127.7, 129.5, 130.0, 133.7, 135.2, 135.2, 144.5, 144.5, 158.0.

TLC: R_f = 0.41 (CH:EA = 5:1).

Lab book number(s): MWa192.

1-Phenyl-2,5,8,11-tetraoxatridecane



$C_{15}H_{24}O_4$, MW = 268.35 g / mol

Diethylene glycol monoethyl ether (134 mg, 1.0 mmol, 1.0 eq.), ((2-bromoethoxy)methyl)benzene (430 mg, 2.0 mmol, 2.0 eq.) and potassium *tert*-butoxide (168 mg, 1.5 mmol, 1.5 eq.) were dissolved in *tert*-butanol (10 mL). The mixture was stirred for 18 h at 30 °C followed by 1 d at 60 °C. The solvent was removed under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 221 mg (82 %, 820 μmol).

Appearance: colorless oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.20 (t, *J* = 7.0 Hz, 3H), 3.51 (q, *J* = 6.9 Hz, 2H), 3.56 – 3.59 (m, 2H), 3.61 – 3.69 (m, 10H), 4.56 (s, 2H), 7.24 – 7.29 (m, 1H), 7.29 – 7.36 (m, 4H).

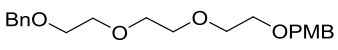
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 15.2, 66.7, 69.5, 69.9, 70.7, 70.7, 70.8, 73.3, 127.6, 127.8, 128.4, 138.4.

TLC: R_f = 0.20 (CH:EA = 5:1).

LC-MS: Mass (ESI), calculated = 269.2 $[M+H]^+$, found = 269.2.
[5-100 % Solvent B, 2.6 min]: R_t = 1.6 min.
98 % purity (220 nm).

Lab book number(s): MWa341.

1-(4-methoxyphenyl)-12-phenyl-2,5,8,11-tetraoxadodecane



$C_{21}H_{28}O_5$, MW = 360.45 g / mol

2-(2-(Benzyloxy)ethoxy)ethanol (9.8 mg, 50 μmol, 1.0 eq.), 1-[(2-bromoethoxy)Methyl]-4-methoxybenzene (24.5 mg, 110 μmol, 2.0 eq.) and potassium *tert*-butoxide (8.4 mg, 1.5 mmol, 1.5 eq.) were dissolved in *tert*-butanol (1 mL). The mixture was stirred for 18 h at at 70 °C. The solvent was removed under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 15.3 mg (85 %, 42.5 μmol).

Appearance: colorless oil.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 3.55 – 3.74 (m, 12H), 3.80 (s, 3H), 4.50 (s, 2H), 4.57 (s, 2H), 6.84 – 6.90 (m, 2H), 7.21 – 7.35 (m, 4H), 7.34 (dd, *J* = 4.1, 0.9 Hz, 3H).

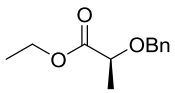
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 55.4, 69.3, 69.6, 70.8, 73.0, 73.4, 113.9, 127.7, 127.9, 128.5, 129.5, 130.5, 138.5, 159.3.

TLC: R_f = 0.40 (CH:EA = 1:1).

LC-MS: Mass (ESI), calculated = 378.2 $[M+NH_4]^+$, found = 378.2.
[5-100 % Solvent B, 3.2 min]: R_t = 2.1 min.
99 % purity (220 nm).

Lab book number(s): MWa442.

Ethyl (*S*)-2-(benzyloxy)propanoate



$C_{12}H_{16}O_3$, MW = 208.26 g / mol

Ethyl (S)-2-hydroxypropanoate (115 μL, 1.0 mmol, 1.0 eq.) was dissolved in THF (dry, 10 mL) and cooled to 0 °C under argon. Sodium hydride (24 mg, 1.0 mmol, 1.0 eq.) was slowly added and the solution was stirred for 30 min at 0 °C. Benzyl bromide (179 μL, 1.5 mmol, 1.5 eq.) and tetrabutylammonium iodide (37 mg, 0.1 mmol, 0.1 eq.) were added and the mixture was stirred for 18 h at 0 °C to room temperature. Water (100 mL) was added and the mixture was extracted with DCM (2 x 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by column chromatography (30 g SiO_2, CH:EA = 10:1).

Yield: 90 mg (43 %, 430 μmol).

Appearance: yellow oil.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 1.20 (t, *J* = 7.1 Hz, 3H), 1.34 (d, *J* = 6.8 Hz, 3H), 3.96 (q, *J* = 6.8 Hz, 1H), 4.12 (qd, *J* = 7.1, 1.5 Hz, 2H), 4.36 (d, *J* = 11.7 Hz, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 7.16 – 7.31 (m, 5H).

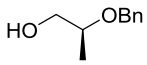
^{13}**C-NMR** (75 MHz, Chloroform-*d*): δ = 14.4, 18.8, 60.9, 72.1, 74.2, 127.9, 128.0, 128.5, 137.8, 173.3.

TLC: R_f = 0.36 (CH:EA = 9:1).

LC-MS: Mass (ESI), calculated = 209.1 $[M+H]^+$, found = 209.0.
[5-100 % Solvent B, 2.6 min]: R_t = 1.8 min.
93 % purity (220 nm).

Lab book number(s): MWa354.

(*S*)-2-(Benzyloxy)propan-1-ol



$C_{10}H_{214}O_2$, MW = 166.22 g / mol

Ethyl (*S*)-2-(benzyloxy)propanoate (90 mg, 430 μmol, 1.0 eq.) was dissolved in THF (1 mL, dry) under argon. The mixture was cooled to 0 °C and LAH (1 M in THF, 473 μL, 473 μmol, 1.1 eq.) was added slowly. The mixture was stirred for 1h at 0 °C to room temperature. The mixture was cooled to 0 °C and NaOH (aq, 1 M, 1mL) and water (20 mL) were added. The mixture was extracted with DCM (4 x 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure.

Yield: 63 mg (89 %, 379 μmol).

Appearance: slightly yellow oil.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.08 (d, *J* = 6.2 Hz, 3H), 2.25 (s, 1H), 3.33 – 3.62 (m, 3H), 4.39 (d, *J* = 11.7 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 7.14 – 7.29 (m, 5H).

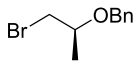
^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 16.0, 66.4, 70.9, 75.7, 127.7, 127.8, 128.5, 138.6.

TLC: R_f = 0.11 (CH:EA = 9:1).

LC-MS: Mass (ESI), calculated = 513.3 $[M+H]^+$, found = 513.2.
[5-100 % Solvent B, 2.6 min]: R_t = 1.4 min.
97 % purity (220 nm).

Lab book number(s): MWa356.

(*S*)-(((1-Bromopropan-2-yl)oxy)methyl)benzene



$C_{10}H_{13}BrO$, MW = 229.12 g / mol

(*S*)-2-(Benzyloxy)propan-1-ol (63 mg, 379 μmol, 1.0 eq.) was dissolved in DCM (5 mL) under argon. Tetrabromomethane (151 mg, 455 μmol, 1.2 eq.) was added and the mixture was cooled to 0 °C. Triphenylphosphine (119 mg, 455 μmol, 1.2 eq.) was added and the mixture was stirred for 18 h at 0 °C to room temperature. Additional tetrabromomethane (0.3 eq.) and triphenylphosphine (0.3 eq.) were added and the mixture was stirred for 5 h at room temperature. The solution was concentrated under reduced pressure and the obtained product was purified by column chromatography (20 g SiO_2, CH:EA 1:1).

Yield: 83 mg (95 %, 362 μmol).

Appearance: slightly yellow oil.

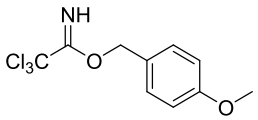
^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.23 (d, *J* = 6.2 Hz, 3H), 3.30 (dd, *J* = 10.4, 5.7 Hz, 1H), 3.37 (dd, *J* = 10.4, 5.0 Hz, 1H), 3.65 (qd, *J* = 6.0, 5.0 Hz, 1H), 4.50 (s, 2H), 7.14 – 7.32 (m, 5H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 19.0, 36.6, 71.2, 74.3, 127.8, 127.8, 128.5, 138.3.

TLC: R_f = 0.82 (CH:EA = 1:1).

Lab book number(s): MWa359.

4-Methoxybenzyl 2,2,2-trichloroacetimidate



$C_{10}H_{10}Cl_3NO_2$, MW = 282.55 g / mol

Sodium hydride (0.15 g, 6.2 mmol, 0.1 eq.) was dissolved in DEE (70 mL) under argon. (4-Methoxyphenyl)methanol (8.54 g, 61.8 mmol, 1.0 eq.) in DEE (10 mL) was slowly added and the mixture was stirred for 30 min at room temperature. The mixture was cooled to 0 °C and trichloroacetonitrinle (6.8 mL, 68 mmol, 1.1 eq.) was added slowly. The mixture was stirred for 4 h at 0 °C to room temperature and afterwards concentrated under reduced pressure. The obtained product was purified by flash chromatography.

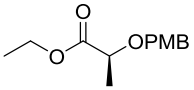
Yield: 12.3 g (70 %, 43.6 mmol).

Appearance: yellow oil.

TLC: R_f = 0.44 (CH:EA = 9:1).

Lab book number(s): MWa443 / MWa481 / MWa505 / MWa507

Ethyl (*S*)-2-((4-methoxybenzyl)oxy)propanoate



$C_{13}H_{18}O_4$, MW = 238.28 g / mol

Variant 1:
(-)-Ethyl L-lactate (4.3 g, 36.3 mmol, 1.0 eq.) and 4-methoxybenzyl 2,2,2-trichloroacetimidate (12.3 g, 43.6 mmol, 1.2 eq.) were dissolved in DEE (dry, 100 mL) and cooled to 0 °C under argon. Trifluormethanesulfonic acid (65 μL, 0.7 mmol, 0.02 eq.) was added and the mixture was stirred at 0 °C to room temperature for 1 h. The reaction was quenched with Sodium hydrogen carbonate (sat., aq, 200 mL) and the mixture was extracted with DEE (3 x 200 mL). The combined organic phases

were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Variant 2:
(-)-Ethyl L-lactate (11.8 g, 100 mmol, 1.0 eq.) and 1-(chloromethyl)-4-methoxybenzene (23.5 g, 150 mmol, 1.5 eq.), DIPEA (27.9 mL, 160 mmol, 1.6 eq.) and sodium iodide (1.5 g, 10 mmol, 0.1 eq.) were stirred at 150 °C for 2 h under argon. Water (100 mL) was added and the mixture was extracted with DCM (3 x 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: Variant 1: 5.1 g (59 %, 21.3 mmol).
Variant 2: 16.6 g (70 %, 69.7 mmol).

Appearance: colorless oil.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.31 (t, *J* = 7.2 Hz, 3H), 1.43 (d, *J* = 6.9 Hz, 3H), 3.80 (s, 3H), 3.99 – 4.11 (m, 1H), 4.22 (qd, *J* = 7.1, 1.4 Hz, 2H), 4.40 (d, *J* = 11.3 Hz, 1H), 4.63 (d, *J* = 11.2 Hz, 1H), 6.84 – 6.94 (m, 2H), 7.27 – 7.35 (m, 2H).

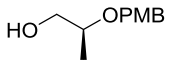
^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 14.3, 18.7, 55.2, 60.8, 71.6, 73.7, 113.8, 129.6, 159.4, 173.3.

TLC: R_f = 0.18 (CH:EA = 9:1).

LC-MS: Mass (ESI), calculated = 261.1 $[M+Na]^+$, found = 261.2.
[5-100 % Solvent B, 3.0 min]: R_t = 2.0 min.
83 % purity (220 nm).

Lab book number(s): Variant 1: MWa446 / MWa482
Variant 2: MWa518

(*S*)-2-((4-Methoxybenzyl)oxy)propan-1-ol



$C_{11}H_{16}O_3$, MW = 196.25 g / mol

Ethyl (*S*)-2-((4-methoxybenzyl)oxy)propanoate (5.0 g, 21.0 mmol, 1.0 eq.) was dissolved in THF (50 mL, dry) under argon. The mixture was cooled to 0 °C and LAH (1 M in THF, 23.1 mL, 23.1 mmol, 1.1 eq.) was added slowly. The mixture was stirred for 2 h at 0 °C to room temperature. Sodium hydroxide (aq, 1 M, 1 mL) and water (5 mL) were added. The solution was filtered and rinsed with DEE. The filtrate was washed with Brine (30 mL) and the organic phase was dried over $MgSO_4$ and concentrated under reduced pressure.

Yield: 4.1 g (quant., 21.0 mmol).

Appearance: colorless oil.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.19 (d, *J* = 6.1 Hz, 3H), 2.27 (s, 1H), 3.46 – 3.71 (m, 3H), 3.82 (s, 3H), 4.44 (d, *J* = 11.2 Hz, 1H), 4.61 (d, *J* = 11.3 Hz, 1H), 6.88 – 6.98 (m, 2H), 7.26 – 7.34 (m, 2H).

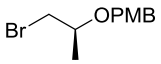
^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 15.9, 55.3, 66.3, 70.5, 75.3, 113.9, 129.4, 130.5, 159.3.

TLC: R_f = 0.18 (CH:EA = 2:1).

LC-MS: [30-100 % Solvent B, 3.2 min]: R_t = 1.5 min.
> 99 % purity (220 nm).

Lab book number(s): MWa447 / MWa 485 / MWa531

(*S*)-1-(((1-bromopropan-2-yl)oxy)methyl)-4-methoxybenzene



$C_{11}H_{15}BrO_2$, MW = 259.14 g / mol

(*S*)-2-((4-Methoxybenzyl)oxy)propan-1-ol (200 mg, 1.02 mmol, 1.0 eq.) and carbon tetrabromide (405 mg, 1.22 mmol, 1.2 eq.) were dissolved in DCM (10 mL). The mixture was cooled to 0 °C and triphenylphosphine (320 mg, 1.22 mmol, 1.2 eq.) was added. The mixture was stirred at 0 °C to room temperature for 5 d. The solution was concentrated under reduced pressure. The obtained product was purified by flash chromatography.

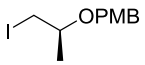
Yield: 132 mg (50 %, 0.51 μmol).

Appearance: slightly yellow oil.

TLC: R_f = 0.11 (CH:EA = 3:1).

Lab book number(s): MWa451

(*S*)-1-(((1-Iodopropan-2-yl)oxy)methyl)-4-methoxybenzene



$C_{11}H_{15}IO_2$, MW = 306.14 g / mol

(*S*)-2-((4-Methoxybenzyl)oxy)propan-1-ol (200 mg, 1.02 mmol, 1.0 eq.), triphenylphosphine (320 mg, 1.22 mmol, 1.2 eq.) and imidazole (208 mg, 3.06 mmol, 3.0 eq.) were dissolved in DCM (10 mL). The mixture was cooled to 0 °C and iodide (337 mg, 1.33 mmol, 1.3 eq.) was added. The mixture was stirred for 18 h at 0 °C to room temperature. Sodium sulfite (aq, 1.75 M, 10 mL) was added and the mixture was extracted with DCM (2 x 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

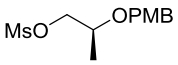
Yield: 191 mg (61 %, 0.62 mmol).

Appearance: slightly yellow oil.

TLC: R_f = 0.10 (CH:EA = 3:1).

Lab book number(s): MWa449.

(*S*)-2-((4-Methoxybenzyl)oxy)propyl methanesulfonate



$C_{12}H_{18}O_5S$, MW = 274.33 g / mol

(*S*)-2-((4-Methoxybenzyl)oxy)propan-1-ol (200 mg, 1.02 mmol, 1.0 eq.), triethylamine (0.43 mL, 3.06 mmol, 3.0 eq.) and 4-dimethylaminopyridine (25 mg, 0.20 mmol, 0.2 eq.) were dissolved in DCM (5 mL) and cooled to 0 °C. Methanesulfonyl chloride (118 μL, 1.53 mmol, 1.5 eq.) was added and the mixture stirred for 18 h at 0 °C to room temperature. Water (5 mL) was added and the solution was extracted with DCM (3 x 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 280 mg (quant., 1.02 mmol).

Appearance: slightly yellow oil.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 1.24 (d, *J* = 6.4 Hz, 3H), 2.99 (s, 3H), 3.80 (s, 4H), 4.11 – 4.31 (m, 2H), 4.45 – 4.59 (m, 2H), 6.81 – 6.92 (m, 2H), 7.24 – 7.31 (m, 2H).

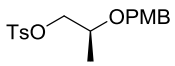
^{13}**C-NMR** (75 MHz, Chloroform-*d*): δ = 16.4, 37.5, 55.3, 70.9, 72.2, 72.6, 113.9, 129.4, 130.1, 159.3.

TLC: R_f = 0.25 (CH:EA = 3:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 1.9 min.
85 % purity (220 nm).

Lab book number(s): MWa456.

(*S*)-2-((4-methoxybenzyl)oxy)propyl 4-methylbenzenesulfonate



$C_{18}H_{22}O_5S$, MW = 350.43 g / mol

The product was synthesized from alcohol **134** (1000 mg, 5.1 mmol, 1.0 eq.) according to general procedure C. The obtained product was purified by flash chromatography.

Yield: 1780 mg (99 %, 5.1 mmol).

Appearance: slightly yellow oil.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.17 (d, *J* = 6.4 Hz, 3H), 2.46 (s, 3H), 3.77 (td, *J* = 6.1, 4.5 Hz, 1H), 3.82 (s, 3H), 4.01 (dd, *J* = 5.3, 2.6 Hz, 2H), 4.46 (d, *J* = 3.9 Hz, 2H), 6.84 – 6.93 (m, 2H), 7.20 – 7.25 (m, 2H), 7.32 – 7.37 (m, 2H), 7.76 – 7.85 (m, 2H).

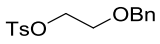
^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 16.8, 21.7, 55.3, 71.0, 72.0, 72.8, 113.8, 128.0, 129.3, 129.9, 130.1, 144.8, 159.2.

TLC: R_f = 0.35 (CH:EA = 3:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.2 min.
> 99 % purity (220 nm).

Lab book number(s): MWa450 / MWa468 / MWa477 / MWa487 / MWa532.

2-(Benzyloxy)ethyl 4-methylbenzenesulfonate



$C_{16}H_{18}O_4S$, MW = 306.38 g / mol

2-(Benzyloxy)ethan-1-ol (4.0 mL, 28.2 mmol, 1.0 eq.), triethylamine (11.8 mL,85.5 mmol, 3.0 eq.) and 4-dimethylaminopyridine (0.7 g, 5.6 mmol, 0.2 eq.) were dissolved in DCM (100 mL) and cooled to 0 °C. *p*-Toluenesulfonyl chloride (8.1 g, 42.2 mmol, 1.5 eq.) was added and the mixture stirred for 3 h at 0 °C to room temperature. Water (100 mL) was added and the mixture was extracted with DCM (3 x 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 5.8 g (66 %, 18.7 mmol).

Appearance: colorless oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 2.45 (s, 3H), 3.66 – 3.71 (m, 2H), 4.19 – 4.24 (m, 2H), 4.50 (s, 2H), 7.27 – 7.30 (m, 2H), 7.33 (q, *J* = 7.3 Hz, 5H), 7.80 – 7.84 (m, 2H).

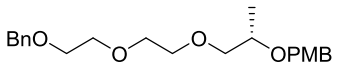
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 21.7, 67.5, 69.4, 73.2, 127.7, 127.8, 128.0, 128.4, 129.9, 133.0, 137.6, 144.8.

TLC: R_f = 0.38 (CH:EA = 3:1).

LC-MS: Mass (ESI), calculated = 324.1 $[M+NH_4]^+$, found = 324.2.
[5-100 % Solvent B, 3.0 min]: R_t = 2.1 min.
> 99 % purity (220 nm).

Lab book number(s): MWa502.

(*S*)-1-(4-Methoxyphenyl)-3-methyl-12-phenyl-2,5,8,11-tetraoxadodecane



$C_{22}H_{30}O_5$, MW = 374.48 g / mol

The product was synthesized from 2-(2-(benzyloxy)ethoxy)ethanol (35 mg, 100 μmol, 1.0 eq.) and tosylate **135** (35 mg, 100 μmol, 2.0 eq.) according to general procedure D. The obtained product was purified by flash chromatography.

Yield: 16.6 mg (89 %, 44.4 μmol).

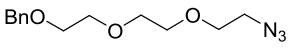
Appearance: colorless oil.

TLC: R_f = 0.25 (CH:EA = 3:1).

LC-MS: Mass (ESI), calculated = 392.3 $[M+NH_4]^+$, found = 392.2.
[5-100 % Solvent B, 3.0 min]: R_t = 2.2 min.
> 99 % purity (220 nm).

Lab book number(s): MWa467.

((2-(2-(2-Azidoethoxy)ethoxy)ethoxy)methyl)benzene



$C_{13}H_{19}N_3O_3$, MW = 265.31 g / mol

2-(2-(Benzyloxy)ethoxy)ethanol (9.8 mg, 50 μmol, 1.0 eq.), 2-azidoethyl 4-methylbenzenesulfonate (24.1 mg, 100 μmol, 2.0 eq.), sodium iodide (3.7 mg, 25 μmol, 0.5 eq.) and potassium *tert*-butoxide (8.4 mg, 75 μmol, 1.5 eq.) were dissolved in *tert*-butanol (0.5 mL). The mixture was stirred for 18 h at room temperature. Additional sodium iodide (3.7 mg, 25 μmol, 0.5 eq.) and potassium *tert*-butoxide (8.4 mg, 75 μmol, 1.5 eq.) were added and the mixture was stirred for 4 d at room temperature. The solvent was removed under reduced pressure. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 8.0 mg (61 %, 23 μmol).

Appearance: colorless oil.

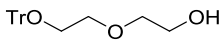
^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.68 (d, *J* = 33.3 Hz, 2H), 3.40 (t, *J* = 5.1 Hz, 2H), 3.67 (q, *J* = 4.6, 3.3 Hz, 2H), 3.71 (d, *J* = 5.0 Hz, 6H), 4.60 (s, 2H), 7.28 – 7.33 (m, 1H), 7.37 (d, *J* = 4.4 Hz, 4H).

TLC: R_f = 0.10 (CH:EA = 1:1).

LC-MS: Mass (ESI), calculated = 288.2 $[M+Na]^+$, found = 288.2.
[5-100 % Solvent B, 2.6 min]: R_t = 1.6 min.
83 % purity (220 nm).

Lab book number(s): MWa527.

2-(2-(Trityloxy)ethoxy)ethan-1-ol



$C_{23}H_{24}O_3$, MW = 348.44 g / mol

Diethylene glycol (11.3 mL, 120 mmol, 3.0 eq.), triethylamine (11.2 mL, 80 mmol, 2.0 eq.) and 4-dimethylaminopyridine (0.5 g, 4.0 mmol, 0.1 eq.) were dissolved in DCM (40 mL) and cooled to 0 °C. Trityl chloride (11.2 g, 40 mmol, 1.0 eq.) was added and the mixture was stirred for 4 h at 0 °C to room temperature. Water (40 mL) was added and the solution was extracted with DCM (3 x 40 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 9.1 g (65 %, 26.0 mmol).

Appearance: white solid.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 3.28 (dd, *J* = 5.7, 4.4 Hz, 2H), 3.61 – 3.64 (m, 2H), 3.68 (dd, *J* = 5.6, 4.5 Hz, 2H), 3.75 (dd, *J* = 5.3, 3.9 Hz, 2H), 7.22 – 7.26 (m, 3H), 7.28 – 7.32 (m, 6H), 7.45 – 7.49 (m, 6H).

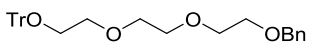
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 61.9, 63.4, 70.7, 72.4, 86.7, 127.1, 127.9, 128.8, 144.1.

TLC: R_f = 0.32 (CH:EA = 2:1).

LC-MS: Mass (ESI), calculated = 371.2 $[M+Na]^+$, found = 371.2.
[5-100 % Solvent B, 3.0 min]: R_t = 2.2 min.
[30-100 % Solvent B, 3.0 min]: R_t = 2.2 min.
> 99 % purity (220 nm).

Lab book number(s): MWa440 / MWa490 / MWa540.

1,1,1,12-Tetraphenyl-2,5,8,11-tetraoxadodecane



$C_{32}H_{34}O_4$, MW = 482.62 g / mol

2-(2-(Trityloxy)ethoxy)ethan-1-ol (139 mg, 400 μmol, 1.0 eq.), 2-(benzyloxy)ethyl 4-methylbenzenesulfonate (245 mg, 800 μmol, 2.0 eq.) and potassium *tert*-butoxide (67 mg, 600 μmol, 1.5 eq.) were dissolved in *tert*-butanol (2 mL). The mixture was stirred for 18 h at 80 °C. Additional potassium *tert*-butoxide (67 mg, 600 μmol, 1.5 eq.) was added and the mixture was stirred for 4 h at 80 °C. The solvent was removed under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 191 mg (99 %, 396 μmol).

Appearance: colorless oil.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 3.69 – 3.83 (m, 12H), 4.65 (d, *J* = 5.3 Hz, 2H), 7.26 – 7.46 (m, 15H), 7.53 – 7.61 (m, 5H).

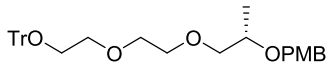
^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 63.4, 69.6, 70.8, 70.8, 70.9, 70.9, 73.3, 86.6, 127.0, 127.7, 127.8, 127.8, 128.4, 128.8, 138.4, 144.2.

TLC: R_f = 0.55 (CH:EA = 2:1).

LC-MS: Mass (ESI), calculated = 500.3 $[M+NH_4]^+$, found = 500.2.
[5-100 % Solvent B, 3.0 min]: R_t = 2.6 min.
75 % purity (220 nm).

Lab book number(s): MWa629.

(*S*)-12-(4-Methoxyphenyl)-10-methyl-1,1,1-triphenyl-2,5,8,11-tetraoxadodecane



$C_{34}H_{38}O_5$, MW = 526.67 g / mol

The product was synthesized from alcohol **152** (35 mg, 100 μmol, 1.0 eq.) and tosylate **135** (70 mg, 200 μmol, 2.0 eq.) according to general procedure D. The obtained product was purified by flash chromatography.

Yield: 49 mg (93 %, 93 μmol).

Appearance: colorless oil.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.08 (d, *J* = 6.3 Hz, 3H), 3.16 (t, *J* = 5.2 Hz, 2H), 3.34 – 3.50 (m, 2H), 3.54 – 3.75 (m, 10H), 4.45 (d, *J* = 5.4 Hz, 2H), 6.71 – 6.79 (m, 2H), 7.08 – 7.25 (m, 11H), 7.33 – 7.44 (m, 6H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 17.4, 55.4, 63.5, 70.9, 71.0, 71.1, 73.7, 75.6, 86.7, 113.8, 127.0, 127.9, 128.8, 129.3, 131.2, 144.3, 159.2.

TLC: R_f = 0.55 (CH:EA = 3:1).

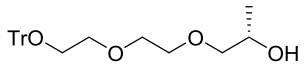
LC-MS: Mass (ESI), calculated = 544.3 $[M+NH_4]^+$, found = 544.2.

[5-100 % Solvent B, 3.0 min]: R_t = 2.6 min.

84 % purity (220 nm).

Lab book number(s): MWa470 / MWa493 / MWa544.

(*S*)-1-(2-(2-(Trityloxy)ethoxy)ethoxy)propan-2-ol



$C_{26}H_{30}O_4$, MW = 406.52 g / mol

(*S*)-12-(4-Methoxyphenyl)-10-methyl-1,1,1-triphenyl-2,5,8,11-tetraoxadodecane (49 mg, 93.0 μmol, 1.0 eq.) was dissolved in DCM and water (1.2 mL, 50:1). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (25 mg, 112 μmol, 1.2 eq.) was added and the mixture was stirred for 10 min at room temperature. The mixture was quenched with sodium hydrogen carbonate (sat., aq, 2 mL) and extracted with DCM (3 x 5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 31 mg (82 %, 76 μmol).

Appearance: colorless oil.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.15 (d, *J* = 6.4 Hz, 3H), 3.26 – 3.36 (m, 3H), 3.56 (dd, *J* = 9.8, 3.0 Hz, 1H), 3.66 – 3.80 (m, 6H), 3.94 – 4.06 (m, 1H), 7.22 – 7.38 (m, 9H), 7.46 – 7.56 (m, 6H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 18.5, 63.3, 66.4, 70.8, 86.6, 127.0, 127.8, 128.7, 144.1.

TLC: R_f = 0.16 (CH:EA = 2:1).

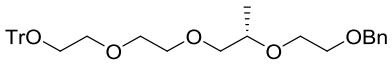
LC-MS: Mass (ESI), calculated = 424.2 $[M+NH_4]^+$, found = 424.2.

[5-100 % Solvent B, 3.0 min]: R_t = 2.2 min.

> 99 % purity (220 nm).

Lab book number(s): MWa473 / MWa498 / MWa548.

(*S*)-10-Methyl-1,1,1,15-tetraphenyl-2,5,8,11,14-pentaoxapentadecane



$C_{35}H_{40}O_5$, MW = 540.70 g / mol

(*S*)-1-(2-(2-(Trityloxy)ethoxy)ethoxy)propan-2-ol (650 mg, 1.60 mmol, 1.0 eq.), ((2-bromoethoxy)methyl)benzene (506 μL, 3.20 mmol, 2.0 eq.), sodium iodide (120 mg, 0.80 mmol, 0.5 eq.) and potassium *tert*-butoxide (269 mg, 2.40 mmol, 1.5 eq.) were dissolved in *tert*-butanol (20 mL). The mixture was stirred for 18 h at 30 °C followed by 24 h at 60 °C. Additional potassium *tert*-butoxide (269 mg, 2.40 mmol, 1.5 eq.), sodium iodide (120 mg, 0.80 mmol, 0.5 eq.) and ((2-bromoethoxy)methyl)benzene (506 μL, 3.20 mmol, 2.0 eq.) were added and the mixture was stirred for 2 d at 60 °C. The solvent was removed under reduced pressure. The crude product was dissolved in DCM and filtered. The solvent was removed under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 854 mg (99 %, 1.58 mmol).

Appearance: colorless oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.23 (d, *J* = 6.3 Hz, 3H), 3.30 (t, *J* = 5.2 Hz, 2H), 3.52 (dd, *J* = 10.2, 4.7 Hz, 1H), 3.59 – 3.67 (m, 3H), 3.70 – 3.78 (m, 9H), 4.61 (s, 2H), 7.28 (d, *J* = 7.3 Hz, 3H), 7.32 – 7.41 (m, 12H), 7.53 (d, *J* = 7.8 Hz, 6H).

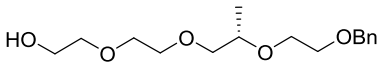
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 17.4, 63.4, 68.7, 69.9, 70.8, 70.9, 71.0, 73.2, 75.2, 75.4, 86.6, 127.0, 127.6, 127.8, 127.8, 128.4, 128.8, 138.5, 144.2.

TLC: R_f = 0.48 (CH:EA = 3:1).

LC-MS: Mass (ESI), calculated = 563.3 $[M+Na]^+$, found = 563.2.
[5-100 % Solvent B, 3.0 min]: R_t = 2.6 min.
88 % purity (220 nm).

Lab book number(s): MWa508 / MWa561.

(*S*)-6-Methyl-1-phenyl-2,5,8,11-tetraoxatridecan-13-ol



$C_{16}H_{26}O_5$, MW = 298.38 g / mol

(*S*)-10-Methyl-1,1,1,15-tetraphenyl-2,5,8,11,14-pentaoxapentadecane (854 mg, 1.58 mmol, 1.0 eq.) was dissolved in DCM:TFA (49:1, 60 mL). The mixture was stirred for 3 h at room temperature. Sodium hydrogen carbonate (aq, sat., 30 mL) was added and the solution was extracted with DCM (3 x 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 390 mg (83 %, 1.31 mmol).

Appearance: colorless oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.18 (d, *J* = 6.4 Hz, 3H), 3.45 (dd, *J* = 10.3, 4.5 Hz, 1H), 3.53 (dd, *J* = 10.3, 6.0 Hz, 1H), 3.61 – 3.69 (m, 7H), 3.68 – 3.77 (m, 2H), 3.77 – 3.80 (m, 2H), 4.46 – 4.50 (m, 2H), 4.59 (s, 2H), 7.29 (ddt, *J* = 8.5, 5.1, 2.7 Hz, 1H), 7.33 – 7.39 (m, 4H).

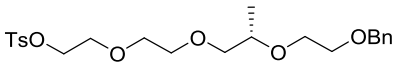
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 17.2, 67.1, 68.2, 68.7, 69.9, 70.9, 73.3, 75.2, 75.3, 127.6, 127.8, 128.4, 138.5.

TLC: R_f = 0.07 (CH:EA = 1:1).

LC-MS: Mass (ESI), calculated = 299.2 $[M+H]^+$, found = 299.2.
[5-100 % Solvent B, 3.0 min]: R_t = 1.6 min.

Lab book number(s): MWa568.

(*S*)-6-Methyl-1-phenyl-2,5,8,11-tetraoxatridecan-13-yl 4-methylbenzenesulfonate



$C_{23}H_{32}O_7S$, MW = 452.56 g / mol

(*S*)-6-Methyl-1-phenyl-2,5,8,11-tetraoxatridecan-13-ol (200 mg, 670 μmol, 1.0 eq.), triethylamine (280 μL, 2.01 mmol, 3.0 eq.) and 4-dimethylaminopyridine (16 mg, 134 μmol, 0.2 eq.) were dissolved in DCM (5 mL) and cooled to 0 °C. *p*-Toluenesulfonyl chloride (192 mg, 1.01 mmol, 1.5 eq.) was added and the mixture stirred for 18 h at 0 °C to room temperature followed by 24 h at 30 °C. Water (15 mL) was added and the solution was extracted with DCM (3 x 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 225 mg (74 %, 497 μmol).

Appearance: slightly yellow oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.14 – 1.18 (m, 3H), 2.44 (s, 3H), 3.41 (dd, *J* = 10.2, 4.4 Hz, 1H), 3.49 (dd, *J* = 10.4, 6.1 Hz, 1H), 3.57 (d, *J* = 3.5 Hz, 3H), 3.59 – 3.65 (m, 2H), 3.64 – 3.78 (m, 6H), 4.15 (t, *J* = 4.9 Hz, 2H), 4.56 – 4.59 (m, 2H), 7.26 – 7.31 (m, 1H), 7.32 – 7.37 (m, 6H), 7.80 (d, *J* = 8.1 Hz, 2H).

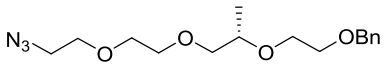
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 17.0, 21.6, 68.5, 68.7, 69.3, 69.8, 70.7, 70.7, 73.2, 75.0, 75.2, 127.6, 127.7, 127.7, 127.8, 128.0, 128.4, 129.8, 133.0, 138.3, 144.8.

TLC: R_f = 0.30 (CH:EA = 1:1).

LC-MS: Mass (ESI), calculated = 453.2 $[M+Na]^+$, found =453.2.
[5-100 % Solvent B, 3.0 min]: R_t = 2.2 min.
> 99 % purity (220 nm).

Lab book number(s): MWa570.

(*S*)-13-Azido-6-methyl-1-phenyl-2,5,8,11-tetraoxatridecane



$C_{16}H_{25}N_3O_4$, MW = 323.39 g / mol

(*S*)-6-Methyl-1-phenyl-2,5,8,11-tetraoxatridecan-13-yl 4-methylbenzenesulfonate (225 mg, 497 μmol, 1.0 eq.) and sodium azide (65 mg, 994 μmol, 2.0 eq.) were dissolved in DMF (5 mL). The mixture was stirred for 3 h at 70 °C. The solvent was removed under reduced pressure. The crude product was dissolved in DCM and filtered through Celite. The solvent was removed under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 118 mg (73 %, 365 μmol).

Appearance: slightly yellow oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.19 (d, *J* = 6.4 Hz, 3H), 3.37 (t, *J* = 5.1 Hz, 2H), 3.46 (dd, *J* = 10.3, 4.6 Hz, 1H), 3.55 (dd, *J* = 10.3, 6.0 Hz, 1H), 3.57 – 3.78 (m, 11H), 4.59 (s, 2H), 7.29 (tt, *J* = 5.9, 2.8 Hz, 1H), 7.33 – 7.38 (m, 4H).

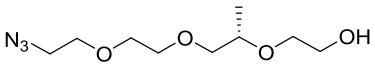
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 17.2, 50.8, 68.7, 69.8, 70.1, 70.8, 70.9, 73.2, 75.1, 75.4, 127.6, 127.7, 128.4, 138.5.

TLC: R_f = 0.13 (CH:EA = 1:1)

LC-MS: Mass (ESI), calculated = 346.2 $[M+Na]^+$, found = 346.2.
[5-100 % Solvent B, 3.0 min]: R_t = 2.0 min.
90 % purity (220 nm).

Lab book number(s): MWa573.

(*S*)-2-((1-(2-(2-Azidoethoxy)ethoxy)propan-2-yl)oxy)ethan-1-ol



$C_9H_{19}N_3O_4$, MW = 233.27 g / mol

(*S*)-13-Azido-6-methyl-1-phenyl-2,5,8,11-tetraoxatridecane (118 mg, 365 μmol, 1.0 eq.) was stirred in hydrochloric acid (37 %, aq, 10 mL) for 18 h at room temperature. Water (30 mL) was added and the solution was extracted with DCM (3 x 30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure.

Yield: 85 mg (quant., 365 μmol).

Appearance: colorless oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.12 (d, *J* = 6.4 Hz, 3H), 3.38 (t, *J* = 5.1 Hz, 2H), 3.43 – 3.47 (m, 2H), 3.55 (dq, *J* = 7.3, 3.5 Hz, 1H), 3.60 – 3.75 (m, 10H), 5.29 (s, 1H).

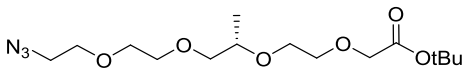
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 16.9, 50.7, 61.9, 70.0, 70.6, 70.6, 70.7, 75.0, 75.4.

TLC: R_f = 0.08 (CH:EA = 1:2)

LC-MS: Mass (ESI), calculated = 234.1 $[M+H]^+$, found = 234.2.
[5-100 % Solvent B, 3.0 min]: R_t = 1.3 min.
69 % purity (220 nm).

Lab book number(s): MWa575.

***tert*-Butyl (*S*)-14-azido-7-methyl-3,6,9,12-tetraoxatetradecanoate**



$C_{15}H_{29}N_3O_6$, MW = 347.41 g / mol

(*S*)-2-((1-(2-(2-Azidoethoxy)ethoxy)propan-2-yl)oxy)ethan-1-ol (85 mg, 365 μmol, 1.0 eq.) and potassium *tert*-butoxide (61 mg, 548 μmol, 1.5 eq.) were dissolved in *tert*-butanol (10 mL). *tert*-Butyl 2-bromoacetate (108 μL, 730 μmol, 2.0 eq.) was added and the mixture was stirred for 18 h at 30 °C. The solution was concentrated under reduced pressure. DCM (50 mL) was added and the solution was filtered and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 95 mg (75 %, 273 μmol).

Appearance: colorless oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.14 (dd, *J* = 6.3, 1.3 Hz, 3H), 1.46 (s, 9H), 3.37 (t, *J* = 5.1 Hz, 2H), 3.39 – 3.44 (m, 1H), 3.50 (ddd, *J* = 10.3, 6.1, 1.3 Hz, 1H), 3.59 – 3.73 (m, 11H), 4.01 (d, *J* = 1.4 Hz, 2H).

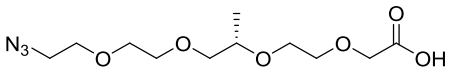
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 17.1, 28.1, 50.7, 68.6, 69.0, 70.0, 70.7, 70.8, 71.0, 75.0, 75.2, 81.4, 169.7.

TLC: R_f = 0.45 (CH:EA = 1:1).

LC-MS: Mass (ESI), calculated = 370.2 $[M+Na]^+$, found = 370.2.
[5-100 % Solvent B, 3.0 min]: R_t = 1.9 min.
> 99 % purity (220 nm).

Lab book number(s): MWa577.

(*S*)-14-Azido-7-methyl-3,6,9,12-tetraoxatetradecanoic acid



$C_{11}H_{21}N_3O_6$, MW = 291.30 g / mol

tert-Butyl (*S*)-14-azido-7-methyl-3,6,9,12-tetraoxatetradecanoate (95 mg, 273 μmol, 1.0 eq.) and lithium hydroxide (65 mg, 2.7 mmol, 10.0 eq.) were dissolved in THF:water (1:1, 30 mL). The mixture was stirred for 18 h at room temperature. Hydrochloric acid (1 M, 50 mL) was added and the mixture was extracted with DCM (3 x 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure.

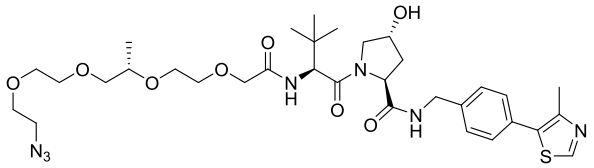
Yield: 80 mg (quant, 273 μmol).

Appearance: colorless oil.

TLC: R_f = 0.15 (CH:EA = 1:1, 1 % HCOOH)

Lab book number(s): MWa579.

(2*S*,4*R*)-1-((2*S*,10*S*)-17-Azido-2-(tert-butyl)-10-methyl-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{33}H_{49}N_7O_8S$, MW = 703.86 g / mol

The product was synthesized from *tert*-butyl protected amine **56** (145 mg, 273 μmol, 1.0 eq.) and carboxylic acid **168** (80 mg, 273 μmol, 1.0 eq.) according to general procedure E. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 83 mg (43 % o2s, 118 μmol).

Appearance: white solid.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 0.98 (s, 9H), 1.12 – 1.18 (m, 3H), 2.09 – 2.17 (m, 1H), 2.44 (ddd, *J* = 13.3, 8.1, 4.8 Hz, 1H), 2.54 (d, *J* = 1.5 Hz, 3H), 3.37 (t, *J* = 5.0 Hz, 2H), 3.40 – 3.44 (m, 1H), 3.48 – 3.53 (m, 1H), 3.59 – 3.74 (m, 12H), 4.02 (dd, *J* = 14.4, 9.8 Hz, 3H), 4.35 (dd, *J* = 15.2, 5.4 Hz, 1H), 4.49 – 4.59 (m, 3H), 4.71 (t, *J* = 7.9 Hz, 1H), 7.27 – 7.32 (m, 1H), 7.33 – 7.40 (m, 4H), 7.50 (t, *J* = 6.1 Hz, 1H), 8.99 (s, 1H).

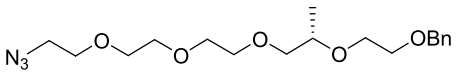
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 14.9, 17.1, 26.4, 35.1, 36.2, 43.1, 50.7, 56.8, 57.2, 58.8, 68.5, 70.0, 70.1, 70.2, 70.6, 70.7, 71.4, 75.1, 75.3, 128.2, 129.4, 133.1, 139.0, 146.2, 151.7, 170.7, 171.2, 171.2.

TLC: R_f(intermediate) = 0.11 (DCM:MeOH = 20:1, 1 % TEA).
R_f =0.15 (DCM:MeOH = 20:1).

LC-MS: Mass (ESI), calculated = 704.3 $[M+H]^+$, found = 704.4.
[5-100 % Solvent B, 3.0 min]: R_t = 1.8 min.
98 % purity (220 nm).

Lab book number(s): MWa580.

(*S*)-16-Azido-6-methyl-1-phenyl-2,5,8,11,14-pentaoxahexadecane



$C_{18}H_{29}N_3O_5$, MW = 367.45 g / mol

(*S*)-6-Methyl-1-phenyl-2,5,8,11-tetraoxatridecan-13-ol (150 mg, 503 μmol, 1.0 eq.), 2-azidoethyl 4-methylbenzenesulfonate (243 μL, 1006 μmol, 2.0 eq.), sodium iodide (38 mg, 251 μmol, 0.5 eq.) and potassium *tert*-butoxide (85 mg, 754 μmol, 1.5 eq.) were dissolved in *tert*-butanol (40 mL). The mixture was stirred for 18 h at 30 °C. The solvent was removed under reduced pressure. The crude product was dissolved in DCM and filtered. The solvent was removed under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 30 mg (16 %, 1.6 mmol).

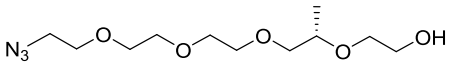
Appearance: colorless oil.

TLC: R_f = 0.12 (CH:EA = 1:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 1.9 min.
> 99 % purity (220 nm).

Lab book number(s): MWa585.

(*S*)-14-Azido-4-methyl-3,6,9,12-tetraoxatetradecan-1-ol



$C_{11}H_{23}N_3O_5$, MW = 277.32 g / mol

(*S*)-16-Azido-6-methyl-1-phenyl-2,5,8,11,14-pentaoxahexadecane (27 mg, 73 μmol, 1.0 eq.) was stirred in hydrochloric acid (37 %, aq, 2 mL) for 18 h at room temperature. Additional hydrochloric acid (37 %, aq, 2 mL) was added and the mixture was stirred for 24 h at room temperature. Water (30 mL) was added and the solution was extracted with DCM (3 x 30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure.

Yield: 20 mg (quant., 73 μmol).

Appearance: colorless oil.

^{1}**H-NMR** (500 MHz, Chloroform-*d*): δ = 1.12 (d, *J* = 6.3 Hz, 3H), 2.81 (s, 1H), 3.38 (t, *J* = 5.1 Hz, 2H), 3.45 (d, *J* = 5.5 Hz, 2H), 3.54 (ddt, *J* = 9.8, 7.8, 1.8 Hz, 1H), 3.58 – 3.78 (m, 14H).

^{13}**C-NMR** (126 MHz, Chloroform-*d*): δ = 16.9, 50.7, 62.0, 70.0, 70.6, 70.6, 70.7, 70.7, 75.0, 75.4.

TLC: R_f = 0.06 (CH:EA = 1:2)

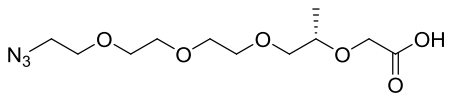
LC-MS: Mass (ESI), calculated = 278.2 $[M+H]^+$, found = 278.2.

[5-100 % Solvent B, 3.0 min]: R_t = 1.4 min.

71 % purity (220 nm).

Lab book number(s): MWa590.

(*S*)-14-Azido-4-methyl-3,6,9,12-tetraoxatetradecanoic acid



$C_{11}H_{21}N_3O_6$, MW = 291.30 g / mol

The product was synthesized from alcohol **170** (20 mg, 73 μmol, 1.0 eq.) according to general procedure G.

Yield: 20 mg (95 %, 67 μmol).

Appearance: colorless oil.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.17 (d, J = 6.2 Hz, 3H), 1.27 (s, 2H), 3.41 (t, J = 5.0 Hz, 2H), 3.46 – 3.79 (m, 13H).

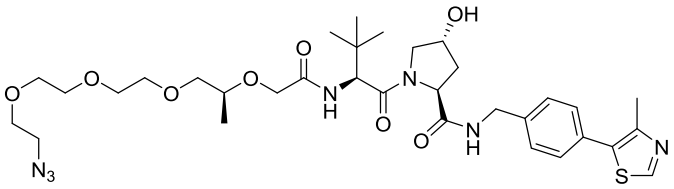
TLC: R_f = 0.11 (CH:EA = 1:1, 1 % HCOOH)

LC-MS: Mass (ESI), calculated = 314.1 $[M+Na]^+$, found = 314.2.

[5-100 % Solvent B, 3.0 min]: R_t = 1.4 min.

Lab book number(s): MWa595.

(2*S*,4*R*)-1-((2*S*,7*S*)-17-Azido-2-(*tert*-butyl)-7-methyl-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{33}H_{49}N_7O_8S$, MW = 703.86 g / mol

The product was synthesized from *tert*-butyl protected amine **56** (36 mg, 67 μmol, 1.0 eq.) and carboxylic acid **171** (20 mg, 67 μmol, 1.0 eq.) according to general procedure E. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 21 mg (45 % o2s, 30 μmol).

Appearance: white solid.

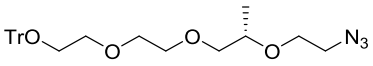
^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 0.96 (s, 9H), 1.13 (d, J = 6.3 Hz, 3H), 2.06 – 2.20 (m, 1H), 2.42 – 2.52 (m, 1H), 2.53 (s, 3H), 3.37 (t, J = 5.1 Hz, 2H), 3.45 – 3.53 (m, 2H), 3.64 (d, J = 3.6 Hz, 12H), 4.01 – 4.14 (m, 3H), 4.34 (dd, J = 15.1, 5.3 Hz, 1H), 4.45 – 4.60 (m, 3H), 4.72 (t, J = 8.0 Hz, 1H), 7.32 – 7.41 (m, 4H), 7.46 (dd, J = 14.6, 7.3 Hz, 2H), 8.92 (s, 1H).

TLC: R_f(intermediate) = 0.11 (DCM:MeOH = 20:1, 1 % TEA).
R_f =0.15 (DCM:MeOH = 20:1).

LC-MS: Mass (ESI), calculated = 704.3 $[M+H]^+$, found = 704.4.
[5-100 % Solvent B, 3.0 min]: R_t = 1.8 min.
98 % purity (220 nm).

Lab book number(s): MWa598.

(*S*)-13-Azido-10-methyl-1,1,1-triphenyl-2,5,8,11-tetraoxatridecane



$C_{28}H_{33}N_3O_4$, MW = 475.59 g / mol

The product was synthesized from alcohol **154** (100 mg, 246 μmol, 1.0 eq.) and tosylate **4a** (119 mg, 492 μmol, 2.0 eq.) according to general procedure F. The obtained product was purified by flash chromatography.

Yield: 115 mg (98 %, 242 μmol).

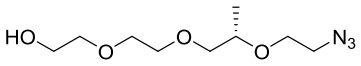
Appearance: colorless oil.

TLC: R_f = 0.42 (CH:EA = 2:1).

LC-MS: Mass (ESI), calculated = 498.3 $[M+H]^+$, found = 498.2.
[5-100 % Solvent B, 3.0 min]: R_t = 2.6 min.
84 % purity (220 nm).

Lab book number(s): MWa517 / MWa551.

(*S*)-2-(2-(2-(2-Azidoethoxy)propoxy)ethoxy)ethan-1-ol



$C_9H_{19}N_3O_4$, MW = 233.27 g / mol

(*S*)-13-Azido-10-methyl-1,1,1-triphenyl-2,5,8,11-tetraoxatridecane (115 mg, 242 μmol, 1.0 eq.) was dissolved in DCM:TFA (9:1, 10 mL). The mixture was stirred for 2 h at room temperature. Sodium hydrogen carbonate (aq, sat., 20 mL) was added and the solution was extracted with DCM (3 x 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 49 mg (85 %, 210 μmol).

Appearance: colorless oil.

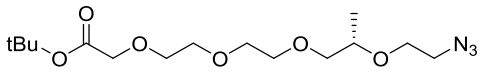
^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.21 (d, *J* = 6.5 Hz, 3H), 2.58 (s, 1H), 3.34 (qt, *J* = 13.1, 5.0 Hz, 1H), 3.42 – 3.50 (m, 2H), 3.53 (dd, *J* = 10.8, 6.4 Hz, 1H), 3.57 – 3.60 (m, 3H), 3.60 – 3.68 (m, 4H), 3.68 – 3.72 (m, 4H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 16.7, 51.1, 61.9, 68.3, 70.5, 70.8, 72.6, 73.7, 75.5.

TLC: R_f = 0.08 (CH:EA = 1:2)

Lab book number(s): MWa562.

***tert*-Butyl (*S*)-14-azido-11-methyl-3,6,9,12-tetraoxatetradecanoate**



$C_{15}H_{29}N_3O_6$, MW = 347.41 g / mol

(*S*)-2-(2-(2-(2-Azidoethoxy)propoxy)ethoxy)ethan-1-ol (49 mg, 210 μmol, 1.0 eq.) and potassium *tert*-butoxide (35 mg, 315 μmol, 1.5 eq.) were dissolved in *tert*-butanol (5 mL). *tert*-Butyl 2-bromoacetate (62 μL, 420 μmol, 2.0 eq.) was added and the mixture was stirred for 18 h at 30 °C. The solution was concentrated under reduced pressure. DCM (50 mL) was added and the solution was filtered and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

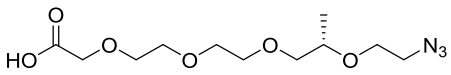
Yield: 34 mg (47 %, 97 μmol).

Appearance: colorless oil.

TLC: R_f = 0.40 (CH:EA = 1:2).

Lab book number(s): MWa564.

(*S*)-14-Azido-11-methyl-3,6,9,12-tetraoxatetradecanoic acid



$C_{11}H_{21}N_3O_6$, MW = 291.30 g / mol

tert-Butyl (*S*)-14-azido-11-methyl-3,6,9,12-tetraoxatetradecanoate (34 mg, 97 μmol, 1.0 eq.) and lithium hydroxide (23 mg, 970 μmol, 10.0 eq.) were dissolved in THF:water (1:1, 10 mL). The mixture was stirred for 6 h at room temperature. Hydrochloric acid (1 M, 30 mL) was added and the mixture was extracted with DCM (3 x 30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure.

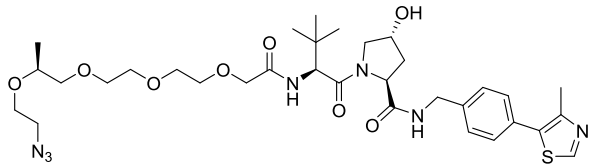
Yield: 27 mg (96 %, 93 μmol).

Appearance: colorless oil.

TLC: R_f = 0.12 (CH:EA = 1:1, 1 % HCOOH)
R_f = 0.40 (CH:EA = 1:2).

Lab book number(s): MWa565.

(2*S*,4*R*)-1-((2*S*,14*S*)-17-Azido-2-(*tert*-butyl)-14-methyl-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{33}H_{49}N_7O_8S$, MW = 703.86 g / mol

The product was synthesized from *tert*-butyl protected amine **56** (49 mg, 93 μmol, 1.0 eq.) and carboxylic acid **158** (27 mg, 93 μmol, 1.0 eq.) according to general procedure E. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 17 mg (26 % o2s, 24 μmol).

Appearance: white solid.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 0.96 (s, 9H), 1.15 (d, *J* = 6.3 Hz, 3H), 2.12 (dd, *J* = 13.5, 8.1 Hz, 1H), 2.47 – 2.56 (m, 4H), 3.27 – 3.38 (m, 2H), 3.39 – 3.52 (m, 2H), 3.59 – 3.74 (m, 12H), 3.94 – 4.05 (m, 2H), 4.08 (d, *J* = 11.4 Hz, 1H), 4.35 (dd, *J* = 15.1, 5.3 Hz, 1H), 4.45 – 4.59 (m, 3H), 4.72 (t, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 7.36 (s, 4H), 7.41 (t, *J* = 6.2 Hz, 1H), 8.89 (s, 1H).

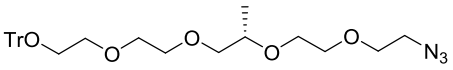
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 15.2, 16.9, 26.4, 34.9, 35.9, 43.2, 51.0, 56.7, 57.3, 58.5, 68.1, 70.1, 70.3, 70.4, 70.6, 70.8, 71.2, 75.3, 128.3, 129.5, 129.9, 132.7, 138.8, 146.9, 151.3, 170.7, 170.8, 171.4.

TLC: R_f(intermediate) = 0.11 (DCM:MeOH = 20:1, 1 % TEA).
R_f =0.15 (DCM:MeOH = 20:1).

LC-MS: Mass (ESI), calculated = 704.3 $[M+H]^+$, found = 704.4.
[5-100 % Solvent B, 3.0 min]: R_t = 1.8 min.
98 % purity (220 nm).

Lab book number(s): MWa567.

(*S*)-16-Azido-10-methyl-1,1,1-triphenyl-2,5,8,11,14-pentaoxahexadecane



$C_{30}H_{37}N_3O_5$, MW = 519.64 g / mol

The product was synthesized from alcohol **154** (500 mg, 1.2 mmol, 1.0 eq.) and tosylate **4b** (702 mg, 2.5 mmol, 2.0 eq.) according to general procedure F. The obtained product was purified by flash chromatography.

Yield: 320 mg (50 %, 0.6 μmol).

Appearance: colorless oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.19 (d, *J* = 6.3 Hz, 3H), 1.30 (s, 2H), 3.28 (t, *J* = 5.2 Hz, 2H), 3.35 (t, *J* = 5.1 Hz, 2H), 3.49 (dd, *J* = 10.2, 4.6 Hz, 1H), 3.56 – 3.60 (m, 1H), 3.60 – 3.69 (m, 3H), 3.68 – 3.74 (m, 8H), 7.23 – 7.27 (m, 3H), 7.32 (dd, *J* = 8.5, 6.9 Hz, 6H), 7.48 – 7.53 (m, 6H).

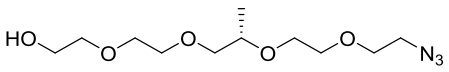
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 17.2, 50.7, 63.4, 68.7, 70.0, 70.7, 70.9, 70.9, 70.9, 75.1, 75.4, 86.6, 127.0, 127.8, 128.8, 144.2.

TLC: R_f = 0.42 (CH:EA = 2:1)

LC-MS: Mass (ESI), calculated = 542.3 $[M+Na]^+$, found = 542.2.
[5-100 % Solvent B, 3.0 min]: R_t = 2.5 min.
87 % purity (220 nm).

Lab book number(s): MWa552.

(*S*)-14-Azido-8-methyl-3,6,9,12-tetraoxatetradecan-1-ol



$C_{11}H_{23}N_3O_5$, MW = 277.32 g / mol

(*S*)-16-Azido-10-methyl-1,1,1-triphenyl-2,5,8,11,14-pentaoxahexadecane (320 mg, 616 μmol, 1.0 eq.) was dissolved in DCM:TFA (9:1, 25 mL). The mixture was stirred for 2 h at room temperature. Sodium hydrogen carbonate (aq, sat., 50 mL) was added and the solution was extracted with DCM (3 x 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 56 mg (33 %, 202 μmol).

Appearance: colorless oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.12 (d, *J* = 6.4 Hz, 3H), 2.74 (s, 1H), 3.34 (t, *J* = 5.1 Hz, 2H), 3.40 (dd, *J* = 10.2, 4.3 Hz, 1H), 3.47 (dd, *J* = 10.2, 6.2 Hz, 1H), 3.55 – 3.58 (m, 2H), 3.59 – 3.69 (m, 12H).

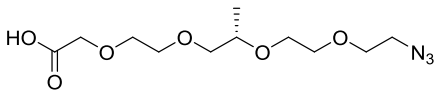
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 16.9, 50.7, 61.7, 68.5, 70.1, 70.4, 70.8, 70.9, 72.6, 75.1, 75.2.

TLC: R_f = 0.05 (CH:EA = 1:2)

LC-MS: Mass (ESI), calculated = 278.2 $[M+H]^+$, found = 278.2.
[5-100 % Solvent B, 3.0 min]: R_t = 1.4 min.
> 99 % purity (220 nm).

Lab book number(s): MWa563.

(*S*)-14-Azido-8-methyl-3,6,9,12-tetraoxatetradecanoic acid



$C_{11}H_{21}N_3O_6$, MW = 291.30 g / mol

The product was synthesized from alcohol **160** (56 mg, 202 μmol, 1.0 eq.) according to general procedure G.

Yield: 59 mg (quant., 202 μmol).

Appearance: colorless oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.20 (d, *J* = 46.5 Hz, 7H), 3.04 – 4.47 (m, 9H), 7.68 – 9.64 (m, 1H).

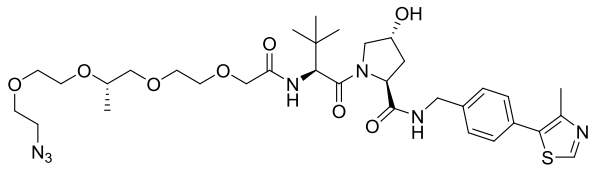
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 16.7, 50.7, 68.4, 68.7, 70.0, 70.5, 70.9, 71.2, 75.0, 75.2, 173.0.

TLC: R_f = 0.11 (CH:EA = 1:1, 1 % HCOOH)

LC-MS: Mass (ESI), calculated = 314.1 $[M+Na]^+$, found = 314.2.
[5-100 % Solvent B, 3.0 min]: R_t = 1.4 min.
92 % purity (220 nm).

Lab book number(s): MWa566.

(2*S*,4*R*)-1-((2*S*,11*S*)-17-Azido-2-(*tert*-butyl)-11-methyl-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{33}H_{49}N_7O_8S$, MW = 703.86 g / mol

The product was synthesized from *tert*-butyl protected amine **56** (107 mg, 202 μmol, 1.0 eq.) and carboxylic acid **161** (59 mg, 202 μmol, 1.0 eq.) according to general procedure E. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 81 mg (57 % o2s, 115 μmol).

Appearance: white solid.

^{1}**H-NMR** (500 MHz, Chloroform-*d*): δ = 0.96 (s, 9H), 1.12 (d, *J* = 6.3 Hz, 3H), 2.13 (dd, *J* = 13.5, 7.9 Hz, 1H), 2.40 (ddd, *J* = 12.9, 8.2, 4.5 Hz, 1H), 2.53 (s, 3H), 3.35 (t, *J* = 5.1 Hz, 2H), 3.41 (dd, *J* = 10.4, 4.6 Hz, 1H), 3.48 (dd, *J* = 10.4, 6.0 Hz, 1H), 3.58 – 3.70 (m, 12H), 3.93 – 4.06 (m, 3H), 4.34 (dd, *J* = 15.3, 5.4 Hz, 1H), 4.48 – 4.58 (m, 3H), 4.68 (t, *J* = 8.0 Hz, 1H), 7.31 – 7.39 (m, 5H), 7.48 (t, *J* = 6.1 Hz, 1H), 9.09 (s, 1H).

^{13}**C-NMR** (126 MHz, Chloroform-*d*): δ = 14.5, 17.0, 26.4, 35.2, 36.4, 43.2, 50.8, 56.9, 57.4, 59.0, 68.6, 70.1, 70.2, 70.2, 70.7, 70.9, 71.2, 75.2, 75.2, 128.4, 129.0, 129.5, 133.7, 139.4, 145.5, 152.3, 171.0, 171.3, 171.4.

TLC: R_f(intermediate) = 0.11 (DCM:MeOH = 20:1, 1 % TEA).

R_f =0.15 (DCM:MeOH = 20:1).

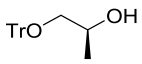
LC-MS: Mass (ESI), calculated = 704.3 $[M+H]^+$, found = 704.4.

[5-100 % Solvent B, 3.0 min]: R_t = 1.8 min.

97 % purity (220 nm).

Lab book number(s): MWa571.

(*S*)-1-(Trityloxy)propan-2-ol



$C_{22}H_{22}O_2$, MW = 318.42 g / mol

(*S*)-Propane-1,2-diol (1.0 mL, 13.0 mmol, 1.0 eq.), triethylamine (2.9 mL, 20.8 mmol, 1.6 eq.) were dissolved in DCM (dry, 20 mL) and cooled to 0 °C under argon. Trityl chloride (3.6 g, 13.0 mmol, 1.0 eq.) was added and the mixture was stirred for 18 h at 0 °C to room temperature. The mixture was concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 3.1 g (74 %, 9.7 mmol).

Appearance: white solid.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.11 – 1.20 (m, 3H), 2.46 (s, 1H), 3.03 – 3.11 (m, 1H), 3.16 – 3.24 (m, 1H), 3.97 – 4.08 (m, 1H), 7.27 – 7.32 (m, 3H), 7.32 – 7.40 (m, 6H), 7.45 – 7.54 (m, 6H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 19.1, 67.1, 69.1, 86.7, 127.1, 127.9, 128.7, 143.9.

TLC: R_f = 0.52 (CH:EA = 1:1).

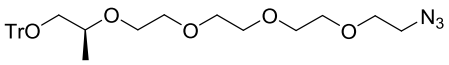
LC-MS: Mass (ESI), calculated = 341.2 $[M+Na]^+$, found = 341.2.

[5-100 % Solvent B, 3.0 min]: R_t = 2.2 min.

99 % purity (220 nm).

Lab book number(s): MWa576.

(*S*)-16-Azido-4-methyl-1,1,1-triphenyl-2,5,8,11,14-pentaoxahexadecane



$C_{30}H_{37}N_3O_5$, MW = 519.64 g / mol

The product was synthesized from alcohol **173** (318 mg, 1.0 mmol, 1.0 eq.) and tosylate **4d** (747 mg, 2.0 mmol, 2.0 eq.) according to general procedure F. The obtained product was purified by flash chromatography.

Yield: 95 mg (18 %, 183 μmol).

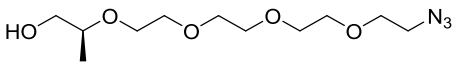
Appearance: colorless oil.

TLC: R_f = 0.45 (CH:EA = 2:1).

LC-MS: Mass (ESI), calculated = 542.3 $[M+Na]^+$, found = 542.2.
[5-100 % Solvent B, 3.0 min]: R_t = 2.5 min.
60 % purity (220 nm).

Lab book number(s): MWa586.

(*S*)-14-Azido-2-methyl-3,6,9,12-tetraoxatetradecan-1-ol



$C_{11}H_{23}N_3O_5$, MW = 277.32 g / mol

(*S*)-16-Azido-4-methyl-1,1,1-triphenyl-2,5,8,11,14-pentaoxahexadecane (95 mg, 183 μmol, 1.0 eq.) was dissolved in DCM:TFA (9:1, 10 mL). The mixture was stirred for 2 h at room temperature. Sodium hydrogen carbonate (aq, sat., 20 mL) was added and the solution was extracted with DCM

(3 x 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 18 mg (35 %, 65 μmol).

Appearance: colorless oil.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.10 (d, *J* = 6.2 Hz, 3H), 2.65 (s, 3H), 3.36 – 3.42 (m, 2H), 3.43 – 3.49 (m, 1H), 3.54 – 3.60 (m, 2H), 3.61 – 3.70 (m, 14H).

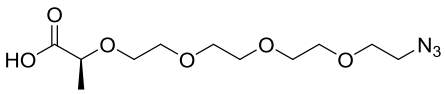
^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 16.3, 50.8, 66.4, 68.2, 70.1, 70.6, 70.7, 70.7, 70.8, 70.9, 77.0.

TLC: R_f = 0.09 (CH:EA = 1:2)

LC-MS: Mass (ESI), calculated = 278.2 $[M+H]^+$, found = 278.2.
[5-100 % Solvent B, 3.0 min]: R_t = 1.4 min.

Lab book number(s): MWa592.

(*S*)-14-Azido-2-methyl-3,6,9,12-tetraoxatetradecanoic acid



$C_{11}H_{21}N_3O_6$, MW = 291.30 g / mol

The product was synthesized from alcohol **175** (18 mg, 65 μmol, 1.0 eq.) according to general procedure G.

Yield: 15 mg (76 %, 50 μmol).

Appearance: colorless oil.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.25 (s, 2H), 1.45 (d, *J* = 6.9 Hz, 3H), 3.40 (t, *J* = 5.0 Hz, 2H), 3.67 (ddt, *J* = 6.2, 4.3, 2.3 Hz, 12H), 3.81 – 3.88 (m, 1H).

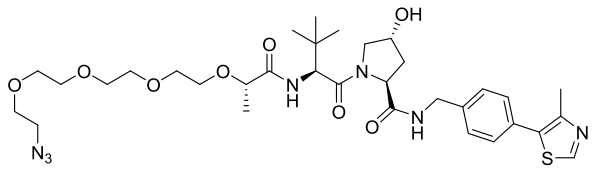
TLC: R_f = 0.11 (CH:EA = 1:1, 1 % HCOOH)

LC-MS: Mass (ESI), calculated = 314.1 $[M+Na]^+$, found = 314.2.

[5-100 % Solvent B, 3.0 min]: R_t = 1.4 min.

Lab book number(s): MWa594.

(2*S*,4*R*)-1-((2*S*,5*S*)-17-Azido-2-(*tert*-butyl)-5-methyl-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



$C_{33}H_{49}N_7O_8S$, MW = 703.86 g / mol

The product was synthesized from *tert*-butyl protected amine **56** (27 mg, 50 μmol, 1.0 eq.) and carboxylic acid **176** (15 mg, 50 μmol, 1.0 eq.) according to general procedure E. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 15 mg (42 % o2s, 21 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.94 (s, 9H), 1.37 (d, J = 6.8 Hz, 3H), 2.06 – 2.17 (m, 1H), 2.52 (s, 4H), 3.37 (t, J = 5.1 Hz, 2H), 3.55 – 3.72 (m, 15H), 3.88 (q, J = 6.8 Hz, 1H), 4.11 (d, J = 11.4 Hz, 1H), 4.35 – 4.45 (m, 4H), 4.74 (t, J = 7.9 Hz, 1H), 7.36 (s, 5H), 8.79 (s, 1H).

TLC: R_f(intermediate) = 0.11 (DCM:MeOH = 20:1, 1 % TEA).

R_f =0.15 (DCM:MeOH = 20:1).

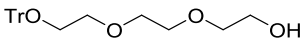
LC-MS: Mass (ESI), calculated = 704.3 $[M+H]^+$, found = 704.4.

[5-100 % Solvent B, 3.0 min]: R_t = 1.8 min.

> 99 % purity (220 nm).

Lab book number(s): MWa597.

2-(2-(2-(Trityloxy)ethoxy)ethoxy)ethan-1-ol



$C_{25}H_{28}O_4$, MW = 392.50 g / mol

Triethylene glycol (4.5 g, 30.0 mmol, 3.0 eq.), triethylamine (2.8 mL, 20.0 mmol, 2.0 eq.) and 4-dimethylaminopyridine (122 mg, 1.00 mmol, 0.1 eq.) were dissolved in DCM (10 mL) and cooled to 0 °C. Trityl chloride (2.8 mg, 10.0 mmol, 1.0 eq.) was added and the mixture was stirred for 18 h at 0 °C to room temperature. Water (10 mL) was added and the solution was extracted with DCM (3 x 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 2.0 g (51 %, 5.1 mmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 2.55 (s, 1H), 3.31 (t, *J* = 5.1 Hz, 2H), 3.64 – 3.69 (m, 2H), 3.70 – 3.80 (m, 8H), 7.23 – 7.38 (m, 9H), 7.49 – 7.56 (m, 6H).

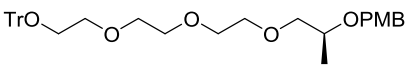
^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 61.8, 63.3, 70.6, 70.7, 70.9, 72.6, 86.7, 127.0, 127.8, 128.8, 144.1.

TLC: R_f = 0.35 (CH:EA = 2:1).

LC-MS: Mass (ESI), calculated = 415.2 $[M+Na]^+$, found = 415.2.
[30-100 % Solvent B, 3.0 min]: R_t = 2.2 min.
> 99 % purity (220 nm).

Lab book number(s): MWa515 / MWa588.

(*S*)-15-(4-Methoxyphenyl)-13-methyl-1,1,1-triphenyl-2,5,8,11,14-pentaoxapentadecane



$C_{36}H_{42}O_6$, MW = 570.73 g / mol

The product was synthesized from 2-(2-(2-(trityloxy)ethoxy)ethoxy)ethan-1-ol (700 mg, 1.78 mmol, 1.0 eq eq.) and tosylate **135** (1.25 g, 3.57 mmol, 2.0 eq.) according to general procedure D. The obtained product was purified by flash chromatography.

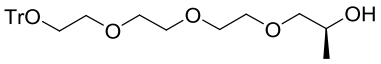
Yield: 1.02 g (quant, 1.78 mmol).

Appearance: colorless oil.

TLC: R_f = 0.57 (CH:EA = 3:1).

Lab book number(s): MWa589.

(*S*)-1,1,1-Triphenyl-2,5,8,11-tetraoxatetradecan-13-ol



$C_{28}H_{34}O_5$, MW = 450.58 g / mol

(*S*)-15-(4-Methoxyphenyl)-13-methyl-1,1,1-triphenyl-2,5,8,11,14-pentaoxapentadecane (1.02 g, 1.78 mmol, 1.0 eq.) was dissolved in DCM:water (20.4 mL, 50:1). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (485 mg, 2.14 mmol, 1.2 eq.) was added and the mixture was stirred for 30 min at room temperature. The mixture was quenched with sodium hydrogen carbonate (sat., aq, 100 mL) and extracted with DCM (3 x 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 344 mg (43 %, 763 μmol).

Appearance: colorless oil.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.14 (d, *J* = 6.4 Hz, 3H), 2.91 (s, 1H), 3.23 – 3.35 (m, 3H), 3.51 (dd, *J* = 9.8, 3.0 Hz, 1H), 3.61 – 3.79 (m, 10H), 3.93 – 4.05 (m, 1H), 7.19 – 7.38 (m, 9H), 7.46 – 7.58 (m, 6H).

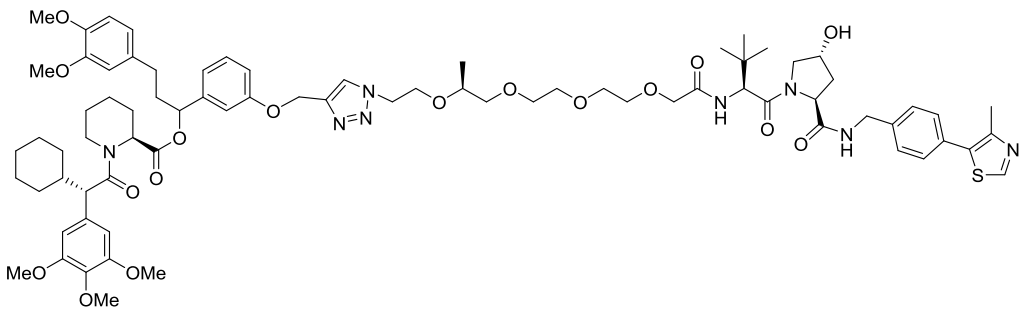
^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 18.6, 63.4, 66.3, 70.6, 70.7, 70.7, 70.8, 77.0, 86.6, 127.0, 127.8, 128.8, 144.2.

TLC: R_f = 0.18 (CH:EA = 2:1).

LC-MS: Mass (ESI), calculated = 473.2 $[M+H]^+$, found = 473.2.
[5-100 % Solvent B, 3.0 min]: R_t = 2.3 min.
> 99 % purity (220 nm).

Lab book number(s): MWa593.

3-(3,4-Dimethoxyphenyl)-1-(3-((1-((4*S*,16*S*)-16-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-4,17,17-trimethyl-14-oxo-3,6,9,12-tetraoxa-15-azaoctadecyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{76}H_{102}N_8O_{17}S$, MW = 1431.75 g / mol

The product was synthesized from (2*S*,4*R*)-1-((2*S*,14*S*)-17-azido-2-(*tert*-butyl)-14-methyl-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (7.0 mg, 10.0 μmol, 1.0 eq.) and alkyne **A10** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 8.9 mg (62 %, 6.2 μmol).

Appearance: white solid.

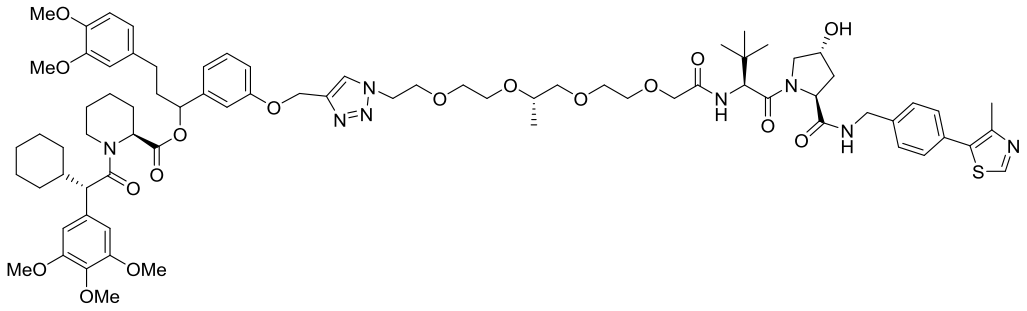
TLC: R_f = 0.15 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.4 min.
[50-100 % Solvent B, 3.0 min]: R_t = 1.8 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+Na]^+$ calculated for $C_{76}H_{102}N_8O_{17}S$ = 1453.69759; found = 1453.69765.

Lab book number(s): MWa600.

3-(3,4-Dimethoxyphenyl)-1-(3-((1-((7*S*,16*S*)-16-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-7,17,17-trimethyl-14-oxo-3,6,9,12-tetraoxa-15-azaoctadecyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (601)



$C_{76}H_{102}N_8O_{17}S$, MW = 1431.75 g / mol

The product was synthesized from (2*S*,4*R*)-1-((2*S*,11*S*)-17-azido-2-(*tert*-butyl)-11-methyl-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (7.0 mg, 10.0 μmol, 1.0 eq.) and alkyne **A10** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 12.2 mg (85 %, 8.5 μmol).

Appearance: white solid.

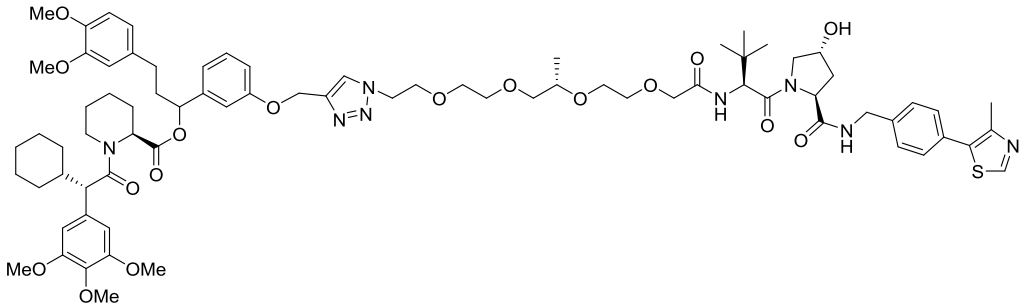
TLC: R_f = 0.15 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.4 min.
[50-100 % Solvent B, 3.0 min]: R_t = 1.8 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+Na]^+$ calculated for $C_{76}H_{102}N_8O_{17}S$ = 1453.69759; found = 1453.69726.

Lab book number(s): MWa601.

3-(3,4-Dimethoxyphenyl)-1-(3-((1-((8*S*,16*S*)-16-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-8,17,17-trimethyl-14-oxo-3,6,9,12-tetraoxa-15-azaoctadecyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{76}H_{102}N_8O_{17}S$, MW = 1431.75 g / mol

The product was synthesized from (2*S*,4*R*)-1-((2*S*,10*S*)-17-azido-2-(*tert*-butyl)-10-methyl-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (7.0 mg, 10.0 μmol, 1.0 eq.) and alkyne **A10** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.7 mg (75 %, 7.5 μmol).

Appearance: white solid.

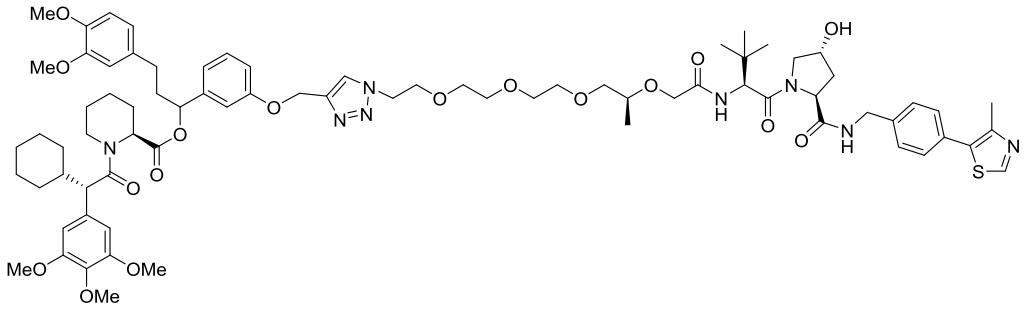
TLC: R_f = 0.15 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.4 min.
[50-100 % Solvent B, 3.0 min]: R_t = 1.8 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+Na]^+$ calculated for $C_{76}H_{102}N_8O_{17}S$ = 1453.69759; found = 1453.69781.

Lab book number(s): MWa602.

3-(3,4-Dimethoxyphenyl)-1-(3-((1-((11*S*,16*S*)-16-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-11,17,17-trimethyl-14-oxo-3,6,9,12-tetraoxa-15-azaoctadecyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{76}H_{102}N_8O_{17}S$, MW = 1431.75 g / mol

The product was synthesized from (2*S*,4*R*)-1-((2*S*,7*S*)-17-azido-2-(*tert*-butyl)-7-methyl-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (7.0 mg, 10.0 μmol, 1.0 eq.) and alkyne **A10** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.3 mg (72 %, 7.2 μmol).

Appearance: white solid.

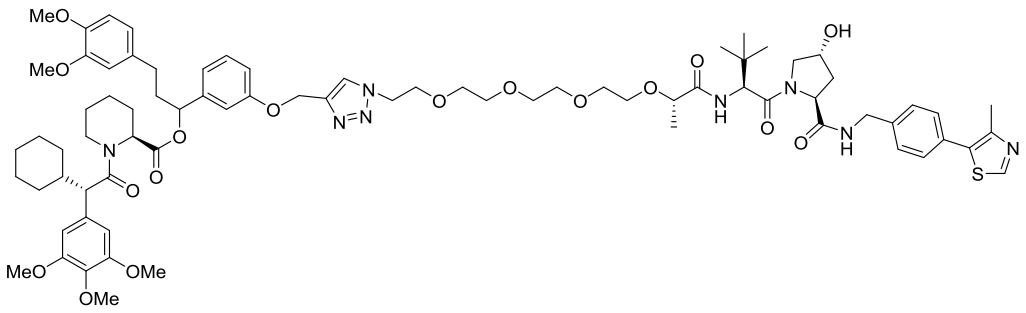
TLC: R_f = 0.15 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.4 min.
[50-100 % Solvent B, 3.0 min]: R_t = 1.8 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{76}H_{102}N_8O_{17}S$ = 1431.71564; found = 1431.71624.

Lab book number(s): MWa603.

3-(3,4-Dimethoxyphenyl)-1-(3-((1-((13*S*,16*S*)-16-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-13,17,17-trimethyl-14-oxo-3,6,9,12-tetraoxa-15-azaoctadecyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (2*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{76}H_{102}N_8O_{17}S$, MW = 1431.75 g / mol

The product was synthesized from (2*S*,4*R*)-1-((2*S*,5*S*)-17-azido-2-(*tert*-butyl)-5-methyl-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (7.0 mg, 10.0 μmol, 1.0 eq.) and alkyne **A10** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.7 mg (75 %, 7.5 μmol).

Appearance: white solid.

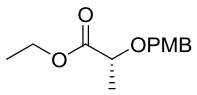
TLC: R_f = 0.15 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.4 min.
[50-100 % Solvent B, 3.0 min]: R_t = 1.8 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+Na]^+$ calculated for $C_{76}H_{102}N_8O_{17}S$ = 1431.71564; found = 1431.71614.

Lab book number(s): MWa604.

Ethyl (*R*)-2-((4-methoxybenzyl)oxy)propanoate



$C_{13}H_{18}O_4$, MW = 238.28 g / mol

(-)-Ethyl D-lactate (12.5 g, 106 mmol, 1.0 eq.) and 1-(chloromethyl)-4-methoxybenzene (25.0 g, 160 mmol, 1.5 eq.), DIPEA (29.6 mL, 170 mmol, 1.6 eq.) and sodium iodide (1.6 g, 10.6 mmol, 0.1 eq.) were stirred for 2 h at 150 °C under argon. Water (100 mL) was added and the mixture was extracted with DCM (3 x 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 8.9 g (35 %, 37.4 mmol).

Appearance: colorless oil.

^{1}**H-NMR** (500 MHz, Chloroform-*d*): δ = 1.32 (t, *J* = 7.2 Hz, 3H), 1.43 (d, *J* = 7.1 Hz, 3H), 3.81 (d, *J* = 3.5 Hz, 3H), 4.05 (q, *J* = 6.9 Hz, 1H), 4.23 (qq, *J* = 6.8, 3.0 Hz, 2H), 4.41 (d, *J* = 11.3 Hz, 1H), 4.64 (d, *J* = 11.2 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H).

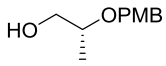
^{13}**C-NMR** (75 MHz, Chloroform-*d*): δ = 14.3, 18.7, 55.3, 60.8, 71.6, 73.7, 113.8, 129.7, 159.4, 173.4.

TLC: R_f = 0.18 (CH:EA = 9:1).

LC-MS: Mass (ESI), calculated = 261.1 $[M+Na]^+$, found = 261.2.
[5-100 % Solvent B, 3.0 min]: R_t = 2.0 min.
85 % purity (220 nm).

Lab book number(s): MWa534.

(*R*)-2-((4-Methoxybenzyl)oxy)propan-1-ol



$C_{11}H_{16}O_3$, MW = 196.25 g / mol

Ethyl (*R*)-2-((4-methoxybenzyl)oxy)propanoate (8.80 g, 37.0 mmol, 1.0 eq.) was dissolved in THF (80 mL, dry) under argon. The mixture was cooled to 0 °C and LAH in THF (1 M, 41.0 mL, 41.0 mmol, 1.1 eq.) was added slowly. The mixture was allowed to warm to room temperature and was stirred for 2 h. Sodium hydroxide (aq, 1 M, 2 mL) and water (10 mL) were added. The solution was filtered and rinsed with DEE. The filtrate was washed with Brine (50 mL) and the organic phase was dried over $MgSO_4$ and concentrated under reduced pressure.

Yield: 7.30 g (quant., 37.0 mmol).

Appearance: slightly yellow oil.

^{1}**H-NMR** (500 MHz, Chloroform-*d*): δ = 1.18 (d, *J* = 6.3 Hz, 3H), 2.27 – 2.47 (m, 1H), 3.50 (ddd, *J* = 11.0, 7.0, 2.8 Hz, 1H), 3.55 – 3.62 (m, 1H), 3.67 (ddq, *J* = 10.1, 7.0, 3.5 Hz, 1H), 3.81 (d, *J* = 3.0 Hz, 3H), 4.44 (d, *J* = 11.3 Hz, 1H), 4.59 (d, *J* = 11.2 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 2H), 7.26 – 7.33 (m, 2H).

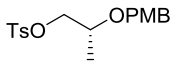
^{13}**C-NMR** (126 MHz, Chloroform-*d*): δ = 15.9, 55.3, 66.3, 70.5, 75.3, 113.9, 129.4, 130.6, 159.3.

TLC: R_f = 0.18 (CH:EA = 2:1).

LC-MS: Mass (ESI), calculated = 219.1 $[M+Na]^+$, found = 219.0.
[5-100 % Solvent B, 2.6 min]: R_t = 1.2 min.
85 % purity.

Lab book number(s): MWa537.

(*R*)-2-((4-Methoxybenzyl)oxy)propyl 4-methylbenzenesulfonate



$C_{18}H_{22}O_5S$, MW = 350.43 g / mol

The product was synthesized from alcohol **141** (7.3 g, 37.0 mmol, 1.0 eq.) according to general procedure C. The obtained product was purified by flash chromatography.

Yield: 9.5 g (73 %, 27.0 mmol).

Appearance: slightly yellow oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.17 (d, *J* = 6.4 Hz, 3H), 2.45 (s, 3H), 3.72 – 3.81 (m, 1H), 3.82 (d, *J* = 1.4 Hz, 3H), 3.96 – 4.06 (m, 2H), 4.41 – 4.51 (m, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 7.8 Hz, 2H).

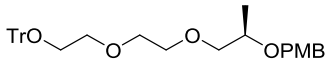
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 16.8, 21.7, 55.3, 71.0, 72.0, 72.8, 113.8, 128.0, 129.3, 129.9, 130.2, 133.0, 144.8, 159.3.

TLC: R_f = 0.35 (CH:EA = 3:1).

LC-MS: Mass (ESI), calculated = 373.1 $[M+Na]^+$, found = 373.0.
[5-100 % Solvent B, 3.0 min]: R_t = 2.2 min.
98 % purity (220 nm).

Lab book number(s): MWa539.

(*R*)-12-(4-Methoxyphenyl)-10-methyl-1,1,1-triphenyl-2,5,8,11-tetraoxadodecane



$C_{34}H_{38}O_5$, MW = 526.67 g / mol

The product was synthesized from alcohol **152** (139 mg, 400 μmol, 1.0 eq.)and tosylate **142** (280 mg, 800 μmol, 2.0 eq.) according to general procedure D. The obtained product was purified by flash chromatography.

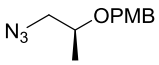
Yield: 171 mg (81 %, 324 μmol).

Appearance: colorless oil.

TLC: R_f = 0.55 (CH:EA = 3:1).

Lab book number(s): MWa630.

(*S*)-1-(((1-Azidopropan-2-yl)oxy)methyl)-4-methoxybenzene



$C_{11}H_{15}N_3O_2$, MW = 221.26 g / mol

(S)-2-((4-methoxybenzyl)oxy)propyl 4-methylbenzenesulfonate (3.10 g, 8.9 mmol, 1.0 eq.) and sodium azide (1.16 g, 17.8 mmol, 2.0 eq.) were dissolved in DMF (90 mL). The mixture was stirred for 18 h at 70 °C. The solvent was removed under reduced pressure. The crude product was dissolved in DCM and filtered through Celite. The solvent was removed under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 1.71 g (87 %, 7.7 mmol).

Appearance: slightly yellow oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.24 (d, *J* = 6.3 Hz, 3H), 3.22 (dd, *J* = 12.8, 3.9 Hz, 1H), 3.32 (dd, *J* = 12.8, 6.8 Hz, 1H), 3.74 (td, *J* = 6.4, 4.0 Hz, 1H), 3.83 (s, 3H), 4.52 (d, *J* = 11.3 Hz, 1H), 4.59 (d, *J* = 11.3 Hz, 1H), 6.89 – 6.95 (m, 2H), 7.30 – 7.35 (m, 2H).

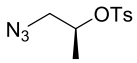
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 17.5, 55.3, 55.8, 70.7, 73.8, 113.9, 129.3, 130.3, 159.3.

TLC: R_f = 0.72 (CH:EA = 1:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.0 min.
87 % purity (220 nm).

Lab book number(s): MWa488.

(*S*)-1-Azidopropan-2-yl 4-methylbenzenesulfonate



$C_{10}H_{13}N_3O_3S$, MW = 255.29 g / mol

(*S*)-1-(((1-Azidopropan-2-yl)oxy)methyl)-4-methoxybenzene (1.65 g, 7.45 mmol, 1.0 eq.) was dissolved in DCM:TFA (9:1, 100 mL). The mixture was stirred for 30 min at room temperature. Water (50 mL) was added and the solution was extracted with DCM (3 x 50 mL). combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure.
TLC: R_f = 0.32 (CH:EA = 1:1)
Crude (*S*)-1-azidopropan-2-ol (0.75 g, 7.45 mmol, 1.0 eq.), triethylamine (3.1 mL, 22.4 mmol, 3.0 eq.) and 4-dimethylaminopyridine (182 mg, 1.49 mmol, 0.2 eq.) were dissolved in DCM (75 mL) and cooled to 0 °C. *p*-Toluenesulfonyl chloride (2.13 g, 11.2 mmol, 1.5 eq.) was added and the mixture was stirred for 18 h at 0 °C to room temperature. Water (80 mL) was added and the solution was extracted with DCM (3 x 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 274 mg (14 % o2s, 1.1 mmol).

Appearance: slightly yellow oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.34 (dd, *J* = 6.4, 1.0 Hz, 3H), 2.47 (s, 3H), 3.29 – 3.41 (m, 2H), 4.70 (pd, *J* = 6.3, 4.3 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.81 – 7.86 (m, 2H).

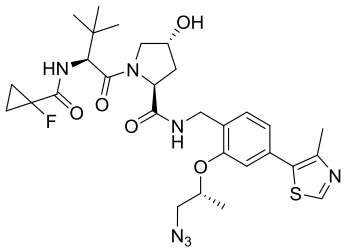
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 18.4, 21.7, 55.1, 77.3, 127.8, 129.9, 133.8, 145.0.

TLC: R_f = 0.40 (CH:EA = 2:1).

LC-MS: Mass (ESI), calculated = 273.1 $[M+NH_4]^+$, found = 273.2.
[5-100 % Solvent B, 3.0 min]: R_t = 2.0 min.
99 % purity (220 nm).

Lab book number(s): MWa492 + MWa496.

(2*S*,4*R*)-*N*-(2-(((*R*)-1-Azidopropan-2-yl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{29}H_{38}FN_7O_5S$, MW = 615.73 g / mol

The product was synthesized from alcohol **7** (53 mg, 100 μmol, 1.0 eq.) and tosylate **187** (34 mg, 135 μmol, 1.35 eq) according to general procedure H. The obtained product was purified by flash chromatography.

Yield: 48 mg (78 %, 78 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.95 (s, 9H), 1.20 – 1.36 (m, 5H), 1.38 (d, *J* = 6.2 Hz, 3H), 2.02 – 2.10 (m, 1H), 2.50 (s, 4H), 3.48 (dd, *J* = 12.9, 3.8 Hz, 1H), 3.56 (dd, *J* = 12.9, 6.3 Hz, 1H), 3.64 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.67 – 3.71 (m, 1H), 3.94 (dt, *J* = 11.3, 1.9 Hz, 1H), 4.39 (dd, *J* = 15.1, 5.5 Hz, 1H), 4.51 (dd, *J* = 15.1, 6.5 Hz, 2H), 4.54 – 4.58 (m, 1H), 4.61 (tt, *J* = 6.3, 3.1 Hz, 1H),

4.69 (t, *J* = 7.7 Hz, 1H), 6.87 (d, *J* = 1.6 Hz, 1H), 6.96 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.07 (dd, *J* = 9.0, 3.6 Hz, 1H), 7.31 (t, *J* = 6.1 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 8.67 (s, 1H).

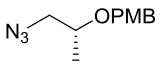
^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 13.7, 16.1, 17.2, 26.3, 35.6, 36.0, 38.8, 55.6, 56.6, 57.4, 58.6, 70.1, 73.2, 79.1, 113.3, 122.2, 127.3, 129.8, 131.7, 132.1, 148.5, 150.4, 154.9, 170.1, 170.2, 170.7.

TLC: R_f = 0.23 (EA).

LC-MS: Mass (ESI), calculated = 616.3 $[M+H]^+$, found = 616.2.
[5-100 % Solvent B, 10.5 min]: R_t = 6.7 min.
[5-100 % Solvent B, 3.0 min]: R_t = 1.9 min.
98 % purity (220 nm).

Lab book number(s): MWa500.

(*R*)-1-(((1-Azidopropan-2-yl)oxy)methyl)-4-methoxybenzene



$C_{11}H_{15}N_3O_2$, MW = 221.26 g / mol

(*R*)-2-((4-Methoxybenzyl)oxy)propyl 4-methylbenzenesulfonate (3.50 g, 10.0 mmol, 1.0 eq.) and sodium azide (1.30 g, 20.0 mmol, 2.0 eq.) were dissolved in DMF (50 mL). The mixture was stirred for 18 h at 70 °C. The solvent was removed under reduced pressure. The crude product was dissolved in DCM and filtered through Celite. The solvent was removed under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 1.82 g (82 %, 8.2 mmol).

Appearance: colorless oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.24 (d, *J* = 6.3 Hz, 3H), 3.22 (dd, *J* = 12.7, 3.4 Hz, 1H), 3.32 (dd, *J* = 12.7, 6.7 Hz, 1H), 3.71 – 3.77 (m, 1H), 3.83 (s, 3H), 4.52 (d, *J* = 11.3 Hz, 1H), 4.59 (d, *J* = 11.3 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H).

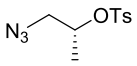
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 17.5, 55.3, 55.8, 70.7, 73.8, 113.9, 129.3, 130.3, 159.3.

TLC: R_f = 0.72 (CH:EA = 1:1).

LC-MS: Mass (ESI), calculated = 244.1 $[M+Na]^+$, found = 244.0.
[5-100 % Solvent B, 3.0 min]: R_t = 2.0 min.
98 % purity (220 nm).

Lab book number(s): MWa541.

(*R*)-1-Azidopropan-2-yl 4-methylbenzenesulfonate



$C_{10}H_{13}N_3O_3S$, MW = 255.29 g / mol

(*R*)-1-(((1-Azidopropan-2-yl)oxy)methyl)-4-methoxybenzene (1.82 g, 8.2 mmol, 1.0 eq.) was dissolved in DCM:TFA (9:1, 100 mL). The mixture was stirred for 30 min at room temperature. Water (50 mL) was added and the solution was extracted with DCM (3 x 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure.
TLC: R_f = 0.27 (CH:EA = 2:1).
Crude (*R*)-1-Azidopropan-2-ol (0.83 g, 8.2 mmol, 1.0 eq.), triethylamine (3.4 mL, 24.6 mmol, 3.0 eq.) and 4-dimethylaminopyridine (195 mg, 1.6 mmol, 0.2 eq.) were dissolved in DCM (75 mL) and cooled to 0 °C. *p*-Toluenesulfonyl chloride (2.35 g, 12.3 mmol, 1.5 eq.) was added and the mixture was stirred for 18 h at 0 °C to room temperature. Water (80 mL) was added and the solution was extracted with DCM (3 x 80 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 711 mg (34 % o2s, 2.8 mmol).

Appearance: yellow oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.29 – 1.34 (m, 3H), 2.43 – 2.47 (m, 3H), 3.28 – 3.38 (m, 2H), 4.68 (pdd, *J* = 6.3, 4.2, 2.2 Hz, 1H), 7.34 – 7.38 (m, 2H), 7.82 (dq, *J* = 8.6, 2.3 Hz, 2H).

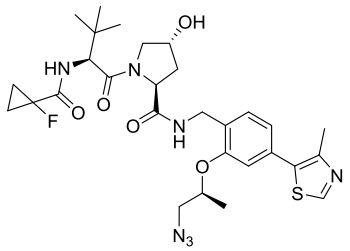
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 18.3, 21.6, 55.0, 77.4, 127.8, 129.9, 133.7, 145.1.

TLC: R_f = 0.41 (CH:EA = 2:1).

LC-MS: Mass (ESI), calculated = 273.1 $[M+NH_4]^+$, found = 273.2.
[5-100 % Solvent B, 3.0 min]: R_t = 2.0 min.
98 % purity (220 nm).

Lab book number(s): MWa546 + MWa547.

(2*S*,4*R*)-*N*-(2-(((*S*)-1-Azidopropan-2-yl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{29}H_{38}FN_7O_5S$, MW = 615.73 g / mol

The product was synthesized from alcohol **7** (53 mg, 100 μmol, 1.0 eq.) and tosylate **189** (34 mg, 135 μmol, 1.35 eq) according to general procedure H. The obtained product was purified by flash chromatography.

Yield: 51 mg (82 %, 82 μmol).

Appearance: white solid.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 0.98 (s, 9H), 1.25 – 1.39 (m, 5H), 1.44 (d, *J* = 6.2 Hz, 3H), 2.12 (ddt, *J* = 13.5, 8.1, 2.1 Hz, 1H), 2.50 (ddd, *J* = 12.8, 7.7, 4.7 Hz, 1H), 2.55 (s, 3H), 3.33 (s, 1H), 3.49 (dd, *J* = 12.9, 3.8 Hz, 1H), 3.57 (dd, *J* = 13.0, 6.5 Hz, 1H), 3.66 (dd, *J* = 11.3, 3.8 Hz, 1H), 4.02 (dt, *J* = 11.5, 1.9 Hz, 1H), 4.48 – 4.59 (m, 4H), 4.64 (tt, *J* = 6.4, 3.2 Hz, 1H), 4.72 (t, *J* = 7.9 Hz, 1H), 6.92 (d, *J* = 1.6 Hz, 1H), 7.00 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.09 (dd, *J* = 9.0, 3.7 Hz, 1H), 7.24 (t, *J* = 6.1 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 8.70 (s, 1H).

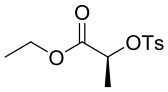
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 13.7, 13.8, 16.1, 17.4, 26.3, 35.4, 36.0, 38.7, 55.6, 56.6, 57.4, 58.6, 70.2, 73.4, 79.1, 113.3, 122.3, 127.3, 129.9, 131.6, 132.3, 148.5, 150.4, 155.0, 170.3, 170.6, 170.8.

TLC: R_f = 0.23 (EA).

LC-MS: Mass (ESI), calculated = 616.3 $[M+H]^+$, found = 616.2.
[5-100 % Solvent B, 10.5 min]: R_t = 6.7 min.
[5-100 % Solvent B, 3.0 min]: R_t = 1.9 min.
98 % purity (220 nm).

Lab book number(s): MWa550.

Ethyl (*S*)-2-(tosyloxy)propanoate



$C_{12}H_{16}O_5S$, MW = 272.32 g / mol

The product was synthesized from ethyl (*S*)-2-hydroxypropanoate (1.44 g, 12.2 mmol, 1.0 eq.) according to general procedure C. The obtained product was purified by flash chromatography.

Yield: 2.37 g (71 %, 8.7 mmol).

Appearance: colorless oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.21 (q, *J* = 6.9, 6.1 Hz, 3H), 1.51 (t, *J* = 5.6 Hz, 3H), 2.45 (d, *J* = 5.3 Hz, 3H), 4.12 (p, *J* = 6.7 Hz, 2H), 4.93 (t, *J* = 6.8 Hz, 1H), 7.35 (t, *J* = 6.9 Hz, 2H), 7.82 (t, *J* = 6.6 Hz, 2H).

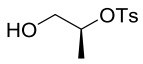
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 13.9, 18.4, 21.6, 61.8, 74.2, 128.0, 129.8, 133.4, 145.1, 169.0.

TLC: R_f = 0.41 (CH:EA = 3:1).

LC-MS: Mass (ESI), calculated = 273.1 $[M+H]^+$, found = 273.2.
[5-100 % Solvent B, 3.0 min]: R_t = 2.0 min.
93 % purity (220 nm).

Lab book number(s): MWa478

(*S*)-1-Hydroxypropan-2-yl 4-methylbenzenesulfonate



$C_{10}H_{14}O_4S$, MW = 230.28 g / mol

Ethyl (*S*)-2-(tosyloxy)propanoate (1.90 g, 7.0 mmol, 1.0 eq.) and lithium chloride (0.69 g, 16.3 mmol, 2.3 eq.) were dissolved in THF:EtOH (1:2, dry, 60 mL) under argon. The mixture was cooled to - 5 °C and sodium borohydride (0.62 g, 16.3 mmol, 2.3 eq.) was added slowly. The mixture was allowed to warm to room temperature and was stirred for 18 h. Chloroform (150 mL) and sodium sulfate (sat., aq, 150 mL) were added and the mixture was stirred for 1 h. The solution was filtered and rinsed with chloroform. The filtrate was washed with Brine (100 mL) and the organic phase was dried over $MgSO_4$ and concentrated under reduced pressure.

Yield: 1.09 g (68 %, 4.73 mmol).

Appearance: colorless oil.

^{1}**H-NMR** (500 MHz, Chloroform-*d*): δ = 1.19 – 1.25 (m, 3H), 2.43 (d, *J* = 2.3 Hz, 3H), 3.58 – 3.64 (m, 2H), 4.66 (tdd, *J* = 9.0, 4.4, 2.8 Hz, 1H), 7.34 (dd, *J* = 8.1, 1.8 Hz, 2H), 7.80 (dd, *J* = 8.3, 1.8 Hz, 2H).

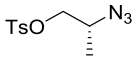
^{13}**C-NMR** (126 MHz, Chloroform-*d*): δ = 16.9, 21.6, 65.4, 80.6, 127.8, 129.9, 133.8, 144.9.

TLC: R_f = 0.15 (CH:EA = 2:1).
R_f = 0.45 (CH:EA = 1:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 1.6 min.
> 99 % purity (220 nm).

Lab book number(s): MWa483 / MWa486.

(*R*)-2-Azidopropyl 4-methylbenzenesulfonate



$C_{10}H_{13}N_3O_3S$, MW = 255.29 g / mol

(*S*)-1-Hydroxypropan-2-yl 4-methylbenzenesulfonate (100 mg, 434 μmol, 1.0 eq.) and sodium azide (56 mg, 868 μmol, 2.0 eq.) were dissolved in DMF (5 mL). The mixture was stirred for 18 h at 70 °C. Brine (30 mL) was added and the solution was extracted with DCM (2 x 40 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure.
TLC: R_f = 0.29 (CH:EA = 2:1).
Crude (*R*)-2-azidopropan-1-ol (44 mg, 434 μmol, 1.0 eq.), triethylamine (181 μL, 1302 μmol, 3.0 eq.) and 4-dimethylaminopyridine (11 mg, 87 μmol, 0.2 eq.) were dissolved in DCM (5 mL) and cooled to 0 °C. *p*-Toluenesulfonyl chloride (124 mg, 651 μmol, 1.5 eq.) was added and the mixture stirred at 0 °C to room temperature for 3 h. Water (5 mL) was added and the solution was extracted with DCM (3 x 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 24 mg (22 % o2s, 94 μmol).

Appearance: colorless oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.01 – 1.06 (m, 3H), 2.24 – 2.30 (m, 3H), 3.54 (ddd, *J* = 11.0, 5.5, 3.3 Hz, 1H), 3.70 – 3.76 (m, 1H), 3.79 – 3.85 (m, 1H), 7.15 – 7.21 (m, 2H), 7.62 (td, *J* = 5.8, 2.7 Hz, 2H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 15.7, 21.7, 55.6, 72.1, 127.9, 130.0, 132.5, 145.3.

TLC: R_f = 0.44 (CH:EA = 2:1).

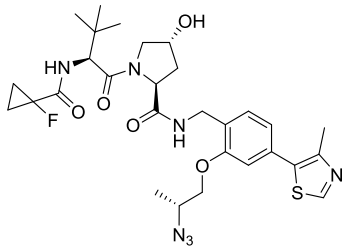
LC-MS: Mass (ESI), calculated = 273.1 $[M+NH_4]^+$, found = 273.2.

[5-100 % Solvent B, 3.0 min]: R_t = 2.0 min.

99 % purity (220 nm).

Lab book number(s): MWa489 + MWa491 / MWa494 + MWa495.

(2*S*,4*R*)-*N*-(2-((*R*)-2-Azidopropoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{29}H_{38}FN_7O_5S$, MW = 615.73 g / mol

The product was synthesized from alcohol **7** (53 mg, 100 μmol, 1.0 eq.) and tosylate **182** (34 mg, 135 μmol, 1.35 eq) according to general procedure H. The obtained product was purified by flash chromatography.

Yield: 41 mg (66 %, 66 μmol).

Appearance: white solid.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 0.96 (s, 9H), 1.28 (td, *J* = 9.9, 9.3, 2.8 Hz, 2H), 1.29 – 1.36 (m, 3H), 1.37 – 1.41 (m, 3H), 2.09 (ddt, *J* = 13.1, 8.2, 1.8 Hz, 1H), 2.52 (s, 4H), 3.66 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.93 – 4.07 (m, 4H), 4.43 (dd, *J* = 15.2, 5.4 Hz, 1H), 4.51 – 4.61 (m, 3H), 4.72 (t, *J* = 7.7 Hz, 1H), 6.84 (d, *J* = 1.7 Hz, 1H), 6.99 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.09 (dd, *J* = 9.0, 3.6 Hz, 1H), 7.34 (t, *J* = 6.1 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 8.69 (s, 1H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 13.7, 16.1, 16.2, 26.3, 35.6, 36.1, 38.6, 56.5, 56.6, 57.4, 58.7, 70.1, 71.7, 79.1, 112.1, 122.3, 126.6, 129.6, 131.6, 132.2, 148.6, 150.4, 155.9, 170.1, 170.7, 170.9.

TLC: R_f = 0.25 (EA).

LC-MS: Mass (ESI), calculated = 616.3 $[M+H]^+$, found = 616.2.

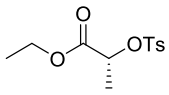
[5-100 % Solvent B, 10.5 min]: R_t = 6.8 min.

[5-100 % Solvent B, 3.0 min]: R_t = 1.9 min.

> 99 % purity (220 nm).

Lab book number(s): MWa497.

Ethyl (*R*)-2-(tosyloxy)propanoate



$C_{12}H_{16}O_5S$, MW = 272.32 g / mol

The product was synthesized from ethyl (*R*)-2-hydroxypropanoate (1.44 g, 12.2 mmol, 1.0 eq.) according to general procedure C. The obtained product was purified by flash chromatography.

Yield: 1.67 g (50 %, 6.1 mmol).

Appearance: colorless oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.17 (t, *J* = 7.2 Hz, 3H), 1.47 (d, *J* = 7.0 Hz, 3H), 2.41 (s, 3H), 4.05 – 4.11 (m, 3H), 4.89 (q, *J* = 6.9 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.78 (d, *J* = 8.2 Hz, 2H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 13.9, 18.4, 21.6, 61.8, 74.2, 128.0, 129.8, 133.4, 145.1, 169.0.

TLC: R_f = 0.41 (CH:EA = 3:1).

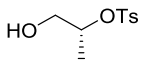
LC-MS: Mass (ESI), calculated = 273.1 $[M+H]^+$, found = 273.2.

[5-100 % Solvent B, 3.0 min]: R_t = 2.0 min.

98 % purity (220 nm).

Lab book number(s): MWa499.

(*R*)-1-hydroxypropan-2-yl 4-methylbenzenesulfonate



$C_{10}H_{14}O_4S$, MW = 230.28 g / mol

Ethyl (R)-2-(tosyloxy)propanoate (1.67 g, 6.1 mmol, 1.0 eq.) and lithium chloride (0.78 g, 18.4 mmol, 3.0 eq.) were dissolved in THF:EtOH (1:2, dry, 60 mL) under argon. The mixture was cooled to - 5 °C and sodium borohydride (0.70 g, 18.4 mmol, 3.0 eq.) was added slowly. The mixture was allowed to warm to room temperature and was stirred for 18 h. Chloroform (150 mL) and sodium sulfate (sat., aq, 150 mL) were added and the mixture was stirred for 1 h. The solution was filtered and rinsed with chloroform. The filtrate was washed with Brine (100 mL) and the organic phase was dried over $MgSO_4$ and concentrated under reduced pressure.

Yield: 0.84 g (59 %, 3.6 mmol).

Appearance: colorless oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.24 (d, *J* = 6.5 Hz, 3H), 2.45 (s, 3H), 3.59 – 3.66 (m, 2H), 4.63 – 4.73 (m, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 8.3 Hz, 2H).

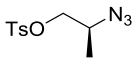
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 16.9, 21.6, 65.5, 80.7, 127.8, 129.9, 133.9, 144.9.

TLC: R_f = 0.45 (CH:EA = 1:1).

LC-MS: Mass (ESI), calculated = 248.1 $[M+NH_4]^+$, found = 248.2.
[5-100 % Solvent B, 3.0 min]: R_t = 1.6 min.
> 99 % purity (220 nm).

Lab book number(s): MWa501.

(*S*)-2-azidopropyl 4-methylbenzenesulfonate



$C_{10}H_{13}N_3O_3S$, MW = 255.29 g / mol

(*R*)-1-hydroxypropan-2-yl 4-methylbenzenesulfonate (837 mg, 3.6 mmol, 1.0 eq.) and sodium azide (473 mg, 7.3 μmol, 2.0 eq.) were dissolved in DMF (30 mL). The mixture was stirred for 18 h at 70 °C. Brine (100 mL) was added and the solution was extracted with DCM (2 x 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The solvent was removed under reduced pressure.

TLC: R_f = 0.29 (CH:EA = 2:1).

Crude (*S*)-2-azidopropan-1-ol (367 mg, 3.6 mmol, 1.0 eq.), triethylamine (1.5 mL, 10.9 mmol, 3.0 eq.) and 4-dimethylaminopyridine (89 mg, 0.7 mmol, 0.2 eq.) were dissolved in DCM (40 mL) and cooled to 0 °C. *p*-Toluenesulfonyl chloride (1039 mg, 5.5 mmol, 1.5 eq.) was added and the mixture stirred at 0 °C to room temperature for 18 h. Water (40 mL) was added and the solution was extracted with DCM (3 x 400 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 187 mg (20 % o2s, 0.7 mmol).

Appearance: colorless oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.25 (d, *J* = 6.7 Hz, 3H), 2.48 (s, 3H), 3.72 – 3.78 (m, 1H), 3.94 (dd, *J* = 10.3, 6.9 Hz, 1H), 4.02 (dd, *J* = 10.3, 4.4 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.83 (dd, *J* = 8.6, 1.9 Hz, 2H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 15.9, 21.8, 55.7, 72.1, 128.1, 130.1, 132.7, 145.3.

TLC: R_f = 0.44 (CH:EA = 2:1).

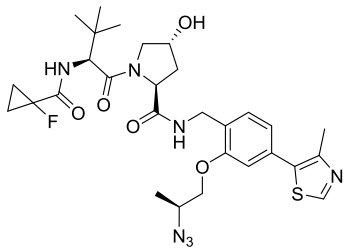
LC-MS: Mass (ESI), calculated = 273.1 $[M+NH_4]^+$, found = 273.2.

[5-100 % Solvent B, 3.0 min]: R_t = 1.9 min.

99 % purity (220 nm).

Lab book number(s): MWa503 + MWa504.

(2*S*,4*R*)-*N*-(2-((*S*)-2-azidopropoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{29}H_{38}FN_7O_5S$, MW = 615.73 g / mol

The product was synthesized from alcohol **7** (53 mg, 100 μmol, 1.0 eq.) and tosylate **189** (34 mg, 135 μmol, 1.35 eq) according to general procedure H. The obtained product was purified by flash chromatography.

Yield: 52 mg (83 %, 83 μmol).

Appearance: white solid.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 0.96 (s, 9H), 1.28 (td, *J* = 9.9, 9.3, 2.8 Hz, 2H), 1.29 – 1.36 (m, 3H), 1.37 – 1.41 (m, 3H), 2.09 (ddt, *J* = 13.1, 8.2, 1.8 Hz, 1H), 2.52 (s, 4H), 3.66 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.93 – 4.07 (m, 4H), 4.43 (dd, *J* = 15.2, 5.4 Hz, 1H), 4.51 – 4.61 (m, 3H), 4.72 (t, *J* = 7.7 Hz, 1H), 6.84 (d, *J* = 1.7 Hz, 1H), 6.99 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.09 (dd, *J* = 9.0, 3.6 Hz, 1H), 7.34 (t, *J* = 6.1 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 8.69 (s, 1H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 13.7, 16.1, 16.2, 26.3, 35.6, 36.1, 38.6, 56.5, 56.6, 57.4, 58.7, 70.1, 71.7, 79.1, 112.1, 122.3, 126.6, 129.6, 131.6, 132.2, 148.6, 150.4, 155.9, 170.1, 170.7, 170.9.

TLC: R_f = 0.24 (EA).

LC-MS: Mass (ESI), calculated = 616.3 $[M+H]^+$, found = 616.2.

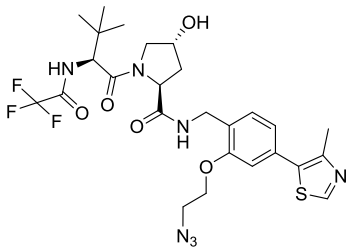
[5-100 % Solvent B, 10.5 min]: R_t = 6.8 min.

[5-100 % Solvent B, 3.0 min]: R_t = 1.9 min.

> 99 % purity (220 nm).

Lab book number(s): MWa497.

(2*S*,4*R*)-*N*-(2-(2-Azidoethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{26}H_{32}F_3N_7O_5S$, MW = 611.64 g / mol

The product was synthesized from (2S,4R)-1-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-4-hydroxy-*N*-(2-hydroxy-4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (HWS02NP, 109 mg, 200 μmol, 1.0 eq.) and tosylate **4a** (65 mg, 270 μmol, 1.35 eq) according to general procedure H. The obtained product was purified by flash chromatography.

Yield: 100 mg (82 %, 163 μmol).

Appearance: white solid.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 0.94 (s, 9H), 2.07 – 2.15 (m, 1H), 2.38 (ddd, *J* = 12.8, 7.8, 4.8 Hz, 1H), 2.49 (s, 3H), 3.65 – 3.72 (m, 3H), 3.76 – 3.81 (m, 1H), 4.16 – 4.21 (m, 2H), 4.42 (dd, *J* = 15.4, 5.6 Hz, 1H), 4.49 – 4.58 (m, 2H), 4.60 (d, *J* = 9.0 Hz, 1H), 4.65 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 1.6 Hz, 1H), 6.98 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.16 (d, *J* = 9.1 Hz, 1H), 7.22 (t, *J* = 6.1 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 8.67 (s, 1H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 14.2, 16.0, 26.2, 36.5, 36.5, 38.7, 50.4, 56.8, 57.8, 59.2, 67.1, 70.0, 112.0, 117.0, 122.3, 126.5, 129.5, 131.6, 132.2, 148.5, 150.5, 156.0, 156.8, 169.5, 170.8.

TLC: R_f = 0.18 (EA).

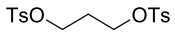
LC-MS: Mass (ESI), calculated = 612.2 $[M+H]^+$, found = 612.2.

[5-100 % Solvent B, 3.0 min]: R_t = 1.9 min.

97 % purity (220 nm).

Lab book number(s): MWa516.

Propane-1,3-diyl bis(4-methylbenzenesulfonate)



$C_{17}H_{20}O_6S_2$, MW = 384.46 g / mol

Propane-1,3-diol (510 μL, 7.0 mmol, 1.0 eq.), triethylamine (5.9 mL, 42.0 mmol, 6.0 eq.) and 4-dimethylaminopyridine (340 mg, 2.8 mmol, 0.4 eq.) were dissolved in DCM (60 mL) and cooled to 0 °C. *p*-Toluenesulfonyl chloride (4.00 g, 21.0 mmol, 3.0 eq.) was added and the mixture stirred for 2 h at 0 °C to room temperature. Water (60 mL) was added and the solution was extracted with DCM (3 x 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 1.84 g (68 %, 4.8 mmol).

Appearance: white solid.

^{1}**H-NMR** (500 MHz, Chloroform-*d*): δ = 2.02 (p, *J* = 6.0 Hz, 2H), 2.47 (s, 6H), 4.08 (t, *J* = 6.0 Hz, 4H), 7.37 (d, *J* = 7.9 Hz, 4H), 7.76 (d, *J* = 8.0 Hz, 4H).

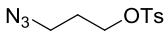
^{13}**C-NMR** (75 MHz, Chloroform-*d*): δ = 21.8, 28.8, 66.0, 128.0, 130.1, 132.7, 145.2.

TLC: R_f = 0.71 (CH:EA = 1:1).

LC-MS: Mass (ESI), calculated = 385.1 $[M+H]^+$, found = 385.0.
[5-100 % Solvent B, 3.0 min]: R_t = 2.1 min.
> 99 % purity (220 nm).

Lab book number(s): MWa535.

3-azidopropyl 4-methylbenzenesulfonate



$C_{10}H_{13}N_3O_3S$, MW = 255.29 g / mol

Propane-1,3-diyl bis(4-methylbenzenesulfonate) (1.84 g, 4.7 mmol, 1.0 eq.) and sodium azide (0.30 g, 4.7 mmol, 1.0 eq.) were dissolved in DMF (40 mL). The mixture was stirred for 18 h at 70 °C. The solvent was removed under reduced pressure. The crude product was dissolved in DCM and filtered through Celite. The solvent was removed under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 295 mg (25 %, 1.2 mmol).

Appearance: colorless oil.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.89 (p, *J* = 6.3 Hz, 2H), 2.46 (s, 3H), 3.38 (t, *J* = 6.5 Hz, 2H), 4.11 (t, *J* = 6.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 2H).

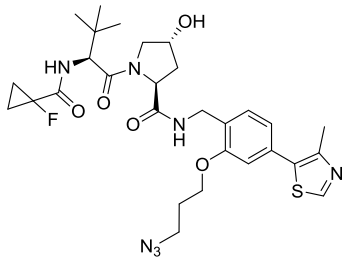
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 21.6, 28.4, 47.3, 67.1, 127.9, 130.0, 132.7, 145.1.

TLC: R_f = 0.46 (CH:EA = 2:1).

LC-MS: Mass (ESI), calculated = 278.1 $[M+Na]^+$, found = 278.0.
[5-100 % Solvent B, 2.6 min]: R_t = 1.7 min.
72 % purity (220 nm).

Lab book number(s): MWa536.

(2*S*,4*R*)-*N*-(2-(3-Azidopropoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{29}H_{38}FN_7O_5S$, MW = 615.73 g / mol

The product was synthesized from alcohol **7** (53 mg, 100 μmol, 1.0 eq.) and tosylate **192** (34 mg, 135 μmol, 1.35 eq) according to general procedure H. The obtained product was purified by flash chromatography.

Yield: 40 mg (65 %, 65 μmol).

Appearance: white solid.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 0.91 (s, 9H), 1.23 – 1.35 (m, 4H), 2.02 – 2.08 (m, 1H), 2.09 – 2.15 (m, 2H), 2.51 (s, 4H), 3.52 – 3.64 (m, 4H), 3.94 (d, *J* = 11.3 Hz, 1H), 4.09 (td, *J* = 6.0, 4.2 Hz, 2H), 4.39 (dd, *J* = 14.9, 5.4 Hz, 1H), 4.46 – 4.56 (m, 3H), 4.71 (t, *J* = 7.7 Hz, 1H), 6.86 (d, *J* = 1.6 Hz, 1H), 6.95 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.07 (dd, *J* = 9.0, 3.6 Hz, 1H), 7.34 (dd, *J* = 12.6, 6.9 Hz, 2H), 8.67 (s, 1H).

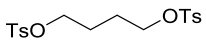
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 13.8, 16.2, 26.4, 28.8, 35.6, 35.8, 38.8, 48.3, 56.6, 57.5, 58.6, 64.9, 70.2, 79.2, 112.1, 121.9, 126.3, 129.7, 131.8, 132.4, 148.6, 150.5, 156.5, 170.2, 170.5, 171.1.

TLC: R_f = 0.24 (EA).

LC-MS: Mass (ESI), calculated = 616.3 $[M+H]^+$, found = 616.2.
[5-100 % Solvent B, 3.0 min]: R_t = 1.9 min.
93 % purity (220 nm).

Lab book number(s): MWa542.

Butane-1,4-diyl bis(4-methylbenzenesulfonate)



$C_{18}H_{22}O_6S_2$, MW = 398.49 g / mol

Butane-1,4-diol (600 μL, 7.0 mmol, 1.0 eq.), triethylamine (5.9 mL, 42.0 mmol, 6.0 eq.) and 4-dimethylaminopyridine (340 mg, 2.8 mmol, 0.4 eq.) were dissolved in DCM (60 mL) and cooled to 0 °C. *p*-Toluenesulfonyl chloride (4.0 g, 21.0 mmol, 3.0 eq.) was added and the mixture stirred for 2 h at 0 °C to room temperature. Water (60 mL) was added and the solution was extracted with DCM (3 x 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 1.73 g (62 %, 4.3 mmol).

Appearance: white solid.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 1.70 (s, 4H), 2.46 (s, 6H), 3.99 (s, 4H), 7.36 (d, *J* = 7.9 Hz, 4H), 7.76 (d, *J* = 7.4 Hz, 4H).

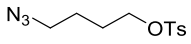
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 21.7, 25.0, 69.4, 127.8, 129.9, 132.9, 145.0.

TLC: R_f = 0.74 (CH:EA = 1:1).

LC-MS: Mass (ESI), calculated = 399.1 $[M+H]^+$, found = 399.0.
[5-100 % Solvent B, 3.0 min]: R_t = 2.2 min.
> 99 % purity (220 nm).

Lab book number(s): MWa543.

4-Azidobutyl 4-methylbenzenesulfonate



$C_{11}H_{15}N_3O_3S$, MW = 269.32 g / mol

Butane-1,4-diyl bis(4-methylbenzenesulfonate) (1.73 g, 4.3 mmol, 1.0 eq.) and sodium azide (280 mg, 4.3 mmol, 1.0 eq.) were dissolved in DMF (40 mL). The mixture was stirred for 3 d at 70 °C. The solvent was removed under reduced pressure. The crude product was dissolved in DCM and filtered through Celite. The solvent was removed under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 109 mg (9 %, 405 μmol).

Appearance: colorless oil.

^{1}**H-NMR** (500 MHz, Chloroform-*d*): δ = 1.59 – 1.66 (m, 2H), 1.70 – 1.76 (m, 2H), 2.46 (s, 3H), 3.26 (t, *J* = 6.7 Hz, 2H), 4.06 (t, *J* = 6.2 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.78 – 7.81 (m, 2H).

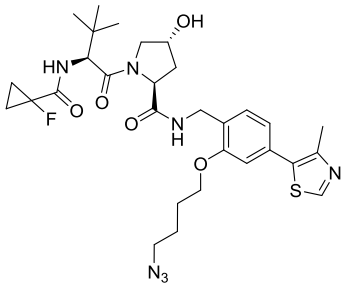
^{13}**C-NMR** (126 MHz, Chloroform-*d*): δ = 21.6, 25.0, 26.1, 50.7, 69.7, 127.9, 129.9, 132.9, 144.9.

TLC: R_f = 0.51 (CH:EA = 2:1).

LC-MS: Mass (ESI), calculated = 292.1 $[M+Na]^+$, found = 292.0.
[5-100 % Solvent B, 3.0 min]: R_t = 2.1 min.
97 % purity (220 nm).

Lab book number(s): MWa545.

(2*S*,4*R*)-*N*-(2-(4-Azidobutoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{30}H_{40}FN_7O_5S$, MW = 629.75 g / mol

The product was synthesized from alcohol **7** (53 mg, 100 μmol, 1.0 eq.) and tosylate **195** (36 mg, 135 μmol, 1.35 eq) according to general procedure H. The obtained product was purified by flash chromatography.

Yield: 53 mg (84 %, 84 μmol).

Appearance: white solid.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ = 0.93 (s, 9H), 1.25 – 1.36 (m, 4H), 1.78 – 1.88 (m, 2H), 1.91 – 1.98 (m, 2H), 2.08 (tdd, *J* = 9.2, 4.3, 2.9 Hz, 1H), 2.52 (s, 4H), 3.39 (t, *J* = 6.7 Hz, 2H), 3.64 (dd, *J* = 11.1, 4.1 Hz, 1H), 3.79 (s, 1H), 3.94 (dt, *J* = 11.3, 1.9 Hz, 1H), 4.04 (td, *J* = 6.1, 2.0 Hz, 2H), 4.40 (dd, *J* = 15.0, 5.4 Hz, 1H), 4.47 – 4.60 (m, 3H), 4.72 (t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 1.6 Hz, 1H), 6.95 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.09 (dd, *J* = 9.0, 3.6 Hz, 1H), 7.32 – 7.37 (m, 2H), 8.68 (s, 1H).

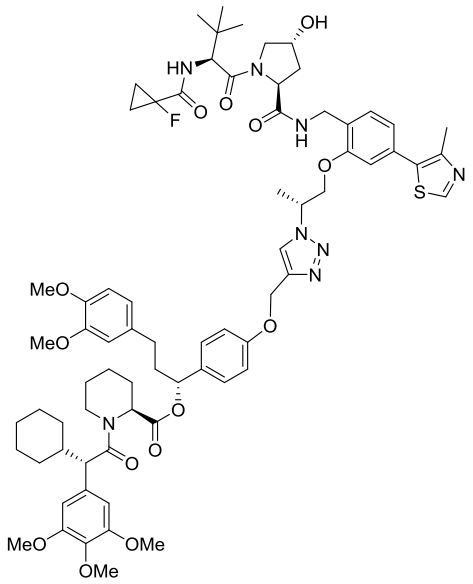
^{13}C-NMR (126 MHz, Chloroform-*d*): δ = 13.7, 13.7, 16.1, 25.7, 26.3, 26.5, 35.6, 35.9, 38.7, 51.1, 56.6, 57.3, 58.6, 67.4, 70.1, 79.2, 112.0, 121.6, 126.3, 129.3, 131.8, 132.2, 148.4, 150.4, 156.5, 170.0, 170.6, 170.9.

TLC: R_f = 0.26 (EA).

LC-MS: Mass (ESI), calculated = 630.3 $[M+H]^+$, found = 630.2.
[5-100 % Solvent B, 3.0 min]: R_t = 2.0 min.
97 % purity (220 nm).

Lab book number(s): MWa549.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-((1-((*R*)-1-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)propan-2-yl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{72}H_{91}FN_8O_{14}S$, MW = 1343.62 g / mol

The product was synthesized from (2*S*,4*R*)-*N*-(2-((*R*)-2-azidopropoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (6.2 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 11.8 mg (88 %, 8.8 μmol).

Appearance: white solid.

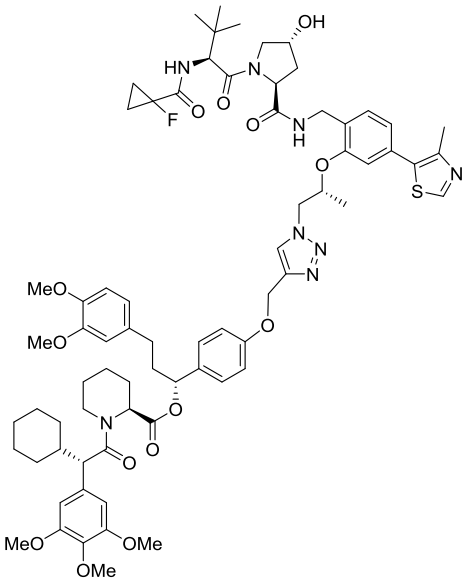
TLC: R_f = 0.15 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 3.0 min]: R_t = 2.2 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{72}H_{91}FN_8O_{14}S$ = 1343.64323; found = 1343.64382.

Lab book number(s): MWa554.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-((1-((*R*)-2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)propyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{72}H_{91}FN_8O_{14}S$, MW = 1343.62 g / mol

The product was synthesized from (2*S*,4*R*)-*N*-(2-(((*R*)-1-azidopropan-2-yl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (6.2 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 12.3 mg (92 %, 9.2 μmol).

Appearance: white solid.

TLC: R_f = 0.15 (DCM:MeOH = 10:1).

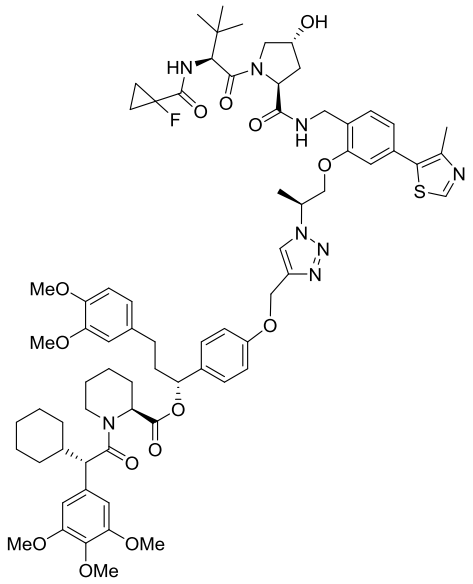
LC-MS: [30-100 % Solvent B, 3.0 min]: R_t = 2.2 min.

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{72}H_{91}FN_8O_{14}S$ = 1343.64323; found = 1343.64367.

Lab book number(s): MWa555.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(4-((1-((*S*)-1-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)propan-2-yl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{72}H_{91}FN_8O_{14}S$, MW = 1343.62 g / mol

The product was synthesized from (2*S*,4*R*)-*N*-(2-((*S*)-2-azidopropoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (6.2 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.4 mg (78 %, 7.8 μmol).

Appearance: white solid.

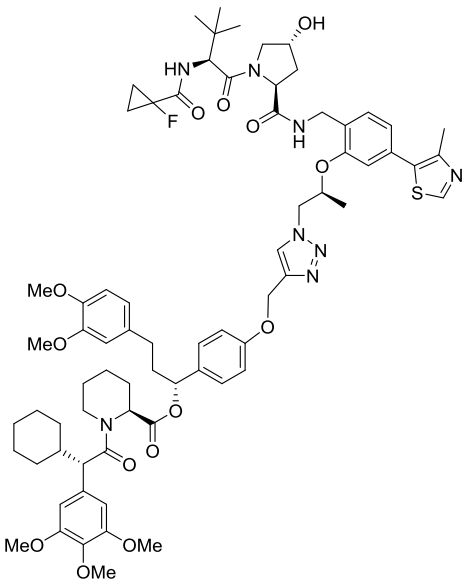
TLC: R_f = 0.15 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 3.0 min]: R_t = 2.2 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{72}H_{91}FN_8O_{14}S$ = 1343.64323; found = 1343.64370.

Lab book number(s): MWa556.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-((1-((*S*)-2-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)propyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{72}H_{91}FN_8O_{14}S$, MW = 1343.62 g / mol

The product was synthesized from (2*S*,4*R*)-*N*-(2-(((*S*)-1-azidopropan-2-yl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (6.2 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 9.0 mg (67 %, 6.7 μmol).

Appearance: white solid.

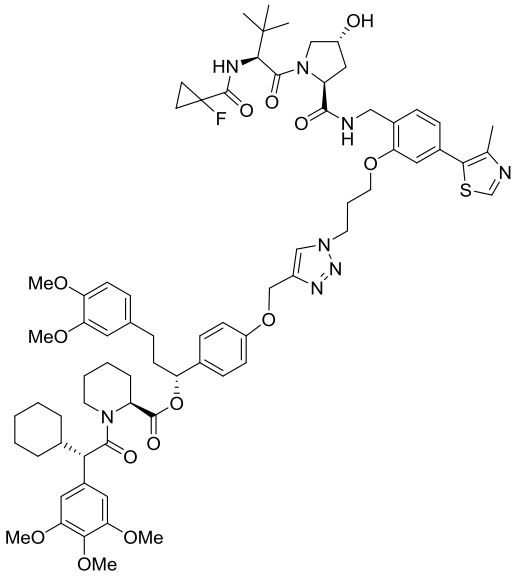
TLC: R_f = 0.15 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 3.0 min]: R_t = 2.2 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{72}H_{91}FN_8O_{14}S$ = 1343.64323; found = 1343.64376.

Lab book number(s): MWa557.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-((1-(3-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)propyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{72}H_{91}FN_8O_{14}S$, MW = 1343.62 g / mol

The product was synthesized from (2*S*,4*R*)-*N*-(2-(3-azidopropoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (6.2 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to

general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.0 mg (75 %, 7.5 μmol).

Appearance: white solid.

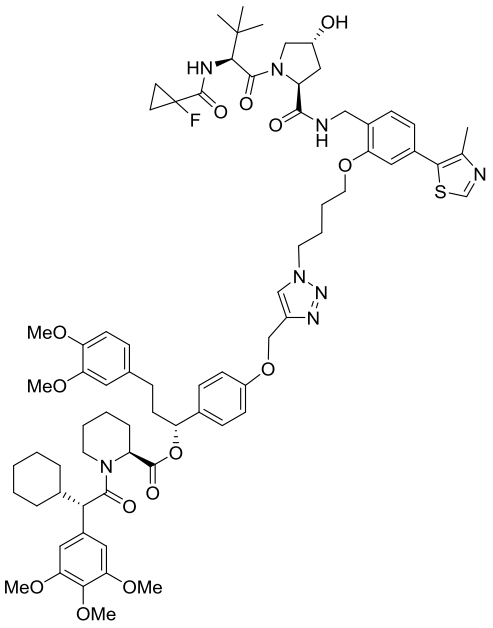
TLC: R_f = 0.15 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 3.0 min]: R_t = 2.2 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{72}H_{91}FN_8O_{14}S$ = 1343.64323; found = 1343.64340.

Lab book number(s): MWa558.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-((1-(4-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)butyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{73}H_{93}FN_8O_{14}S$, MW = 1357.65 g / mol

The product was synthesized from (2*S*,4*R*)-*N*-(2-(4-azidobutoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (6.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.2 mg (75 %, 7.5 μmol).

Appearance: white solid.

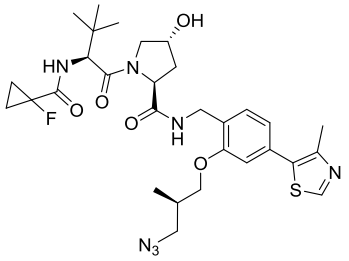
TLC: R_f = 0.16 (DCM:MeOH = 10:1).

LC-MS: [30-100 % Solvent B, 3.0 min]: R_t = 2.2 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{73}H_{93}FN_8O_{14}S$ = 1357.65888; found = 1357.65911.

Lab book number(s): MWa559.

(2*S*,4*R*)-*N*-(2-((*R*)-3-Azido-2-methylpropoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{30}H_{40}FN_7O_5S$, MW = 629.75 g / mol

The product was synthesized from alcohol **7** (53 mg, 100 μmol, 1.0 eq.) and (*R*)-3-azido-2-methylpropyl 4-methylbenzenesulfonate (MZh008, 36 mg, 135 μmol, 1.35 eq) according to general procedure H. The obtained product was purified by flash chromatography.

Yield: 44 mg (70 %, 70 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.95 (s, 9H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.25 – 1.39 (m, 4H), 2.04 – 2.17 (m, 1H), 2.24 – 2.38 (m, 1H), 2.47 – 2.61 (m, 4H), 3.44 – 3.59 (m, 2H), 3.65 (dd, *J* = 11.2, 3.9 Hz, 1H), 3.87 – 4.06 (m, 3H), 4.37 – 4.62 (m, 4H), 4.74 (t, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 1.6 Hz, 1H), 6.97 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.10 (dd, *J* = 8.9, 3.6 Hz, 1H), 7.33 – 7.44 (m, 2H), 8.93 (s, 1H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 13.8, 14.0, 15.0, 15.3, 26.4, 33.9, 35.5, 36.0, 38.8, 54.4, 56.7, 57.6, 58.7, 70.0, 70.3, 79.9, 112.1, 121.9, 127.0, 129.7, 131.3, 132.9, 147.0, 151.6, 156.7, 170.3, 170.7, 171.2.

TLC: R_f = 0.26 (EA).

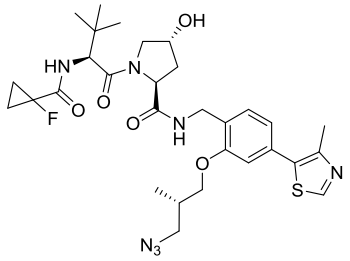
LC-MS: Mass (ESI), calculated = 630.3 $[M+H]^+$, found = 630.2.

[5-100 % Solvent B, 3.0 min]: R_t = 2.0 min.

> 99 % purity (220 nm).

Lab book number(s): MWa605.

(2*S*,4*R*)-*N*-(2-((*S*)-3-Azido-2-methylpropoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{30}H_{40}FN_7O_5S$, MW = 629.75 g / mol

The product was synthesized from alcohol **7** (53 mg, 100 μmol, 1.0 eq.) and (*S*)-3-azido-2-methylpropyl 4-methylbenzenesulfonate (MZh019, 36 mg, 135 μmol, 1.35 eq) according to general procedure H. The obtained product was purified by flash chromatography.

Yield: 45 mg (71 %, 71 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.95 (s, 9H), 1.16 (d, *J* = 6.9 Hz, 3H), 1.23 – 1.44 (m, 4H), 2.04 – 2.17 (m, 1H), 2.25 – 2.40 (m, 1H), 2.48 – 2.61 (m, 4H), 3.46 – 3.55 (m, 2H), 3.65 (dd, *J* = 11.3, 3.9 Hz, 1H), 3.90 – 4.05 (m, 3H), 4.37 – 4.62 (m, 4H), 4.74 (t, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 1.6 Hz, 1H), 6.97 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.10 (dd, *J* = 8.9, 3.6 Hz, 1H), 7.31 – 7.44 (m, 2H), 8.94 (s, 1H).

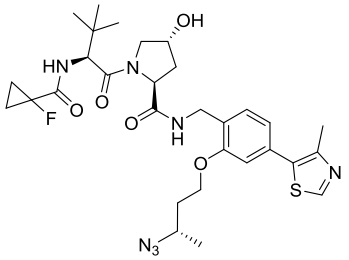
^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 13.8, 13.9, 15.0, 15.3, 26.4, 33.9, 35.5, 36.0, 38.8, 54.4, 56.7, 57.6, 58.7, 70.1, 70.3, 79.9, 112.1, 121.9, 127.0, 129.7, 131.3, 133.0, 147.0, 151.6, 156.7, 170.4, 170.7, 171.2.

TLC: R_f = 0.26 (EA).

LC-MS: Mass (ESI), calculated = 630.3 $[M+H]^+$, found = 630.2.
[5-100 % Solvent B, 3.0 min]: R_t = 2.0 min.
96 % purity (220 nm).

Lab book number(s): MWa606.

(2*S*,4*R*)-*N*-(2-((*S*)-3-Azidobutoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{30}H_{40}FN_7O_5S$, MW = 629.75 g / mol

The product was synthesized from alcohol **7** (53 mg, 100 μmol, 1.0 eq.) and (*S*)-3-azidobutyl 4-methylbenzenesulfonate (MZh034, 36 mg, 135 μmol, 1.35 eq) according to general procedure H. The obtained product was purified by flash chromatography.

Yield: 42 mg (67 %, 67 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.94 (s, 9H), 1.25 – 1.37 (m, 4H), 1.40 (d, *J* = 6.5 Hz, 3H), 1.89 – 2.18 (m, 2H), 2.51 – 2.63 (m, 4H), 3.64 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.89 (ddd, *J* = 9.0, 6.6, 4.7 Hz, 1H), 3.99 (d, *J* = 11.3 Hz, 1H), 4.04 – 4.23 (m, 2H), 4.41 (dd, *J* = 14.9, 5.3 Hz, 1H), 4.48 – 4.59 (m, 3H), 4.74 (t, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 1.6 Hz, 1H), 6.97 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.09 (dd, *J* = 8.9, 3.6 Hz, 1H), 7.36 (dd, *J* = 7.0, 3.7 Hz, 2H), 8.82 (s, 1H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 13.8, 13.9, 15.7, 19.8, 26.4, 35.5, 35.9, 35.9, 38.9, 54.9, 56.6, 57.6, 58.6, 64.9, 70.3, 79.8, 112.1, 121.9, 126.7, 129.7, 131.9, 132.4, 147.8, 151.1, 156.7, 170.3, 170.6, 171.1.

TLC: R_f = 0.26 (EA).

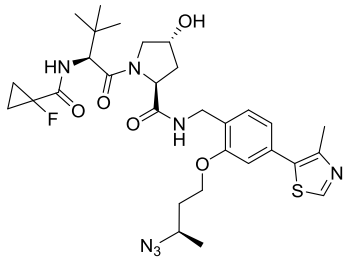
LC-MS: Mass (ESI), calculated = 630.3 $[M+H]^+$, found = 630.2.

[5-100 % Solvent B, 3.0 min]: R_t = 2.0 min.

> 99 % purity (220 nm).

Lab book number(s): MWa607.

(2*S*,4*R*)-*N*-(2-((*R*)-3-Azidobutoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{30}H_{40}FN_7O_5S$, MW = 629.75 g / mol

The product was synthesized from alcohol **7** (53 mg, 100 μmol, 1.0 eq.) and (*R*)-3-azidobutyl 4-methylbenzenesulfonate (MZh033, 36 mg, 135 μmol, 1.35 eq) according to general procedure H. The obtained product was purified by flash chromatography.

Yield: 51 mg (81 %, 81 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 0.95 (s, 9H), 1.21 – 1.36 (m, 4H), 1.38 (d, *J* = 6.5 Hz, 3H), 1.86 – 2.22 (m, 3H), 2.39 – 2.50 (m, 1H), 2.56 (s, 3H), 3.66 (dd, *J* = 11.3, 3.7 Hz, 1H), 3.75 – 3.88 (m, 1H), 3.99 (d, *J* = 11.4 Hz, 1H), 4.06 – 4.15 (m, 2H), 4.41 (dd, *J* = 15.3, 5.5 Hz, 1H), 4.51 (dd, *J* = 15.2, 7.0 Hz, 3H), 4.70 (t, *J* = 7.9 Hz, 1H), 6.85 (d, *J* = 1.6 Hz, 1H), 6.94 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.10 (dd, *J* = 8.8, 3.8 Hz, 1H), 7.36 – 7.45 (m, 2H), 9.21 (s, 1H).

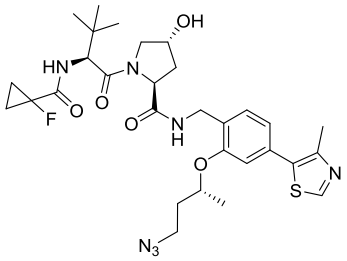
^{13}**C-NMR** (75 MHz, Chloroform-*d*): δ = 13.8, 13.9, 14.3, 19.7, 26.4, 35.5, 35.8, 36.2, 38.9, 54.9, 56.8, 57.8, 59.0, 65.1, 70.3, 79.8, 111.9, 121.9, 127.6, 129.8, 130.0, 134.2, 145.1, 152.7, 156.8, 170.6, 171.2, 171.2.

TLC: R_f = 0.26 (EA).

LC-MS: Mass (ESI), calculated = 630.3 $[M+H]^+$, found = 630.4.
[5-100 % Solvent B, 3.0 min]: R_t = 2.0 min.
93 % purity (220 nm).

Lab book number(s): MWa614.

(2*S*,4*R*)-*N*-(2-(((*R*)-4-Azidobutan-2-yl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{30}H_{40}FN_7O_5S$, MW = 629.75 g / mol

The product was synthesized from alcohol **7** (53 mg, 100 μmol, 1.0 eq.) and (*S*)-4-azidobutan-2-yl 4-methylbenzenesulfonate (MZh040, 36 mg, 135 μmol, 1.35 eq) according to general procedure H. The obtained product was purified by flash chromatography.

Yield: 22 mg (35 %, 35 μmol).

Appearance: white solid.

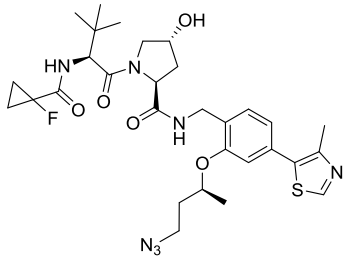
^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.00 (s, 9H), 1.24 – 1.45 (m, 7H), 1.94 (dtd, *J* = 14.3, 7.2, 4.5 Hz, 1H), 2.03 – 2.21 (m, 2H), 2.59 (s, 4H), 3.48 – 3.57 (m, 2H), 3.67 (dd, *J* = 11.4, 3.7 Hz, 1H), 4.05 (d, *J* = 11.4 Hz, 1H), 4.42 – 4.81 (m, 7H), 6.90 – 7.00 (m, 2H), 7.12 (dd, *J* = 8.8, 3.7 Hz, 1H), 7.32 (t, *J* = 6.3 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 9.10 (s, 1H).

TLC: R_f = 0.26 (EA).

LC-MS: Mass (ESI), calculated = 630.3 $[M+H]^+$, found = 630.0.
[5-100 % Solvent B, 3.0 min]: R_t = 1.9 min.
> 99 % purity (220 nm).

Lab book number(s): MWa635.

(2*S*,4*R*)-*N*-(2-(((*S*)-4-Azidobutan-2-yl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



$C_{30}H_{40}FN_7O_5S$, MW = 629.75 g / mol

The product was synthesized from alcohol **7** (53 mg, 100 μmol, 1.0 eq.) and (*R*)-4-azidobutan-2-yl 4-methylbenzenesulfonate (MZh041, 36 mg, 135 μmol, 1.35 eq) according to general procedure H. The obtained product was purified by flash chromatography.

Yield: 25 mg (53 %, 40 μmol).

Appearance: white solid.

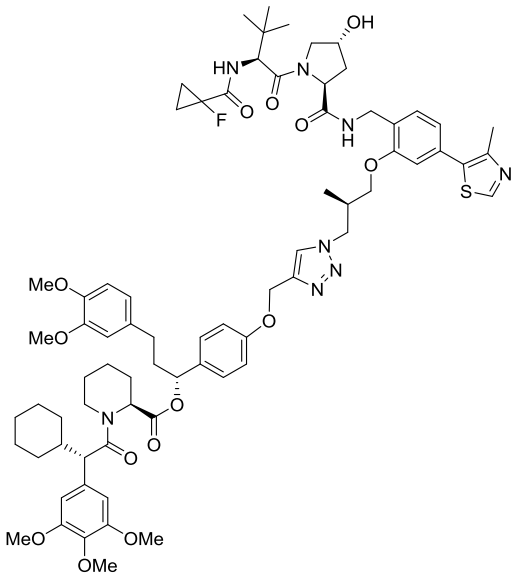
^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 0.95 (s, 9H), 1.27 – 1.43 (m, 7H), 1.90 – 2.02 (m, 1H), 2.05 – 2.19 (m, 2H), 2.46 – 2.60 (m, 4H), 3.46 – 3.71 (m, 3H), 4.02 (d, *J* = 11.4 Hz, 1H), 4.35 – 4.69 (m, 6H), 4.73 (t, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 1.6 Hz, 1H), 6.96 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.11 (dd, *J* = 8.9, 3.6 Hz, 1H), 7.38 (t, *J* = 6.7 Hz, 2H), 9.00 (s, 1H).

TLC: R_f = 0.26 (EA).

LC-MS: Mass (ESI), calculated = 630.3 $[M+H]^+$, found = 630.0.
[5-100 % Solvent B, 3.0 min]: R_t = 2.0 min.
87 % purity (220 nm).

Lab book number(s): MWa636.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-((1-((*R*)-3-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)-2-methylpropyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{73}H_{93}FN_8O_{14}S$, MW = 1357.65 g / mol

The product was synthesized from (2*S*,4*R*)-*N*-(2-((*R*)-3-Azido-2-methylpropoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (6.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 9.3 mg (69 %, 6.9 μmol).

Appearance: white solid.

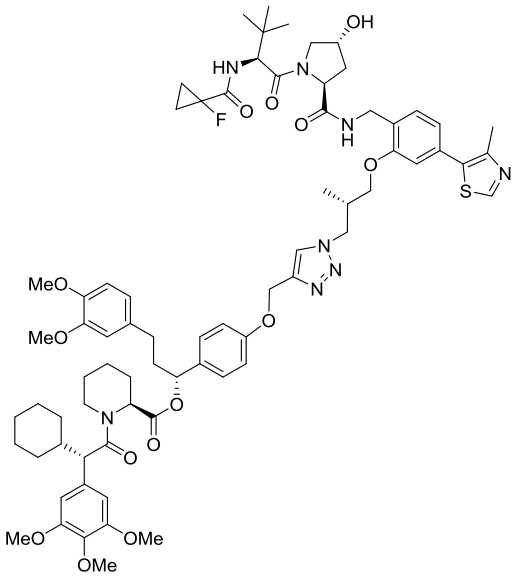
TLC: R_f = 0.15 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.5 min.
[50-100 % Solvent B, 3.0 min]: R_t = 2.0 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{73}H_{93}FN_8O_{14}S$ = 1357.65888; found = 1357.66055.

Lab book number(s): MWa610.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-((1-((*S*)-3-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)-2-methylpropyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{73}H_{93}FN_8O_{14}S$, MW = 1357.65 g / mol

The product was synthesized from (2*S*,4*R*)-*N*-(2-((*S*)-3-Azido-2-methylpropoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (6.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 9.5 mg (71 %, 7.1 μmol).

Appearance: white solid.

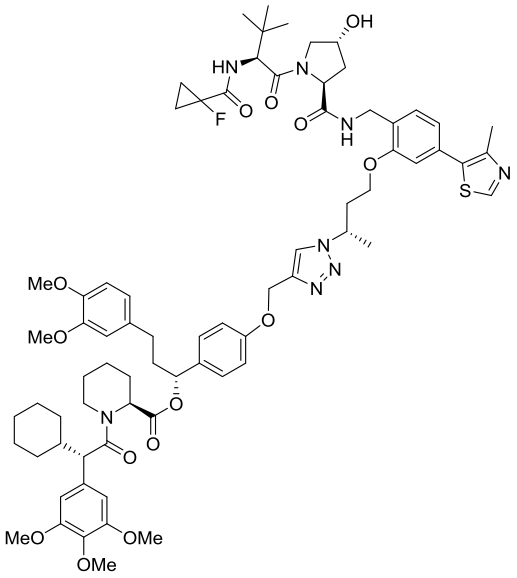
TLC: R_f = 0.15 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.5 min.
[50-100 % Solvent B, 3.0 min]: R_t = 2.0 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{73}H_{93}FN_8O_{14}S$ = 1357.65888; found = 1357.65905.

Lab book number(s): MWa611.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-((1-((*S*)-4-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)butan-2-yl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{73}H_{93}FN_8O_{14}S$, MW = 1357.65 g / mol

The product was synthesized from (2*S*,4*R*)-*N*-(2-((*S*)-3-Azidobutoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (6.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 8.2 mg (61 %, 6.1 μmol).

Appearance: white solid.

TLC: R_f = 0.15 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.5 min.

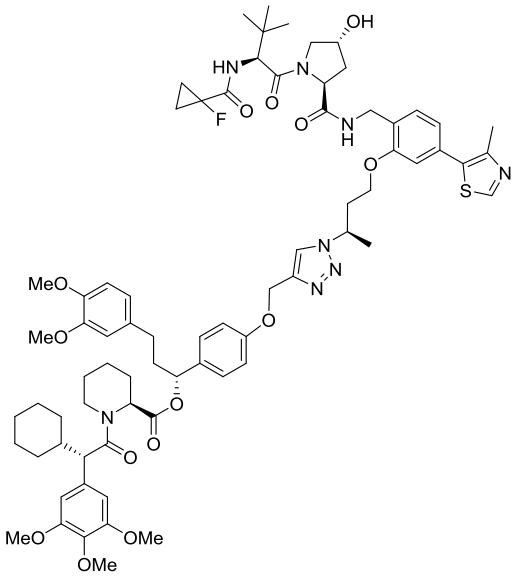
[50-100 % Solvent B, 3.0 min]: R_t = 1.9 min.

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{73}H_{93}FN_8O_{14}S$ = 1357.65888; found = 1357.65911.

Lab book number(s): MWa612.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-((1-((*R*)-4-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)butan-2-yl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{73}H_{93}FN_8O_{14}S$, MW = 1357.65 g / mol

The product was synthesized from (2*S*,4*R*)-*N*-(2-((*R*)-3-Azidobutoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide(6.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 10.0 mg (75 %, 7.5 μmol).

Appearance: white solid.

TLC: R_f = 0.15(DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.5 min.

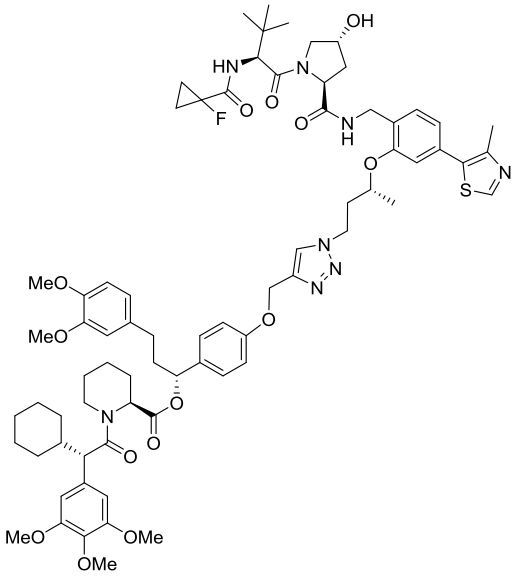
[50-100 % Solvent B, 3.0 min]: R_t = 2.0 min.

> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{73}H_{93}FN_8O_{14}S$ = 1357.65888; found = 1357.65816.

Lab book number(s): MWa648.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-((1-((*R*)-3-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)butyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{73}H_{93}FN_8O_{14}S$, MW = 1357.65 g / mol

The product was synthesized from (2*S*,4*R*)-*N*-(2-(((*R*)-4-Azidobutan-2-yl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (6.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 7.2 mg (54 %, 5.4 μmol).

Appearance: white solid.

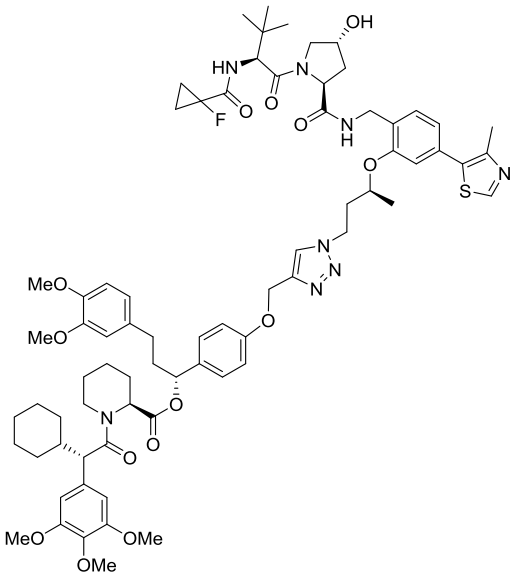
TLC: R_f = 0.15 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.5 min.
[50-100 % Solvent B, 3.0 min]: R_t = 2.0 min.
98 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{73}H_{93}FN_8O_{14}S$ = 1357.65888; found = 1357.65817.

Lab book number(s): MWa649.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-((1-((*S*)-3-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)butyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{73}H_{93}FN_8O_{14}S$, MW = 1357.65 g / mol

The product was synthesized from (2*S*,4*R*)-*N*-(2-(((*S*)-4-Azidobutan-2-yl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (6.3 mg, 10.0 μmol, 1.0 eq.) and alkyne **A14** (7.3 mg, 10.0 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 7.4 mg (55 %, 5.5 μmol).

Appearance: white solid.

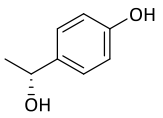
TLC: R_f = 0.15 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.5 min.
[50-100 % Solvent B, 3.0 min]: R_t = 2.0 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{73}H_{93}FN_8O_{14}S$ = 1357.65888; found = 1357.65878.

Lab book number(s): MWa650.

(*R*)-4-(1-Hydroxyethyl)phenol



$C_8H_{10}O_2$, MW = 138.17 g / mol

1-(4-Hydroxyphenyl)ethan-1-one (200 mg, 1.5 mmol, 1.0 eq.) was dissolved in *iso*-propanole (12 mL) and degassed by argon. $RuCl_2$[(S)-dm-segphos®][(S)-daipen] (36 mg, 0.03 mmol, 0.02 eq.) was added and the mixture was sparged with H_2. Potassium *tert*-butoxide (494 mg, 4.4 mmol, 3.0 eq.) was added and the mixture was stirred for 4 d at room temperature. The mixture was concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 94 mg (46 %, 680 μmol).

Appearance: white solid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.29 (d, J = 6.4 Hz, 3H), 4.62 (q, J = 6.4 Hz, 1H), 4.96 (s, 1H), 6.68 – 6.75 (m, 2H), 7.11 – 7.17 (m, 2H), 9.20 (s, 1H).

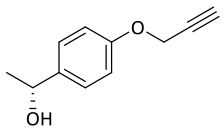
^{13}C-NMR (75 MHz, DMSO-d_6): δ = 26.4, 68.3, 115.1, 126.9, 138.1, 156.4.

TLC: R_f = 0.10 (DCM:MeOH = 20:1).

LC-MS: Mass (ESI), calculated = 139.1 $[M+H]^+$, found = 120.8.
[5-100 % Solvent B, 3.0 min]: R_t = 1.0 min.
99 % purity (220 nm).

Lab book number(s): MWa626.

(*R*)-1-(4-(Prop-2-yn-1-yloxy)phenyl)ethan-1-ol



$C_{11}H_{12}O_2$, MW = 176.22 g / mol

(*R*)-4-(1-Hydroxyethyl)phenol (94 mg, 680 μmol, 1.0 eq.), 3-bromoprop-1-yne (97 mg, 816 μmol, 1.2 eq.) and potassium carbonate (940 mg, 6800 μmol, 10.0 eq.) were stirred in acetone (4 mL) for 4 d at room temperature. The mixture was filtered and concentrated under reduced pressure. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 41 mg (36 %, 232 μmol).

Appearance: white solid.

^{1}**H-NMR** (300 MHz, Chloroform-*d*): δ = 1.47 (d, J = 6.5 Hz, 3H), 1.93 (s, 1H), 2.52 (t, J = 2.4 Hz, 1H), 4.68 (d, J = 2.4 Hz, 2H), 4.85 (q, J = 6.5 Hz, 1H), 6.92 – 6.99 (m, 2H), 7.28 – 7.35 (m, 2H).

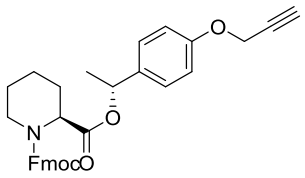
^{13}**C-NMR** (75 MHz, Chloroform-*d*): δ = 25.1, 56.0, 70.0, 75.6, 78.7, 115.0, 126.8, 139.1, 157.0.

TLC: R_f = 0.41 (CH:EA = 1:1).

LC-MS: Mass (ESI), calculated = 159.1 $[M+H-H_2O]^+$, found = 159.4.
[5-100 % Solvent B, 3.0 min]: R_t = 1.6 min.
99 % purity (220 nm).

Lab book number(s): MWa631.

1-((9H-Fluoren-9-yl)methyl) 2-((*R*)-1-(4-(prop-2-yn-1-yloxy)phenyl)ethyl) (*S*)-piperidine-1,2-dicarboxylate



$C_{32}H_{31}NO_5$, MW = 509.60 g / mol

(*S*)-1-(((9H-Fluoren-9-yl)methoxy)carbonyl)piperidine-2-carboxylic acid (82 mg, 232 μmol, 1.0 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (53 mg, 278 μmol, 1.2 eq.) and 4-dimethylaminopyridine (8.6 mg, 70 μmol, 0.3 eq.) were cooled to 0 °C under argon. DCM (dry, 4 mL) and (*R*)-1-(4-(prop-2-yn-1-yloxy)phenyl)ethan-1-ol (41 mg, 232 μmol, 1.0 eq.) were added and the mixture was stirred for 15 min at 0 °C followed by 2 h at room temperature. The solution was concentrated under reduced pressure. The obtained product was purified by flash chromatography.

Yield: 70 mg (59 %, 137 μmol).

Appearance: white foam.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 1.15 – 1.36 (m, 1H), 1.44 – 1.61 (m, 4H), 1.65 – 1.79 (m, 3H), 2.32 (t, *J* = 10.4 Hz, 1H), 2.47 – 2.58 (m, 1H), 2.91 – 3.25 (m, 1H), 4.03 – 4.56 (m, 4H), 4.57 – 4.72 (m, 2H), 4.93 (dd, *J* = 46.8, 5.4 Hz, 1H), 5.90 – 6.01 (m, 1H), 6.84 – 7.03 (m, 2H), 7.20 – 7.49 (m, 6H), 7.59 (dd, *J* = 32.1, 7.4 Hz, 2H), 7.73 – 7.85 (m, 2H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ = 20.7, 22.0, 24.8, 26.9, 42.0, 47.3, 55.8, 67.7, 72.9, 73.1, 75.6, 78.5, 114.8, 114.9, 120.0, 125.0, 125.2, 127.1, 127.6, 127.7, 134.2, 141.3, 143.9, 144.2, 157.3, 170.9.

TLC: R_f = 0.55 (CH:EA = 1:1).

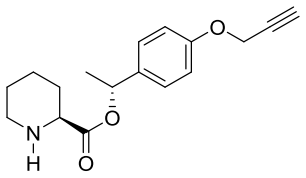
LC-MS: Mass (ESI), calculated = 532.2 $[M+Na]^+$, found = 532.0.

[5-100 % Solvent B, 3.0 min]: R_t = 2.6 min.

> 99 % purity (220 nm).

Lab book number(s): MWa653.

(*R*)-1-(4-(Prop-2-yn-1-yloxy)phenyl)ethyl (*S*)-piperidine-2-carboxylate



$C_{17}H_{21}NO_3$, MW = 437.54 g / mol

1-((9H-Fluoren-9-yl)methyl) 2-((*R*)-1-(4-(prop-2-yn-1-yloxy)phenyl)ethyl) (*S*)-piperidine-1,2-dicarboxylate (40 mg, 78 μmol, 1.0 eq.) and 4-methylpiperidine (38 μL, 322 μmol, 4.1 eq) were dissolved in DCM (300 μL) and the mixture was stirred for 2 h at room temperature. The obtained product was purified by by flash chromatography.

Yield: 22 mg (quant., 78 μmol).

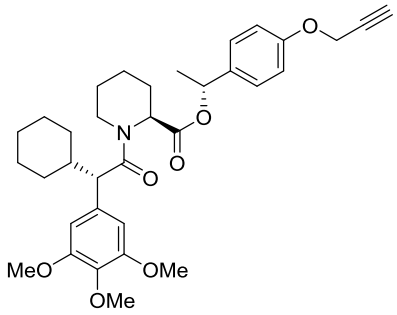
Appearance: yellow oil.

TLC: R_f = 0.26 (CH:EA = 1:1, 3 % TEA).

LC-MS: Mass (ESI), calculated = 288.2 $[M+H]^+$, found = 288.0.
[5-100 % Solvent B, 3.0 min]: R_t = 1.5 min.
98 % purity (220 nm).

Lab book number(s): MWa654.

(*R*)-1-(4-(Prop-2-yn-1-yloxy)phenyl)ethyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{34}H_{43}NO_7$, MW = 577.72 g / mol

The product was synthesized from (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylic acid (VBu308, 24 mg, 78 μmol, 1.0 eq.) and amine **203** (5.8 mg, 10 μmol, 1.0 eq.) according to general procedure I. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 33 mg (73 %, 57 μmol).

Appearance: white solid.

^{1}**H-NMR** (500 MHz, Chloroform-*d*): δ = 0.74 (q, *J* = 13.8, 12.8 Hz, 1H), 1.03 – 1.74 (m, 15H), 1.85 (d, *J* = 12.7 Hz, 1H), 2.00 – 2.31 (m, 2H), 2.47 – 2.57 (m, 1H), 2.62 – 3.10 (m, 1H), 3.39 (dd, *J* = 15.8, 9.7 Hz, 1H), 3.74 – 3.88 (m, 9H), 3.97 (dd, *J* = 32.2, 12.8 Hz, 1H), 4.63 – 4.70 (m, 2H), 5.28 – 5.49 (m, 1H), 5.69 – 6.03 (m, 1H), 6.38 – 6.56 (m, 3H), 6.77 – 6.87 (m, 2H), 6.95 – 7.00 (m, 1H), 7.32 (t, *J* = 7.2 Hz, 1H).

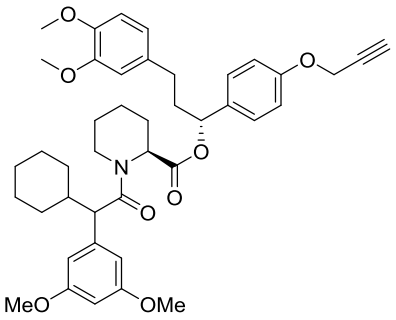
^{13}**C-NMR** (126 MHz, Chloroform-*d*): δ = 20.9, 22.0, 25.6, 26.1, 26.2, 26.3, 26.6, 26.8, 30.7, 32.8, 41.3, 44.0, 52.5, 55.9, 56.2, 60.9, 72.8, 75.6, 78.6, 105.8, 114.7, 127.4, 133.5, 134.4, 137.0, 153.3, 157.3, 170.2, 173.0.

TLC: R_f = 0.26 (CH:EA = 2:1).

LC-MS: Mass (ESI), calculated = 578.3 $[M+H]^+$, found = 578.0.
[5-100 % Solvent B, 3.0 min]: R_t = 2.5 min.
> 99 % purity (220 nm).

Lab book number(s): MWa655.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-(prop-2-yn-1-yloxy)phenyl)propyl (2*S*)-1-(2-cyclohexyl-2-(3,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{42}H_{51}NO_8$, MW = 697.87 g / mol

The product was synthesized from 2-cyclohexyl-2-(3,5-dimethoxyphenyl)acetic acid (FKN735, 6.4 mg, 23 μmol, 1.0 eq.) and amine **94** (10 mg, 23 μmol, 1.0 eq.) according to general procedure I. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: D1: 5 mg (31 %, 7.2 μmol).
D2: 4 mg (25 %, 5.7 μmol).

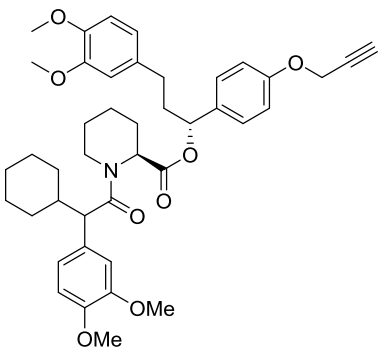
Appearance: white solid.

TLC: R_f = 0.34 (CH:EA = 2:1).

LC-MS: D1: Mass (ESI), calculated = 720.4 $[M+Na]^+$, found = 720.0.
[5-100 % Solvent B, 3.0 min]: R_t = 2.5 min.
> 99 % purity.
D2: Mass (ESI), calculated = 720.4 $[M+Na]^+$, found = 720.0.
[5-100 % Solvent B, 3.0 min]: R_t = 2.5 min.
> 99 % purity (220 nm).

Lab book number(s): MWa657.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-(prop-2-yn-1-yloxy)phenyl)propyl (2*S*)-1-(2-cyclohexyl-2-(3,4-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{42}H_{51}NO_8$, MW = 697.87 g / mol

The product was synthesized from 2-cyclohexyl-2-(3,4-dimethoxyphenyl)acetic acid (FKN029, 6.4 mg, 23 μmol, 1.0 eq.) and amine **94** (10 mg, 23 μmol, 1.0 eq.) according to general procedure I. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: D1: 4 mg (25 %, 5.7 μmol).
D2: 5 mg (31 %, 7.2 μmol).

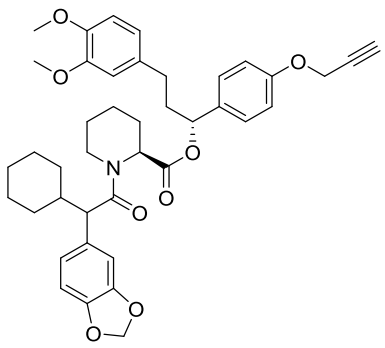
Appearance: white solid.

TLC: R_f = 0.35 (CH:EA = 2:1).

LC-MS: D1: Mass (ESI), calculated = 720.4 $[M+Na]^+$, found = 720.0.
[5-100 % Solvent B, 3.0 min]: R_t = 2.5 min.
> 99 % purity (220 nm).
D2: Mass (ESI), calculated = 720.4 $[M+Na]^+$, found = 720.0.
[5-100 % Solvent B, 3.0 min]: R_t = 2.5 min.
> 99 % purity (220 nm).

Lab book number(s): MWa658.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-(prop-2-yn-1-yloxy)phenyl)propyl (2*S*)-1-(2-(benzo[d][1,3]dioxol-5-yl)-2-cyclohexylacetyl)piperidine-2-carboxylate



$C_{41}H_{47}NO_8$, MW = 681.84.87 g / mol

The product was synthesized from 2-(benzo[d][1,3]dioxol-5-yl)-2-cyclohexylacetic acid (FKN224, 6.0 mg, 23 μmol, 1.0 eq.) and amine **94** (10 mg, 23 μmol, 1.0 eq.) according to general procedure I. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: D1: 5 mg (32 %, 7.3 μmol).
D2: 3 mg (19 %, 4.4 μmol).

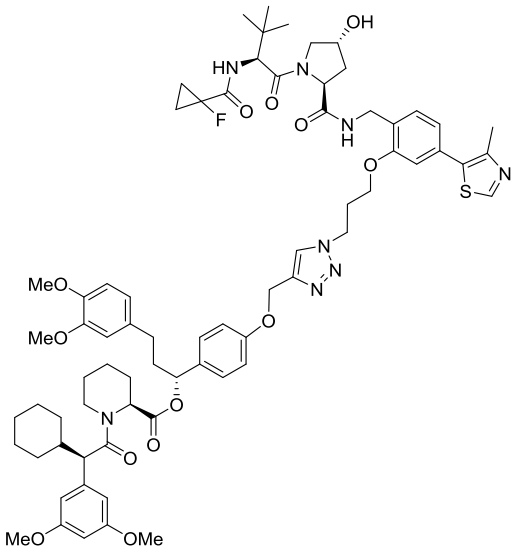
Appearance: white solid.

TLC: R_f = 0.33 (CH:EA = 2:1).

LC-MS: D1: Mass (ESI), calculated = 682.3 $[M+Na]^+$, found = 682.0.
[5-100 % Solvent B, 3.0 min]: R_t = 2.5 min.
> 99 % purity (220 nm).
D2: Mass (ESI), calculated = 682.3 $[M+Na]^+$, found = 682.0.
[5-100 % Solvent B, 3.0 min]: R_t = 2.6 min.
> 99 % purity (220 nm).

Lab book number(s): MWa659.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-((1-(3-(2-(((2*S*,4*R*)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)propyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (*S*)-1-((*R*)-2-cyclohexyl-2-(3,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{71}H_{89}FN_8O_{13}S$, MW = 1313.59 g / mol

The product was synthesized from (2*S*,4*R*)-*N*-(2-(3-azidopropoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (4.4 mg, 7.2 μmol, 1.0 eq.) and alkyne **197_D2** (5.0 mg, 7.2 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 5.0 mg (53 %, 3.8 μmol).

Appearance: white solid.

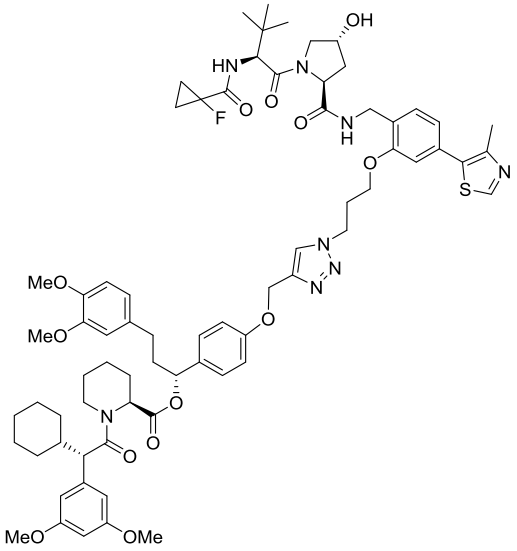
TLC: R_f = 0.16 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.5 min.
93 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{71}H_{89}FN_8O_{13}S$ = 1313.63266; found = 1313.63350.

Lab book number(s): MWa660.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-((1-(3-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)propyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,5-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{71}H_{89}FN_8O_{13}S$, MW = 1313.59 g / mol

The product was synthesized from (2*S*,4*R*)-*N*-(2-(3-azidopropoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (3.5 mg, 5.7 μmol, 1.0 eq.) and alkyne **197_D1** (4.0 mg, 5.7 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 3.0 mg (40 %, 2.3 μmol).

Appearance: white solid.

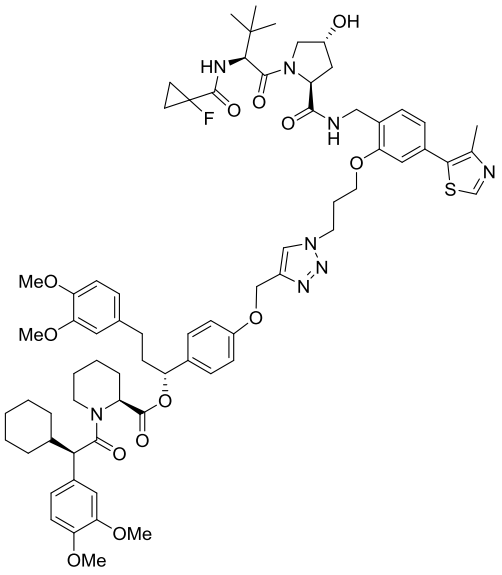
TLC: R_f = 0.16 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.5 min.
91 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{71}H_{89}FN_8O_{13}S$ = 1313.63266; found = 1313.63397.

Lab book number(s): MWa661.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-((1-(3-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)propyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (*S*)-1-((*R*)-2-cyclohexyl-2-(3,4-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{71}H_{89}FN_8O_{13}S$, MW = 1313.59 g / mol

The product was synthesized from (2*S*,4*R*)-*N*-(2-(3-azidopropoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (3.5 mg, 5.7 μmol, 1.0 eq.) and alkyne **198_D2** (4.0 mg, 5.7 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 6.0 mg (80 %, 4.6 μmol).

Appearance: white solid.

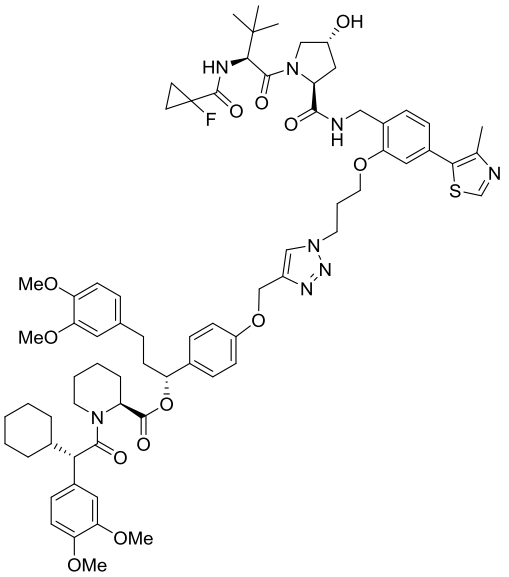
TLC: R_f = 0.17 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.4 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{71}H_{89}FN_8O_{13}S$ = 1313.63266; found = 1313.63361.

Lab book number(s): MWa662.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-((1-(3-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)propyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4-dimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{71}H_{89}FN_8O_{13}S$, MW = 1313.59 g / mol

The product was synthesized from (2*S*,4*R*)-*N*-(2-(3-azidopropoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (4.4 mg, 7.2 μmol, 1.0 eq.) and alkyne **198_D1** (5.0 mg, 7.2 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 6.0 mg (64 %, 4.6 μmol).

Appearance: white solid.

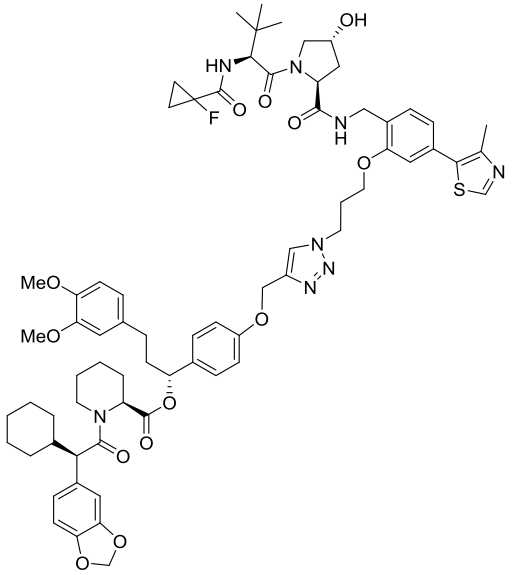
TLC: R_f = 0.17 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.4 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{71}H_{89}FN_8O_{13}S$ = 1313.63266; found = 1313.63295.

Lab book number(s): MWa663.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-((1-(3-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)propyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (*S*)-1-((*R*)-2-(benzo[d][1,3]dioxol-5-yl)-2-cyclohexylacetyl)piperidine-2-carboxylate



$C_{70}H_{85}FN_8O_{13}S$, MW = 1297.55 g / mol

The product was synthesized from (2*S*,4*R*)-*N*-(2-(3-azidopropoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (4.5 mg, 7.3 μmol, 1.0 eq.) and alkyne **199_D2** (5.0 mg, 7.3 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 7.0 mg (74 %, 5.4 μmol).

Appearance: white solid.

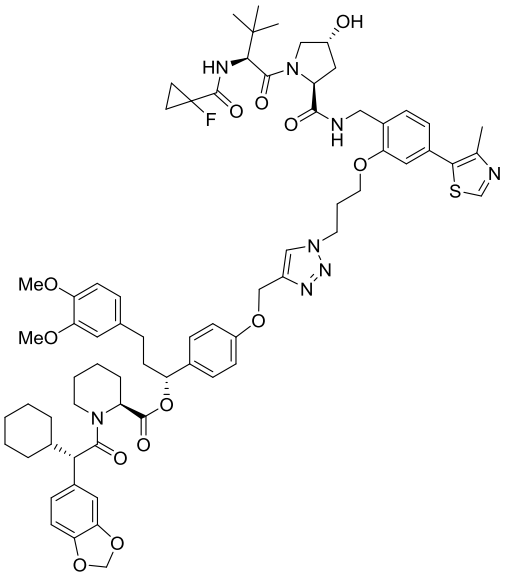
TLC: R_f = 0.16 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.5 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{70}H_{85}FN_8O_{13}S$ = 1297.60136; found = 1297.60209.

Lab book number(s): MWa664.

(*R*)-3-(3,4-Dimethoxyphenyl)-1-(4-((1-(3-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)propyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl (*S*)-1-((*S*)-2-(benzo[d][1,3]dioxol-5-yl)-2-cyclohexylacetyl)piperidine-2-carboxylate



$C_{70}H_{85}FN_8O_{13}S$, MW = 1297.55 g / mol

The product was synthesized from (2*S*,4*R*)-*N*-(2-(3-azidopropoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (2.7 mg, 4.4 μmol, 1.0 eq.) and alkyne **199_D1** (3.0 mg, 4.4 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 4.0 mg (70 %, 3.1 μmol).

Appearance: white solid.

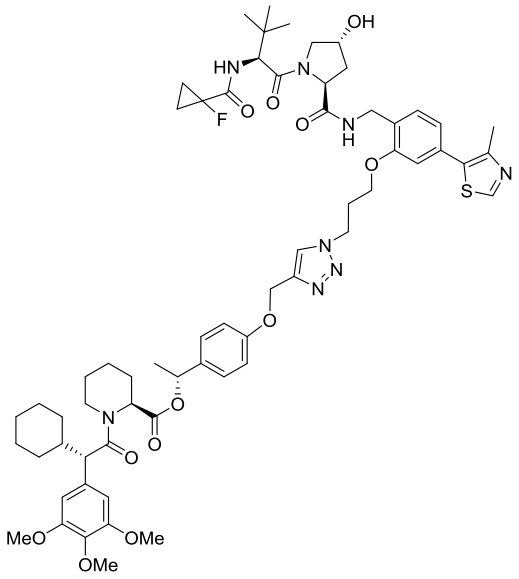
TLC: R_f = 0.16 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.5 min.
> 99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{70}H_{85}FN_8O_{13}S$ = 1297.60136; found = 1297.60116.

Lab book number(s): MWa665.

(*R*)-1-(4-((1-(3-(2-(((2*S*,4*R*)-1-((*S*)-2-(1-Fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)methyl)-5-(4-methylthiazol-5-yl)phenoxy)propyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)ethyl (*S*)-1-((*S*)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate



$C_{63}H_{81}FN_8O_{12}S$, MW = 1193.44 g / mol

The product was synthesized from (2*S*,4*R*)-*N*-(2-(3-azidopropoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (6.2 mg, 10 μmol, 1.0 eq.) and alkyne **204** (5.8 mg, 10 μmol, 1.0 eq.) according to general procedure A. The obtained product was purified by preparative HPLC. The product was dried by lyophilisation.

Yield: 8.1 mg (68 %, 6.8 μmol).

Appearance: white solid.

TLC: R_f = 0.18 (DCM:MeOH = 10:1).

LC-MS: [5-100 % Solvent B, 3.0 min]: R_t = 2.4 min.
99 % purity (220 nm).

HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{63}H_{81}FN_8O_{12}S$ = 1193.57515; found = 1193.57591.

Lab book number(s): MWa666.

8. List of abbreviations

Abbreviation	Meaning
ACN	Acetonitrile
ATP	Adenosine triphosphate
AMP	Adenosine monophosphate
CH	Cyclohexane
CRBN	Cereblon
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DDQ	2,3-Dichlor-5,6-dicyano-1,4-benzochinon
DIBAL-H	Diisobutylaluminiumhydrid
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
EA	Ethyl acetate
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
FKBP	FK506 binding protein
FP	Fluorescence Polarization
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GR	glucocorticoid receptor
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HEK293T	Human embryonic kidney 293 cells with mutated SV40 large T antigen
HOBT	Hydroxybenzotriazole
HSP	Heat shock protein
HTRF	Homogeneous Time Resolved Fluorescence
HPLC	High-performance liquid chromatography
IAPs	Apoptosis proteins
K_D	Dissociation constant
LAH	Lithium aluminium hydride
LC	Liquid chromatogrphy
LDA	Lithiumdiisopropylamid
L-E3LL	Linker-E3-ligase-ligand

LG	Leaving group
LHMDS	Lithiumhexamethyldisilazid
MDM2	Mouse double minute 2
MS	Mass spectrometry
NanoBRET	Nano-bioluminescence resonance energy transfer
n.d.	Not detected
NF-*k*B	Nuclear Factor 'Kappa-Light-Chain-Enhancer' of Activated B-Cells
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
opc	one-point cooperativity value
PG	Protecting group
PHLPP	Leucine-rich repeat protein phosphatases
PMB	*p*-Methoxybenzyl
POI	Protein of interest
Pom	Pomalidomide
PPIase	Peptidylprolyl isomerase
PROTAC	Proteolysis targeting chimera
q	Quartet
rt	room temperature
s	Singlet
sat.	Saturated
SHRs	Steroid hormone receptors
t	Triplet
TBAF	Tetra-*N*-butylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMS	Trimethylsilyl
TPD	Targeted protein degradation
TPR	Tetratricopeptide repeat
UPS	Ubiquitin proteasome system
VCB	VHL-elongin C-elongin B complex
VHL	Von Hippel-Lindau

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10. Spectra of key compounds

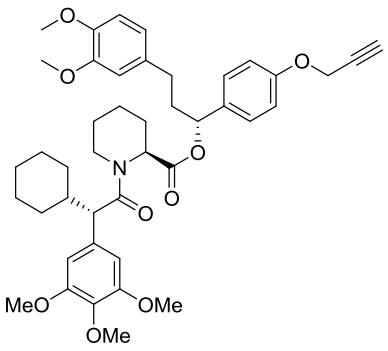

Figure 33: Structure of MWa406 (**A14**; **95**).

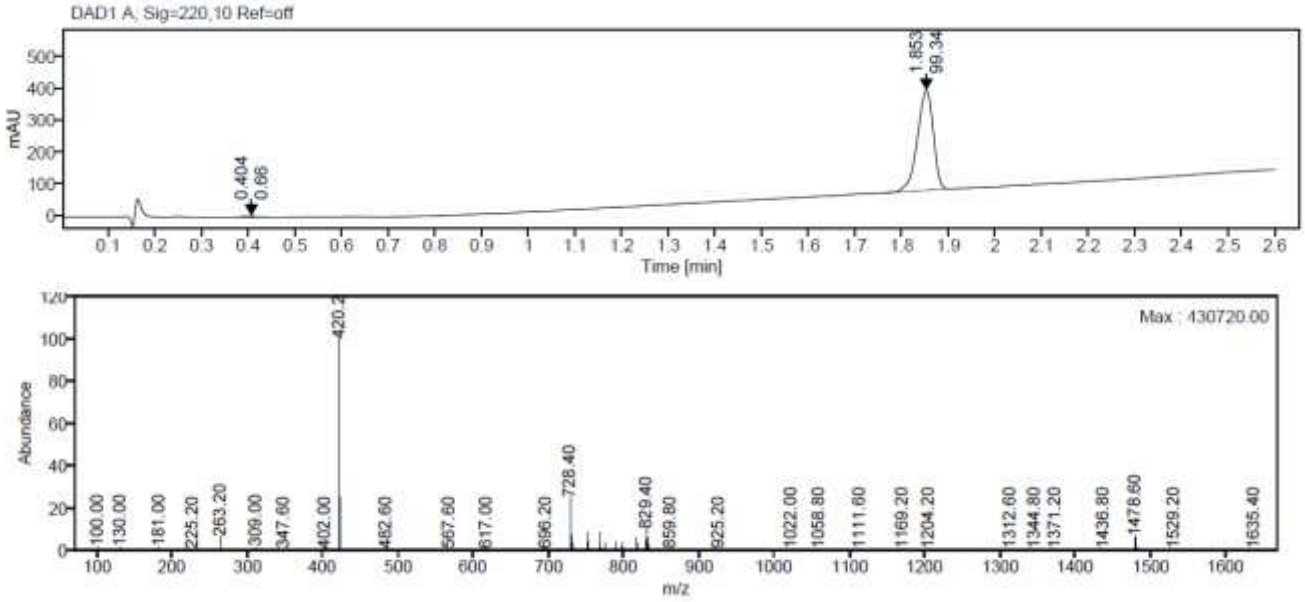

Figure 34: LC-MS of MWa406 (**A14**; **95**; 50-100 % solvent B).

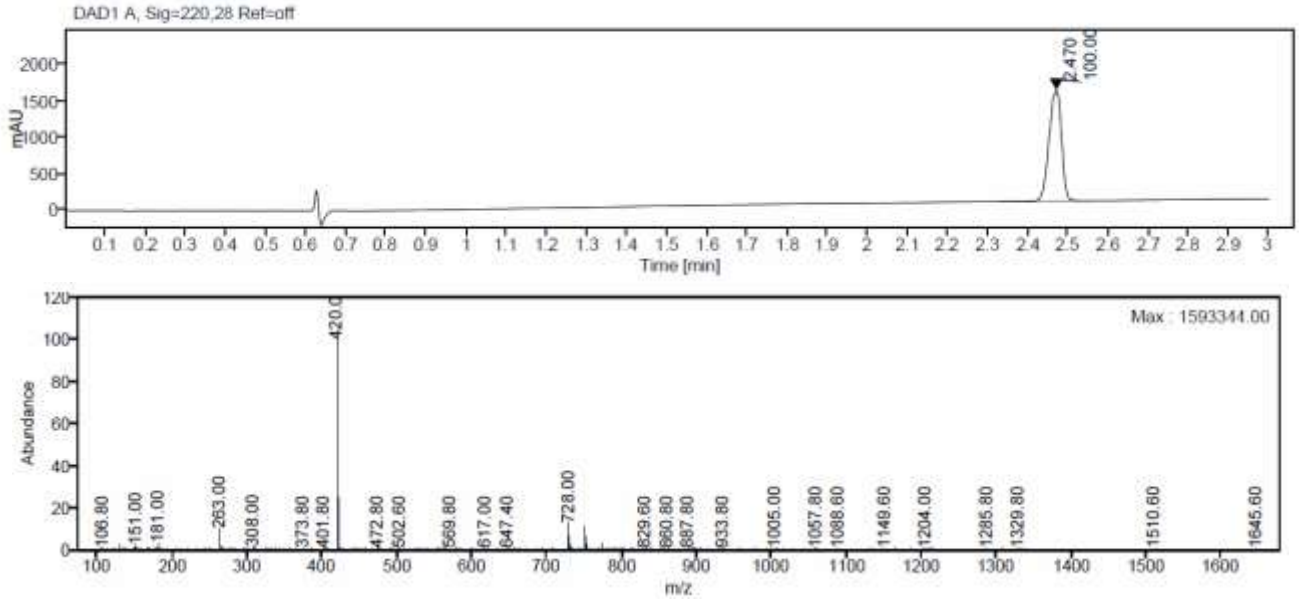

Figure 35: LC-MS of MWa647 (**A14**; **95**; 5-100 % solvent B).

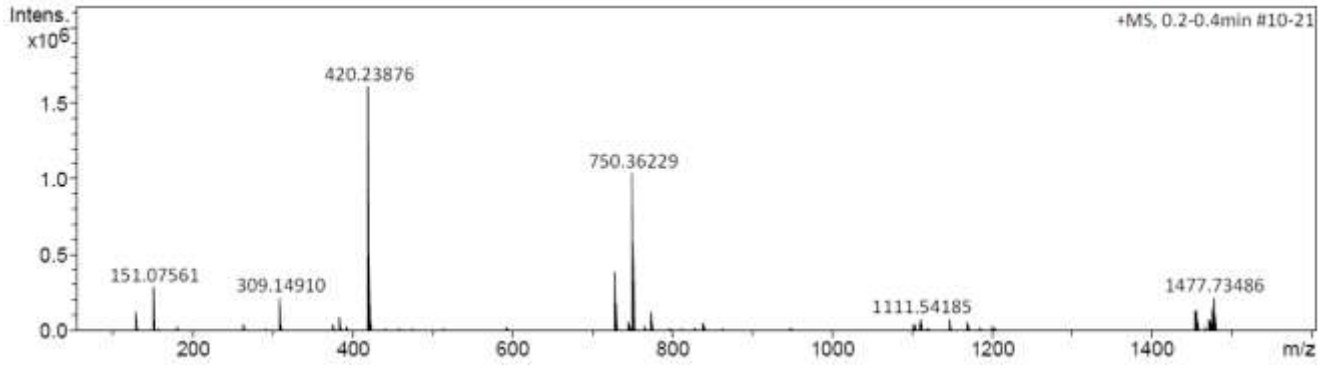

Figure 36: HRMS of MWa406 (**A14**; **95**).

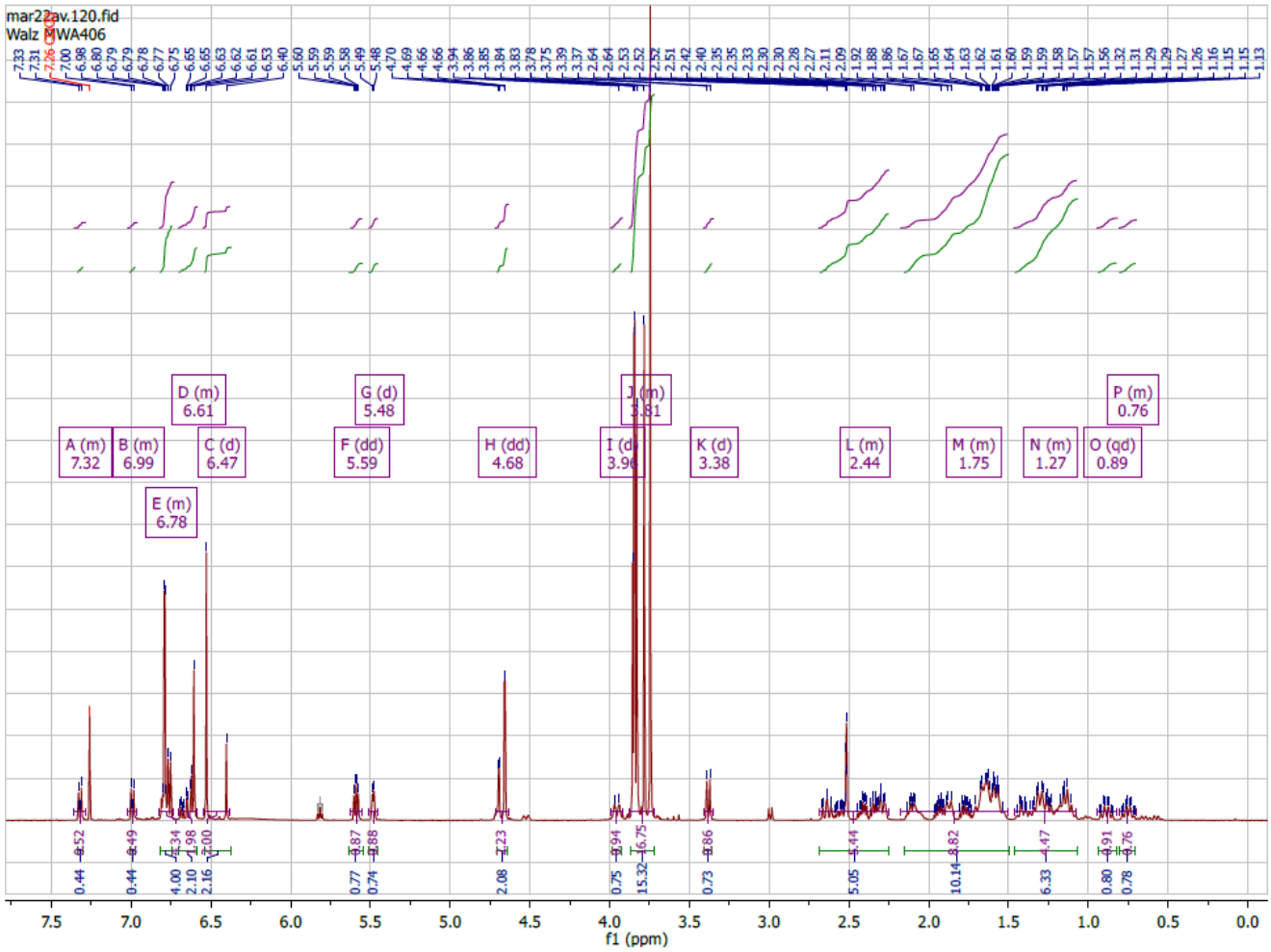

Figure 37: ^{1}H-NMR of MWa406 (**A14**; **95**).

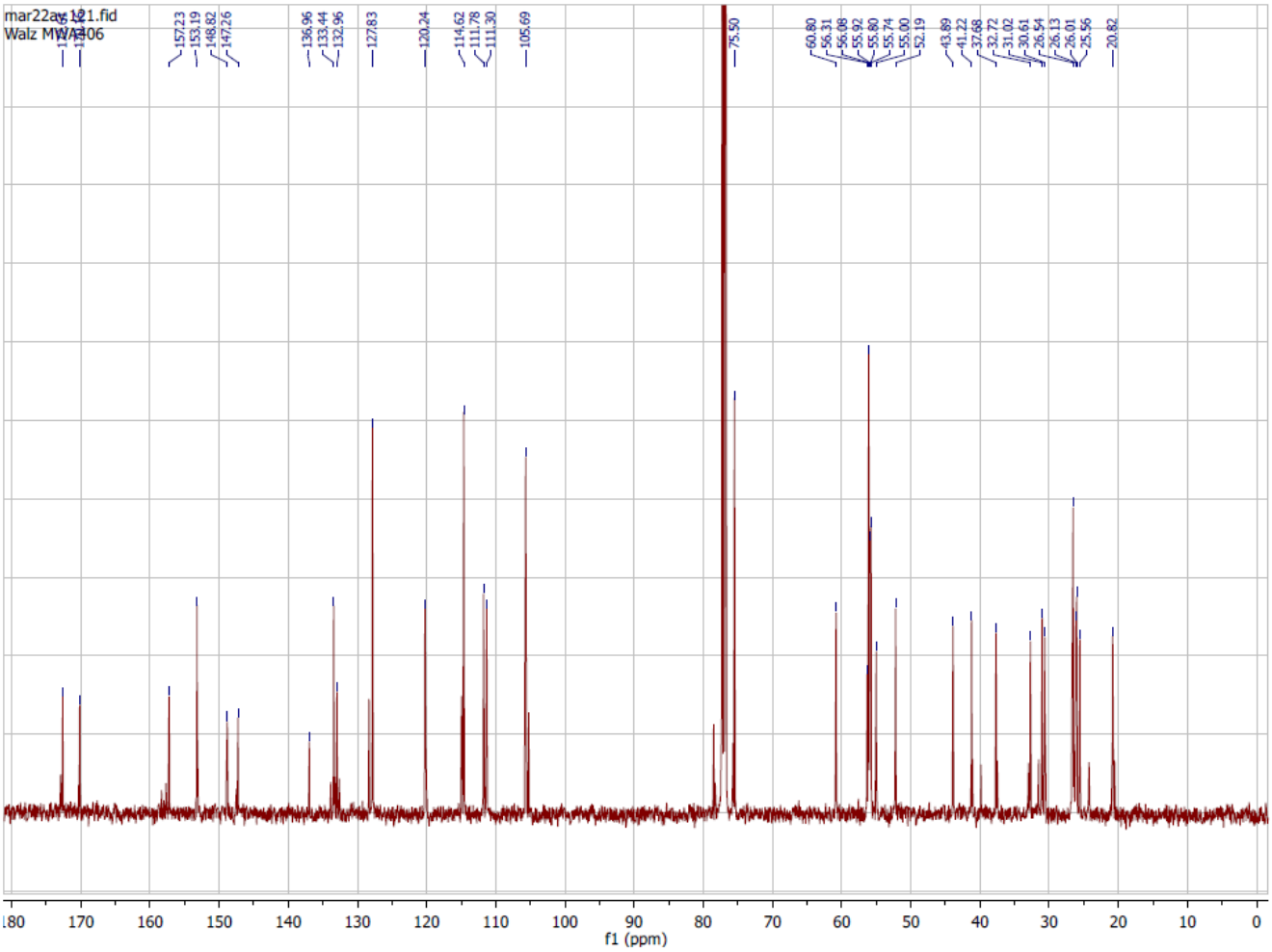

Figure 38: ^{13}C-NMR of MWa406 (**A14**; **95**).

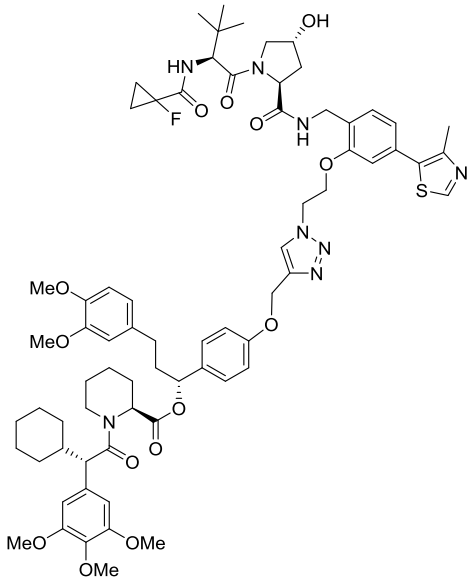

Figure 39: Structure of of MWa421 (**107a**).

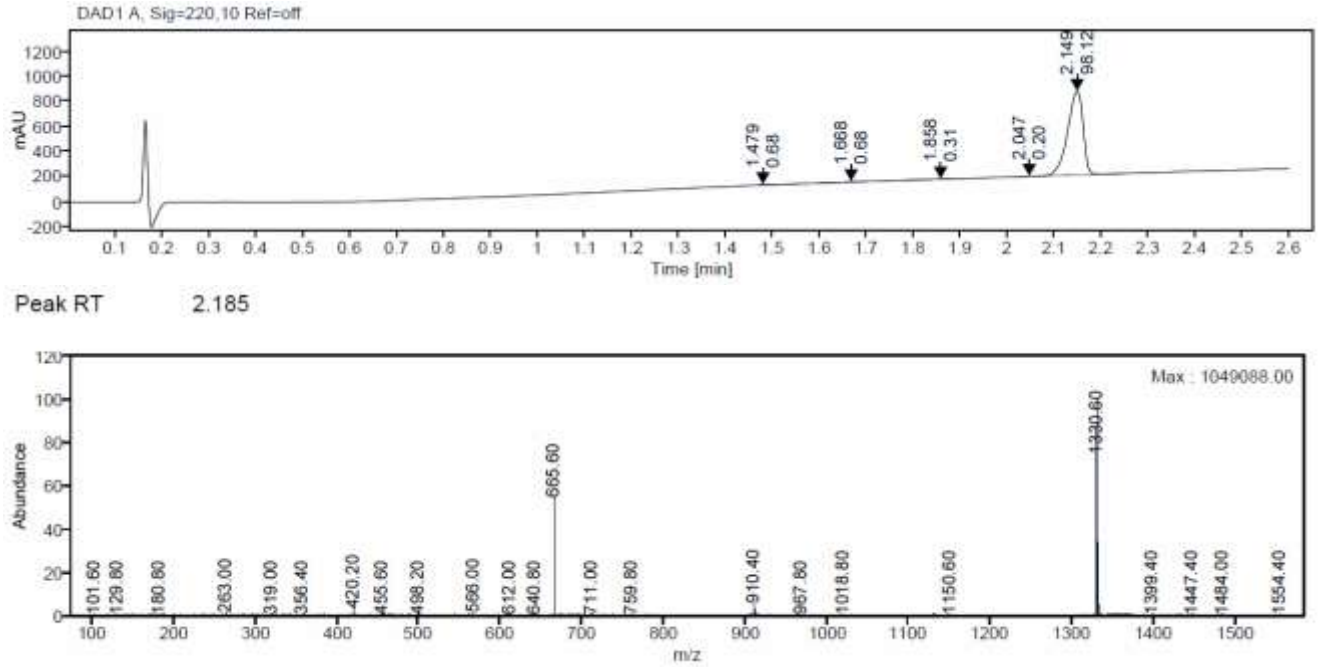

Figure 40: LC-MS of MWa421 (**107a**; 5-100 % solvent B).

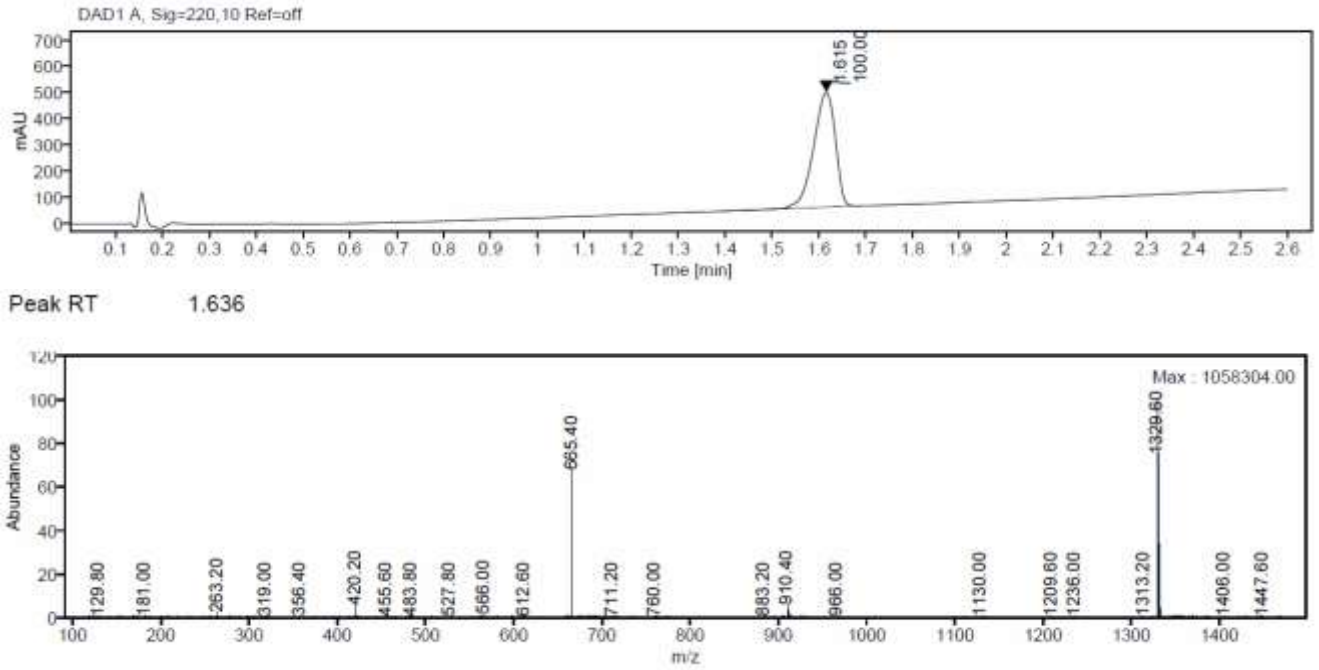

Figure 41: LC-MS of MWa421 (**107a**; 50-100 % solvent B).

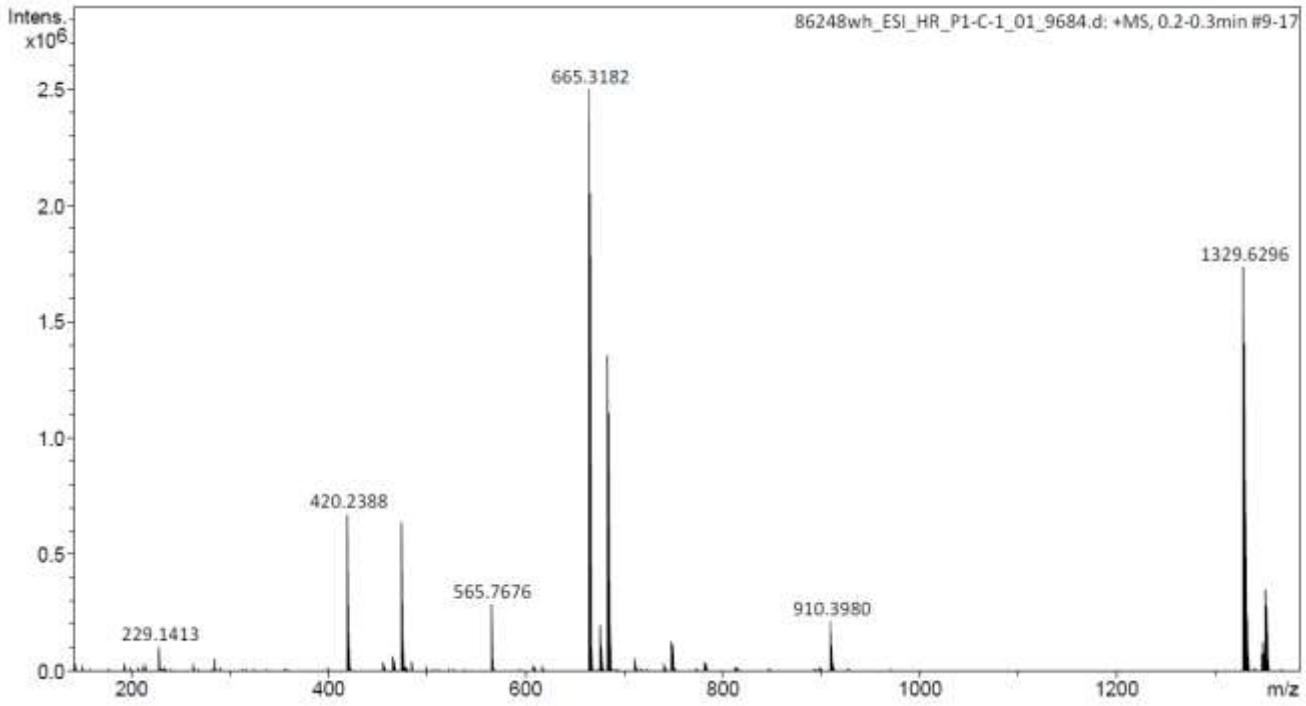

Figure 42: HRMS of MWa421 (**107a**).

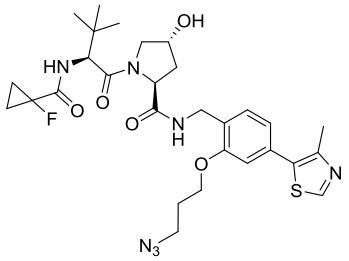

Figure 43: Structure of MWa542.

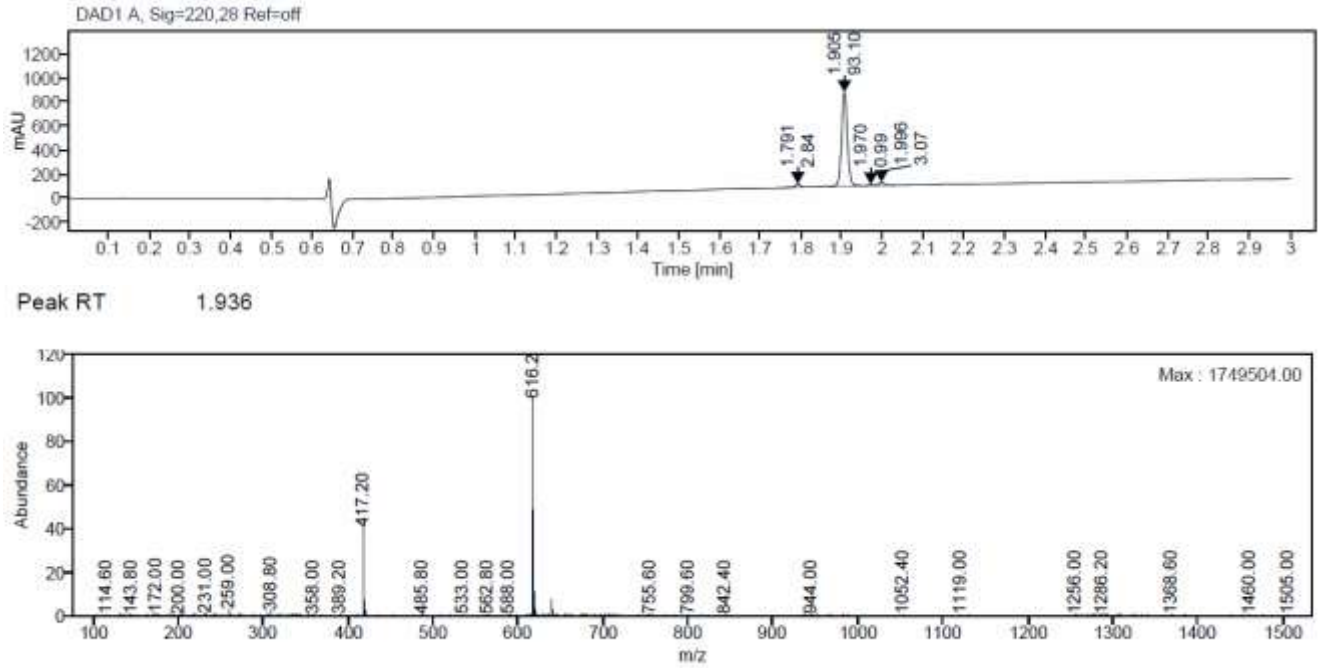

Figure 44: LC-MS of MWa542 (5-100 % solvent B).

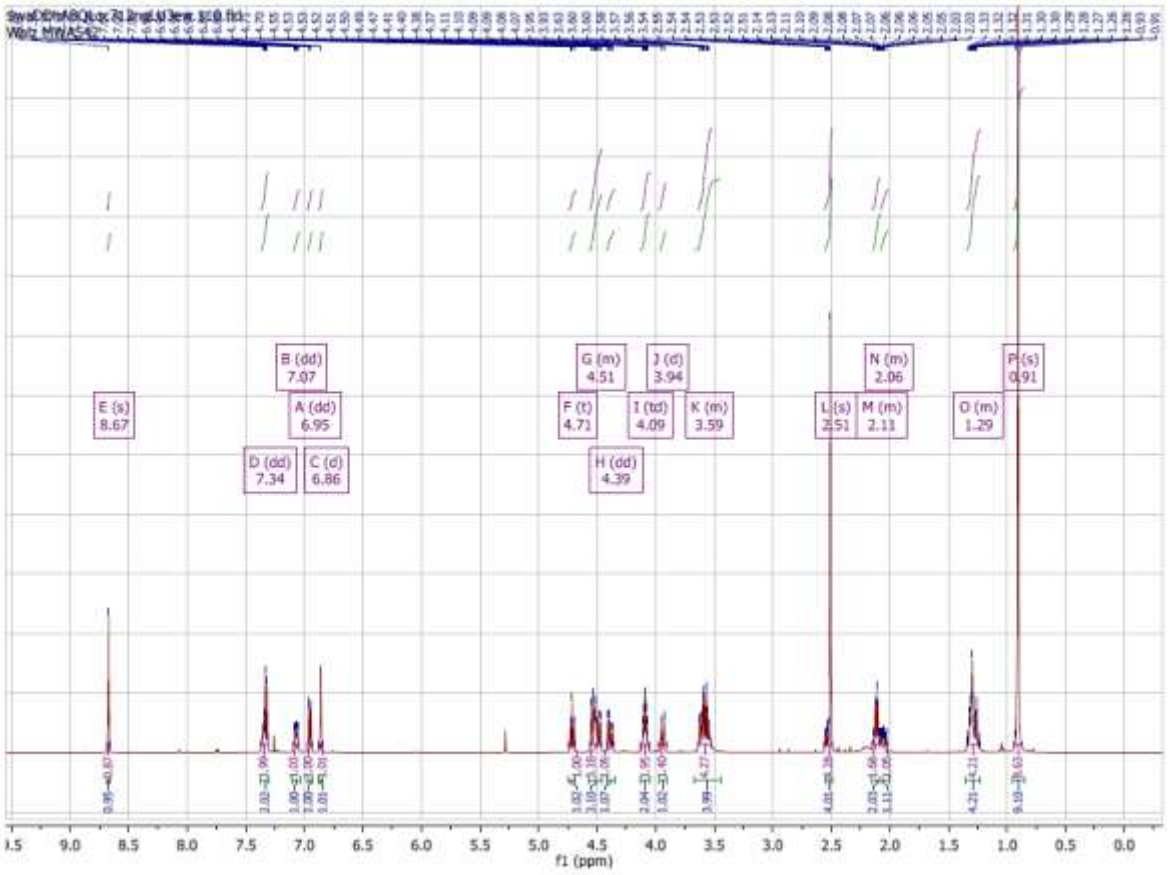

Figure 45: ^{1}H-NMR of MWa542.

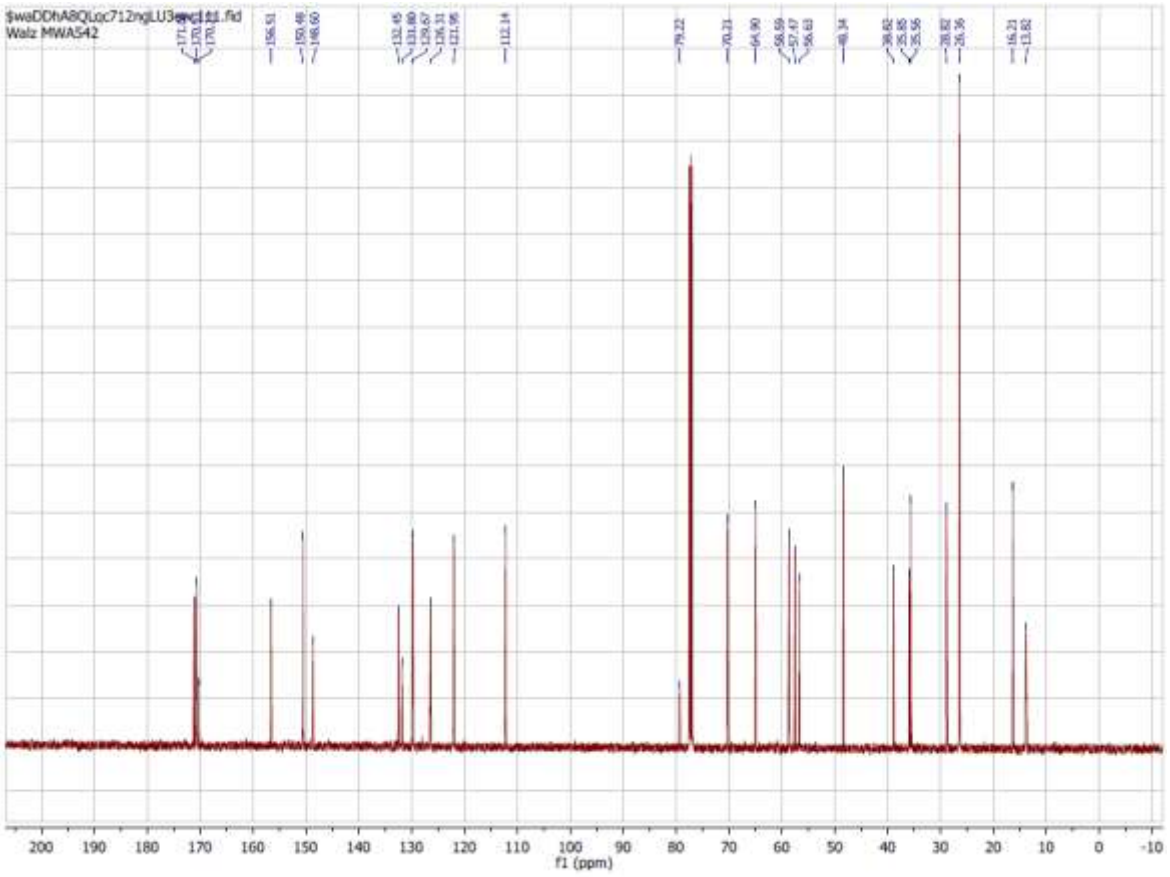

Figure 46: ^{13}C-NMR of MWa542.

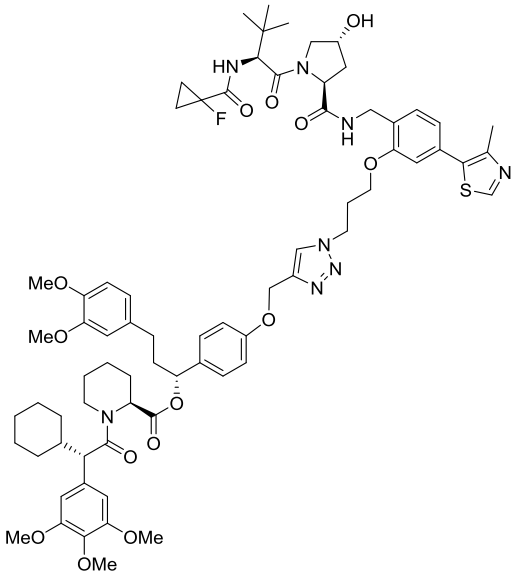

Figure 47: Structure of MWa558 (**196**).

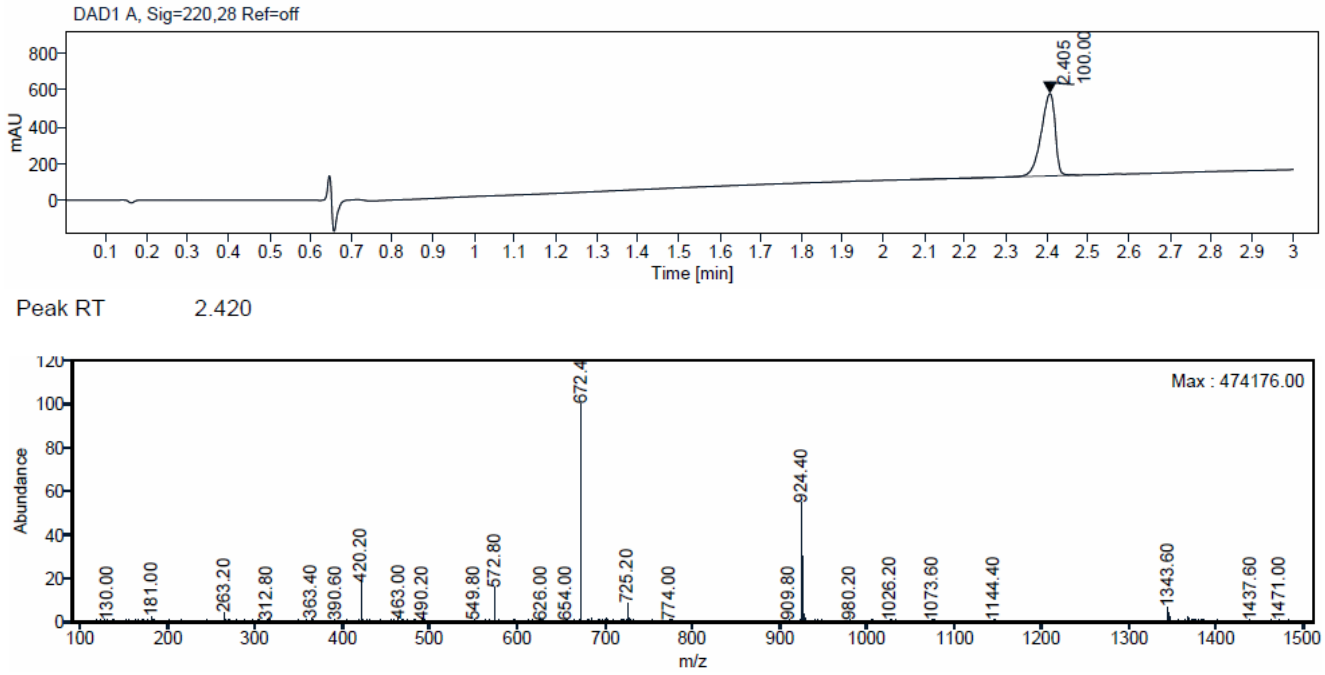

Figure 48: LC-MS of MWa558 (**196**; 5-100 % solvent B).

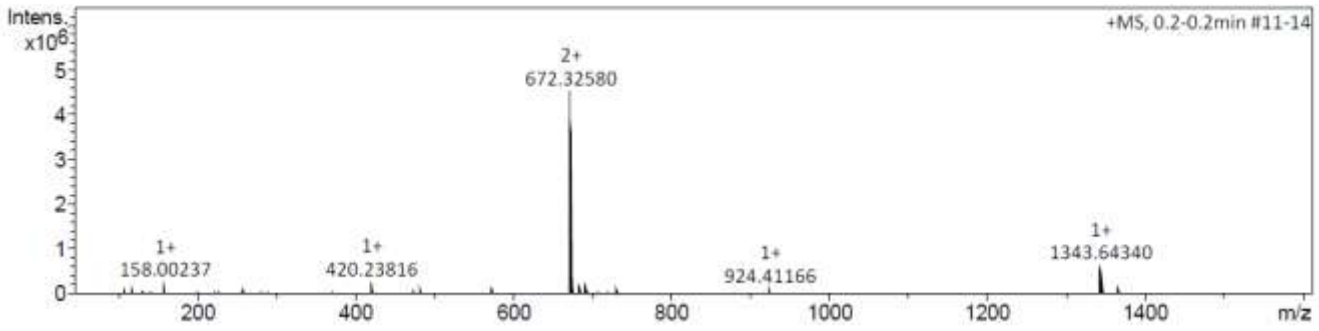

Figure 49: HRMS of MWa558 (**196**).

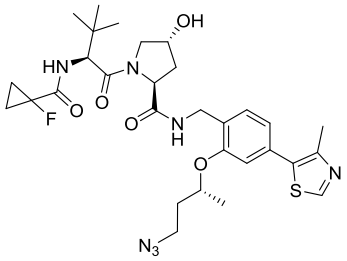

Figure 50: Structure of MWa635.

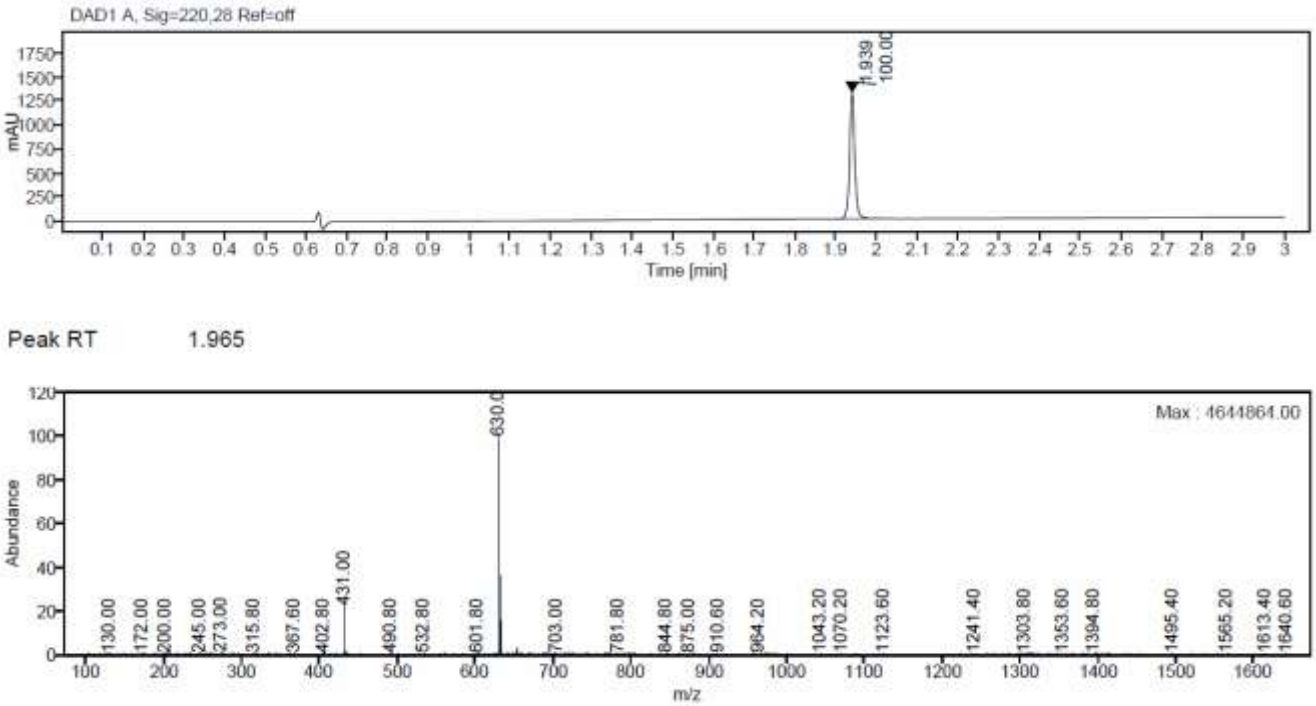

Figure 51: LC-MS of MWa635 (5-100 % solvent B).

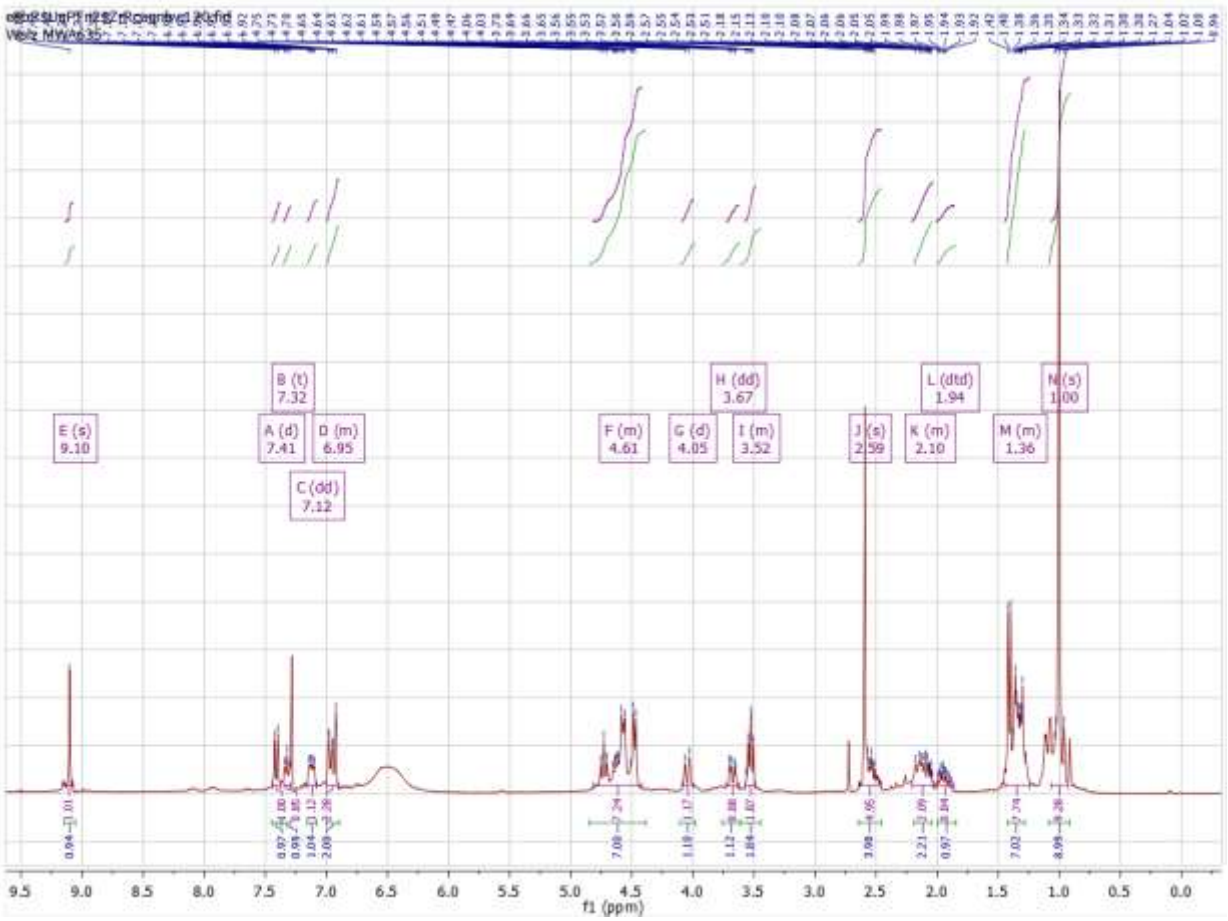

Figure 52: ^{1}H-NMR of MWa635.

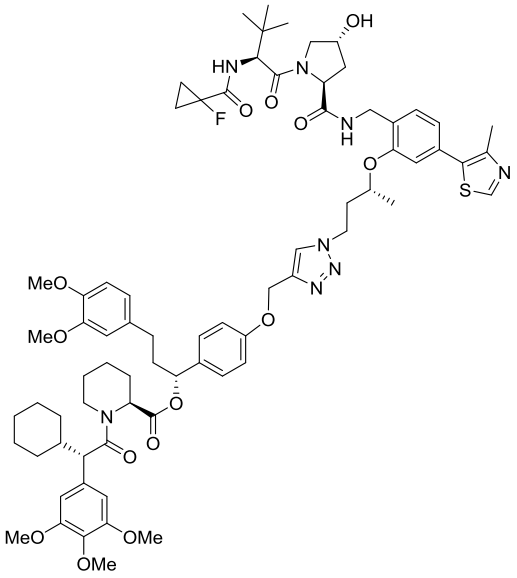

Figure 53: Structure of MWa649.

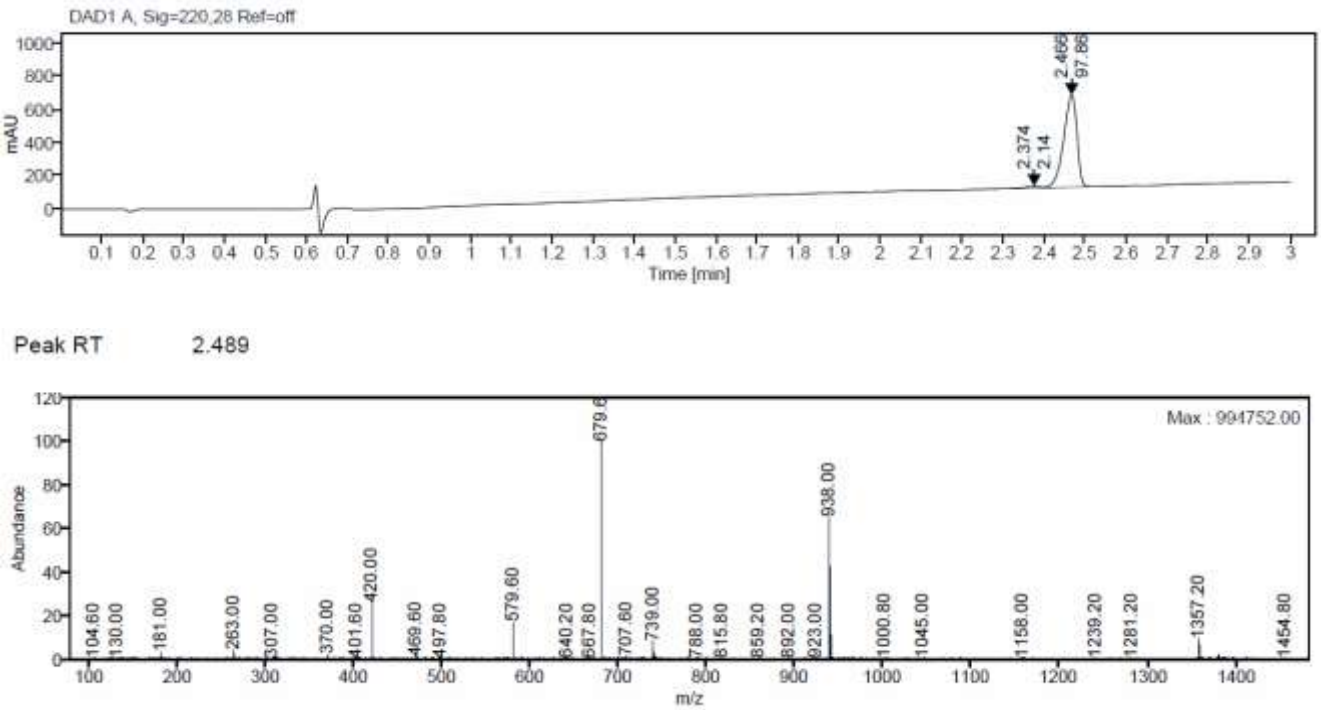

Figure 54: LC-MS of MWa649 (5-100 % solvent B).

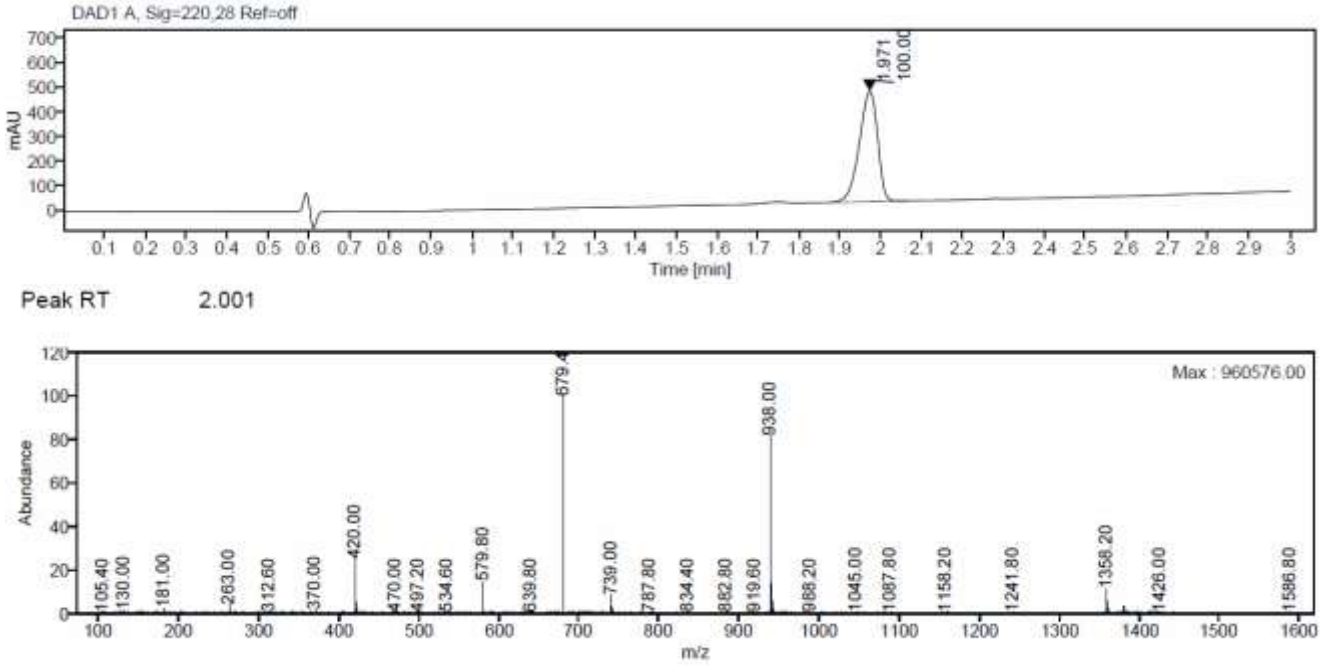

Figure 55: LC-MS of MWa649 (50-100 % solvent B).

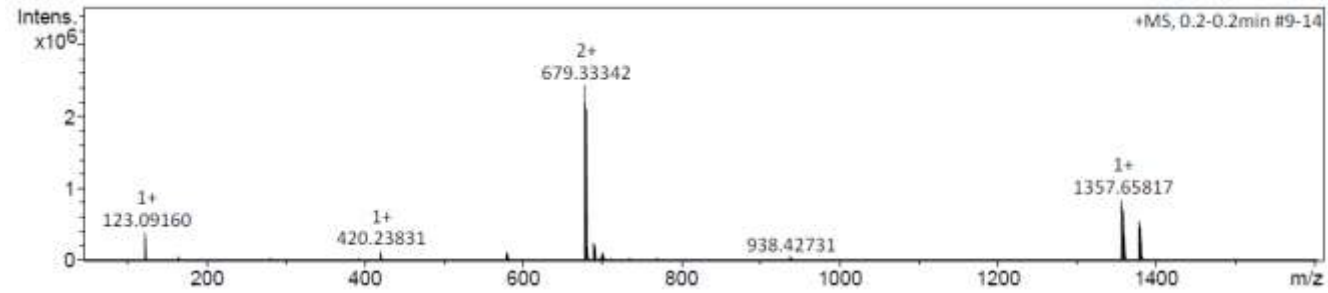

Figure 56: HRMS of MWa649.