Design, synthesis and biological evaluation of novel FKBP51 ligands

Design, Synthese und biologische Evaluierung von neuartigen FKBP51 Liganden

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Abstract

The FK506-binding protein 51 (FKBP51) has emerged as an attractive new drug target for mood disorders, obesity and chronic pain. The most advanced FKBP51 ligands of the SAFit class are highly selective against the anti-target FKBP52, but only poorly discriminate against the homologs FKBP12 and FKBP12.6. To improve SAFit-like compounds we employed a structure-based approach:

Envisioning enhanced properties of macrocycles like increased oral bioavailability, metabolic stability and selectivity compared to the linear SAFit-construct, we designed and synthesized FKBP-binding macrocycles. These macrocycles were synthesized via ring-closing-metathesis and a solid-phase assisted approach. Surprisingly, we observed that many of these macrocyclic analogs have a novel high preference for FKBP51 over FKBP12 and FKBP12.6 and that they bind with a new binding mode featuring a transient conformation that is disfavored for the small FKBPs. These findings represent the structural basis for enhanced selectivity and a new chemical scaffold for selective FKBP51 ligands.

Furthermore, we present the rational design and synthesis of novel A and B ring derivatives of SAFit1 (an essential building block of SAFit-ligands). Reducing the size of SAFit to explore the necessary interactions and subsequently combining the most favorable moieties resulted in novel diaza-chalcone derivatives. These compounds reached similar FKBP51 selectivity and affinity in comparison to SAFit1 and most importantly displayed a reduced weight by up to 132 g/mol. Additionally, a compound series of A/B ring-analogs was synthesized by *Click* reaction, which displayed a new preference for FKBP12.6 over FKBP12. This may offer new possibilities to alter FKBP selectivities.

Zusammenfassung

Das Protein FKBP51 (FK506-binding protein 51) ist ein attraktives Wirkstoffziel für die Behandlung von psychischen Krankheiten, Adipositas und chronischem Schmerz. Die bestentwickelten FKBP51 Liganden der SAFit-Klasse binden hochselektiv an FKBP51 und nicht das anti-target FKBP52. Allerdings binden die SAFit Liganden die stark homologen off-targets FKBP12 und 12.6. Im Rahmen dieser Arbeit wurde ein Struktur-basierter Ansatz verfolgt, um diese Bindeeigenschaften der SAFit ähnlichen Verbindungen zu verbessern:

Hierzu wurden unter Zuhilfenahme des SAFit Grundgerüstes Makrozyklen durch Ringschluss-Metathese, sowie Festphasen-Peptid-Synthese synthetisiert. Diese neuartigen Makrozyklen präferieren die Bindung an FKBP51 und binden nicht mehr an FKBP12 und 12.6. Eine Erklärung für diese spezifische Eigenschaft konnte mit Hilfe von Kokristallstrukturen postuliert werden. Der makrozyklische Ligand bindet nur eine transiente Konformation der Proteine, die bei FKBP51 bevorzugt vorliegt. Diese neue Ligandenklasse bildet eine strukturelle Grundlage für die Entwicklung von hochselektiven FKBP51 Liganden.

Des Weiteren wurden neuartige A/B-Ringsysteme (essentieller Baustein von SAFit-Liganden) synthetisiert, um SAFit-Derivate zu finden, welche verbesserte Eigenschaften hinsichtlich Molekülmasse und Größe aufweisen. Insbesondere zeigten Diazachalkone im Vergleich zu SAFit1 ähnliche FKBP51 Selektivität und Affinität auf. Zusätzlich konnte die Molekülmasse um 132 g/mol verringert werden. Zudem zeigte eine weitere Serie von A/B-Ringsystemen, welche über eine *Click*-Reaktion synthetisiert wurden, eine bis dato unbekannte, bevorzugte Bindung von FKBP12.6 gegenüber FKBP12. Diese Ergebnisse könnten uns neue Möglichkeiten zur Steuerung und Anpassung der Eigenschaften für FKBP Liganden liefern.

Declaration of contributions

The synthesis of compounds **NG67** and **NG72** were conducted by Niklas Gutfreund as part of his master thesis under my supervision. Preliminary works towards meta OH substituted macrocycles were conducted by Matthias Roth as part of his master thesis under my supervision. Details can be found in their master thesis. Compound **77** was kindly provided by Tim Heymann.

The measurement of binding affinities was conducted by Tim Heymann, Stefanie Merz and Patrick Purder. The tracer used in these measurements (MTQ238 or FTSP11) was provided by Dr. Tianqi Mao and synthesized according to Dr. Sebastian Pomplun. Details can be found in their dissertations.

Co-crystallization of ligands with FKBPs and corresponding diffraction measurement were performed in cooperation with Dr. Andreas Bracher and Dr. Christian Meyners.

Molecular dynamics simulations were perfomed by Dr. Daniel Tietze.

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1. Introduction

1.1. FKBP51 vs. FKBP52 and the selective ligand class SAFit

The FK506-binding protein 51 (FKBP51, encoded by the FKBP5 gene) shows peptidyl-prolyl cis-trans isomerase (PPIase) activity and belongs to the class of immunophilins known to bind the macrocyclic, natural compounds and immunosuppressive drugs FK506 (Tacrolimus) and Rapamycin (Sirolimus, **Figure 1A**).[1]

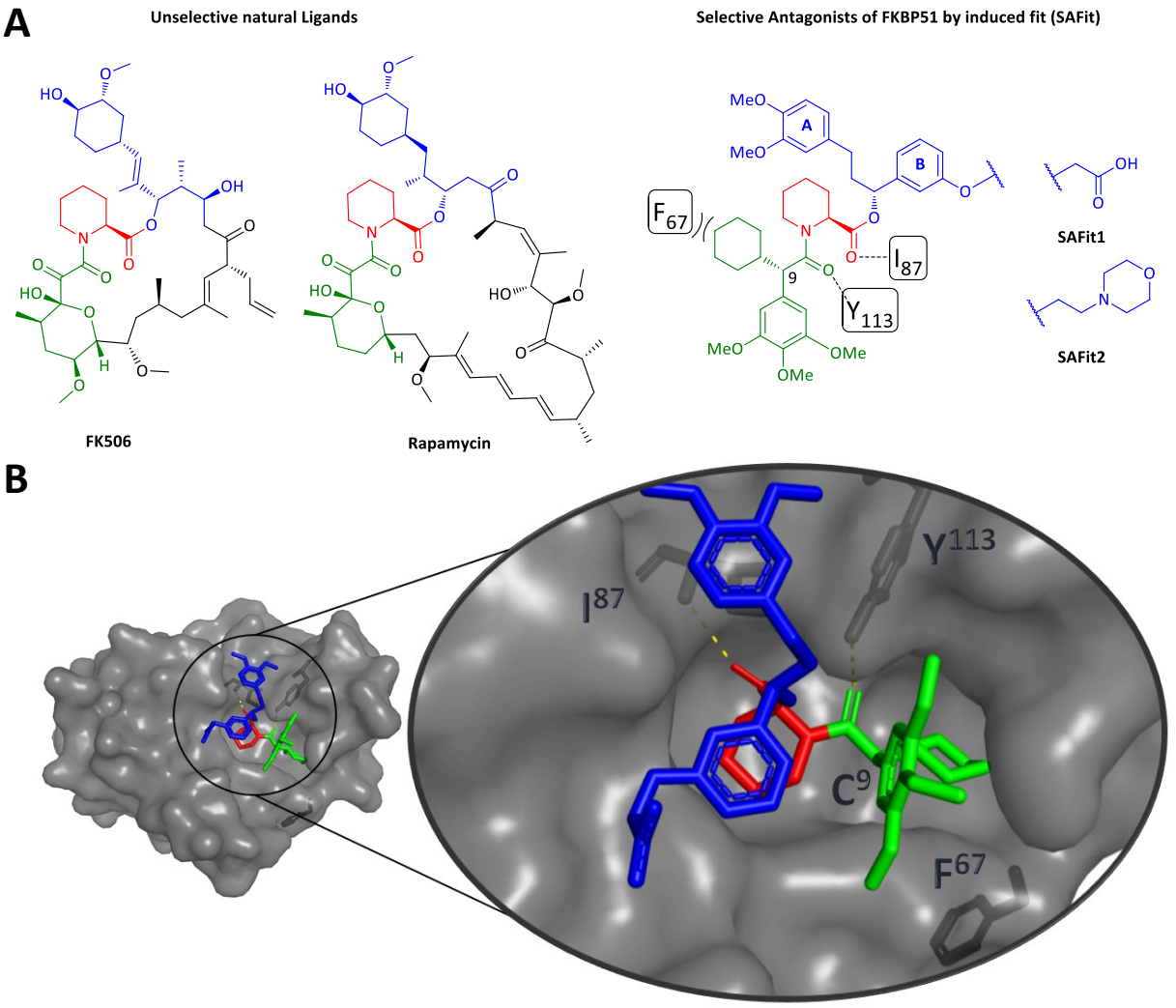


Figure 1. A) The chemical structure of the FKBP ligands FK506, Rapamycin and the FKBP51-selective ligand SAFit1. The key interactions of SAFit1 and 2 with FKBP51 is indicated. **B)** SAFit1 in complex with the FK1 domain of FKBP51 with the highlighted key interactions. (Unpublished crystal structure of SAFit1, kindly provided by Dr. Christian Meyners)

FKBP51 works in association with the heat shock protein 90 (Hsp90) as a cochaperone and decreases glucocorticoid receptor (GR) signaling.[2] In contrast, the close and homologous protein FKBP52 functions as a facilitator of GR signaling (**Figure 2**).[3] FKBP51 structurally consists of an *N*-terminal FK1 domain, which displays PPIase activity, a PPIase-like FK2 domain and a C-terminal tetratrico peptide repeat (TPR) domain. The FK1 domain implements the PPIase site with the ligand-binding pocket. The

FK2 domain also has a typical FKBP-like structure, but it neither shows isomerase activity nor does it bind FK506 or Rapamycin.[4, 5]

Interestingly, FKBP51 emerged as a promising drug target for stress-related diseases like depression,[6-13] obesity,[14, 15] and chronic pain[16-18] due to the findings that FKBP51 knockout mice displayed enhanced stress-coping behavior, attenuated weight gain in a high-fat diet model and increased pain durability. In contrast, FKBP52 knockout mice displayed adverse effects such as impaired sex organ development,[19, 20] which highlights the necessity of highly selective ligands for drug development.[21]

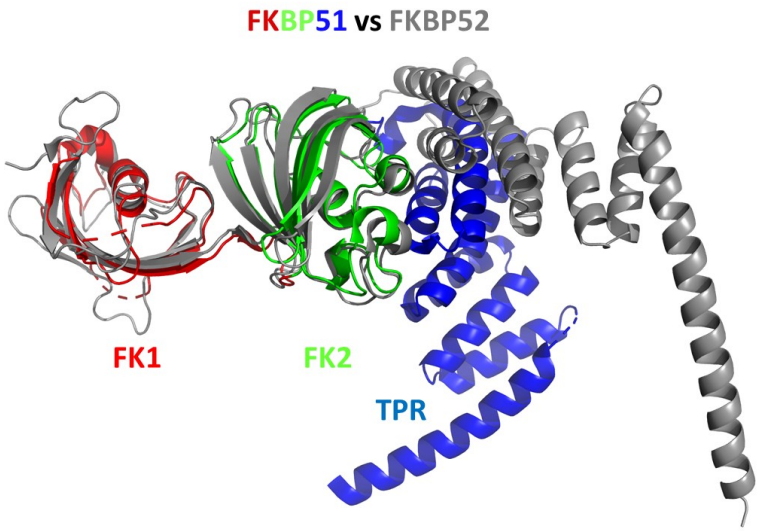


Figure 2. High structural homology between FKBP51 (colored cartoon, pdb-ID: 1kt0) and FKBP52 (grey cartoon, pdb-ID: 1q1c, 1p5q) displayed by an overlay. Both proteins consist of three domains: The FK1 domain with the active PPIase site, the FK2 domain with a homologous structure to the FK1 domain but with no PPIase activity and the TPR domain necessary for Hsp90 binding.

The FKBP51 selective ligands SAFit1 and 2 developed by the Hausch group are binding by a factor of >10000 towards FKBP51 over FKBP52.[13] The cyclohexyl ring at the C^9 position displaces in FKBP51 the amino acid F^{67} forming a new pocket (**Figure 1B**). The formation of this transient pocket is unfavored in FKBP52.[13] In vivo testing of SAFit2 phenocopied the results observed in FKBP51 knockout mice. The mice showed increased stress-coping behavior,[13] attenuated weight gain, together with antidiabetic effects,[15] reduction of chronic pain,[16, 18] reduction of NF-κB driven inflammatory pathways[12] and slight reduction of conditioned alcohol consumption.[22]

1.2. FKBP12 and 12.6

FKBP12 and its isoform 12.6 are, with a molecular weight of 12 kDa, its smallest members of the FKBP family. Both contain the PPIase core domain, which is highly homologous to the PPIase-domains in many FKBPs (FK1 domain of FKBP51, **Figure 3**).

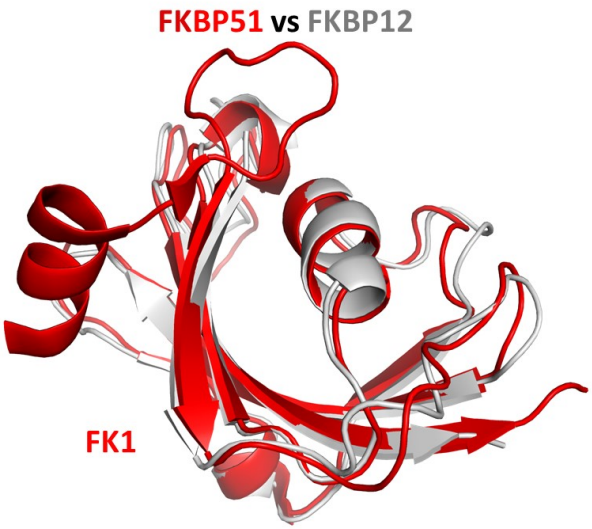


Figure 3. High structural homology between the FKBP51 FK1 domain (colored cartoon, pdb-ID: 3o5q) and FKBP12 (grey cartoon, pdb-ID: 1fkj) displayed by an overlay. FKBP12 consists only of the FK1 domain.

FKBP12 is well known to form a trimeric complex with the natural drug FK506 and calcineurin[23], an enzyme involved in the T-cell activation cascade[24]. In association with Rapamycin, the complex binds to the FRB (FKBP-Rapamycin binding) domain of the protein called mammalian target of Rapamycin (mTOR).[25] Formation of these complexes and thus inhibition of pathways regulated by these proteins leads to an immunosuppressive response, which is used to inhibit allograft rejection in post-transplantation patients.[26-30]

FKBP12 is essential for mammalian life and occurs in most tissues and is together with FKBP12.6 a cofactor of the ryanodine receptor (RyR),[31-33] where they play an important role in fine-tuning the excitability of smooth or heart muscle. Knock-out of FKBP12 in mice produced an embryonic lethal phenotype due to severe cardiac defects also attributed to interference with the ryanodine receptor,[34, 35] which intracellularly modulates Ca^{2+}-signaling in myocytes to evoke muscle contraction. Recent cryoelectron microscopy structures have elucidated the FKBP binding site in the ryanodine receptor complex, where FKBP12 and FKBP12.6 occupied identical positions.[36, 37] While the RyR1-FKBP12 complex is present in skeletal muscle, the homologous RyR2 and FKBP12.6 seem to have evolved as a specialized system to control cardiac muscle stimulation in mammals.[1] Various studies have investigated the role of FKBP12 and FKBP12.6 and their interaction levels with different ryanodine receptors, however, with highly controversial findings. Future development of selective tool compounds might give a better insight into their respective function.

1.3. Development of SAFit ligands

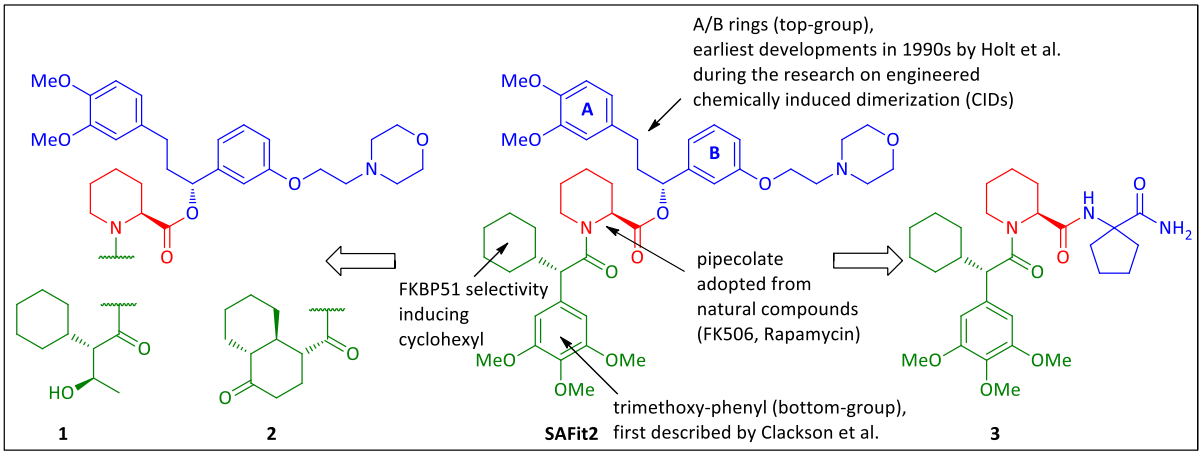


Figure 4. Ligand development of the SAFit-class. Examples of the variants of the bottom-group (green) and top-group (blue) during structure-affinity-relationship studies (SAR). These new moieties displayed reduced size but also reduced affinity towards FKBP51 in the micromolar ranges. Earliest developments on the top-group and the bottom-group by Holt et al. and Clackson et al.[38, 39]

The FKBP51-selective SAFit-class was developed by serendipity, during works on a bump and hole approach on FKBP51 and 52. Gaali et al.[13] prepared a ligand series (iFit), which should only bind the F67V-engineered mutants of FKBP51 and 52, to be able to observe the phenotype of selective binding in *vitro*. This system was analogous to the already developed system of the FKBP12 mutant F36V, using analogs of the Shld ligand developed by Clackson et al.[39] In a fluorescence polarization assay, Gaali et al. noticed that the iFit ligands retained weak affinity to the wildtype FKBP51 but not to FKBP52. A co-crystal structure (pdb-ID: 4tw6) revealed a flip of F67 in the FKBP51-FK1 domain by an induced-fit or a conformational selection. Further SAR studies on the selectivity inducing moiety singled out the cyclohexyl ring to be most efficient in high selectivity *vs.* FKBP52 and high-affinity binding of FKBP51.

Due to SAFits lack of drug-like chemical properties further development was aimed at identifying size-reducing moieties. Especially the trimethoxyphenyl was extensively modulated in previous SAR studies (green, **Figure 4**). Several trimethoxy-analogs and analogs implementing a hydroxyl group mimicking part of the hemiacetal moiety in FK506 at the C^{10}, which forms a hydrogen bond with D68 (**1, Figure 4**) did decrease the size of SAFit but also reduced affinity towards micromolar ranges.[40] More recently a novel decaline like bicyclic scaffold rigidifying the bottom-part (**2, Figure 4**) was developed by Feng et al.,[41] which also displayed FKBP51 selectivity vs FKBP52 and bound in the submicromolar range. Both SARs still leaving the trimethoxy bottom-group of SAFit as best moiety for now. The top-group (A/B ring, blue, **Figure 4**) of SAFit1 is needed for high-affinity binding, although no specific interactions can be found in the co-crystal structure of SAFit1. The removal of this group leads to a decrease in affinity towards the µM range.[42] Substitution by several smaller pipecolic acid amides with a plethora of natural and unnatural amino acids provided smaller sized compounds of the SAFit-class (**3, Figure 4**), which displayed FKBP51 selectivity and reached submicromolar affinities. These results altogether

suggest the need for new approaches towards drug-like and selective FKBP51 ligand development, which will be addressed in this thesis.

2. Aim

Although SAFit has already quite advanced functional properties the drug-like qualities are lacking. Blood-brain-barrier penetration is quite low, its molecular weight is too high and its metabolic stability is still low.[13] Another crucial point is that SAFit-like compounds still bind other FKBPs, including FKBP12 and its isoform FKBP12.6 (for SAFit1: K_i^{FKBP12}: 135 nM, $K_i^{FKBP12.6}$: 26 nM). As mentioned above, knock-outs of these ubiquitous immunophilins in mice produced an embryonic lethal phenotype, which was linked to interference with a ryanodine receptor.[34] An inhibition of FKBP12 and 12.6 as off-targets over a prolonged time might be disadvantageous for a drug's mode of action. We set out employing two different approaches for the modulation of SAFit's properties.

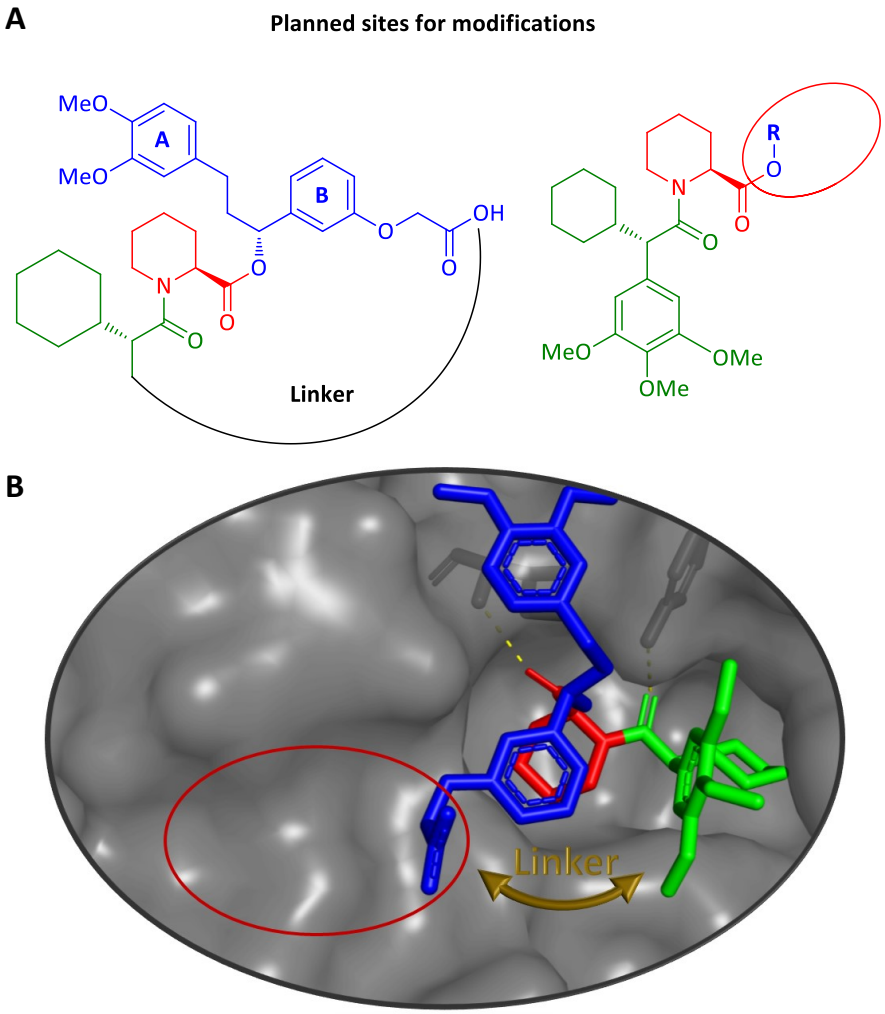


Figure 5. A) The planned sites for modifications to alter the properties of the SAFit-class compounds are indicated by highlighting the site for macrocyclization (linker) and a new shallow binding site on the surface of the protein (red ellipse). **B)** SAFit1 in the co-crystal structure with the highlighted modification sites as described above.

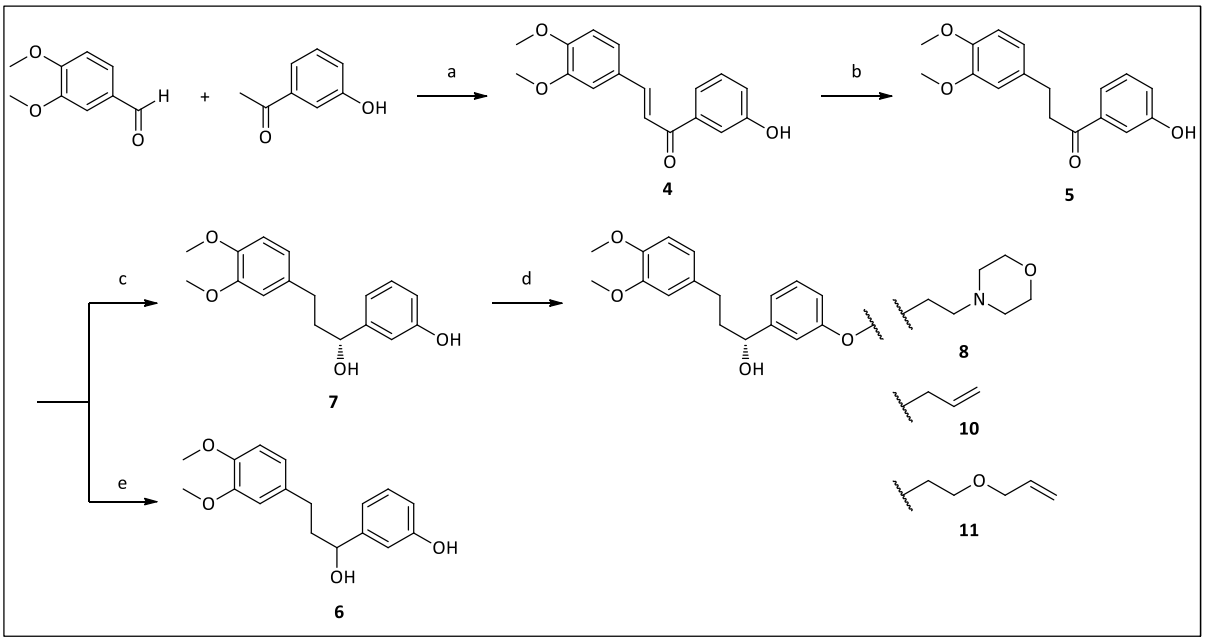
Our first objective was to rationally design novel and FKBP51 selective macrocycles. Macrocyclization is a popular approach in drug discovery to improve drug-like properties for compounds outside the rule-of-five (Ro5) space[43-45]. Macrocycles are thought to have better affinities and selectivities as well as improved ADME properties compared to their non-cyclic counterparts and are often synthesized to improve oral bioavailability, which is especially important for compounds in the non-Ro5-chemical space.[43-45] Altogether, macrocyclization is thought to be crucial for the unexpectedly benign properties of the clinically used natural products FK506, Rapamycin and Cyclosporin as well as close analogs thereof.[46] Indeed, the groups of Holt and Luengo et al. already developed macrocyclic FKBP12 ligands binding in the nanomolar range.[38, 47] Structural simplification of natural macrocycles like Sangliferin A led to efficient inhibitors of cyclophilin.[48, 49] Systematic exploration of macrocyclic analogs of Rapamycin led to the identification of novel non-immunosuppressive FKBP ligands and novel inhibitors for hENT1[50] and GLUT1.[50] Starting with the crystal structure of the linear SAFit1 displaying a highly conserved binding mode and to maintain the FKBP51 selectivity, we chose to keep the pipecolate, the chalcone-derived A/B rings and cyclohexyl ring constant and insert a linker between the last two (**Figure 5**).

The second objective was to find new binding interactions of the SAFit1 A/B ring by systematically analyzing the effects of small variations through *Claisen-Schmidt* reactions. As mentioned above, co-crystal structures of SAFit and analogs showed that this ligand moiety has only unspecific contacts with the surface of the protein (**Figure 5**) but is still needed for high-affinity binding. Additionally, we thought to develop a fast and easily approachable library employing the *Huisgen-Sharpless-Meldal* (*Click*) reaction to reach further into the shallow binding pocket located on the protein's surface as well as to develop smaller sized top-groups to find options to improve our current best ligand SAFit (red ellipse, **Figure 5**).

3. Results and discussion

3.1. Upscaled synthesis of SAFit's A/B ring

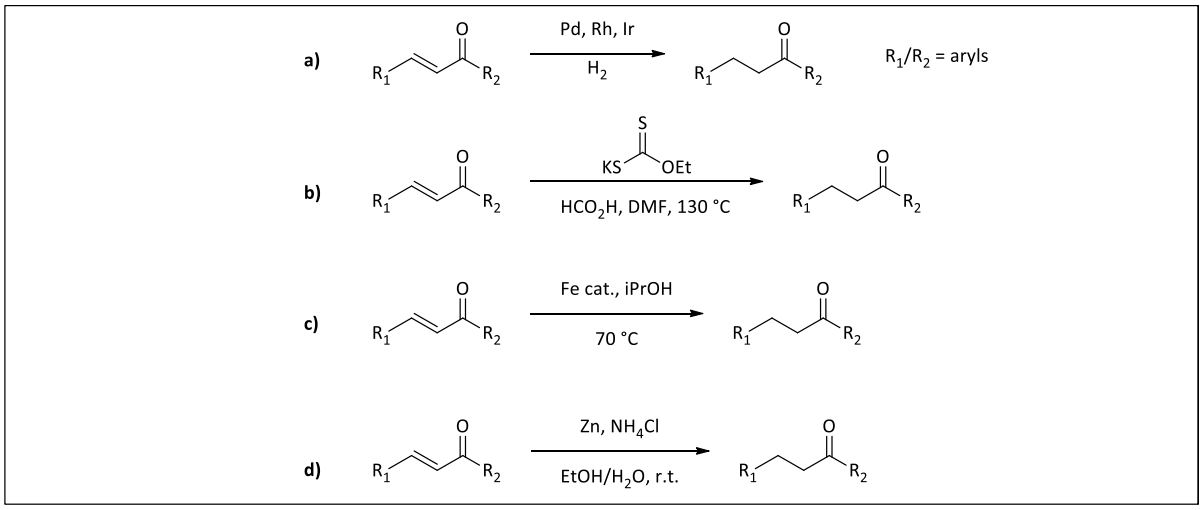
SAFit's A/B ring was essential for our planned syntheses and due to an increased demand of SAFit2 in mouse and rat model experiments, an efficient, cheap, high-yielding, multigram scale synthesis was required. Therefore, we started to revise and optimize the synthesis of the A/B ring of SAFit as previously reported by Gaali et al.[13]



Scheme 1. a) KOH, H_2O/EtOH, 0°C – r.t.; b) Zn powder, NH_4Cl, MeOH/THF; c) $RuCl_2$[(S)-(DM-SEGPHOS)][(S)-DAIPEN], K_2CO_3, iPrOH/THF; d) allylbromide or 4-(2-chloroethyl)morpholine hydrochloride or **9**, K_2CO_3, MeCN; e) $NaBH_4$, THF.

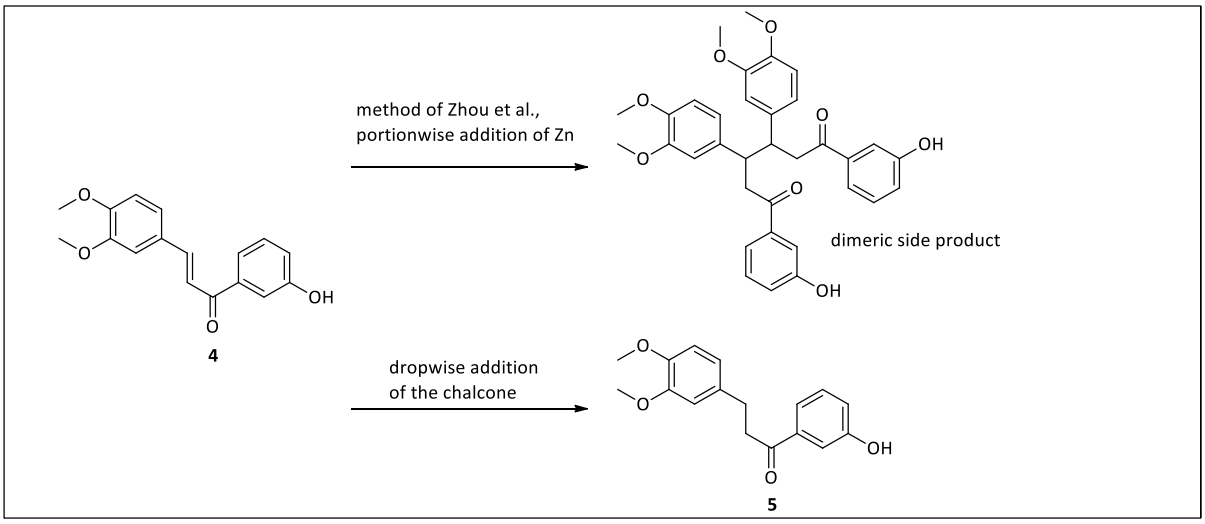
The reaction sequence starts with the *Claisen-Schmidt* reaction of the respective ketone and aldehyde providing the chalcone **4**, which was recrystallized and gave in an upscaled setup of 100 g aldehyde moderate yields of 56%. The aldol condensation was also conducted on a smaller scale (50 g) and reached up to 90%.[51] Regarding the cheap starting materials and simple reaction setup, we did not further optimize the reaction. Gaali et al.[13] further processed the chalcone in an autoclave at 40 bar hydrogen pressure to chemoselectively reduce the double bond via *Lindlar* catalyst (**5**). The reaction yielded satisfying amounts (76%) but took 3-4 days and was limited to the size of the autoclave's reaction chamber, which could only take up 200 mL per batch. Due to these limitations, we looked for alternative reduction methods. Standard procedures to gain α, β-saturated ketones by reduction usually involve the use of comparatively expensive transition metals such as palladium, ruthenium or iridium and high pressures of hydrogen or higher temperatures in combination with a different hydrogen source (**Scheme 2**).[52-55] Alternative methods with cheaper catalysts were developed such as iron catalysts with isopropanol as hydrogen source, but they still require a ligand as well as heating.[56] A recent report of upscaled Shld synthesis included a method using Pd/C and NH_4HCO_3 for the chalcone

reduction, but only with a moderate yield of 68%.[57] A cheap alternative is reported by Zhou and Li et al., which uses zinc and ammonium chloride or ammonium acetate that allows the reduction of α,β-saturated ketones in very short reaction times in good to excellent yields (85-95%).[58, 59]



Scheme 2. a) Reduction of α,β-saturated ketones using a transition metal and hydrogen, **b)** reduction using different hydrogen sources such as formic acid and xanthate at high temperatures, **c)** chemoselective reduction by iron catalysis under milder conditions, **d)** zinc reduction at room temperature.

Our first trials in reducing the chalcone **4** in the manner of Zhou et al. gave some product and mostly a side product, which quickly precipitated as white, quite insoluble solid and was identified by MS (m/z = 553.12) and NMR to be a dimer of the reduced chalcone (**Scheme 3**). The reaction mechanism is not described in the literature but it is postulated to react via radicals, which could explain the dimerization reaction. Zhou et al. dissolved their starting materials and reactants in H_2O/THF and added Zn powder portion-wise in 15 min steps.



Scheme 3. The side reaction towards the dimeric side product and the simple change resulting in product **5** in high yield (81%).

We thought of a method to prevent the dimerization reaction by having our starting material as diluted as possible, which can be achieved by the drop-wise addition of the chalcone to a vigorously stirring

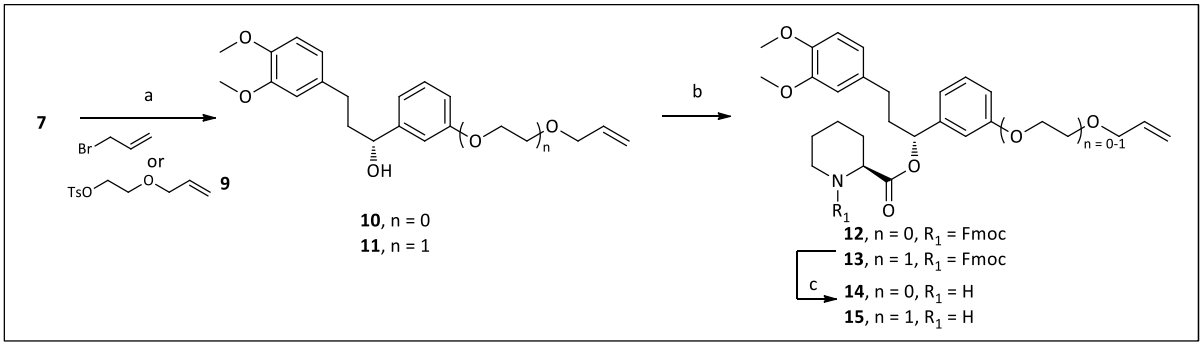
slurry of Zn powder and NH_4Cl in MeOH/THF. The results were astounding as we were able to isolate pure product **5** in high amounts (81%) in a very fast and upscaled reaction setup with 50 g starting material. This reaction setup was also tested for various chalcone derivatives (3.3.1) but seems to work best with the SAFit top-group. One of the problems was the solubility of the chalcones in MeOH. A change in the solvent (EtOH, DMF, THF) did not work, as the reaction worked best with a solvent being able to dissolve some of the salt (NH_4Cl) together with the organic starting material (chalcone). Using mixtures with water made the workups very complex and often lead to prolonged workup and also to an increased side product ratio. Although not universally applicable, this procedure can be regarded as an improvement for the SAFit A/B ring synthesis.

After the chalcone reduction, Gaali et al. already introduced the carboxylic ester or morpholine group onto the phenol, then reduced the ketone asymmetrically. Here we thought to first synthesize the chiral alcohol, which then can be diversified into several different top groups through S_N reaction at the reactive phenol. To be able to measure the enantiomeric ratio (*er*) by chiral column we synthesized the racemic alcohol **6** via $NaBH_4$ reduction. For the asymmetric reduction, we tried several newer and cheaper catalyst systems than those that have been used before.[51] We found the *Noyori* catalyst $RuCl_2$[(*S*)-(DM-SEGPHOS)][(*S*)-DAIPEN] at 10 bar H_2 and with K_2CO_3 as activating base to be the most satisfying regarding yields (87%), *er* (99.33/0.67), and handling. The reaction worked with 40 g starting material in an autoclave (Roth, Model II) and purification was done by simple precipitation in cooled DCM, which gave pure product **7**. Later on, in subsequent experiments, we noticed this catalyst was also able to reduce the ketone already at 1 bar hydrogen pressure using KOtBu as base giving similar results in yield (73%) and *er* (99.63/0.37), which increases handling speed of the reaction setup even more as the laborious step with the autoclave can be omitted. Further reaction of the chiral alcohol with 4-(2-chloroethyl)morpholine hydrochloride provided the SAFit2 A/B ring **8** in a quantitative yield. Other linkers were applied as well and worked likewise with excellent yields (compounds **10** and **11**). The overall yield of the whole reaction sequence amounted to 63%. This is quite an enhancement regarding the scale and handling of the reaction and the overall yield of the former sequence (53%,[60] calculated with crude yields). A portion of the SAFit2 A/B ring was used in the complete synthesis of SAFit2 in cooperation with Michael Bauder (TU Darmstadt, Doctoral student). Furthermore, we sent a sample of SAFit 2 to the group of Prof. Dr. Christian Müller at the University Clinic Erlangen whose group evaluated that SAFit2 reduces the alcohol consumption and reinstatement of the conditioned alcohol effects in mice.[22]

3.2. Macrocyclization of SAFit

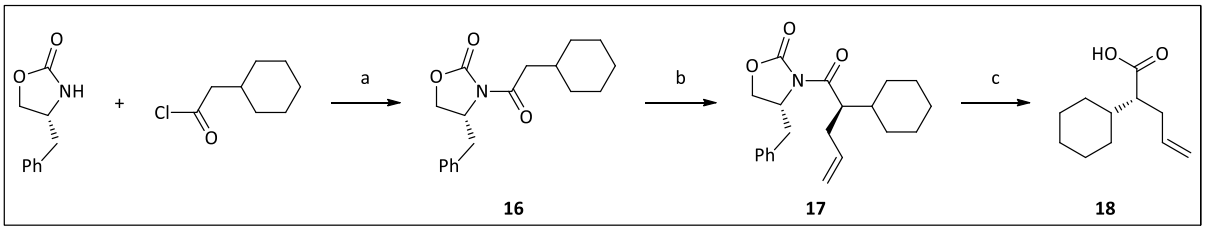
3.2.1. Macrocyclization through ring-closing-metathesis (RCM)

Based on the structure-affinity relationship findings on SAFit analogs[13, 40-42] and the highly conserved binding mode (**Figure 1B**), we chose to keep the pipecolate, the chalcone-derived A/B rings and cyclohexyl ring constant and to cyclize between the latter two. For macrocyclization several options are available. Macrolactamization, -lactonization and ring-closing metathesis (RCM) are the most popular ones in organic chemistry. We first chose to conduct RCM as the double bond located at the linker can be easily modified and thus gave us more diversity in our final products, which also minimized the amount of work to synthesize several derivatives. The synthesis started from the chiral alcohol **7** (**Scheme 1**), which was coupled with allyl bromide or linker **9** providing compounds **10** and **11** (**Scheme 4**). After coupling with Fmoc-*S*-pipecolate (**12**/**13**), the constructs were deprotected resulting in the free secondary amines **14** and **15**.



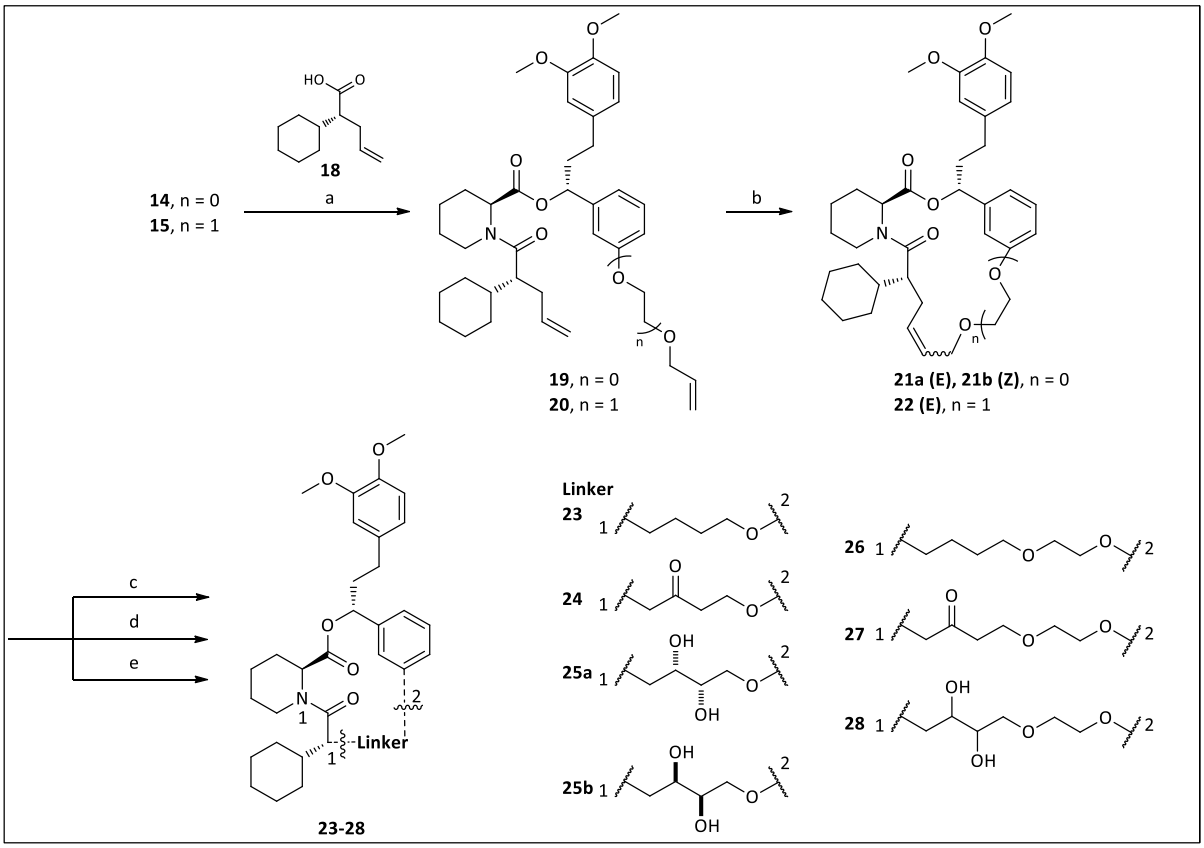
Scheme 4. a) K_2CO_3, allyl bromide or **9**, MeCN, rt; b) DCC, DMAP, Fmoc-*S*-pipecolate, DCM; c) 20% 4-methyl piperidine in DMF.

To insert the selectivity inducing moiety as in SAFit, we synthesized the chiral cyclohexyl bearing compound **18** as described by Feng et al. (**Scheme 5**).[40]



Scheme 5. a) N-BuLi, THF; b) LiHMDS, allyl bromide, THF; c) LiOH, H_2O_2, THF/H_2O.

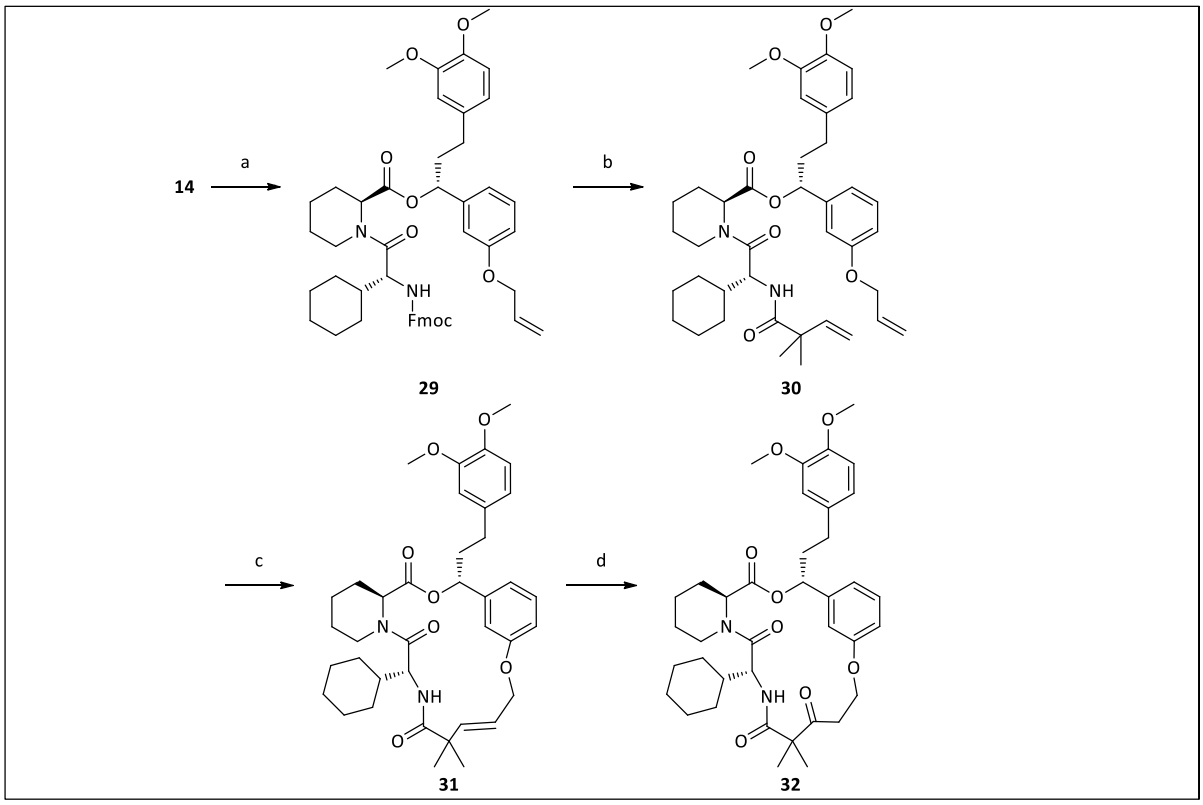
2-Cyclohexylacetyl chloride is coupled with the *Evans* auxiliary (**16**) and further reacted with allyl bromide (**17**), then deprotected to get the chiral carboxylic acid **18**.



Scheme 6. a) **18**, HATU, HOAt, DIPEA, DMF; b) Grubbs-2 cat., DCM; c) Wilkinson cat. or Pt/C, DCM/MeOH, 1 bar H_2; d) $PdCl_2$, *p*-benzoquinone, THF/H_2O; e) OsO_4, NMO, Ac/H_2O.

18 was coupled with the amines **14** and **15** under a standard peptide coupling method providing the linear amides **19** and **20** (**Scheme 6**). The ring-closing metathesis was conducted as described by Lee and Grubbs[61], which gave us excellent yields of the macrocycles **21** and **22** (86% and 92%). For **21** we were able to separate both E and Z isomer, which were in an 89:11 ratio present in the crude mixture and for the larger macrocycle **22** we only isolated the E-isomer as determined by NMR. To introduce additional functionalities into the linker, we further derivatized the E-isomers by *Wilkinson* or Pt/C reduction (**23**/**26**), by *Wacker*-Oxidation (**24**/**27**) as described by Miller et al.[62] or dihydroxylation (**25**/**28**), which resulted in only one Wacker product respectively. The dihydroxylated diastereomeric mixture was separable for the smaller macrocycle. For the larger macrocycle, we only got an inseparable dihydroxylated diastereomeric mixture.

Partially based on the macrocyclic FKBP12 ligands by Holt et al.[38] we additionally synthesized geminal methyl bearing compound **31** (**Scheme 7**). Starting from the amine **14** we coupled cyclohexyl glycine (**29**), which we deprotected with DBU within 3 minutes and directly reacted with the acid chloride of 2,2-dimethylbut-3-enoic acid. The Fmoc deprotection of **29** underwent under standard conditions (20% 4-methyl piperidine in DMF, 15 min, r.t.) a side reaction, in which the deprotected amine cleaved off the piperidine and formed a diketopiperazine. The side product having a mass of 250 g/mol was confirmed via LCMS in the deprotection solution.



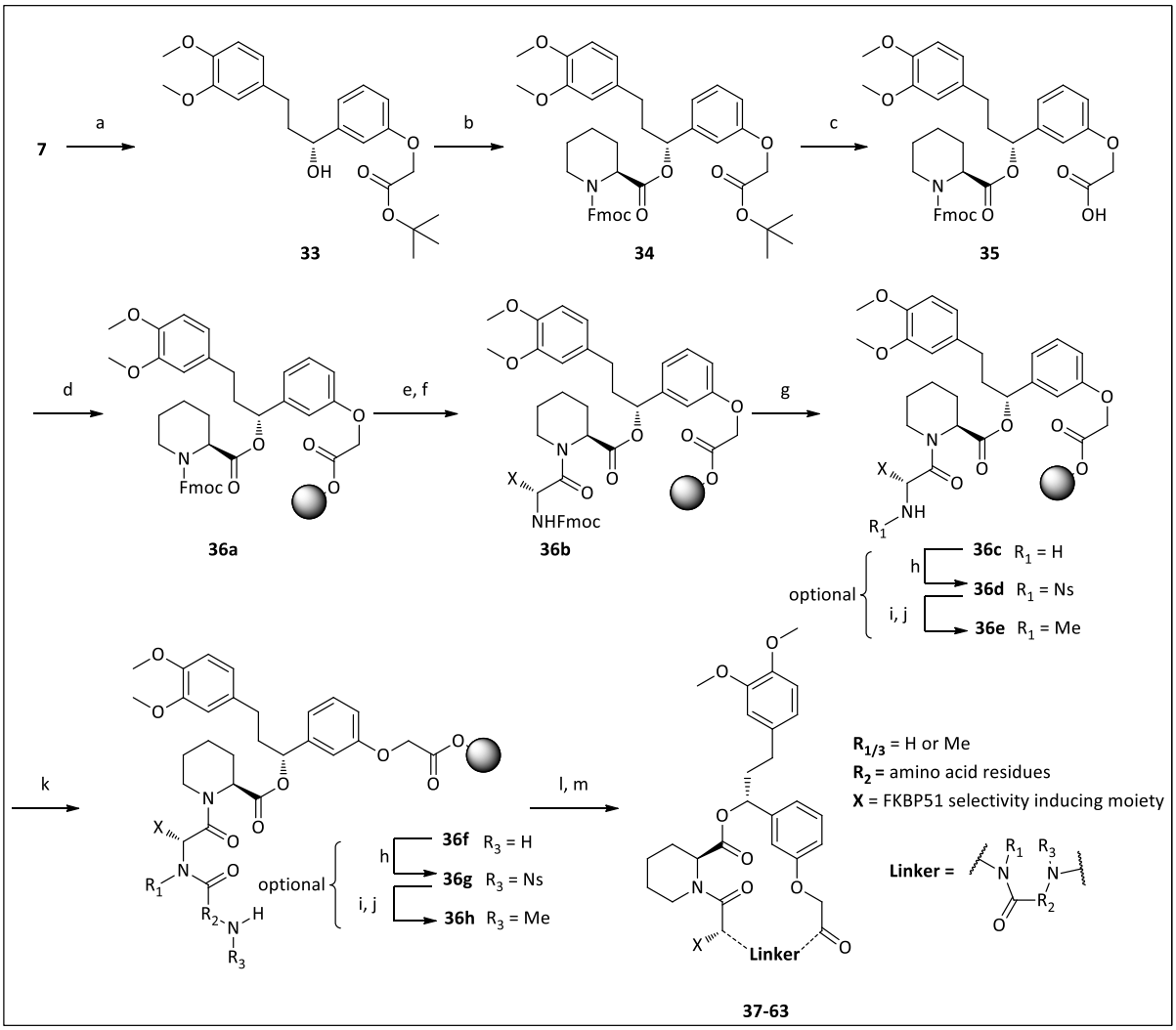
Scheme 7. a) Fmoc-D-Chg-OH, HATU, HOAt, DIPEA, DMF; b) DBU, DCM, 3 min, then 2,2-dimethylbut-3-enoic acid chloride is added c) Grubbs-2 cat., *p*-benzoquinone, toluene, 80°C; d) $PdCl_2$, *p*-benzoquinone, THF/H_2O.

To prevent this, we screened the reaction with differing concentrations of 4-methyl piperidine in time dependency but only got again diketopiperazine as a side product. Thus, we changed the base to DBU, which is known to deprotect Fmoc very rapidly. Here we also observed side product formation, but only after reaction times over 5 minutes. The diketopiperazine formation, unfortunately, was favored in the subsequent coupling of 2,2-dimethylbut-3-enoic acid via HATU coupling. We therefore freshly prepared the acid chloride and added it directly to the DBU deprotection solution, which provided us with compound **30** in good yield (74% over two steps). The RCM of the linear construct was first conducted as described above in DCM at 30°C but did not show conversion. Due to that we changed the solvent system to toluene and heated stepwise to 80°C until we observed conversion. Unfortunately, LCMS analysis revealed a majorly running side reaction with the metathesis catalysts, where the aromatic allyl must have undergone double bond transfer towards the vinyl ether and subsequently been cleaved off. The alkene isomerization side reaction with ruthenium catalysts was already described by Cadot et al.[63] and its prevention by Hong et al.[64]. The addition of *p*-benzoquinone is postulated to work as a ruthenium hydride quencher, the species, which is believed to conduct the side reaction. Indeed, *p*-benzoquinone worked with our system as well, although the yield of **31** was still mediocre (38%), possibly due to steric hindrance caused by the geminal methyls. Due to low amounts of the compound, we conducted only the well-behaving *Wacker* oxidation (**32**) as the derivatization method.

Unfortunately, almost none of the macrocycles closed by RCM did not show detectable binding to FKBP51 in a fluorescence polarization assay.[65] Gratifyingly, the 18-membered dihydroxylated macrocycle **28** of the larger macrocycle bound to FKBP51 with a K_i of 1.2 µM. Surprisingly, however, **28** did not bind to FKBP12 or FKBP12.6 and as expected no binding to FKBP52 was observed (see supplement Figure 17). The second compound showing detectable affinity was the macrocycle **32**, which bound FKBP51 with a K_i of 0.78 µM, no FKBP52, FKBP12 1.9 µM and FKBP12.6 7.6 µM. What most piqued our interest was the novel FKBP51 selectivity of compound **28** over FKBP12 and 12.6, which we further investigated by the synthesis of macrolactams with similar sizes of 17-19 membered rings.

3.2.2. Macrocyclization through macrolactamization

We set out to investigate the unprecedented but highly desired FKBP51 selectivity of the RCM macrocycle **28** in more detail, utilizing amino acids to rapidly explore the effect of the linker.



Scheme 8. a) *tert*-butyl bromoacetate, K_2CO_3, MeCN; b) Fmoc-*S*-Pip-OH, DCC, DMAP, DCM; c) 20% TFA in DCM; d) 2-CTC resin, DIPEA, DCM; e) 20% 4-methyl piperidine in DMF, rt, 3x10 min; f) Fmoc-D-Chg-OH, HATU, HOAt, DIPEA, DMF; g) 5% 4-methyl piperidine in DMF, 0°C, 3x5 min; h) NosCl, Collidine, DMF; i) PPh_3, dry MeOH, DIAD, dry THF, rt, 3x10 min; j) β-mercapto

ethanol, DBU, DMF, rt, 3x10 min; k) Fmoc-AA-OH, HATU, HOAt, DIPEA, DMF; l) 20% HFIP in DCM; m) 1 mM in DMF, HATU, DIPEA.

Applying the Fmoc solid-phase peptide synthesis (SPPS) strategy, we started from the chiral alcohol **7**, which we coupled with *tert*-butyl bromoacetate (**33**), then with Fmoc-*S*-pipecolate (**34**, **Scheme 8**). The precursor for all final substances was deprotected with TFA (**35**) and loaded onto 2-chloro trityl (2-CTC) resin (**36a**). After Fmoc deprotection we introduced D-cyclohexyl glycine as the FKBP52-discriminating moiety (**36b**) and synthesized varying macrocycles with differing linkers achieved by the incorporation of natural and unnatural amino acids. Optionally, we *N*-methylated the amino acids to probe the influence of the now blocked amide groups. *N*-methylation is often used as a tool to enhance compounds' metabolic stability. Additionally, one might enhance and rigidify the cycle's conformation to get a favorable entropic contribution upon ligand binding.[66, 67] The Fmoc deprotection of **36b** underwent under standard conditions (20% 4-methyl piperidine in DMF, 15 min, r.t.), as already mentioned above, a diketopiperazine side product formation. To suppress this, the reaction was done with 5% 4-methyl piperidine in DMF at 0°C in 5 min.[68] This was only possible on solid-phase and not in solution since a longer reaction time under these enhanced conditions showed again an increased amount of side product. Finally, the linear peptides were cleaved from the resin and cyclized in the crude state by macrolactamization (**37**-**63**). Here we diluted down to 1 mM in DMF and cyclized with the coupling reagent HATU overnight. These macrocyclization conditions worked for all linear constructs presented here. Other coupling conditions with the reagents DPPA and PyBOP were tested as well but did not surpass formerly mentioned conditions.

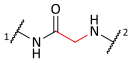
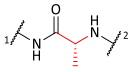
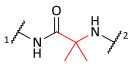
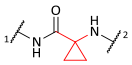
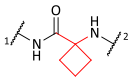
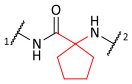
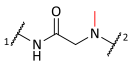
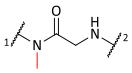
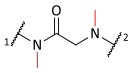
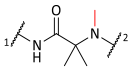
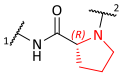
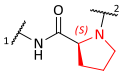
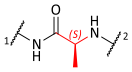
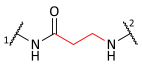
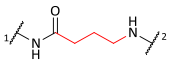
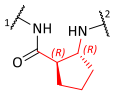
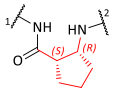
We additionally synthesized a library screening for differing selectivity inducing moieties (**X**), where we simply exchanged the cyclohexyl by several suiting D-amino acids and kept the second amino acid constant as Aib.

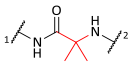
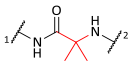
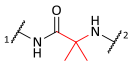
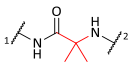
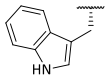
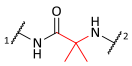
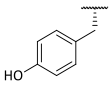
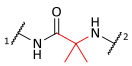
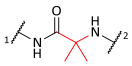
3.2.3. Binding affinities (Fluorescence polarization assay)

All final compounds were screened for affinity towards the FKBPs 51, 52, 12 and 12.6 in a competitive fluorescence polarization assay.[65, 69] Gratifyingly, most of the macrocycles with amino acid-based linkers bound to FKBP51 in the low to submicromolar range (**Table 1**). Most importantly, however, none of the macrocycles did show any affinity towards FKBP12, FKB12.6, or FKBP52. The glycine derivative **37** had an affinity of 2.3 µM, which gradually increased with an increasing substitution (**38** (D-Ala): 1.0 µM, **39** (Aib): 0.29 µM). For the geminal cyclic amino acids, the affinity slightly decreased with size (**40**: 0.40 µM, **41**: 0.40 µM, **42**: 1.3 µM).

N-methylation of glycine did not affect affinity majorly [**43** (R_3 = Me): 3.1 µM)]. Likewise, single *N*-methylation of the D-Chg [**44** (R_1 = Me): 0.96 µM] had no considerable effect on the affinity and the double *N*-methylated compound **45** showed a decrease in binding affinity towards FKBP51. The *N*-methylated Aib analog **46** also displayed this behavior.

Table 1. Affinities of macrocycles with amino acid-containing linker determined by a competitive fluorescence polarization assay; [a] standard error from three independent measurements; [b] values derived from literature[29, 70]; [c] error from two independent measurements; *82% purity with a 75:25 diastereomeric mixture.

Cmpd. Nr. (Journal)	Purity 254 nm [%]	X	Linker	FKBP51FK1	FKBP12	FKBP12.6
				K_i [µM]		
SAFit1		**Figure 1**		0.004±0.001[a]	0.163±0.009[a]	0.019±0.002[a]
FK506		**Figure 1**		0.104[b]	0.0006[b]	0.004[b]
37 (AV011)	95			2.30±0.05[c]	>80	>80
38 (AV022)	96			1.00	>80	>80
39 (AV023/183)	99			0.29±0.05[a]	>80	>80
40 (AV075)	96			0.40±0.05[a]	>80	>80
41 (AV293)	99			0.40	>80	>80
42 (AV076)	98			1.30	>80	>80
43 (AV658)	99			3.10	>80	>80
44 (AV087)	98			0.96±0.14[c]	>80	>80
45 (AV160)	97			5.30±0.50[c]	>80	>80
46 (AV168)	89			0.37	>80	>80
47 (AV041)	99			0.80	>80	>80
48 (AV042)	99			5.10	>80	>80
49 (AV021)	96			17	>80	>80
50 (AV024)	99			7.40	>80	>80
51 (AV077)	99			>80	>80	>80
52 (AV079)	99			1.80	>80	>80
53 (AV078)	99			>80	>80	>80

54* **(AV419)**	82			1.30	>80	>80
55 (424)	99			2.50	>80	>80
56 (AV422)	99			4.70	>80	>80
57 (425)	84			>80	>80	>80
59 (AV454)	99			>80	>80	>80
61 (AV458)	89			>80	>80	>80
63 (AV457)	99			>80	>80	>80

Unfortunately, we could not synthesize the other *N*-methylated Aib analogs. The coupling of the highly sterically hindered Aib to the *N*-methylated D-Chg simply did not occur under various coupling conditions. (HATU + Fmoc-AIB-OH, Fmoc-Aib-Cl, Fmoc-Aib-F, Nos-Aib-Cl).[71, 72] *N*-cyclization [**47** (D-Pro): 0.80 µM] did, similarly to *N*-methylation not increase binding significantly. In contrast, the L-Pro derivative (**48**: 5.1 µM) displayed even worse affinity compared to D-Pro and similarly the L-Ala derivative (**49**: 17 µM) in comparison to D-Ala.

Longer amino acid linkers reduced affinity [**50** (β-Ala): 7.4 µM and GABA **51** (no binding)], which could be compensated by appropriate rigidification as in **52** (1.8 µM; other diastereomer **53** inactive). Some of the crude linear constructs were also tested in the FP-assay. These displayed mostly no binding or binding in a higher magnitude than their cyclic counterparts (>20 µM), underlining the significance of the macrocyclization.

Additionally, we proved that the cyclohexyl moiety is best suited for selectivity as well as high affinity at least in the range of commercially available natural and unnatural amino acids. All tested derivatives (**54**-**63**) showed decreased affinities towards FKBP51 but also displayed selectivity over FKBP12 and 12.6. The residues D-Phg, D-Trp, D-His and D-Tyr (**57**-**63**) did not show any binding.

The affinities of compounds **37** and **40** for FKBP51FK1 determined by FP-assay (**Figure 6**) were again confirmed by isothermal titration calorimetry (ITC), yielding an enthalpy-driven K_d = 3.6 µM ± 0.9 µM for **37** and K_d = 0.6 µM ± 0.1 µM for **40** respectively (**Figure 7,** data measured and provided by Dr. Christian Meyners).

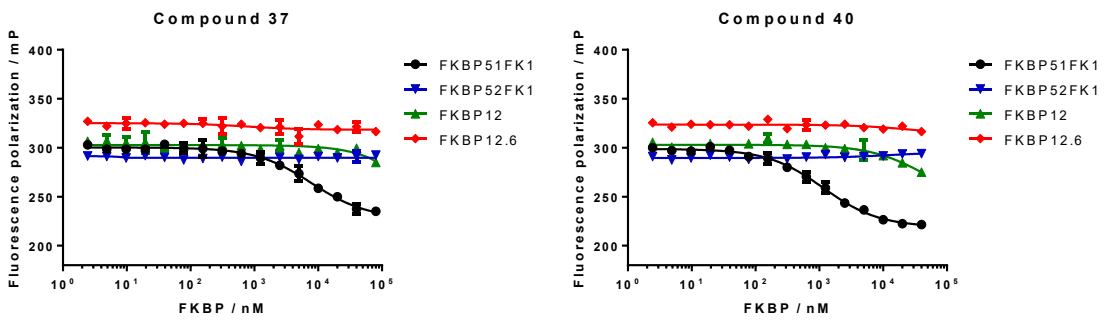


Figure 6. FP-Assay binding curves of compounds **37** and **40**.

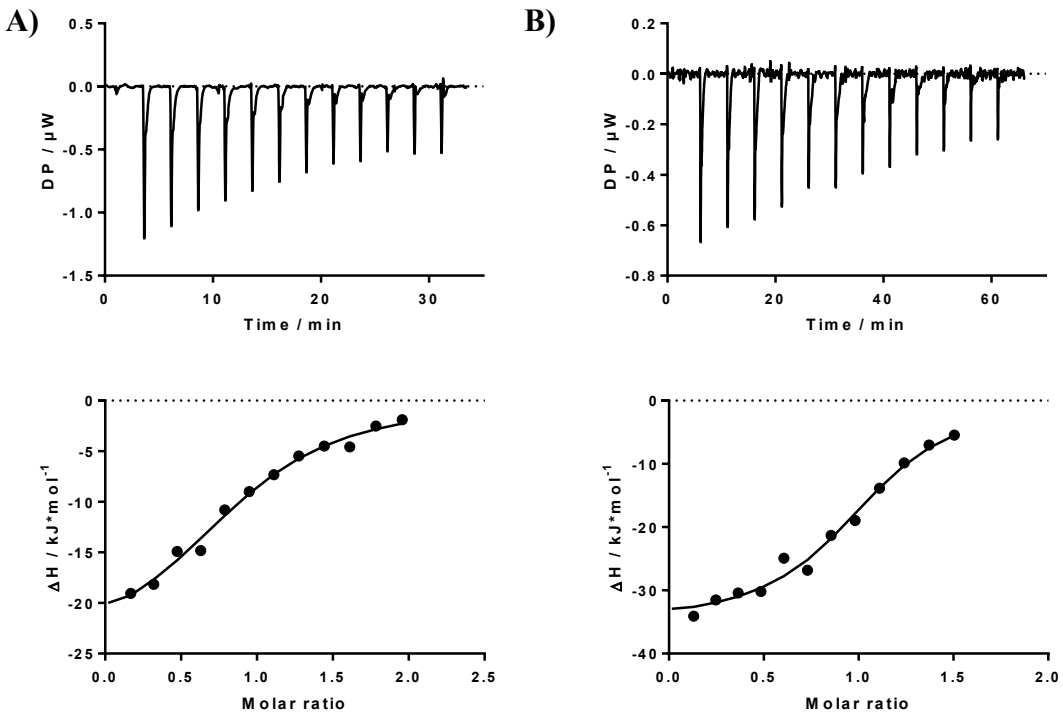


Figure 7. A) Binding of compound **37** to FKBP51FK1 determined by isothermal titration calorimetry at 25 °C. A 20 µM solution FKBP51FK1 formulated in 20 mM HEPES pH 8.0, 20 mM NaCl, 5% glycerol and 2% DMSO was placed in the sample cell of a PEAK-ITC instrument. The syringe was filled with a 200 µM solution of **37** formulated in the same buffer. After equilibration, the compound was titrated into the sample cell by 12 injections of 3 µl each. The obtained data were analyzed using the provided software package and fitted to a one-site binding model yielding a K_d-value of 3600 ± 900 nM (mean ± SD from 3 independent experiments). **B)** Binding of compound **40** to FKBP51FK1 determined by isothermal titration calorimetry at 25 °C. A 13 µM solution FKBP51FK1 formulated in 20 mM HEPES pH 8.0, 20 mM NaCl, 5% glycerol and 2% DMSO was placed in the sample cell of a PEAK-ITC instrument. The syringe was filled with a 100 µM solution of **40** formulated in the same buffer. After equilibration, the compound was titrated into the sample cell by 12 injections of 3 µl each. The obtained data were analyzed using the provided software package and fitted to a one-site binding model yielding a K_d-value of 600 ± 100 nM (mean ± SD from 3 independent experiments); Data provided by Dr. Christian Meyners.

3.2.4. Structural basis for FKBP51 selectivity by co-crystal structures

To clarify the structural basis for the unprecedented selectivity of the peptidic macrocycles, we solved in cooperation with Dr. Andreas Bracher from the Max Planck Institue of Biochemistry (Martinsried, Munich) and Dr. Christian Meyners (TU Darmstadt, AK Hausch) the crystal structures of compound **37**, **40** and **46** (PDB-ID: 7aot, 7aou and 7awf) in complex with FKBP51FK1 A19T.[73] As expected, the interactions of the pipecolate, the A- and B-rings, as well as the cyclohexyl group with FKBP51, were completely conserved in comparison to previous FKBP51-SAFit cocrystal structures (**Figure 8**).

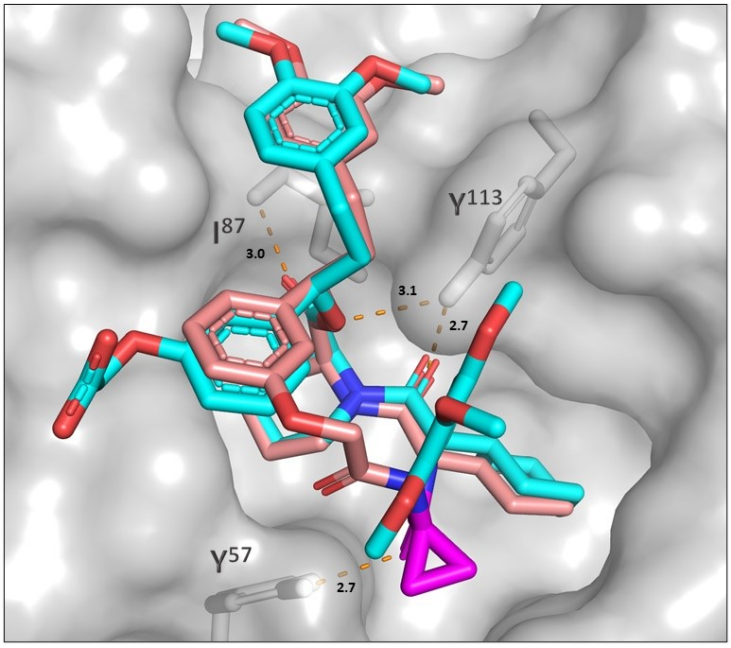


Figure 8. Crystal structure of the FK1 domain of FKBP51 in complex with **40** (pink-colored sticks, linker region in magenta, PDB-ID: 7aou), key interactions with the residues I^{87}, Y^{113} and Y^{57} indicated as orange broken line (distance in Å) in overlap with the crystal structure of SAFit1 (cyan-colored sticks, not published, provided by Dr. Christian Meyners) indicating the conservation of the key interactions. Due to the high similarity of the co-crystal structure of compounds **37**, **40** and **46**, only **40** is depicted.

This includes a displacement of F^{67}, which is responsible for the strong selectivity vs. FKBP52 of SAFit-like ligands.[13, 40-42] However, the β3b strand which contains F^{67} and which previously was shown to display enhanced basal mobility[74] was substantially rearranged (**Figure 9**).

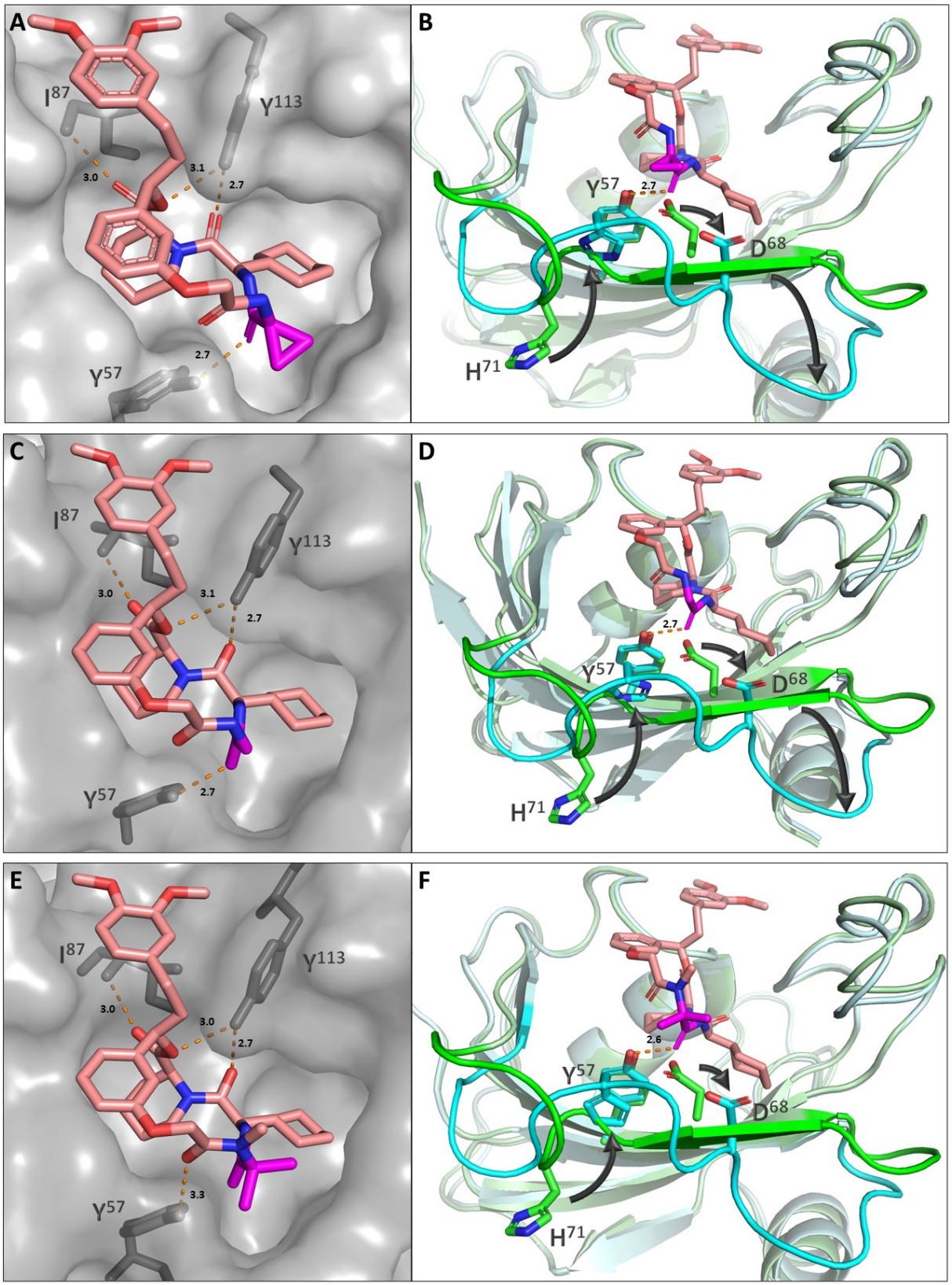


Figure 9. A) Crystal structure of the FK1 domain of FKBP51 in complex with **40** (pink-colored sticks), key interactions with the residues I^{87}, Y^{113} and Y^{57} indicated as orange broken line (distance in Å). **B)** Crystal structure of the FK1 domain of FKBP51 (pale cyan) in complex with **40** (pink-colored sticks) superimposed to the structure of the SAFit1-analog iFit4 in complex with FKBP51FK1 (pale green, pdb-ID: 4tw7, iFit4 has been omitted for clarity). The β3b strand is highlighted in cyan and green, respectively, and key residues Y^{57}, D^{68} and H^{71} are shown as sticks. The key carbonyl of **40** displacing D^{68} is highlighted in magenta and the new hydrogen bond between Y^{57} and D^{68} in complex with **40** is indicated as an orange broken line.

C) Same display of compound **37** as described in A. **D)** Same display of compound **37** as described under point B. **E)** Same display of compound **46** as described in A. **F)** Same display of compound **46** as described under point B.

Strikingly, we observed that a carbonyl group of **37**, **40** and **46** displaced D^{68} and replaced it as a hydrogen bond acceptor for the ε-hydroxyl group of Y^{57}. The rearrangement of the β3b strand is stabilized by an inward flip of H^{71}, which partially replaces S^{70} and substitutes the former as a hydrogen bond donor for the backbone carbonyl of Y^{57}. A similar inward flip of H^{71} has previously been observed for FKBP51 in complex with Rapamycin and FRB (pdb: 4drh).[75] Intriguingly, H^{71} is replaced in FKBP12 and FKBP12.6 by an arginine (R^{40} in FKBP12/12.6 numbering), which can be expected to be less efficient in stabilizing the **37**/**40**/**46**-binding conformation, providing a molecular rationale for the discrimination *vs.* FKBP12/12.6 observed for the macrocycles.

The macrocyclic ligands selectivity and its weaker binding affinity in comparison to SAFit1 might also be explained by the molecular dynamics (MD) simulation of compound **40** bound to the FKBP51FK1 domain (**Figure 10**). In cooperation with Dr. Daniel Tietze, we employed the program YASARA to calculate a 200 ns MD simulation of the protein-ligand complex in aqueous solution at room temperature, with structural snapshots taken every 100 ps. The protein itself did not show significant changes like secondary structure unfolding or refolding during the whole MD simulation, indicated by the mostly constant rmsd. The linker of compound **40** displays higher flexibility indicated by the average B-factor, which could keep the β3b strand also in its rearranged form. On the other hand, a too flexible ligand might also have several conformations, which do not fit well into the protein's pocket, leading in comparison to the SAFit ligands to weaker affinity.

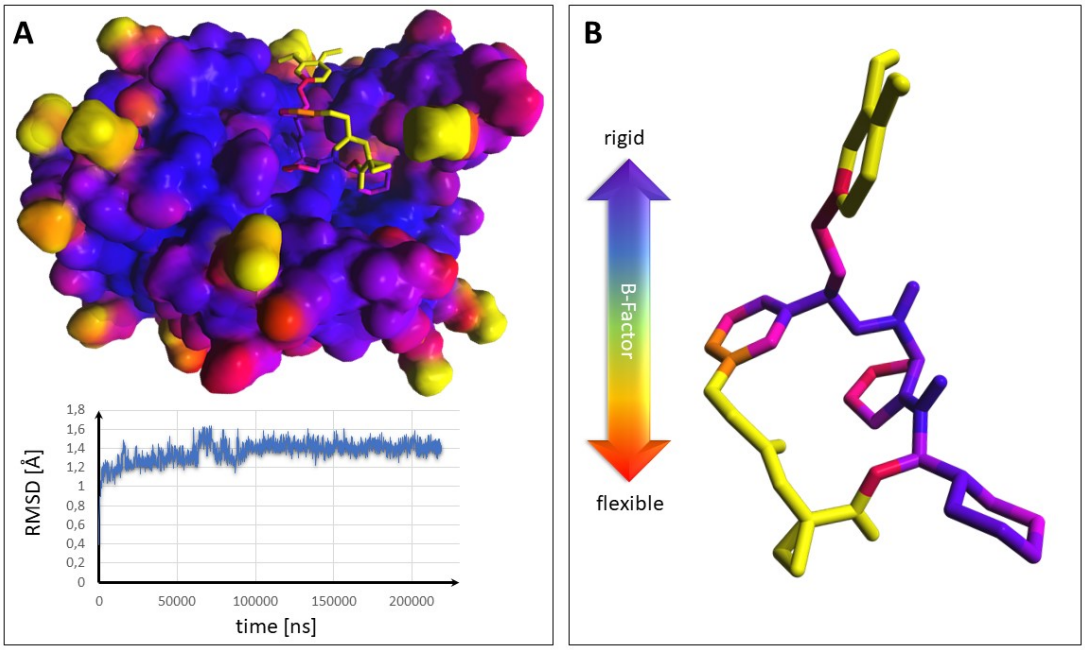
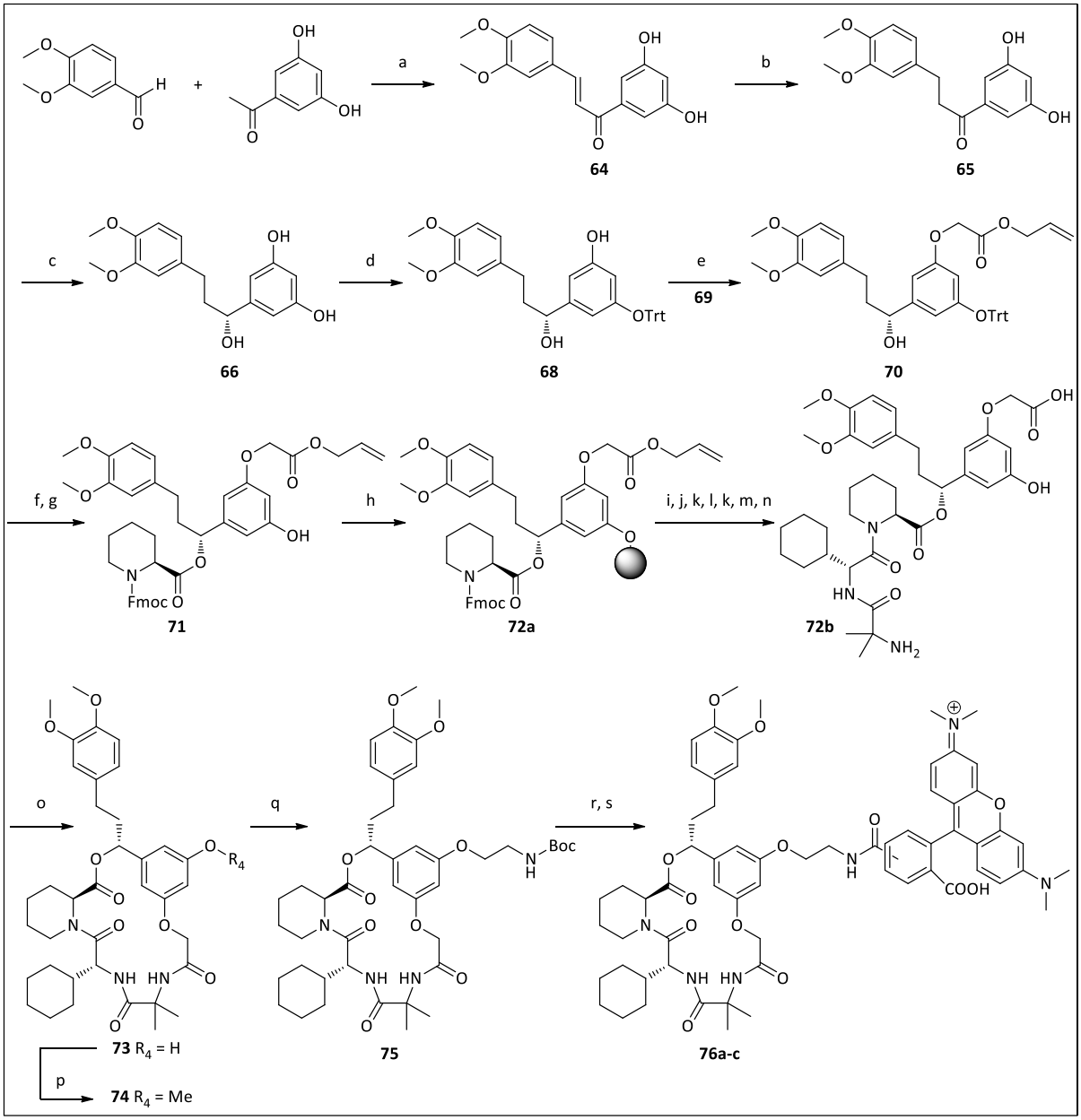


Figure 10. A) The ligand **40** bound to the FKBP51FK1 domain is MD simulated for 200 ns in a water shell at r.t. by employing the Yasara molecular modeling program.[76, 77] The average B-factor is displayed in the color code from blue to red. The relatively stable rmsd value over time indicates no extreme changes in the overall structure. **B)** A zoomed-in view of the averaged ligand conformation of compound **40** and its flexibility indicated by the B-factor coloring.

Nonetheless, our results provide the first ligands that robustly discriminate between FKBP51 and FKBP12 and FKBP12.6 and provide a structural basis for the rational design for further lead optimization. As mentioned above, FKBP12 and FKBP12.6 are cofactors of the ryanodine receptor[31-33] and play an important role in fine-tuning the excitability of smooth or heart muscle. FKBP12 knockout or knockdown leads to severe cardiac defects,[34, 35] underscoring the importance of selectivity for FKBP51 over FKBP12/12.6 in FKBP51-based therapies.

3.2.5. Fluorescent macrocyclic tracer as proof of concept of selective FKBP51 binding

We decided to synthesize a probe to further elucidate these highly selective ligands by attaching a TAMRA fluorophore (**76, Scheme 9**) with the best binding compound **39** (**Table 1**). Starting from the co-crystal structure (**Figure 8**) we thought to add the fluorophores linker onto the B ring in meta position, where the exit vector would behave like a prolongation of the carboxylic acid of SAFit1.



Scheme 9. Reaction scheme for the meta B ring modification and the TAMRA coupled fluorescent tracer. a) NaOH, EtOH/H_2O, 0°C-rt; b) Zn, NH_4Cl, MeOH; c) $RuCl_2$[(*S*)-(DM-SEGPHOS)][(*S*)-DAIPEN], THF, 10 bar H_2, KOtBu, rt; d) TrtCl, K_2CO_3, MeCN; e) **76**, K_2CO_3, MeCN; f) DCC, Fmoc-*S*-Pipecolate, DMAP, DCM; g) 1% TFA in DCM; h) 2-CTC-resin, DIPEA, DCM; i) 20% 4-methyl piperidine in DMF, 3x10 min; j) Fmoc-D-Chg-OH, HATU, HOAt, DIPEA, DMF; k) 5% 4-Me-piperidine in DMF, 0°C, 3x5 min; l) Fmoc-Aib-OH, HATU, HOAt, DIPEA, DMF; m) $Pd(OAc)_2$, morpholine, PPh_3, THF; n) 20% HFIP in DCM; o) HATU, pentafluoro phenol, 1 mM in DMF, p) MeI, K_2CO_3, q) Ag_2CO_3, tert-butyl (2-bromoethyl) carbamate; (MeCN) r) DCM/TFA, 4/1 s) TEA, 5 (6)-NHS-TAMRA, (DMF).

Preliminary works towards the synthesis route were performed by the master student Matthias Roth under my supervision.[51] We started with the *Claisen-Schmidt* reaction of the respective ketone and

aldehyde providing the chalcone **64**, which was chemo-selectively (**65**) and then asymmetrically reduced (**66**). The racemic alcohol (**67**) was synthesized using $NaBH_4$ reduction to determine the enantiomeric ratio via chiral column HPLC. The diphenol needed protection for further handling, which was achieved by mono tritylation (**68**) followed by reaction with the freshly prepared linker allyl 2-bromoacetate (**69**). Compound **70** was then coupled with Fmoc-*S*-pipecolate and the trityl group was removed yielding **71**. The free phenol was loaded onto 2-CTC resin (**72a**) and further coupled under standard SPPS conditions providing **72b**. The linear construct was cyclized in solution (**73**) and further methylated (**74**). For the macrocyclization reaction with HATU, a side product with a mass corresponding to the uronium salt of the phenol was observed. Attempts of removing this group under basic conditions did also result in ring-opening. Thus, we tried different coupling reagents (DPPA, PyBOP, HBTU) and additives (HOAt, pentafluorophenol). Fortunately, we were able to prevent the side reaction by using HATU together with an excess of pentafluorophenol as a scavenger of the reactive species. The meta hydroxy (**73**) and its methoxy (**74**) analog were tested in an FP-assay (**Table 2**) and displayed a slightly decreased affinity towards FKBP51 (0.37-0.39 µM) in comparison to its parent compound **39** and no binding of FKBP52, 12 and 12.6.

Table 2. Ki values were determined by a competitive fluorescence polarization assay; [a] standard error from three independent measurements.

Cmpd.	R_4	FKBP51FK1
		K_i [µM]
39	No substituent	0.29±0.05[a]
73	H	0.37
74	Me	0.39

The macrocyclic tracer was synthesized starting from compound **73**. First, a linker was added by a nucleophilic substitution reaction with *tert*-butyl-(2-bromoethyl) carbamate, which was deprotected with TFA and finally coupled with an *N*-hydroxy succinimide activated 5-(6)-TAMRA fluorophore providing the regioisomers of compound **76**. The regioisomers stemming from the used regioisomeric fluorophor could be separated and three fractions were obtained: **76a** (pure regioisomer 1), **76b** (mixed fraction of both isomers 34 to 66 ratio) and **76c** (regioisomer 2 still containing 12% isomer 1).

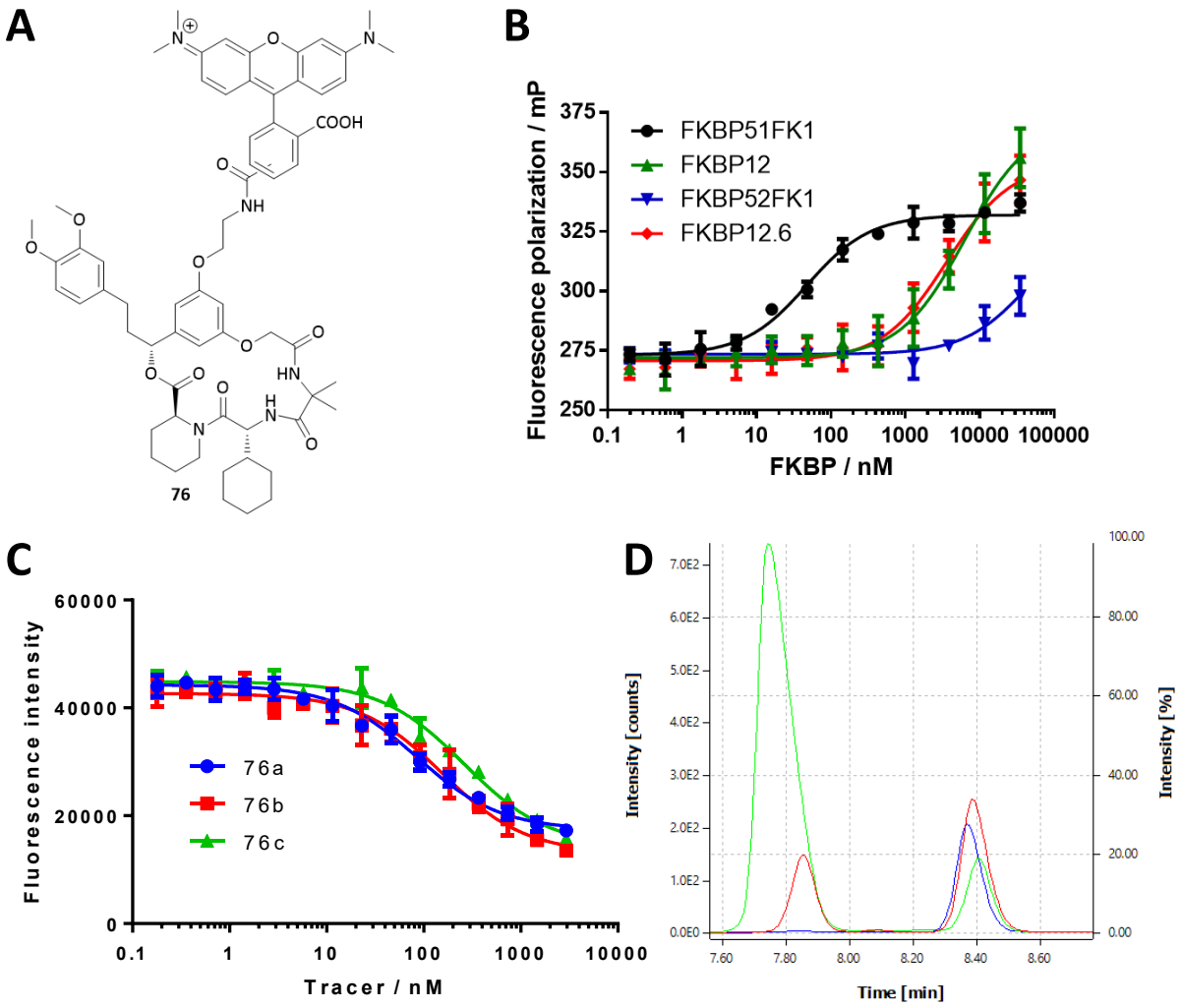


Figure 11. A) Structure of the TAMRA labeled tracer **76a** 5 or 6-TAMRA regioisomer. **B)** Binding of the TAMRA-tracer **76a** to FKBPs 51, 52, 12 and 12.6 determined by a fluorescence polarization assay yielding K_d-values of 45 ± 7 nM for FKBP51FK1, 6 ± 1.4 µM for FKBP12, >80 µM for FKBP52FK1 and 3.6 ± 0.8 µM for FKBP12.6. The error bars represent the standard deviation of three independent experiments. **C)** The FRET assay of **76** with fluorescein-labeled FKBP51FK1 domain. A serial dilution series of the tracer was placed in a microplate and supplemented with 5 nM of fluorescein-labeled FKBP51FK1. The binding of the tracer resulted in quenching of the fluorescein signal observable as a decrease in the fluorescence intensity at 530 nm upon excitation at 485 nm. The obtained data were plotted against the tracer concentration and fitted to a binary binding model yielding for **76a** a K_d-value of 80 ± 10 nM, for **76b** a K_d-value of 150 ±25 nM and **76c** a K_d-value of 380 ± 35 nM. The error bars represent the standard deviation of three independent experiments. **D**) The overlay of the analytical HPLC chromatogram of **76a** (blue), **76b** (red) and **76c** (green) displaying the ratio of the regioisomers.

All three fractions were tested for binding in a FRET-assay with **76a** having the highest affinity (K_d = 80 ± 10 nM; **Figure 11C**). The FRET was measured with a fluorescein-labeled FKBP51FK1 domain (C103A/C107I/E140C, with the fluoresceine label on cysteine 140). The affinity of the tracer **76a** was further confirmed in an FP-assay, which bound directly to FKBP51 (K_d = 45 ± 7 nM) but poorly to FKBP12, FKBP12.6 or FKBP52 (**Figure 11B**) confirming the high preference of FKBP51 by the macrocyclic structures. The sudden rise in affinity can be explained by additional interactions of the TAMRA with the surface of the protein. Unfortunately, due to the low quantity, the large structure of this compound and rotamers in the NMR we could not elucidate, which of the regioisomers was the more potent one.

Synthesis of the tracer with the pure NHS-TAMRA fluorophore should give more insight in future works.

3.2.6. More insight into the structural basis for selectivity by co-crystal structures

To get further insight into the structural basis for the unprecedented selectivity of the macrocycles, we solved another two co-crystal structures of the latest compounds, the dihydrophenyl glycine containing compound **54** and the meta methoxylated compound **74** in complex with FKBP51FK1 A19T (**Figure 12A** and **B**). Similar to the co-crystal structure of **40** the key-interactions with FKBP51 were completely conserved in comparison to the SAFit1 co-crystal structure along with the displacement of D^{68} by the carbonyl in the macrocycles (**Figure 12C**). Unexpectedly, the unfolding of the β3b strand, as well as the flip of His^{71} did not happen for both of those complexes. These findings suggest a more complex mechanism underlying the high selectivity of these macrocycles but all contain the rearrangement or displacement of D^{68} and disruption of the hydrogen-bond with Y^{57}, which is the current best rationale to explain the specific binding mode of the peptidic macrocycles.

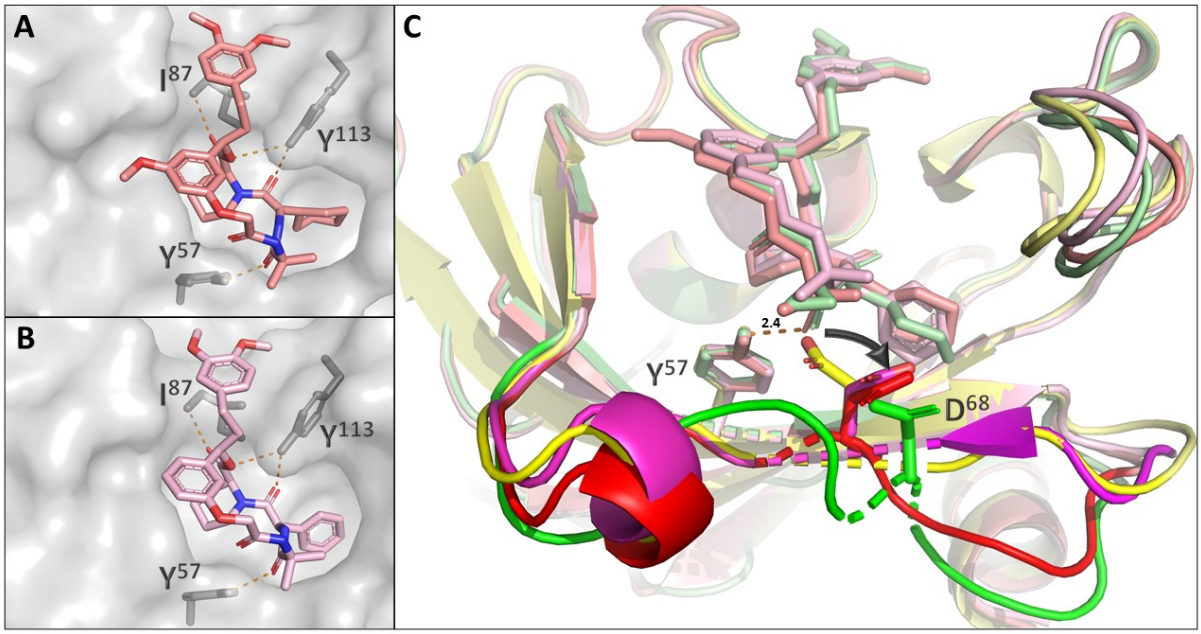


Figure 12. A) Crystal structure of the FK1 domain of FKBP51 in complex with compound **74** (salmon-colored sticks), key interactions with the residues I^{87}, Y^{113} and Y^{57} indicated as orange broken line. **B)** Crystal structure of the FK1 domain of FKBP51 in complex with compound **54** (light-pink-colored sticks), key interactions with the residues I^{87}, Y^{113} and Y^{57} indicated as orange broken line. **C)** Overlay of the crystal structure of the FK1 domain of FKBP51 in complex with **40**, **54** and **74** (pale green-, light-pink- and salmon-colored sticks respectively) superimposed to the structure of the SAFit1-analog iFit4 in complex with FKBP51FK1 (yellow-colored, pdb-ID: 4tw7, iFit4 has been omitted for clarity). The β3b strand is highlighted in green, magenta and red respectively, and key residues Y^{57}, D^{68} and H^{71} are shown as sticks. The key carbonyl of **40**, **54** and **74** displacing D^{68} and the new hydrogen bond is indicated as an orange broken line. The unfolding of the β3b strand, as well as the flip of His^{71} in the complexes of **54** and **74** is not present. Indicating that only the displacement of D^{68} might be more essential for the newfound selectivity over FKBP12 and 12.6.

3.3. Structure-Affinity-Relationships (SAR) of the SAFit A and B ring

3.3.1. Synthesis of novel A/B rings by Claisen-Schmidt chalcone synthesis

We started to explore the essential moieties for high-affinity binding by systematically analyzing the effects of small variations as we aimed to discover the essential binding interactions of the SAFit1 A/B rings. We either exchanged the A or the B ring (**Figure 13**) in the original SAFit structure and kept the other with methoxy substituents constant.

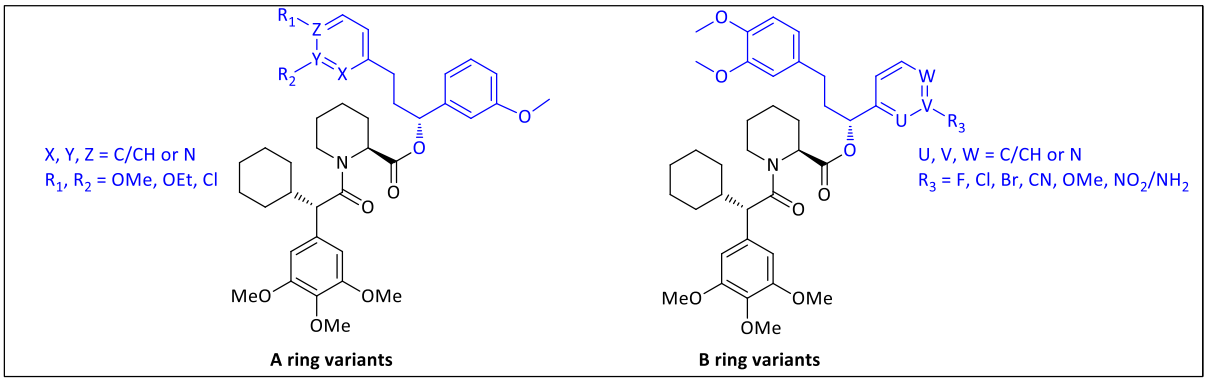
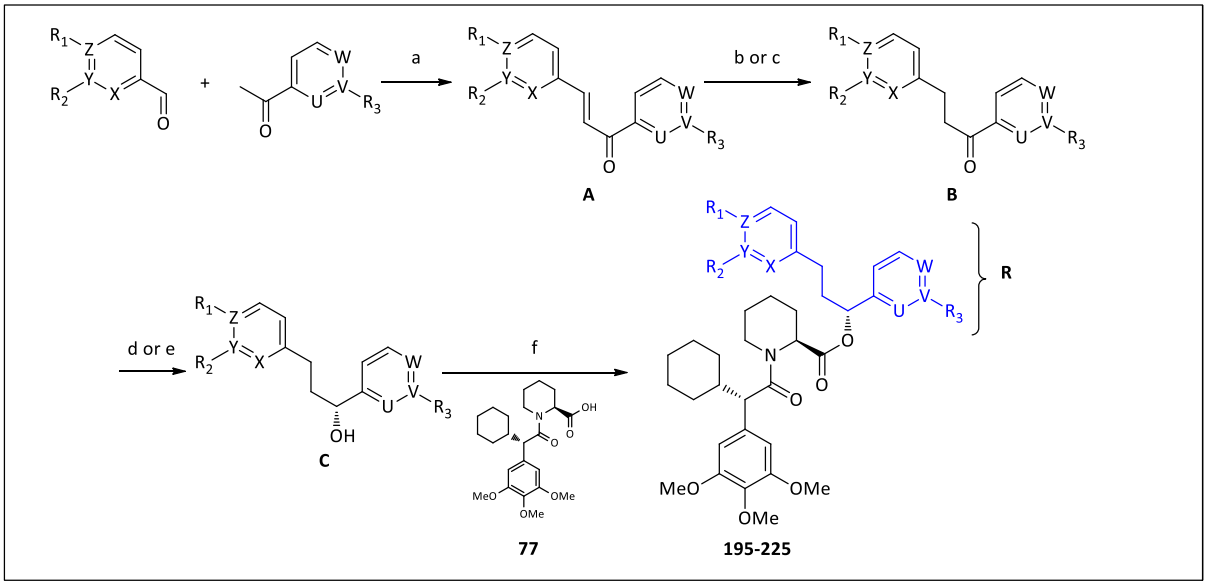


Figure 13. Screening for novel A/B rings. Either the A or B ring was kept constant and the other was varied to be able to compare the influence of differing residues.

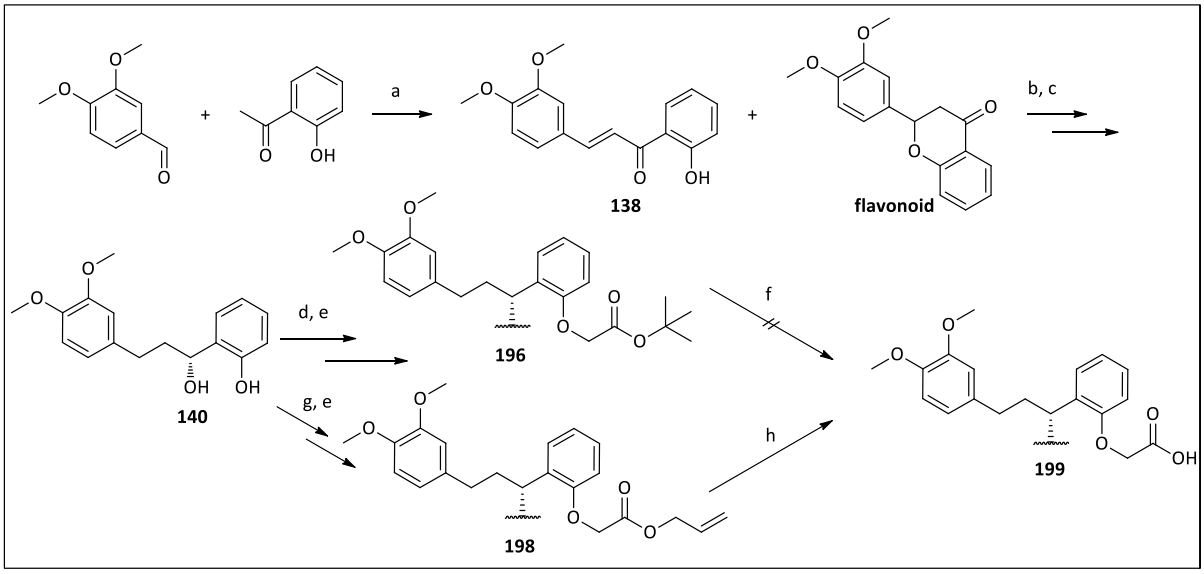
The synthesis began as described for the upscaled synthesis of the SAFit A/B ring (**Scheme 1**) with the *Claisen-Schmidt* reaction, providing the chalcones (**A**, **Scheme 10**).



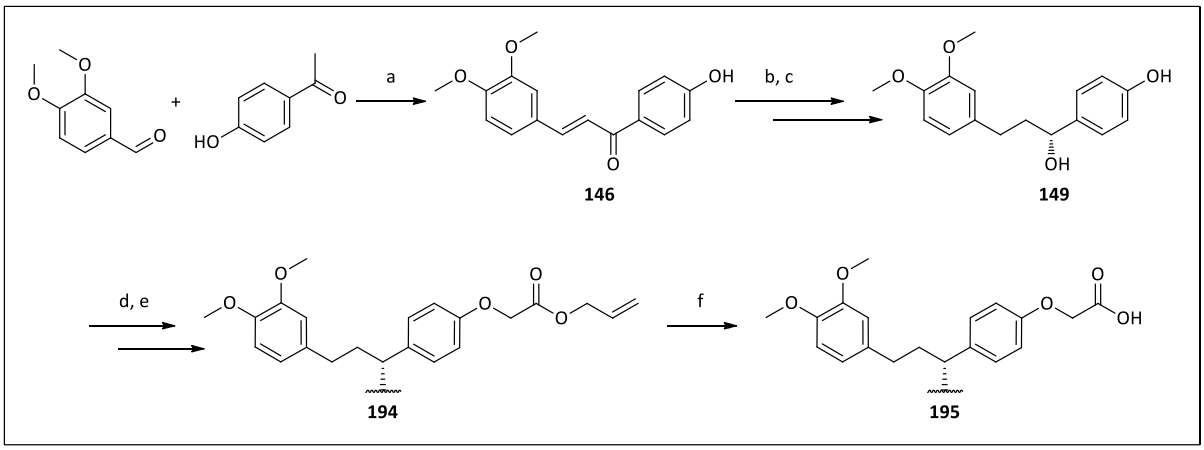
Scheme 10. General synthesis pathway of the A/B ring derivatives for library A. a) NaOH or KOH or Na_2CO_3, ($EtOH/H_2O$); b) Pd/C, 1 bar H_2, (MeOH); c) Zn powder, NH_4Cl, (THF/MeOH); d) CBS cat., BH_3*SMe_2, (THF); e) $RuCl_2$[(S)-(DM-SEGPHOS)][(S)-DAIPEN], (THF), 10 bar H_2, KO*t*Bu; f) **77**, DIC, DMAP, (DCM).

The *Claisen-Schmidt* reaction conditions were modified where necessary. Especially for the insertion of pyridines, we had to optimize due to extensive side reactions. At standard *Claisen-Schmidt* conditions, we observed for pyridine containing top-groups direct *Michael-Addition* of the product

chalcone to the reactants, which gave a complex product mixture barely containing the target products. This was partially prevented by excess usage of the aldehyde and dropwise addition of the ketone (See conditions in the experimental procedures). The reduction (**B**, **Scheme 10**) was done either with Zn/NH_4Cl or $Pd/C + H_2$, where Pd/C worked best for the heteroaromatic- and pyridine chalcones. An asymmetric *Noyori* or *Corey-Bakshi-Shibata* (CBS) reduction provided the chiral alcohol (**C**, **Scheme 10**). We opted for conducting an asymmetric reduction of pyridine containing top groups by *Noyori* catalyst as we observed in the CBS reduction a stable complex formation with the required borane reagent, which often needed excess addition of borane due to the scavenging of the reagent and after reaction an additional deprotection step with concentrated HCl. The *ee* of the alcohol was determined via chiral HPLC using a racemate as a reference, which was synthesized by $NaBH_4$ reduction. The top-groups were then coupled with the building block **77 (Scheme 10)**[13] using the recently published *Steglich* esterification method of Jorgensen et al.,[57] which gave a mixture of diastereomers up to 10% of the final compounds. Coupling under normal *Steglich* conditions (1.0 eq DCC, 0.1 eq DMAP) gave highly diastereomeric mixtures. The final compounds contained ≤ 5% diastereomer after purification as determined by analytical HPLC. Otherwise less pure compounds are marked in the following tables. To evaluate which attachment point on the B ring is the most suiting we also thought of synthesizing regioismers of SAFit1, with changes in the position of the carboxylic acid. Having the phenol on the *para* or *ortho* position required changes in the synthesis (**Scheme 11**). Especially with the "*ortho*-SAFit" (**199**) we initially found in literature research that the *Claisen-Schmidt* synthesis would need the protection of the phenol because the chalcone (**138**) would undergo a further reaction towards the flavonoid[78] We first tried the *Claisen-Schmidt* under slightly modified conditions and got enough product for our purposes (33%). If an increased yield is needed one might try trityl (Trt) or methoxymethyl (Mom) protection of the phenol prior to the *Claisen-Schmidt* reaction. Further synthesis towards the chiral alcohol (**140**) succeeded only with the CBS catalyst, the *Noyori* conditions did not work, probably due to good chelating properties of the starting material. Further synthesis was performed as described for SAFit1[13], which included coupling of the chiral alcohol with the *tert*-butyl protected carboxylic acid, then further coupling of the bottom-core construct **77** as discussed above (**Scheme 10**). The final tert butyl deprotection of **196** under acidic conditions, unfortunately, additionally cleaved the internal ester, which is not observed within the SAFit synthesis. This likewise occurred for the *para*-regioisomer. Other deprotection conditions with $ZnBr_2$ or $Yb(OTf_3)$ as suggested by Greene and Wuts also cleaved the internal ester.[79] Thus, we had to exchange the protecting group and coupled the chiral alcohols with the prior synthesized, allyl protected compound **69**. Final products **195** and **199** were obtained after deprotection with palladium acetate under basic conditions.



Scheme 11. Synthesis of the ortho-SAFit **199**. a) NaOH, EtOH; b) Pd/C, H_2, THF; c) *S*-CBS, BH_3*SMe_2, THF; d) K_2CO_3, *tert*-butyl bromoacetate, MeCN; e) **77**, DMAP, DIC, DCM; f) 30% TFA in DCM; g) K_2CO_3, **69**, MeCN; h) $Pd(OAc)_2$, morpholine, PPh_3, THF.



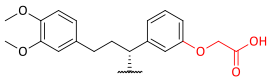
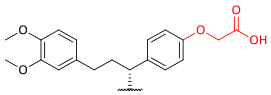
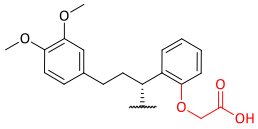
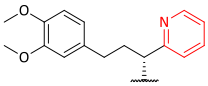
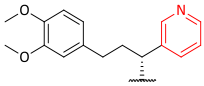
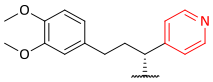
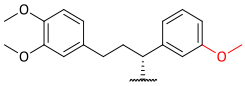
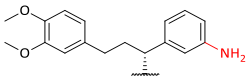
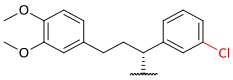
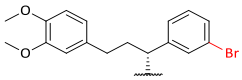
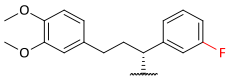
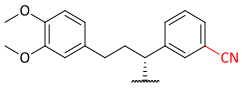
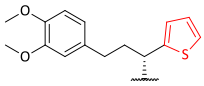
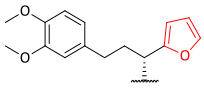
Scheme 12. Synthesis of the para-SAFit **195**. a) KOH, EtOH; b) Zn-Powder, NH_4Cl, MeOH/THF; c) *Noyori,* KOtBu, iPrOH, H_2; d) K_2CO_3, **69**, MeCN; e) **77**, DMAP, DIC, DCM; f) $Pd(OAc)_2$, morpholine, PPh_3, THF.

3.3.2. Binding affinities (Fluorescence polarization assay)

All final compounds were tested for affinity in a competitive fluorescence polarization assay (FP-assay) towards the FKBPs 51, 52, 12 and 12.6.[65] **Table 3** comprising all B ring derivatizations compares the final compounds with SAFit1 (FKBP51: 4 nM). All tested derivatives bound less towards FKBP51. The *para* and *ortho*-analogs of SAFit1 (**195** and **199**) displayed interesting changes in selectivity. The *para*-SAFit1-analog binds FKBP51 (4 nM) as strong as SAFit1 but loses in selectivity towards FKBP52. The *ortho*-analog loses affinity towards FKBP51 (170 nM) but remains highly 51 selective. These results strongly suggest the original meta position of SAFit1 as the optimal derivatization point, as we did with the following compounds. The *ortho*-pyridine compound **200** (*ortho*-pyridine) again underscores these findings as it showed complete loss of high affinity against FKBP51 (1 µM). The best compounds with binding affinities around 30 nM included the *meta*- and *para*-pyridines (**201** and **202**) as well as the aniline **204**. Halogens, as well as the nitrile substitutions, showed decreased affinity (**205-208).** The

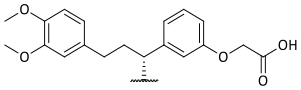
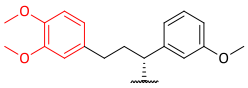
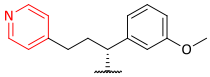
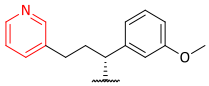
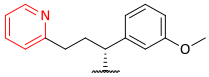
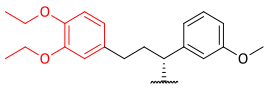
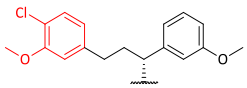
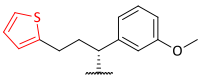
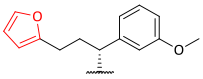
methoxy B ring derivative **209** was used as a reference for the A ring derivatives (**Table 4**). The thiophene (**210**) and furan (**211**) heteroaromatics displayed the lowest affinity in this series.

Table 3. Library of the B ring SAFit variants. K_i values were determined by a competitive fluorescence polarization assay. [a] error values calculated from two independent assays.

Cmpd.	A/B ring R (Scheme 10)	FKBP51FK1	FKBP52FK1	FKBP12	FKBP12.6
				K_i [nM]	
SAFit1		3	>10000	172	17
195		4	1500	15	5
199		170	>10000	1800	>10000
200		1030±49[a]	>10000	>10000	>10000
201		23±7[a]	>10000	175±14[a]	72±23[a]
202		26±5[a]	>10000[a]	110±22[a]	41±14[a]
209		71±3[a]	>10000	690±29[a]	180±10[a]
204		32±22[a]	>10000	303±83[a]	96±48[a]
205		63	>10000	480	140
206		66	>10000	380	70
207		110	>10000	870	230
208		99	>10000	1000	260
210		145	>10000	785	250
211		150	>10000	910	200

Instead of the carboxylic acid in SAFit1, we installed a methoxy group on the B ring for the series of A ring derivatives (**Table 4**). This was conducted due to the additional deprotection step of the carboxylic acid we would have had for each final compound. Thus, we synthesized compound **209** as a reference to be able to compare the A ring derivatives with SAFit1. The FP-assay revealed that all pyridine compounds (**212**-**214**) bound better than the control compound **209**. This indicates that the two methoxy substituents of the A ring of SAFit are replaceable. Removing these would give us already an improved molecular weight of 60 g/mol. Additionally, SAFit1's FKBP51 affinity is 18 times higher than compound **209**, which indicates that by combining the pyridine top-groups with the carboxylic acid on the B ring or creating a diaza A/B ring with decreased molecular weight should also bind effectively.

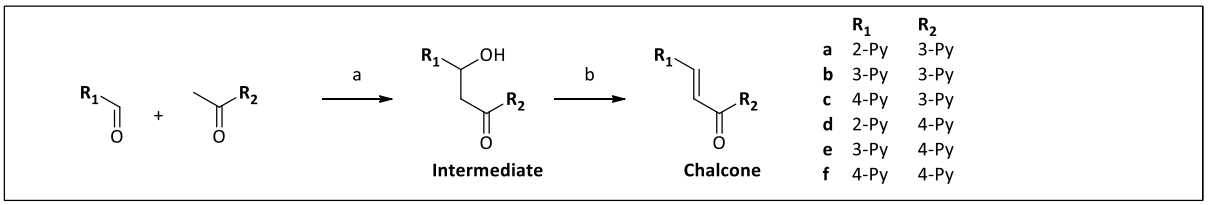
Table 4. Library of the A ring SAFit variants. K_i values were determined by a competitive fluorescence polarization assay. [a] error values calculated from two independent assays.

Cmpd.	A/B ring R (Scheme 10)	FKBP51FK1	FKBP52FK1	FKBP12	FKBP12.6
		K_i [nM]			
SAFit1		3	>10000	172	17
209		71±3[a]	>10000	690±29[a]	180±10[a]
212		22±5[a]	>10000	230±41[a]	190±120[a]
213		21±3[a]	>10000	350±16[a]	220±60[a]
214		28±0[a]	>10000	460±70[a]	380±60[a]
215		88	>10000	550	77
216		90	>10000	390	2100
217		98	>10000	420	200
218		140	>10000	930	560

3.3.3. Extended SAR – Synthesis of diaza-chalcones

To extend the findings of the A or B ring derivatives we combined their best binders and synthesized diaza-chalcones. The general chalcone synthesis employing the *Claisen-Schmidt* method did not reward us with product at all. The procedures using KOH as base reported by Basnet and Jeong et al. mostly delivered complex side product mixtures consisting of dimers and oligomers, which made

product isolation difficult.[80, 81] Vatsadze et al. described the formation of cyclic, dimeric and trimeric side products that occurred during their attempts of synthesis of diaza chalcones. Interestingly, only the synthesis of the 4, 4-diaza-chalcone using Na_2CO_3 in pure H_2O worked in good yields.[82] Unfortunately, their approach did only give single-digit yields for the other pyridine combinations. After monitoring the reaction by LCMS we noticed that the aldol intermediate formed extremely quick (**Scheme 13**) and longer reaction times increased side product formation. We, therefore, altered the reaction conditions by quenching the fast reactions after 5-10 minutes to extract the intermediate (**Scheme 10**).

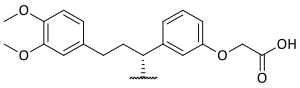
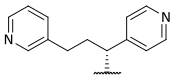
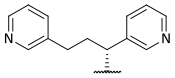
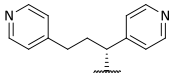
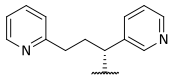
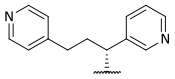
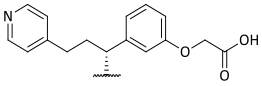


Scheme 13. Modified synthesis of the diaza-chalcones. a) Na_2CO_3, (H_2O), 5 min, 0°C; b) dry load onto SiO_2, 120°C, 1 h.

To transform the intermediate to the chalcone we directly loaded the crude extract onto silica (dry load), which we subsequently heated to 120°C to condensate the intermediate to the chalcone. The silica visibly turned from white to yellow as the reaction proceeded. The resulting dry load was directly used for silica column chromatography. With this optimized method, we were able to get all 6 combinations of diaza-chalcones in moderate yields from 27-66%. As little literature exists describing the synthesis for these diaza-chalcones this synthesis method can be regarded as novel. Further synthesis was conducted as described in **Scheme 10**. Unfortunately, the yield of the asymmetric reduction was quite low. The diaza compounds' ability to chelate metals might have also increased the difficulties in handling these. The final synthesis of the 2,4-diaza compound (**Scheme 13d**), unfortunately, did not deliver enough yield and was not repeated because of very similar results of the diaza-chalcones in the FP-assay.

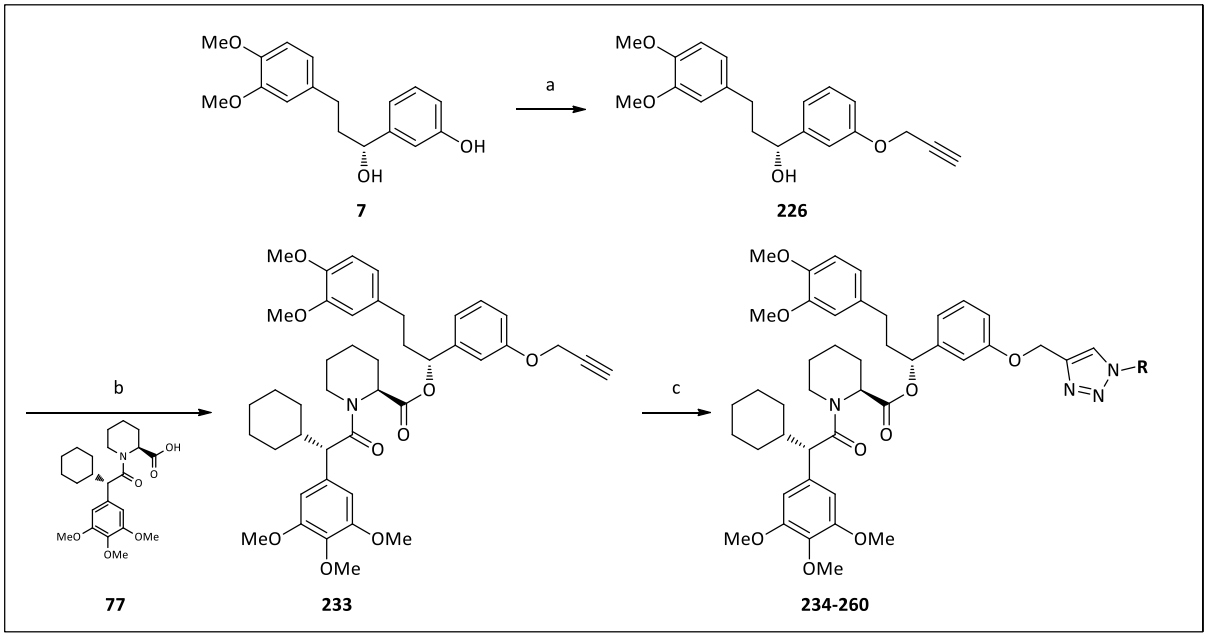
We additionally synthesized one B ring carboxylic acid-bearing compound with pyridine as A ring (**225**). The FP-assay results of the combinations are given in **Table 5**. The diaza compounds **219**-**222** bound quite similar compared to SAFit1 with a reduced affinity by factor 10 (~40 nM). Only compound **223** exhibited decreased FKBP51 binding affinity (90 nM). All of them kept similar selectivities towards FKBP12 and 12.6. Due to their high-affinity binding and decrease in molecular weight by 132 g/mol in comparison to SAFit1, it seems pyridines are a suiting replacement of the methoxy groups. Additionally, compound **225**, the combination of *para*-pyridine on the A ring together with SAFits carboxylic acid on the B ring displayed the best FKBP51 binding affinity in the combinatorial series with 20 nM.

Table 5. Combination of the best binding ligands of the A and B ring series. K_i values were determined by a competitive fluorescence polarization assay.

Cmpd.	A/B ring combination R (Scheme 10)	FKBP51FK1	FKBP52FK1	FKBP12	FKBP12.6
		K_i [nM]			
SAFit1		5	>10000	110	21
219		35	>10000	180	90
220		40	>10000	450	150
221		40	>10000	280	70
222		43	>10000	610	270
223		90	>10000	600	390
225		20	>10000	550	190

3.4. SAR of SAFit A/B ring triazole derivatives

3.4.1. Synthesis of SAFit A/B ring derivatives by Click reaction



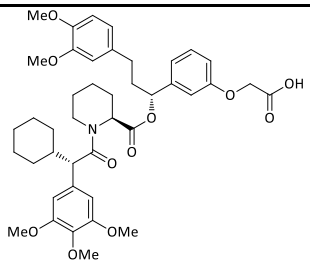
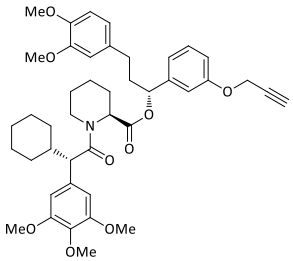
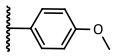
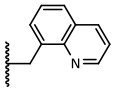
Scheme 14. Synthesis of the SAFit-like precursor for Click-reaction and final compound synthesis. a) K_2CO_3, propargyl bromide, (MeCN); b) DIC, DMAP, (DCM), 0°C - r.t.; c) $CuSO_4$, **R**-N_3, sodium ascorbate, (*t*BuOH/H_2O).

To further explore derivatives of the seemingly important carboxylic acid site on the B ring of SAFit1, we thought to synthesize a precursor, from which we would be able to quickly derivatize via *Click-*

reaction. Bioisosterical modifications of ligands are often regarded to alter a ligands' physicochemical properties.[83] As the carboxyl group of SAFit1 protrudes into a shallow, but a quite broad pocket (**Figure 5B**) we thought to shape our ligands properties by inserting triazoles as isosteres of carboxylic acid esters of SAFit1. We, therefore, synthesized a suitable precursor, starting with the chiral alcohol **7** (**Scheme 14**). Here we chose to keep the dimethoxybenzene as A ring, due to the increased synthesis complexity of the pyridines. Compound **7** was coupled with propargyl bromide giving compound **226**, which was coupled with construct **77** providing precursor **233**. This construct was "clicked" with several commercially available azides providing the new compound library (**Table 6**). The amines for compounds **235**-**241** were after the *Click* reaction Boc deprotected with TFA in DCM.

3.4.2. Binding affinities (Fluorescence polarization assay)

Table 6: Library of the clicked top-group derivatives. K_i values were determined by a competitive fluorescence polarization assay; [a] values and error from two independent experiments.

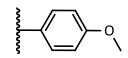
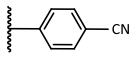
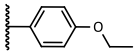
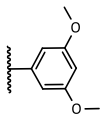
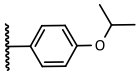
Cmpd.	R (Scheme 14)	FKBP51FK1	FKBP52FK1	FKBP12	FKBP12.6
		K_i [nM]			
SAFit1		4±1[a]	>10000	163±9[a]	19±2[a]
233		100	>10000	410	90
235		7	300	5	6
237		8	610	28	11
239		10	460	35	12
241		11	2600	77	16
242		14±2[a]	>10000	>10000	16±5[a]
243		30	>10000	180	22

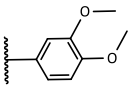
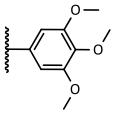
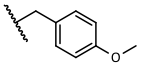
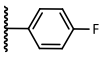
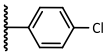
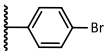
Interestingly, a general trend of loss of selectivity towards FKBP52 was observed with ligands containing a longer linker with a primary or secondary amine at the terminus (compounds **235-241**). This could be caused by the difference in the amino acid 85 (Q^{85} for FKBP51 and E^{85} for FKBP52) in the binding pockets of 51 and 52, which is positioned in distance compatible with the linker length. Furthermore, all ligands showed FKBP12 and 12.6 binding analogous to SAFit1. An astounding exception was compound **242**, which showed a remarkable preference for FKBP51 (14±2 nM) and FKBP12.6 (16±5 nM) and no FKBP12 binding (FP-assay binding curves see **Figure 14**). This is especially interesting since no tool compound distinguishing between FKBP12 and 12.6 was published up to this date.

3.4.3. Extended SAR

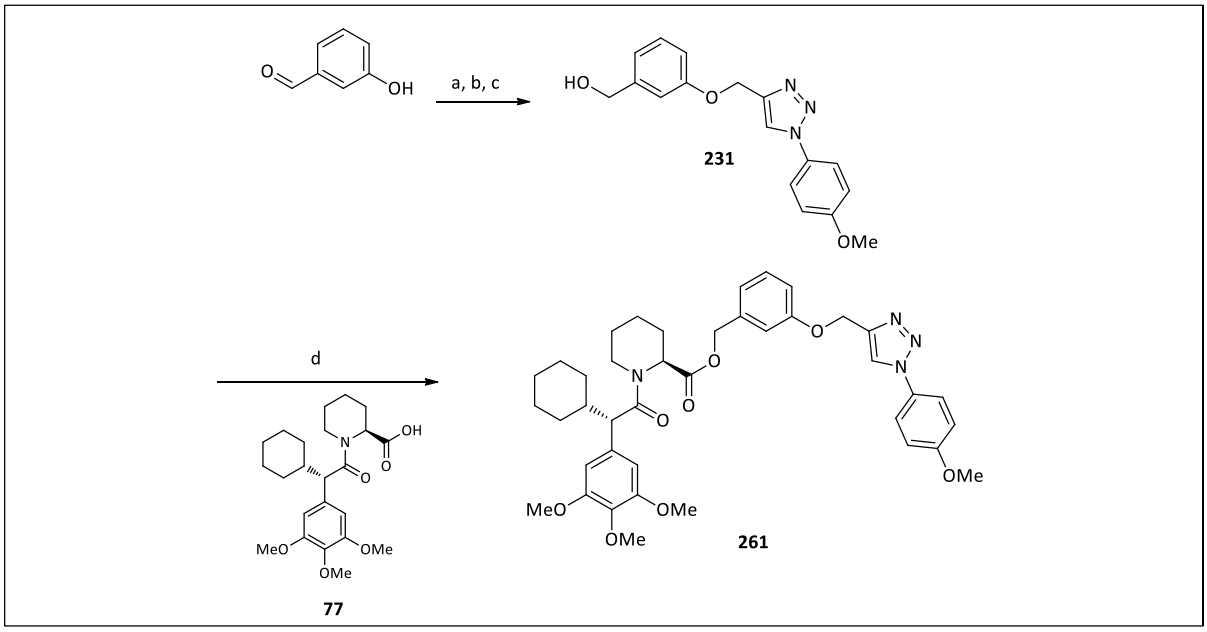
These novel findings were further explored in an extended SAR. Especially compound **242**, which bears the *p*-anisole moiety, showed remarkable properties. Therefore, we synthesized an extended library, which comprises *para*-anisole derivatives and analogs (pyridines, halogenated aromatics, increased alkyl residues). The azides were commercially purchased, only the 1-azido-3,4,5-trimethoxybenzene was synthesized from the aniline according to the procedure of Odlo et al.[84] All final compound analogs of parent compound **242** displayed in the FP-assay a preference of FKBP51 over 52 (**Table 7**). Noticeably, compounds **244-246** having the nitrile, ethoxy group and 3,5-dimethoxy substituent displayed the same selectivity profile but they did not reach its level of affinity. Insertion of the isopropoxy group loses in FKBP12.6 affinity, but still exerts selectivity over FKBP12 (**247**). Alternating the position and increasing the number of methoxy groups as well as increasing linker length by one methylene unit to a benzyl in compounds **248**-**251** abolished this newfound preference. The exchange of the methoxy group to halogens or pyridines also did not exert the FKBP12.6 preference (**252**-**260**).

Table 7. Extended Library of the "clicked" final compounds. K_i values were determined by a competitive fluorescence polarization assay; [a] values and error from two independent experiments.

Cmpd.	R (Scheme 14)	FKBP51FK1	FKBP52FK1	FKBP12	FKBP12.6
		K_i [nM]			
242		14±2[a]	>10000	>10000	16±5[a]
244		23	>10000	>10000	21
245		45	>10000	>10000	42
246		80	>10000	>10000	60
247		90	>10000	>10000	2800

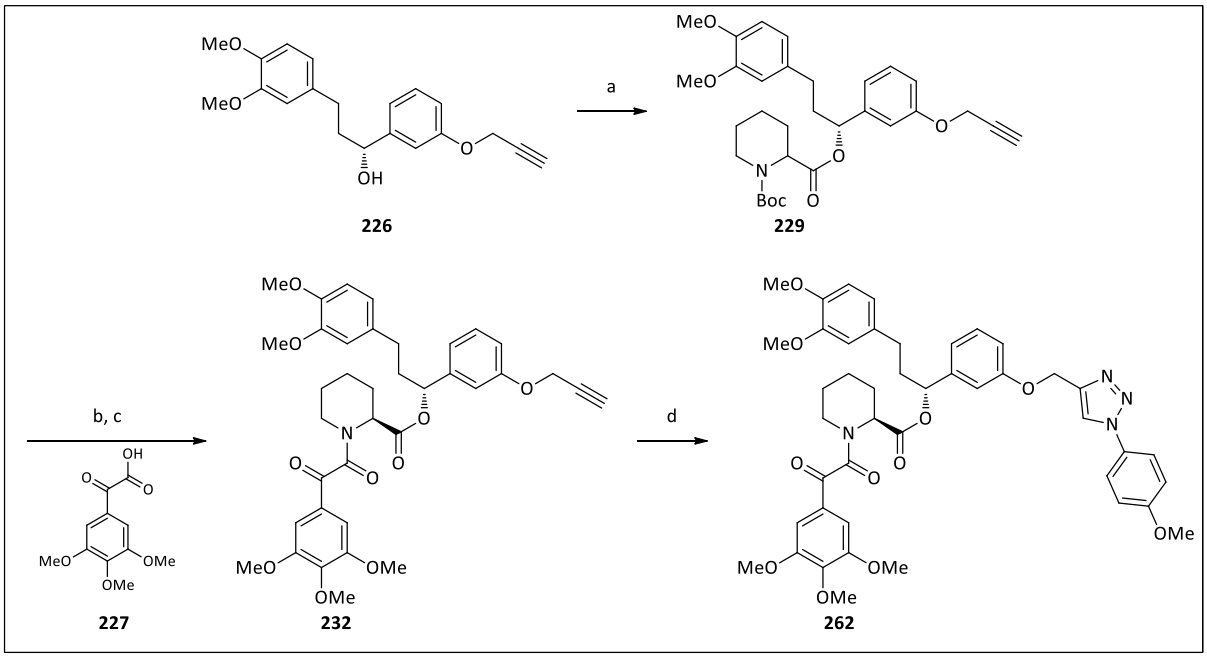
248		32	>10000	700	19
249		34	>10000	670	15
250		46	>10000	7300	60
251		45	>10000	240	50
252		23	>10000	190	15
253		24	>10000	250	20
254		43	>10000	360	16
255		24	>10000	3600	170
256		35	>10000	3900	50
257		33	>10000	6500	26
258		46	10000	>10000	26
259		30	>10000	1200	21
260		41	>10000	1700	21

We further synthesized compound **261** to ascertain if the selective properties of compound **242** remain when we decrease the size by leaving out the A ring (**Scheme 15**). This also simplified the overall synthesis due to one less chiral center. Here we started with 3-hydroxy benzaldehyde, which was coupled with propargyl bromide, then clicked with *p*-azido anisole providing compound **231** and finally coupled with compound **77** resulting in compound **261**.



Scheme 15. The synthesis of compound **261**, the truncated version of **242**. a) propargyl bromide, K_2CO_3, (MeCN); b) *p*-azido anisole, $CuSO_4$, sodium ascorbate, (*t*BuOH/H_2O); c) $NaBH_4$, (MeOH); d) **77**, DIC, DMAP, (DCM).

We additionally synthesized compound **262** where the cyclohexyl on the bottom-group is exchanged with a pipecolate diketo amide (**Scheme 16**). FKBP ligands having this specific structure were shown to bind primarily to FKBP12 and FKBP12.6 while having a micromolar affinity towards FKBP51 and 52.[85] By possibly abolishing the binding of FKBP51 and 52, we hoped for a possible selection between only FKBP12 and 12.6.

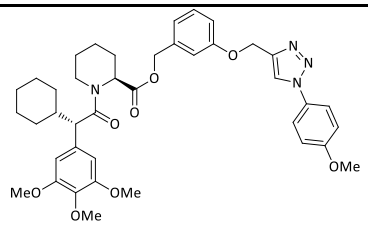
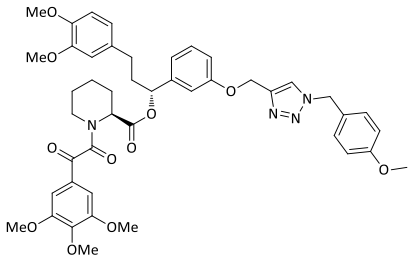


Scheme 16. Synthesis of compound **262** the diketo analog of **242**. a) DCC, DMAP, Boc-*S*-Pip-OH, (DCM); b) TFA/DCM, 1/2; c) HATU, HOAt, DIPEA, (DMF); d) *p*-azido anisole, $CuSO_4$, sodium ascorbate, (*t*BuOH/H_2O).

The synthesis started with **226** which was coupled with Boc-*S*-Pipecolate (**229**), deprotected and coupled with compound **227**, which was synthesized as previously reported[85] giving us compound **232**. This was clicked with *p*-azido anisole providing final compound **262**.

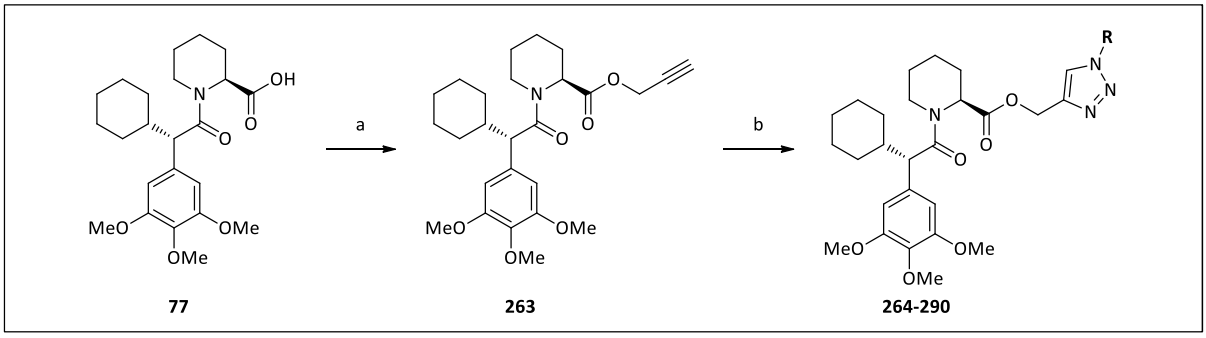
Compound **261** with decreased top-group size lost in affinity towards FKBP51 and did not show any binding towards FKBP52, 12 and 12.6 (**Table 8**). The A ring in the parent compound **242** might work as a lever to force the B ring into the right position, explaining the necessity of the complete A/B ring construct. The diketo analog (**262**) displayed as expected no FKBP51 and 52 binding. Unfortunately, the compound lost in FKBP12.6 preference and bound both FKBP12 and 12.6 in the nanomolar range. This highlights the importance of the cyclohexyl ring, which could induce a necessary chain flip needed for FKBP12.6 preference.

Table 8. Extended library of derivatives of compound **242**. K_i values were determined by a competitive fluorescence polarization assay.

Cmpd.	Structure	FKBP51FK1	FKBP52FK1	FKBP12	FKBP12.6
		K_i [nM]			
261		440	>10000	>10000	>10000
262		>10000	>10000	46	36

3.4.4. Synthesis of minimized SAFit derivatives by Click reaction

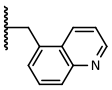
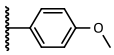
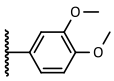
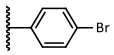
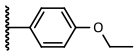
The same approach of a “clicked” library was conducted for a minimized precursor construct (**Scheme 17**), which gave us a suitable starting point to search for smaller top-groups in broad variability. The precursor was synthesized starting from compound **77**, which was coupled with propargyl bromide providing us with precursor **263**. Compound **263** was clicked with the same azide pool as previously used leading to the library of SAFit derivatives with reduced size (**Table 9**).

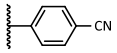
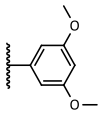
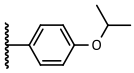
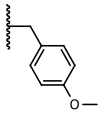
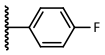
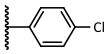
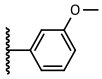
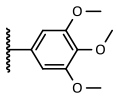


Scheme 17. Synthesis of the smaller precursor for the *Click* reaction and final compound synthesis. a) DIPEA, propargyl bromide, (MeCN); b) $CuSO_4$, **R**-N_3, sodium ascorbate, (*t*BuOH/H_2O).

In comparison to their bigger SAFit analogs we determined generally weaker binding affinities in the micromolar range towards FKBP51, but also found high FKBP51 selectivity. The terminal amines also showed mostly selective FKBP51 binding but already in the micromolar range (**265**-**272**). Compound **273**, one of the most affine compounds of this series, still had a sub-micromolar affinity of 350 nM towards FKBP51 and did not show FKBP52, 12 and 12.6 binding. Many analogs of compound **273** also showed selective FKBP51 binding, but with decreased affinities (**274**-**280**). Insertion of halogens or pyridines, as well as several methoxy analogs (**281-290**), did not display the same selectivity.

Table 9. Library of the minimized "clicked" compounds. Ki values were determined by a competitive fluorescence polarization assay; [a] values and error from two independent experiments.

Cmpd.	R (Scheme 17)	FKBP51FK1	FKBP52FK1	FKBP12	FKBP12.6
		K_i [nM]			
263		3100	>80000	>80000	3200
265		930	>80000	>80000	>80000
266		1200	>80000	>80000	5000
268		1200	>80000	>80000	1900
270		2300	>80000	>80000	>80000
272		2800	>80000	>80000	>80000
273		350±30[b]	>80000	>80000	>80000
274		300±10[a]	>80000	>80000	>80000
275		550	>80000	>80000	>80000
276		590	>80000	>80000	>80000

277		630	>80000	>80000	>80000
278		1100	>80000	>80000	>80000
279		1150	>80000	>80000	>80000
280		2600	>80000	>80000	>80000
281		880	>80000	10000	>80000
282		680	>80000	3000	1200
283		1100	>80000	1000	1300
284		2000	>80000	9400	>80000
285		380	>80000	2700	1500
286		360	>80000	>80000	6500
287		780	>80000	7800	1000
288		700	>80000	>80000	>80000
289		780	>80000	>80000	>80000
290		880	>80000	>80000	>80000

3.4.5. Structural basis for selectivities postulated by modeling into co-crystal structures

An explanation for the unprecedented high selectivity for compound **242** as well for **273** might be explained by the amino acids postulated to surround these new moieties when bound to FKBPs (**Figure 14**). As we could not obtain co-crystal structures, we modeled these compounds onto the co-crystal structure of SAFit1 with FKBP51 and superimposed the published FKBP12 and 12.6 rapamycin complexes. The FKBP12.6 preference of **242** might be explained by the residues differences in position 49 (arginine for FKBP12.6 and valine for FKBP12, **Figure 14A**). Similarly, compound **273** can interact with several differing residues in the shallow pocket, which becomes clear by superimposing FKBP51 with FKBP12 and 12.6. Especially FKBP51's valine 78 differs strongly from lysine 47 in FKBP12 and 12.6 (**Figure 14B**).

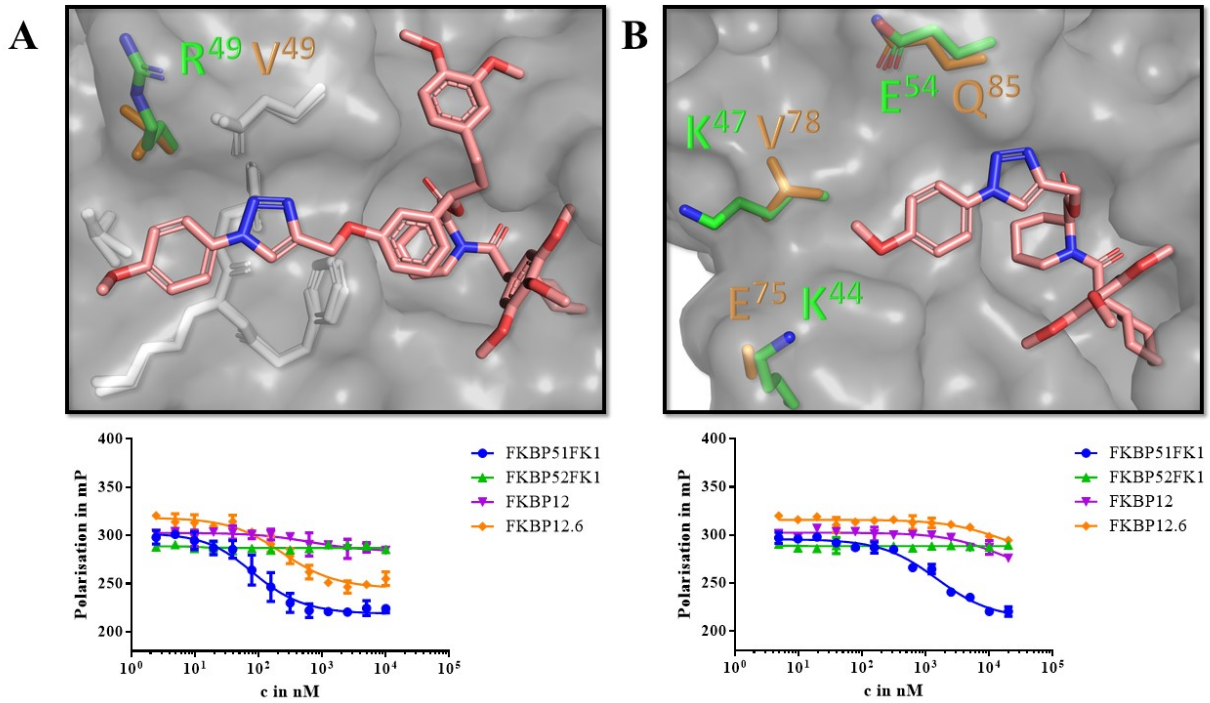
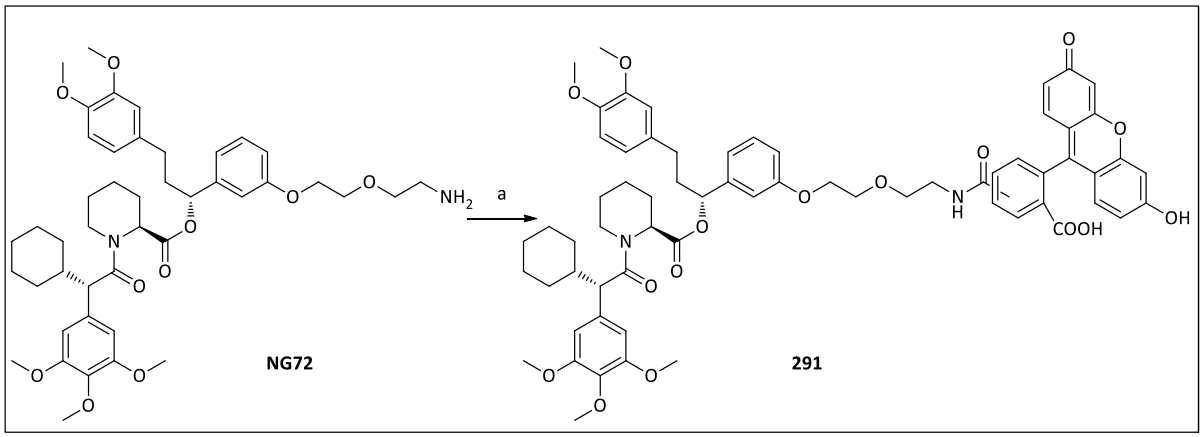


Figure 14. A) Compound **242** modeled onto the structure of SAFit1 (pink sticks). FKBP12.6 (pdb-ID: 1c9h, grey surface) and FKBP12 (pdb-ID: 1fkl) are overlapped. The shallow pocket formed by homologous amino acids is depicted in grey sticks, the differing residues are colored as green sticks in the case of FKBP12.6 (R49) and orange sticks for FKBP12 (V49). The binding curves of the FP-assay are depicted below. **B)** Compound **273** modeled onto the structure of SAFit1 (pink sticks). FKBP51 (gray surface, residues as orange sticks) is overlapped with FKBP12 and 12.6 (green sticks) and the differing residues highlighted. FKBP12 and 12.6 are highly homologous, thus only FKBP12 is displayed as green sticks for clarity. E75 is only defined as a stub in the crystal structure due to insufficient electron density of the solvent-exposed residue. The binding curves of the FP-assay are depicted below.

3.5. Synthesis of fluorescent SAFit ligands as tool compounds

To provide a SAFit tool compound for biochemical studies, we synthesized fluorescent analogs of SAFit.

3.5.1. Fluoresceine labeled SAFit

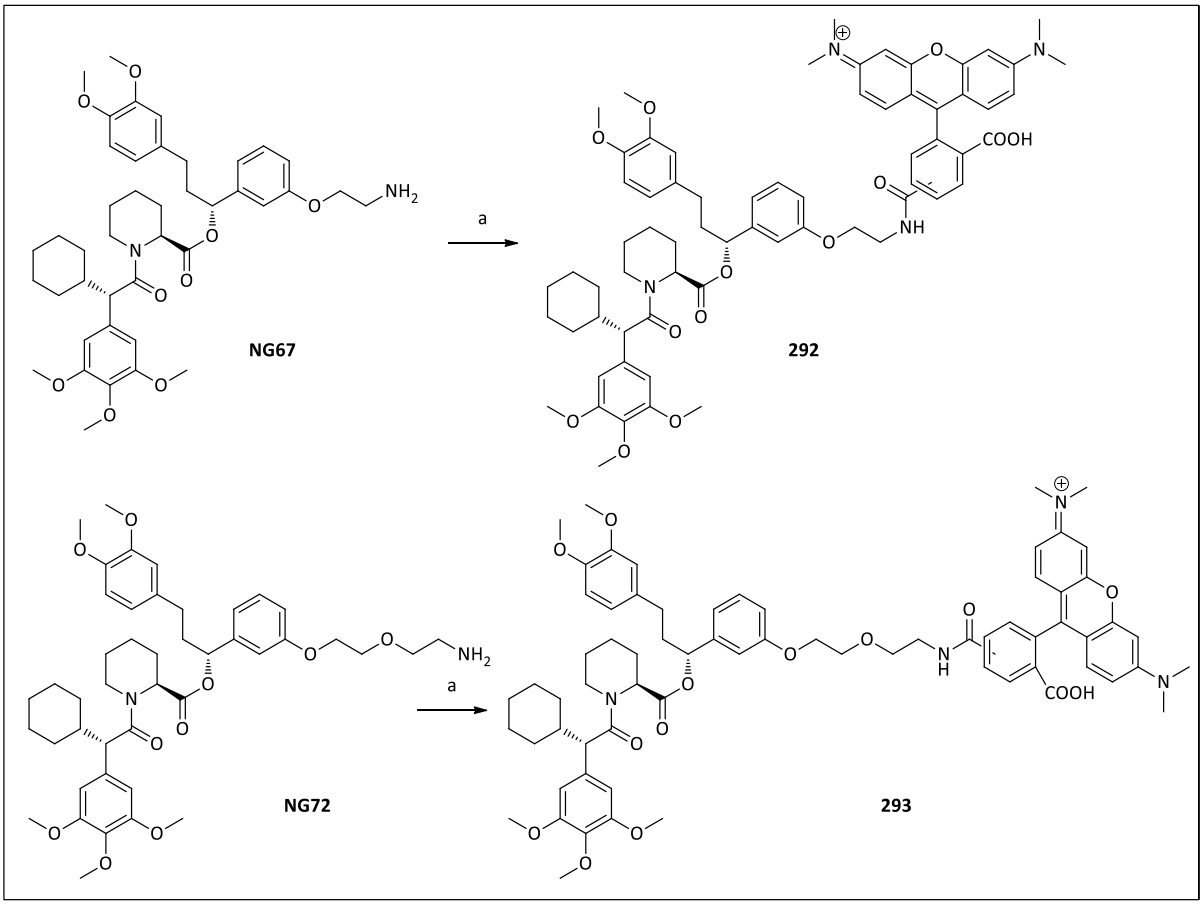


Scheme 18. Synthesis of the fluoresceine labeled compound **291** a) 5(6)-NHS-fluoresceine, TEA, DMF.

5(6)-NHS-fluoresceine was coupled towards the amine linker of **NG72**. The SAFit analog **NG72** was prior synthesized by Niklas Gutfreund during his master thesis under my supervision.[86] The fluorescent tracer **291** (**Scheme 18**) was used to check differences in affinity of several FKBP51FK1 mutants through active site titrations (Unpublished data, Anna Charalampidou, AK Hausch) and in a flow cytometry screening (FACS – fluorescence-activated cell sorting) of randomized FKBP51 mutants (Unpublished data, Andreas Christmann, AK Kolmar).

3.5.2. TAMRA labeled SAFit

5(6)-NHS-TAMRA was coupled towards the amine linkers of **NG72** and **NG67**. The SAFit analog **NG72** and **NG67** were synthesized by Niklas Gutfreund during his master thesis under my supervision.[86] The fluorescent tracers **292** and **293** (**Scheme 19**) were used in FRET experiments with a FITC-FKBP51FK1 domain to measure binding curves, as well as kinetics (Unpublished data, Christian Meyners, AK Hausch).



Scheme 19. Synthesis of the TAMRA labeled compound **291** a) 5(6)-NHS-TAMRA, TEA, DMF.

3.6. Crystal structures and refinement of BR175, BR179, SP597, SP464, SP468 and AntaB

In addition to the mentioned co-crystal structures above, we co-crystallized and refined in cooperation with Dr. Andreas Bracher several bicyclic FKBP binding ligands (BR175, BR179, SP597, SP464, SP468, **Figure 15**), which were used for structure-activity relationship studies in the doctoral thesis of Jürgen Kolos (AK Hausch, TU Darmstadt). For the refinement process, data and PDB-IDs: see Refinement data 5.5.9, **Table 12**. Additionally, we solved the crystal structure of Antascomicine B (AntaB), which is a natural compound known to bind to FKBPs analogous to FK506 and Rapamycin.[87]

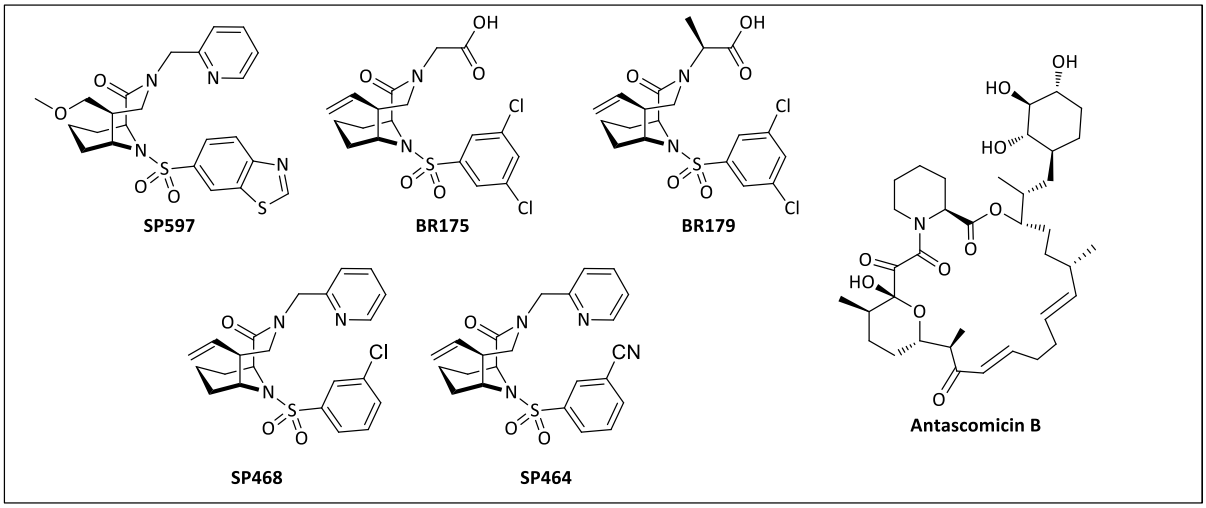


Figure 15. Structures of the bicylic compounds BR175, BR179, SP597, SP464, SP468 and AntaB co-crystallized with FKBP51 FK1.

3.7. Refit of the $G_{q/11}$ protein ligand YM-254890

In cooperation with Dr. Daniel Tietze we worked on a refit of the $G_{q/11}$ protein ligand YM-254890. The natural compound YM-254890 showed antithrombotic and thrombolytic efficacy in rat models [88-91] and the closely related depsipeptide FR-900359 directly targets melanoma cells in mouse xenograft models[92], making these compounds a focus of interest in drug research.

A new found cis-conformation solved by Dr. Daniel Tietze in NMR experiments in aqueous solvent was fitted in the published co-crystal structure 3ah8. Here the ligand displayed prior a trans-conformation, which was fitted by conformational analysis in organic solvent. As the ligands native conformation should resemble more closely to the cis-conformation in water, we refitted the ligand structure as follows. The reflection data of 3ah8 was converted by the structure factor tool (SF-tool) of the Protein Data Bank (PDB) to get the respective reflection data in a mtz-file format.[93] The mtz-file together with the pdb of 3ah8 was used in the programs *CCP4i2* and *Coot* to create an omit-map of the structure. The original ligand was removed and via *REFMAC5* refined to get the difference density map showing the positive density at the ligand site.[94-102] For further ligand fitting the restraints of the YM-ligand was calculated using the program *prodrg* in the interface of *CCP4i*[103] The ligand was then manually

fitted into the binding pocket using *Coot*.[96] Finally, the protein ligand complex was refined with 10 cycles in *REFMAC5* with standard settings in *CCP4i2*. No further refinement was conducted. To compare the two different ligands conformations, the original PDB-ligand structure was also refined under the same conditions using *REFMAC5* together with the omit-map getting the final R- and R-free-values for both structures (**Table 10**, **Figure 16**). The R values are used in crystallography as data quality check. The best possible number would be 0, indicating a perfect agreement between the simulated diffraction pattern of the crystallographic model and the experimental X-ray diffraction data. Typical values are between 0.15-0.25 (lower numbers for high resolution structures). R free is used as control for the R value to prevent possible bias in the structure building. Here only 90% of the reflections are used in refinement and then compared with the other non-used 10%. The R free value should be as close as possible to the R value.

Table 10. R values for 3ah8 crystal structure reanalysis. [a] Fit of original into omit-map.

	3ah8[a]	**YM-Refit**
R-work	0.22	0.29
R-free	0.26	0.33

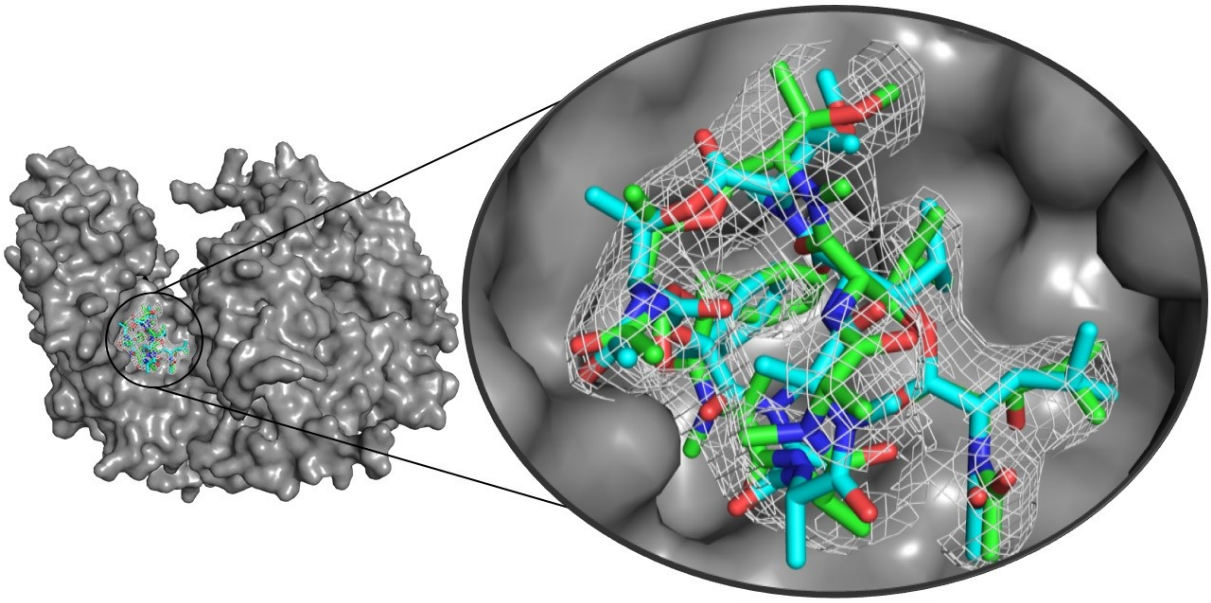


Figure 16. Superimposition of the refitted G_q bound YM-254890 ligand (green sticks, NMR in H_2O) with the published crystal structure (cyan sticks, NMR in organic solvent, PDB-ID: 3ah8). Electron density grid (gray) is shown at an RMSD of 1 Å.

As the R-value and overall B factor only give a view of the global fit and the published crystal structures resolution is not optimal (2.9 Å), which means the comparison of the global fit is not a satisfactory reference value, we conducted a further experiment to get an evaluation of the local fit for both ligands as it was suggested in Deller et al.[104] Therefore, we calculated the RSCC (real space correlation

coefficient) using the software *MolProbity* in the *Phenix* suite.[105, 106] The RSCC defines the positioning of the object into the surrounding electron density. The RSCC values range between 0 (bad) and 1 (good), where the value 1 describes the best possible fit (**Table 11**). [104] Both ligands have the same or nearly the same fit, which would mean our newly found conformation is also a valid solution of the crystal structure. These results were published as part of the publication "Structural and Dynamical Basis of G Protein Inhibition by YM254890 and FR900359: An Inhibitor in Action".[91]

Table 11. RSCC values and reanalysis of the crystal structure 3AH8 via MolProbity in the Phenix suite.

	3AH8 (fit of original into omit-map)	**YM-Refit**
RSCC (ligand)	0.915	0.914
B-factor (ligand)	121.67	106.08
Occupancy (ligand)	1.00	1.00
R-work (global)	0.22	0.29
R-free (global)	0.25	0.31
B-factor (global)	108.03	110.63
RMS angles (global)	1.62	1.57
RMS bonds (global)	0.01	0.01
Resolution [Å]	19.65 – 2.90	19.65 – 2.90

4. Conclusion

This thesis presents the first macrocyclic ligands that robustly bind the drug target FKBP51 and discriminate against the essential and homologous proteins FKBP52, FKBP12 and FKBP12.6. Macrocyclization of the currently most advanced ligand SAFit (SAFit1: FKBP51: 4 nM, FKBP12.6: 19 nM, FKBP12: 163 nM) resulted in FKBP51-specific binding ligands and provides a structural basis for rational design and further lead optimization of FKBP51 specific ligands (**39**: FKBP51: 290 nM, **40** FKBP51: 400 nM, **Figure 17** and **Figure 18**).

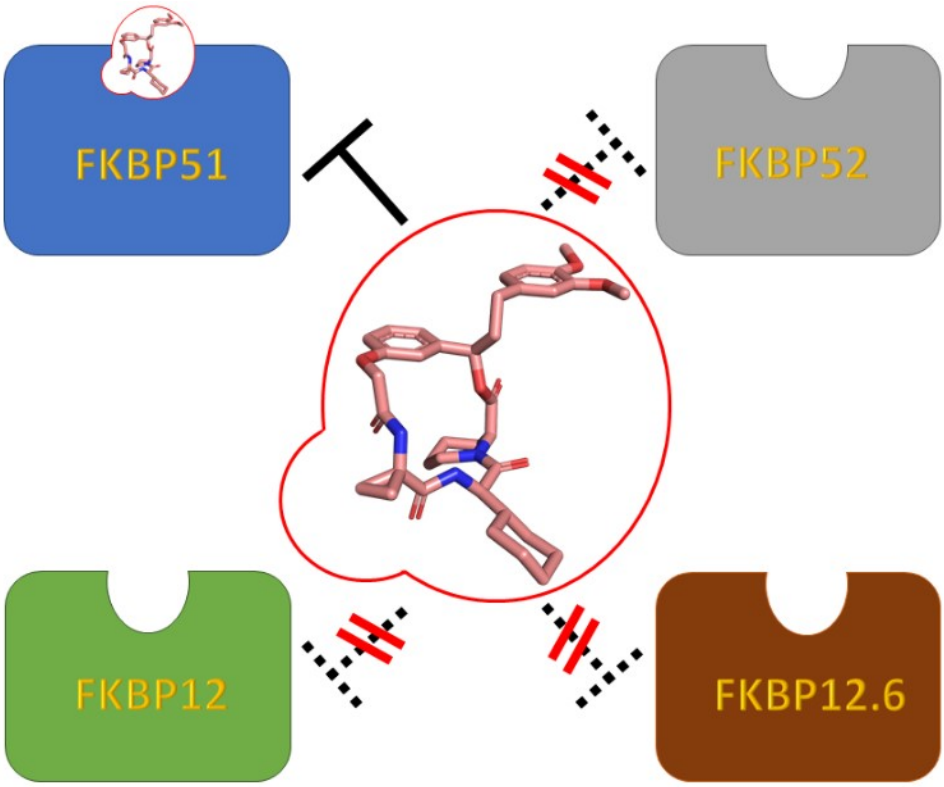


Figure 17. Macrocyclic ligand **40** with selective binding of FKBP51.

Co-crystal structures of the macrocycles in complex with FKBP51 gave first insights into a plausible mechanism for the FKBP51 selectivity. Disruption of an intermolecular hydrogen bond of the protein by a carbonyl in the macrocycle leads to a new, transient protein conformation, which might be disfavored by FKBP12 and 12.6. FKBP12 and FKBP12.6 are cofactors of the ryanodine receptor[31-33] and play an important role in fine-tuning the excitability of smooth or heart muscle. FKBP12 knockout or knockdown leads to severe cardiac defects in mice[34, 35], underscoring the importance of selectivity for FKBP51 over FKBP12/12.6 in FKBP51-based therapies.

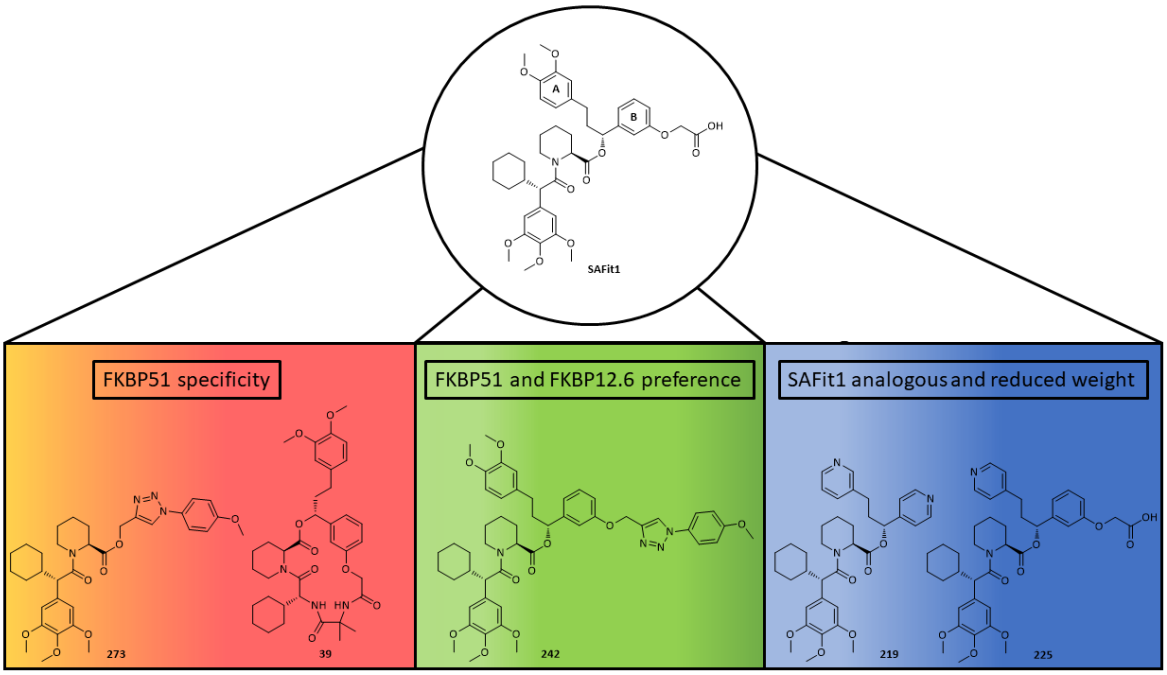


Figure 18. Overview of the best binding ligands structures of this thesis and their specifications.

We further explored the A/B-rings of SAFit as they do not show any specific interactions in the co-crystal structure with FKBP51, but are definitely needed for high-affinity binding. We synthesized >40 SAFit derivatives with differing moieties on the A/B rings and determined that pyridines can be used to replace the methoxy groups of SAFit (**225**: FKBP51: 20 nM). Further synthesis of diaza chalcones, having reduced weight in comparison to SAFit1, were also among the ligands with comparable affinity and selectivity profile of SAFit1 (**219**: FKBP51: 35 nM).

Further research into new A/B rings by fast and simple *Click* chemistry resulted in a wide variety of ligands, where one significantly differed in the FP-assays. Compound **242** displayed preferred binding of FKBP51 and FKBP12.6, but not FKBP12. The differences in the function of FKBP12 and 12.6 are until now not completely understood. The development of a discriminating tool compound thereof would help in the research of the physiological roles of those proteins. Compound **242** and it's analogs presented here are to my knowledge the first pharmacological agents that can discriminate between FKBP12 and FKB12.6.

Additionally, employing *Click* chemistry, we found a new smaller A/B ring structure (**273**: FKBP51: 350 nM), which also specifically binds FKBP51. The binding mechanism could be explained by the differences in the amino acids surrounding the new moiety. A prospective co-crystal structure of both the specific binding as well as partially discriminating ligand will give more insights in the future. Increasing the affinity of the macrocyclic ligands is still a major factor, as well as finding new types of linkers, which are not based on peptidic bonds. This could also improve metabolic stability.

5. Materials and Methods

5.1. Nuclear magnetic resonance spectroscopy (NMR)

^{1}H, ^{13}C-NMR spectra were recorded at the NMR department of chemistry of the Technische Universität Darmstadt (TUD) on a Bruker AC 300, AR300 or DRX500. Chemical shifts for ^{1}H and ^{13}C are given in ppm (δ). Deuterated chloroform ($CDCl_3$), dimethyl sulfoxide (DMSO-d_6), dichloromethane (CD_2Cl_2) and tetrahydrofuran (THF-d_8) were used as solvents and the spectra calibrated according to their corresponding peak. The multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of triplets (dt), multiplet (m). In case of rotamers, which were found for all SAFit-like analogs, the major peaks were selected and reported.

5.2. HPLC and MS

5.2.1. Liquid chromatography coupled with mass spectrometry (LC-MS)

Pump: Beckman System Gold 125 Solvent Module

Detector: Beckman System Gold 199 Detector Module

Column: YMC Pack Pro C8, 100 × 4.6 mm, 3 µm

Solvent A: 95% H_2O, 5% MeCN, 0.1% Formic acid

Solvent B: 95% MeCN, 5% H_2O, 0.1% Formic acid

Method: 0-100% B in 19 min, 1 mL/min

MS: LCQ Deca XP Plus

Ionization: ESI

5.2.2. High-resolution mass spectrometry (HRMS)

High resolution MS was performed at the MS department of the Technical University Darmstadt.

MS: Impact II, Fa. Bruker Daltonik

Mass range: 20 – 40.000 m/z

Detector: qTOF

Accuracy: <2 ppm

Ionization: ESI

5.3. High-performance liquid chromatography (HPLC)

5.3.1. Analytical HPLC

Pump: Dionex System Summit Pump

Detector: UVD380

Column: Phenomenex Jupiter 4 µ Proteo 90Å, 250 × 4.6 mm, 4 micron

Solvent A: 95% H_2O, 5% MeCN, 0.1% TFA

Solvent B: 95% MeCN, 5% H_2O, 0.1% TFA

Methods: Described at the specific compounds; the purity of each compound is given in percentage of the main compounds peak area.

5.3.2. Chiral HPLC

Pump: Beckman System Gold 125S Solvent Module

Detector: Beckman System Gold Diode Array Detector Module 168

Column: Daicel chemical industries Ltd, Chiralcel OD-H, Normal Phase analytical column, 250 × 4.6 mm, 5 µm

Solvent A: *n*-Hexane

Solvent B: *iso*-Propanol

Method: Described at the specific compounds

5.3.3. Semi-preparative HPLC

Pump: Beckman System Gold 126 NMP Programmable Solvent Module

Detector: Beckman System Gold 166 Programmable Detector Module

Column: Phenomenex Jupiter 4µ Proteo 90Å, 250 × 10 mm, 4 micron

Solvent A: H_2O, 0.1% TFA

Solvent B: MeCN, 0.1% TFA

Methods: Described at the specific compounds

5.4. Column chromatography

5.4.1. Manual chromatography

Silicagel: Kieselgel 60 Roth, 0.04-0.063 mm, 230-400 mesh

5.4.2. Flash chromatography

Automated flash chromatography was performed with an Interchim Puriflash 430 with UV detection.

5.4.3. Thin-layer chromatography (TLC)

Aluminum plates coated with silica 60 F_{254} were used for analytical chromatography (Merck). The compound spots were visualized by UV light and/or by staining the TLC plate with one of the solutions given below and if needed carefully heated by a heat gun.

Hanessians: 5 g $Ce(SO_4)_2$, 25 g $NH_4Mo_7O_{24}$*4 H_2O, 40 mL H_2O, 50 mL H_2SO_4

Ninhydrin: 0.5 g Ninhydrin, 100 mL EtOH, 5 mL AcOH

$KMnO_4$: 1.5 g $KMnO_4$, 10 g K_2CO_3, 1.25 mL 10% NaOH in 200 mL H_2O

5.5. Procedure of co-crystallization

5.5.1. Crystallization of 37 and 40

Complexes were prepared by mixing FKBP51 at 2.5 mM with a slight molar excess of 20 mM ligand dissolved in DMSO. Crystallization was performed at 20°C using the hanging drop vapor-diffusion method, equilibrating mixtures of 1 µl protein complex and 1 µl reservoir against 500 µl reservoir solution. Crystals were obtained after seeding with reservoir solutions containing 30-60% PEG-3350, 0.2 M NH_4-acetate and HEPES-NaOH pH 7.5.

The complex of compound **37** was crystallized and refined by Andreas Bracher and compound **40**, BR179, BR175, SP597, SP468, SP464 and AntaB were crystallized in cooperation, measured and refined by myself. Complexes **54** and **74** were crystallized, measured and refined by Dr. Christian Meyners.

5.5.2. Structure solution and refinement of 37 and 40

Diffraction data were collected at the European Synchrotron Radiation Facility (ESRF) in Grenoble, France and the Swiss Light Source (SLS). Diffraction data were integrated with XDS[107] and further processed with the implemented programs of the CCP4i and CCP4i2 interface (Collaborative Computational Project).[94, 108] The data reduction was conducted with Aimless.[108-110] Crystal structures were solved by molecular replacement employing the program Molrep.[111, 112] Iterative model improvement and refinement were performed with Coot[96] and Refmac5.[97, 99-102] The dictionaries for the compounds were generated with PRODRG implemented in CCP4i.[103] Residues facing solvent channels without detectable side-chain density were truncated at Cβ.

5.5.3. Crystallization of BR179

Complexes were prepared by mixing FKBP51 at 2.19 mM with BR179 at 6.25 mM. Crystallization was performed at 20°C using the hanging drop vapor-diffusion method, equilibrating mixtures of 1 µl protein complex and 1 µl reservoir against 500 µl reservoir solution (tray A324, drop D5, 20.11.2015). Crystals were obtained after seeding with reservoir solutions containing 38% PEG-3350, 0.2 M NH4-acetate and HEPES-NaOH pH 7.5.

5.5.4. Structure solution and refinement of BR179

Diffraction data were collected at beamline ID30B of the European Synchrotron Radiation Facility (ESRF) in Grenoble, France (15.12.2015). Further processing was conducted as described under paragraph 5.5.2.

5.5.5. Crystallization of BR175

Complexes were prepared by mixing FKBP51 at 2.19 mM with BR175 at 2.5 mM. Crystallization was performed at 20°C using the hanging drop vapor-diffusion method, equilibrating mixtures of 1 µl protein complex and 1 µl reservoir against 500 µl reservoir solution (tray A330, drop A5, 20.12.2016).

Crystals were obtained after seeding with reservoir solutions containing 38% PEG-3350, 0.2 M NH4-acetate and HEPES-NaOH pH 7.5.

5.5.6. Structure solution and refinement of BR175

Diffraction data were collected at beamline ID29 of the European Synchrotron Radiation Facility (ESRF) in Grenoble, France (4.02.2017). The GrenADeS/EDNA (Ref. PMID: 23682196) pipeline was used for data processing. Further processing was conducted as described under paragraph 5.5.2.

5.5.7. Crystallization of SP597

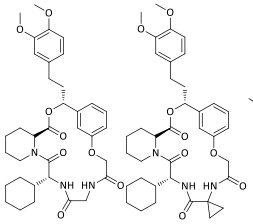
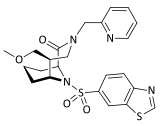
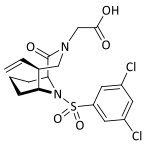
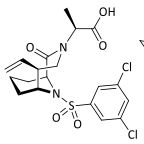
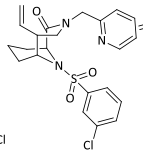
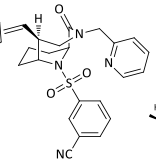
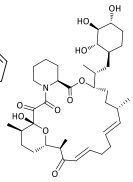
Complexes were prepared by mixing FKBP51 at 2.19 mM with SP597 at 2.5 mM. Crystallization was performed at 20°C using the hanging drop vapor-diffusion method, equilibrating mixtures of 1 µl protein complex and 1 µl reservoir against 500 µl reservoir solution (tray A330, drop B4 or B6, 20.12.2016). Crystals were obtained after seeding with reservoir solutions containing 36% or 40% PEG-3350, 0.2 M NH4-acetate and HEPES-NaOH pH 7.5.

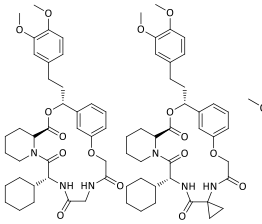
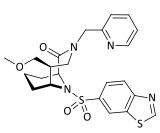
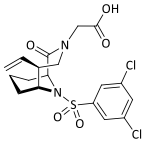
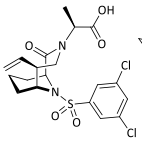
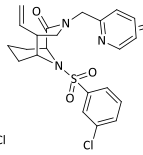
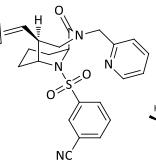
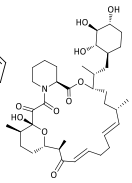
5.5.8. Structure solution and refinement of SP597

Diffraction data were collected at beamline ID29 of the European Synchrotron Radiation Facility (ESRF) in Grenoble, France (4.02.2017). The GrenADeS/EDNA (Ref. PMID: 23682196) pipeline was used for data processing. Further processing was conducted as described under paragraph 5.5.2.

5.5.9. Refinement data

Table 12. Refinement data of compounds 37, 40, SP597, BR175, BR179, SP468, SP464 and Antascomicin B (AntaB). Refinement data for46, 54 and 74 not shown (Correspondence: Christian Meyners, AK Hausch)

Lig. Name	37	40	SP597	BR175	BR179	SP468	SP464	AntaB
Lig. Structure								
PDB-ID	7AOT	7AOU	7APQ	7APT	7APS	Not published	Not published	Not published
FKBP51fk1 A19T	13-140	13-140	13-140	13-140	13-140	13-140	13-140	13-140
Synchrotron	ESRF	ESRF	ESRF	ESRF	ESRF	ESRF	ESRF	ESRF
Beamline	ID30B	ID23-1	ID29	ID29	ID30B	ID23-1	ID23-1	ID23-1
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
a (Å)	43.504	43.410	41.82	41.92	34.81	41.900	42.018	42.010
b (Å)	49.633	49.460	54.61	54.55	39.92	54.810	54.593	54.890
c (Å)	59.903	59.590	56.46	56.28	43.55	56.690	56.357	56.590
α (°)	90	90	90	90	74.06	90	90	90
β (°)	90	90	90	90	76.11	90	90	90
γ (°)	90	90	90	90	74.05	90	90	90
Integration software	XDS	*GrenADES/ EDNA*	*GrenADeS/EDNA/XDS*	*GrenADeS/EDNA/XDS*	*XDS*	*GrenADES/ EDNA*	*GrenADES/ EDNA*	*GrenADES/ EDNA*
Resolution limits (Å)	49.63 – 0.85	38.06-1.16	39.28-1.09 (1.11-1.09)	39.17-1.15 (1.15-1.13)	37.42-0.94 (0.95-0.94)	39.44-0.90 (0.92-0.90)	19.69-0.92 (0.94-0.92)	39.40-0.89 (0.90-0.89)
⟨*I*/σ(*I*)⟩	22.1 (1.4)	9.8 (2.1)	5.9 (2.0)	9.5 (2.0)	16.3 (1.2)	16.2 (1.9)	14.5 (1.6)	8.4 (2.0)
Multiplicity	5.7 (3.3)	1.6 (1.9)	3.5 (3.2)	3.2 (2.6)	3.7 (3.1)	1.0 (1.0)	1.0 (1.0)	1.0 (1.0)
Completeness (%)	97.1 (72.4)	98.9 (97.7)	100 (99.8)	100 (99.9)	85.9 (76.0)	99.4 (93.9)	100 (100)	100 (99.5)
Refinement program	Refmac5	*Refmac5*	*REFMAC*	*REFMAC*	*REFMAC*	*REFMAC*	*REFMAC*	*REFMAC*
Resolution range (Å)	30 – 0.85	29.80-1.16	30.00-1.09	28.62-1.13	30.00-0.94	39.44-0.90	19.69-0.92	28.74-0.89
Reflections_{all}	105556	45040	54712	48910	119854	96245	90448	101731
$\text{Reflections}_{free}$	5557	2243	2760	2536	6102	4720	4539	5078
R_{work}	0.122	0.150	0.181	0.167	0.141	0.147	0.144	0.144
R_{free}	0.138	0.179	0.215	0.216	0.165	0.150	0.165	0.150
Protein No. of atoms (B-Factor)	2109 (11.5)	2076 (17.2)	2077 (15.3)	2096 (19.5)	2211 (15.5), 2244 (12.7)	1987 (12.7)	2250 (12.0)	2181 (12.5)

Lig. Name	37	40	SP597	BR175	BR179	SP468	SP464	AntaB
Lig. Structure								
PDB-ID	7AOT	7AOU	7APQ	7APT	7APS	Not published	Not published	Not published
Ligand No. of atoms (B-Factor)	91 (8.0)	95 (13.7)	122 (22.4)	47 (19.8)	50 (9.5), 50 (12.5)	108 (13.3)	55 (13.6)	101 (17.8)
Water No. of atoms (B-Factor)	223 (23.4)	152 (27.4)	118 (16.7)	155 (30.7)	141 (23.9), 131 (21.9)	147 (21.5)	220 (30.7)	213 (21.9)
R.m.s.d. bonds (Å)	0.030	0.015	0.015	0.021	0.014	0.009	0.014	0.009
R.m.s.d. angles (°)	2.522	1.971	1.888	2.200	1.950	1.670	2.124	1.613

5.6. Fluorescence polarisation assay

Competitive fluorescence polarization assays (FP-Assays) were performed by my colleagues Tim Heyman, Stephanie Merz and Patrick Purder (TU Darmstadt). The fluorescence polarization assay was performed according to Kozany et al.[65] The assay plates were measured with a plate reader Tecan Genios Pro at excitation/emission values of 535/590 nm. The data were analyzed using Prism 6.0 (GraphPad Software). The K_d values were calculated by fitting to the equation provided in Kozany et al. (Supporting Information, Appendix 3).[65]

5.7. Isothermal titration calorimetry

The isothermal titration calorimetry (ITC) experiments were performed by Dr. Christian Meyners (TU Darmstadt) with a MicroCal PEAQ-ITC isothermal titration calorimeter (Malvern).

5.8. Solvents and reagents

Reagents were obtained from abcr, Sigma Aldrich, Alfa Aesar, Fluka, Merck, Novabiochem, Carl Roth, Bachem, Acros Organics and Oxchem and used without further purification. Compound **77** was kindly provided by my colleague Tim Heymann. Compounds NG72 and NG67 were kindly provided by the master student Niklas Gutfreund, working under my supervision.

5.9. General procedures

5.9.1. Autoclave

Autoclave for hydrogenation reactions: Modell type II 250 mL, Carl Roth

Hydrogen: Air Liquide, Klasse 5.0

5.9.2. Test cleavage

After washing the resin with DCM (3×) a few resin beads are taken and transferred into an Eppendorf tube. 1 mL of a 20% HFIP in DCM solution is added and the product cleaved off the resin for 15 min. The solvent is evaporated under the air stream and the solid leftover is dissolved in acetonitrile + 0.1% HCOOH (HPLC grade), filtered by syringe PTFE-filter and analyzed by LC-MS.

5.9.3. Chloranil test

After washing the resin with DCM (3×) a few resin beads are taken from the filter syringe and transferred into an Eppendorf tube. Then 1-2 drops of a 2% acetaldehyde in DMF solution and 1-2 drops of a 2% chloranil in DMF solution are added to the resin. Deprotected secondary amines are confirmed by a quickly blue coloring of the beads, primary amines can also be confirmed but the reaction takes several minutes.

5.9.4. Kaiser test

After washing the resin with DCM (3×) a few resin beads are taken from the filter syringe and transferred into an Eppendorf tube. Then 1-2 drops of a 0.5 g ninhydrin in 10 mL EtOH solution, 1-2 drops of a 2 g Phenol in 0.5 mL EtOH solution and 1-2 drops of a mixture of 0.2 mL 0.001 M KCN in H_2O mixed with 9.8 mL pyridine are added to the resin. The tube is carefully heated by a heat gun for 1-2 minutes. Deprotected primary amines are confirmed by a purple coloring of the beads.

5.9.5. SPPS and macrocyclization

a) **Resin Loading:** 2-Chlorotrityl chloride resin (2.0 eq) is placed into a dried and heated flask and swelled for 30 min in 30 mL/g resin dry DCM at r.t. under argon protection. The compound to load (1.0 eq) is dissolved in a minimum amount dry DCM and mixed with DIPEA (4 eq) and the resulting mixture is then added to the resin and stirred at r.t. overnight. After complete loading (TLC check of the solution) the resin is capped for 30 min by addition of 100 µL/g resin dry

MeOH and DIPEA (1.0 eq). The resin is then filtered, washed with DMF (3×), DCM (3×) and dried in the desiccator overnight and the loading *l* determined as follows:[67]

$$\frac{(m_{total} - m_{resin}) \cdot 10^3}{(MW - 36.46) \cdot m_{total}} = l \ {}^{mmol}/_{g}$$

b) **1st deprotection:** The needed amount of resin calculated by the resin loading is transferred to a syringe with filter fritt. The resin is swelled for 20 min in DCM, then washed with DMF 3x. The pipecolate is Fmoc deprotected by shaking in 20% 4-methyl piperidine in DMF (3x10 min). The completion of the reaction is monitored on LCMS by test cleavage (5.9.2) as well as by Chloranil-test (5.9.3).

c) **1st AA coupling:** Fmoc-AA-OH, (3.0 eq respectively to the resin loading), HATU (3.0 eq) and HOAt (3.0 eq) are dissolved in a minimum amount of DMF by sonication. Then DIPEA (6.0 eq) is added and the mixture is drawn up into the filter syringe filled with loaded resin. The syringe is mixed by shaking for 2 h or with especially hindered substrates overnight. Finally, the solvent is removed and the resin is washed with DMF (3×), THF (3×), DCM (3×). The coupling is confirmed via test cleavage (5.9.2) and/or by Chloranil-test (5.9.3).

d) **2nd deprotection:** The Fmoc protecting group is removed by the addition of 5% 4-methyl piperidine in DMF solution pre-cooled in an ice bath to 4 °C to the filter syringes. After 5 min the deprotection solution is removed and the resin is washed with DMF (1×). The completion of the reaction is confirmed via test cleavage (5.9.2) and/or by Kaiser Test (5.9.4). The deprotection procedure is repeated two times if needed. After the final step the resin is washed with DMF (3×), then DCM (3×).

e) **Nosyl protection (optional for *N*-methylation):** *o*-Nitrobenzensulfonychloride (4.0 eq) is dissolved in NMP and 2, 4, 6-collidine (10.0 eq) is added. The mixture is drawn up into the syringe with resin and reacted for 15 min. This procedure is repeated 2x. After the final step the resin is washed with DMF (3×), then DCM (3×). The completion of the reaction is confirmed via test cleavage (5.9.2) and/or by Kaiser-test (5.9.4).

f) ***N*-methylation (optional for *N*-methylation):** The resin is washed with dry THF (3x) and a solution of PPh_3 (5.0 eq) and dry MeOH (10.0 eq) in dry THF is added. Then DIAD (5.0 eq) diluted in dry THF is added portion-wise (Caution! Exothermic reaction!). After 10 min the reaction mixture is discarded, the resin washed with dry THF and the procedure repeated 2x. After the final step the resin is washed with DMF (3×), then DCM (3×). The completion of the reaction is confirmed via test cleavage (5.9.2).

g) **Nosyl deprotection (optional for *N*-methylation):** DBU (5.0 eq) and beta-mercaptoethanol (10.0 eq) are dissolved in NMP. The mixture is drawn up into the syringe with resin and reacted for 10 min. This procedure is repeated 2x After the final step the resin is washed with DMF

(3×), then DCM (3×). The completion of the reaction is confirmed via test cleavage (5.9.2) and/or by Chloranil-test (5.9.3).

h) **2nd AA coupling:** Repeat entry **c)**.

i) **3rd deprotection:** Repeat entry **d)**; in case of the meta OH B ring derivative, another deprotection for the allyl is done by the addition of premixing $Pd(OAc)_2$ (0.1 eq), PPh_3 (1.0 eq) and morpholine (2.0 eq) in THF. After addition to the syringe, the resin is mixed for 20 min. The completion of the reaction is confirmed via test cleavage (5.9.2)

j) **2nd *N*-methylation (optional):** Repeat entry **e)**, **f)** and **g)**.

k) **Cleavage from resin:** The resin is transferred to a round bottom flask and stirred in 20 mL/g resin 20% HFIP in DCM for 2 h. The resin is filtered off and washed with DCM. The solvent is removed and the crude linear product is identified by LCMS.

l) **Macrocyclization:** The crude linear product is dissolved in DMF (1.0 mM) then HATU (3.0 eq) and DIPEA (5.0 eq) added. In the case of the meta OH B ring derivative another method is used: HATU (1.0 eq), DIPEA (3.0 eq) and pentafluorophenol (10.0 eq) in NMP (1 mM). The reaction is stirred at r.t. overnight and the solvent removed under reduced pressure. The crude product is purified by silica column chromatography and/or semi-preparative HPLC.

5.9.6. Click reaction

Alkyne (1.0 eq) and azide (1.5 eq) are dissolved in 2 mL *t*BuOH. Then $CuSO_4$ (1.5 eq) is dissolved in 2 mL H_2O and added to the solution. Finally, sodium ascorbate (1.5 eq) is added.

After complete reaction (1-2 h), monitored by TLC and LCMS, the mixture is diluted with DCM and washed with H_2O (3×). The organic phase is dried with $MgSO_4$, filtered and the solvent removed under reduced pressure and the crude product purified.

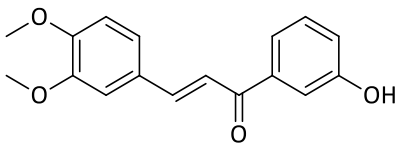
5.9.7. Steglich esterification

Alcohol (1.0 eq), the carboxylic acid (1.1 eq) and DMAP (4 eq) are dissolved in 5 mL dry DCM and cooled to 0°C for 15 min. Then DIC (1.1 eq) is added. The mixture is stirred for 15 min at 0°C, then overnight at rising temperature to room temperature. After complete conversion, the solvent is removed and the crude product is purified.

6. Experimental procedures

6.1. Upscaled synthesis of the SAFit A/B ring

(E)-3-(3,4-dimethoxyphenyl)-1-(3-hydroxyphenyl)prop-2-en-1-one (AV483)



Chemical Formula: $C_{17}H_{16}O_4$
Exact Mass: 284,10
Molecular Weight: 284,31

4

3-Hydroxyacetophenon (81.93 g, 0.60 mol, 1.0 eq) and 3,4-Dimethoxybenzaldehyde (100 g, 0.60 mol, 1 eq) are dissolved in 800 mL EtOH. The mixture is cooled to 0°C for 30 min, then cooled KOH (135 g, 2.41 mol, 4 eq) dissolved in 500 mL H_2O is added dropwise in 1 h. The mixture is stirred under slowly rising temperatures overnight. After complete conversion, the reaction mixture is cooled by adding 1 kg ice and acidified with 600 mL 6 M HCl. Then 250 mL H_2O is added dropwise to precipitate the product. After stirring overnight the precipitate is filtered, washed with H_2O and dried on the rotivap, then via a high vacuum pump. The pure product **4** is obtained as a yellow-beige solid.

Yield 96 g (56%).

TLC (CH/EE, 2/1): R_f (**4**) = 0.22.

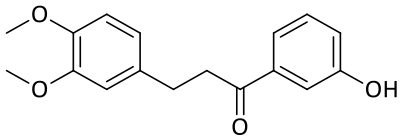
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.76 (d, *J* = 15.6 Hz, 1H), 7.65 (dd, *J* = 1.6, 2.5 Hz, 1H), 7.55 (ddd, *J* = 1.0, 1.6, 7.7 Hz, 1H), 7.39 – 7.31 (m, 2H), 7.20 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.16 – 7.09 (m, 2H), 7.05 (s, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 191.05, 156.66, 151.64, 149.27, 145.75, 139.72, 129.82, 127.77, 123.38, 120.75, 120.35, 119.91, 115.30, 111.22, 110.37, 56.01.

LC-MS (30-100% B, 19 min): t_R (**4**) = 7.65 min, m/z: calculated = 285.10 $[M+H]^+$, found = 285.18 $[M+H]^+$.

RP-HPLC (30 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**4**) = 7.60 min (99% Purity).

3-(3,4-dimethoxyphenyl)-1-(3-hydroxyphenyl)propan-1-one (AV328/AV330/AV332/AV334/AV409/AV487/AV489)



Chemical Formula: $C_{17}H_{18}O_4$
Exact Mass: 286,12
Molecular Weight: 286,32

5

Zn powder (115 g, 1.76 mol, 10.0 eq) and NH_4Cl (94 g, 1.76 mol, 10.0 eq) are added to a flask and suspended in 500 mL MeOH. **4** (50 g, 0.18 mol, 1.0 eq) is dissolved in 250 mL MeOH and 180 mL THF and added dropwise to the vigorously stirring suspension in 3 h. After complete addition, the mixture is filtered and washed with MeOH. 1.5 L H_2O is added slowly to the filtrate under stirring to precipitate the product. The mixture is stirred overnight to facilitate full precipitation, then filtered, washed with H_2O and dried on the rotivap. The pure product **5** is obtained as a beige-white solid.

Yield 41 g (81%).

TLC (CH/EE, 2/1): R_f (**5**) = 0.34.

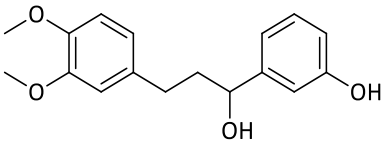
^{1}H-NMR (300 MHz, DMSO-d_6): δ 9.73 (s, 1H), 7.48 – 7.38 (m, 1H), 7.38 – 7.26 (m, 2H), 7.01 (ddd, *J* = 1.1, 2.5, 8.1 Hz, 1H), 6.92 – 6.67 (m, 3H), 3.73 (s, 2H), 3.70 (s, 3H), 3.27 (dd, *J* = 7.0, 8.1 Hz, 2H), 2.86 (t, *J* = 7.5 Hz, 2H).

^{13}C-NMR (75 MHz, DMSO-d_6): δ 199.13, 157.53, 148.59, 147.02, 138.04, 133.66, 129.70, 120.09, 120.03, 118.85, 114.02, 112.41, 111.87, 55.50, 55.37, 29.22.

LC-MS (30-100% B, 19 min): t_R (**5**) = 7.67 min, m/z: calculated = 287.12 $[M+H]^+$, found = 287.10 $[M+H]^+$.

RP-HPLC (30 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**5**) = 7.34 min (99% Purity).

3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenol (AV141)



Chemical Formula: $C_{17}H_{20}O_4$
Exact Mass: 288,14
Molecular Weight: 288,34

6

5 (100 mg, 0.35 mmol, 1.0 eq) is dissolved in 5 mL THF. $NaBH_4$ (13.56 mg, 0.35 mmol, 1.0 eq) is added and the reaction stirred at r.t. overnight. The mixture is quenched with 1 mL 3 M HCl. The THF is removed under reduced pressure and the aqueous phase diluted with H_2O, then extracted with DCM (3×10 mL) The crude product is purified by column chromatography (CH/EE, 3/2). The pure product **6** is obtained as a beige-white solid.

Yield 86 mg (85%).

TLC (CH/EE, 3/2): R_f (**6**) = 0.26.

^{1}H-NMR (300 MHz, DMSO-*d*$_6$): δ 7.13 (td, *J* = 3.5, 7.8 Hz, 1H), 6.86 (t, *J* = 2.0 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.76 – 6.70 (m, 2H), 6.66 (dt, *J* = 2.3, 6.9 Hz, 2H), 4.58 (dd, *J* = 5.3, 7.7 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 2.59 (qdd, *J* = 4.1, 6.4, 14.1 Hz, 2H), 2.14 – 1.86 (m, 2H).

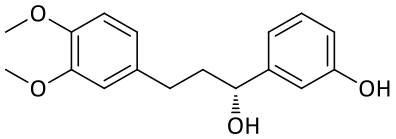
^{13}C-NMR (75 MHz, DMSO-*d*$_6$): δ 156.34, 148.83, 147.22, 146.07, 134.41, 129.76, 120.38, 118.19, 114.91, 112.94, 112.06, 111.50, 73.98, 56.01, 55.91, 40.30, 31.63.

LC-MS (30-100% B, 19 min): t_R (**6**) = 9.05 min, m/z: calculated = 271.12 $[M-OH]^+$, found = 271.06 $[M-OH]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**6**) = 10.94 min (92% Purity).

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**6**) = 16.30 + 18.25 min (*er* = 50.50/49.50).

(R)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenol (AV142/AV200/AV497)



Chemical Formula: $C_{17}H_{20}O_4$
Exact Mass: 288,14
Molecular Weight: 288,34

7

K_2CO_3 (19.30 g, 0.14 mol, 1.0 eq) is filled into an autoclave (Roth, Model II). **5** (40 g, 0.14 mol, 1.0 eq) is dissolved in 150 mL iPrOH and 50 mL THF and added to the autoclave. The solution is sparged with argon for 10 min, then $RuCl_2$[(S)-(DM-SEGPHOS)][(S)-DAIPEN] (1.35 g, 1 mmol, 0.008 eq) is added and the autoclave closed, then flushed 3x with H_2, then 10 bar H_2 applied. After 2 d reaction time, the mixture is transferred to a beaker and filtered through celite and washed with MeOH. The solvent is removed under reduced pressure. The crude product is dissolved in EE and 2 g activated charcoal added. Then the mixture is filtered through 500 g silica using a gradient of CH/EE 2/1 going up to CH/EE 1/1. The product fractions are combined, the solvent removed and the brown oily product then dissolved in a minimum amount DCM under heating to reflux. The product precipitates by cooling the DCM under airstream. After filtering and washing with cooled DCM the pure product **7** is obtained as white solid.

Yield 34.9 g (87%).

TLC (CH/EE, 1/1): R_f (**7**) = 0.35.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.15 (td, *J* = 1.5, 7.9 Hz, 1H), 6.86 (t, *J* = 2.0 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.77 – 6.72 (m, 2H), 6.67 (dt, *J* = 1.8, 10.2 Hz, 2H), 4.59 (t, *J* = 6.6 Hz, 1H), 3.81 (s, 3H), 3.79 (d, *J* = 1.5 Hz, 3H), 2.74 – 2.52 (m, 4H), 2.13 – 1.87 (m, 2H).

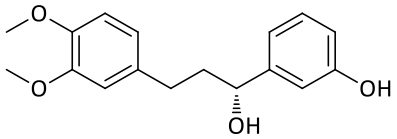
^{13}C-NMR (126 MHz, $CDCl_3$): δ 156.28, 148.89, 147.28, 146.16, 134.40, 129.83, 120.39, 118.28, 114.91, 112.94, 112.05, 111.51, 74.00, 56.05, 55.95, 40.38, 31.66.

LC-MS (30-100% B, 19 min): t_R (**7**) = 5.97 min, m/z: calculated = 271.32 $[M-OH]^+$, found = 271.17 $[M-OH]^+$.

RP-HPLC (30 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**7**) = 4.93 min (99% Purity).

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**7**) = 16.30 + 18.25 min (*er* = 99.33/0.67).

(R)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenol (AV526)



Chemical Formula: $C_{17}H_{20}O_4$
Exact Mass: 288,14
Molecular Weight: 288,34

7

5 (100 mg, 0.35 mmol, 1.0 eq) is suspended in 5 mL iPrOH. $RuCl_2$[(S)-(DM-SEGPHOS)][(S)-DAIPEN] (6 mg, 3 µmol, 0.008 eq) is added, then the mixture is sparged with argon for 10 min. A 1 M solution of KOtBu in tBuOH (0.35 mL, 1.0 eq) is added and the flask flushed with H_2 for 3 min, then 1 bar H_2 applied overnight. The solvent is removed under reduced pressure. The crude product is purified by silica column chromatography (CH/EE, 1/1) and pure product **7** is obtained as white solid.

Yield 73 mg (73%).

TLC (CH/EE, 1/1): R_f (**7**) = 0.35.

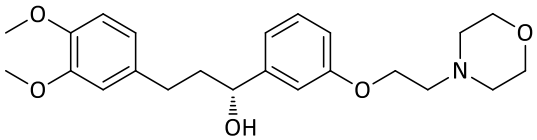
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.16 (t, J = 7.8 Hz, 1H), 6.86 (t, J = 2.0 Hz, 1H), 6.82 (d, J = 7.6 Hz, 1H), 6.77 – 6.72 (m, 2H), 6.70 – 6.65 (m, 2H), 4.60 (dd, J = 5.3, 7.8 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.69 – 2.51 (m, 2H), 2.12 – 1.90 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 156.31, 148.91, 147.29, 146.24, 134.44, 129.82, 120.39, 118.24, 114.89, 112.94, 112.05, 111.51, 73.97, 56.06, 55.96, 40.43, 31.68, 29.82.

RP-HPLC (30 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**7**) = 4.89 min (99% Purity).

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**7**) = 16.30 + 18.25 min (*er* = 99.63/0.37).

(R)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propan-1-ol (AV531)



Chemical Formula: $C_{23}H_{31}NO_5$
Exact Mass: 401,22
Molecular Weight: 401,50

8

7 (23.47 g, 80 mmol, 1.0 eq) is dissolved in 270 mL MeCN. K_2CO_3 (45.00 g, 330 mmol, 4.0 eq) and 4-(2-chloroethyl)morpholine hydrochloride (15.15 g, 80 mmol, 1.0 eq) are added. The reaction is stirred at reflux overnight. After complete conversion, the suspension is filtered, washed with MeCN and the solvent removed under reduced pressure. The crude product **8** is obtained as slightly brown oil and used without further purification.

Yield 32.17 g (quant.).

TLC (EE/MeOH, 20/1): R_f (**8**) = 0.34.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.22 (m, 1H), 6.97 – 6.91 (m, 2H), 6.87 – 6.77 (m, 2H), 6.81 – 6.69 (m, 2H), 4.66 (dd, *J* = 5.1, 7.9 Hz, 1H), 4.10 (t, *J* = 5.7 Hz, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.75 – 3.69 (m, 4H), 2.79 (t, *J* = 5.7 Hz, 2H), 2.75 – 2.60 (m, 2H), 2.57 (dd, *J* = 3.7, 5.7 Hz, 4H), 2.16 – 1.95 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 158.97, 148.91, 147.27, 146.68, 134.49, 129.53, 120.27, 118.54, 113.62, 112.20, 111.91, 111.39, 73.66, 66.90, 65.77, 57.71, 56.00, 55.90, 54.12, 40.73, 31.73.

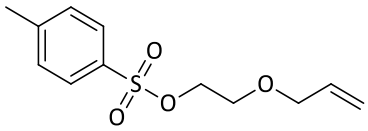
LC-MS (0-100% B, 19 min): t_R (**8**) = 7.10 min, m/z: calculated = 402.22 $[M+H]^+$, found = 402.36 $[M+H]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**8**) = 9.25 min (97% Purity).

6.2. Macrocycles through RCM

6.2.1. Building blocks

2-(allyloxy)ethyl 4-methylbenzenesulfonate (AV170)



Chemical Formula: $C_{12}H_{16}O_4S$
Exact Mass: 256,08
Molecular Weight: 256,32

9

2-(Allyloxy)ethanol (1.91 g, 0.02 mol, 1 eq) and pyridine (2.96 g, 0.04 mol, 2.0 eq) are dissolved in 30 mL dry DCM and cooled to 0°C for 10 min. Then *p*-toluenesulfonyl chloride is added portion-wise. The reaction is stirred at slowly rising temperature to r.t. overnight. Complete conversion is checked by TLC and LCMS. The reaction mixture is diluted with 30 mL DCM washed with 2 M HCl (2 × 30 mL), 4% $NaHCO_3$ (1 × 40 mL), then H_2O (1 × 40 mL) and brine (1 × 50 mL). The organic phase is dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by manual column chromatography (CH/EE, 5/1). Product **9** is obtained as a slightly yellow oil.

Yield: 2.72 g (57%).

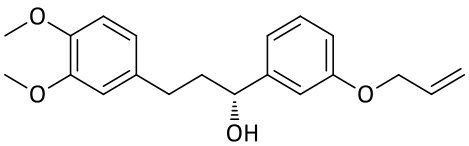
TLC (CH/EE, 5/1, v/v): R_f (**9**) = 0.25.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.82 – 7.77 (m, 2H), 7.36 – 7.31 (m, 2H), 5.81 (ddt, J = 5.5, 10.3, 17.2 Hz, 1H), 5.22 (dq, J = 1.6, 17.3 Hz, 1H), 5.16 (dq, J = 1.4, 10.4 Hz, 1H), 4.17 (ddd, J = 0.9, 3.7, 5.8 Hz, 2H), 3.94 (dt, J = 1.4, 5.5 Hz, 2H), 3.65 – 3.59 (m, 2H), 2.44 (s, 3H), 1.57 (d, J = 1.7 Hz, 0H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 144.90, 134.26, 133.27, 129.94, 128.12, 117.53, 72.31, 69.37, 67.59, 21.76.

LC-MS (0-100% B, 19 min): t_R (**9**) = 11.4 min, m/z: calculated = 257.08 $[M+H]^+$, found = 257.09 $[M+H]^+$.

(R)-1-(3-(allyloxy)phenyl)-3-(3,4-dimethoxyphenyl)propan-1-ol (AV123/AV144/AV146/AV212)



Chemical Formula: $C_{20}H_{24}O_4$
Exact Mass: 328,17
Molecular Weight: 328,40

10

7 (2.16 g, 7.49 mmol, 1.0 eq), K_2CO_3 (1.14 g, 8.24 mmol, 1.1 eq) and allyl bromide (997 mg, 8.24 mmol, 1.1 eq) are dissolved in 70 mL MeCN. The reaction is stirred overnight at r.t. After complete conversion, the mixture is filtered over celite and washed with MeCN. The solvent is removed under reduced pressure and the crude product purified by silica filtration (CH/EE, 3/2). Compound **10** is obtained as a white solid.

Yield 2.31 g (94%)

TLC (CH/EE, 3/2, v/v): R_f (**10**) = 0.53.

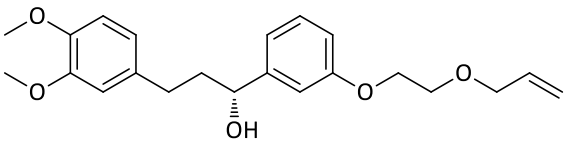
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.24 (ddd, *J* = 1.0, 7.0, 8.2 Hz, 1H), 6.91 (dd, *J* = 1.4, 7.3 Hz, 2H), 6.86 – 6.78 (m, 1H), 6.77 (d, *J* = 0.8 Hz, 1H), 6.73 (d, *J* = 1.8 Hz, 1H), 6.71 (s, 1H), 6.13 – 5.98 (m, 1H), 5.41 (dq, *J* = 1.6, 17.3 Hz, 1H), 5.28 (dq, *J* = 1.4, 10.5 Hz, 1H), 4.64 (dd, *J* = 5.3, 7.7 Hz, 1H), 4.52 (dt, *J* = 1.5, 5.2 Hz, 2H), 3.84 (d, *J* = 1.5 Hz, 6H), 2.65 (qdd, *J* = 6.4, 9.2, 13.8 Hz, 2H), 2.20 – 1.91 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 158.81, 148.86, 147.21, 146.44, 134.45, 133.29, 129.53, 120.25, 118.46, 117.70, 113.76, 112.38, 111.83, 111.32, 73.77, 68.80, 55.96, 55.85, 40.63, 31.68.

LC-MS (0-100%, 19 min): t_R (**10**) = 10.47 min, m/z: calculated = 311.17 $[M-OH]^+$, found = 311.03 $[M-OH]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**10**) = 14.75 min (97% Purity).

(R)-1-(3-(2-(allyloxy)ethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propan-1-ol (AV176/AV178)



Chemical Formula: $C_{22}H_{28}O_5$
Exact Mass: 372,19
Molecular Weight: 372,45

11

7 (969 mg, 3.36 mmol, 1.0 eq), K_2CO_3 (697 g, 5 mmol, 1.5 eq) and **9** (861 mg, 3.4 mmol, 1.1 eq) are dissolved in 20 mL MeCN. The reaction is stirred overnight after heating to reflux. After complete conversion, the mixture is filtered over celite and washed with acetone. The solvent is removed under reduced pressure and the crude product purified by column chromatography (CH/EE, 3/1). Compound **11** is obtained as a beige oil.

Yield 1.18 g (94%)

TLC (CH/EE, 1/1, v/v): R_f (**11**) = 0.46.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.26 (td, *J* = 2.8, 7.9 Hz, 1H), 6.99 – 6.90 (m, 2H), 6.89 – 6.77 (m, 1H), 6.77 – 6.66 (m, 2H), 5.95 (ddt, *J* = 5.0, 10.1, 16.2 Hz, 1H), 5.32 (dd, *J* = 2.7, 17.2 Hz, 1H), 5.22 (d, *J* =

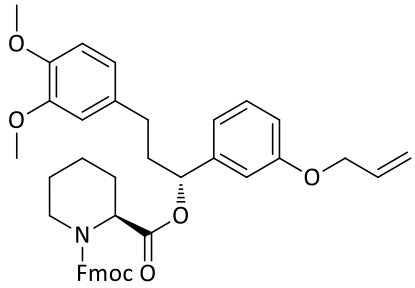
10.3 Hz, 1H), 4.72 – 4.60 (m, 1H), 4.19 – 4.03 (m, 5H), 3.86 (d, *J* = 2.9 Hz, 6H), 3.84 – 3.72 (m, 2H), 2.66 (qdd, *J* = 2.7, 8.4, 13.8, 16.1 Hz, 2H), 2.13 – 1.92 (m, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 159.06, 148.91, 147.25, 146.45, 134.61, 134.50, 129.51, 120.26, 118.51, 117.37, 113.66, 112.33, 111.90, 111.40, 73.77, 72.41, 68.57, 67.47, 55.99, 55.88, 40.65, 31.67, 26.97.

LC-MS (30-100%, 19 min): t_R (**11**) = 10.93 min, m/z: calculated = 354.17 $[M-OH]^+$, 390.22 $[M+NH_4]^+$, found = 355.10 $[M-OH]^+$, 390.04 $[M+NH_4]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**11**) = 14.54 min (93% Purity).

(S)-1-((9H-fluoren-9-yl)methyl) 2-((R)-1-(3-(allyloxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl) piperidine-1,2-dicarboxylate (AV126/161)



Chemical Formula: $C_{41}H_{43}NO_7$
Exact Mass: 661,30
Molecular Weight: 661,78

12

10 (1.29 g, 3.47 mmol, 1.0 eq) and Fmoc-*S*-pipecolate (1.99 g, 5.66 mmol, 1.1 eq) are dissolved in 40 mL dry DCM and cooled to 0°C for 15 min. DMAP (70 mg, 0.57 mmol, 0.1 eq) is added and stirred until dissolved, then DCC (1.17 g, 5.66 mmol, 1.1 eq) is added. The mixture is stirred for 15 min. Finally, the ice bath is removed and the reaction stirred overnight at r.t. The reaction mixture is filtered, washed with DCM and the solvent removed under reduced pressure. The crude product is purified by silica column chromatography (CH/EE, 5/1) and pure product **12** obtained as a white foam.

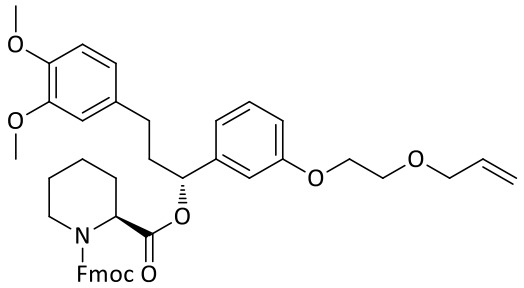
Yield 3.16 g (93%).

TLC (CH/EE, 5/1, v/v): R_f (**12**) = 0.22.

LC-MS (70-100% B, 19 min): t_R (**12**) = 7.70 min, m/z: calculated = 679.30 $[M+H]^+$, found = 679.02 $[M+H]^+$.

RP-HPLC (70 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**12**) = 11.12 min (99% Purity).

(S)-1-((9H-fluoren-9-yl)methyl) 2-((R)-1-(3-(2-(allyloxy)ethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl) piperidine-1,2-dicarboxylate (AV116/AV182)



Chemical Formula: $C_{43}H_{47}NO_8$
Exact Mass: 705,33
Molecular Weight: 705,84

13

11 (1.29 g, 3.47 mmol, 1.0 eq) and Fmoc-*S*-pipecolate (1.30 g, 3.81 mmol, 1.1 eq) are dissolved in 20 mL dry DCM and cooled to 0°C for 15 min. DMAP (50 mg, 0.38 mmol, 0.1 eq) is added and stirred until dissolved, then DCC (0.8 g, 3.81 mmol, 1.1 eq) is added. The mixture is stirred for 15 min. Finally, the ice bath is removed and the reaction stirred overnight at r.t. The reaction mixture is filtered, washed with DCM and the solvent removed under reduced pressure. The crude product is purified by silica column chromatography (CH/EE, 4/1) and pure product **13** obtained as a white foam.

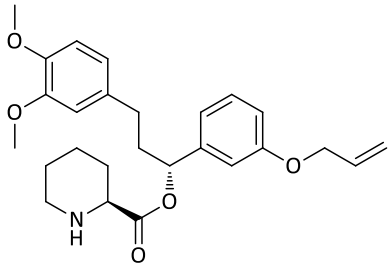
Yield 2.17 g (89%).

TLC (CH/EE, 4/1, v/v): R_f (**13**) = 0.22.

LC-MS (50-100% B, 19 min): t_R (**13**) = 12.27 min, m/z: calculated = 723.36 $[M+NH_4]^+$, found = 723.07 $[M+NH_4]^+$.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**13**) = 16.82 min (99% Purity).

(S)-(R)-1-(3-(allyloxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl piperidine-2-carboxylate (AV129/AV185)



Chemical Formula: $C_{26}H_{33}NO_5$
Exact Mass: 439,24
Molecular Weight: 439,54

14

12 (3.15 g, 4.76 mmol, 1.0 eq) is dissolved in 40 mL DCM and 10% 4-methyl piperidine (4.4 mL) is added. The reaction is stirred at r.t. for 2 h, then diluted with 50 mL DCM, washed with 1 M HCl (4x50 mL) and brine (1x50 mL). The organic phase is dried with $MgSO_4$, filtered and the solvent removed. The crude product is purified by silica column chromatography (CH/EE, 2/1 +1% TEA + 2% MeOH) and the pure product **14** obtained as a colorless oil.

Yield 1.85 g (89%).

TLC (CH/EE, 2/1 +1% TEA + 2% MeOH, v/v): R_f (**14**) = 0.25.

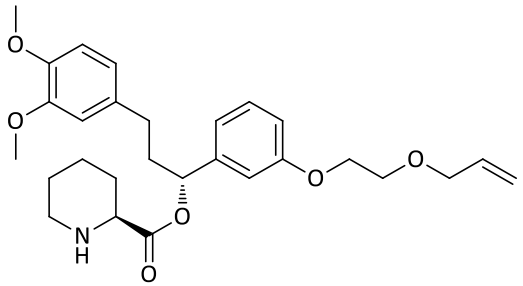
^{1}H-NMR (300 MHz, Chloroform-*d*): δ 7.24 (t, J = 7.8 Hz, 1H), 6.96 – 6.85 (m, 2H), 6.83 (ddd, J = 1.0, 2.6, 8.3 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.67 (d, J = 7.9 Hz, 2H), 6.05 (ddt, J = 5.3, 10.5, 17.1 Hz, 1H), 5.77 (dd, J = 5.7, 7.9 Hz, 1H), 5.41 (dq, J = 1.6, 17.2 Hz, 1H), 5.28 (dq, J = 1.4, 10.5 Hz, 1H), 4.52 (dt, J = 1.5, 5.3 Hz, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.37 (dd, J = 3.2, 9.7 Hz, 1H), 3.07 (dt, J = 3.4, 11.9 Hz, 1H), 2.72 – 2.45 (m, 3H), 2.34 – 2.15 (m, 1H), 2.15 – 1.96 (m, 3H), 1.87 – 1.74 (m, 1H), 1.70 – 1.37 (m, 4H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ 172.95, 158.83, 149.03, 147.47, 141.94, 133.77, 133.31, 129.65, 120.27, 119.15, 117.83, 114.07, 113.34, 111.84, 111.47, 75.64, 68.94, 58.87, 56.05, 55.98, 45.78, 38.07, 31.47, 29.41, 25.97, 24.27.

LC-MS (0-100% B, 19 min): t_R (**14**) = 8.32 min, m/z: calculated = 440.24 $[M+H]^+$,
found = 440.23 $[M+H]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**14**) = 12.95 min (93% Purity).

((S)-(R)-1-(3-(2-(allyloxy)ethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl piperidine-2-carboxylate (AV184)



Chemical Formula: $C_{28}H_{37}NO_6$
Exact Mass: 483,26
Molecular Weight: 483,60

15

13 (2.17 g, 3.08 mmol, 1.0 eq) is dissolved in 30 mL DCM and 10% 4-methyl piperidine (3.3 mL) is added. The reaction is stirred at r.t. for 2 h, then diluted with 50 mL DCM, washed with 1 M HCl (4x50 mL) and brine (1x50 mL). The organic phase is dried with $MgSO_4$, filtered and the solvent

removed. The crude product is purified by silica column chromatography (CH/EE, 2/1 +1% TEA + 2% MeOH) and the pure product **15** obtained as a colorless oil.

Yield 1.23 g (83%).

TLC (CH/EE, 2/1 +1% TEA + 2% MeOH, v/v): R_f (**15**) = 0.25.

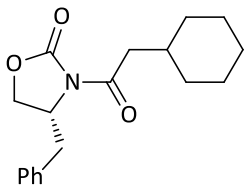
^{1}H-NMR (300 MHz, Chloroform-*d*): δ 7.23 (t, J = 8.0 Hz, 1H), 6.90 (dt, J = 1.2, 5.6 Hz, 2H), 6.83 (ddd, J = 1.0, 2.6, 8.2 Hz, 1H), 6.77 (d, J = 7.9 Hz, 1H), 6.66 (d, J = 7.8 Hz, 2H), 5.93 (ddt, J = 5.7, 10.4, 17.3 Hz, 1H), 5.76 (dd, J = 5.7, 7.9 Hz, 1H), 5.37 – 5.25 (m, 1H), 5.20 (dq, J = 1.4, 10.4 Hz, 1H), 4.16 – 4.05 (m, 4H), 3.85 (s, 3H), 3.84 (s, 3H), 3.82 – 3.74 (m, 2H), 3.36 (dd, J = 3.2, 9.7 Hz, 1H), 3.11 – 3.00 (m, 1H), 2.70 – 2.44 (m, 3H), 2.31 – 2.16 (m, 1H), 2.12 – 1.96 (m, 4H), 1.80 (dt, J = 3.8, 7.8 Hz, 1H), 1.69 – 1.36 (m, 3H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ 172.81, 158.92, 148.89, 147.33, 141.78, 134.53, 133.65, 129.49, 120.14, 119.08, 117.33, 113.77, 113.19, 111.71, 111.34, 75.51, 72.37, 68.49, 67.42, 58.73, 55.92, 55.86, 45.66, 37.94, 31.33, 29.28, 25.84, 24.15.

LC-MS (0-100% B, 19 min): t_R (**15**) = 8.65 min, m/z: calculated = 484.26 $[M+H]^+$, found = 484.18 $[M+H]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**15**) = 12.97 min (98% Purity).

(R)-4-benzyl-3-(2-cyclohexylacetyl)oxazolidin-2-one (AV187)



Chemical Formula: $C_{18}H_{23}NO_3$
Exact Mass: 301,17
Molecular Weight: 301,38

16

To a solution of (*R*)-4-benzyloxazolidin-2-one (4.54 g, 25.64 mmol, 1 eq) in THF (50 mL) is added a 2.5 M *N*-butyllithium solution in hexane (13.32 ml, 33.30 mmol, 1.5 eq) dropwise in 10 min at -78°C and the mixture is stirred at that temperature for 1.5 h. To the mixture is added 2-cyclohexylacetyl chloride (1.30 mL, 8.47 mmol, 1.5 eq) dropwise in 10 min at -78°C. The reaction is stirred for 2.5 h at -78°C and is then slowly warmed to r.t. After stirring overnight, the reaction mixture is quenched with sat. NH_4Cl solution. The aqueous layer is extracted with Et_2O. The combined organic layers are dried over $MgSO_4$, filtrated and concentrated under reduced pressure. Finally, the crude product is purified by manual chromatography (CH/EE – 8/1). Compound **16** is obtained as a white crystalline compound.

Yield 7.52 g (97%)

TLC (CH/EE, 8/1, v/v): R_f (**16**) = 0.31.

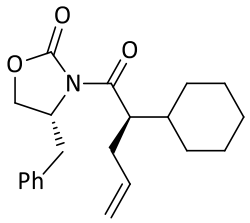
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.36 – 7.30 (m, 2H), 7.30 – 7.25 (m, 1H), 7.24 – 7.19 (m, 2H), 4.68 (ddt, *J* = 9.6, 7.6, 3.1 Hz, 1H), 4.22 – 4.13 (m, 2H), 3.31 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.88 (dd, *J* = 15.9, 6.6 Hz, 1H), 2.82 – 2.72 (m, 2H), 1.91 (dddt, *J* = 14.8, 7.8, 6.8, 3.4 Hz, 1H), 1.78 (ttt, *J* = 9.1, 3.7, 1.8 Hz, 2H), 1.72 (dqd, *J* = 12.6, 3.4, 1.4 Hz, 2H), 1.66 (dtt, *J* = 13.1, 3.4, 1.6 Hz, 1H), 1.35 – 1.25 (m, 2H), 1.17 (qt, *J* = 12.7, 3.5 Hz, 1H), 1.10 – 0.98 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 172.75, 153.56, 135.49, 129.55, 129.08, 127.46, 66.22, 55.35, 42.82, 38.15, 34.45, 33.28, 33.23, 26.28.

LC-MS (0-100% B, 19 min): t_R (**16**) = 12.96 min, m/z: calculated = 302.18 $[M+H]^+$, found = 302.04 $[M+H]^+$.

RP-HPLC (30 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**16**) = 14.6 min (92% Purity).

(R)-4-benzyl-3-((R)-2-cyclohexylpent-4-enoyl)oxazolidin-2-one (AV188)



Chemical Formula: $C_{21}H_{27}NO_3$
Exact Mass: 341,20
Molecular Weight: 341,44

17

16 (7.48 g, 25 mmol, 1 eq) is dissolved in dry THF and added to a dried flask under argon protection, then cooled under stirring for 30 min at -78°C. A 1 M solution of LiHMDS in THF (37.23 ml, 37 mmol. 1.5 eq) is slowly added in 45 min and the solution is then stirred for 45 min at -78°C. Then 3-bromoprop-1-ene (3.22 ml, 37 mmol, 1.5 eq) is added dropwise in 10 min and the solution is stirred at -78°C with slowly rising temperature to r.t. overnight. The mixture is quenched with sat. NH_4Cl solution (100 mL) and the aqueous layer extracted with Et_2O (3×100 mL). The combined organic layers are washed with brine, dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product is purified by manual chromatography (Cy + 5% EE). Compound **17** is obtained as a white solid.

Yield 7.10 g (84%)

TLC (Cy + 5% EE, v/v): R_f (**17**) = 0.15.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.29 – 7.09 (m, 5H), 5.74 (dddd, *J* = 6.2, 7.7, 10.2, 16.6 Hz, 1H), 5.00 (dq, *J* = 1.6, 17.2 Hz, 1H), 4.93 (ddd, *J* = 1.2, 2.0, 10.2 Hz, 1H), 4.67 – 4.53 (m, 1H), 4.05 – 4.02 (m, 2H), 3.84

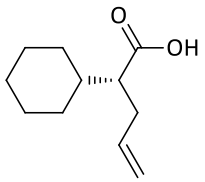
(ddd, *J* = 5.0, 7.5, 9.2 Hz, 1H), 3.22 (dd, *J* = 3.3, 13.3 Hz, 1H), 2.55 (dd, *J* = 10.0, 13.3 Hz, 1H), 2.44 – 2.29 (m, 2H), 1.82 – 1.48 (m, 7H), 1.24 – 0.82 (m, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 175.90, 153.31, 135.77, 135.69, 129.50, 128.98, 127.32, 116.95, 65.79, 55.74, 47.50, 40.17, 38.17, 33.88, 31.27, 29.78, 27.00, 26.40.

LC-MS (50-100% B, 19 min): t_R (**17**) = 10.38 min, m/z: calculated = 342.20 $[M+H]^+$, found = 342.13 $[M+H]^+$.

RP-HPLC (30 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**17**) = 17.06 min (99% Purity).

(R)-2-cyclohexylpent-4-enoic acid (AV189)



Chemical Formula: $C_{11}H_{18}O_2$
Exact Mass: 182,13
Molecular Weight: 182,26

18

Lithium hydroxide (2.22 g, 93 mmol, 4.5 eq) and a 30 wt% hydrogen peroxide solution (8.34 g, 74 mmol, 3.6 eq) are added to a solution of **17** (7.05 g, 21 mmol, 1 eq) in THF/H_2O (215 mL/135 mL, 8/5). The resulting solution is stirred at r.t overnight. Then the reaction mixture is quenched with 100 mL sat. Na_2SO_3 solution, acidified with conc. HCl to pH = 1 and extracted with DCM (3×100 mL). The organic layers are combined, washed with brine and dried over $MgSO_4$ and the mixture is concentrated under reduced pressure. The crude product is purified by column chromatography (CH/EE, 5/1). Compound **18** is obtained as a colorless oil.

Yield 2.53 g (68%)

TLC (CH/EE, 5/1, v/v): R_f (**18**) = 0.14.

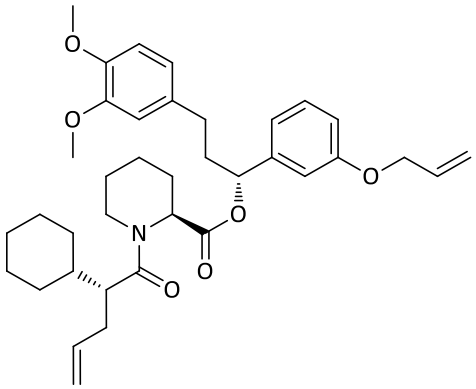
^{1}H-NMR (500 MHz, $CDCl_3$): δ 11.45 (s, 1H), 5.77 (ddt, *J* = 6.7, 10.1, 17.0 Hz, 1H), 5.07 (dq, *J* = 1.5, 17.1 Hz, 1H), 5.01 (dt, *J* = 1.4, 10.1 Hz, 1H), 2.32 (ddt, *J* = 1.4, 6.6, 7.9 Hz, 2H), 2.30 – 2.23 (m, 1H), 1.83 – 1.63 (m, 4H), 1.58 (dddd, *J* = 3.2, 6.7, 11.2, 14.5 Hz, 1H), 1.31 – 0.96 (m, 5H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 181.70, 135.84, 116.76, 51.79, 39.76, 33.49, 30.95, 30.58, 26.45, 26.41.

LC-MS (0-100%, 19 min): t_R (**18**) = 11.52 min, m/z: calculated = 183.26 $[M+H]^+$, 224.29 $[M+MeCN+H]^+$, found = 183.09 $[M+H]^+$, 223.78 $[M+MeCN+H]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**18**) = 14.24 min (95% Purity).

(S)-(R)-1-(3-(allyloxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((R)-2-cyclohexylpent-4-enoyl)piperidine-2-carboxylate (AV132/AV190)



Chemical Formula: $C_{37}H_{49}NO_6$
Exact Mass: 603,36
Molecular Weight: 603,79

19

18 (456 mg, 2.50 mmol, 1.1 eq) is dissolved in 5 mL DMF, HATU (951 mg, 2.50 mmol, 1.1 eq) and DIPEA (1160 µL, 6.83 mmol, 3.0 eq) are added and the mixture stirred for 5 min. Then a solution of **14** (1.0 g, 2.28 mmol, 1.0 eq) in 15 mL DMF is added. The reaction is stirred at r.t overnight. The solvent is removed under reduced pressure. The crude product is purified by silica column chromatography (CH/EE, 7/1) to obtain pure product **19** as sticky resin.

Yield 900 mg (68%).

TLC (CH/EE, 7/1, v/v): R_f (**19**) = 0.21.

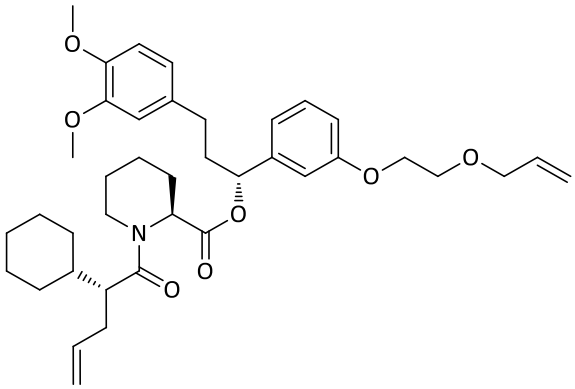
^{1}H-NMR (300 MHz, Chloroform-*d*): δ 7.27 – 7.19 (m, 1H), 6.93 – 6.81 (m, 3H), 6.80 – 6.73 (m, 1H), 6.71 – 6.62 (m, 2H), 6.11 – 5.98 (m, 1H), 5.93 – 5.81 (m, 1H), 5.81 – 5.72 (m, 1H), 5.64 – 5.53 (m, 1H), 5.46 – 5.36 (m, 1H), 5.32 – 5.24 (m, 2H), 5.10 – 4.96 (m, 1H), 4.96 – 4.88 (m, 1H), 4.56 – 4.49 (m, 2H), 3.98 – 3.87 (m, 1H), 3.84 (d, J = 2.2 Hz, 6H), 3.15 – 3.01 (m, 1H), 2.66 – 2.39 (m, 3H), 2.38 – 2.17 (m, 3H), 2.13 – 1.94 (m, 1H), 1.87 (d, J = 13.2 Hz, 1H), 1.80 – 1.48 (m, 9H), 1.46 – 1.04 (m, 4H), 1.03 – 0.70 (m, 2H).

^{13}C-NMR (75 MHz, Chloroform-*d*): δ 174.76, 170.86, 170.43, 158.77, 148.96, 148.89, 147.33, 141.71, 141.34, 136.81, 136.40, 133.68, 133.37, 133.26, 133.13, 129.74, 129.63, 120.24, 120.16, 119.30, 119.15, 117.84, 117.73, 116.75, 116.07, 114.37, 114.26, 113.38, 113.27, 111.76, 111.67, 111.33, 76.21, 68.85, 56.33, 55.98, 55.88, 51.97, 47.47, 46.88, 43.84, 40.38, 40.13, 38.09, 37.77, 34.80, 34.53, 32.02, 31.74, 31.50, 31.35, 30.46, 30.20, 27.10, 26.54, 26.47, 26.44, 26.21, 25.72, 21.25, 21.16

LC-MS (70-100% B, 19 min): t_R (**19**) = 8.48 min, m/z: calculated = 604.36 $[M+H]^+$,
found = 604.13 $[M+H]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**19**) = 17.15 min (98% Purity).

(S)-(R)-1-(3-(2-(allyloxy)ethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((R)-2-cyclohexylpent-4-enoyl)piperidine-2-carboxylate (AV124/AV125/AV191)



Chemical Formula: $C_{39}H_{53}NO_7$
Exact Mass: 647,38
Molecular Weight: 647,84

20

18 (415 mg, 2.27 mmol, 1.1 eq) is dissolved in 5 mL DMF, HATU (865 mg, 2.27 mmol, 1.1 eq) and DIPEA (1055 µL, 6.20 mmol, 3.0 eq) are added and the mixture stirred for 5 min. Then a solution of **15** (1.0 g, 2.07 mmol, 1.0 eq) in 10 mL DMF is added. The reaction is stirred at r.t overnight. The solvent is removed under reduced pressure. The crude product is purified by silica column chromatography (CH/EE, 7/1) to obtain pure product **20** as sticky resin.

Yield 1.20 g (90%).

TLC (CH/EE, 7/1, v/v): R_f (**20**) = 0.23.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ 7.23 (t, J = 7.4, 8.3 Hz, 1H), 6.93 – 6.87 (m, 2H), 6.86 – 6.80 (m, 1H), 6.80 – 6.73 (m, 1H), 6.69 – 6.61 (m, 2H), 6.01 – 5.86 (m, 1H), 5.85 – 5.71 (m, 2H), 5.59 (d, J = 5.7 Hz, 1H), 5.35 – 5.24 (m, 1H), 5.24 – 5.15 (m, 1H), 5.09 – 4.95 (m, 1H), 4.95 – 4.87 (m, 1H), 4.15 – 4.03 (m, 6H), 3.95 – 3.88 (m, 1H), 3.86 – 3.81 (m, 6H), 3.81 – 3.72 (m, 2H), 3.14 – 3.01 (m, 1H), 2.74 – 2.13 (m, 7H), 1.93 – 1.79 (m, 1H), 1.79 – 1.50 (m, 9H), 1.42 – 1.01 (m, 4H), 1.01 – 0.66 (m, 2H).

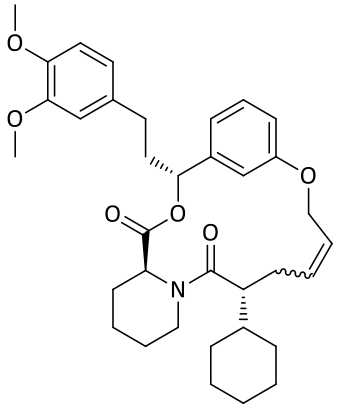
^{13}C-NMR (75 MHz, Chloroform-*d*): δ 174.75, 174.46, 170.83, 170.40, 158.97, 148.95, 148.88, 147.45, 147.31, 141.64, 141.28, 136.80, 136.39, 134.62, 134.57, 133.67, 133.37, 129.71, 129.60, 120.22, 120.14, 119.34, 119.18, 117.47, 117.41, 116.74, 116.06, 114.18, 114.13, 113.35, 113.22, 111.75, 111.65, 111.31, 76.22, 72.44, 68.56, 68.52, 67.49, 60.45, 56.33, 55.97, 55.88, 51.96, 47.44, 46.86, 43.83, 40.37, 40.12, 39.23, 38.06, 37.77, 34.79, 34.52, 32.01, 31.73, 31.47, 31.33, 30.45, 30.19, 29.78, 28.29, 27.10, 26.53, 26.47, 26.43, 26.32, 26.21, 25.71, 25.12, 21.24, 21.13, 14.28.

LC-MS (70-100% B, 19 min): t_R (**20**) = 8.42 min, m/z: calculated = 648.38 $[M+H]^+$, found = 648.06 $[M+H]^+$.

RP-HPLC (70 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**20**) = 9.99 min (99% Purity).

6.2.2. Macrocycles

(2R,5S,12R,14Z)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-3,17-dioxa-10-azatricyclo[16.3.1.0^{5},^{10}]docosa-1(22),14,18,20-tetraene-4,11-dione (AV137/AV153/AV201)



Chemical Formula: $C_{35}H_{45}NO_6$
Exact Mass: 575,32
Molecular Weight: 575,73

21a (E-isomer) and **b** (Z-isomer)

19 (536 mg, 0.89 mmol, 1.0 eq) is dissolved in 1.8 L dry DCM (0.5 mM) in a dried flask with a condenser. The solution is sparged continuously with argon and heated to 30°C. The system is equilibrated for 45 min, then Grubbs 2nd generation catalyst (75 mg, 0.089, 0.1 eq) is added. After 2.5 h the solution is filtered through a silica plug and the product eluted with 300 mL EE. The solvent is removed under reduced pressure and the crude mixture purified by manual silica column chromatography (CH/EE, 4/1) to obtain pure products **21a** (E-isomer) and **b** (Z-isomer).

Yield (21a) 441 mg (86%), (**21b**) 44 mg (9%).

TLC (CH/EE, 4/1, v/v): R_f (**21a**) = 0.25, R_f (**21b**) = 0.35.

^{1}H-NMR (500 MHz, THF-d$_8$, 21a): δ 7.10 (t, J = 7.3 Hz, 1H), 7.05 – 7.01 (m, 1H), 6.80 – 6.73 (m, 1H), 6.75 (d, J = 8.1 Hz, 1H), 6.72 (d, J = 2.0 Hz, 1H), 6.72 – 6.66 (m, 1H), 6.62 (dd, J = 2.1, 8.1 Hz, 1H), 5.91 (dt, J = 6.6, 8.0, 15.5 Hz, 1H), 5.64 (dd, J = 4.9, 8.3 Hz, 1H), 5.64 – 5.58 (m, 1H), 5.56 (ddd, J = 4.7, 7.4, 15.7 Hz, 1H), 4.64 – 4.49 (m, 2H), 3.73 (d, J = 13.1 Hz, 6H), 3.68 – 3.60 (m, 1H), 2.57 – 2.30 (m, 6H), 2.27 – 2.19 (m, 1H), 2.12 – 2.03 (m, 1H), 2.04 – 1.93 (m, 1H), 1.80 – 1.66 (m, 4H), 1.67 – 1.54 (m, 4H), 1.52 – 1.45 (m, 1H), 1.44 – 1.33 (m, 1H), 1.32 – 1.24 (m, 1H), 1.24 – 1.09 (m, 3H), 1.07 – 0.96 (m, 1H), 0.92 – 0.83 (m, 1H).

^{13}C-NMR (126 MHz, THF-d$_8$, 21a): δ 172.35, 171.44, 160.69, 150.91, 149.26, 142.09, 135.88, 134.76, 129.51, 127.89, 121.12, 120.34, 118.78, 113.71, 113.41, 111.32, 78.16, 69.15, 56.46, 56.29, 52.35, 48.51, 44.24, 42.47, 38.51, 32.61, 31.86, 31.26, 29.76, 28.06, 27.87, 27.49, 26.88, 26.84, 21.75.

^{1}H-NMR (500 MHz, THF-d$_8$, 21b): δ 7.11 (t, J = 7.9 Hz, 1H), 6.79 – 6.75 (m, 2H), 6.74 (d, J = 2.0 Hz, 1H), 6.70 (d, 1H), 6.69 – 6.65 (m, 2H), 5.73 (dd, J = 3.7, 8.5 Hz, 1H), 5.49 – 5.44 (m, 1H), 5.36 – 5.28 (m, 1H), 5.23 (dt, J = 2.1, 4.0, 11.3 Hz, 1H), 5.10 (dt, J = 2.6, 4.3, 11.0 Hz, 1H), 4.63 (dq, J = 2.8, 16.0 Hz, 1H), 3.98 – 3.91 (m, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.50 (td, J = 3.0, 13.0 Hz, 1H), 2.76 – 2.68 (m, 1H), 2.66 – 2.60 (m, 2H), 2.56 – 2.45 (m, 1H), 2.29 – 2.17 (m, 1H), 2.17 – 2.10 (m, 1H), 2.10 – 2.00 (m, 2H), 1.90 – 1.82 (m, 1H), 1.80 – 1.62 (m, 10H), 1.62 – 1.41 (m, 1H), 1.34 – 0.95 (m, 4H).

^{13}C-NMR (126 MHz, THF-d$_8$, 21b): δ 176.07, 172.84, 159.27, 150.98, 149.33, 142.82, 135.20, 131.01, 129.76, 129.14, 121.20, 118.07, 117.87, 113.91, 113.53, 110.81, 75.45, 65.21, 56.47, 56.34, 52.22, 47.35, 44.10, 42.28, 39.03, 32.42, 32.05, 31.25, 30.06, 27.86, 27.66, 27.57, 27.54, 26.58, 20.76.

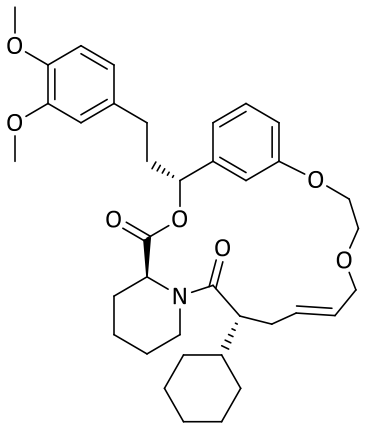
LC-MS (50-100% B, 19 min): t_R (**21a**) = 11.75 min, m/z: calculated = 576.32 $[M+H]^+$, found = 576.05 $[M+H]^+$, t_R (**21b**) = 11.94 min, m/z: calculated = 576.32 $[M+H]^+$, found = 576.35 $[M+H]^+$.

HRMS (ESI, 21a): calculated = 576.33196 $[M+H]^+$, found = 576.33244 $[M+H]^+$, err [ppm] = 0.82.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**21a**) = 15.77 min (99% Purity).

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**21b**) = 16.48 min (98% Purity).

(2R,5S,12R,14E)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-3,17,20-trioxa-10-azatricyclo[19.3.1.0^5,^{10}]pentacosa-1(25),14,21,23-tetraene-4,11-dione (AV128/AV135/AV202)



Chemical Formula: $C_{36}H_{49}NO_7$
Exact Mass: 607,35
Molecular Weight: 607,78

22

19 (592 mg, 0.91 mmol, 1.0 eq) is dissolved in 1.8 L dry DCM (0.5 mM) in a dried flask with a condenser. The solution is sparged continuously with argon and heated to 30°C. The system is equilibrated for 45 min, then Grubbs 2nd generation catalyst (78 mg, 0.091, 0.1 eq) is added. After 2.5 h the solution is filtered through a silica plug and the product eluted with 200 mL EE. The solvent is removed under

reduced pressure and the crude mixture purified by manual silica column chromatography (CH/EE, 4/1) to obtain pure product **22**.

Yield 519 mg (92%).

TLC (CH/EE, 3/1, v/v): R_f (**22**) = 0.25.

^{1}H-NMR (500 MHz, CD_2Cl_2): δ 7.28 – 7.19 (m, 1H), 7.11 (t, J = 2.1 Hz, 1H), 6.94 – 6.90 (m, 1H), 6.85 (ddd, J = 0.9, 2.5, 8.2 Hz, 1H), 6.82 – 6.77 (m, 1H), 6.75 – 6.68 (m, 2H), 5.69 (dd, J = 5.1, 8.8 Hz, 1H), 5.64 (ddd, J = 1.3, 5.8, 15.0 Hz, 1H), 5.59 (d, J = 5.9 Hz, 0H), 5.52 (dt, J = 5.7, 15.4 Hz, 1H), 5.47 (d, 1H), 5.44 – 5.36 (m, 0H), 4.23 – 4.18 (m, 2H), 3.90 (d, 2H), 3.81 (d, J = 5.3 Hz, 6H), 3.72 – 3.57 (m, 2H), 3.18 (td, J = 3.1, 12.8 Hz, 1H), 2.71 – 2.63 (m, 1H), 2.63 – 2.52 (m, 2H), 2.47 – 2.40 (m, 1H), 2.31 – 2.21 (m, 3H), 2.14 – 2.03 (m, 1H), 1.87 – 1.81 (m, 1H), 1.79 – 1.53 (m, 8H), 1.48 – 1.35 (m, 2H), 1.31 – 1.20 (m, 3H), 1.20 – 1.08 (m, 1H), 1.04 – 0.91 (m, 2H).

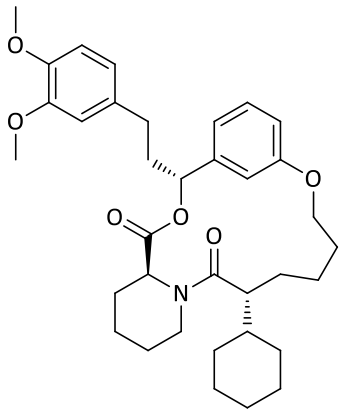
^{13}C-NMR (126 MHz, CD_2Cl_2): δ 175.05, 171.89, 159.50, 149.76, 148.15, 142.51, 134.50, 132.19, 129.94, 128.32, 120.82, 120.12, 116.69, 115.33, 112.77, 112.32, 76.58, 71.79, 69.78, 68.93, 56.42, 56.34, 56.30, 52.49, 47.49, 44.22, 40.84, 38.32, 32.93, 32.30, 31.89, 30.55, 27.41, 27.10, 27.02, 26.14, 21.43.

LC-MS (50-100% B, 19 min): t_R (**22**) = 10.67 min, m/z: calculated = 620.35 $[M+H]^+$,
found = 620.39 $[M+H]^+$.

HRMS (ESI): calculated = 620.35818 $[M+H]^+$, found = 620.35870 $[M+H]^+$, err [ppm] = 0.84.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**22**) = 14.72 min (99% Purity).

(2R,5S,12R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-3,17-dioxa-10-azatricyclo[16.3.1.0^{5},^{10}]docosa-1(22),18,20-triene-4,11-dione (AV152/AV171/AV172/AV174/AV217)



Chemical Formula: $C_{35}H_{47}NO_6$
Exact Mass: 577,34
Molecular Weight: 577,75

23

21a (48 mg, 0.083 mmol, 1.0 eq) is dissolved in 3 mL dry MeOH and the solvent sparged with argon for 5 min, Then Pt/C (2 mg, 0.0008 mmol, 0.01 eq) is added and the slurry sparged with H_2 for 10 min. Then the reaction is stirred at 1 bar H_2 for 2 h. The mixture is filtered over SiO_2 and eluted with MeOH. The solvent is removed and the crude product is purified by semi-preparative HPLC.

prep-HPLC (70 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**23**) = 6.80 min.

Yield 16 mg (33%).

^{1}H-NMR (500 MHz, THF-d$_8$): δ 7.12 (d, J = 7.4 Hz, 1H), 7.04 (dd, J = 1.5, 2.6 Hz, 1H), 6.77 (dd, J = 2.6, 7.7 Hz, 2H), 6.74 (d, J = 2.1 Hz, 1H), 6.72 (dt, J = 1.2, 7.5 Hz, 1H), 6.64 (dd, J = 2.1, 8.1 Hz, 1H), 5.70 (dd, J = 6.2, 7.4 Hz, 1H), 5.66 (d, J = 5.1 Hz, 1H), 4.28 – 4.16 (m, 1H), 4.17 – 4.01 (m, 1H), 3.78 (d, J = 15.2 Hz, 4H), 3.75 (s, 3H), 3.73 (s, 3H), 2.72 – 2.59 (m, 1H), 2.57 – 2.50 (m, 1H), 2.53 – 2.44 (m, 2H), 2.39 – 2.28 (m, 1H), 2.21 – 2.13 (m, 1H), 2.09 – 1.98 (m, 1H), 1.79 (ddd, J = 7.0, 10.3, 14.4 Hz, 2H), 1.70 (d, J = 13.8 Hz, 3H), 1.68 – 1.56 (m, 6H), 1.56 – 1.44 (m, 2H), 1.46 – 1.34 (m, 2H), 1.35 – 1.24 (m, 1H), 1.26 – 1.18 (m, 1H), 1.21 – 1.07 (m, 1H), 1.09 – 0.88 (m, 2H).

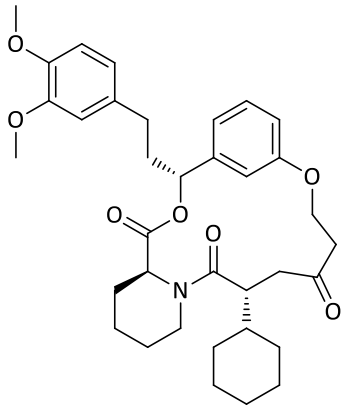
^{13}C-NMR (126 MHz, THF-d$_8$): δ 173.73, 171.66, 160.77, 150.95, 149.30, 142.46, 134.83, 129.71, 121.14, 120.22, 118.47, 113.76, 113.45, 112.38, 77.96, 68.69, 56.46, 56.29, 52.27, 46.09, 44.27, 42.34, 38.56, 33.11, 32.01, 30.87, 30.72, 30.32, 27.79, 27.69, 27.61, 27.32, 26.98, 25.98, 21.56.

LC-MS (70-100% B, 19 min): t_R (**23**) = 7.60 min, m/z: calculated = 578.34 $[M+H]^+$, found = 578.42 $[M+H]^+$.

HRMS (ESI): calculated = 578.34761 $[M+H]^+$, found = 578.34766 $[M+H]^+$, err [ppm] = 0.08.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**23**) = 15.89 min (99% Purity)

(2R,5S,12R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-3,17-dioxa-10-azatricyclo[16.3.1.0^{5},^{10}]docosa-1(22),18,20-triene-4,11,14-trione (AV240)



Chemical Formula: $C_{35}H_{45}NO_7$
Exact Mass: 591,32
Molecular Weight: 591,73

24

21a (34 mg, 0.059 mmol, 1.0 eq) is dissolved in 0.7 mL THF and add 0.1 mL H_2O (7/1, ratio). *p*-benzoquinone (7 mg, 0.06 mmol, 1.1 eq) is added, then $PdCl_2$ (2 mg, 0.01 mmol, 0.2 eq). The reaction is stirred overnight at r.t. The solvent is removed under reduced pressure and the crude product is purified by silica column chromatography (CH/EE, 3/1) and pure **24** is obtained.

Yield 27 mg (77%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.19 (t, J = 7.8 Hz, 1H), 6.87 (t, J = 2.1 Hz, 1H), 6.81 – 6.75 (m, 3H), 6.71 – 6.65 (m, 2H), 5.65 (dd, J = 5.3, 7.9 Hz, 1H), 5.39 – 5.33 (m, 1H), 4.46 – 4.33 (m, 2H), 3.91 – 3.87 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.36 (td, J = 2.8, 13.3 Hz, 1H), 3.15 – 3.08 (m, 1H), 3.08 – 3.02 (m, 2H), 2.92 (ddd, J = 5.8, 8.2, 16.7 Hz, 1H), 2.67 – 2.58 (m, 2H), 2.54 (dt, J = 4.9, 16.7 Hz, 1H), 2.49 – 2.43 (m, 1H), 2.33 – 2.21 (m, 1H), 2.15 – 2.05 (m, 2H), 1.80 – 1.60 (m, 5H), 1.59 – 1.47 (m, 1H), 1.33 – 1.16 (m, 2H), 1.16 – 1.06 (m, 1H), 1.06 – 0.85 (m, 2H).

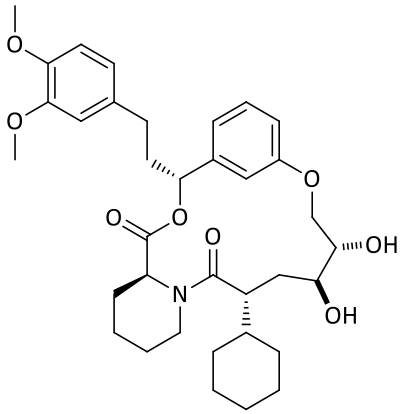
^{13}C-NMR (126 MHz, $CDCl_3$): δ 207.80, 174.87, 171.62, 159.77, 149.06, 147.46, 141.64, 133.91, 129.33, 120.31, 119.60, 117.04, 114.99, 111.89, 111.53, 76.04, 65.66, 56.09, 56.00, 51.59, 43.64, 43.58, 42.51, 42.38, 40.36, 37.20, 31.59, 31.37, 30.00, 27.06, 26.67, 26.57, 26.39, 25.57, 19.84.

LC-MS (50-100% B, 19 min): t_R (**24**) = 10.43 min, m/z: calculated = 592.32 $[M+H]^+$, found = 592.34 $[M+H]^+$.

HRMS (ESI): calculated = 592.32688 $[M+H]^+$, found = 592.32709 $[M+H]^+$, err [ppm] = 0.35.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**24**) = 12.76 min (99% Purity)

(2R,5S,12R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-14,15-dihydroxy-3,17-dioxa-10-azatricyclo[16.3.1.0^{5},^{10}]docosa-1(22),18,20-triene-4,11-dione (AV219/AV222)



Chemical Formula: $C_{35}H_{47}NO_8$
Exact Mass: 609,33
Molecular Weight: 609,75

25a and **b**

21a (53 mg, 0.092 mmol, 1.0 eq) is dissolved in 2 mL acetone and add 220 µL H_2O (9/1, ratio). NMO (16 mg, 0.14 mmol, 1.5 eq) is added, then OsO_4 (23 µL, 0.002 mmol, 0.02 eq) of a 2.5 w% solution in *t*BuOH. The reaction is stirred overnight at r.t. The reaction is quenched with 1 mL sat. $Na_2S_2O_{3(aq)}$ solution and stirred for 15 min. The mixture is diluted with H_2O and extracted with DCM (3x15 mL). The organic phase is washed with 15 mL sat. $CuSO_{4(aq)}$ solution, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by semi-preparative HPLC and pure diastereomers **25a** and **b** are obtained.

prep-HPLC (60 – 80% B, 10 mL/min, 20 min, 254 nm): t_R (**25**) = 6.80 min.

Yield (25a) 15 mg (26%), (**25b**) 13 mg (23%).

TLC (CH/EE, 1/1, v/v): R_f (**25**) = 0.35.

^{1}H-NMR (500 MHz, $CDCl_3$, 25a): δ 7.24 – 7.22 (m, 1H), 7.17 (dd, J = 7.4, 8.3 Hz, 1H), 6.89 – 6.83 (m, 1H), 6.77 (d, J = 7.9 Hz, 1H), 6.75 – 6.71 (m, 1H), 6.69 – 6.64 (m, 2H), 5.67 (dd, J = 5.6, 8.3 Hz, 1H), 5.63 (d, J = 4.6 Hz, 1H), 4.44 (dd, J = 6.1, 12.8 Hz, 1H), 4.10 (dd, J = 5.7, 12.8 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.76 – 3.72 (m, 1H), 3.72 – 3.63 (m, 2H), 3.27 (s, 3H), 2.66 – 2.56 (m, 2H), 2.53 – 2.44 (m, 2H), 2.44 – 2.35 (m, 1H), 2.35 – 2.23 (m, 1H), 2.14 – 2.01 (m, 2H), 1.90 – 1.81 (m, 1H), 1.79 – 1.52 (m, 7H), 1.54 – 1.31 (m, 2H), 1.28 – 0.89 (m, 4H).

^{13}C-NMR (126 MHz, $CDCl_3$, 25a): 174.59, 170.21, 158.97, 148.99, 147.44, 140.67, 133.46, 129.39, 120.27, 120.20, 117.98, 111.87, 111.50, 109.88, 78.00, 72.13, 69.95, 69.83, 56.07, 55.98, 52.17, 44.46, 44.14, 41.66, 36.98, 32.98, 31.80, 31.08, 29.35, 26.82, 26.65, 26.33, 25.67, 20.38, 1.96.

^{1}H-NMR (500 MHz, $CDCl_3$, 25b): δ 7.24 (t, J = 7.8 Hz, 1H), 7.09 – 7.07 (m, 1H), 6.93 – 6.89 (m, 1H), 6.88 – 6.85 (m, 1H), 6.79 (d, J = 7.9 Hz, 1H), 6.70 – 6.65 (m, 2H), 5.65 (t, J = 7.1 Hz, 1H), 5.54 – 5.49

(m, 1H), 4.36 (dd, J = 2.8, 12.6 Hz, 1H), 4.24 (dd, J = 6.1, 12.6 Hz, 1H), 3.90 – 3.88 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.68 – 3.63 (m, 1H), 3.61 – 3.56 (m, 1H), 2.96 (td, J = 2.7, 13.4 Hz, 1H), 2.76 – 2.68 (m, 1H), 2.61 – 2.52 (m, 2H), 2.46 – 2.35 (m, 1H), 2.20 – 2.14 (m, 1H), 2.14 – 2.06 (m, 1H), 2.03 – 1.93 (m, 1H), 1.83 (d, J = 12.9 Hz, 1H), 1.77 – 1.55 (m, 4H), 1.55 – 1.36 (m, 1H), 1.29 – 1.04 (m, 3H), 1.04 – 0.83 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$, 25b): δ 176.39, 171.95, 159.08, 149.07, 147.55, 140.97, 133.35, 130.22, 120.56, 120.36, 118.73, 112.53, 111.87, 111.56, 77.79, 72.74, 70.52, 68.89, 56.10, 56.00, 52.39, 44.35, 43.38, 41.28, 36.14, 34.10, 32.12, 31.37, 30.36, 26.57, 26.53, 26.44, 25.55, 20.13.

LC-MS (50-100% B, 19 min): t_R (**25a**) = 6.38 min, m/z: calculated = 610.33 $[M+H]^+$, found = 610.40 $[M+H]^+$, t_R (**25b**) = 7.12 min, m/z: calculated = 610.33 $[M+H]^+$, found = 610.44 $[M+H]^+$.

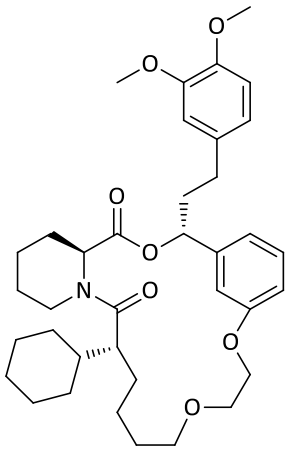
HRMS (ESI, 25a): calculated = 610.33744 $[M+H]^+$, found = 610.33760 $[M+H]^+$, err [ppm] = 0.26.

HRMS (ESI, 25b): calculated = 610.33744 $[M+H]^+$, found = 610.33762 $[M+H]^+$, err [ppm] = 0.28.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 254 nm): t_R (**25a**) = 6.49 min (99% Purity).

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 254 nm): t_R (**25b**) = 7.46 min (95% Purity).

(2R,5S,12R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-3,17,20-trioxa-10-azatricyclo[19.3.1.0^5,^{10}]pentacosa-1(25),21,23-triene-4,11-dione (AV339)



Chemical Formula: $C_{37}H_{51}NO_7$
Exact Mass: 621,37
Molecular Weight: 621,80

26

22 (30 mg, 0.048 mmol, 1.0 eq), $RuCl(PPh_3)_3$ (22 mg, 0.024 mmol, 0.5 eq) are dissolved in 3 mL toluene. The solution is sparged with H_2 for 10 min and then the reaction is stirred under 1 bar H_2 atmosphere overnight at r.t. The solvent is removed and the crude product purified by silica column chromatography (CH/EE, 3/1) to obtain pure product **26**.

Yield 28 mg (93%).

TLC (CH/EE, 3/1, v/v): R_f (**26**) = 0.25.

^{1}H-NMR (500 MHz, CD_2Cl_2): δ 7.23 (t, J = 7.9 Hz, 1H), 7.20 (t, J = 2.1 Hz, 1H), 6.92 – 6.89 (m, 1H), 6.89 – 6.86 (m, 1H), 6.77 (d, J = 8.6 Hz, 1H), 6.71 – 6.65 (m, 2H), 5.81 (dd, J = 5.6, 8.3 Hz, 1H), 5.66 – 5.61 (m, 1H), 4.26 – 4.11 (m, 2H), 3.97 – 3.91 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.67 (ddd, J = 2.7, 4.9, 11.5 Hz, 1H), 3.59 – 3.48 (m, 2H), 3.39 (ddd, J = 4.8, 7.2, 9.3 Hz, 1H), 3.02 – 2.94 (m, 1H), 2.68 – 2.57 (m, 1H), 2.57 – 2.47 (m, 2H), 2.32 – 2.26 (m, 1H), 2.26 – 2.18 (m, 1H), 2.09 – 1.99 (m, 1H), 1.91 – 1.83 (m, 1H), 1.82 – 1.48 (m, 11H), 1.46 – 1.33 (m, 5H), 1.30 – 1.17 (m, 2H), 1.17 – 1.06 (m, 1H), 1.01 – 0.84 (m, 2H).

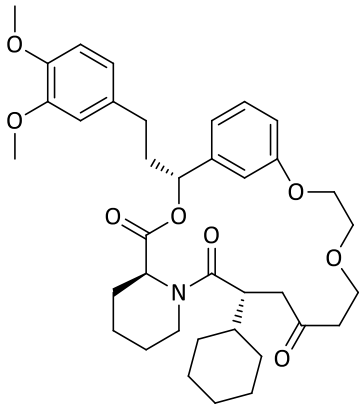
^{13}C-NMR (126 MHz, CD_2Cl_2): δ 175.49, 171.39, 159.24, 149.04, 147.44, 141.78, 133.93, 129.52, 121.03, 120.38, 117.24, 116.19, 112.00, 111.52, 76.08, 71.45, 70.44, 69.15, 56.09, 55.99, 51.99, 46.95, 44.07, 41.19, 38.22, 30.68, 30.60, 30.55, 27.07, 26.94, 26.64, 26.59, 25.76, 25.27, 21.02.

LC-MS (70-100% B, 19 min): t_R (**26**) = 8.41 min, m/z: calculated = 622.37 $[M+H]^+$, found = 622.50 $[M+H]^+$.

HRMS (ESI): calculated = 622.37383 $[M+H]^+$, found = 622.37352 $[M+H]^+$, err [ppm] = 0.50.

RP-HPLC (70 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**26**) = 8.35 min (99% Purity).

(2R,5S,12R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-3,17,20-trioxa-10-azatricyclo[19.3.1.0^5,^{10}]pentacosa-1(25),21,23-triene-4,11,14-trione (AV248)



Chemical Formula: $C_{37}H_{49}NO_8$
Exact Mass: 635,35
Molecular Weight: 635,79

27

22 (50 mg, 0.081 mmol, 1.0 eq) is dissolved in 0.7 mL THF and add 0.1 mL H_2O (7/1, ratio). *p*-benzoquinone (10 mg, 0.09 mmol, 1.1 eq), then $PdCl_2$ (4 mg, 0.016 mmol, 0.4 eq) are added. The reaction is stirred overnight at r.t. The solvent is removed under reduced pressure and the crude product is purified by semi-preparative HPLC and pure **27** obtained.

prep-HPLC (60 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**27**) = 7.93 min.

Yield 23 mg (45%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.20 (t, J = 7.9 Hz, 1H), 7.05 (t, J = 2.0 Hz, 1H), 6.83 (d, J = 1.2, 7.8 Hz, 1H), 6.82 – 6.76 (m, 2H), 6.71 – 6.66 (m, 2H), 5.73 (dd, J = 5.4, 8.1 Hz, 1H), 5.45 (d, 1H), 4.16 – 4.09 (m, 2H), 3.93 (d, J = 13.3 Hz, 1H), 3.90 – 3.81 (m, 6H), 3.76 – 3.70 (m, 2H), 3.69 – 3.61 (m, 1H), 3.25 – 3.18 (m, 1H), 3.16 – 3.08 (m, 1H), 2.83 (dd, J = 6.0, 17.9 Hz, 1H), 2.76 (ddd, J = 4.9, 8.3, 16.4 Hz, 1H), 2.66 (dd, J = 6.1, 18.1 Hz, 1H), 2.63 – 2.50 (m, 2H), 2.43 (dt, J = 5.0, 16.4 Hz, 1H), 2.31 – 2.16 (m, 2H), 2.13 – 2.01 (m, 1H), 1.91 – 1.82 (m, 1H), 1.77 – 1.57 (m, 7H), 1.57 – 1.50 (m, 1H), 1.49 – 1.35 (m, 2H), 1.31 – 1.18 (m, 2H), 1.19 – 1.05 (m, 1H), 1.03 – 0.79 (m, 2H).

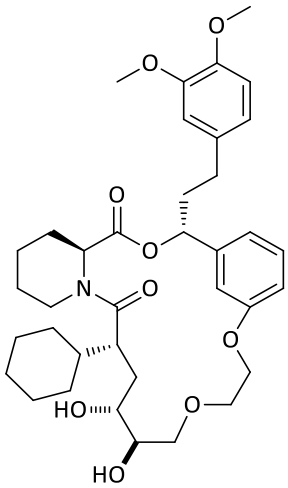
^{13}C-NMR (126 MHz, $CDCl_3$): δ 207.55, 174.71, 171.04, 159.35, 149.05, 147.48, 141.88, 133.88, 129.41, 120.37, 119.60, 114.89, 114.43, 111.98, 111.53, 76.07, 69.79, 68.59, 66.15, 56.09, 56.02, 52.09, 44.00, 43.86, 43.04, 41.14, 40.57, 37.99, 31.74, 31.28, 30.25, 26.91, 26.62, 26.51, 26.43, 25.64, 20.87.

LC-MS (50-100% B, 19 min): t_R (**27**) = 9.88 min, m/z: calculated = 636.35 $[M+H]^+$, found = 636.44 $[M+H]^+$.

HRMS (ESI): calculated = 636.35309 $[M+H]^+$, found = 636.35343 $[M+H]^+$, err [ppm] = 0.52.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 254 nm): t_R (**27**) = 10.91 min (99% Purity)

(2R,5S,12R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-14,15-dihydroxy-3,17,20-trioxa-10-azatricyclo[19.3.1.0^{5},^{10}]pentacosa-1(25),21,23-triene-4,11-dione (AV246)



Chemical Formula: $C_{37}H_{51}NO_9$
Exact Mass: 653,36
Molecular Weight: 653,80

28

22 (53 mg, 0.086 mmol, 1.0 eq) is dissolved in 2 mL acetone and add 220 µL H_2O (9/1, ratio). NMO (12 mg, 0.1 mmol, 1.2 eq), then OsO_4 (21 µL, 0.002 mmol, 0.02 eq) of a 2.5 w% solution in *t*BuOH are added. The reaction is stirred overnight at r.t. The reaction is quenched with 1 mL sat. $Na_2S_2O_{3(aq)}$ solution and stirred for 15 min. The mixture is diluted with H_2O and extracted with DCM (3x15 mL).

The organic phase is washed with 15 mL sat. $CuSO_{4(aq)}$ solution, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by semi-preparative HPLC and pure **28** obtained. (Diastereomers could not be separated on either semi-prep. HPLC or analytical RP-HPLC)

prep-HPLC (55 – 65% B, 10 mL/min, 10 min, 254 nm): t_R (**28**) = 9.25 min.

Yield 19 mg (34%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.26 (m, 1H), 7.25 – 7.21 (m, 1H), 7.01 (t, J = 2.0 Hz, 1H), 6.93 – 6.85 (m, 2H), 6.81 – 6.74 (m, 1H), 6.71 – 6.65 (m, 2H), 5.76 (dd, J = 5.9, 8.1 Hz, 0.57H), 5.70 (dd, J = 5.2, 8.3 Hz, 0.43H), 5.58 (d, J = 1.9, 6.2 Hz, 0.50H), 5.55 (d, 0.64H), 4.35 – 4.15 (m, 2H), 4.05 (d, J = 13.6 Hz, 0.42H), 3.91 – 3.81 (m, 6H), 3.79 – 3.42 (m, 6H), 3.40 – 3.29 (m, 0.53H), 3.24 – 3.09 (m, 0.51H), 3.03 – 2.85 (m, 1H), 2.82 – 2.46 (m, 2H), 2.40 – 2.20 (m, 2H), 2.17 – 1.95 (m, 1H), 1.95 – 1.80 (m, 1H), 1.80 – 1.34 (m, 8H), 1.30 – 0.87 (m, 4H).

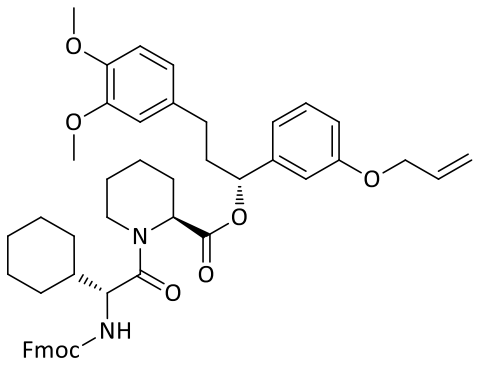
^{13}C-NMR (126 MHz, $CDCl_3$): δ 176.10, 175.88, 172.13, 171.46, 159.37, 158.55, 149.14, 149.06, 147.60, 147.49, 141.68, 141.42, 133.75, 133.66, 129.85, 129.75, 129.55, 120.54, 120.33, 119.94, 117.36, 116.91, 116.16, 116.01, 111.95, 111.58, 111.52, 76.46, 74.79, 73.53, 73.16, 72.15, 70.67, 70.64, 70.46, 69.86, 69.63, 69.34, 56.10, 56.04, 56.00, 52.19, 52.16, 44.25, 44.07, 44.03, 42.82, 41.62, 41.22, 37.94, 37.37, 34.09, 33.41, 31.93, 31.67, 31.53, 31.49, 30.45, 29.80, 27.11, 26.83, 26.75, 26.70, 26.68, 26.56, 26.54, 26.46, 25.70, 25.62, 21.04, 20.89.

LC-MS (50-100% B, 19 min): t_R (**28**) = 7.68 min, m/z: calculated = 654.36 $[M+H]^+$, found = 654.51 $[M+H]^+$.

HRMS (ESI): calculated = 654.36366 $[M+H]^+$, found = 654.36352 $[M+H]^+$, err [ppm] = 0.21.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 254 nm): t_R (**28**) = 7.95 min (99% Purity, 1/1 dr determined by NMR).

(S)-(R)-1-(3-(allyloxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((R)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-cyclohexylacetyl)piperidine-2-carboxylate (AV134/AV186)



Chemical Formula: $C_{49}H_{56}N_2O_8$
Exact Mass: 800,40
Molecular Weight: 800,98

29

HATU (761 mg, 2 mmol, 1.1 eq), HOAt (272 mg, 2 mmol, 1.1 eq), Fmoc-D-Chg-OH (760 mg, 2 mmol, 1.1 eq) are dissolved in 5 ml dry DMF and 5 ml dry DCM. Then DIPEA (930 µL, 5.5 mmol, 3.0 eq) is added. The solution is stirred for 10 min, then added to a solution of **14** (800 mg, 1.8 mmol, 1.0 eq) in 12 ml dry DCM in a dried flask under argon atmosphere. The reaction is stirred at r.t. overnight. The solvent is removed under reduced pressure and the crude product purified by silica column chromatography (CH/EE, 5/1) and pure **29** is obtained as a white foam.

Yield 1.45 g (99%).

TLC (CH/EE, 3/1, v/v): R_f (**29**) = 0.25.

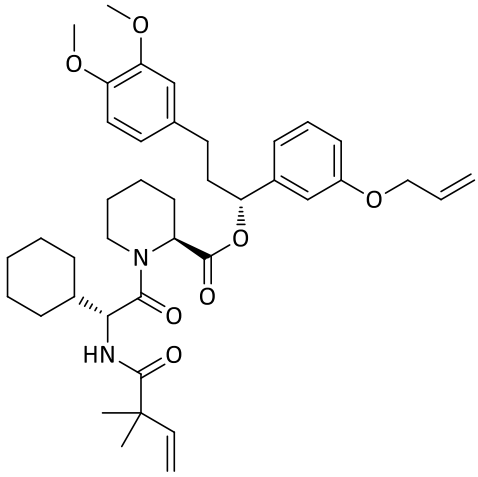
^{1}H-NMR (500 MHz, Chloroform-*d*): δ 7.77 – 7.73 (m, 2H), 7.64 – 7.53 (m, 2H), 7.42 – 7.35 (m, 2H), 7.35 – 7.24 (m, 3H), 6.97 – 6.77 (m, 4H), 6.76 – 6.60 (m, 3H), 6.11 – 6.00 (m, 1H), 5.83 – 5.79 (m, 0H), 5.72 (dd, J = 5.6, 8.0 Hz, 1H), 5.66 (d, J = 9.0 Hz, 1H), 5.47 – 5.37 (m, 2H), 5.34 – 5.25 (m, 1H), 4.71 – 4.64 (m, 1H), 4.56 – 4.50 (m, 2H), 4.46 – 4.31 (m, 1H), 4.30 – 4.11 (m, 2H), 3.91 (d, J = 13.7 Hz, 1H), 3.89 – 3.79 (m, 6H), 3.36 – 3.24 (m, 1H), 2.59 – 2.45 (m, 2H), 2.41 – 2.26 (m, 1H), 2.25 – 2.15 (m, 1H), 2.15 – 1.96 (m, 1H), 1.85 – 1.56 (m, 8H), 1.54 – 1.40 (m, 2H), 1.40 – 1.05 (m, 6H), 0.95 – 0.81 (m, 1H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ 171.88, 171.05, 170.18, 170.03, 158.95, 158.83, 156.37, 149.00, 147.46, 144.18, 143.87, 141.66, 141.37, 133.61, 133.33, 133.20, 129.77, 127.80, 127.72, 127.14, 125.27, 120.33, 120.25, 119.99, 119.28, 119.04, 117.80, 117.70, 114.56, 114.41, 113.39, 113.24, 111.97, 111.84, 111.57, 111.49, 76.44, 68.90, 67.01, 56.64, 56.08, 56.00, 55.95, 55.15, 52.76, 47.38, 43.96, 41.90, 40.50, 39.75, 38.14, 37.91, 31.59, 31.17, 30.10, 29.80, 28.45, 27.81, 26.95, 26.29, 26.19, 26.00, 25.84, 25.41, 24.81, 21.17, 21.07.

LC-MS (50-100% B, 19 min): t_R (**29**) = 12.90 min, m/z: calculated = 801.40 $[M+H]^+$, found = 801.21 $[M+H]^+$.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**29**) = 18.92 min (97% Purity).

(S)-(R)-1-(3-(allyloxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((R)-2-cyclohexyl-2-(2,2-dimethylbut-3-enamido)acetyl)piperidine-2-carboxylate (AV205/AV208/AV210/AV211/AV215/AV220)



Chemical Formula: $C_{40}H_{54}N_2O_7$
Exact Mass: 674,39
Molecular Weight: 674,87

30

29 (50 mg, 0.06 mmol, 1.0 eq) is dissolved in 2.5 mL dry DCM and 25 µL DBU (0.17 mmol, 2.65 eq) is added. The reaction is stirred for 3 min, then a solution of 2,2-dimethylbut-3-enoic acid (28 µL, 0.24 mmol, 2.0 eq) prior stirred in $SOCl_2$ (26 µL, 0.36 mmol, 3 eq) at 70°C for 2 h is added. The reaction is stirred for 20 min, then the solvent removed under reduced pressure and the crude product purified by semi-preparative HPLC (70-100%, 10 min) and pure product **30** obtained.

Yield 31 mg (74%).

TLC (CH/EE, 3/2, v/v): R_f (**30**) = 0.45.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ 7.30 – 7.21 (m, 1H), 6.95 – 6.89 (m, 1H), 6.89 – 6.86 (m, 1H), 6.86 – 6.83 (m, 2H), 6.81 – 6.74 (m, 1H), 6.70 – 6.62 (m, 3H), 6.11 – 5.99 (m, 1H), 5.99 – 5.88 (m, 1H), 5.70 (dd, J = 5.9, 7.8 Hz, 1H), 5.45 – 5.38 (m, 1H), 5.35 – 5.31 (m, 1H), 5.31 – 5.25 (m, 1H), 5.25 – 5.18 (m, 1H), 5.18 – 5.10 (m, 1H), 4.90 (dd, J = 6.1, 8.7 Hz, 1H), 4.59 – 4.47 (m, 3H), 3.93 (d, J = 13.8 Hz, 1H), 3.87 – 3.84 (m, 6H), 3.25 (td, J = 2.9, 13.3 Hz, 1H), 2.67 – 2.41 (m, 2H), 2.40 – 2.30 (m, 1H), 2.30 – 2.14 (m, 1H), 2.13 – 1.95 (m, 1H), 1.82 – 1.56 (m, 7H), 1.51 – 1.38 (m, 2H), 1.31 – 1.26 (m, 4H), 1.21 (s, 2H), 1.16 – 0.93 (m, 2H), 0.91 – 0.69 (m, 1H).

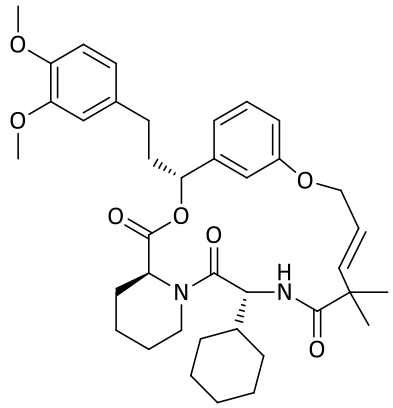
^{13}C-NMR (126 MHz, Chloroform-*d*): δ 176.78, 176.64, 171.91, 171.44, 169.99, 158.86, 149.09, 147.54, 142.60, 142.51, 141.59, 141.40, 133.63, 133.37, 133.24, 129.86, 120.40, 120.30, 119.29, 119.07, 117.81, 117.76, 115.26, 115.16, 114.68, 114.47, 113.34, 113.27, 112.02, 111.89, 111.60, 76.51, 68.97,

68.92, 56.83, 56.11, 56.02, 53.48, 53.26, 52.95, 45.51, 44.10, 41.85, 40.19, 40.08, 38.17, 37.98, 31.64, 31.25, 30.26, 30.00, 28.44, 27.95, 27.05, 26.27, 26.20, 26.00, 25.81, 25.73, 25.41, 24.98, 24.88, 24.69, 24.64, 21.14, 21.05.

LC-MS (50-100% B, 19 min): t_R (**30**) = 11.61 min, m/z: calculated = 675.39 $[M+H]^+$, found = 675.03 $[M+H]^+$.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**30**) = 15.70 min (95% Purity).

(2R,5S,12R,16E)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-15,15-dimethyl-3,19-dioxa-10,13-diazatricyclo[18.3.1.0^5,^{10}]tetracosa-1(24),16,20,22-tetraene-4,11,14-trione (AV216/AV218/AV221/AV224/AV341Fr2)



Chemical Formula: $C_{38}H_{50}N_2O_7$
Exact Mass: 646,36
Molecular Weight: 646,81

31

30 (68 mg, 0.1 mmol, 1.0 eq) is dissolved in 200 mL toluene (0.5 mM) in a dried flask with a condenser. The solution is sparged continuously with argon and heated to 80°C. The system is equilibrated for 30 min, then p-benzoquinone (6 mg, 0.05 mmol, 0.5 eq) and Grubbs 2nd generation catalyst (9 mg, 0.01, 0.1 eq) is added. After stirring overnight and continuous argon sparging toluene is refilled and another portion of Grubbs catalyst (3 mg) added. The reaction is continuously stirred for 3 d, then the solvent removed under reduced pressure. The crude product is filtered through silica and eluted with EE, then purified by semi-preparative HPLC (70-100%, 10 min).

Yield 25 mg (38%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.20 (t, J = 7.9 Hz, 1H), 6.96 – 6.92 (m, 1H), 6.84 (ddd, J = 1.0, 2.6, 8.2 Hz, 1H), 6.79 – 6.75 (m, 2H), 6.69 – 6.62 (m, 2H), 6.49 (d, J = 8.2 Hz, 1H), 5.86 – 5.78 (m, 1H), 5.70 (ddd, J = 4.8, 5.9, 16.0 Hz, 1H), 5.64 – 5.58 (m, 1H), 5.20 – 5.17 (m, 1H), 4.74 – 4.71 (m, 1H), 4.71 – 4.69 (m, 1H), 4.60 (ddd, J = 1.3, 5.9, 14.2 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.76 (d, J = 13.5 Hz, 1H), 3.26 (td, J = 3.0, 13.0 Hz, 1H), 2.64 – 2.46 (m, 2H), 2.35 – 2.21 (m, 1H), 2.21 – 2.12 (m, 1H), 2.12 – 2.01 (m, 1H),

1.78 – 1.66 (m, 5H), 1.66 – 1.60 (m, 4H), 1.59 – 1.53 (m, 1H), 1.51 – 1.38 (m, 1H), 1.35 (s, 3H), 1.23 (s, 3H), 1.21 – 0.93 (m, 4H).

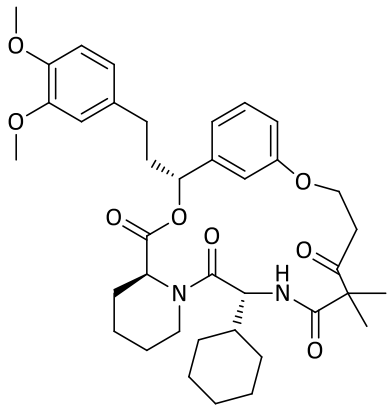
^{13}C-NMR (126 MHz, $CDCl_3$): δ 175.54, 172.12, 171.44, 158.92, 149.07, 147.52, 141.24, 139.22, 133.76, 129.44, 124.83, 120.30, 119.77, 116.35, 112.06, 111.91, 111.54, 76.91, 68.10, 56.10, 56.01, 53.54, 53.20, 52.62, 44.86, 43.84, 42.13, 37.46, 31.42, 30.27, 27.99, 26.54, 26.30, 26.26, 26.13, 25.72, 25.21, 20.09.

LC-MS (50-100% B, 19 min): t_R (**31**) = 10.70 min, m/z: calculated = 647.37 $[M+H]^+$, found = 647.41 $[M+H]^+$.

HRMS (ESI): calculated = 647.369208 $[M+H]^+$, found = 647.36980 $[M+H]^+$, err [ppm] = 1.11.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**31**) = 11.81 min (86% Purity)

(2R,5S,12R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-15,15-dimethyl-3,19-dioxa-10,13-diazatricyclo[18.3.1.0^5,^{10}]tetracosa-1(24),20,22-triene-4,11,14,16-tetrone (AV341Fr1)



Chemical Formula: $C_{38}H_{50}N_2O_8$
Exact Mass: 662,36
Molecular Weight: 662,81

32

31 (10 mg, 0.015 mmol, 1.0 eq) is dissolved in 0.7 mL THF and 0.1 mL H_2O (7/1, ratio) added. *p*-benzoquinone (4 mg, 0.04 mmol, 2 eq), then $PdCl_2$ (2 mg, 0.015 mmol, 1.0 eq) are added. The reaction is stirred over 3 d at r.t. The solvent is removed under reduced pressure and the crude product is purified by preparative HPLC (70-100%, 10 min).

Yield 1 mg (10%).

LC-MS (70-100% B, 19 min): t_R (**32**) = 5.91 min, m/z: calculated = 663.36 $[M+H]^+$, found = 663.45 $[M+H]^+$.

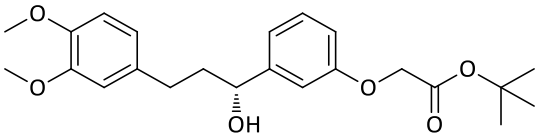
HRMS (ESI): calculated = 663.36399 $[M+H]^+$, found = 663.36359 $[M+H]^+$, err [ppm] = 0.61.

RP-HPLC (70 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**32**) = 5.84 min (77% Purity)

6.3. Cyclopeptides

6.3.1. Building blocks

(R)-tert-butyl 2-(3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenoxy)acetate (AV145/AV150/TR05)



Chemical Formula: $C_{23}H_{30}O_6$
Exact Mass: 402,20
Molecular Weight: 402,48

33

7 (4.00 g, 14 mmol, 1.0 eq) is dissolved in 120 mL MeCN. K_2CO_3 (2.90 g, 21 mmol, 1.5 eq) and *tert*-butyl bromoacetate (2.98 g, 15 mmol, 1.1 eq) are added. After 3 h the suspension is filtered, washed with MeCN and the solvent removed under reduced pressure. The crude product is purified by silica column chromatography (CH/EE, 2/1) and pure **33** obtained as resinous oil.

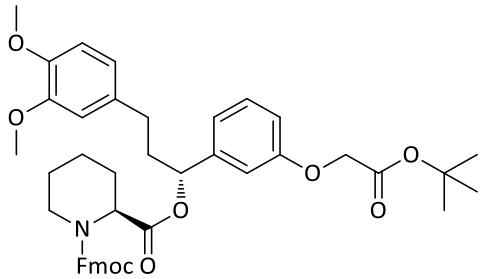
Yield 5.34 g (96%).

TLC (CH/EE, 2/1): R_f (**33**) = 0.36.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.27 (m, 1H), 6.96 (m, 2H), 6.81 (m, 2H), 6.74 (m, 2H), 4.67 (dd, 1H), 4.53 (s, H), 3.87 (m, 6H), 2.65 (m, 2H), 2.03 (m, 3H), 1.50 (s, 9H).

LC-MS (0-100% B, 19 min): t_R (**33**) = 11.49 min, m/z: calculated = 420.24 $[M+NH_4]^+$, found = 420.09 $[M+NH_4]^+$.

(S)-1-((9H-fluoren-9-yl)methyl) 2-((R)-1-(3-(2-(tert-butoxy)-2-oxoethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl) piperidine-1,2-dicarboxylate (AV003/094/TR06)



Chemical Formula: $C_{44}H_{49}NO_9$
Exact Mass: 735,34
Molecular Weight: 735,86

34

Compound **33** (1.5 g, 3.73 mmol, 1 eq) and (*S*)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)piperidine-2-carboxylic acid (1.44 g, 4.10 mmol, 1.1 eq) are dissolved in 15 mL of dry DCM and added to a dried flask under argon protection. The mixture is then cooled to 0°C for 15 min. First DMAP (66 mg, 0,54 mmol) and after 5 min DCC (1.12 g, 5.42 mmol) were added under constant stirring. The ice bath is removed after stirring for 15 min. The reaction mixture is then stirred at r.t. overnight. For purification, the suspension is filtered and washed with Et_2O (2×75 mL) and DCM (1×50 mL). The solvent is removed under vacuum and the crude product is purified via column chromatography (CH/EE , 3/1). The pure product **34** is obtained as a white solid.

Yield 2.41 g (88%)

TLC (CH/EE, 2/1, v/v): R_f (**34**) = 0.50.

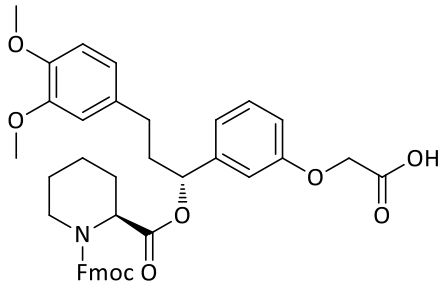
^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.79 – 7.73 (m, 1H), 7.74 – 7.68 (m, 1H), 7.63 – 7.55 (m, 1H), 7.46 (dd, *J* = 20.4, 7.6 Hz, 1H), 7.43 – 7.15 (m, 4H), 6.98 – 6.92 (m, 1H), 6.90 (t, *J* = 2.1 Hz, 1H), 6.84 – 6.73 (m, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 6.68 – 6.57 (m, 2H), 5.76 (dd, *J* = 8.2, 5.6 Hz, 1H), 4.95 (dd, *J* = 75.5, 5.5 Hz, 1H), 4.54 – 4.23 (m, 4H), 3.82 (d, *J* = 10.3 Hz, 6H), 3.22 – 2.94 (m, 1H), 2.51 (tt, *J* = 28.8, 7.9 Hz, 2H), 2.37 – 2.15 (m, 2H), 2.03 (s, 1H), 1.73 (dddd, *J* = 21.4, 10.8, 7.3, 4.2 Hz, 3H), 1.47 (s, 9H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ = δ 170.92, 167.87, 158.10, 156.39, 155.92, 148.92, 147.35, 143.91, 141.73, 141.52, 141.30, 133.52, 133.41, 129.66, 127.66, 127.05, 125.08, 120.12, 119.95, 113.98, 113.28, 111.78, 111.40, 82.31, 76.43, 76.17, 67.79, 65.80, 65.67, 60.36, 55.82, 54.92, 54.57, 47.26, 42.04, 41.89, 38.04, 31.14, 28.03, 26.83, 24.80, 24.56, 21.73, 21.02, 20.82, 20.73, 20.55, 14.21.

LC-MS (80-100% B, 19 min): t_R (**34**) = 5.62 min, m/z: calculated = 736.35 $[M+H]^+$,
found = 736.33$[M+H]^+$.

HPLC-RP (70 – 100% B, 1.0 mL/min, 20 min): t_R (**34**) = 18.67 min (99% Purity).

2-(3-((R)-1-(((S)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid (AV095)



Chemical Formula: $C_{40}H_{41}NO_9$
Exact Mass: 679,28
Molecular Weight: 679,75

35

Compound **34** (2.40 g, 3.53 mmol, 1 eq) is dissolved in 15 mL of dry DCM and stirred at r.t. under argon protection. 6.5 mL TFA (30%) is added and the reaction stirred for 1 h. TFA and solvent are removed under reduced pressure and the remaining TFA is co-evaporated with toluene and then DCM. The crude product is purified via manual column chromatography (Cy/EE – 7/3 + 1% TFA). Product **35** is obtained after drying overnight at high vacuum as a resinous solid.

Yield 2.25 g (quant.)

TLC (CH/EE/TFA, 7/3/0.2, v/v): R_f (**35**) = 0.19.

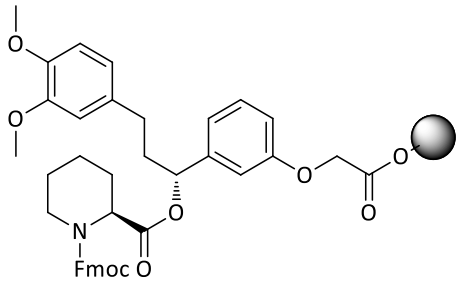
^{1}H-NMR (400 MHz, Chloroform-*d*): δ = 7.80 – 7.68 (m, 2H), 7.54 (t, *J* = 6.3 Hz, 1H), 7.50 – 7.30 (m, 2H), 7.32 – 7.16 (m, 3H), 6.94 (dd, *J* = 13.3, 7.5 Hz, 1H), 6.89 – 6.80 (m, 2H), 6.77 (t, *J* = 8.6 Hz, 1H), 6.67 (d, *J* = 9.8 Hz, 1H), 6.64 – 6.55 (m, 1H), 5.82 – 5.63 (m, 1H), 5.00 (d, *J* = 5.6 Hz, 1H), 4.65 (d, *J* = 5.5 Hz, 1H), 4.55 (s, 1H), 4.49 – 4.34 (m, 2H), 4.24 (t, *J* = 7.1 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 0H), 4.13 – 3.99 (m, 1H), 3.85 (d, *J* = 2.2 Hz, 6H), 3.79 (s, 1H), 3.21 – 3.10 (m, 1H), 2.68 – 2.42 (m, 1H), 2.38 – 2.15 (m, 1H), 2.09 (s, 1H), 2.08 – 2.00 (m, 1H), 1.73 (d, *J* = 38.5 Hz, 2H), 1.44 (d, *J* = 12.7 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 2H).

^{13}C-NMR (101 MHz, Chloroform-*d*): δ = 172.87, 172.73, 170.82, 159.13, 158.71, 157.85, 157.69, 157.16, 156.91, 148.94, 147.42, 143.87, 143.65, 143.59, 142.14, 141.58, 141.42, 133.60, 133.45, 130.01, 127.92, 127.27, 125.09, 124.95, 120.67, 120.44, 120.14, 120.02, 115.26, 114.52, 113.12, 111.94, 111.64, 111.29, 68.57, 65.24, 64.88, 61.27, 56.10, 56.01, 55.12, 54.80, 47.20, 42.26, 42.13, 38.10, 37.87, 31.48, 31.28, 27.04, 26.92, 24.76, 24.49, 21.21, 20.81, 20.59, 14.23.

ESI-MS: m/z: calculated = 702.74 $[M+Na]^+$, found = 702.13 $[M+Na]^+$.

RP-HPLC (50 – 100% B, 1.0 mL/min, 20 min): t_R (**35**) = 10.72 min (91% Purity).

Resin bound 2-(3-((R)-1-(((S)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid (AV098/AV177)

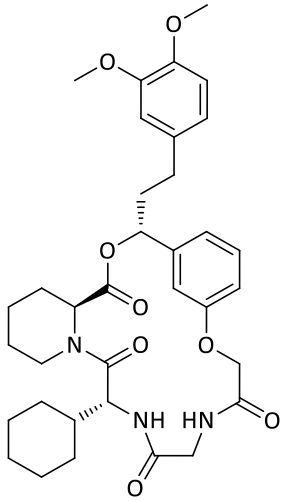


36

Synthesis according to 5.9.5.

6.3.2. Macrocycles

(2R,5S,12R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^{5},^{10}]tetracosa-1(24),20,22-triene-4,11,14,17-tetrone (AV011/148)



Chemical Formula: $C_{35}H_{45}N_3O_8$
Exact Mass: 635,32
Molecular Weight: 635,75

37

Starting materials: Resin: **36** (0.17 mmol), 1st AA: Fmoc-D-Chg-OH, 2nd AA: Fmoc-Gly-OH, General Procedure 5.9.5.

prep-HPLC (80 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**37**) = 9.50 min.

Yield 11 mg (10%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.21 (m, 1H), 7.14 (d, J = 9.1 Hz, 1H), 6.96 – 6.87 (m, 3H), 6.88 – 6.82 (m, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.69 – 6.61 (m, 2H), 5.67 – 5.59 (m, 1H), 5.26 – 5.18 (m, 1H), 4.82 – 4.74 (m, 1H), 4.69 – 4.57 (m, 2H), 4.57 – 4.43 (m, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.80 – 3.73 (m, 1H), 3.37 (dd, J = 4.3, 14.8 Hz, 1H), 3.16 (td, J = 2.9, 13.2 Hz, 1H), 2.66 – 2.39 (m, 1H), 2.37 – 2.22 (m,

1H), 2.21 – 2.11 (m, 1H), 2.10 – 1.98 (m, 1H), 1.94 – 1.79 (m, 2H), 1.80 – 1.67 (m, 2H), 1.69 – 1.53 (m, 8H), 1.54 – 1.34 (m, 1H), 1.30 – 1.10 (m, 2H), 1.09 – 0.93 (m, 2H).

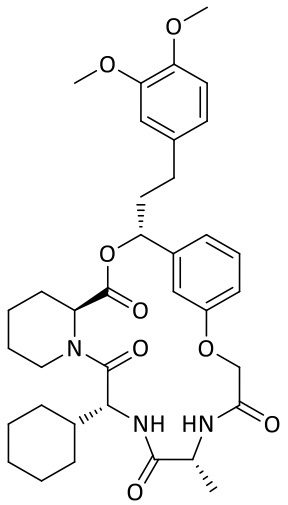
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.01, 171.50, 170.31, 169.37, 157.84, 149.02, 147.48, 141.76, 133.42, 129.96, 121.32, 120.27, 116.67, 111.78, 111.49, 111.44, 109.57, 76.65, 66.89, 56.06, 55.98, 53.59, 52.56, 44.00, 43.88, 41.12, 37.32, 31.35, 30.12, 28.14, 26.41, 26.11, 26.03, 25.22, 19.99.

LC-MS (80-100% B, 19 min): t_R (**37**) = 2.30 min, m/z: calculated = 636.33 $[M+H]^+$, found = 636.07 $[M+H]^+$.

HRMS (ESI): calculated = 636.32794 $[M+H]^+$, found = 636.32770 $[M+H]^+$, err [ppm] = 0.37.

RP-HPLC (0 – 100% B, 1.5 mL/min, 30 min, 220 nm): t_R (**37**) = 19.87 min (93% Purity)

(2R,5S,12R,15R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-15-methyl-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^{5,10}]tetracosa-1(24),20,22-triene-4,11,14,17-tetrone (AV022)



Chemical Formula: $C_{36}H_{47}N_3O_8$
Exact Mass: 649,34
Molecular Weight: 649,77

38

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Chg-OH, 2nd AA: Fmoc-D-Ala-OH, General Procedure 5.9.5.

Silica column chromatography: DCM/MeOH, 8/2, v/v.

prep-HPLC (80 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**38**) = 11.80 min.

Yield 17 mg (19%).

^{1}H-NMR (800 MHz, DMSO-d_6 + CD_2Cl_2): δ 8.31 (d, J = 7.2 Hz, 1H), 7.75 (d, J = 9.0 Hz, 1H), 7.20 (t, J = 7.8 Hz, 1H), 6.90 – 6.86 (m, 1H), 6.87 – 6.82 (m, 3H), 6.78 (d, J = 2.0 Hz, 1H), 6.67 (dd, J = 2.0, 8.1 Hz, 1H), 5.62 (dd, J = 5.0, 8.6 Hz, 1H), 5.08 – 5.04 (m, 1H), 4.73 (d, J = 15.8 Hz, 1H), 4.61 (d, J = 15.8 Hz, 1H), 4.48 (dd, J = 7.0, 9.1 Hz, 1H), 4.08 (p, J = 7.3 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.70 – 3.65 (m, 1H), 3.00 – 2.93 (m, 1H), 2.59 – 2.52 (m, 1H), 2.49 – 2.43 (m, 1H), 2.17 – 2.10 (m, 1H), 2.06 – 1.99 (m,

2H), 1.79 – 1.72 (m, 1H), 1.72 – 1.68 (m, 1H), 1.67 – 1.58 (m, 6H), 1.58 – 1.54 (m, 1H), 1.40 – 1.33 (m, 2H), 1.31 (d, J = 7.3 Hz, 3H), 1.22 – 1.11 (m, 2H), 1.09 – 1.03 (m, 1H), 0.98 – 0.89 (m, 2H).

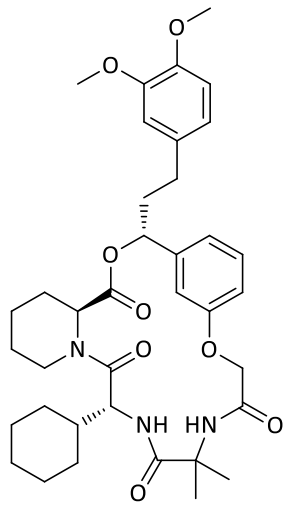
^{13}C-NMR (201 MHz, DMSO-d_6 + CD_2Cl_2): δ 172.16, 171.15, 170.56, 167.97, 158.76, 148.66, 147.06, 141.43, 133.34, 128.95, 120.00, 119.50, 116.36, 112.26, 111.89, 110.08, 75.41, 65.71, 55.51, 55.37, 52.48, 52.10, 50.28, 42.48, 40.25, 37.37, 30.71, 30.11, 27.16, 26.02, 25.87, 25.67, 25.61, 24.46, 19.53, 18.04.

LC-MS (0-100% B, 19 min): t_R (**38**) = 12.00 min, m/z: calculated = 650.34 $[M+H]^+$, found = 650.09 $[M+H]^+$.

HRMS (ESI): calculated = 650.34359 $[M+H]^+$, found = 650.34361 $[M+H]^+$, err [ppm] = 0.03.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**38**) = 20.35 min (96% Purity)

(2R,5S,12R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-15,15-dimethyl-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^5,^{10}]tetracosa-1(24),20,22-triene-4,11,14,17-tetrone (AV023/183)



Chemical Formula: $C_{37}H_{49}N_3O_8$
Exact Mass: 663,35
Molecular Weight: 663,80

39

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Chg-OH, 2nd AA: Fmoc-Aib-OH, General Procedure 5.9.5.

Silica column chromatography: DCM/Ac, 10/1, v/v.

TLC (DCM/Ac, 10/1): R_f (**39**) = 0.35.

Yield 257 mg (83%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.73 (d, J = 9.0 Hz, 1H), 7.25 – 7.19 (m, 1H), 6.99 – 6.96 (m, 1H), 6.85 – 6.80 (m, 2H), 6.77 (d, J = 8.0 Hz, 1H), 6.68 – 6.62 (m, 2H), 6.48 (s, 1H), 5.65 (dd, J = 5.7, 7.6 Hz, 1H), 5.25 – 5.20 (m, 1H), 4.69 (dd, J = 6.1, 9.1 Hz, 1H), 4.64 (d, J = 16.1 Hz, 1H), 4.54 (d, J = 16.1 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.81 – 3.75 (m, 1H), 3.28 (td, J = 3.1, 13.1 Hz, 1H), 2.62 – 2.44 (m, 2H), 2.31 –

2.20 (m, 1H), 2.16 – 2.10 (m, 1H), 2.08 – 2.00 (m, 1H), 1.99 (s, 1H), 1.82 (s, 1H), 1.78 (s, 3H), 1.77 – 1.60 (m, 10H), 1.41 (s, 3H), 1.30 – 1.17 (m, 2H), 1.16 – 0.97 (m, 2H).

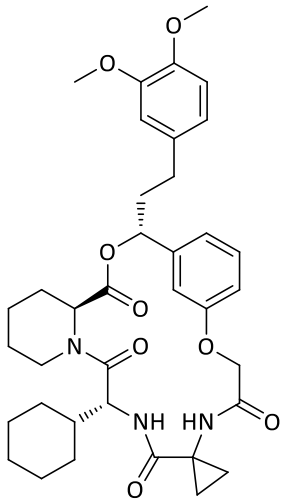
^{13}C-NMR (126 MHz, $CDCl_3$): δ 174.04, 172.32, 171.69, 169.57, 157.60, 149.07, 147.53, 142.13, 133.55, 129.78, 120.64, 120.27, 115.19, 111.84, 111.54, 110.27, 76.29, 66.95, 58.76, 56.08, 56.00, 53.63, 52.52, 51.94, 43.83, 41.40, 37.83, 31.25, 30.34, 26.45, 26.20, 26.12, 25.47, 25.22, 24.81, 19.89.

LC-MS (50-100% B, 19 min): t_R (**39**) = 8.25 min, m/z: calculated = 664.35 $[M+H]^+$, found = 664.32 $[M+H]^+$.

HRMS (ESI): calculated = 664.35924 $[M+H]^+$, found = 664.36019 $[M+H]^+$, err [ppm] = 1.42.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**39**) = 12.57 min (99% Purity)

(2'R,5'S,12'R)-12'-cyclohexyl-2'-[2-(3,4-dimethoxyphenyl)ethyl]-3',19'-dioxa-10',13',16'-triazaspiro[cyclopropane-1,15'-tricyclo[18.3.1.0^5,^{10}]tetracosane]-1'(24'),20',22'-triene-4',11',14',17'-tetrone (AV075)



Chemical Formula: $C_{37}H_{47}N_3O_8$
Exact Mass: 661,34
Molecular Weight: 661,78

40

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Chg-OH, 2nd AA: Fmoc-1-amino-1-cyclopropanecarboxylic acid, General Procedure 5.9.5.

Silica column chromatography: DCM/MeOH, 95/5, v/v.

prep-HPLC (80 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**40**) = 10.40 min.

Yield 27 mg (77%).

^{1}H-NMR (599 MHz, DMSO-d_6 + CD_2Cl_2): δ 8.12 (s, 1H), 7.46 (d, J = 9.0 Hz, 1H), 6.77 (t, J = 7.8 Hz, 1H), 6.51 (d, J = 2.4 Hz, 1H), 6.43 – 6.38 (m, 3H), 6.35 – 6.31 (m, 1H), 6.24 (dd, J = 2.1, 8.0 Hz, 1H), 5.22 (dd, J = 5.3, 8.3 Hz, 1H), 4.61 (dd, J = 2.7, 6.3 Hz, 1H), 4.34 (d, J = 16.0 Hz, 1H), 4.10 (d, J = 15.9 Hz, 1H), 4.04 (t, J = 8.2 Hz, 1H), 3.30 (s, 3H), 3.27 (s, 4H), 3.17 (d, J = 13.7 Hz, 1H), 2.50 (t, J = 12.5 Hz, 1H), 2.05

– 1.96 (m, 1H), 1.75 – 1.67 (m, 1H), 1.66 – 1.54 (m, 3H), 1.40 – 1.28 (m, 1H), 1.30 – 1.13 (m, 6H), 1.13 – 1.03 (m, 2H), 0.98 – 0.86 (m, 2H), 0.85 – 0.66 (m, 2H), 0.66 – 0.55 (m, 1H), 0.55 – 0.41 (m, 3H), 0.39 – 0.29 (m, 1H).

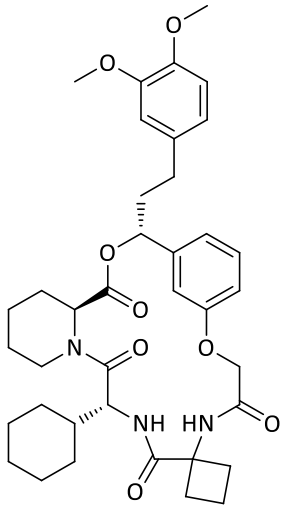
^{13}C-NMR (126 MHz, DMSO-d_6 + CD_2Cl_2): δ 185.63, 185.35, 184.66, 183.74, 173.34, 163.11, 161.51, 155.74, 147.84, 143.26, 134.47, 133.90, 131.29, 126.72, 126.36, 124.21, 90.10, 79.77, 69.99, 69.84, 67.92, 66.88, 56.94, 54.96, 52.06, 48.52, 45.21, 44.85, 41.57, 40.47, 40.38, 40.27, 40.14, 38.96, 34.12, 30.32, 28.75.

LC-MS (0-100% B, 19 min): t_R (**40**) = 12.24 min, m/z: calculated = 662.34 $[M+H]^+$, found = 662.32 $[M+H]^+$.

HRMS (ESI): calculated = 662.34359 $[M+H]^+$, found = 662.34412 $[M+H]^+$, err [ppm] = 0.79.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**40**) = 19.97 min (96% Purity)

(2'R,5'S,12'R)-12'-cyclohexyl-2'-[2-(3,4-dimethoxyphenyl)ethyl]-3',19'-dioxa-10',13',16'-triazaspiro[cyclobutane-1,15'-tricyclo[18.3.1.0^5,^{10}]tetracosane]-1'(24'),20',22'-triene-4',11',14',17'-tetrone (AV293)



Chemical Formula: $C_{38}H_{49}N_3O_8$
Exact Mass: 675,35
Molecular Weight: 675,81

41

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Chg-OH, 2nd AA: Fmoc-1-amino-1-cyclobutanecarboxylic acid, General Procedure 5.9.5.

Silica column chromatography: DCM/Ac, 10/1, v/v.

TLC (DCM/Ac, 10/1): R_f (**41**) = 0.55.

prep-HPLC (50 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**41**) = 8.00 min.

Yield 38 mg (29%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.87 (d, J = 9.5 Hz, 1H), 7.23 – 7.17 (m, 1H), 6.89 – 6.83 (m, 2H), 6.81 – 6.72 (m, 2H), 6.64 – 6.61 (m, 2H), 6.57 (s, 1H), 5.60 (t, J = 6.6 Hz, 1H), 5.26 (q, J = 2.1 Hz, 1H), 4.75 (d, J = 16.5 Hz, 1H), 4.71 (dd, J = 6.4, 9.5 Hz, 1H), 4.58 (d, J = 16.6 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.81 – 3.77 (m, 1H), 3.22 – 3.14 (m, 1H), 2.94 – 2.85 (m, 1H), 2.78 – 2.69 (m, 1H), 2.59 – 2.52 (m, 1H), 2.52 – 2.40 (m, 1H), 2.29 – 2.17 (m, 1H), 2.14 – 2.06 (m, 1H), 2.03 – 1.81 (m, 4H), 1.80 – 1.59 (m, 11H), 1.51 – 1.38 (m, 1H), 1.31 – 1.19 (m, 2H), 1.19 – 1.09 (m, 1H), 1.08 – 1.00 (m, 1H).

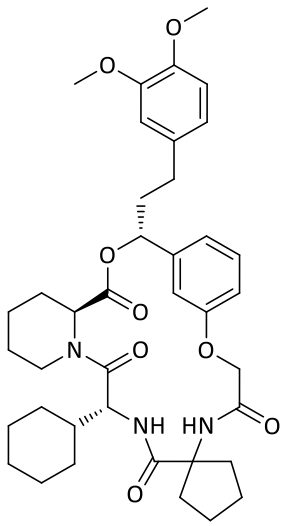
^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.13, 171.95, 171.45, 169.89, 157.76, 149.01, 147.45, 142.16, 133.47, 129.75, 120.72, 120.20, 116.94, 111.76, 111.47, 107.68, 76.51, 66.58, 59.87, 56.03, 55.95, 53.44, 52.32, 43.81, 41.27, 38.36, 32.25, 31.12, 30.36, 29.36, 28.06, 26.49, 26.20, 26.14, 26.08, 25.31, 19.94, 15.71.

LC-MS (50-100% B, 19 min): t_R (**41**) = 9.47 min, m/z: calculated = 676.36 $[M+H]^+$, found = 676.48 $[M+H]^+$.

HRMS (ESI): calculated = 676.35924 $[M+H]^+$, found = 676.35936 $[M+H]^+$, err [ppm] = 0.17.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**41**) = 8.78 min (99% Purity)

(2'R,5'S,12'R)-12'-cyclohexyl-2'-[2-(3,4-dimethoxyphenyl)ethyl]-3',19'-dioxa-10',13',16'-triazaspiro[cyclopentane-1,15'-tricyclo[18.3.1.0^{5},^{10}]tetracosane]-1'(24'),20',22'-triene-4',11',14',17'-tetrone (AV076)



Chemical Formula: $C_{39}H_{51}N_3O_8$
Exact Mass: 689,37
Molecular Weight: 689,84

42

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Chg-OH, 2nd AA: Fmoc-1-amino-1-cyclopentanecarboxylic acid, General Procedure 5.9.5.

prep-HPLC (80 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**42**) = 5.01 min.

Silica column chromatography: DCM/MeOH, 95/5, v/v.

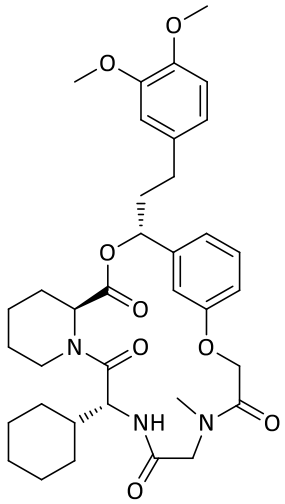
Yield 4 mg (4%).

LC-MS (50-100% B, 19 min): t_R (**42**) = 13.04 min, m/z: calculated = 690.37 $[M+H]^+$, found = 690.36 $[M+H]^+$.

HRMS (ESI): calculated = 690.37487 $[M+H]^+$, found = 690.37549 $[M+H]^+$, err [ppm] = 0.90.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**42**) = 21.33 min (98% Purity)

(2R,5S,12R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-16-methyl-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^{5,10}]tetracosa-1(24),20,22-triene-4,11,14,17-tetrone (AV658)



Chemical Formula: $C_{36}H_{47}N_3O_8$
Exact Mass: 649,34
Molecular Weight: 649,77

43

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Chg-OH, 2nd AA: Fmoc-Gly-OH, General Procedure 5.9.5.

prep-HPLC (60 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**43**) = 4.60 min.

Silica column chromatography: DCM + 2% MeOH, v/v.

Yield 30 mg (19%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.23 (t, J = 7.9 Hz, 1H), 6.96 (s, 1H), 6.80 – 6.73 (m, 3H), 6.69 – 6.61 (m, 2H), 5.73 – 5.67 (m, 1H), 5.41 – 5.35 (m, 1H), 4.89 (t, J = 7.8 Hz, 1H), 4.72 (d, J = 12.6 Hz, 1H), 4.49 (d, J = 12.6 Hz, 1H), 4.06 (q, J = 17.3 Hz, 2H), 3.92 – 3.85 (m, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.28 – 3.18 (m, 1H), 3.07 (s, 3H), 2.62 – 2.51 (m, 2H), 2.25 – 2.02 (m, 2H), 1.83 – 1.62 (m, 12H), 1.54 – 1.38 (m, 1H), 1.30 – 0.98 (m, 5H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 171.69, 170.83, 168.72, 167.77, 157.99, 149.01, 147.46, 142.02, 133.74, 129.52, 120.27, 119.53, 114.01, 111.90, 111.72, 111.47, 75.87, 68.30, 56.07, 56.01, 53.72, 53.55, 53.08, 52.11, 43.94, 42.00, 37.99, 35.78, 30.84, 30.15, 28.60, 26.19, 26.14, 26.07, 25.29, 19.77.

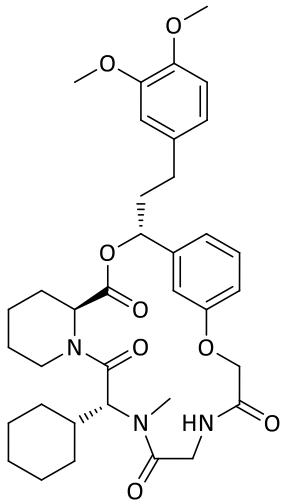
LC-MS (50-100% B, 19 min): t_R (**43**) = 7.07 min, m/z: calculated = 650.34 $[M+H]^+$,

found = 650.51 $[M+H]^+$.

HRMS (ESI): calculated = 650.34359 $[M+H]^+$, found = 650.34345 $[M+H]^+$, err [ppm] = 0.22.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**43**) = 6.77 min (99% Purity)

(2R,5S,12R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-13-methyl-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^{5},^{10}]tetracosa-1(24),20,22-triene-4,11,14,17-tetrone (AV087)



Chemical Formula: $C_{36}H_{47}N_3O_8$
Exact Mass: 649,34
Molecular Weight: 649,77

44

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Chg-OH, 2nd AA: Fmoc-Gly-OH, General Procedure 5.9.5.

Silica column chromatography: DCM/MeOH, 95/5, v/v.

prep-HPLC (80 – 90% B, 10 mL/min, 15 min, 254 nm): t_R (**44**) = 11.38 min.

Yield 1 mg (1%).

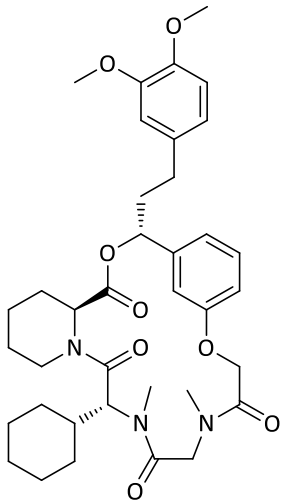
LC-MS (0-100% B, 19 min): t_R (**44**) = 12.03 min, m/z: calculated = 650.34 $[M+H]^+$,

found = 650.19 $[M+H]^+$.

HRMS (ESI): calculated = 650.34359 $[M+H]^+$, found = 650.34372 $[M+H]^+$, err [ppm] = 0.20.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**44**) = 19.72 min (98% Purity)

(2R,5S,12R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-13,16-dimethyl-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^{5},^{10}]tetracosa-1(24),20,22-triene-4,11,14,17-tetrone (AV160)



Chemical Formula: $C_{37}H_{49}N_3O_8$
Exact Mass: 663,35
Molecular Weight: 663,80

45

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Chg-OH, 2nd AA: Fmoc-Gly-OH, General Procedure 5.9.5.

prep-HPLC (50 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**45**) = 11.75 min.

Yield 6 mg (30%).

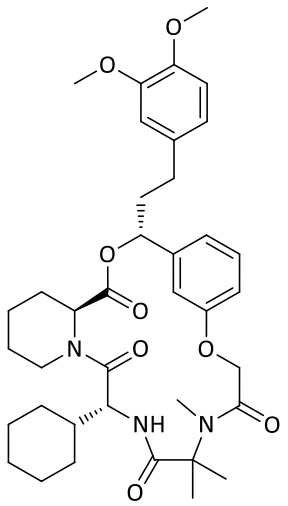
LC-MS (50-100% B, 19 min): t_R (**45**) = 7.14 min, m/z: calculated = 664.35 $[M+H]^+$,

found = 664.14 $[M+H]^+$.

HRMS (ESI): calculated = 664.35924 $[M+H]^+$, found = 664.35913 $[M+H]^+$, err [ppm] = 0.17.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**45**) = 19.93 min (97% Purity)

((2R,5S,12R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-15,15,16-trimethyl-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^{5},^{10}]tetracosa-1(24),20,22-triene-4,11,14,17-tetrone (AV168)



Chemical Formula: $C_{38}H_{51}N_3O_8$
Exact Mass: 677,37
Molecular Weight: 677,83

46

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Chg-OH, 2nd AA: Fmoc-AIB-OH, General Procedure 5.9.5.

prep-HPLC (70 – 90% B, 10 mL/min, 25 min, 254 nm): t_R (**46**) = 16.25 min.

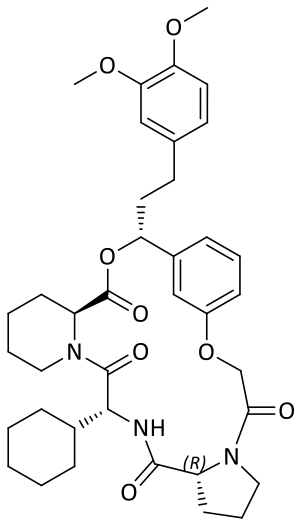
Yield 15 mg (21%).

LC-MS (50-100% B, 19 min): t_R (**46**) = 7.64 min, m/z: calculated = 678.37 $[M+H]^+$,

found = 678.41 $[M+H]^+$.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**46**) = 9.34 min (89% Purity)

(9R,12R,19S,22R)-12-cyclohexyl-22-[2-(3,4-dimethoxyphenyl)ethyl]-2,21-dioxa-5,11,14-triazatetracyclo[21.3.1.0^{5},^{9}.0^{14},^{19}]heptacosa-1(26),23(27),24-triene-4,10,13,20-tetrone (AV041)



Chemical Formula: $C_{38}H_{49}N_3O_8$
Exact Mass: 675,35
Molecular Weight: 675,81

47

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Chg-OH, 2nd AA: Fmoc-D-Pro-OH, General Procedure 5.9.5.

Silica column chromatography: DCM/MeOH, 9/1, v/v.

prep-HPLC (65 – 68% B, 10 mL/min, 14 min, 254 nm): t_R (**48**) = 11.80 min.

Yield 7 mg (7%).

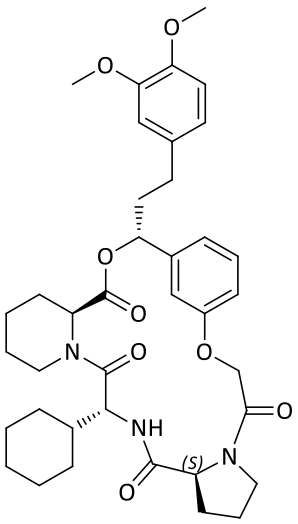
LC-MS (0-100% B, 19 min): t_R (**47**) = 12.38 min, m/z: calculated = 676.36 $[M+H]^+$,

found = 676.18 $[M+H]^+$.

HRMS (ESI): calculated = 676.35924 $[M+H]^+$, found = 676.35889 $[M+H]^+$, err [ppm] = 0.52.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**47**) = 20.25 min (99% Purity)

(9S,12R,19S,22R)-12-cyclohexyl-22-[2-(3,4-dimethoxyphenyl)ethyl]-2,21-dioxa-5,11,14-triazatetracyclo[21.3.1.0^{5},^{9}.0^{14},^{19}]heptacosa-1(26),23(27),24-triene-4,10,13,20-tetrone (AV042)



Chemical Formula: $C_{38}H_{49}N_3O_8$
Exact Mass: 675,35
Molecular Weight: 675,81

48

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Chg-OH, 2nd AA: Fmoc-L-Pro-OH, General Procedure 5.9.5.

Silica column chromatography: DCM/MeOH, 9/1, v/v.

prep-HPLC (65 – 68% B, 10 mL/min, 14 min, 254 nm): t_R (**48**) = 11.80 min.

Yield 4 mg (4%).

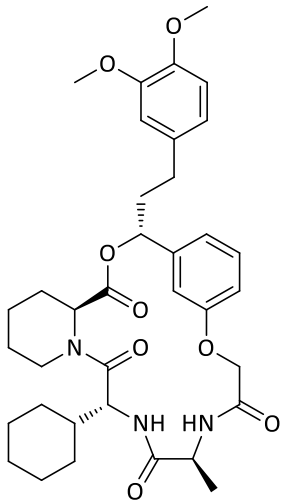
LC-MS (0-100% B, 19 min): t_R (**48**) = 12.03 min, m/z: calculated = 676.36 $[M+H]^+$,

found = 676.18 $[M+H]^+$.

HRMS (ESI): calculated = 676.35924 $[M+H]^+$, found = 676.35941 $[M+H]^+$, err [ppm] = 0.24.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**48**) = 19.82 min (99% Purity)

(2R,5S,12R,15S)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-15-methyl-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^{5},^{10}]tetracosa-1(24),20,22-triene-4,11,14,17-tetrone (AV021)



Chemical Formula: $C_{36}H_{47}N_3O_8$
Exact Mass: 649,34
Molecular Weight: 649,77

49

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Chg-OH, 2nd AA: Fmoc-L-Ala-OH, General Procedure 5.9.5.

Silica column chromatography: DCM/MeOH, 8/2, v/v.

prep-HPLC (80 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**49**) = 11.80 min.

Yield 27 mg (28%).

^{1}H-NMR (800 MHz, DMSO-d_6 + CD_2Cl_2): δ 8.30 (d, J = 9.0 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.29 – 7.25 (m, 1H), 6.96 (ddd, J = 1.0, 2.6, 8.2 Hz, 1H), 6.93 – 6.89 (m, 1H), 6.83 (d, J = 8.1 Hz, 1H), 6.75 (d, J = 2.0 Hz, 1H), 6.74 – 6.71 (m, 1H), 6.65 (dd, J = 2.0, 8.1 Hz, 1H), 5.73 (t, J = 7.1 Hz, 1H), 5.23 – 5.20 (m, 1H), 4.68 (d, J = 16.1 Hz, 1H), 4.64 – 4.58 (m, 1H), 4.46 (t, J = 9.0 Hz, 1H), 4.42 (d, J = 16.1 Hz, 1H), 3.99 – 3.92 (m, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 2.64 – 2.56 (m, 1H), 2.48 – 2.37 (m, 2H), 2.15 – 2.07 (m, 2H), 2.06 – 1.99 (m, 1H), 1.74 – 1.60 (m, 5H), 1.60 – 1.54 (m, 2H), 1.52 – 1.42 (m, 2H), 1.40 – 1.21 (m, 2H), 1.16 (d, J = 6.8 Hz, 3H), 1.14 – 1.07 (m, 2H), 0.97 – 0.80 (m, 2H).

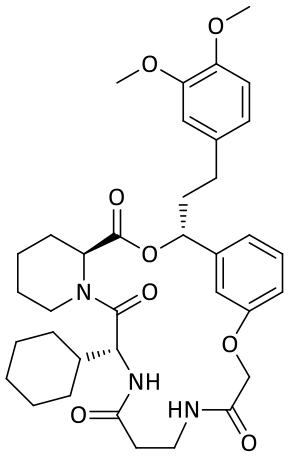
^{13}C-NMR (201 MHz, DMSO-d_6 + CD_2Cl_2): δ 171.15, 170.52, 170.43, 167.86, 158.41, 148.63, 147.05, 140.21, 133.18, 129.53, 121.86, 119.97, 117.71, 112.25, 111.87, 110.35, 75.05, 68.11, 55.51, 55.34, 54.90, 51.85, 51.66, 46.78, 43.37, 35.15, 30.72, 29.31, 27.98, 26.17, 25.77, 25.41, 25.36, 25.10, 20.19, 18.21.

LC-MS (0-100% B, 19 min): t_R (**49**) = 12.34 min, m/z: calculated = 650.34 $[M+H]^+$,
found = 650.07 $[M+H]^+$.

HRMS (ESI): calculated = 650.34359 $[M+H]^+$, found = 650.34358 $[M+H]^+$, err [ppm] = 0.01.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**49**) = 20.72 min (96% Purity)

(2R,5S,12R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-3,20-dioxa-10,13,17-triazatricyclo[19.3.1.0^{5},^{10}]pentacosa-1(25),21,23-triene-4,11,14,18-tetrone (AV024)



Chemical Formula: $C_{36}H_{47}N_3O_8$
Exact Mass: 649,34
Molecular Weight: 649,77

50

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Chg-OH, 2nd AA: Fmoc-β-Ala-OH, General Procedure 5.9.5.

Silica column chromatography: DCM/MeOH, 9/1, v/v.

prep-HPLC (80 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**50**) = 9.60 min.

Yield 14 mg (16%).

^{1}H-NMR (800 MHz, DMSO-*d*$_6$ + CD_2Cl_2): δ 7.93 (d, J = 9.1 Hz, 1H), 7.82 – 7.78 (m, 1H), 7.24 (t, J = 7.9 Hz, 1H), 6.89 – 6.86 (m, 1H), 6.86 – 6.82 (m, 2H), 6.77 (d, J = 2.0 Hz, 1H), 6.74 – 6.71 (m, 1H), 6.69 (dd, J = 2.0, 8.1 Hz, 1H), 5.58 (dd, J = 5.3, 8.2 Hz, 1H), 5.17 – 5.13 (m, 1H), 4.71 – 4.67 (m, 1H), 4.46 (d, J = 15.4 Hz, 1H), 4.40 (d, J = 15.4 Hz, 1H), 4.03 – 3.97 (m, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.59 – 3.53 (m, 1H), 3.18 – 3.13 (m, 1H), 3.13 – 3.06 (m, 1H), 2.58 – 2.52 (m, 1H), 2.48 – 2.40 (m, 2H), 2.32 – 2.27 (m, 1H), 2.10 – 2.05 (m, 1H), 2.05 – 1.98 (m, 2H), 1.77 – 1.69 (m, 3H), 1.69 – 1.64 (m, 1H), 1.64 – 1.56 (m, 5H), 1.42 – 1.32 (m, 1H), 1.28 – 1.06 (m, 5H), 1.05 – 0.92 (m, 2H).

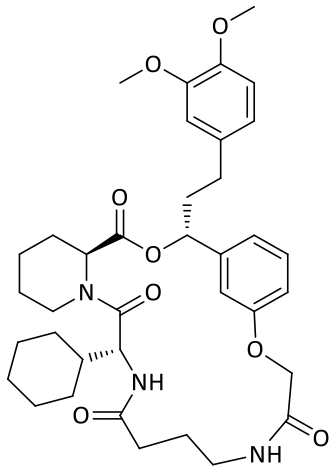
^{13}C-NMR (201 MHz, DMSO-*d*$_6$ + CD_2Cl_2): δ 170.89, 170.83, 170.40, 167.51, 158.36, 148.65, 147.05, 141.88, 133.26, 129.34, 120.09, 119.68, 114.92, 112.28, 111.89, 111.34, 74.62, 67.48, 55.49, 55.36, 54.90, 52.76, 51.86, 43.31, 37.31, 34.31, 34.24, 30.39, 29.65, 27.58, 26.38, 25.81, 25.65, 25.59, 24.76, 20.19.

LC-MS (0-100% B, 19 min): t_R (**50**) = 11.97 min, m/z: calculated = 650.35 $[M+H]^+$,
found = 650.04 $[M+H]^+$.

HRMS (ESI): calculated = 650.34359 $[M+H]^+$, found = 650.34363 $[M+H]^+$, err [ppm] = 0.05.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**50**) = 19.73 min (99% Purity)

(2R,5S,12R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-3,21-dioxa-10,13,18-triazatricyclo[20.3.1.0^{5},^{10}]hexacosa-1(26),22,24-triene-4,11,14,19-tetrone (AV077)



Chemical Formula: $C_{37}H_{49}N_3O_8$
Exact Mass: 663,35
Molecular Weight: 663,80

51

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Chg-OH, 2nd AA: Fmoc-GABA-OH, General Procedure 5.9.5.

Silica column chromatography: DCM/MeOH, 95/5, v/v.

prep-HPLC (80 – 100% B, 10 mL/min, 20 min, 254 nm): t_R (**51**) = 10.20 min.

Yield 8 mg (5%).

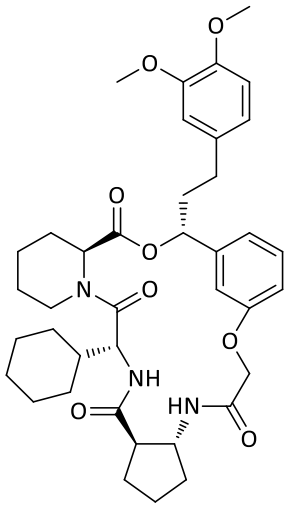
LC-MS (0-100% B, 19 min): t_R (**51**) = 11.72 min, m/z: calculated = 664.35 $[M+H]^+$,

found = 664.31 $[M+H]^+$.

HRMS (ESI): calculated = 664.35924 $[M+H]^+$, found = 664.35929 $[M+H]^+$, err [ppm] = 0.07.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**51**) = 19.23 min (99% Purity)

(2R,5S,12R,15R,19R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-3,23-dioxa-10,13,20-triazatetracyclo[22.3.1.0^{5},^{10}.0^{15},^{19}]octacosa-1(28),24,26-triene-4,11,14,21-tetrone (AV079)



Chemical Formula: $C_{39}H_{51}N_3O_8$
Exact Mass: 689,37
Molecular Weight: 689,84

52

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Chg-OH, 2nd AA: (1R,2R)-Fmoc-2-amino-1-cyclopentanecarboxylic acid, General Procedure 5.9.5.

prep-HPLC (90 – 96% B, 10 mL/min, 10 min, 254 nm): t_R (**52**) = 5.10 min.

Yield 3 mg (3%).

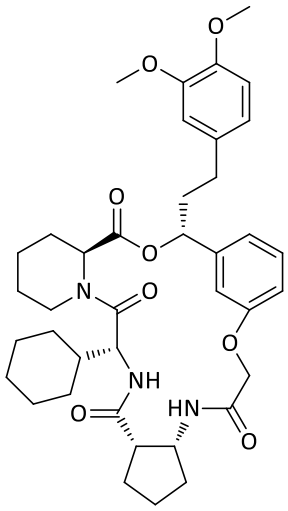
LC-MS (0-100% B, 19 min): t_R (**52**) = 12.31 min, m/z: calculated = 690.37 $[M+H]^+$,

found = 690.32 $[M+H]^+$.

HRMS (ESI): calculated = 690.37489 $[M+H]^+$, found = 690.37473 $[M+H]^+$, err [ppm] = 0.23.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**52**) = 20.33 min (99% Purity)

(2R,5S,12R,15S,19R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-3,23-dioxa-10,13,20-triazatetracyclo[22.3.1.0^{5},^{10}.0^{15},^{19}]octacosa-1(28),24,26-triene-4,11,14,21-tetrone (AV078)



Chemical Formula: $C_{39}H_{51}N_3O_8$
Exact Mass: 689,37
Molecular Weight: 689,84

53

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Chg-OH, 2nd AA: (1S,2R)-Fmoc-2-amino-1-cyclopentanecarboxylic acid, General Procedure 5.9.5.

prep-HPLC (90 – 96% B, 10 mL/min, 10 min, 254 nm): t_R (**53**) = 5.10 min.

Yield 2 mg (4%).

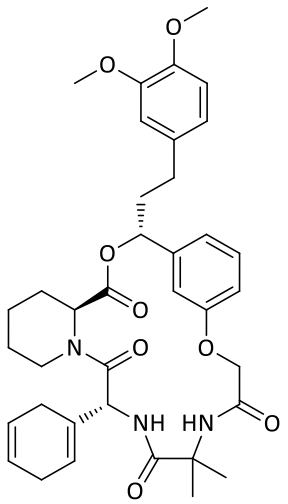
LC-MS (0-100% B, 19 min): t_R (**53**) = 12.69 min, m/z: calculated = 690.37 $[M+H]^+$,

found = 690.28 $[M+H]^+$.

HRMS (ESI): calculated = 690.37489 $[M+H]^+$, found = 690.37455 $[M+H]^+$, err [ppm] = 0.50.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**53**) = 21.03 min (99% Purity)

(2R,5S,12R)-12-(cyclohexa-1,4-dien-1-yl)-2-[2-(3,4-dimethoxyphenyl)ethyl]-15,15-dimethyl-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^{5},^{10}]tetracosa-1(24),20,22-triene-4,11,14,17-tetrone (AV419)



Chemical Formula: $C_{37}H_{45}N_3O_8$
Exact Mass: 659,32
Molecular Weight: 659,77

54

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Dhphg-OH, 2nd AA: Fmoc-AIB-OH, General Procedure 5.9.5.

Silica column chromatography: DCM/Ac, 10/1, v/v.

TLC (DCM/Ac, 10/1): R_f (**54**) = 0.35.

Yield 7 mg (8%).

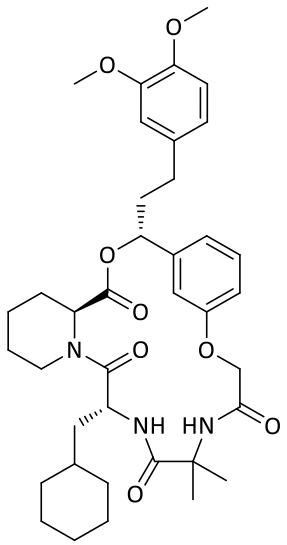
LC-MS (50-100% B, 19 min): t_R (**54**) = 6.87 min, m/z: calculated = 660.33 $[M+H]^+$,

found = 660.64 $[M+H]^+$.

HRMS (ESI): calculated = 660.32794 $[M+H]^+$, found = 660.32819 $[M+H]^+$, err [ppm] = 0.38.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**54**) = 7.35 min (82% Purity)

(2R,5S,12R)-12-(cyclohexylmethyl)-2-[2-(3,4-dimethoxyphenyl)ethyl]-15,15-dimethyl-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^{5},^{10}]tetracosa-1(24),20,22-triene-4,11,14,17-tetrone (AV424)



Chemical Formula: $C_{38}H_{51}N_3O_8$
Exact Mass: 677,37
Molecular Weight: 677,83

55

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Cha-OH, 2nd AA: Fmoc-AIB-OH, General Procedure 5.9.5.

Silica column chromatography: DCM/Ac, 20/1, v/v.

TLC (DCM/Ac, 15/1): R_f (**55**) = 0.30.

Yield 24 mg (25%).

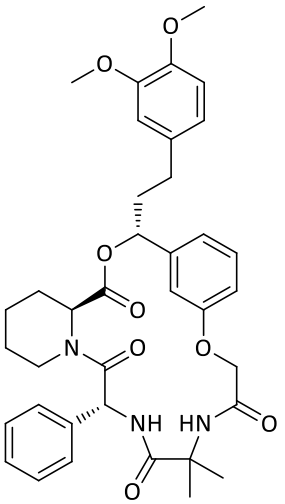
LC-MS (50-100% B, 19 min): t_R (**55**) = 9.26 min, m/z: calculated = 678.37 $[M+H]^+$,

found = 678.64 $[M+H]^+$.

HRMS (ESI): calculated = 678.37489 $[M+H]^+$, found = 678.37543 $[M+H]^+$, err [ppm] = 0.79.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**55**) = 10.40 min (99% Purity)

(2R,5S,12R)-2-[2-(3,4-dimethoxyphenyl)ethyl]-15,15-dimethyl-12-phenyl-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^{5},^{10}]tetracosa-1(24),20,22-triene-4,11,14,17-tetrone (AV422)



Chemical Formula: $C_{37}H_{43}N_3O_8$
Exact Mass: 657,31
Molecular Weight: 657,75

56

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Phg-OH, 2nd AA: Fmoc-AIB-OH, General Procedure 5.9.5.

Silica column chromatography: DCM/Ac, 12/1, v/v.

TLC (DCM/Ac, 10/1): R_f (**56**) = 0.25.

Yield 10 mg (11%).

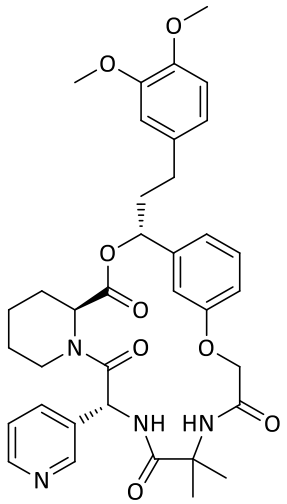
LC-MS (50-100% B, 19 min): t_R (**56**) = 6.99 min, m/z: calculated = 672.33 $[M+H]^+$,

found = 672.46 $[M+H]^+$.

HRMS (ESI): calculated = 672.32794 $[M+H]^+$, found = 672.32778 $[M+H]^+$, err [ppm] = 0.24.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**56**) = 7.26 min (99% Purity)

(2R,5S,12R)-2-[2-(3,4-dimethoxyphenyl)ethyl]-15,15-dimethyl-12-(pyridin-3-yl)-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^{5,10}]tetracosa-1(24),20,22-triene-4,11,14,17-tetrone (AV425)



Chemical Formula: $C_{36}H_{42}N_4O_8$
Exact Mass: 658,30
Molecular Weight: 658,74

57

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Pyg-OH, 2nd AA: Fmoc-Gly-OH, General Procedure 5.9.5.

prep-HPLC (40 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**57**) = 5.42 min.

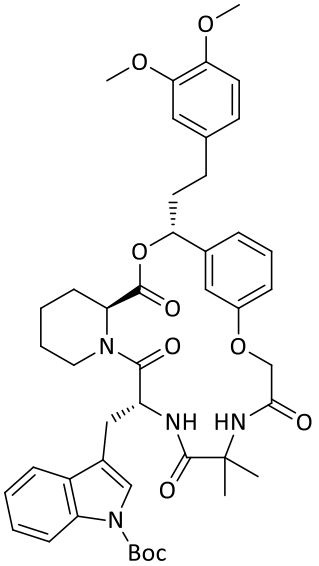
Yield 4 mg (4%).

LC-MS (0-100% B, 19 min): t_R (**57**) = 8.73 min, m/z: calculated = 673.30 $[M+H]^+$,

found = 673.66 $[M+H]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**57**) = 11.39 min (84% Purity)

tert-butyl 3-{[(2R,5S,12R)-2-[2-(3,4-dimethoxyphenyl)ethyl]-15,15-dimethyl-4,11,14,17-tetraoxo-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^{5},^{10}]tetracosa-1(24),20,22-trien-12-yl]methyl}-2,3-dihydro-1H-indole-1-carboxylate (AV420)



Chemical Formula: $C_{45}H_{54}N_4O_{10}$
Exact Mass: 810,38
Molecular Weight: 810,93

58

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Trp-OH, 2nd AA: Fmoc-AIB-OH, General Procedure 5.9.5.

Silica column chromatography: DCM/Ac, 15/1, v/v.

TLC (CH/EE, 10/1): R_f (**58**) = 0.35.

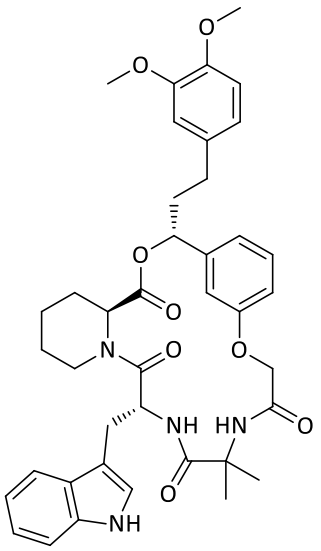
Yield 32 mg (28%).

LC-MS (50-100% B, 19 min): t_R (**58**) = 10.25 min, m/z: calculated = 811.38 $[M+H]^+$,

found = 811.57 $[M+H]^+$.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**58**) = 12.01 min (99% Purity)

(2R,5S,12R)-2-[2-(3,4-dimethoxyphenyl)ethyl]-12-[(1H-indol-3-yl)methyl]-15,15-dimethyl-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^{5},^{10}]tetracosa-1(24),20,22-triene-4,11,14,17-tetrone (AV454)



Chemical Formula: $C_{40}H_{46}N_4O_8$
Exact Mass: 710,33
Molecular Weight: 710,82

59

58 (10 mg, 0.01 mmol, 1.0 eq) is dissolved in 300 µL DCM. 150 µL TFA is added and the reaction stirred for 20 min. The solvent is removed under airstream and the crude product purified by semi-preparative HPLC.

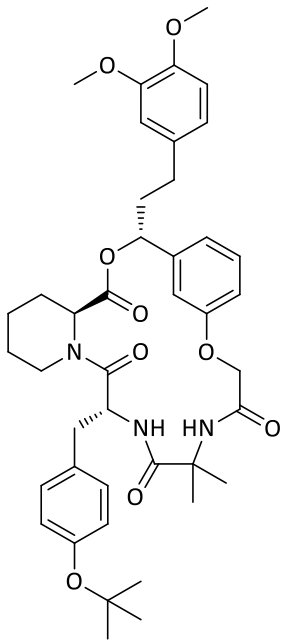
prep-HPLC (50-100% B, 10 mL/min, 15 min, 254 nm): t_R (**59**) = 6.54 min.

Yield 3 mg (33%).

LC-MS (50-100% B, 19 min): t_R (**59**) = 6.19 min, m/z: calculated = 711.33 $[M+H]^+$, found = 711.69 $[M+H]^+$.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**59**) = 6.55 min (99% Purity)

(2R,5S,12R)-12-{[4-(tert-butoxy)phenyl]methyl}-2-[2-(3,4-dimethoxyphenyl)ethyl]-15,15-dimethyl-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^{5},^{10}]tetracosa-1(24),20,22-triene-4,11,14,17-tetrone (AV423)



Chemical Formula: $C_{42}H_{53}N_3O_9$
Exact Mass: 743,38
Molecular Weight: 743,88

60

Starting materials: Resin: **36**, 1st AA: Fmoc-D-Tyr-OH, 2nd AA: Fmoc-AIB-OH, General Procedure 5.9.5.

Silica column chromatography: CH/EE, 12/1, v/v.

TLC (CH/EE, 10/1): R_f (**60**) = 0.38.

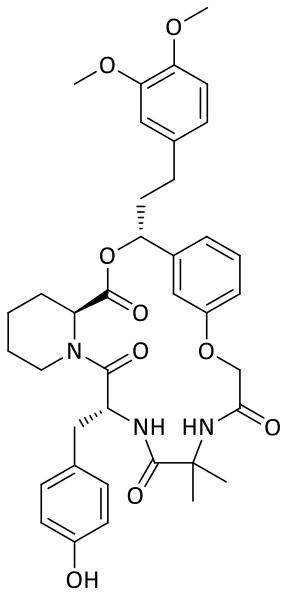
Yield 20 mg (19%).

LC-MS (50-100% B, 19 min): t_R (**60**) = 8.46 min, m/z: calculated = 744.38 $[M+H]^+$,

found = 744.68 $[M+H]^+$.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**60**) = 9.43 min (99% Purity)

(2R,5S,12R)-2-[2-(3,4-dimethoxyphenyl)ethyl]-12-[(4-hydroxyphenyl)methyl]-15,15-dimethyl-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^{5},^{10}]tetracosa-1(24),20,22-triene-4,11,14,17-tetrone (AV458)



Chemical Formula: $C_{38}H_{45}N_3O_9$
Exact Mass: 687,32
Molecular Weight: 687,78

61

60 (12 mg, 0.02 mmol, 1.0 eq) is dissolved in 300 µL DCM. 150 µL TFA is added and the reaction stirred for 40 min. The solvent is removed under airstream and the crude product purified by semi-preparative HPLC.

prep-HPLC (50-100% B, 10 mL/min, 15 min, 254 nm): t_R (**61**) = 7.45 min.

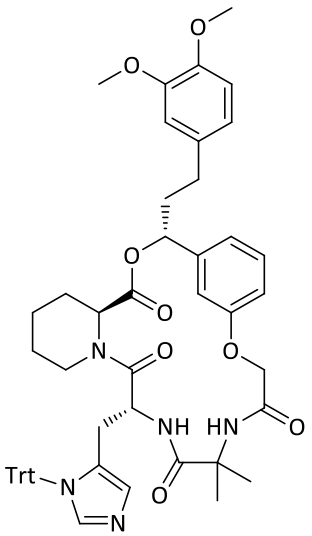
Yield 4 mg (36%).

LC-MS (30-100% B, 19 min): t_R (**61**) = 8.92 min, m/z: calculated = 688.32 $[M+H]^+$,

found = 688.54 $[M+H]^+$.

RP-HPLC (30 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**61**) = 9.35 min (89% Purity)

(2R,5S,12R)-2-[2-(3,4-dimethoxyphenyl)ethyl]-15,15-dimethyl-12-{[1-(triphenylmethyl)-1H-imidazol-5-yl]methyl}-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^{5},^{10}]tetracosa-1(24),20,22-triene-4,11,14,17-tetrone (AV421)



Chemical Formula: $C_{54}H_{57}N_5O_8$
Exact Mass: 903,42
Molecular Weight: 904,06

62

Starting materials: Resin: **36**, 1st AA: Fmoc-D-His-OH, 2nd AA: Fmoc-AIB-OH, General Procedure 5.9.5.

Silica column chromatography: CH/EE, 12/1, v/v.

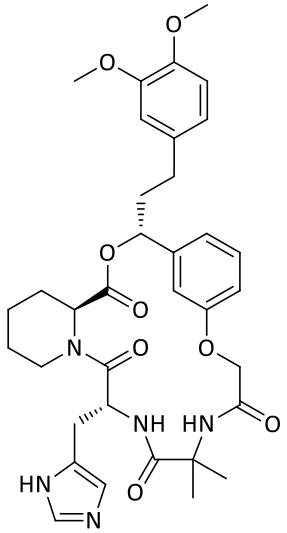
TLC (CH/EE, 10/1): R_f (**62**) = 0.45.

Yield 18 mg (14%).

LC-MS (30-100% B, 19 min): t_R (**62**) = 7.86 min, m/z: calculated = 904.42 $[M+H]^+$,

found = 904.67 $[M+H]^+$.

(2R,5S,12R)-2-[2-(3,4-dimethoxyphenyl)ethyl]-12-[(1H-imidazol-5-yl)methyl]-15,15-dimethyl-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^{5},^{10}]tetracosa-1(24),20,22-triene-4,11,14,17-tetrone (AV457)



Chemical Formula: $C_{35}H_{43}N_5O_8$
Exact Mass: 661,31
Molecular Weight: 661,74

63

62 (18 mg, 0.02 mmol, 1.0 eq) is dissolved in 300 µL DCM. 5 µL TIS, then 150 µL TFA are added and the reaction stirred for 30 min. The solvent is removed under airstream and the crude product purified by semi-preparative HPLC.

prep-HPLC (40 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**63**) = 5.41 min.

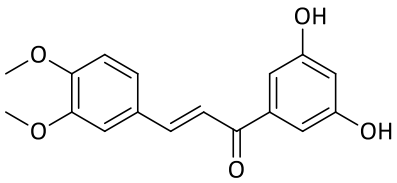
Yield 5 mg (38%).

LC-MS (50-100% B, 19 min): t_R (**63**) = 1.09 min, m/z: calculated = 662.31 $[M+H]^+$, found = 662.76 $[M+H]^+$.

RP-HPLC (30 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**63**) = 6.20 min (99% Purity)

6.3.3. Macrocyclic tracer

(E)-1-(3,5-dihydroxyphenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (AV241/AV243/AV266)



Chemical Formula: $C_{17}H_{16}O_5$
Exact Mass: 300,10
Molecular Weight: 300,31

64

3,5-Dihydroxyacetophenon (6.00 g, 39 mmol, 1.0 eq) and 3,4-dimethoxybenzaldehyde (6.55 g, 39 mol, 1.0 eq) are dissolved in 120 mL EtOH and sparged with argon for 20 min. The solution is cooled to 0°C and cooled NaOH (10.40 g, 350 mmol, 9.0 eq) is dissolved in 120 mL H_2O and slowly added in 10 min. The reaction is stirred under argon at slowly rising temperature to r.t. overnight. The mixture is acidified with conc. HCl and extracted with EE (3×150 mL). The combined organic layers are dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by silica filtration (EE). The product **64** is obtained as a yellow foam.

Yield 8.75 g (74%).

TLC (CH/EE, 1/1): R_f (**64**) = 0.22.

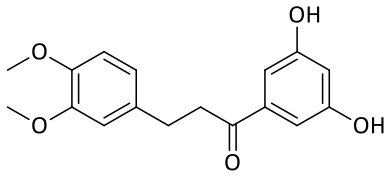
^{1}H-NMR (500 MHz, DMSO-*d*$_6$): δ 9.61 (s, 2H), 7.67 – 7.60 (m, 2H), 7.50 (d, *J* = 2.0 Hz, 1H), 7.34 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.03 – 6.93 (m, 3H), 6.80 (d, *J* = 2.2 Hz, 1H), 6.51 (t, *J* = 2.2 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H).

^{13}C-NMR (126 MHz, DMSO-*d*$_6$): δ 197.74, 189.25, 158.69, 151.26, 149.10, 144.22, 140.08, 138.89, 127.59, 123.83, 120.08, 111.60, 110.72, 107.20, 106.99, 106.57, 106.24, 59.81, 55.76, 55.61, 26.76, 20.76, 14.10.

LC-MS (0-100% B, 19 min): t_R (**64**) = 9.08 min, m/z: calculated = 301.10 $[M+H]^+$,
found = 301.22 $[M+H]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**64**) = 10.95 min (83% Purity).

1-(3,5-dihydroxyphenyl)-3-(3,4-dimethoxyphenyl)propan-1-one (AV269/AV270/AV271/AV272/AV335)



Chemical Formula: $C_{17}H_{18}O_5$
Exact Mass: 302,12
Molecular Weight: 302,32

65

Zn powder (1.4 g, 21 mmol, 5.0 eq) and NH_4Cl (5.5 g, 126 mmol, 30.0 eq) are added to a flask and suspended in 50 mL MeOH. **4** (1.22 g, 4 mmol, 1.0 eq) is dissolved in 30 mL MeOH and added dropwise to the vigorously stirring suspension in 1.5 h. After complete addition, the mixture is filtered and washed with MeOH. The solvent is removed on rotivap, then the solid dissolved in 100 mL H_2O and extracted with EE (3×100 mL). The combined organic layers are dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 1/1). The pure product **65** is obtained as a beige-white solid.

Yield 350 mg (28%).

TLC (CH/EE, 1/1): R_f (**65**) = 0.25.

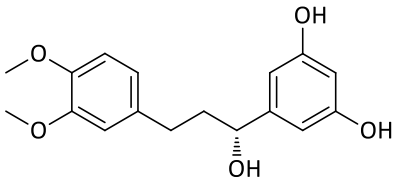
^{1}H-NMR (500 MHz, DMSO-*d*$_6$) δ 9.54 (s, 2H), 6.86 (d, *J* = 2.0 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.80 (d, *J* = 2.2 Hz, 2H), 6.74 (dd, *J* = 2.0, 8.2 Hz, 1H), 6.44 (t, *J* = 2.2 Hz, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.18 (dd, *J* = 7.0, 8.0 Hz, 2H), 2.83 (t, *J* = 7.5 Hz, 2H).

^{13}C-NMR (126 MHz, DMSO) δ 199.02, 158.55, 148.61, 147.04, 138.65, 133.71, 120.02, 112.44, 111.93, 107.01, 105.87, 55.54, 55.41, 29.27.

LC-MS (0-100% B, 19 min): t_R (**65**) = 9.23 min, m/z: calculated = 303.12 $[M+H]^+$, found = 302.92 $[M+H]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**65**) = 10.61 min (99% Purity).

(R)-5-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)benzene-1,3-diol (AV273/AV275/AV277/AV291/AV338)



Chemical Formula: $C_{17}H_{20}O_5$
Exact Mass: 304,13
Molecular Weight: 304,34

66

65 (2.10 g, 6.95 mmol, 1.0 eq) is dissolved in 50 mL THF and added to an autoclave. The solution is sparged with argon for 10 min, then 100 mL iPrOH is added and the solution further sparged with argon for 5 min. $RuCl_2$[(*S*)-(DM-SEGPHOS)][(*S*)-DAIPEN] (84 mg, 0.07 mmol, 0.01 eq) and 1 M KOtBu in *t*BuOH (7 mL, 7 mmol, 1.0 eq) is added and the autoclave closed, then flushed 3x with H_2 and finally 10 bar H_2 applied. After reaction overnight, the mixture is transferred to a flask and the solvent is removed under reduced pressure. The crude product is dissolved in 200 mL EE and washed with 100 mL sat. NH_4Cl solution. The aqueous phase is extracted with EE (3×100 ml). The combined organic layers are dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 1/2). The pure product **66** is obtained as a white solid.

Yield 1.37 g (65%).

TLC (CH/EE, 1/1): R_f (**66**) = 0.14.

^{1}H-NMR (500 MHz, DMSO-*d*$_6$) δ 9.03 (s, 2H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.76 (d, *J* = 2.0 Hz, 1H), 6.68 (dd, *J* = 2.0, 8.1 Hz, 1H), 6.20 (d, *J* = 2.2 Hz, 2H), 6.06 (t, *J* = 2.2 Hz, 1H), 5.03 (d, *J* = 4.3 Hz, 1H), 4.32 (dt, *J* = 4.8, 7.4 Hz, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 2.62 – 2.51 (m, 2H), 2.47 (s, 0H), 1.79 (ddt, *J* = 5.6, 9.0, 11.9 Hz, 2H).

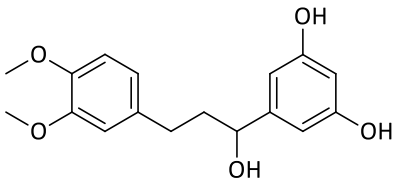
^{13}C-NMR (126 MHz, DMSO) δ 158.04, 148.64, 148.48, 146.85, 134.70, 119.91, 112.25, 111.97, 103.90, 100.83, 71.71, 55.54, 55.39, 40.98, 30.64.

LC-MS (0-100% B, 19 min): t_R (**66**) = 8.53 min, m/z: calculated = 287.11 $[M-OH]^+$, found = 287.12 $[M-OH]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**66**) = 9.06 min (98% Purity).

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**66**) = 20.77 min (er >99/1).

5-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)benzene-1,3-diol (AV274)



Chemical Formula: $C_{17}H_{20}O_5$
Exact Mass: 304,13
Molecular Weight: 304,34

67

65 (70 mg, 0.23 mmol, 1.0 eq) is dissolved in 3 mL THF. $NaBH_4$ (9 mg, 0.23 mmol, 1.0 eq) is added and the reaction stirred at r.t. overnight. The mixture is quenched with 1 mL 3 M HCl. The THF is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 1/1). The pure product **67** is obtained as a beige-white solid.

Yield 50 mg (71%).

TLC (CH/EE, 1/1): R_f (**67**) = 0.13.

^{1}H-NMR (300 MHz, DMSO-*d*$_6$): δ 9.05 (s, 2H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.75 (d, *J* = 2.0 Hz, 1H), 6.67 (dd, *J* = 2.0, 8.1 Hz, 1H), 6.18 (d, *J* = 2.2 Hz, 2H), 6.05 (t, *J* = 2.2 Hz, 1H), 5.04 (d, *J* = 4.3 Hz, 1H), 4.30 (q, *J* = 5.8 Hz, 1H), 3.71 (d, *J* = 6.8 Hz, 6H), 2.65 – 2.51 (m, 1H), 2.45 (d, *J* = 8.2 Hz, 0H), 1.79 (qd, *J* = 4.5, 9.0 Hz, 2H).

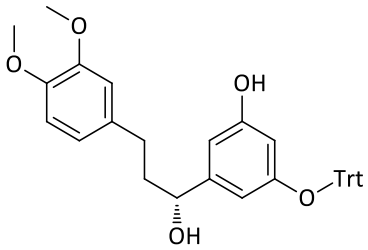
^{13}C-NMR (75 MHz, DMSO-*d*$_6$): δ 158.03, 148.61, 148.48, 146.82, 134.68, 119.90, 112.21, 111.93, 103.88, 100.81, 71.69, 55.53, 55.38, 40.99, 31.13.

LC-MS (0-100% B, 19 min): t_R (**67**) = 8.15 min, m/z: calculated = 287.11 $[M-OH]^+$, found = 287.13 $[M-OH]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**67**) = 9.00 min (95% Purity).

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**67**) = 21.17 + 22.97 min (*er* = 31.38/68.62).

(R)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)-5-(trityloxy)phenol (AV313/AV314/AV317/AV319/AV342)



Chemical Formula: $C_{36}H_{34}O_5$
Exact Mass: 546,24
Molecular Weight: 546,65

68

66 (680 mg, 2.23 mmol, 1.0 eq) is dissolved in 50 mL dry MeCN and added to dried flask under argon atmosphere. Then K_2CO_3 (308 mg, 2.23 mmol, 1.0 eq) and trityl chloride (466 mg, 1.67 mmol, 0.75 eq) are added. The reaction is stirred at r.t. overnight. The mixture is filtered and the solvent removed. The crude product is purified by column chromatography (CH/EE, 2/1 gradient to EE). The pure product **68** is obtained as a yellow solid.

Yield 431 mg (47%).

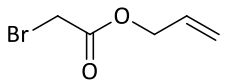
TLC (CH/EE, 2/1): R_f (**68**) = 0.20.

^{1}H-NMR ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 9.01 (s, 1H), 7.41 – 7.38 (m, 6H), 7.30 (dd, *J* = 7.0, 8.5 Hz, 7H), 7.24 – 7.19 (m, 3H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.68 (d, *J* = 2.0 Hz, 1H), 6.58 (dd, *J* = 2.0, 8.2 Hz, 1H), 6.22 (t, *J* = 1.7 Hz, 1H), 6.06 (d, *J* = 2.0 Hz, 1H), 5.98 (t, *J* = 2.2 Hz, 1H), 4.97 (d, *J* = 4.4 Hz, 1H), 4.14 (dt, *J* = 4.7, 7.6 Hz, 1H), 3.72 (d, *J* = 5.2 Hz, 6H), 2.32 (dddd, *J* = 6.2, 9.7, 13.9, 23.5 Hz, 2H), 1.64 – 1.47 (m, 2H).

^{13}C-NMR (126 MHz, DMSO-*d*$_6$): δ 156.99, 156.22, 148.55, 147.35, 146.80, 143.90, 134.58, 128.33, 127.69, 127.04, 119.84, 112.22, 111.92, 109.06, 106.07, 105.93, 89.16, 71.36, 59.70, 55.53, 55.37, 40.80, 30.79, 20.71, 14.04.

LC-MS (50-100% B, 19 min): t_R (**68**) = 8.78 min, m/z: calculated = 569.23 $[M+Na]^+$, found = 596.11 $[M+Na]^+$ (95% Purity)

allyl 2-bromoacetate (AV294)



Chemical Formula: $C_5H_7BrO_2$
Exact Mass: 177,96
Molecular Weight: 179,01

69

Allyl alcohol (1.00 mL, 15 mmol, 1.0 eq) is dissolved in dry DCM in a dried flask under argon atmosphere. Pyridine (1.18 mL, 15 mmol, 1.0 eq) is added and the flask cooled to 0°C for 15 min. Then bromoacetyl bromide (1.40 mL, 16 mmol, 1.1 eq) is added dropwise in 20 min. After 20 min further stirring the ice bath is removed and the reaction stirred at r.t. for 30 min. Finally, the reaction is quenched by addition of 30 mL H_2O, then extracted with DCM (3×50 mL), the combined organic layers washed with brine and dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product **69** is used without further purification.

Yield 2.61 g (quant.).

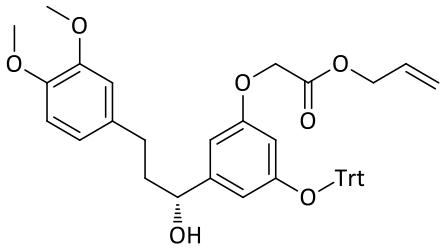
TLC (CH/EE, 4/1, v/v): R_f(**69**) = 0.66.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.06 – 5.82 (m, 1H), 5.44 – 5.23 (m, 2H), 4.67 (dd, *J* = 2.3, 5.8 Hz, 2H), 3.92 – 3.81 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 167.05, 131.35, 119.33, 66.88, 25.82.

EI-MS (303 K): m/z: calculated = 123/121 $[M\text{-}O\text{allyl}]^+$, 99 $[M\text{-}HBr]^+$, 95/93 $[BrCH_2]^+$, 85 $[M\text{-}BrCH_2]^+$, found = 123/121 $[M\text{-}O\text{allyl}]^+$, 99 $[M\text{-}HBr]^+$, 95/93 $[BrCH_2]^+$, 85 $[M\text{-}BrCH_2]^+$.

(R)-allyl 2-(3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)-5-(trityloxy)phenoxy)acetate (AV318/AV320/AV345)



Chemical Formula: $C_{41}H_{40}O_7$
Exact Mass: 644,28
Molecular Weight: 644,75

70

68 (1000 mg, 1.83 mmol, 1.0 eq) is dissolved in 50 mL MeCN. K_2CO_3 (1000 mg, 7.32 mmol, 4.0 eq) and **69** (570 mg, 3.20 mmol, 1.75 eq) are added. The reaction is stirred at r.t. night. After complete conversion, the suspension is filtered, washed with MeCN and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 3/1 then 2/1). The pure product **70** is obtained as a yellow solid.

Yield 910 mg (77%).

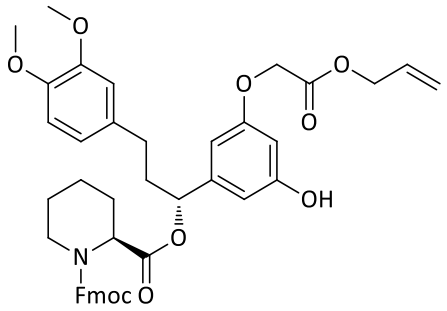
TLC (CH/EE, 1/1): R_f (**70**) = 0.57.

^{1}H-NMR (500 MHz, DMSO-*d*$_6$) δ 7.41 – 7.37 (m, 6H), 7.30 (dd, *J* = 7.0, 8.5 Hz, 6H), 7.25 – 7.20 (m, 3H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.68 (d, *J* = 2.0 Hz, 1H), 6.58 (dd, *J* = 2.0, 8.2 Hz, 1H), 6.36 (dd, *J* = 1.2, 2.5 Hz, 1H), 6.24 (t, *J* = 1.7 Hz, 1H), 6.07 (t, *J* = 2.3 Hz, 1H), 5.86 (ddt, *J* = 5.4, 10.7, 17.3 Hz, 1H), 5.30 – 5.17 (m, 2H), 5.06 (d, *J* = 4.5 Hz, 1H), 4.57 – 4.53 (m, 4H), 4.21 (dt, *J* = 4.9, 7.6 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 2.32 (dddd, *J* = 6.1, 9.7, 13.9, 23.6 Hz, 2H), 1.64 – 1.48 (m, 1H).

^{13}C-NMR (126 MHz, DMSO-*d*$_6$): δ 168.21, 157.39, 156.29, 148.55, 147.73, 146.81, 143.63, 134.49, 132.09, 128.29, 127.78, 127.16, 119.84, 117.94, 113.41, 112.22, 111.91, 111.10, 105.12, 104.90, 89.52, 71.27, 64.74, 64.55, 59.69, 55.53, 55.38, 40.76, 30.75.

LC-MS (70-100% B, 19 min): t_R (**70**) = 6.33 min, m/z: calculated = 667.27 $[M+Na]^+$, found = 667.16 $[M+Na]^+$.

(S)-1-((9H-fluoren-9-yl)methyl) 2-((R)-1-(3-(2-(allyloxy)-2-oxoethoxy)-5-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)propyl) piperidine-1,2-dicarboxylate (AV321/AV346/322/362/323)



Chemical Formula: $C_{43}H_{45}NO_{10}$
Exact Mass: 735,30
Molecular Weight: 735,82

71

70 (910 mg, 1.41 mmol, 1.0 eq) and Fmoc-*S*-pipecolate (546 mg, 1.55 mmol, 1.1 eq) are dissolved in 50 mL dry DCM and cooled to 0°C for 15 min. DMAP (57 mg, 0.47 mmol, 0.3 eq) is added and stirred until dissolved, then DCC (320 mg, 1.55 mmol, 1.1 eq) is added. The mixture is stirred for 15 min. Finally, the ice bath is removed and the reaction stirred overnight at r.t. The reaction mixture is filtered, washed with DCM and the solvent removed under reduced pressure. The crude product is dissolved in 30 mL DCM + 1% TFA and stirred for 5 min. The solvent is removed under reduced pressure and the crude product purified by silica column chromatography (CH/EE, 2/1) and the pure product **71** is obtained as a colorless oil.

Yield 1.05 g (92%).

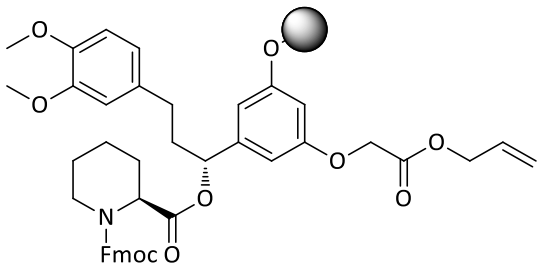
TLC (CH/EE, 2/1, v/v): R_f (**71**) = 0.30.

^{1}H-NMR (500 MHz, Chloroform-*d*): δ 7.79 – 7.72 (m, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.57 (dd, J = 7.6, 11.5 Hz, 1H), 7.46 (dd, J = 7.5, 26.6 Hz, 1H), 7.34 (ddt, J = 7.6, 16.1, 33.4 Hz, 3H), 7.20 (t, J = 7.5 Hz, 1H), 6.77 – 6.70 (m, 1H), 6.68 – 6.53 (m, 2H), 6.45 – 6.41 (m, 2H), 6.30 (d, J = 17.0 Hz, 1H), 5.94 – 5.82 (m, 1H), 5.74 – 5.62 (m, 1H), 5.33 – 5.27 (m, 1H), 5.23 (d, J = 10.5 Hz, 1H), 5.04 – 4.86 (m, 1H), 4.68 – 4.63 (m, 2H), 4.57 (s, 1H), 4.50 (s, 1H), 4.48 – 4.41 (m, 1H), 4.38 – 4.22 (m, 2H), 4.06 (d, J = 16.4 Hz, 1H), 3.87 – 3.74 (m, 6H), 3.22 – 3.13 (m, 1H), 2.90 (t, J = 13.1 Hz, 0H), 2.62 – 2.38 (m, 2H), 2.34 – 2.25 (m, 1H), 2.21 – 1.90 (m, 1H), 1.72 (t, J = 14.4 Hz, 4H), 1.52 – 1.39 (m, 1H), 1.31 (s, 1H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ 159.25, 149.07, 147.52, 143.94, 141.41, 131.53, 127.86, 127.22, 125.19, 120.27, 120.12, 119.25, 111.93, 111.84, 111.55, 107.01, 105.72, 105.27, 101.92, 76.16, 68.03, 66.00, 65.42, 56.09, 55.99, 55.09, 54.67, 47.37, 42.16, 38.08, 31.28, 31.21, 26.96, 24.88, 24.65, 20.80, 14.34.

LC-MS (50-100% B, 19 min): t_R (**71**) = 11.32 min, m/z: calculated = 753.33 $[M+NH_4]^+$, found = 753.73 $[M+NH_4]^+$.

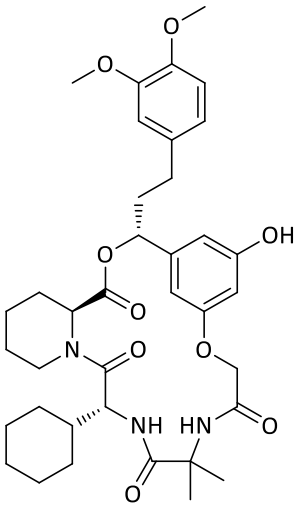
Resin bound (S)-1-((9H-fluoren-9-yl)methyl) 2-((R)-1-(3-(2-(allyloxy)-2-oxoethoxy)-5-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)propyl) piperidine-1,2-dicarboxylate (AV324/AV348/AV363)



72

Synthesis according to 5.9.5.

(2R,5S,12R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-22-hydroxy-15,15-dimethyl-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^{5},^{10}]tetracosa-1(24),20,22-triene-4,11,14,17-tetrone (AV361/AV367/AV331P)



Chemical Formula: $C_{37}H_{49}N_3O_9$
Exact Mass: 679,35
Molecular Weight: 679,80

73

Starting materials: Resin: **72**, 1st AA: Fmoc-D-Chg-OH, 2nd AA: Fmoc-Aib-OH, Procedure 5.9.5.

Silica column chromatography: DCM/MeOH, 30/1, v/v.

TLC (DCM/MeOH, 30/1): R_f(**73**) = 0.25.

Yield 90 mg (20%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.78 (d, J = 8.8 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.68 (d, J = 2.0 Hz, 1H), 6.67 – 6.62 (m, 1H), 6.61 – 6.52 (m, 2H), 6.35 – 6.32 (m, 2H), 5.57 – 5.51 (m, 1H), 5.25 – 5.21 (m, 1H), 4.70 (s, 1H), 4.64 (d, J = 16.4 Hz, 1H), 4.53 (d, J = 16.3 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.85 – 3.81 (m, 1H), 3.31 (t, J = 13.1 Hz, 1H), 2.57 – 2.48 (m, 2H), 2.29 – 2.19 (m, 1H), 2.17 – 2.10 (m, 1H), 2.08 –

1.99 (m, 1H), 1.77 (s, 3H), 1.77 – 1.61 (m, 8H), 1.53 – 1.44 (m, 1H), 1.43 (s, 3H), 1.31 – 1.16 (m, 3H), 1.18 – 1.09 (m, 1H), 1.08 – 0.93 (m, 2H).

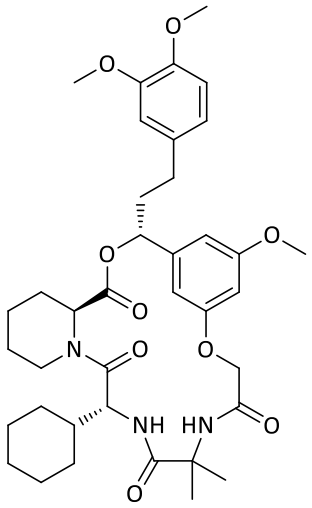
^{13}C-NMR (126 MHz, $CDCl_3$): δ 174.09, 172.12, 171.65, 169.90, 158.71, 158.10, 149.04, 147.47, 142.80, 133.71, 120.26, 111.89, 111.54, 108.63, 102.77, 101.46, 76.57, 66.99, 58.74, 56.09, 56.02, 53.60, 52.49, 43.89, 41.38, 37.73, 31.22, 30.36, 28.17, 26.48, 26.24, 26.19, 26.11, 25.66, 25.31, 24.84, 19.97.

LC-MS (30-100% B, 19 min): t_R (**73**) = 10.92 min, m/z: calculated = 680.35 $[M+H]^+$, found = 680.49 $[M+H]^+$.

HRMS (ESI): calculated = 680.35416 $[M+H]^+$, found = 680.35433 $[M+H]^+$, err [ppm] = 0.25.

RP-HPLC (30 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**73**) = 12.05 min (99% Purity)

(2R,5S,12R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-22-methoxy-15,15-dimethyl-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^5,^{10}]tetracosa-1(24),20,22-triene-4,11,14,17-tetrone (AV389)



Chemical Formula: $C_{38}H_{51}N_3O_9$
Exact Mass: 693,36
Molecular Weight: 693,83

74

73 (5 mg, 0.01 mmol, 1.0 eq) is dissolved in 1 mL dry MeCN and K_2CO_3 (10 mg, 0.1 mmol, 10.0 eq) is added. Then MeI (5 µL, 0.1 mmol, 10.0 eq) is added and the mixture stirred at r.t. overnight. The mixture is diluted with DCM and extracted 1x with 1 M $NaOH_{aq}$. The organic solvent is removed and the crude product purified by semi-preparative HPLC.

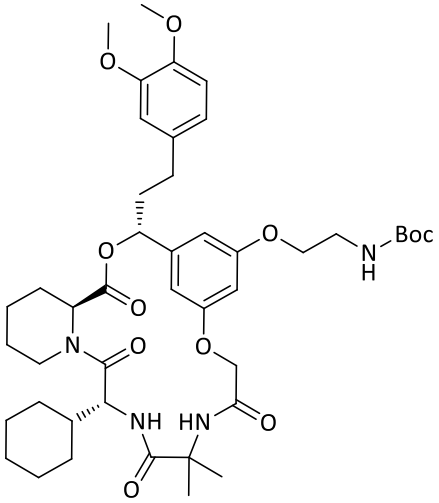
prep-HPLC (70 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**74**) = 3.83 min.

Yield 1 mg (19%).

LC-MS (50-100% B, 19 min): t_R (**74**) = 9.07 min, m/z: calculated = 694.36 $[M+H]^+$, found = 694.47 $[M+H]^+$.

HRMS (ESI): calculated = 694.36981 $[M+H]^+$, found = 694.36967 $[M+H]^+$, err [ppm] = 0.20.

tert-butyl N-(2-{[(2R,5S,12R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-15,15-dimethyl-4,11,14,17-tetraoxo-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^{5},^{10}]tetracosa-1(24),20,22-trien-22-yl]oxy}ethyl)carbamate (AV384)



Chemical Formula: $C_{44}H_{62}N_4O_{11}$
Exact Mass: 822,44
Molecular Weight: 822,98

75

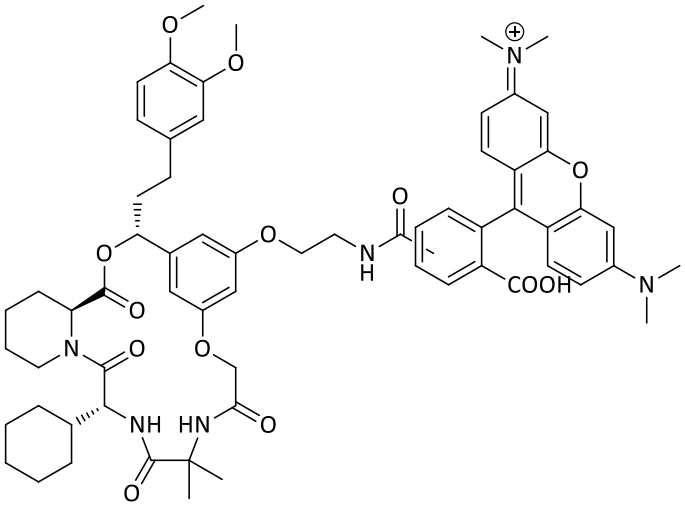
73 (33 mg, 0.048 mmol, 1.0 eq) is dissolved in 1 mL dry MeCN and Ag_2CO_3 (28 mg, 0.1 mmol, 2.0 eq) is added. Then tert-butyl (2-bromoethyl)carbamate (40 mg, 0.16 mmol, 3.0 eq) is added and the mixture stirred at 30°C over 3 d. The mixture is filtered and washed with MeCN. The organic solvent is removed, the crude product purified by semi-preparative HPLC and pure **75** obtained.

prep-HPLC (50 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**75**) = 6.46 min.

Yield 18 mg (45%).

LC-MS (50-100% B, 19 min): t_R (**75**) = 13.68 min, m/z: calculated = 823.44 [M+H]+, found = 823.32 [M+H]+.

9-{2-carboxy-4(5)-[(2-{[(2R,5S,12R)-12-cyclohexyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-15,15-dimethyl-4,11,14,17-tetraoxo-3,19-dioxa-10,13,16-triazatricyclo[18.3.1.0^{5},^{10}]tetracosa-1(24),20,22-trien-22-yl]oxy}ethyl)carbamoyl]phenyl}-6-(dimethylamino)-N,N-dimethyl-3H-xanthen-3-iminium (AV387)



Chemical Formula: $C_{64}H_{75}N_6O_{13}^{+}$
Exact Mass: 1135,54
Molecular Weight: 1136,31

76

75 (18 mg, 0.022 mmol, 1.0 eq) is dissolved in 2 mL dry DCM and 0.5 mL TFA added. After 30 min the solvent is removed under reduced pressure and the TFA co-evaporated with DCM and toluene. The crude product is dissolved in 1.5 mL DMF and 30 µL TEA, then 5 (6)-TAMRA NHS ester (12 mg, 0.022 mmol, 1.0 eq) added. The flask is protected from light by an alumina foil wrapping. After stirring at r.t. overnight the solvent is removed under reduced pressure and the crude product purified by silica column chromatography (DCM + 15 MeOH). The regioisomers could be separated and three fractions were obtained. **76a** (pure regioisomer 1), **76b** (mixed fraction of both isomers), **76c** (regioisomer 2 still containing 12% isomer 1). All fractions were tested in an FRET-Assay, with **76a** having the highest affinity.

TLC (DCM + 15 MeOH, 2/1): R_f (14) = 0.22.

Yield 76a, 10 mg (40%), **76b**, 7 mg (28%), **76c**, 8 mg (32%).

^{1}H-NMR (500 MHz, DMSO-d6, 76a): δ 9.04 (t, J = 5.4 Hz, 1H), 8.47 – 8.43 (m, 1H), 8.26 – 8.19 (m, 1H), 8.17 (s, 1H), 7.55 (t, J = 10.1 Hz, 1H), 7.34 – 7.23 (m, 1H), 6.87 – 6.79 (m, 1H), 6.79 – 6.74 (m, 1H), 6.70 – 6.62 (m, 1H), 6.54 – 6.44 (m, 6H), 6.45 – 6.39 (m, 1H), 5.77 – 5.73 (m, 1H), 5.59 – 5.50 (m, 1H), 5.13 – 5.06 (m, 1H), 4.69 (d, J = 16.1 Hz, 1H), 4.53 (d, J = 15.5 Hz, 1H), 4.51 – 4.46 (m, 1H), 4.16 – 4.04 (m, 2H), 3.76 – 3.67 (m, 6H), 3.69 – 3.63 (m, 2H), 3.32 (s, 12H), 3.20 – 3.06 (m, 1H), 2.94 (s, 6H), 2.09

– 1.89 (m, 4H), 1.72 – 1.55 (m, 9H), 1.53 – 1.41 (m, 1H), 1.36 (s, 3H), 1.34 (s, 3H), 1.28 – 1.16 (m, 2H), 1.18 – 1.08 (m, 1H), 1.08 – 0.81 (m, 3H).

13C-NMR (126 MHz, DMSO-d6, 76a): δ 173.47, 172.88, 170.99, 167.64, 166.71, 160.09, 157.58, 152.11, 151.95, 148.63, 147.03, 143.17, 142.62, 135.82, 134.46, 133.27, 128.39, 126.87, 124.16, 123.20, 119.94, 112.21, 111.88, 108.97, 105.54, 102.14, 97.96, 88.51, 75.12, 65.91, 61.76, 60.96, 56.16, 55.47, 55.36, 54.88, 52.66, 51.68, 43.52, 40.71, 37.58, 33.69, 31.25, 30.62, 30.18, 29.91, 28.64, 27.08, 26.92, 25.78, 25.65, 25.53, 24.99, 24.57, 24.49, 23.16, 23.08.

HRMS (ESI): 76a calculated = 1135.53866 [M]+, found = 1135.54008 [M]+, err [ppm] = 1.25.

HRMS (ESI): 76b calculated = 1135.53866 [M]+, found = 1135.54043 [M]+, err [ppm] = 1.56.

HRMS (ESI): 76c calculated = 1135.53866 [M]+, found = 1135.53983 [M]+, err [ppm] = 1.03.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**76a**) = 8.37 min (99% Purity)

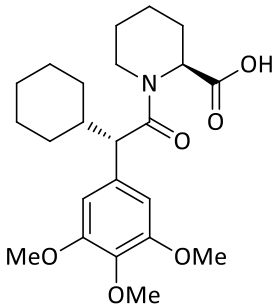
RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**76b**) = 7.85 min, 8.39 (34%, 66%)

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**76c**) = 7.75, 8.40 min (87%, 12%)

6.4. A/B ring derivatization through chalcone synthesis

6.4.1. Building blocks

(S)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylic acid (THE129)

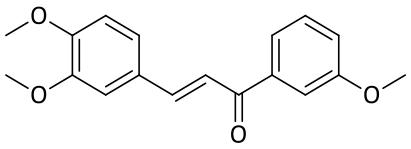


Chemical Formula: $C_{23}H_{33}NO_6$
Exact Mass: 419,23
Molecular Weight: 419,51

77

This precursor was kindly provided by my colleague Tim Heymann. For the synthesis see Jorgensen et al.[57]

(E)-3-(3,4-dimethoxyphenyl)-1-(3-methoxyphenyl)prop-2-en-1-one



Chemical Formula: $C_{18}H_{18}O_4$
Exact Mass: 298,12
Molecular Weight: 298,33

78

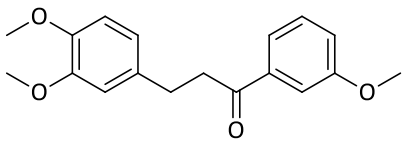
1-(3-methoxyphenyl)ethanon (4.5 g, 30 mmol, 1.0 eq) and 3,4-dimethoxybenzaldehyde (5 g, 30 mmol, 1 eq) are dissolved in 45 mL EtOH. The mixture is cooled to 0°C for 30 min, then cooled KOH (6.7 g, 120 mmol, 4 eq) dissolved in 30 mL H_2O is added dropwise over 30 min. The mixture is stirred under slowly rising temperature overnight. After complete conversion, the reaction mixture is cooled by adding ice and acidified with 6 M HCl to pH=1-2. Then 100 mL H_2O is added dropwise to precipitate the product. The precipitate is filtered, washed with H_2O and dried on the rotivap and under high vacuum. The pure product **78** is obtained as a yellow-beige solid.

Yield 9 g (quant.).

TLC (CH/EE, 2/1): R_f (**78**) = 0.51.

LC-MS (0-100% B, 19 min): t_R (**78**) = 11.28 min, m/z: calculated = 299.12 $[M+H]^+$, found = 299.15 $[M+H]^+$ (95% Purity)

3-(3,4-dimethoxyphenyl)-1-(3-methoxyphenyl)propan-1-one (MedChem17_JS_Zn)



Chemical Formula: $C_{18}H_{20}O_4$
Exact Mass: 300,14
Molecular Weight: 300,35

79

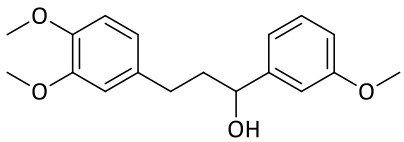
NH_4Ac (52 g, 670 mmol, 100.0 eq) is dissolved in 100 mL H_2O and added to a flask then **78** (2 g, 7 mmol, 1.0 eq) is dissolved in 200 mL EtOH and added. Zn powder (3.3 g, 50 mmol, 7.5 eq) is added in 5 portions in 15 min time steps. After complete addition, the mixture is filtered and washed with EtOH. The EtOH is removed on rotivap and the residual aqueous phase extracted with EE (3x). The combined organic layers are dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by silica column chromatography (CH/EE, 5/1). The pure product **79** is obtained as a beige-white solid.

Yield 0.52 g (26%).

TLC (CH/EE, 3/1): R_f (**79**) = 0.24.

LC-MS (0-100% B, 19 min): t_R (**79**) = 11.27 min, m/z: calculated = 301.14 $[M+H]^+$, found = 300.98 $[M+H]^+$ (95% Purity)

3-(3,4-dimethoxyphenyl)-1-(3-methoxyphenyl)propan-1-ol (AV485_rac)



Chemical Formula: $C_{18}H_{22}O_4$
Exact Mass: 302,15
Molecular Weight: 302,36

80

79 (50 mg, 0.17 mmol, 1.0 eq) is dissolved in 5 mL THF. $NaBH_4$ (13 mg, 0.33 mmol, 2.0 eq) is added and the reaction stirred at r.t. overnight. The mixture is quenched with 1 mL 3 M HCl. The THF is removed under reduced pressure and the aqueous phase diluted with H_2O, then extracted with DCM (3×10 mL) The crude product is purified by column chromatography (CH/EE, 3/1). The pure product **80** is obtained as a beige-white solid.

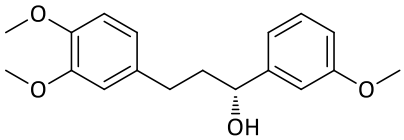
Yield 46 mg (92%).

TLC (CH/EE, 3/1): R_f (**80**) = 0.23.

LC-MS (0-100% B, 19 min): t_R (**80**) = 10.37 min, m/z: calculated = 320.18 $[M+NH_4]^+$, found = 319.99 $[M+NH_4]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**80**) = 13.25 + 13.89 min (*er* = 49.89/50.11).

(R)-3-(3,4-dimethoxyphenyl)-1-(3-methoxyphenyl)propan-1-ol (AV485)



Chemical Formula: $C_{18}H_{22}O_4$
Exact Mass: 302,15
Molecular Weight: 302,36

81

Dissolve *S*-CBS (9 mg, 0.03 mmol, 0.1 eq) in 1.1 mL dry THF and add to a flask under argon atmosphere. Add 20 µL (0.1 eq) of a 2 M BH_3*SMe_2 solution in THF. Dissolve **79** (100 mg, 0.33 mmol, 1.0 eq) in 800 µL dry THF and add to the catalyst. Then 250 µL (1.5 eq) of a 2 M BH_3*SMe_2 solution in THF is added dropwise in 1 h. After complete addition, the reaction is further stirred for 1.5 h, then stopped by the addition of MeOH. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 2/1). The pure product **81** is obtained as a white oil.

Yield 98 g (97%).

TLC (CH/EE, 2/1): R_f (**81**) = 0.27.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.74 – 9.63 (1H, m), 9.37 – 9.32 (2H, m), 9.28 – 9.19 (2H, m), 9.19 – 9.11 (2H, m), 7.09 (1H, dd, J=7.7, 5.3 Hz), 6.28 (3H, s), 6.27 (3H, s), 6.24 (3H, s), 5.22 – 4.99 (2H, m), 4.60 – 4.37 (2H, m)

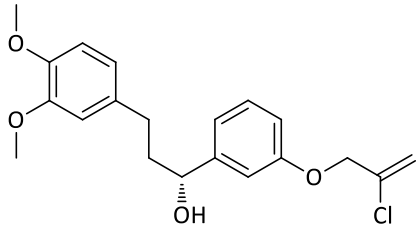
^{13}C-NMR (75 MHz, $CDCl_3$): δ 159.97, 149.05, 147.40, 146.50, 134.54, 129.66, 120.36, 118.37, 113.17, 112.02, 111.62, 111.52, 73.97, 56.10, 55.38, 40.70, 31.79.

LC-MS (30-100% B, 19 min): t_R (**81**) = 8.29 min, m/z: calculated = 320.18 $[M+NH_4]^+$, found = 320.34 $[M+NH_4]^+$.

RP-HPLC (30 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**81**) = 8.37min (99% Purity).

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**81**) = 13.69 + 15.48 min (*er* = 2.52/97.48).

(R)-1-(3-((2-chloroallyl)oxy)phenyl)-3-(3,4-dimethoxyphenyl)propan-1-ol (AV245)



Chemical Formula: $C_{20}H_{23}ClO_4$
Exact Mass: 362,13
Molecular Weight: 362,85

82

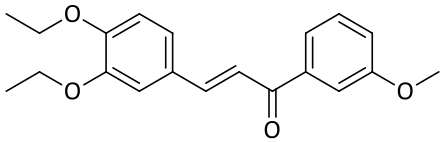
7 (1.9 g, 6.6 mmol, 1.0 eq) is dissolved in 25 mL MeCN. K2CO3 (1.1 g, 7.9 mmol, 1.2 eq) and 2,3-dichloro-1-propene (900 µL, 6.6 mmol, 1.5 eq) are added. The reaction is stirred at 50°C overnight. The mixture is filtered over celite and washed with MeCN. The solvent is removed and the crude product purified by silica column chromatography (CH/EE, 2/1) and **82** obtained as a colorless oil.

Yield 2.12 g (89%).

TLC (CH/EE, 2/1, v/v): R_f (**82**) = 0.35.

LC-MS (50-100% B, 19 min): t_R (**82**) = 12.23min, m/z: calculated = 345.13 $[M-OH]^+$, found = 345.34 $[M-OH]^+$.

(E)-3-(3,4-diethoxyphenyl)-1-(3-methoxyphenyl)prop-2-en-1-one (MedChem17_RR_CS)



Chemical Formula: $C_{20}H_{22}O_4$
Exact Mass: 326,15
Molecular Weight: 326,39

83

3,4-diethoxybenzaldehyde (5.0 g, 26 mmol, 1.0 eq) and 3-methoxyacetophenone (3.84 g, 26 mmol, 1 eq) are dissolved in 40 mL EtOH. The mixture is cooled to 0°C for 15 min, then cooled KOH (5.75 g, 100 mmol, 4 eq) dissolved in 25 mL H_2O added. The reaction is stirred overnight under slowly rising temperature. The mixture is diluted with H_2O (50 mL) and extracted with EE (3×100 mL). The combined organic phases are washed with brine (1×50 mL), dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by manual column chromatography (CH/EE, 5/1) and **83** obtained as a yellow oil.

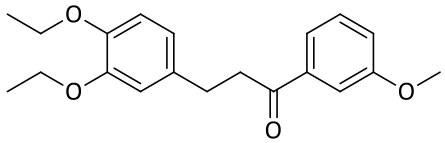
Yield 8.59 g (97%).

TLC (CH/EE, 5/1, v/v): R_f (**83**) = 0.34.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.68 (d, J = 15.6 Hz, 1H), 7.52 (dt, J = 1.3, 7.7 Hz, 1H), 7.49 – 7.45 (m, 1H), 7.36 – 7.29 (m, 2H), 7.16 – 7.09 (m, 2H), 7.04 (ddd, J = 1.0, 2.7, 8.2 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 4.07 (qd, J = 3.8, 7.0 Hz, 4H), 3.80 (s, 3H), 1.41 (td, J = 3.0, 7.0 Hz, 6H).

LC-MS (50-100% B, 19 min): t_R (**83**) = 12.23min, m/z: calculated = 327.15 $[M+H]^+$, found = 327.21 $[M+H]^+$.

3-(3,4-diethoxyphenyl)-1-(3-methoxyphenyl)propan-1-one (MedChem17_RR_Zn)



Chemical Formula: $C_{20}H_{24}O_4$
Exact Mass: 328,17
Molecular Weight: 328,40

84

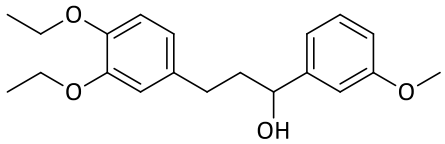
Zn powder (650 mg, 10 mmol, 10.0 eq) and NH_4OAc (10 g, 130 mmol, 130.0 eq) are added to a flask and suspended in 100 mL EtOH and 20 mL H_2O. **83** (430 mg, 1 mmol, 1.0 eq) is dissolved in 30 mL EtOH and added dropwise to the vigorously stirring suspension in 30 min. After complete addition, the mixture is filtered and washed with EtOH. The EtOH is partially removed under reduced pressure, then diluted with 100 mL H_2O and the mixture extracted with EE (3×50 mL). The combined organic phases are dried with $MgSO_4$, then filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 7/1). The pure product **84** is obtained as a beige solid.

Yield 380 mg (88%).

TLC (CH/EE, 7/1, v/v): R_f (**84**) = 0.24.

LC-MS (50-100% B, 19 min): t_R (**84**) = 12.04 min, m/z: calculated = 329.17 $[M+H]^+$, found = 328.94 $[M+H]^+$.

3-(3,4-diethoxyphenyl)-1-(3-methoxyphenyl)propan-1-ol (MedChem17_RR_rac)



Chemical Formula: $C_{20}H_{26}O_4$
Exact Mass: 330,18
Molecular Weight: 330,42

85

84 (50 mg, 0.16 mmol, 1.0 eq) is dissolved in 5 mL iPrOH. $NaBH_4$ (13 mg, 0.33 mmol, 2 eq) is added and the reaction stirred overnight. The mixture is quenched with 5 mL 0.5 M HCl. The aqueous phase is extracted with EE (3×10 mL). The crude product is purified by column chromatography (CH/EE, 3/1). The pure product **85** is obtained as beige-white oil.

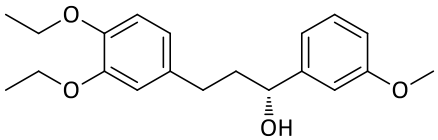
Yield 44 mg (87%).

TLC (CH/EE, 3/1): R_f (**85**) = 0.37.

LC-MS (50-100% B, 19 min): t_R (**85**) = 9.40 min, m/z: calculated = 313.18 $[M-OH]^+$, found = 312.99 $[M-OH]^+$.

Chiral-HPLC (5% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**85**) = 25.18 min, 28.37 min.

(R)-3-(3,4-diethoxyphenyl)-1-(3-methoxyphenyl)propan-1-ol (MedChem17_RR_chiral)



Chemical Formula: $C_{20}H_{26}O_4$
Exact Mass: 330,18
Molecular Weight: 330,42

86

84 (100 mg, 0.32 mmol, 1.0 eq) is dissolved in 9 mL dry THF and added to the flask under argon atmosphere. Then *S*-CBS (0.4 eq) is added and 1.8 eq borane complex in THF solution added dropwise within 1 h. The reaction is stirred overnight after full addition. The mixture is quenched with 5 mL MeOH and stirred for 1 h. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 3/1). The pure product **86** is obtained as a white oil.

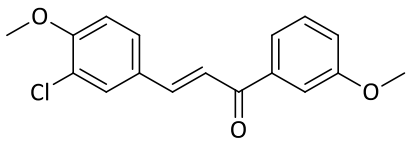
Yield 92 mg (92%).

TLC (CH/EE, 3/1): R_f (**86**) = 0.37.

LC-MS (50-100% B, 19 min): t_R (**86**) = 9.41 min, m/z: calculated = 313.18 $[M-OH]^+$, found = 312.99 $[M-OH]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**86**) = 28.80 min (*er* = 94.05/5.05).

(E)-3-(3-chloro-4-methoxyphenyl)-1-(3-methoxyphenyl)prop-2-en-1-one (MedChem17_SZ_CS)



Chemical Formula: $C_{17}H_{15}ClO_3$
Exact Mass: 302,07
Molecular Weight: 302,75

87

3-chloro-4-methoxybenzaldehyde (5.0 g, 29 mmol, 1.0 eq) and 3-methoxyacetophenone (4.40 g, 29 mmol, 1 eq) are dissolved in 40 mL EtOH. The mixture is cooled to 0°C for 15 min, then cooled KOH (6.60 g, 120 mmol, 4 eq) dissolved in 25 mL H_2O added. The reaction is stirred overnight under slowly rising temperatures. The mixture is diluted with H_2O (50 mL) and extracted with EE (3×100 mL). The combined organic phases are washed with brine (1×50 mL), dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by manual column chromatography (CH/EE, 5/1) and **87** obtained as a yellow oil.

Yield 5.39 g (61%).

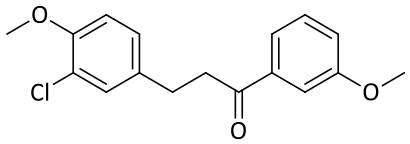
TLC (CH/EE, 5/1, v/v): R_f (**87**) = 0.58.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.40 (d, J = 15.7 Hz, 1H), 3.26 (d, J = 7.7 Hz, 1H), 3.23 – 3.14 (m, 2H), 3.12 – 3.02 (m, 2H), 2.89 – 2.77 (m, 2H), -0.38 (s, 3H), -0.45 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 189.99, 160.00, 155.38, 143.81, 139.48, 134.85, 130.67, 129.68, 125.04, 122.67, 121.48, 121.10, 119.36, 113.07, 111.56, 56.27, 55.56.

LC-MS (50-100% B, 19 min): t_R (**87**) = 12.48 min, m/z: calculated = 303.07 $[M+H]^+$, found = 303.16 $[M+H]^+$.

3-(3-chloro-4-methoxyphenyl)-1-(3-methoxyphenyl)propan-1-one (MedChem17_SZ_Zn)



Chemical Formula: $C_{17}H_{17}ClO_3$
Exact Mass: 304,09
Molecular Weight: 304,77

88

Zn powder (810 mg, 12 mmol, 7.50 eq) and NH_4OAc (13 g, 165 mmol, 100.0 eq) are added to a flask and suspended in 100 mL EtOH and 20 mL H_2O. **87** (500 mg, 1.66 mmol, 1.0 eq) is dissolved in 30 mL

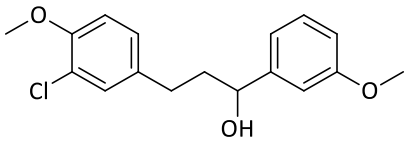
EtOH and added dropwise to the vigorously stirring suspension in 30 min. After complete addition, the mixture is filtered and washed with EtOH. The EtOH is partially removed under reduced pressure, then diluted with 100 mL H_2O and the mixture extracted with EE (3×50 mL). The combined organic phases are dried with $MgSO_4$, then filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 7/1). The pure product **88** is obtained as a beige solid.

Yield 293 mg (58%).

TLC (CH/EE, 7/1, v/v): R_f (**88**) = 0.24.

LC-MS (30-100% B, 19 min): t_R (**88**) = 10.67 min, m/z: calculated = 305.09 $[M+H]^+$, found = 305.00 $[M+H]^+$.

3-(3-chloro-4-methoxyphenyl)-1-(3-methoxyphenyl)propan-1-ol (MedChem17_SZ_rac)



Chemical Formula: $C_{17}H_{19}ClO_3$
Exact Mass: 306,10
Molecular Weight: 306,78

89

88 (60 mg, 0.18 mmol, 1.0 eq) is dissolved in 5 mL iPrOH. $NaBH_4$ (14 mg, 0.47 mmol, 2.0 eq) is added and the reaction stirred overnight. The mixture is quenched with 5 mL 0.5 M HCl. The aqueous phase is extracted with EE (3×10 mL). The crude product is purified by column chromatography (CH/EE, 3/1). The pure product **89** is obtained as beige-white oil.

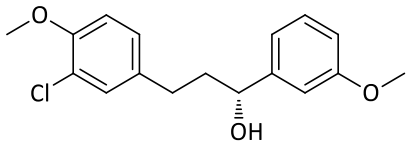
Yield 47 mg (83%).

TLC (CH/EE, 3/1): R_f (**89**) = 0.31.

LC-MS (0-100% B, 19 min): t_R (**89**) = 9.61 min, m/z: calculated = 289.10 $[M-OH]^+$, found = 289.03 $[M-OH]^+$.

Chiral-HPLC (10% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**89**) = 12.15 min, 12.79 min.

(R)-3-(3-chloro-4-methoxyphenyl)-1-(3-methoxyphenyl)propan-1-ol (MedChem17_SZ_chiral)



Chemical Formula: $C_{17}H_{19}ClO_3$
Exact Mass: 306,10
Molecular Weight: 306,78

90

88 (100 mg, 0.32 mmol, 1.0 eq) is dissolved in 9 mL dry THF and added to the flask under argon atmosphere. Then *S*-CBS (0.4 eq) is added. Subsequently, 1.8 eq borane complex in THF solution are added dropwise within 1 h. The reaction is stirred overnight after full addition. The mixture is quenched with 5 mL MeOH and stirred for 1 h. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 3/1). The pure product **90** is obtained as a white oil.

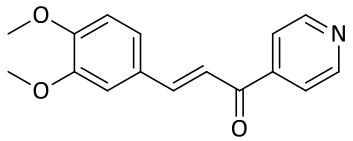
Yield 100 mg (quant.).

TLC (CH/EE, 3/1): R_f (**90**) = 0.31.

LC-MS (0-100% B, 19 min): t_R (**90**) = 9.68 min, m/z: calculated = 289.10 $[M-OH]^+$, found = 289.10 $[M-OH]^+$.

Chiral-HPLC (10% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**90**) = 12.27 min (*er* = 92.90/7.10).

(E)-3-(3,4-dimethoxyphenyl)-1-(pyridin-4-yl)prop-2-en-1-one (AV430/AV432/AV444)



Chemical Formula: $C_{16}H_{15}NO_3$
Exact Mass: 269,11
Molecular Weight: 269,30

91

4-Acetylpyridine (5.0 g, 0.04 mol, 1.0 eq) and 3,4-dimethoxybenzaldehyde (6.86 g, 0.04 mol, 1 eq) are dissolved in 60 mL MeOH. The mixture is cooled to 0°C for 15 min, then cooled KOH (2.78 g, 0.05 mol, 1.2 eq) dissolved in 20 mL H_2O added. The mixture is checked every 10 min by TLC and the reaction stopped after 40 min. The reaction mixture is diluted with sat. $NH_4Cl_{(aq)}$ (50 mL), brine (50 mL) and H_2O (50 mL) and extracted with EE (3×100 mL). The combined organic phases are washed with brine

(1×50 mL), dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by manual column chromatography (CH/EE, 1/1 + 1% TEA) and **91** obtained as yellow oil.

Yield 1.56 g (14%).

TLC (CH/EE, 1/1 + 1% TEA, v/v): R_f (**91**) = 0.22.

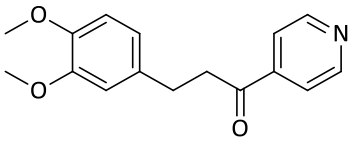
^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.79 – 8.74 (m, 2H), 7.76 – 7.68 (m, 3H), 7.24 – 7.08 (m, 3H), 6.86 (d, J = 8.3 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 189.84, 152.11, 150.74, 149.44, 147.04, 144.82, 127.35, 123.82, 121.57, 119.21, 111.26, 110.27, 56.09, 56.05.

LC-MS (30-100% B, 19 min): t_R (**91**) = 5.43 min, m/z: calculated = 270.11 $[M+H]^+$,
found = 270.21 $[M+H]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**91**) = 8.72 min (99% Purity).

3-(3,4-dimethoxyphenyl)-1-(pyridin-4-yl)propan-1-one (AV502/AV505/AV507)



Chemical Formula: $C_{16}H_{17}NO_3$
Exact Mass: 271,12
Molecular Weight: 271,31

92

Zn powder (2.43 g, 40 mmol, 10.0 eq) and NH_4Cl (1.99 g, 40 mmol, 10.0 eq) are added to a flask and suspended in 20 mL MeOH. **91** (1.0 mg, 4 mmol, 1.0 eq) is dissolved in 50 mL MeOH and added dropwise to the vigorously stirring suspension in 1 h. After complete addition, the mixture is filtered and washed with MeOH. 100 mL H_2O is added to the filtrate and adjusted to pH = 13 with a 10% aqueous NaOH solution. The mixture is extracted with EE (3×50 mL), the combined organic phases dried with $MgSO_4$, then filtered and the solvent removed under reduced pressure. The crude (380 mg) is dissolved in 10 mL DCM and Dess-Martin-Periodinan (650 mg, 1.4 mmol, 1.1 eq) is added. The reaction is stirred at r.t. overnight. 30 mL H_2O is added to the reaction and adjusted to pH = 13 with a 10% aqueous NaOH solution. The mixture is extracted with DCM (3×50 mL). The combined organic phases dried with $MgSO_4$, then filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 2/1). The pure product **92** is obtained as a beige solid.

Yield 90 mg (9%).

TLC (CH/EE, 2/1, v/v): R_f (**92**) = 0.20.

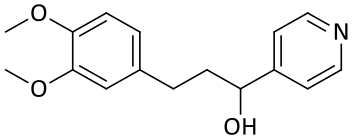
^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.77 – 8.69 (m, 2H), 7.71 – 7.60 (m, 2H), 6.74 – 6.70 (m, 2H), 6.69 (d, *J* = 2.0 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.21 (t, *J* = 7.5 Hz, 2H), 2.95 (t, *J* = 7.4 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 198.64, 150.66, 150.35, 123.78, 121.69, 121.12, 120.19, 111.87, 111.46, 111.22, 55.95, 55.88, 40.98, 29.36.

LC-MS (0-100% B, 19 min): t_R (**92**) = 9.48 min, m/z: calculated = 272.12 $[M+H]^+$, found = 272.21 $[M+H]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**92**) = 8.58 min (99% Purity).

3-(3,4-dimethoxyphenyl)-1-(pyridin-4-yl)propan-1-ol (AV522/AV524)



Chemical Formula: $C_{16}H_{19}NO_3$
Exact Mass: 273,14
Molecular Weight: 273,33

93

92 (60 mg, 0.22 mmol, 1.0 eq) is dissolved in 5 mL iPrOH. $NaBH_4$ (30 mg, 0.79 mmol, 3.6 eq) is added and the reaction stirred at 70°C overnight. The mixture is cooled to r.t. and quenched with 10 mL 3 M HCl. The aqueous phase is adjusted to pH = 13 with 10% $NaOH_{(aq)}$ solution, then extracted with DCM (3×10 mL). The crude product is purified by column chromatography (CH/EE, 1/4). The pure product **93** is obtained as beige-white oil.

Yield 20 mg (33%).

TLC (CH/EE, 1/4): R_f (**93**) = 0.20.

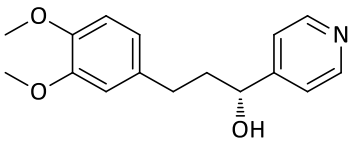
^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.60 – 8.46 (m, 2H), 7.27 (dd, *J* = 2.0, 6.6 Hz, 2H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.74 – 6.66 (m, 2H), 4.70 (dd, *J* = 4.8, 8.0 Hz, 1H), 3.85 (s, 3H), 3.85 (s, 3H), 2.76 – 2.63 (m, 2H), 2.10 – 1.94 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 153.99, 149.81, 149.12, 147.54, 133.96, 121.01, 120.37, 111.93, 111.54, 72.30, 56.09, 56.00, 40.64, 31.48.

LC-MS (0-100% B, 19 min): t_R (**93**) = 6.10 min, m/z: calculated = 274.14 $[M+H]^+$, found = 274.26 $[M+H]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**93**) = 23.89 min, 24.24 min.

(R)-3-(3,4-dimethoxyphenyl)-1-(pyridin-4-yl)propan-1-ol (AV529)



Chemical Formula: $C_{16}H_{19}NO_3$
Exact Mass: 273,14
Molecular Weight: 273,33

94

93 (30 mg, 0.11 mmol, 1.0 eq) is dissolved in 5 mL iPrOH. Then KOtBu (110 µL, 0.11 mmol, 1 eq) is added and the solution is sparged with argon for 5 min. $RuCl_2$[(S)-(DM-SEGPHOS)][(S)-DAIPEN] (2.7 mg, 0.002 mmol, 0.02 eq) is added and the solution sparged with H_2 for 5 min, then the reaction stirred at 1 bar H_2 at r.t. overnight. After full conversion, the solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 1/4). The pure product **94** is obtained as a white oil.

Yield 14 mg (47%).

TLC (CH/EE, 1/4): R_f (**94**) = 0.21.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.56 – 8.49 (m, 2H), 7.28 – 7.26 (m, 2H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.75 – 6.69 (m, 2H), 4.71 (dd, *J* = 4.8, 7.9 Hz, 1H), 3.85 (s, 4H), 3.85 (s, 5H), 2.77 – 2.63 (m, 2H), 2.10 – 1.90 (m, 2H).

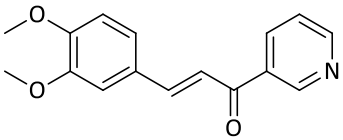
^{13}C-NMR (126 MHz, $CDCl_3$): δ 153.97, 149.82, 149.11, 147.54, 147.54, 133.96, 121.00, 120.36, 111.93, 111.54, 72.30, 56.09, 56.00, 40.64, 31.48.

LC-MS (0-100% B, 19 min): t_R (**94**) = 6.10 min, m/z: calculated = 274.14 $[M+H]^+$,
found = 274.23 $[M+H]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**94**) = 6.39 min (99% Purity).

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**94**) = 22.65 min (>99%).

(E)-3-(3,4-dimethoxyphenyl)-1-(pyridin-3-yl)prop-2-en-1-one (AV481/AV482/AV486)



Chemical Formula: $C_{16}H_{15}NO_3$
Exact Mass: 269,11
Molecular Weight: 269,30

95

3,4-Dimethoxybenzaldehyde (5.0 g, 0.03 mol, 1.0 eq) and 3-acetylpyridine (3.65 g, 0.03 mol, 1 eq) are dissolved in 50 mL MeOH. The mixture is cooled to 0°C for 20 min, then cooled NaOH (1.32 g, 0.05 mol, 1.1 eq) dissolved in 30 mL H_2O is added slowly in 2 min. The mixture is checked every 5 min by TLC and the reaction stopped after 20 min when side reaction is observed. The reaction mixture is diluted with sat. $NH_4Cl_{(aq)}$ (50 mL), brine (50 mL) and H_2O (50 mL) and extracted with EE (3×100 mL). The combined organic phases are washed with brine (1×50 mL), dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is crystallized by dissolving in 10 mL EtOH, 10 mL MeOH and 50 mL EE and the addition of 1.5 mL conc. HCl under stirring. The mixture is kept in the freezer (-20°C) overnight. The crystals are filtered and washed with cold EE and **95** obtained as yellow crystals.

Yield 1.52 g (19%).

TLC (CH/EE, 1/1, v/v): R_f (**95**) = 0.42.

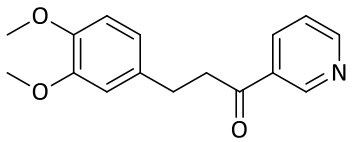
^{1}H-NMR (300 MHz, MeOD): δ 9.32 (dd, *J* = 0.9, 2.3 Hz, 1H), 8.85 (dd, *J* = 1.7, 5.0 Hz, 1H), 8.64 (ddd, *J* = 1.6, 2.2, 8.0 Hz, 1H), 7.89 (d, *J* = 15.5 Hz, 1H), 7.80 – 7.67 (m, 2H), 7.51 (dd, *J* = 2.0, 5.6 Hz, 1H), 7.41 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 4.00 (d, *J* = 2.9 Hz, 3H), 3.96 (d, *J* = 1.0 Hz, 3H).

^{13}C-NMR (75 MHz, MeOD): δ 190.04, 153.61, 152.56, 150.87, 149.51, 147.96, 138.84, 125.77, 125.50, 120.04, 112.68, 112.08, 56.64, 56.48.

LC-MS (0-100% B, 19 min): t_R (**95**) = 9.61 min, m/z: calculated = 270.11 $[M+H]^+$,
found = 270.20 $[M+H]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**95**) = 8.67 min (90% Purity).

3-(3,4-dimethoxyphenyl)-1-(pyridin-3-yl)propan-1-one (AV498)



Chemical Formula: $C_{16}H_{17}NO_3$
Exact Mass: 271,12
Molecular Weight: 271,31

96

Zn powder (2.43 g, 40 mmol, 10.0 eq) and NH_4Cl (1.99 g, 40 mmol, 10.0 eq) are added to a flask and suspended in 20 mL MeOH. **91** (1.0 mg, 4 mmol, 1.0 eq) is dissolved in 100 mL MeOH and added dropwise to the vigorously stirring suspension in 25 min. After complete addition, the mixture is filtered and washed with MeOH. 100 mL H_2O is added to the filtrate and adjusted to pH = 13 with a 10% aqueous NaOH solution. The mixture is extracted with EE (3×50 mL), the combined organic phases are dried with $MgSO_4$, then filtered and the solvent removed under reduced pressure. The crude

product is purified by column chromatography (CH/EE, 1/1). The pure product **96** is obtained as a beige solid.

Yield 250 mg (25%).

TLC (CH/EE, 1/1, v/v): R_f (**96**) = 0.25.

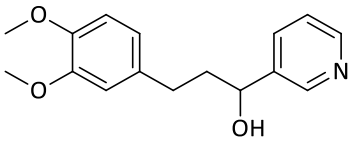
^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.12 – 9.07 (m, 1H), 8.70 (dd, *J* = 1.6, 4.8 Hz, 1H), 8.14 (dt, *J* = 1.9, 8.0 Hz, 1H), 7.38 – 7.29 (m, 1H), 6.77 – 6.66 (m, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.23 (t, *J* = 7.5 Hz, 2H), 2.97 (t, *J* = 7.5 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 198.31, 153.63, 149.74, 149.14, 147.71, 135.45, 133.50, 132.26, 123.78, 120.35, 112.01, 111.59, 56.09, 41.09, 29.66.

LC-MS (0-100% B, 19 min): t_R (**96**) = 9.52 min, m/z: calculated = 272.12 $[M+H]^+$, found = 272.43 $[M+H]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**96**) = 8.23 min (99% Purity).

3-(3,4-dimethoxyphenyl)-1-(pyridin-3-yl)propan-1-ol (AV514)



Chemical Formula: $C_{16}H_{19}NO_3$
Exact Mass: 273,14
Molecular Weight: 273,33

97

96 (20 mg, 0.07 mmol, 1.0 eq) is dissolved in 2 mL iPrOH. $NaBH_4$ (3 mg, 0.07 mmol, 1 eq) is added and the reaction stirred at r.t. overnight. The mixture is quenched with MeOH. The aqueous phase is adjusted to pH = 13 with 10% $NaOH_{(aq)}$ solution, then extracted with DCM (3×10 mL). The crude product is purified by column chromatography (CH/EE, 1/1). The pure product **97** is obtained as beige-white oil.

Yield 17 mg (85%).

TLC (CH/EE, 1/1): R_f (**97**) = 0.15.

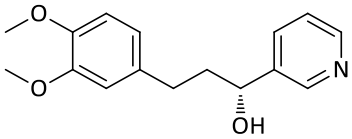
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.55 (d, *J* = 2.3 Hz, 1H), 8.50 (dd, *J* = 1.7, 4.8 Hz, 1H), 7.71 (dt, *J* = 2.0, 7.9 Hz, 1H), 7.28 (ddd, *J* = 0.9, 4.9, 7.9 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.75 – 6.68 (m, 2H), 4.74 (dd, *J* = 5.1, 8.0 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.78 – 2.59 (m, 2H), 2.19 – 1.95 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 149.06, 147.97, 147.53, 140.07, 133.98, 133.79, 123.70, 120.36, 111.91, 111.54, 71.64, 56.10, 56.01, 40.77, 31.64, 29.85.

LC-MS (0-100% B, 19 min): t_R (**97**) = 6.17min, m/z: calculated = 274.14 $[M+H]^+$, found = 274.23 $[M+H]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**97**) = 15.54 min, 16.22 min.

(R)-3-(3,4-dimethoxyphenyl)-1-(pyridin-3-yl)propan-1-ol (AV528)



Chemical Formula: $C_{16}H_{19}NO_3$
Exact Mass: 273,14
Molecular Weight: 273,33

98

96 (30 mg, 0.11 mmol, 1.0 eq) is dissolved in 5 mL iPrOH. Then KOtBu (110 µL, 0.11 mmol, 1 eq) is added and the solution is sparged with argon for 5 min. $RuCl_2$[(S)-(DM-SEGPHOS)][(S)-DAIPEN] (4 mg, 0.003 mmol, 0.03 eq) is added and the solution sparged with H_2 for 5 min, then the reaction stirred at 1 bar H_2 at r.t. overnight. After full conversion, the solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 1/1). The pure product **98** is obtained as a white oil.

Yield 27 mg (90%).

TLC (EE): R_f (**94**) = 0.47.

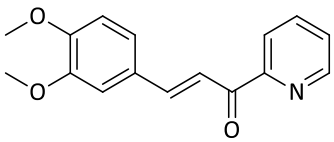
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.50 (d, *J* = 2.2 Hz, 1H), 8.45 (dd, *J* = 1.7, 4.8 Hz, 1H), 7.70 (dt, *J* = 1.9, 7.8 Hz, 1H), 7.29 – 7.21 (m, 1H), 6.77 (s, 2H), 6.74 – 6.65 (m, 2H), 4.72 (dd, *J* = 5.1, 8.0 Hz, 1H), 3.84 (s, 3H), 3.84 (s, 3H), 2.77 – 2.56 (m, 2H), 2.17 – 1.93 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 149.07, 148.85, 147.87, 147.47, 140.26, 134.04, 133.83, 123.66, 120.34, 111.91, 111.51, 71.47, 56.07, 55.98, 40.78, 31.63, 29.82.

LC-MS (0-100% B, 19 min): t_R (**94**) = 6.18 min, m/z: calculated = 274.14 $[M+H]^+$,
found = 274.22 $[M+H]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**94**) = 16.20 min (>99%).

(E)-3-(3,4-dimethoxyphenyl)-1-(pyridin-1-yl)prop-2-en-1-one (MedChem19_17)



Chemical Formula: $C_{16}H_{15}NO_3$
Exact Mass: 269,11
Molecular Weight: 269,30

99

3,4-Dimethoxybenzaldehyde (8.23 g, 0.05 mol, 1.0 eq) and 2-Acetylpyridine (6.00 g, 0.05 mol, 1 eq) are dissolved in 180 mL EtOH. The mixture is cooled to 0°C for 20 min, then cooled KOH (11.13 g, 0.2 mol, 1.1 eq) dissolved in 120 mL H_2O is added slowly in 2 min. The yellow precipitate is filtered, washed with H_2O, dissolved in DCM, dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The yellow solid **99** is further used as crude.

Yield 11.11 g (83%).

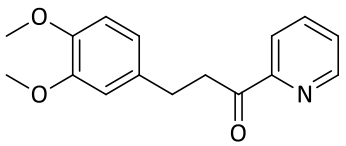
TLC (CH/EE, 1/1, v/v): R_f (**99**) = 0.35.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.72 (ddd, *J* = 0.9, 1.8, 4.8 Hz, 1H), 8.19 – 8.09 (m, 2H), 7.96 – 7.80 (m, 2H), 7.46 (ddd, *J* = 1.3, 4.7, 7.6 Hz, 1H), 7.32 – 7.23 (m, 2H), 6.88 (d, *J* = 8.1 Hz, 1H), 3.95 (s, 3H), 3.91 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 189.38, 154.56, 151.65, 149.33, 148.84, 145.18, 137.12, 128.32, 126.84, 124.03, 123.01, 118.71, 111.14, 110.33, 56.12, 56.08.

LC-MS (0-100% B, 19 min): t_R (**99**) = 11.27 min, m/z: calculated = 270.25 $[M+H]^+$, found = 270.15 $[M+H]^+$.

3-(3,4-dimethoxyphenyl)-1-(pyridin-2-yl)propan-1-one (AV495/AV509/AV646)



Chemical Formula: $C_{16}H_{17}NO_3$
Exact Mass: 271,12
Molecular Weight: 271,31

100

99 (1 g, 4 mmol, 1.0 eq) is dissolved in 50 mL THF and the solution sparged with argon for 5 min. 10 w% Pd/C (0.2 g, 0.05 eq) is added and the slurry sparged with H_2 for 5 min, then stirred under 1 atm H_2 for 2.5 h. After complete conversion, the mixture is filtered and washed with THF. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 2/1). The pure product **100** is obtained as a beige solid.

Yield 530 mg (52%).

TLC (CH/EE, 1/1, v/v): R_f (**100**) = 0.25.

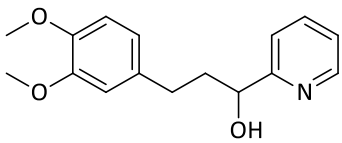
^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.60 (t, *J* = 3.4 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.76 (dt, *J* = 4.5, 9.1 Hz, 1H), 7.44 – 7.31 (m, 1H), 6.73 (d, *J* = 2.8 Hz, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.48 (td, *J* = 2.2, 8.0 Hz, 2H), 2.95 (t, *J* = 7.2 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 201.08, 153.38, 148.92, 148.84, 147.30, 136.86, 134.07, 127.08, 121.79, 120.27, 111.92, 111.31, 55.93, 55.82, 39.54, 29.54.

LC-MS (0-100% B, 19 min): t_R (**100**) = 10.95 min, m/z: calculated = 272.12 $[M+H]^+$, found = 272.03 $[M+H]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**100**) = 11.28 min (98% Purity).

3-(3,4-dimethoxyphenyl)-1-(pyridin-2-yl)propan-1-ol (AV515/AV523/AV525/AV653/AV667)



Chemical Formula: $C_{16}H_{19}NO_3$
Exact Mass: 273,14
Molecular Weight: 273,33

101

100 (50 mg, 0.07 mmol, 1.0 eq) is dissolved in 2 mL iPrOH. $NaBH_4$ (30 mg, 0.70 mmol, 10 eq) is added and the reaction stirred at 70°C overnight. The mixture is diluted with 10 mL H_2O and quenched with a few drops conc. HCl. The aqueous phase is adjusted to pH = 13 with 10% $NaOH_{(aq)}$ solution, then extracted with DCM (3×10 mL). The crude product is purified by column chromatography (CH/EE, 1/1). The pure product **101** is obtained as beige-white oil.

Yield 20 mg (40%).

TLC (CH/EE, 1/1): R_f (**101**) = 0.15.

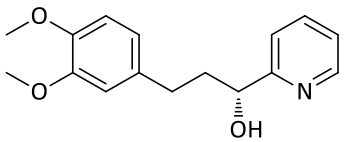
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.60 – 8.54 (m, 1H), 7.69 (td, *J* = 1.6, 7.6 Hz, 1H), 7.31 – 7.25 (m, 1H), 7.22 (ddd, *J* = 1.0, 4.9, 7.6 Hz, 1H), 6.83 – 6.72 (m, 3H), 4.79 (dd, *J* = 3.9, 8.2 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.83 – 2.69 (m, 2H), 2.19 – 2.10 (m, 1H), 1.99 (dddd, *J* = 5.7, 8.5, 9.5, 13.8 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 149.06, 147.97, 147.53, 140.07, 133.98, 133.79, 123.70, 120.36, 111.91, 111.54, 71.64, 56.10, 56.01, 40.77, 31.64, 29.85.

LC-MS (0-100% B, 19 min): t_R (**101**) = 6.26 min, m/z: calculated = 274.14 $[M+H]^+$, found = 274.15 $[M+H]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**101**) = 9.25 min, 9.43 min.

(R)-3-(3,4-dimethoxyphenyl)-1-(pyridin-2-yl)propan-1-ol (AV527)



Chemical Formula: $C_{16}H_{19}NO_3$
Exact Mass: 273,14
Molecular Weight: 273,33

102

100 (20 mg, 0.07 mmol, 1.0 eq) is dissolved in 5 mL iPrOH. Then K_2CO_3 (15 mg, 0.11 mmol, 1.5 eq) is added and the solution is sparged with argon for 5 min. $RuCl_2$[(*S*)-(DM-SEGPHOS)][(*S*)-DAIPEN] (2 mg, 0.002 mmol, 0.02 eq) is added and the solution is added to an autoclave. The autoclave is flushed with H_2 (3x) and the reaction is stirred at 10 bar H_2 at r.t. overnight. After full conversion, the solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 1/1). The pure product **102** is obtained as a white oil.

Yield 15 mg (75%).

TLC (CH/EE, 1/1): R_f (**102**) = 0.24.

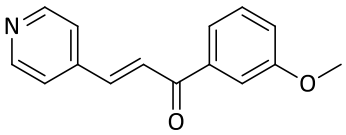
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.57 (dt, *J* = 1.3, 4.9 Hz, 1H), 7.70 (td, *J* = 1.7, 7.6 Hz, 1H), 7.28 (d, *J* = 6.0 Hz, 1H), 7.22 (ddd, *J* = 1.1, 4.9, 7.6 Hz, 1H), 6.79 (ddd, *J* = 2.5, 6.0, 17.0 Hz, 3H), 4.80 (dd, *J* = 3.9, 8.2 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.83 – 2.68 (m, 2H), 2.20 – 1.91 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 162.03, 148.99, 148.33, 147.31, 136.81, 134.80, 122.45, 120.40, 112.06, 111.46, 72.10, 56.08, 55.96, 40.71, 31.37, 29.83.

LC-MS (0-100% B, 19 min): t_R (**102**) = 6.23 min, m/z: calculated = 274.14 $[M+H]^+$, found = 274.17 $[M+H]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**102**) = 9.23 min (*er* = 92.56/7.44).

(E)-1-(3-methoxyphenyl)-3-(pyridin-4-yl)prop-2-en-1-one (AV431/AV434/AV435/AV436/AV443)



Chemical Formula: $C_{15}H_{13}NO_2$
Exact Mass: 239,09
Molecular Weight: 239,27

103

Pyridine-4-carboxaldehyde (14.02 g, 0.09 mol, 2 eq) is dissolved in 40 mL MeOH. The solution is cooled to 0°C for 15 min, then cooled KOH (10.48 g, 0.19 mol, 4.0 eq) dissolved in 30 mL H_2O is added. Subsequently a solution of 3-methoxyacetophenone (5.0 g, 0.05 mol, 1.0 eq) in 20 mL MeOH is added dropwise in 10 min. The mixture is checked every 5 min by TLC and the reaction stopped after 20 min when side reaction is observed. The reaction mixture is diluted with sat. $NH_4Cl_{(aq)}$ (100 mL), brine (50 mL) and extracted with EE (3×100 mL). The combined organic phases are washed with brine (1×50 mL), dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is enriched by manual column chromatography (EE + 3% TEA), then crystallized in iPrOH/H2O – 20/1. Compound **103** is obtained as yellow crystals.

Yield 1 g (9%).

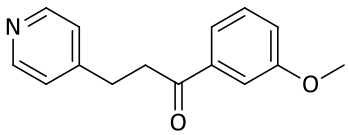
TLC (EE + 3% TEA): R_f (**103**) = 0.42.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.70 – 8.64 (m, 2H), 7.70 – 7.60 (m, 2H), 7.58 (ddd, *J* = 0.9, 1.6, 7.7 Hz, 1H), 7.53 (dd, *J* = 1.5, 2.7 Hz, 1H), 7.48 – 7.44 (m, 2H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.15 (ddd, *J* = 0.9, 2.7, 8.2 Hz, 1H), 3.87 (s, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 189.60, 160.17, 150.64, 142.32, 141.55, 139.00, 129.86, 126.33, 122.15, 121.26, 119.93, 113.11, 55.63.

LC-MS (0-100% B, 19 min): t_R (**103**) = 9.61 min, m/z: calculated = 240.10 $[M+H]^+$, found = 240.25 $[M+H]^+$.

1-(3-methoxyphenyl)-3-(pyridin-4-yl)propan-1-one (AV437/AV445)



Chemical Formula: $C_{15}H_{15}NO_2$
Exact Mass: 241,11
Molecular Weight: 241,29

104

Zn powder (1.34 g, 20 mmol, 10.0 eq) and NH_4Cl (1.10 g, 20 mmol, 10.0 eq) are added to a flask and suspended in 10 mL MeOH. **103** (490 mg, 2 mmol, 1.0 eq) is dissolved in 10 mL MeOH and added dropwise to the vigorously stirring suspension in 10 min. After complete addition, the mixture is filtered and washed with MeOH. 50 mL H_2O is added to the filtrate and adjusted to pH = 13 with a 10% aqueous NaOH solution. The mixture is extracted with EE (3×50 mL), the combined organic phases dried with $MgSO_4$, then filtered and the solvent removed under reduced pressure. The crude is purified by column chromatography (EE). The pure product **104** is obtained as a beige solid.

Yield 320 mg (65%).

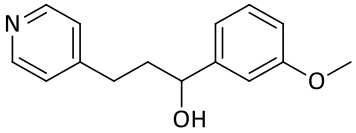
TLC (EE): R_f (**104**) = 0.27.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.52 – 8.48 (m, 2H), 7.52 (ddd, *J* = 1.0, 1.6, 7.6 Hz, 1H), 7.47 (dd, *J* = 1.5, 2.7 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.22 – 7.19 (m, 2H), 7.11 (ddd, *J* = 0.9, 2.7, 8.2 Hz, 1H), 3.85 (s, 3H), 3.36 – 3.23 (m, 2H), 3.08 (t, *J* = 7.4 Hz, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 197.94, 159.93, 150.84, 149.35, 137.92, 129.68, 124.01, 120.56, 119.74, 112.36, 55.46, 38.88, 29.27.

LC-MS (0-100% B, 19 min): t_R (**104**) = 8.90 min, m/z: calculated = 242.11 $[M+H]^+$, found = 242.25 $[M+H]^+$.

1-(3-methoxyphenyl)-3-(pyridin-4-yl)propan-1-ol (AV448)



Chemical Formula: $C_{15}H_{17}NO_2$
Exact Mass: 243,13
Molecular Weight: 243,30

105

104 (50 mg, 0.21 mmol, 1.0 eq) is dissolved in 2 mL iPrOH. $NaBH_4$ (8 mg, 0.21 mmol, 1 eq) is added and the reaction stirred at r.t. overnight. The mixture is diluted with 10 mL MeOH and quenched with a few drops conc. HCl. The solvent removed under reduced pressure. The crude product is purified by column chromatography (EE). The pure product **105** is obtained as a beige-white oil.

Yield 45 mg (90%).

TLC (EE): R_f (**105**) = 0.20.

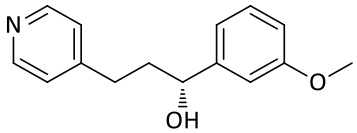
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.46 – 8.39 (m, 2H), 7.29 – 7.23 (m, 1H), 7.17 – 7.10 (m, 2H), 6.91 (dt, *J* = 1.5, 3.7 Hz, 2H), 6.82 (ddd, *J* = 1.1, 2.6, 8.2 Hz, 1H), 4.66 (dd, *J* = 5.1, 7.9 Hz, 1H), 3.80 (d, *J* = 1.1 Hz, 3H), 2.83 – 2.61 (m, 3H), 2.17 – 1.95 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 160.02, 151.55, 149.41, 146.21, 129.76, 124.16, 118.26, 113.25, 111.59, 73.51, 55.39, 39.33, 31.51.

LC-MS (0-100% B, 19 min): t_R (**105**) = 7.26 min, m/z: calculated = 244.13 $[M+H]^+$, found = 244.19 $[M+H]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**105**) = 13.98 min, 16.12 min.

(R)-1-(3-methoxyphenyl)-3-(pyridin-4-yl)propan-1-ol (AV447)



Chemical Formula: $C_{15}H_{17}NO_2$
Exact Mass: 243,13
Molecular Weight: 243,30

106

Dissolve S-CBS (34 mg, 0.12 mmol, 0.1 eq) in 4.1 mL dry THF and add to a flask under argon atmosphere. Add 60 µL (0.1 eq) of a 2 M BH_3*SMe_2 solution in THF. Dissolve **104** (300 mg, 1.24 mmol, 1.0 eq) in 3.1 mL dry THF and add to the catalyst. Then 933 µL (1.5 eq) of a 2 M BH_3*SMe_2 solution in THF is added dropwise in 1 h. After complete addition, the reaction is further stirred for 2 h, then stopped by the addition of MeOH. The formation of product-boron complexes is stopped by the addition of 1.1 eq conc. HCl and further stirring for 1 h. Finally, the mixture is diluted with sat. $NaHCO_3$ solution until basic and extracted with EE (3×20 mL). The combined organic phases are washed with brine (1×50 mL), dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (EE). The pure product **106** is obtained as a white oil.

Yield 217 mg (71%).

TLC (EE): R_f (**106**) = 0.21.

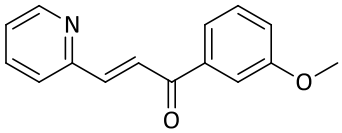
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.42 (dq, *J* = 1.7, 5.6 Hz, 2H), 7.28 – 7.22 (m, 1H), 7.13 – 7.09 (m, 2H), 6.93 – 6.87 (m, 2H), 6.82 (ddd, *J* = 1.1, 2.5, 8.2 Hz, 1H), 4.65 (dd, *J* = 5.1, 7.9 Hz, 1H), 3.80 (d, *J* = 1.3 Hz, 3H), 2.81 – 2.62 (m, 2H), 2.17 – 1.95 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 159.99, 151.49, 149.42, 129.72, 124.13, 118.27, 113.21, 111.57, 73.44, 55.37, 39.35, 31.49.

LC-MS (0-100% B, 19 min): t_R (**106**) = 6.53 min, m/z: calculated = 244.13 $[M+H]^+$, found = 244.23 $[M+H]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**106**) = 15.95 min (*er* = 94.47/5.53).

(E)-1-(3-methoxyphenyl)-3-(pyridin-2-yl)prop-2-en-1-one (AV438)



Chemical Formula: $C_{15}H_{13}NO_2$
Exact Mass: 239,09
Molecular Weight: 239,27

107

Pyridine-2-carboxaldehyde (14.02 g, 0.09 mol, 2 eq) is dissolved in 10 mL MeOH. The solution is cooled to 0°C for 15 min, then cooled NaOH (2.05 g, 0.05 mol, 1.1 eq) dissolved in 18 mL H_2O is added. Subsequently a solution of 3-Methoxyacetophenone (5.0 g, 0.05 mol, 1.0 eq) in 10 mL MeOH is added dropwise in 10 min. The mixture is checked every 5 min by TLC and the reaction stopped after 10 min. The reaction mixture is diluted with sat. $NH_4Cl_{(aq)}$ (50 mL) and extracted with EE (3×100 mL). The combined organic phases are washed with brine (1×50 mL), dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by manual column chromatography (EE + 1% TEA), then precipitated in iPrOH/H2O – 20/1. Compound **107** is obtained as yellow crystals.

Yield 4.23 g (38%).

TLC (EE + 1% TEA): R_f (**107**) = 0.60.

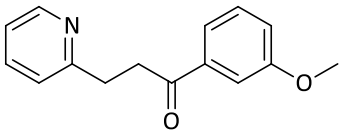
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.68 (m, 1H), 8.09 (d, *J* = 15.3 Hz, 1H), 7.80 – 7.65 (m, 3H), 7.60 (dd, *J* = 1.6, 2.7 Hz, 1H), 7.48 (m, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.29 (ddd, *J* = 1.1, 4.7, 7.6 Hz, 1H), 7.13 (ddd, *J* = 0.9, 2.7, 8.2 Hz, 1H), 3.88 (s, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 190.29, 160.09, 153.33, 150.23, 142.81, 139.37, 137.06, 129.73, 125.90, 125.46, 124.52, 121.58, 119.90, 112.94, 55.63.

LC-MS (0-100% B, 19 min): t_R (**107**) = 11.31 min, m/z: calculated = 240.10 $[M+H]^+$,
found = 240.14 $[M+H]^+$.

RP-HPLC (30 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**95**) = 4.05 min (99% Purity).

1-(3-methoxyphenyl)-3-(pyridin-2-yl)propan-1-one (AV490)



Chemical Formula: $C_{15}H_{15}NO_2$
Exact Mass: 241,11
Molecular Weight: 241,29

108

Zn powder (5.46 g, 84 mmol, 10.0 eq) and NH_4Cl (4.47 g, 84 mmol, 10.0 eq) are added to a flask and suspended in 30 mL MeOH. **107** (2.0 g, 8 mmol, 1.0 eq) is dissolved in 50 mL MeOH and added dropwise to the vigorously stirring suspension in 30 min. After complete addition, the mixture is filtered and washed with MeOH. 200 mL H_2O is added to the filtrate and adjusted to pH = 13 with a 10% aqueous NaOH solution. The mixture is extracted with EE (3×50 mL), the combined organic phases dried with $MgSO_4$, then filtered and the solvent removed under reduced pressure. The crude product **108** is obtained as brown oil and used without further purification.

Yield 1.88 g (93%).

TLC (CH/EE, 2/1, v/v): R_f (**108**) = 0.27.

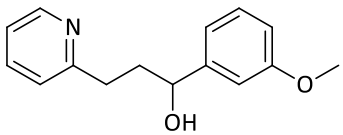
^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.49 (ddd, *J* = 0.9, 1.9, 4.9 Hz, 1H), 7.61 – 7.53 (m, 2H), 7.49 (dd, *J* = 1.6, 2.6 Hz, 1H), 7.33 (dd, *J* = 7.6, 8.2 Hz, 1H), 7.23 (dt, *J* = 1.1, 7.8 Hz, 1H), 7.08 (dtd, *J* = 1.2, 2.9, 7.3 Hz, 2H), 3.82 (s, 3H), 3.48 (td, *J* = 0.6, 7.2 Hz, 2H), 3.22 (t, *J* = 7.2 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 199.06, 160.68, 159.79, 149.21, 138.27, 136.31, 129.50, 123.30, 121.19, 120.75, 119.54, 112.20, 55.39, 37.90, 32.10.

LC-MS (0-100% B, 19 min): t_R (**108**) = 6.65 min, m/z: calculated = 242.11 $[M+H]^+$, found = 242.24 $[M+H]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**108**) = 6.38 min (96% Purity).

1-(3-methoxyphenyl)-3-(pyridin-2-yl)propan-1-ol (AV492)



Chemical Formula: $C_{15}H_{17}NO_2$
Exact Mass: 243,13
Molecular Weight: 243,30

109

108 (50 mg, 0.21 mmol, 1.0 eq) is dissolved in 2 mL iPrOH. $NaBH_4$ (8 mg, 0.21 mmol, 1 eq) is added and the reaction stirred at r.t. overnight. The mixture is diluted with 10 mL MeOH and quenched with a few drops conc. HCl. The solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 1/1). The pure product **109** is obtained as beige-white oil.

Yield 30 mg (60%).

TLC (CH/EE, 1/1): R_f (**109**) = 0.18.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.53 (ddd, *J* = 0.9, 1.8, 4.9 Hz, 1H), 7.63 (td, *J* = 1.9, 7.6 Hz, 1H), 7.30 – 7.23 (m, 1H), 7.22 – 7.14 (m, 2H), 7.03 – 6.95 (m, 2H), 6.81 (dd, *J* = 2.7, 8.2 Hz, 1H), 4.83 (dd, *J* = 4.2, 8.0 Hz, 1H), 3.82 (s, 3H), 3.00 (t, *J* = 6.7 Hz, 2H), 2.31 – 2.12 (m, 2H).

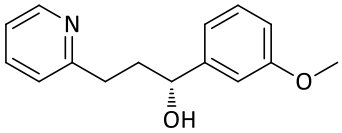
^{13}C-NMR (126 MHz, $CDCl_3$): δ 161.50, 159.83, 148.70, 147.20, 136.98, 129.38, 123.39, 121.33, 118.33, 112.78, 111.39, 73.75, 55.35, 37.99, 34.60.

LC-MS (0-100% B, 19 min): t_R (**109**) = 5.76 min, m/z: calculated = 244.13 $[M+H]^+$, found = 244.11 $[M+H]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**109**) = 1.75 min (98% Purity).

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**109**) = 7.85 min, 8.25 min.

(R)-1-(3-methoxyphenyl)-3-(pyridin-2-yl)propan-1-ol (AV494)



Chemical Formula: $C_{15}H_{17}NO_2$
Exact Mass: 243,13
Molecular Weight: 243,30

110

Dissolve S-CBS (11.5 mg, 0.04 mmol, 0.1 eq) in 1.4 mL dry THF and add to a flask under argon atmosphere. Add 20 µL (0.1 eq) of a 2 M BH_3*SMe_2 solution in THF. Dissolve **108** (100 mg, 0.41 mmol, 1.0 eq) in 1 mL dry THF and add to the catalyst. Then 311 µL (1.5 eq) of a 2 M BH_3*SMe_2 solution in THF is added dropwise in 1 h. After complete addition, the reaction is further stirred for 2 h, then stopped by the addition of MeOH. The formation of product-boron complexes is stopped by the addition of 1.1 eq conc. HCl and further stirring for 1 h. Finally, the mixture is diluted with sat. $NaHCO_3$ solution until basic and extracted with EE (3×20 mL). The combined organic phases are washed with brine (1×50 mL), dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 1/1). The pure product **110** is obtained as a white oil.

Yield 80 mg (80%).

TLC (EE): R_f (**110**) = 0.15.

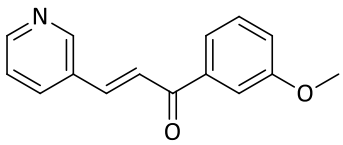
^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.51 (dt, *J* = 1.3, 5.0 Hz, 1H), 7.60 (td, *J* = 1.8, 7.7 Hz, 1H), 7.26 – 7.19 (m, 1H), 7.19 – 7.08 (m, 2H), 6.99 – 6.89 (m, 2H), 6.78 (ddd, *J* = 1.0, 2.7, 8.2 Hz, 1H), 4.80 (dd, *J* = 4.5, 7.6 Hz, 1H), 3.80 (d, *J* = 0.5 Hz, 3H), 2.98 (t, *J* = 6.7 Hz, 2H), 2.27 – 2.09 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 161.52, 159.86, 148.73, 147.20, 136.97, 129.39, 123.39, 121.33, 118.34, 112.81, 111.42, 73.78, 55.36, 37.98, 34.62.

LC-MS (0-100% B, 19 min): t_R (**110**) = 5.76 min, m/z: calculated = 244.13 $[M+H]^+$, found = 244.09 $[M+H]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**110**) = 8.35 min (*er* = 91.43/8.57).

(E)-1-(3-methoxyphenyl)-3-(pyridin-3-yl)prop-2-en-1-one (AV446)



Chemical Formula: $C_{15}H_{13}NO_2$
Exact Mass: 239,09
Molecular Weight: 239,27

111

Pyridine-3-carboxaldehyde (4.21 g, 0.03 mol, 2 eq) is dissolved in 3 mL MeOH. The solution is cooled to 0°C for 15 min, then cooled NaOH (0.62 g, 0.015 mol, 1.1 eq) dissolved in 6 mL H_2O is added. Subsequently a solution of 3-Methoxyacetophenone (1.50 g, 0.01 mol, 1.0 eq) in 3 mL MeOH is added dropwise in 10 min. The mixture is checked every 10 min by TLC and the reaction stopped after 30 min. The reaction mixture is diluted with sat. $NH_4Cl_{(aq)}$ (50 mL) and extracted with EE (3×100 mL). The combined organic phases are washed with brine (1×50 mL), dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is enriched by manual column chromatography (CH/EE, 1/1 + 1% TEA). Compound **111** is obtained as a yellow oil.

Yield 3.21 g (95%).

TLC (CH/EE, 1/1, v/v + 1% TEA**):** R_f (**111**) = 0.29.

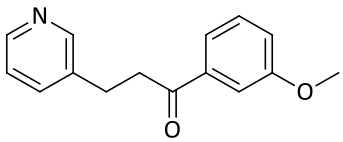
^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.03 (m, 1H), 8.58 – 8.41 (m, 2H), 8.12 (m, 1H), 7.91 (m, 1H), 7.79 – 7.67 (m, 2H), 7.47 – 7.40 (m, 1H), 7.40 – 7.34 (m, 1H), 7.31 (m, 1H), 3.83 (s, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 190.75, 154.76, 152.07, 151.07, 149.96, 140.89, 135.83, 134.66, 129.73, 124.11, 124.02, 123.84, 121.12, 119.63, 113.01, 55.53.

LC-MS (0-100% B, 19 min): t_R (**111**) = 9.38 min, m/z: calculated = 240.10 $[M+H]^+$, found = 240.30 $[M+H]^+$, t_R (Pyridine-3-carboxaldehyde) = 1.71, m/z: calculated = 108.13 $[M+H]^+$, found = 108.30 $[M+H]^+$

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**111**) = 7.91 min (87% Purity), t_R (Pyridine-3-carboxaldehyde) = 1.71.

1-(3-methoxyphenyl)-3-(pyridin-3-yl)propan-1-one (AV491)



Chemical Formula: $C_{15}H_{15}NO_2$
Exact Mass: 241,11
Molecular Weight: 241,29

112

Zn powder (5.46 g, 84 mmol, 10.0 eq) and NH_4Cl (4.47 g, 84 mmol, 10.0 eq) are added to a flask and suspended in 30 mL MeOH. **111** (2.0 g, 8 mmol, 1.0 eq) is dissolved in 50 mL MeOH and added dropwise to the vigorously stirring suspension in 30 min. After complete addition, the mixture is filtered and washed with MeOH. 200 mL H_2O is added to the filtrate and adjusted to pH = 13 with a 10% aqueous NaOH solution. The mixture is extracted with EE (3×50 mL), the combined organic phases dried with $MgSO_4$, then filtered and the solvent removed under reduced pressure. The crude is purified by column chromatography (EE). The pure product **112** is obtained as a yellow solid.

Yield 1.00 g (50%).

TLC (EE): R_f (**112**) = 0.42.

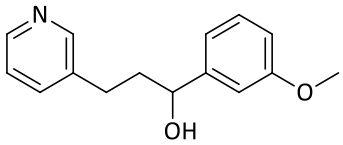
^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.36 – 8.21 (m, 2H), 7.37 (dt, *J* = 2.0, 8.1 Hz, 1H), 7.33 – 7.24 (m, 2H), 7.14 (t, *J* = 7.9 Hz, 1H), 7.00 (dd, *J* = 4.8, 7.9 Hz, 1H), 6.89 (dd, *J* = 2.7, 8.1 Hz, 1H), 3.62 (s, 3H), 3.09 (t, *J* = 7.4 Hz, 2H), 2.86 (t, *J* = 7.4 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 198.20, 159.84, 149.92, 147.60, 137.97, 136.55, 135.97, 129.61, 123.32, 120.54, 119.61, 112.27, 55.39, 39.78, 27.12.

LC-MS (0-100% B, 19 min): t_R (**112**) = 6.73 min, m/z: calculated = 242.11 $[M+H]^+$, found = 242.30 $[M+H]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**112**) = 6.73 min (99% Purity).

1-(3-methoxyphenyl)-3-(pyridin-3-yl)propan-1-ol (AV493)



Chemical Formula: $C_{15}H_{17}NO_2$
Exact Mass: 243,13
Molecular Weight: 243,30

113

112 (50 mg, 0.21 mmol, 1.0 eq) is dissolved in 2 mL iPrOH. $NaBH_4$ (8 mg, 0.21 mmol, 1 eq) is added and the reaction stirred at r.t. overnight. The mixture is diluted with 10 mL MeOH and quenched with a few drops conc. HCl. The solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 1/1). The pure product **113** is obtained as beige-white oil.

Yield 30 mg (60%).

TLC (CH/EE, 1/1): R_f (**113**) = 0.18.

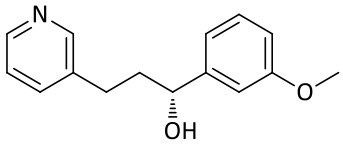
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.44 – 8.33 (m, 2H), 7.51 (dt, *J* = 1.9, 7.7 Hz, 1H), 7.31 – 7.17 (m, 2H), 6.95 – 6.87 (m, 2H), 6.82 (ddd, *J* = 1.1, 2.5, 8.2 Hz, 1H), 4.65 (dd, *J* = 5.1, 7.9 Hz, 1H), 3.80 (s, 3H), 2.81 – 2.63 (m, 2H), 2.16 – 1.95 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 159.98, 149.98, 147.36, 146.40, 137.34, 136.11, 129.71, 123.48, 118.30, 113.22, 111.53, 73.41, 55.37, 40.19, 29.29.

LC-MS (0-100% B, 19 min): t_R (**113**) = 5.90 min, m/z: calculated = 244.13 $[M+H]^+$, found = 244.27 $[M+H]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**113**) = 12.79 min, 14.99 min.

(R)-1-(3-methoxyphenyl)-3-(pyridin-3-yl)propan-1-ol (AV496)



Chemical Formula: $C_{15}H_{17}NO_2$
Exact Mass: 243,13
Molecular Weight: 243,30

114

Dissolve S-CBS (11.5 mg, 0.04 mmol, 0.1 eq) in 1.4 mL dry THF and add to a flask under argon atmosphere. Add 20 µL (0.1 eq) of a 2 M BH_3*SMe_2 solution in THF. Dissolve **112** (100 mg, 0.41 mmol, 1.0 eq) in 1 mL dry THF and add to the catalyst. Then 311 µL (1.5 eq) of a 2 M BH_3*SMe_2 solution in THF is added dropwise in 1 h. After complete addition, the reaction is further stirred for 2 h, then stopped by the addition of MeOH. The formation of product-boron complexes is stopped by the addition of 1.1 eq conc. HCl and further stirring for 1 h. Finally, the mixture is diluted with sat. $NaHCO_3$ solution until basic and extracted with EE (3×20 mL). The combined organic phases are washed with brine (1×50 mL), dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 1/1). The pure product **114** is obtained as a white oil.

Yield 80 mg (80%).

TLC (CH/EE, 1/1, v/v): R_f (**114**) = 0.30.

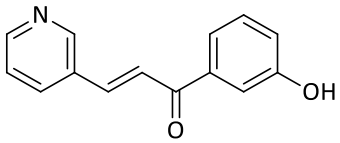
^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.45 – 8.35 (m, 2H), 7.61 (dt, *J* = 2.0, 7.8 Hz, 1H), 7.33 – 7.24 (m, 1H), 7.21 (d, *J* = 8.3 Hz, 1H), 6.89 (dd, *J* = 1.5, 7.3 Hz, 2H), 6.81 – 6.75 (m, 1H), 5.29 (d, *J* = 4.6 Hz, 1H), 4.50 (td, *J* = 4.6, 6.3 Hz, 1H), 3.74 (s, 3H), 2.78 – 2.54 (m, 2H), 1.88 (td, *J* = 6.5, 8.0 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 159.15, 149.54, 147.72, 146.99, 137.37, 135.69, 129.01, 123.37, 117.98, 112.11, 111.26, 71.42, 54.90, 28.64.

LC-MS (0-100% B, 19 min): t_R (**114**) = 5.85 min, m/z: calculated = 244.13 $[M+H]^+$, found = 244.33 $[M+H]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**114**) = 16.10 min (*er* = 87.44/12.56).

(E)-1-(3-hydroxyphenyl)-3-(pyridin-3-yl)prop-2-en-1-one (AV665)



Chemical Formula: $C_{14}H_{11}NO_2$
Exact Mass: 225,08
Molecular Weight: 225,24

115

Pyridine-3-carboxaldehyde (2.00 g, 19 mmol, 1 eq) and 3-hydroxy acetophenone (2.54 g, 19 mmol, 1 eq) are dissolved in 8 mL MeOH. The solution is cooled to 0°C for 15 min, then cooled NaOH (1.6 g, 38 mmol, 2 eq) dissolved in 8 mL H_2O is added. The mixture is stirred for 2.5 h under cooling, then neutralized with conc. HCl, diluted with 40 mL H_2O and the precipitate filtered off and washed with H_2O. The crude product is used in the next steps without further purification. Compound **115** is obtained as yellow solid.

Yield 4.00 g (95%).

TLC (CH/EE, 2/1, v/v**):** R_f (**115**) = 0.15.

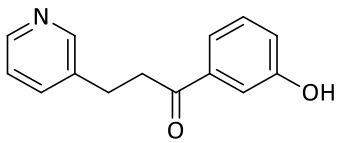
^{1}H-NMR (500 MHz, DMSO-d_6): δ 9.01 (d, J = 2.2 Hz, 1H), 8.61 (dd, J = 1.6, 4.7 Hz, 1H), 8.34 (dt, J = 2.0, 8.0 Hz, 1H), 7.99 (d, J = 15.8 Hz, 1H), 7.74 (d, J = 15.8 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.51 – 7.45 (m, 2H), 7.38 (t, J = 7.9 Hz, 1H), 7.12 – 7.04 (m, 1H).

^{13}C-NMR (126 MHz, DMSO-d_6): δ 188.90, 157.83, 150.93, 150.33, 140.31, 138.71, 135.04, 130.50, 129.84, 124.09, 123.88, 120.51, 119.64, 114.71.

LC-MS (0-100% B, 19 min): t_R (**115**) = 8.53 min, m/z: calculated = 226.24 $[M+H]^+$, found = 226.30 $[M+H]^+$

RP-HPLC (0 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**115**) = 6.18 min (87% Purity)

1-(3-hydroxyphenyl)-3-(pyridin-3-yl)propan-1-one (AV669)



Chemical Formula: $C_{14}H_{13}NO_2$
Exact Mass: 227,09
Molecular Weight: 227,26

116

115 (4.00 g, 18 mmol, 1.0 eq) is dissolved in 100 mL THF. The solution is sparged with argon for 5 min. Then 10 wt% Pd/C (0.94 g, 1 mmol, 0.05 eq) is added and the slurry sparged with H_2 for 10 min. After 3 h the reaction is complete. The mixture is filtered over celite and washed with THF. The solvent is removed and the crude is purified by recrystallization in MeOH. The pure product **116** is obtained as slightly yellow solid.

Yield 2.55 g (63%).

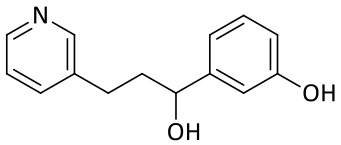
TLC (CH/EE, 1/2, v/v): R_f (**116**) = 0.25.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.13 (d, J = 2.1 Hz, 1H), 7.01 (dd, J = 1.7, 4.8 Hz, 1H), 6.31 (dt, J = 2.0, 7.9 Hz, 1H), 6.05 (dt, J = 1.3, 7.7 Hz, 1H), 6.01 – 5.85 (m, 3H), 5.64 (ddd, J = 1.0, 2.7, 8.1 Hz, 1H), 1.98 (t, J = 7.4 Hz, 2H), 1.55 (t, J = 7.4 Hz, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 198.73, 157.60, 149.75, 147.15, 137.91, 136.70, 135.88, 129.77, 123.31, 120.26, 118.92, 114.08, 39.02, 26.60.

LC-MS (0-100% B, 19 min): t_R (**116**) = 6.36 min, m/z: calculated = 228.09 $[M+H]^+$, found = 228.29 $[M+H]^+$.

3-(1-hydroxy-3-(pyridin-3-yl)propyl)phenol (AV672)



Chemical Formula: $C_{14}H_{15}NO_2$
Exact Mass: 229,11
Molecular Weight: 229,27

117

116 (50 mg, 0.22 mmol, 1.0 eq) is dissolved in 2 mL THF. CeCl3 * 7 H_2O (8 mg, 0.02 mmol, 0.1 eq) is added, then $NaBH_4$ (8 mg, 0.22 mmol, 1 eq) is added slowly and the reaction stirred for 10 min. The

mixture is diluted with 10 mL MeOH and quenched with a few drops conc. HCl. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 1/3). The pure product **117** is obtained as a beige-white solid.

Yield 30 mg (60%).

TLC (CH/EE, 1/3): R_f (**117**) = 0.19.

^{1}H-NMR (500 MHz, DMSO-d_6): δ 9.24 (s, 1H), 8.41 (d, J = 2.3 Hz, 1H), 8.38 (dd, J = 1.6, 4.8 Hz, 1H), 7.60 (dt, J = 2.0, 7.8 Hz, 1H), 7.28 (ddd, J = 0.9, 4.7, 7.8 Hz, 1H), 7.09 (t, J = 7.8 Hz, 1H), 6.77 – 6.75 (m, 1H), 6.73 (dt, J = 1.3, 7.5 Hz, 1H), 6.61 (ddd, J = 1.1, 2.5, 8.1 Hz, 1H), 5.22 (d, J = 4.4 Hz, 1H), 4.43 (dt, J = 5.0, 7.1 Hz, 1H), 2.72 – 2.55 (m, 2H), 1.85 (dddd, J = 2.1, 5.8, 8.5, 10.9 Hz, 2H).

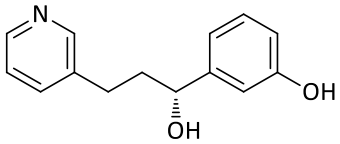
^{13}C-NMR (126 MHz, DMSO-d_6): δ 157.14, 149.53, 147.52, 146.98, 137.41, 135.68, 128.89, 123.37, 116.39, 113.57, 112.62, 71.38, 40.47, 28.61.

LC-MS (0-100% B, 19 min): t_R (**117**) = 5.92 min, m/z: calculated = 230.27 $[M+H]^+$, found = 230.17 $[M+H]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**117**) = 1.85 min (93% Purity).

Chiral-HPLC (10% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**117**) = 41.48 min, 50.13 min.

(R)-3-(1-hydroxy-3-(pyridin-3-yl)propyl)phenol (AV670/AV682)



Chemical Formula: $C_{14}H_{15}NO_2$
Exact Mass: 229,11
Molecular Weight: 229,27

118

116 (500 mg, 2.20 mmol, 1.0 eq) is dissolved in 20 mL THF. Then a 1 M solution of KOtBu in *t*BuOH (3.30 mL, 3.30 mmol, 1.5 eq) is added and the solution is sparged with argon for 5 min. $RuCl_2$[(S)-(DM-SEGPHOS)][(S)-DAIPEN] (107 mg, 0.088 mmol, 0.04 eq) is added. The slurry is sparged with H_2 for 5 min and the reaction is stirred at 1 bar H_2 at r.t. overnight. After full conversion, the mixture is diluted with 50 mL H_2O and extracted with EE (3×). The combined organic phases are washed with brine (1×50 mL), dried with $MgSO_4$, filtered and the solvent removed under reduced pressure The crude product is purified by column chromatography (EE). The pure product **118** is obtained as a beige solid.

Yield 349 mg (70%).

TLC (EE): R_f (**118**) = 0.26.

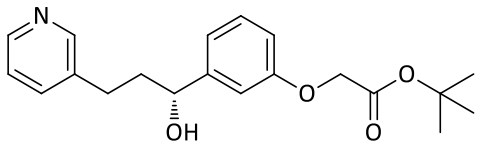
^{1}H-NMR (300 MHz, DMSO-d_6): δ 9.22 (s, 1H), 8.44 – 8.39 (m, 1H), 8.38 (dd, J = 1.6, 4.8 Hz, 1H), 7.60 (dt, J = 2.0, 7.8 Hz, 1H), 7.28 (ddd, J = 0.9, 4.8, 7.8 Hz, 1H), 7.09 (t, J = 7.8 Hz, 1H), 6.77 – 6.71 (m, 2H), 6.61 (ddd, J = 1.1, 2.5, 8.0 Hz, 1H), 5.20 (d, J = 4.5 Hz, 1H), 4.43 (q, J = 6.0 Hz, 1H), 3.31 (s, 3H), 2.75 – 2.53 (m, 2H), 1.91 – 1.78 (m, 2H).

^{13}C-NMR (75 MHz, DMSO-d_6): δ 157.12, 149.50, 147.49, 146.96, 137.39, 135.65, 128.86, 123.34, 116.37, 113.55, 112.61, 71.37, 28.59.

LC-MS (0-100% B, 19 min): t_R (**118**) = 5.80 min, m/z: calculated = 230.27 $[M+H]^+$, found = 230.19 $[M+H]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**118**) = 42.68, 49.55 min (*er* = 1.15/98.85).

(R)-tert-butyl 2-(3-(1-hydroxy-3-(pyridin-3-yl)propyl)phenoxy)acetate (AV679/AV683/AV684/AV685/AV686/AV688/AV689)



Chemical Formula: $C_{20}H_{25}NO_4$
Exact Mass: 343,18
Molecular Weight: 343,42

119

Dissolve **118** (100 mg, 0.43 mmol, 1.0 eq) in 10 mL dry MeCN and add Ag2CO3 (120 mg, 0.43 mmol, 1.0 eq). Then 65 µL (1.0 eq) of *tert*-butyl bromoacetate is added. The mixture is stirred overnight at r.t. After complete conversion, the reaction is filtered, washed with MeCN and the solvent removed. The crude product is purified by column chromatography (CH/EE, 1/1). The pure product **119** is obtained as a beige oil.

Yield 64 mg (42%).

TLC (CH/EE, 1/1, v/v): R_f (**119**) = 0.30.

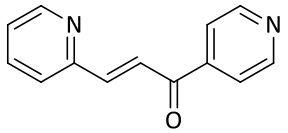
^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.41 (d, J = 2.3 Hz, 1H), 8.38 (dd, J = 1.7, 4.9 Hz, 1H), 7.50 (dt, J = 2.1, 7.8 Hz, 1H), 7.30 – 7.15 (m, 2H), 6.99 – 6.90 (m, 2H), 6.85 – 6.76 (m, 1H), 4.64 (dd, J = 5.1, 8.0 Hz, 1H), 4.52 (s, 2H), 2.84 – 2.62 (m, 2H), 2.18 – 1.89 (m, 2H), 1.48 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 168.11, 158.26, 149.92, 147.32, 146.51, 137.29, 136.12, 129.74, 123.49, 119.14, 113.78, 112.20, 82.51, 73.21, 65.73, 40.20, 29.20, 28.17.

LC-MS (0-100% B, 19 min): t_R (**119**) = 8.18 min, m/z: calculated = 344.42 $[M+H]^+$, found = 344.13 $[M+H]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**119**) = 8.10 min (92% Purity).

(E)-3-(pyridin-2-yl)-1-(pyridin-4-yl)prop-2-en-1-one (AV734/AV743/AV744)



Chemical Formula: $C_{13}H_{10}N_2O$
Exact Mass: 210,08
Molecular Weight: 210,23

120

Pyridine-2-carboxaldehyde (1.00 g, 9.3 mmol, 1 eq) and 4-acetylpyridine (1.13 g, 9.3 mmol, 1 eq) are dissolved in 40 mL H_2O. The solution is cooled to 0°C for 15 min, then Na_2CO_3 (4.00 g, 37.3 mmol, 4 eq) dissolved in 36 mL H_2O is added. The reaction is stopped after the formation of a precipitate is observed (10 min). The mixture is extracted with DCM (3×20 mL), the combined organic phases are washed with brine (1×50 mL), dried with $MgSO_4$, filtered and the crude loaded directly onto SiO_2. The dry-load is then heated under stirring to 120°C for 1 h. The now yellow silica is cooled and directly used as a dry-load for a silica column chromatography (EE + 2% MeOH). Pure compound **120** is obtained as a yellow solid.

Yield 520 mg (27%).

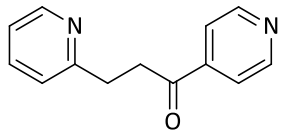
TLC (EE + 2% MeOH**):** R_f (**120**) = 0.30.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.86 – 8.78 (m, 2H), 8.67 (d, J = 4.8 Hz, 1H), 8.00 (d, J = 15.3 Hz, 1H), 7.87 – 7.77 (m, 3H), 7.76 – 7.66 (m, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.29 (dd, J = 4.8, 7.7 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 189.89, 152.67, 150.96, 150.40, 144.61, 143.95, 137.04, 125.87, 124.97, 124.62, 121.64.

LC-MS (0-100% B, 19 min): t_R (**120**) = 8.49 min, m/z: calculated = 211.23 $[M+H]^+$, found = 211.20 $[M+H]^+$.

3-(pyridin-2-yl)-1-(pyridin-4-yl)propan-1-one (AV750/AV754/AV755/AV756/AV757)



Chemical Formula: $C_{13}H_{12}N_2O$
Exact Mass: 212,09
Molecular Weight: 212,25

121

120 (30 mg, 0.14 mmol, 1.0 eq) is dissolved in 5 mL MeOH and sparged for 5 min with argon. Then 10 wt% Pt/C (14 mg, 0.007 mmol, 0.05 eq) is added and the slurry sparged with H_2 for 5 min. The

mixture is filtered after 5 min and washed with MeOH. The solvent is removed under reduced pressure. The crude is purified by column chromatography (EE + 10% MeOH). The pure product **121** is obtained as a white solid.

Yield 18 mg (60%).

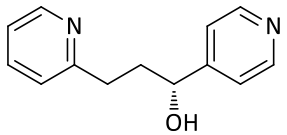
TLC (EE + 10% MeOH**):** R_f (**121**) = 0.32.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.82 – 8.72 (m, 2H), 8.48 (ddd, J = 1.0, 1.9, 4.9 Hz, 1H), 7.77 – 7.70 (m, 2H), 7.59 (td, J = 1.9, 7.7 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.10 (ddd, J = 1.2, 4.9, 7.5 Hz, 1H), 3.54 – 3.46 (m, 2H), 3.24 (t, J = 7.0 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 151.03, 149.32, 136.55, 123.47, 121.52, 121.21, 37.87, 31.70.

LC-MS (0-100% B, 19 min): t_R (**121**) = 1.98 min, m/z: calculated = 213.25 $[M+H]^+$, found = 213.26 $[M+H]^+$.

(R)-3-(pyridin-2-yl)-1-(pyridin-4-yl)propan-1-ol (AV760)



Chemical Formula: $C_{13}H_{14}N_2O$
Exact Mass: 214,11
Molecular Weight: 214,26

122

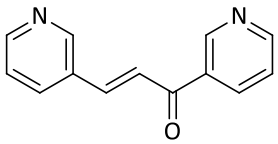
121 (30 mg, 0.14 mmol, 1.0 eq) is dissolved in 5 mL THF. Then a 1 M solution of KOtBu in *t*BuOH (140 µL, 0.14 mmol, 1.0 eq) is added and the solution is sparged with argon for 5 min. $RuCl_2$[(S)-(DM-SEGPHOS)][(S)-DAIPEN] (7 mg, 0.006 mmol, 0.04 eq) is added. The slurry is sparged with H_2 for 5 min and the reaction is stirred at 1 bar H_2 at r.t. overnight. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (EE + 10% MeOH). The pure product **122** is obtained as a yellow solid.

Yield 7 mg (23%).

TLC (EE + 10% MeOH): R_f (**122**) = 0.20.

LC-MS (0-100% B, 19 min): t_R (**122**) = 1.25 min, m/z: calculated = 215.1 $[M+H]^+$, found = 215.09 $[M+H]^+$.

(E)-3-(pyridin-3-yl)-1-(pyridin-3-yl)prop-2-en-1-one (AV735)



Chemical Formula: $C_{13}H_{10}N_2O$
Exact Mass: 210,08
Molecular Weight: 210,23

123

Pyridine-3-carboxaldehyde (1.00 g, 9.3 mmol, 1 eq) and 3-acetylpyridine (1.13 g, 9.3 mmol, 1 eq) are dissolved in 20 mL H_2O. The solution is cooled to 0°C for 15 min, then Na_2CO_3 (4.00 g, 37.3 mmol, 4 eq) dissolved in 36 mL H_2O is added. The reaction is stopped after the formation of a precipitate is observed (40 min). The solid is filtered and washed with H_2O. The crude product is purified by silica column chromatography (EE + 2% MeOH). Compound **123** is obtained as a yellow solid.

Yield 640 mg (33%).

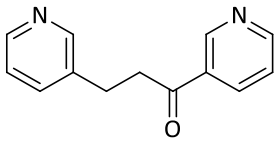
TLC (EE + 2% MeOH): R_f (**123**) = 0.25.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.22 (dd, J = 0.9, 2.3 Hz, 1H), 8.85 (d, J = 2.3 Hz, 1H), 8.80 (dd, J = 1.7, 4.8 Hz, 1H), 8.63 (dd, J = 1.6, 4.8 Hz, 1H), 8.28 (dt, J = 2.0, 7.9 Hz, 1H), 7.95 (dt, J = 2.0, 7.8 Hz, 1H), 7.81 (d, J = 15.8 Hz, 1H), 7.54 (d, J = 15.8 Hz, 1H), 7.45 (ddd, J = 0.9, 4.8, 8.0 Hz, 1H), 7.36 (ddd, J = 0.9, 4.8, 8.0 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 188.59, 153.58, 151.64, 150.29, 149.88, 142.18, 136.00, 134.73, 133.18, 130.35, 123.94, 123.85, 123.22.

LC-MS (0-100% B, 19 min): t_R (**123**) = 7.10 min, m/z: calculated = 211.23 $[M+H]^+$,
found = 211.26 $[M+H]^+$.

3-(pyridin-3-yl)-1-(pyridin-3-yl)propan-1-one (AV748)



Chemical Formula: $C_{13}H_{12}N_2O$
Exact Mass: 212,09
Molecular Weight: 212,25

124

(200 mg, 1.0 mmol, 1.0 eq) is dissolved in 5 mL MeOH and sparged for 5 min with argon. Then 10 wt% Pd/C (100 mg, 1 eq) is added and the slurry sparged with H_2 for 1 min. The mixture is filtered after

10 min and washed with MeOH. The solvent is removed under reduced pressure. The crude is purified by column chromatography (EE + 6% MeOH). The pure product **124** is obtained as a yellow solid.

Yield 100 g (50%).

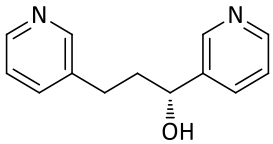
TLC (EE + 6% MeOH): R_f (**124**) = 0.25.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.10 (d, J = 2.3 Hz, 1H), 8.72 (dd, J = 1.7, 4.8 Hz, 1H), 8.48 (d, J = 2.3 Hz, 1H), 8.43 – 8.37 (m, 1H), 8.16 (dt, J = 1.9, 8.1 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.36 (dd, J = 4.9, 8.0 Hz, 1H), 7.18 (dd, J = 4.9, 7.9 Hz, 1H), 3.29 (t, J = 7.3 Hz, 2H), 3.05 (t, J = 7.3 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 197.24, 153.62, 149.75, 149.47, 147.64, 136.27, 136.22, 135.34, 131.89, 123.73, 123.50, 39.99, 26.77.

LC-MS (0-100% B, 19 min): t_R (**124**) = 1.98 min, m/z: calculated = 213.25 $[M+H]^+$, found = 213.25 $[M+H]^+$.

(R)-3-(pyridin-3-yl)-1-(pyridin-3-yl)propan-1-ol (AV758)



Chemical Formula: $C_{13}H_{14}N_2O$
Exact Mass: 214,11
Molecular Weight: 214,26

125

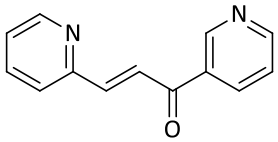
124 (30 mg, 0.14 mmol, 1.0 eq) is dissolved in 5 mL THF. Then a 1 M solution of KOtBu in *t*BuOH (140 µL, 0.14 mmol, 1.0 eq) is added and the solution is sparged with argon for 5 min. $RuCl_2$[(S)-(DM-SEGPHOS)][(S)-DAIPEN] (7 mg, 0.006 mmol, 0.04 eq) is added. The slurry is sparged with H_2 for 5 min and the reaction is stirred at 1 bar H_2 at r.t. overnight. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (EE + 10% MeOH). The pure product **125** is obtained as a white oil.

Yield 7 mg (23%).

TLC (EE + 10% MeOH): R_f (**125**) = 0.24.

LC-MS (0-100% B, 19 min): t_R (**125**) = 1.19 min, m/z: calculated = 215.26 $[M+H]^+$, found = 215.32 $[M+H]^+$.

(E)-3-(pyridin-2-yl)-1-(pyridin-3-yl)prop-2-en-1-one (AV736)



Chemical Formula: $C_{13}H_{10}N_2O$
Exact Mass: 210,08
Molecular Weight: 210,23

126

Pyridine-2-carboxaldehyde (1.00 g, 9.3 mmol, 1 eq) and 3-acetylpyridine (1.13 g, 9.3 mmol, 1 eq) are dissolved in 20 mL H_2O. The solution is cooled to 0°C for 15 min, then Na_2CO_3 (4.00 g, 37.3 mmol, 4 eq) dissolved in 36 mL H_2O is added. The reaction is stopped after the formation of a precipitate is observed (30 min). The mixture is extracted with DCM (3×20 mL), the combined organic phases are washed with brine (1×50 mL), dried with $MgSO_4$, filtered and the crude loaded directly onto SiO_2. The dry-load is then heated under stirring to 120°C for 1 h. The now yellow silica is cooled and directly used as a dry-load for a silica column chromatography (EE + 2% MeOH). Compound **126** is obtained as a yellow oil.

Yield 800 mg (40%).

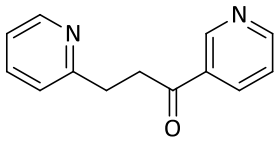
TLC (EE + 2% MeOH): R_f (**126**) = 0.23.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.23 (dd, J = 0.9, 2.3 Hz, 1H), 8.74 (dd, J = 1.7, 4.8 Hz, 1H), 8.63 (ddd, J = 0.9, 1.9, 4.8 Hz, 1H), 8.27 (ddd, J = 1.8, 2.3, 8.0 Hz, 1H), 8.01 (d, J = 15.3 Hz, 1H), 7.74 (d, J = 15.2 Hz, 1H), 7.67 (dd, J = 1.8, 7.7 Hz, 1H), 7.45 – 7.35 (m, 2H), 7.25 (ddd, J = 1.2, 4.7, 7.6 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 189.15, 153.37, 152.75, 150.28, 150.03, 143.80, 136.93, 135.93, 133.14, 125.61, 124.85, 124.74, 123.60.

LC-MS (0-100% B, 19 min): t_R (**126**) = 8.31 min, m/z: calculated = 211.23 $[M+H]^+$,
found = 211.21 $[M+H]^+$.

3-(pyridin-2-yl)-1-(pyridin-3-yl)propan-1-one (AV749)



Chemical Formula: $C_{13}H_{12}N_2O$
Exact Mass: 212,09
Molecular Weight: 212,25

127

126 (200 mg, 0.14 mmol, 1.0 eq) is dissolved in 5 mL MeOH and sparged for 5 min with argon. Then 10 wt% Pd/C (100 mg, 0.007 mmol, 0.1 eq) is added and the slurry sparged with H_2 for 5 min. The mixture is filtered after 10 min and washed with MeOH. The solvent is removed under reduced pressure. The crude is purified by column chromatography (EE + 6% MeOH). The pure product **127** is obtained as a yellow solid.

Yield 60 mg (30%).

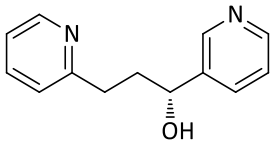
TLC (EE + 6% MeOH): R_f (**127**) = 0.42.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.17 (d, J = 2.2 Hz, 1H), 8.73 (dd, J = 1.7, 4.9 Hz, 1H), 8.46 (d, J = 4.9 Hz, 1H), 8.22 (dt, J = 2.0, 8.1 Hz, 1H), 7.57 (td, J = 1.8, 7.7 Hz, 1H), 7.37 (dd, J = 4.9, 8.0 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 7.08 (dd, J = 5.0, 7.5 Hz, 1H), 3.49 (t, J = 7.1 Hz, 2H), 3.23 (t, J = 7.1 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 198.30, 160.14, 153.40, 149.69, 149.24, 136.55, 135.48, 132.28, 123.65, 123.46, 121.46, 37.89, 31.69.

LC-MS (0-100% B, 19 min): t_R (**127**) = 1.83 min, m/z: calculated = 213.25 $[M+H]^+$, found = 213.22 $[M+H]^+$.

(R)-3-(pyridin-2-yl)-1-(pyridin-3-yl)propan-1-ol (AV759)



Chemical Formula: $C_{13}H_{14}N_2O$
Exact Mass: 214,11
Molecular Weight: 214,26

128

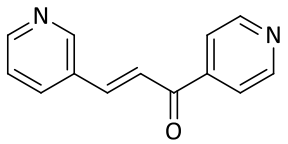
127 (20 mg, 0.12 mmol, 1.0 eq) is dissolved in 5 mL THF. Then a 1 M solution of KOtBu in *t*BuOH (140 µL, 0.14 mmol, 1.2 eq) is added and the solution is sparged with argon for 5 min. $RuCl_2$[(S)-(DM-SEGPHOS)][(S)-DAIPEN] (7 mg, 0.006 mmol, 0.04 eq) is added. The slurry is sparged with H_2 for 5 min and the reaction is stirred at 1 bar H_2 at r.t. overnight. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (EE + 10% MeOH). The pure product **128** is obtained as a yellow oil.

Yield 8 mg (40%).

TLC (EE + 10% MeOH): R_f (**128**) = 0.18.

LC-MS (0-100% B, 19 min): t_R (**128**) = 1.30 min, m/z: calculated = 215.11 $[M+H]^+$, found = 215.15 $[M+H]^+$.

(E)-3-(pyridin-3-yl)-1-(pyridin-4-yl)prop-2-en-1-one (AV745)



Chemical Formula: $C_{13}H_{10}N_2O$
Exact Mass: 210,08
Molecular Weight: 210,23

129

Pyridine-3-carboxaldehyde (1.00 g, 9.3 mmol, 1 eq) and 4-acetylpyridine (1.13 g, 9.3 mmol, 1 eq) are dissolved in 40 mL H_2O. The solution is cooled to 0°C for 15 min, then Na_2CO_3 (4.00 g, 37.3 mmol, 4 eq) dissolved in 36 mL H_2O is added. The reaction is stopped after the formation of a precipitate is observed (7 min). The mixture is extracted with DCM (3×20 mL), the combined organic phases are washed with brine (1×50 mL), dried with $MgSO_4$, filtered and the crude loaded directly onto SiO_2. The dry-load is then heated under stirring to 120°C for 1 h. The now yellow silica is cooled and directly used as dry-load for a silica column chromatography (EE + 2% MeOH). Compound **129** is obtained as a yellow oil.

Yield 1.11 g (57%).

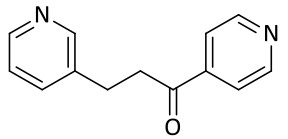
TLC (EE + 2% MeOH**):** R_f (**129**) = 0.20.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.87 – 8.74 (m, 3H), 8.66 – 8.50 (m, 1H), 7.92 (dd, J = 2.0, 7.9 Hz, 1H), 7.81 – 7.67 (m, 3H), 7.46 (d, J = 15.9 Hz, 1H), 7.34 (dd, J = 4.9, 8.0 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 189.23, 151.71, 150.97, 150.23, 143.85, 142.89, 134.76, 130.15, 123.90, 122.93, 121.47.

LC-MS (0-100% B, 19 min): t_R (**129**) = 6.88 min, m/z: calculated = 211.23 $[M+H]^+$, found = 211.26 $[M+H]^+$.

3-(pyridin-3-yl)-1-(pyridin-4-yl)propan-1-one (AV751/AV762)



Chemical Formula: $C_{13}H_{12}N_2O$
Exact Mass: 212,09
Molecular Weight: 212,25

130

129 (200 mg, 0.95 mmol, 1.0 eq) is dissolved in 20 mL MeOH and sparged for 5 min with argon. Then 10 wt% Pt/C (19 mg, 0.01 mmol, 0.01 eq) is added and the slurry sparged with H_2 for 5 min. The mixture

is filtered after 20 min and washed with MeOH. The solvent is removed under reduced pressure. The crude is purified by column chromatography (EE + 10% MeOH). The pure product **130** is obtained as a yellow solid.

Yield 38 g (19%).

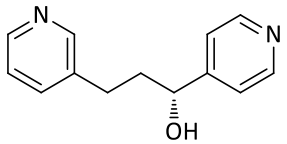
TLC (EE + 10% MeOH): R_f (**130**) = 0.20.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.83 – 8.77 (m, 2H), 8.56 – 8.49 (m, 1H), 8.46 (dd, J = 1.6, 4.8 Hz, 1H), 7.72 – 7.67 (m, 2H), 7.57 (dt, J = 2.0, 7.9 Hz, 1H), 7.22 (ddd, J = 0.9, 4.8, 7.8 Hz, 1H), 3.31 (t, J = 7.3 Hz, 2H), 3.09 (t, J = 7.3 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 198.01, 151.20, 150.04, 148.03, 142.47, 136.16, 136.13, 123.57, 121.03, 40.20, 26.84.

LC-MS (0-100% B, 19 min): t_R (**130**) = 1.95 min, m/z: calculated = 213.25 $[M+H]^+$, found = 213.23 $[M+H]^+$.

(R)-3-(pyridin-3-yl)-1-(pyridin-4-yl)propan-1-ol (AV764)



Chemical Formula: $C_{13}H_{14}N_2O$
Exact Mass: 214,11
Molecular Weight: 214,26

131

130 (30 mg, 0.14 mmol, 1.0 eq) is dissolved in 5 mL THF. Then a 1 M solution of KOtBu in *t*BuOH (140 µL, 0.14 mmol, 1.0 eq) is added and the solution is sparged with argon for 5 min. $RuCl_2$[(S)-(DM-SEGPHOS)][(S)-DAIPEN] (7 mg, 0.006 mmol, 0.04 eq) is added. The slurry is sparged with H_2 for 5 min and the reaction is stirred at 1 bar H_2 at r.t. overnight. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (EE + 10% MeOH). The pure product **131** is obtained as a yellow oil.

Yield 7 mg (23%).

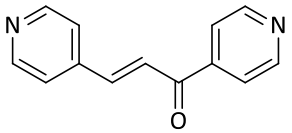
TLC (EE + 10% MeOH): R_f (**131**) = 0.20.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.57 – 8.51 (m, 2H), 8.42 (d, J = 2.2 Hz, 1H), 8.37 (dd, J = 1.6, 4.8 Hz, 1H), 7.51 (dt, J = 2.0, 7.9 Hz, 1H), 7.30 – 7.26 (m, 2H), 7.20 (dd, J = 4.8, 7.8 Hz, 1H), 4.67 (dd, J = 4.5, 8.4 Hz, 1H), 2.77 (t, J = 7.8 Hz, 2H), 2.15 – 1.93 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 153.91, 149.98, 149.92, 147.50, 136.94, 136.19, 123.64, 120.93, 71.59, 40.02, 28.95.

LC-MS (0-100% B, 19 min): t_R (**131**) = 1.22 min, m/z: calculated = 215.11 $[M+H]^+$, found = 215.21 $[M+H]^+$.

(E)-3-(pyridin-4-yl)-1-(pyridin-4-yl)prop-2-en-1-one (AV746)



Chemical Formula: $C_{13}H_{10}N_2O$
Exact Mass: 210,08
Molecular Weight: 210,23

132

Pyridine-4-carboxaldehyde (1.00 g, 9.3 mmol, 1 eq) and 4-acetylpyridine (1.13 g, 9.3 mmol, 1 eq) are dissolved in 40 mL H_2O. The solution is cooled to 0°C for 15 min, then Na_2CO_3 (2.00 g, 19.0 mmol, 2 eq) dissolved in 36 mL H_2O is added. The reaction is stopped after the formation of a precipitate is observed (7 min). The mixture is extracted with DCM (3×20 mL), the combined organic phases are washed with brine (1×50 mL), dried with $MgSO_4$, filtered and the crude loaded directly onto SiO_2. The dry-load is then heated under stirring to 120°C for 1 h. The now yellow silica is cooled and directly used as dry-load for a silica column chromatography (EE + 2% MeOH). Compound **132** is obtained as a yellow oil.

Yield 830 mg (42%).

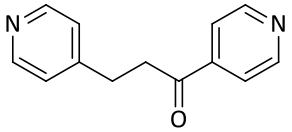
TLC (EE + 2% MeOH): R_f (**132**) = 0.20.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.87 – 8.78 (m, 2H), 8.73 – 8.65 (m, 2H), 7.78 – 7.73 (m, 2H), 7.70 (d, J = 15.8 Hz, 1H), 7.54 (d, J = 15.8 Hz, 1H), 7.47 – 7.43 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 189.33, 151.08, 150.87, 143.60, 143.51, 141.48, 125.15, 122.12, 121.49.

LC-MS (0-100% B, 19 min): t_R (**132**) = 6.00 min, m/z: calculated = 211.23 $[M+H]^+$, found = 211.23 $[M+H]^+$.

3-(pyridin-4-yl)-1-(pyridin-4-yl)propan-1-one (AV752/AV763)



Chemical Formula: $C_{13}H_{12}N_2O$
Exact Mass: 212,09
Molecular Weight: 212,25

133

132 (200 mg, 0.95 mmol, 1.0 eq) is dissolved in 20 mL MeOH and sparged for 5 min with argon. Then 10 wt% Pt/C (19 mg, 0.01 mmol, 0.01 mg) is added and the slurry sparged with H_2 for 5 min. The mixture is filtered after 35 min and washed with MeOH. The solvent is removed under reduced pressure. The crude is purified by column chromatography (EE + 10% MeOH). The pure product **133** is obtained as a yellow solid.

Yield 100 mg (50%).

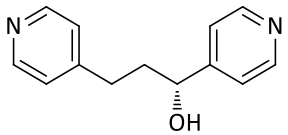
TLC (EE + 10% MeOH): R_f (**133**) = 0.42.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.87 – 8.73 (m, 2H), 8.58 – 8.39 (m, 2H), 7.74 – 7.60 (m, 2H), 7.19 – 7.06 (m, 2H), 3.31 (t, J = 7.3 Hz, 2H), 3.06 (t, J = 7.3 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 197.71, 151.12, 149.90, 149.80, 142.36, 123.92, 120.98, 39.25, 28.81.

LC-MS (0-100% B, 19 min): t_R (**133**) = 1.78 min, m/z: calculated = 213.25 $[M+H]^+$, found = 213.26 $[M+H]^+$.

(R)-3-(pyridin-4-yl)-1-(pyridin-4-yl)propan-1-ol (AV765)



Chemical Formula: $C_{13}H_{14}N_2O$
Exact Mass: 214,11
Molecular Weight: 214,26

134

133 (30 mg, 0.14 mmol, 1.0 eq) is dissolved in 5 mL THF. Then a 1 M solution of KO*t*Bu in *t*BuOH (140 µL, 0.14 mmol, 1.0 eq) is added and the solution is sparged with argon for 5 min. $RuCl_2$[(*S*)-(DM-SEGPHOS)][(*S*)-DAIPEN] (7 mg, 0.006 mmol, 0.04 eq) is added. The slurry is sparged with H_2 for 5 min and the reaction is stirred at 1 bar H_2 at r.t. overnight. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (EE + 10% MeOH). The pure product **134** is obtained as a white oil.

Yield 14 mg (47%).

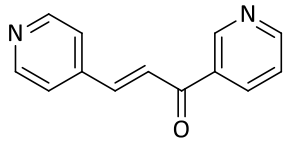
TLC (EE + 10% MeOH): R_f (**134**) = 0.20.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.54 – 8.47 (m, 2H), 8.44 – 8.39 (m, 2H), 7.31 – 7.26 (m, 2H), 7.13 – 7.08 (m, 2H), 4.69 (dd, J = 4.8, 7.9 Hz, 1H), 2.85 – 2.69 (m, 2H), 2.13 – 1.94 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 153.81, 150.79, 149.94, 149.74, 124.07, 120.94, 71.77, 39.23, 31.15.

LC-MS (0-100% B, 19 min): t_R (**134**) = 1.48 min, m/z: calculated = 215.11 $[M+H]^+$, found = 215.18 $[M+H]^+$.

(E)-3-(pyridin-4-yl)-1-(pyridin-3-yl)prop-2-en-1-one (AV747)



Chemical Formula: $C_{13}H_{10}N_2O$
Exact Mass: 210,08
Molecular Weight: 210,23

135

Pyridine-4-carboxaldehyde (1.00 g, 9.3 mmol, 1 eq) and 3-acetylpyridine (1.13 g, 9.3 mmol, 1 eq) are dissolved in 40 mL H_2O. The solution is cooled to 0°C for 15 min, then Na_2CO_3 (4.00 g, 37.3 mmol, 4 eq) dissolved in 36 mL H_2O is added. The reaction is stopped after the formation of a precipitate is observed (10 min). The mixture is extracted with DCM (3×20 mL), the combined organic phases are washed with brine (1×50 mL), dried with $MgSO_4$, filtered and the crude loaded directly onto SiO_2. The dry-load is then heated under stirring to 120°C for 1 h. The now yellow silica is cooled and directly used as dry-load for a silica column chromatography (EE + 3% MeOH). Compound **135** is obtained as a yellow oil.

Yield 1.3 g (66%).

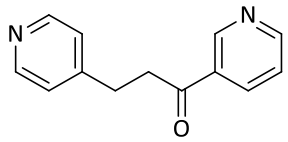
TLC (EE + 2% MeOH)**:** R_f (**135**) = 0.20.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.22 (dd, J = 0.9, 2.3 Hz, 1H), 8.81 (dd, J = 1.7, 4.8 Hz, 1H), 8.72 – 8.65 (m, 2H), 8.33 – 8.25 (m, 1H), 7.78 – 7.55 (m, 2H), 7.51 – 7.41 (m, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 188.62, 153.76, 150.86, 149.92, 142.77, 141.68, 136.04, 132.96, 125.41, 123.91, 122.15.

LC-MS (0-100% B, 19 min): t_R (**135**) = 6.24 min, m/z: calculated = 211.08 $[M+H]^+$, found = 211.24 $[M+H]^+$.

3-(pyridin-4-yl)-1-(pyridin-3-yl)propan-1-one (AV753)



Chemical Formula: $C_{13}H_{12}N_2O$
Exact Mass: 212,09
Molecular Weight: 212,25

136

135 (200 mg, 1.0 mmol, 1.0 eq) is dissolved in 5 mL MeOH and sparged for 5 min with argon. Then 10 wt% Pd/C (100 mg, 0.1 eq) is added and the slurry sparged with H_2 for 5 min. The mixture is filtered

after 5 min and washed with MeOH. The solvent is removed under reduced pressure. The crude is purified by column chromatography (EE + 6% MeOH). The pure product **136** is obtained as a yellow solid.

Yield 50 g (25%).

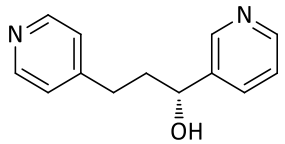
TLC (EE + 6% MeOH): R_f (**136**) = 0.25.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.20 – 9.11 (m, 1H), 8.77 (dd, J = 1.7, 4.9 Hz, 1H), 8.54 – 8.44 (m, 2H), 8.21 (dt, J = 2.0, 8.0 Hz, 1H), 7.41 (ddd, J = 0.9, 4.8, 8.0 Hz, 1H), 7.21 – 7.10 (m, 2H), 3.33 (t, J = 7.3 Hz, 2H), 3.08 (t, J = 7.3 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 197.12, 153.85, 149.98, 149.92, 149.61, 135.40, 131.93, 123.96, 123.84, 39.23, 28.93.

LC-MS (0-100% B, 19 min): t_R (**136**) = 1.98 min, m/z: calculated = 213.25 $[M+H]^+$, found = 213.23 $[M+H]^+$.

(R)-3-(pyridin-4-yl)-1-(pyridin-3-yl)propan-1-ol (AV761)



Chemical Formula: $C_{13}H_{14}N_2O$
Exact Mass: 214,11
Molecular Weight: 214,26

137

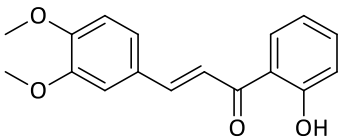
136 (30 mg, 0.14 mmol, 1.0 eq) is dissolved in 5 mL THF. Then a 1 M solution of KO*t*Bu in *t*BuOH (140 µL, 0.14 mmol, 1.0 eq) is added and the solution is sparged with argon for 5 min. $RuCl_2$[(*S*)-(DM-SEGPHOS)][(*S*)-DAIPEN] (7 mg, 0.006 mmol, 0.04 eq) is added. The slurry is sparged with H_2 for 5 min and the reaction is stirred at 1 bar H_2 at r.t. overnight. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (EE + 10% MeOH). The pure product **137** is obtained as a white oil.

Yield 10 mg (33%).

TLC (EE + 10% MeOH): R_f (**137**) = 0.20.

LC-MS (0-100% B, 19 min): t_R (**137**) = 1.83 min, m/z: calculated = 215.34 $[M+H]^+$, found = 215.26 $[M+H]^+$.

(E)-3-(3,4-dimethoxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (AV623/AV628)



Chemical Formula: $C_{17}H_{16}O_4$
Exact Mass: 284,10
Molecular Weight: 284,31

138

2-Hydroxy acetophenone (4.10 g, 30 mmol, 1 eq) and 3,4-dimethoxybenzaldehyde (5.00 g, 30 mmol, 1 eq) are dissolved in 90 mL EtOH. NaOH (2.41 g, 60 mmol, 2.0 eq) dissolved in 6 mL EtOH is dropwise added in 10 min. The reaction is stirred for 2 d. The precipitate is filtered and washed with cooled EtOH. The solvent is removed and the crude product is purified by recrystallization in EtOH. The crystals are filtered off, dissolved in 70 mL 1 M HCl and extracted with DCM (3x50 mL), the combined organic phases dried with $MgSO_4$ and the solvent removed under reduced pressure. Compound **138** is obtained as yellow solid.

Yield 2.89 g (33%).

TLC (CH/EE, 3/1, v/v): R_f (**138**) = 0.34

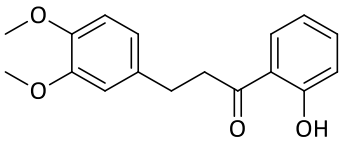
^{1}H-NMR (300 MHz, $CDCl_3$): δ 12.90 (s, 1H), 7.95 – 7.85 (m, 2H), 7.56 – 7.44 (m, 2H), 7.32 – 7.25 (m, 1H), 7.18 (d, J = 2.1 Hz, 1H), 7.03 (dd, J = 1.2, 8.4 Hz, 1H), 6.99 – 6.89 (m, 2H), 3.97 (s, 3H), 3.94 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 193.73, 163.72, 152.01, 149.51, 145.80, 136.31, 129.68, 127.79, 123.72, 120.27, 118.88, 118.77, 117.99, 111.37, 110.53, 56.19.

LC-MS (30-100% B, 19 min): t_R (**138**) = 10.65 min, m/z: calculated = 285.31 $[M+H]^+$, found = 285.17 $[M+H]^+$.

RP-HPLC (30 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**138**) = 10.43 min (98% Purity).

3-(3,4-dimethoxyphenyl)-1-(2-hydroxyphenyl)propan-1-one (AV499/AV632)



Chemical Formula: $C_{17}H_{18}O_4$
Exact Mass: 286,12
Molecular Weight: 286,32

139

138 (700 mg, 1.7 mmol, 1.0 eq) is dissolved in 40 mL THF and flushed with argon for 5 min. Then 10 wt% Pd/C (30 mg, 0.01 eq) is added and the mixture flushed with H_2 for 10 min. The reaction is stirred under 1 atm H_2 for 60 min, then filtered over celite, the solvent removed and the crude product recrystallized in MeOH. The pure product **139** is obtained as a white solid.

Yield 605 mg (86%).

TLC (CH/EE, 4/1, v/v): R_f (**139**) = 0.30.

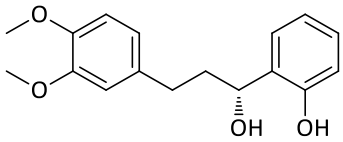
^{1}H-NMR (300 MHz, $CDCl_3$): δ 12.23 (s, 1H), 7.67 (dd, *J* = 1.6, 8.1 Hz, 1H), 7.39 (ddd, *J* = 1.7, 7.2, 8.4 Hz, 1H), 6.91 (ddd, *J* = 0.4, 1.2, 8.4 Hz, 1H), 6.81 (ddd, *J* = 1.2, 7.2, 8.2 Hz, 1H), 6.72 (q, *J* = 1.9 Hz, 2H), 6.69 (d, *J* = 1.8 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.27 – 3.17 (m, 2H), 2.95 (dd, *J* = 6.9, 8.3 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 205.59, 162.47, 149.00, 147.57, 136.37, 133.37, 129.85, 120.25, 119.34, 118.94, 118.58, 111.95, 111.55, 55.99, 55.90, 40.28, 29.81.

LC-MS (30-100% B, 19 min): t_R (**139**) = 10.18 min, m/z: calculated = 287.12 $[M+H]^+$, found = 287.16 $[M+H]^+$.

RP-HPLC (30 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**139**) = 11.36 min (99% Purity).

(R)-2-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenol (AV634/AV645)



Chemical Formula: $C_{17}H_{20}O_4$
Exact Mass: 288,14
Molecular Weight: 288,34

140

S-CBS (31 mg, 0.11 mmol, 0.1 eq) is dissolved in 3.7 mL dry THF and added to a flask under argon atmosphere. 55 µL (0.1 eq) of a 2 M BH_3*SMe_2 solution in THF is added. **139** (315 mg, 1.10 mmol, 1.0 eq) is dissolved in 2.70 mL dry THF and added to the catalyst. Then 825 µL (1.5 eq) of a 2 M BH_3*SMe_2 solution in THF is added dropwise in 1 h. After complete addition, the reaction is further stirred for 2 h, then stopped by the addition of MeOH and quenched for 1 h. The solvent is removed under reduced pressure. The crude product is purified by silica column chromatography (CH/EE, 4/1). The pure product **140** is obtained as a colorless solid.

Yield 170 mg (53%).

TLC (CH/EE, 4/1): R_f (**140**) = 0.25.

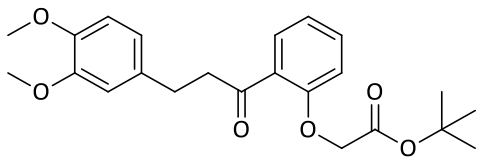
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.19 – 7.14 (m, 1H), 6.90 (ddd, J = 1.3, 7.9, 27.8 Hz, 2H), 6.86 – 6.77 (m, 2H), 6.76 – 6.71 (m, 2H), 4.84 (dd, J = 5.3, 8.3 Hz, 1H), 3.86 (d, J = 1.1 Hz, 3H), 3.85 (d, J = 1.1 Hz, 3H), 2.78 – 2.62 (m, 2H), 2.30 – 2.05 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 155.71, 149.09, 147.48, 133.99, 129.12, 127.43, 127.26, 120.38, 119.90, 117.38, 111.90, 111.52, 75.57, 56.09, 56.01, 38.66, 31.70.

LC-MS (30-100% B, 19 min): t_R (**140**) = 7.25 min, m/z: calculated = 269.32 $[M-H_2O]^+$, found = 269.44 $[M-H_2O]^+$.

RP-HPLC (30 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**140**) = 6.18 min (99% Purity).

tert-butyl 2-(2-(3-(3,4-dimethoxyphenyl)propanoyl)phenoxy)acetate (AV534/AV541/AV554)



Chemical Formula: $C_{23}H_{28}O_6$
Exact Mass: 400,19
Molecular Weight: 400,46

141

139 (86 mg, 0.30 mmol, 1.0 eq) is dissolved in 3 mL MeCN. K_2CO_3 (83 mg, 0.6 mmol, 2.0 eq) and *tert*-butyl bromoacetate (53 µL 0.36 mmol, 1.2 eq) is added. The reaction is stirred at 70°C overnight. After complete conversion, the suspension is filtered, washed with MeCN and the solvent removed under reduced pressure. The crude product **141** is obtained as a colorless oil and used without further purification.

Yield 120 mg (quant.).

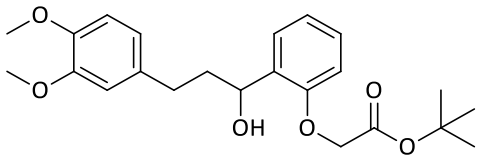
TLC (CH/EE, 2/1): R_f (**141**) = 0.33.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.68 (dd, *J* = 1.9, 7.7 Hz, 1H), 7.45 – 7.38 (m, 1H), 7.06 – 6.97 (m, 1H), 6.82 – 6.78 (m, 4H), 4.58 (s, 2H), 3.86 (s, 3H), 3.84 (d, *J* = 0.5 Hz, 3H), 3.42 (dd, *J* = 7.1, 8.2 Hz, 2H), 2.99 (t, *J* = 7.6 Hz, 2H), 1.45 (d, *J* = 0.6 Hz, 9H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 201.98, 167.28, 156.77, 148.95, 147.34, 134.52, 133.26, 130.75, 129.07, 121.71, 120.42, 112.17, 112.13, 111.41, 82.80, 66.07, 56.08, 55.93, 45.73, 30.18, 28.15.

LC-MS (50-100% B, 19 min): t_R (**141**) = 8.03 min, m/z: calculated = 423.15 $[M+Na]^+$, found = 422.98 $[M+Na]^+$.

tert-butyl 2-(2-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenoxy)acetate (AV539/AV542)



Chemical Formula: $C_{23}H_{30}O_6$
Exact Mass: 402,20
Molecular Weight: 402,48

142

141 (10 mg, 0.03 mmol, 1.0 eq) is dissolved in 2 mL MeOH. $CeCl_3$ (12 mg, 0.03 mmol, 1.2 eq) and subsequently $NaBH_4$ (1.8 mg, 0.05 mmol, 2.0 eq) is added and the reaction stirred at r.t. overnight. The mixture is diluted with 2 mL MeOH and quenched with a few drops of glacial acetic acid. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 3/1). The pure product **142** is obtained as a colorless oil.

Yield 7 mg (70%).

TLC (CH/EE, 3/1): R_f (**142**) = 0.25.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.30 – 7.25 (m, 2H), 7.22 (td, *J* = 1.8, 7.8 Hz, 1H), 6.98 (tq, *J* = 1.3, 7.4 Hz, 1H), 6.81 – 6.73 (m, 4H), 4.87 (dd, *J* = 5.1, 8.4 Hz, 1H), 4.62 – 4.51 (m, 2H), 3.86 (t, *J* = 1.3 Hz, 3H), 3.85 (d, *J* = 0.9 Hz, 3H), 2.87 – 2.57 (m, 2H), 2.30 – 2.06 (m, 2H), 1.50 – 1.47 (m, 9H).

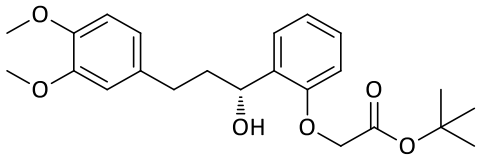
^{13}C-NMR (126 MHz, $CDCl_3$): δ 168.16, 155.61, 148.94, 147.24, 135.08, 133.12, 128.50, 127.89, 121.92, 120.39, 112.10, 112.01, 111.40, 82.99, 71.30, 66.07, 56.10, 55.96, 38.64, 32.24, 28.22.

LC-MS (50-100% B, 19 min): t_R (**142**) = 6.78 min, m/z: calculated = 425.19 $[M+Na]^+$, found = 425.20 $[M+H]^+$.

RP-HPLC (30 – 100% B, 1.0 mL/min, 15 min, 220 nm): t_R (**142**) = 10.25 min (96% Purity).

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**142**) = 10.21 min, 12.13 min.

(R)-tert-butyl 2-(2-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenoxy)acetate (AV543/AV557)



Chemical Formula: $C_{23}H_{30}O_6$
Exact Mass: 402,20
Molecular Weight: 402,48

143

K_2CO_3 (100 mg, 0.60 mmol, 2.0 eq) is filled into an autoclave (Roth, Model II). **141** (120 mg, 0.30 mmol, 1.0 eq) is dissolved in 20 mL iPrOH and added to the autoclave. The solution is sparged with argon for 10 min, then $RuCl_2$[(*S*)-(DM-SEGPHOS)][(*S*)-DAIPEN] (20 mg, 0.02 mmol, 0.05 eq) is added and the autoclave closed, then flushed 3x with H_2 and 10 bar H_2 applied. After 5 d reaction time, the mixture is transferred to a beaker and filtered through celite and washed with MeOH. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 4/1).
The pure product **143** is obtained as a colorless oil.

Yield 95 mg (78%).

TLC (CH/EE, 2/1): R_f (**143**) = 0.33.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.24 (m, 1H), 7.22 (td, *J* = 1.8, 7.9 Hz, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.83 – 6.70 (m, 5H), 4.87 (dd, *J* = 5.2, 8.4 Hz, 1H), 4.62 – 4.50 (m, 2H), 3.86 (s, 3H), 3.85 (s, 4H), 2.73 (dddd, *J* = 6.0, 10.0, 14.1, 77.2 Hz, 2H), 2.39 – 2.06 (m, 2H), 1.48 (d, *J* = 2.1 Hz, 9H).

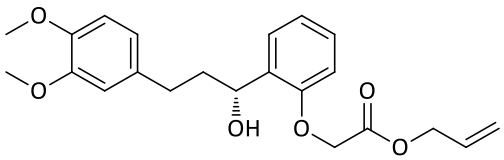
^{13}C-NMR (126 MHz, $CDCl_3$): δ 168.16, 155.61, 148.94, 147.23, 135.08, 133.12, 128.50, 127.89, 121.92, 120.39, 112.10, 112.01, 111.40, 82.99, 71.30, 66.07, 56.10, 55.96, 38.64, 32.24, 29.85, 28.22.

LC-MS (50-100% B, 19 min): t_R (**143**) = 6.78 min, m/z: calculated = 425.19 $[M+Na]^+$,
found = 425.16 $[M+Na]^+$.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**143**) = 6.65 min (95% Purity).

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**7**) = 10.25 min (*er* = 81.57/18.43).

(R)-allyl 2-(2-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenoxy)acetate (AV635/AV647)



Chemical Formula: $C_{22}H_{26}O_6$
Exact Mass: 386,17
Molecular Weight: 386,44

144

140 (145 mg, 0.5 mmol, 1.0 eq) is dissolved in 10 mL MeCN and K_2CO_3 (140 mg, 1 mmol, 2.0 eq) and **69** (120 mg, 0.65 mmol, 1.3 eq) are added. The reaction is stirred at r.t. overnight. The slurry is filtered and the solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 2/1). The pure product **144** is obtained as a colorless oil.

Yield 131 mg (67%).

TLC (CH/EE, 2/1): R_f (**144**) = 0.30.

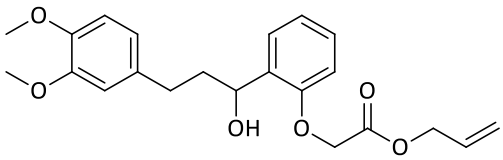
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.31 (dd, J = 1.7, 7.6 Hz, 1H), 7.25 – 7.12 (m, 1H), 7.00 (td, J = 1.0, 7.5 Hz, 1H), 6.89 (ddd, J = 1.4, 7.9, 24.5 Hz, 1H), 6.84 – 6.70 (m, 3H), 5.91 (ddt, J = 5.9, 10.4, 16.6 Hz, 1H), 5.33 (dq, J = 1.5, 17.2 Hz, 1H), 5.27 (dq, J = 1.3, 10.4 Hz, 1H), 4.92 (dd, J = 5.1, 8.3 Hz, 1H), 4.70 (m, 4H), 3.85 (m, 6H), 2.84 – 2.59 (m, 2H), 2.29 – 2.02 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 168.76, 155.28, 148.91, 147.21, 134.99, 133.23, 131.36, 128.53, 127.85, 122.16, 120.36, 119.47, 112.07, 111.94, 111.39, 70.88, 66.18, 65.53, 56.07, 55.93, 38.72, 32.15.

LC-MS (50-100% B, 19 min): t_R (**144**) = 9.55 min, m/z: calculated = 369.42 $[M\text{-}OH+H]^+$, found = 369.33 $[M\text{-}OH+H]^+$.

RP-HPLC (30 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**144**) = 8.91 min (98% Purity).

allyl 2-(2-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenoxy)acetate (AV637/AV640/AV642)



Chemical Formula: $C_{22}H_{26}O_6$
Exact Mass: 386,17
Molecular Weight: 386,44

145

144 (15 mg, 0.04 mmol, 1.0 eq) is dissolved in 2 mL dry THF. $CeCl_3$ (14 mg, 0.04 mmol, 1.0 eq) and subsequently $NaBH_4$ (1.5 mg, 0.05 mmol, 1.0 eq) is added and the reaction stirred for 5 min. The mixture is diluted with 2 mL MeOH and quenched with a few drops of glacial acetic acid. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 2/1). The pure product **145** is obtained as a colorless oil.

Yield 15 mg (quant.).

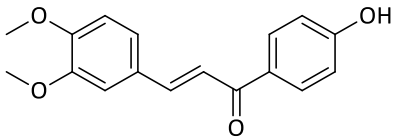
TLC (CH/EE, 2/1): R_f (**145**) = 0.31.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.32 (dd, J = 1.7, 7.5 Hz, 1H), 7.23 (ddd, J = 1.7, 7.4, 8.1 Hz, 1H), 7.00 (td, J = 1.0, 7.4 Hz, 1H), 6.80 – 6.74 (m, 4H), 5.91 (ddt, J = 5.9, 10.5, 17.1 Hz, 1H), 5.34 (dq, J = 1.5, 17.2 Hz, 1H), 5.27 (dq, J = 1.2, 10.5 Hz, 1H), 4.93 (dd, J = 5.1, 8.3 Hz, 1H), 4.76 – 4.66 (m, 4H), 3.86 (s, 3H), 3.85 (s, 3H), 2.73 (dddd, J = 5.9, 10.0, 13.9, 74.0 Hz, 2H), 2.26 – 2.08 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 168.74, 155.29, 148.93, 147.23, 135.02, 133.30, 131.39, 128.53, 127.86, 122.17, 120.37, 119.47, 112.08, 111.93, 111.39, 70.86, 66.18, 65.55, 56.09, 55.95, 38.75, 32.18.

LC-MS (50-100% B, 19 min): t_R (**145**) = 9.64 min, m/z: calculated = 369.42 $[M\text{-}OH+H]^+$, found = 369.29 $[M\text{-}OH+H]^+$.

(E)-3-(3,4-dimethoxyphenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (AV553/AV559)



Chemical Formula: $C_{17}H_{16}O_4$
Exact Mass: 284,10
Molecular Weight: 284,31

146

3,4-Dimethoxybenzaldehyde (5.0 g, 30 mmol, 1 eq) and 4'-hydroxyacetophenon (4.1 g, 30 mmol, 1 eq) are dissolved in 70 mL EtOH. KOH (13.5 g, 240 mmol, 8.0 eq) is added directly. The reaction is stirred over two days. The mixture is cooled to 0°C, diluted with H_2O (200 mL) and acidified with conc. HCl until precipitation is observed. After stirring overnight, the precipitate is filtered, washed with H_2O, dissolved in EE, dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The product **146** is used as crude in further reactions.

Yield 6.4g (75%).

TLC (CH/EE, 2/1, v/v**):** R_f (**146**) = 0.20.

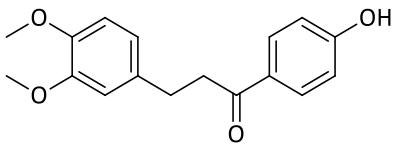
^{1}H-NMR (500 MHz, DMSO-d_6): δ 10.38 (s, 1H), 8.12 – 8.01 (m, 2H), 7.80 (dd, *J* = 1.3, 15.4 Hz, 1H), 7.65 (dd, *J* = 1.3, 15.4 Hz, 1H), 7.52 (d, *J* = 1.6 Hz, 1H), 7.35 (dt, *J* = 1.6, 8.3 Hz, 1H), 7.00 (dd, *J* = 1.3, 8.4 Hz, 1H), 6.91 (dd, *J* = 1.4, 8.6 Hz, 2H), 3.86 (d, *J* = 1.3 Hz, 3H), 3.81 (d, *J* = 1.3 Hz, 3H).

^{13}C-NMR (126 MHz, DMSO-d_6): δ 187.05, 161.99, 151.01, 149.01, 143.17, 131.03, 129.36, 127.73, 123.57, 119.67, 115.29, 111.55, 110.65, 55.72, 55.56.

LC-MS (30-100% B, 19 min): t_R (**146**) = 7.25 min, m/z: calculated = 285.31 $[M+H]^+$,
found = 285,23 $[M+H]^+$.

RP-HPLC (30 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**146**) = 6.39 min (99% Purity).

3-(3,4-dimethoxyphenyl)-1-(4-hydroxyphenyl)propan-1-one (AV565)



Chemical Formula: $C_{17}H_{18}O_4$
Exact Mass: 286,12
Molecular Weight: 286,32

147

Zn powder (11.50 g, 180 mmol, 10.0 eq) and NH_4Cl (9.41 g, 180 mmol, 10.0 eq) are added to a flask and suspended in 50 mL MeOH. **146** (5.00 g, 18 mmol, 1.0 eq) is dissolved in 50 mL THF and diluted

with 50 mL MeOH, then added dropwise to the vigorously stirring suspension in 40 min. After complete addition, the mixture is filtered and washed with MeOH. The mixture is then concentrated by 100 mL under reduced pressure. 100 mL H_2O is added, to precipitate the product. The crude product is filtered and recrystallized in MeOH. The pure product **147** is obtained as a white solid.

Yield 2.55 g (51%).

TLC (CH/EE, 2/1, v/v): R_f (**147**) = 0.23.

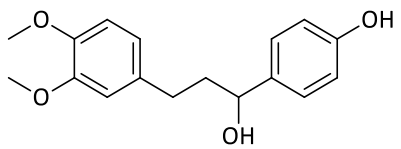
^{1}H-NMR (500 MHz, DMSO-d_6): δ 10.30 (s, 1H), 7.97 – 7.78 (m, 2H), 6.87 (d, *J* = 2.0 Hz, 1H), 6.85 (s, 1H), 6.84 – 6.80 (m, 2H), 6.75 (dd, *J* = 2.0, 8.2 Hz, 1H), 3.73 (d, *J* = 0.8 Hz, 3H), 3.70 (d, *J* = 0.7 Hz, 3H), 3.21 (t, *J* = 7.6 Hz, 2H), 2.84 (t, *J* = 7.6 Hz, 2H).

^{13}C-NMR (126 MHz, DMSO-d_6): δ 197.38, 161.90, 148.61, 147.02, 133.88, 130.43, 128.31, 120.06, 115.15, 112.45, 111.90, 55.54, 55.40, 29.47.

LC-MS (30-100% B, 19 min): t_R (**147**) = 7.32 min, m/z: calculated = 287.12 $[M+H]^+$, found = 287.13 $[M+H]^+$.

RP-HPLC (30 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**147**) = 6.04 min (79% Purity).

4-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenol (AV572)



Chemical Formula: $C_{17}H_{20}O_4$
Exact Mass: 288,14
Molecular Weight: 288,34

148

147 (50 mg, 0.17 mmol, 1.0 eq) is dissolved in 2 mL iPrOH. $CeCl_3$ (68 mg, 0.17 mmol, 1.0 eq) and subsequently $NaBH_4$ (12 mg, 0.34 mmol, 2.0 eq) is added and the reaction stirred at r.t. overnight. The mixture is diluted with 2 mL MeOH and quenched with a few drops of glacial acetic acid. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 2/1). The pure product **148** is obtained as a white solid.

Yield 50 mg (quant.).

TLC (CH/EE, 1/2): R_f (**148**) = 0.50.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.23 – 7.18 (m, 2H), 6.83 – 6.76 (m, 3H), 6.73 – 6.68 (m, 2H), 4.62 (dd, *J* = 5.6, 7.7 Hz, 1H), 3.84 (s, 6H), 2.62 (dddd, *J* = 6.1, 9.5, 14.0, 39.1 Hz, 2H), 2.17 – 1.91 (m, 2H).

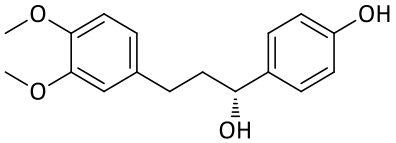
^{13}C-NMR (126 MHz, $CDCl_3$): δ 155.49, 148.97, 147.32, 136.62, 134.56, 127.58, 120.38, 115.50, 112.00, 111.50, 73.78, 56.09, 55.97, 40.54, 31.86, 29.84.

LC-MS (30-100% B, 19 min): t_R (**148**) = 5.50 min, m/z: calculated = 270.12 $[M-H_2O]^+$, found = 269.45 $[M-H_2O]^+$.

RP-HPLC (30 – 100% B, 1.0 mL/min, 15 min, 220 nm): t_R (**148**) = 4.71 min (96% Purity).

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**148**) = 19.88 min, 20.24 min.

(R)-4-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenol (AV570)



Chemical Formula: $C_{17}H_{20}O_4$
Exact Mass: 288,14
Molecular Weight: 288,34

149

147 (300 mg, 1 mmol, 1.0 eq) is dissolved in 10 mL iPrOH. Then KOtBu (117 µL, 1 mmol, 1 eq) is added and the solution is sparged with argon for 5 min. $RuCl_2$[(S)-(DM-SEGPHOS)][(S)-DAIPEN] (25 mg, 0.02 mmol, 0.02 eq) is added and the solution sparged with H_2 for 5 min, then the reaction stirred at 1 bar H_2 at r.t. over three days. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 3/1). The pure product **149** is obtained as a white solid.

Yield 254 mg (84%).

TLC (CH/EE, 1/1, v/v): R_f (**149**) = 0.29.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.26 (d, *J* = 0.8 Hz, 1H), 7.24 – 7.21 (m, 2H), 6.84 – 6.80 (m, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.74 – 6.69 (m, 2H), 4.63 (dd, *J* = 5.5, 7.8 Hz, 1H), 3.91 – 3.81 (m, 6H), 2.71 – 2.55 (m, 2H), 2.19 – 1.93 (m, 2H).

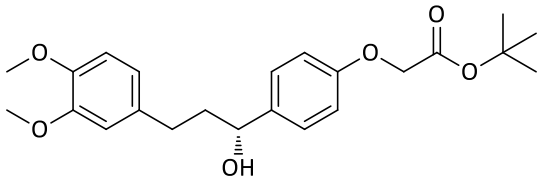
^{13}C-NMR (126 MHz, $CDCl_3$): δ 136.87, 134.58, 127.57, 120.36, 115.48, 111.98, 111.48, 73.71, 60.58, 56.10, 55.98, 40.64, 31.89, 21.19, 14.34.

LC-MS (30-100% B, 19 min): t_R (**149**) = 5.42 min, m/z: calculated = 270.12 $[M-H_2O]^+$, found = 269.40 $[M-H_2O]^+$.

RP-HPLC (30 – 100% B, 1.0 mL/min, 15 min, 220 nm): t_R (**148**) = 4.71 min (99% Purity).

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**149**) = 19.83 min (*er* = 94.44/5.56).

(R)-tert-butyl 2-(4-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenoxy)acetate (AV582)



Chemical Formula: $C_{23}H_{30}O_6$
Exact Mass: 402,20
Molecular Weight: 402,48

150

149 (30 mg, 0.10 mmol, 1.0 eq) is dissolved in 3 mL MeCN. K_2CO_3 (29 mg, 0.2 mmol, 2.0 eq) and *tert*-butyl bromoacetate (18 µL 0.12 mmol, 1.2 eq) is added. The reaction is stirred at r.t. overnight. After complete conversion, the suspension is filtered, washed with MeCN and the solvent removed under reduced pressure. The crude product **150** is obtained as a colorless oil and used without further purification.

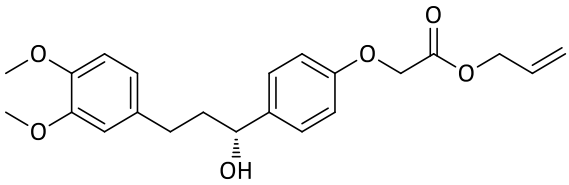
Yield 41 mg (quant.).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.24 (m, 2H), 6.88 (dt, *J* = 1.7, 8.8 Hz, 2H), 6.78 (dd, *J* = 0.8, 8.0 Hz, 1H), 6.74 – 6.68 (m, 2H), 4.66 – 4.60 (m, 1H), 4.50 (d, *J* = 0.9 Hz, 2H), 3.87 – 3.83 (m, 6H), 2.71 – 2.54 (m, 2H), 2.16 – 1.92 (m, 2H), 1.48 (d, *J* = 0.9 Hz, 9H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 168.14, 157.60, 149.00, 147.34, 137.76, 134.55, 127.35, 120.32, 114.74, 111.94, 111.45, 82.51, 73.57, 65.91, 56.08, 55.97, 40.66, 31.84, 28.19, 27.95.

LC-MS (50-100% B, 19 min): t_R (**141**) = 6.00 min, m/z: calculated = 425.19 $[M+Na]^+$, found = 425.40 $[M+Na]^+$.

(R)-allyl 2-(4-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenoxy)acetate (AV608)



Chemical Formula: $C_{22}H_{26}O_6$
Exact Mass: 386,17
Molecular Weight: 386,44

151

149 (30 mg, 0.10 mmol, 1.0 eq) is dissolved in 3 mL MeCN. K_2CO_3 (29 mg, 0.21 mmol, 2.0 eq) and **69** (23 mg 0.13 mmol, 1.2 eq) are added. The reaction is stirred at r.t. overnight. After complete conversion, the suspension is filtered, washed with MeCN and the solvent removed under reduced

pressure. The crude product **151** is purified by silica column chromatography (CH/EE, 2/1) and obtained as a colorless oil.

Yield 28 mg (70%).

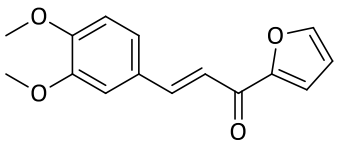
TLC (CH/EE, 3/2): R_f (**151**) = 0.35.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.24 – 7.17 (m, 3H), 6.85 – 6.80 (m, 2H), 6.71 (d, J = 8.0 Hz, 1H), 6.65 (d, J = 9.0 Hz, 2H), 5.85 (ddt, J = 5.8, 10.2, 16.5 Hz, 1H), 5.26 (dd, J = 1.5, 17.1 Hz, 1H), 5.22 – 5.15 (m, 1H), 4.67 – 4.60 (m, 2H), 4.58 (s, 3H), 3.78 (d, J = 1.5 Hz, 6H), 2.55 (tdd, J = 7.2, 11.3, 14.2 Hz, 2H), 2.10 – 1.83 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 168.73, 157.45, 149.01, 147.36, 138.08, 134.50, 131.54, 127.42, 120.32, 119.25, 114.83, 111.94, 111.46, 73.52, 65.99, 65.57, 56.08, 55.97, 40.67, 31.82.

LC-MS (50-100% B, 19 min): t_R (**151**) = 4.70 min, m/z: calculated = 404.20 $[M+NH_4]^+$, found = 404.65 $[M+NH_4]^+$.

(E)-3-(3,4-dimethoxyphenyl)-1-(furan-2-yl)prop-2-en-1-one (MedChem19_CS2_14)



Chemical Formula: $C_{15}H_{14}O_4$
Exact Mass: 258,09
Molecular Weight: 258,27

152

3,4-Dimethoxybenzaldehyde (1.50 g, 9 mmol, 1 eq) and 4'-Hydroxyacetophenon (0.91 mL, 9 mmol, 1 eq) are dissolved in 30 mL EtOH and cooled to 0°C. KOH (2.04 g, 36 mmol, 4.0 eq) is dissolved in 20 mL H_2O, cooled and added slowly to the solution. The reaction is stirred for 2 h, then ice added and acidified with conc. HCl. The resulting precipitate is filtered and washed with H_2O, then dissolved in EE, dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The product **152** is obtained as yellow solid and used as crude in further reactions.

Yield 1.64 g (70%).

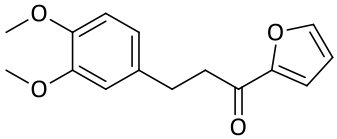
TLC (CH/EE, 1/1, v/v**):** R_f (**152**) = 0.25.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.74 (d, *J* = 15.7 Hz, 1H), 7.56 (dd, *J* = 0.8, 1.7 Hz, 1H), 7.27 – 7.20 (m, 2H), 7.15 (dd, *J* = 2.0, 8.3 Hz, 1H), 7.08 (d, *J* = 1.9 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.50 (dd, *J* = 1.7, 3.6 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 178.14, 153.96, 151.63, 149.36, 146.34, 144.18, 127.85, 123.44, 119.16, 117.20, 112.57, 111.25, 110.29, 56.09.

LC-MS (0-100% B, 19 min): t_R (**152**) = 8.23 min, m/z: calculated = 259.27 $[M+H]^+$, found = 259.20 $[M+H]^+$.

3-(3,4-dimethoxyphenyl)-1-(furan-2-yl)propan-1-one (MedChem19_Zn1_14)



Chemical Formula: $C_{15}H_{16}O_4$
Exact Mass: 260,10
Molecular Weight: 260,29

153

Zn powder (6.42 g, 120 mmol, 10.0 eq) and NH_4Cl (7.85 g, 120 mmol, 10.0 eq) are added to a flask and suspended in 50 mL MeOH. **152** (3.10 g, 12 mmol, 1.0 eq) is dissolved in 200 mL MeOH, then added dropwise to the vigorously stirring suspension in 2 h. After complete addition, the mixture is filtered and washed with MeOH. The filtrate is concentrated under reduced pressure, then diluted with 100 mL H_2O and extracted with DCM (3×100 mL). The combined organic layers are dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 3/1). The pure product **153** is obtained as a white solid.

Yield 740 mg (24%).

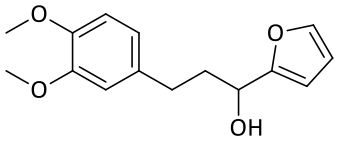
TLC (CH/EE, 3/1, v/v): R_f (**153**) = 0.22.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.56 (dd, *J* = 0.8, 1.7 Hz, 1H), 7.15 (dd, *J* = 0.8, 3.5 Hz, 1H), 6.80 – 6.73 (m, 3H), 6.51 (dd, *J* = 1.7, 3.5 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.15 – 3.09 (m, 2H), 2.98 (dd, *J* = 6.8, 8.3 Hz, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 188.66, 152.86, 149.06, 147.60, 146.38, 133.75, 120.33, 117.06, 112.30, 112.04, 111.55, 56.06, 55.97, 40.50, 29.77.

LC-MS (0-100% B, 19 min): t_R (**153**) = 7.98 min, m/z: calculated = 261.29 $[M+H]^+$, found = 261.01 $[M+H]^+$.

3-(3,4-dimethoxyphenyl)-1-(furan-2-yl)propan-1-ol (AV573)



Chemical Formula: $C_{15}H_{18}O_4$
Exact Mass: 262,12
Molecular Weight: 262,30

154

153 (20 mg, 0.08 mmol, 1.0 eq) is dissolved in 2 mL iPrOH. $NaBH_4$ (3 mg, 0.08 mmol, 1.0 eq) is added and the reaction stirred at r.t. overnight. The mixture is diluted with 2 mL MeOH and quenched with a few drops of glacial acetic acid. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 3/1). The pure product **154** is obtained as a colorless oil.

Yield 19 mg (95%).

TLC (CH/EE, 3/1): R_f (**154**) = 0.20.

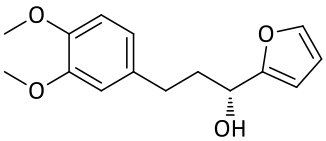
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.45 – 7.35 (m, 1H), 6.85 – 6.69 (m, 3H), 6.34 (dd, *J* = 1.9, 3.3 Hz, 1H), 6.25 (d, *J* = 3.3 Hz, 1H), 4.69 (q, *J* = 6.4 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.80 – 2.59 (m, 2H), 2.23 – 2.09 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 156.75, 149.06, 147.46, 142.14, 134.24, 120.42, 112.01, 111.50, 110.30, 106.11, 67.15, 56.10, 55.98, 37.33, 31.50.

LC-MS (30-100% B, 19 min): t_R (**154**) = 7.05 min, m/z: calculated = 245.10 $[M-OH]^+$, found = 245.20 $[M-OH]^+$.

RP-HPLC (30 – 100% B, 1.0 mL/min, 15 min, 220 nm): t_R (**154**) = 6.03 min (99% Purity).

(R)-3-(3,4-dimethoxyphenyl)-1-(furan-2-yl)propan-1-ol (MedChem19_chir_14/AV571)



Chemical Formula: $C_{15}H_{18}O_4$
Exact Mass: 262,12
Molecular Weight: 262,30

155

S-CBS (21 mg, 0.07 mmol, 0.1 eq) is dissolved in 2.6 mL dry THF and added to a flask under argon atmosphere. 40 µL (0.1 eq) of a 2 M BH_3*SMe_2 solution in THF is added. **153** (200 mg, 0.70 mmol, 1.0 eq) is dissolved in 2.6 mL dry THF and added to the catalyst. Then 600 µL (1.5 eq) of a 2 M BH_3*SMe_2 solution in THF is added dropwise in 1 h. After complete addition, the reaction is further stirred for 2 h, then stopped by the addition of MeOH and quenched for 1 h. The solvent is removed under reduced pressure. The crude product **155** is obtained as a yellow oil and used without purification.

Yield 170 mg (84%).

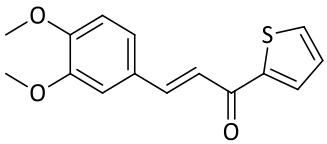
TLC (CH/EE, 3/1, v/v): R_f (**155**) = 0.14.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 0.8, 1.8 Hz, 1H), 6.84 – 6.70 (m, 3H), 6.34 (dd, *J* = 1.8, 3.3 Hz, 1H), 6.24 (d, *J* = 3.2 Hz, 1H), 4.68 (td, *J* = 3.9, 6.7 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.79 – 2.57 (m, 2H), 2.16 (td, *J* = 6.5, 7.8 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 156.75, 149.04, 147.44, 142.12, 134.24, 120.41, 112.00, 111.49, 110.30, 106.10, 67.14, 56.09, 55.97, 37.32, 31.49.

LC-MS (0-100% B, 19 min): t_R (**155**) = 7.15 min, m/z: calculated = 245.29 $[M-OH]^+$, found = 245.22 $[M-OH]^+$.

(E)-3-(3,4-dimethoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one (MedChem19_CS_12)



Chemical Formula: $C_{15}H_{14}O_3S$
Exact Mass: 274,07
Molecular Weight: 274,33

156

3,4-Dimethoxybenzaldehyde (6.54 g, 40 mmol, 1 eq) and 1-(thiophene-2-yl)ethanone (5.00 g, 40 mmol, 1 eq) are dissolved in 30 mL EtOH and cooled to 0°C. KOH (2.04 g, 36 mmol, 4.0 eq) is dissolved in 20 mL H_2O, cooled and added slowly to the solution. The reaction is stirred for 4 h, then ice is added and acidified to pH = 1 with conc. HCl. 50 mL H_2O is added to the mixture, then extracted with DCM (3×100 mL), dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The product **156** is obtained as yellow solid and used as crude in further reactions.

Yield 10.89 g. (10.97 max. yield)

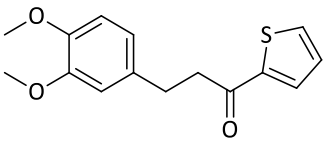
TLC (DCM + 0.1% MeOH**):** R_f (**156**) = 0.23.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.85 – 7.70 (m, 1H), 7.68 – 7.56 (m, 2H), 7.41 (dd, *J* = 1.9, 8.2 Hz, 1H), 7.36 (d, *J* = 1.9 Hz, 1H), 7.24 – 7.15 (m, 1H), 7.15 – 7.09 (m, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.61, 149.75, 144.29, 133.83, 133.63, 132.52, 131.60, 130.27, 128.25, 128.18, 126.93, 123.25, 119.65, 111.30, 110.53, 110.42, 109.10, 56.11.

LC-MS (30-100% B, 19 min): t_R (**156**) = 9.07 min, m/z: calculated = 275.07 $[M+H]^+$, found = 275.29 $[M+H]^+$.

3-(3,4-dimethoxyphenyl)-1-(thiophen -2-yl)propan-1-one (MedChem19_Zn_12/AV589)



Chemical Formula: $C_{15}H_{16}O_3S$
Exact Mass: 276,08
Molecular Weight: 276,35

157

156 (220 mg, 0.80 mmol, 1.0 eq) is added to a flask under argon atmosphere and dissolved in 5 mL dry MeOH. 10 wt% Pd on carbon (42 mg, 0.04 mmol, 0.05 eq) is added to the solution. The mixture is sparged with H_2 for 5 min then stirred at 1 atm H_2 for 1 h. After complete conversion, the reaction is filtered, washed with DCM and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 4/1). The pure product **157** is obtained as a white solid.

Yield 77 mg (35%).

TLC (CH/EE, 3/1, v/v): R_f (**157**) = 0.29.

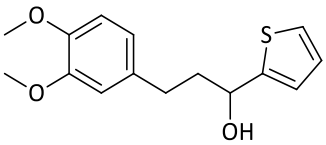
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.67 (dd, *J* = 1.1, 3.8 Hz, 1H), 7.60 (dd, *J* = 1.2, 4.9 Hz, 1H), 7.09 (dd, *J* = 3.7, 5.0 Hz, 1H), 6.78 (ddd, *J* = 1.5, 7.4, 10.9 Hz, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.19 (dd, *J* = 6.9, 8.3 Hz, 2H), 3.01 (dd, *J* = 6.9, 8.3 Hz, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 192.34, 149.00, 147.54, 144.30, 133.69, 133.62, 131.89, 128.15, 120.28, 111.97, 111.48, 56.00, 55.91, 41.44, 30.19.

LC-MS (30-100% B, 19 min): t_R (**157**) = 8.92 min, m/z: calculated = 277.08 $[M+H]^+$,
found = 277.03 $[M+H]^+$.

RP-HPLC (30 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**157**) = 8.02 min (99% Purity).

3-(3,4-dimethoxyphenyl)-1-(thiophen -2-yl)propan-1-ol (MedChem19_rac_12/AV593)



Chemical Formula: $C_{15}H_{18}O_3S$
Exact Mass: 278,10
Molecular Weight: 278,37

158

157 (20 mg, 0.07 mmol, 1.0 eq) is dissolved in 2 mL iPrOH. $NaBH_4$ (3 mg, 0.08 mmol, 1.0 eq) is added and the reaction stirred at r.t. for 1 h. The mixture is diluted with 2 mL MeOH and quenched with two

drops sat. NH_4Cl solution. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 3/1). The pure product **158** is obtained as a colorless oil.

Yield 20 mg (quant.).

TLC (CH/EE, 3/1): R_f (**158**) = 0.60.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.26 (dd, *J* = 1.7, 4.6 Hz, 1H), 7.04 – 6.95 (m, 3H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.77 – 6.69 (m, 2H), 4.96 – 4.89 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.70 (qdd, *J* = 6.3, 9.2, 13.9 Hz, 2H), 2.26 – 2.07 (m, 2H).

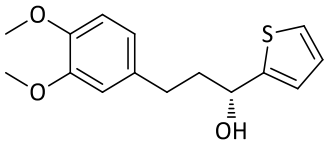
^{13}C-NMR (126 MHz, $CDCl_3$): δ 149.04, 148.68, 147.43, 134.18, 126.79, 124.78, 124.00, 120.40, 111.98, 111.49, 69.63, 56.08, 55.97, 41.01, 31.75.

LC-MS (30-100% B, 19 min): t_R (**158**) = 7.97 min, m/z: calculated = 261.08 $[M-OH]^+$, found = 261.28 $[M-OH]^+$.

RP-HPLC (0 – 100% B, 1.0 mL/min, 15 min, 220 nm): t_R (**158**) = 10.37 min (99% Purity).

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**158**) = 13.40 min, 13.98 min.

(R)-3-(3,4-dimethoxyphenyl)-1-(thiophen -2-yl)propan-1-ol (MedChem19_chir_12)



Chemical Formula: $C_{15}H_{18}O_3S$
Exact Mass: 278,10
Molecular Weight: 278,37

159

S-CBS (6 mg, 0.02 mmol, 0.1 eq) is dissolved in 100 µL dry THF and added to a flask under argon atmosphere. 11 µL (0.1 eq) of a 2 M BH_3*SMe_2 solution in THF is added. **157** (64 mg, 0.23 mmol, 1.0 eq) is dissolved in 750 µL dry THF and added to the catalyst. Then 170 µL (1.5 eq) of a 2 M BH_3*SMe_2 solution in THF is added dropwise in 1 h. After complete addition, the reaction is further stirred for 2 h, then stopped by the addition of MeOH and quenched for 1 h. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (DCM + 1% MeOH). The pure product **159** is obtained as a colorless oil.

Yield 23 mg (35%).

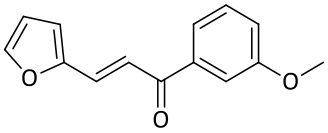
TLC (DCM + 1% MeOH): R_f (**159**) = 0.37.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.28 – 7.27 (m, 1H), 6.98 (d, *J* = 4.6 Hz, 2H), 6.80 (d, *J* = 7.9 Hz, 1H), 6.74 (d, *J* = 7.7 Hz, 2H), 4.93 (d, *J* = 10.9 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.69 (p, *J* = 7.2, 7.8 Hz, 2H), 2.20 (s, 2H).

LC-MS (0-100% B, 19 min): t_R (**159**) = 8.07 min, m/z: calculated = 261.08 $[M-OH]^+$, found = 261.08 $[M-OH]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**159**) = 13.99 min (*er* = 94.86/5.14).

(E)-3-(furan-2-yl)-1-(3-methoxyphenyl)prop-2-en-1-one (MedChem19_CS_11)



Chemical Formula: $C_{14}H_{12}O_3$
Exact Mass: 228,08
Molecular Weight: 228,24

160

Furan-2-carbaldehyde (3.20 g, 33 mmol, 1 eq) and 3'-methoxyacetophenon (5.00 g, 33 mmol, 1 eq) are dissolved in 150 mL EtOH and cooled to 0°C. KOH (2.04 g, 36 mmol, 4.0 eq) is dissolved in 100 mL H_2O, cooled and added slowly to the solution. The reaction is stirred for 3 , then ice added and acidified with conc. HCl. The resulting precipitate is filtered and washed with H_2O, then dissolved in DCM, dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The product **160** is obtained as a yellow oil and used as crude in further reactions.

Yield 7.40 g (7.45 g max. yield).

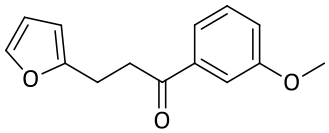
TLC (DCM/MeOH, 100/1, v/v**):** R_f (**160**) = 0.60.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.50 – 7.43 (m, 1H), 7.42 – 7.37 (m, 1H), 7.38 – 7.31 (m, 1H), 7.29 (s, 1H), 7.27 – 7.18 (m, 1H), 6.95 (ddt, *J* = 1.0, 2.7, 7.1 Hz, 1H), 6.55 (d, *J* = 3.4 Hz, 1H), 6.36 (s, 0H), 3.71 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 160.03, 151.81, 145.05, 139.69, 130.80, 129.67, 121.12, 119.52, 119.48, 116.32, 112.83, 112.79, 55.58, 55.55.

LC-MS (30-100% B, 19 min): t_R (**160**) = 10.15 min, m/z: calculated = 229.24 $[M+H]^+$, found = 229.15 $[M+H]^+$.

3-(furan-2-yl)-1-(3-methoxyphenyl)propan-1-one (MedChem19_Zn_11)



Chemical Formula: $C_{14}H_{14}O_3$
Exact Mass: 230,09
Molecular Weight: 230,26

161

Zn powder (10.03 g, 153 mmol, 10.0 eq) and NH_4Cl (8.20 g, 153 mmol, 10.0 eq) are added to a flask and suspended in 30 mL MeOH. **160** (3.50 g, 15 mmol, 1.0 eq) is dissolved in 35 mL MeOH and added dropwise to the vigorously stirring suspension over 2 h. After complete addition, the mixture is filtered and washed with MeOH. The filtrate is concentrated under reduced pressure, then diluted with 100 mL H_2O and extracted with DCM (3×100 mL). The combined organic layers are dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/DCM, 1/1 then CH/DCM, 1/4). The pure product **161** is obtained as grey oil.

Yield 1.26 g (37%).

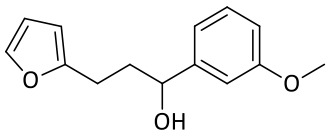
TLC (CH/DCM, 1/4): R_f (**161**) = 0.44.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.54 (ddd, *J* = 1.0, 1.6, 7.6 Hz, 1H), 7.51 – 7.48 (m, 1H), 7.36 (ddd, *J* = 0.4, 7.6, 8.1 Hz, 1H), 7.30 (dd, *J* = 0.9, 1.9 Hz, 1H), 7.10 (ddd, *J* = 1.0, 2.7, 8.3 Hz, 1H), 6.28 (dd, *J* = 1.9, 3.2 Hz, 1H), 6.05 (dq, *J* = 0.9, 3.2 Hz, 1H), 3.84 (s, 3H), 3.34 – 3.27 (m, 2H), 3.13 – 3.04 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 198.47, 159.97, 154.84, 141.17, 138.23, 129.67, 120.73, 119.67, 112.41, 110.33, 105.40, 55.50, 37.11, 22.66.

LC-MS (0-100% B, 19 min): t_R (**161**) = 12.67 min, m/z: calculated = 231.26 $[M+H]^+$, found = 231.17 $[M+H]^+$.

3-(furan-2-yl)-1-(3-methoxyphenyl)propan-1-ol (MedChem19_rac_11)



Chemical Formula: $C_{14}H_{16}O_3$
Exact Mass: 232,11
Molecular Weight: 232,28

162

161 (100 mg, 0.43 mmol, 1.0 eq) is dissolved in 5 mL iPrOH. $NaBH_4$ (33 mg, 0.43 mmol, 1.0 eq) is added and the reaction stirred at r.t. overnight. The mixture is diluted with 2 mL MeOH and quenched with a

few drops conc. HCl. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 3/1). The pure product **162** is obtained as a grey oil.

Yield 91 mg (91%).

TLC (CH/EE, 2/1): R_f (**162**) = 0.50.

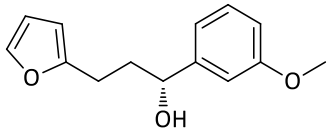
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.22 (dd, *J* = 0.9, 1.9 Hz, 1H), 7.21 – 7.12 (m, 1H), 6.84 (ddt, *J* = 0.7, 2.5, 5.1 Hz, 2H), 6.74 (ddd, *J* = 1.1, 2.5, 8.2 Hz, 1H), 6.20 (dd, *J* = 1.9, 3.2 Hz, 1H), 5.92 (dq, *J* = 0.9, 3.3 Hz, 1H), 4.60 (dd, *J* = 5.6, 7.6 Hz, 1H), 3.73 (s, 3H), 2.69 – 2.58 (m, 2H), 2.13 – 1.90 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 159.97, 155.67, 146.22, 141.07, 129.67, 118.32, 113.26, 111.53, 110.25, 105.15, 73.74, 55.37, 37.26, 24.53.

LC-MS (30-100% B, 19 min): t_R (**162**) = 8.78 min, m/z: calculated = 233.28 $[M+H]^+$, found = 233.13 $[M+H]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**162**) = 6.75 min, 7.25 min.

(R)-3-(furan-2-yl)-1-(3-methoxyphenyl)propan-1-ol (MedChem19_chiral_11)



Chemical Formula: $C_{14}H_{16}O_3$
Exact Mass: 232,11
Molecular Weight: 232,28

163

S-CBS (24 mg, 0.08 mmol, 0.1 eq) is dissolved in 2.9 mL dry THF and added to a flask under argon atmosphere. 50 µL (0.1 eq) of a 2 M BH_3*SMe_2 solution in THF is added. **161** (200 mg, 0.90 mmol, 1.0 eq) is dissolved in 2.9 mL dry THF and added to the catalyst. Then 650 µL (1.5 eq) of a 2 M BH_3*SMe_2 solution in THF is added dropwise in 1.5 h. After complete addition, the reaction is further stirred for 2 h, then stopped by the addition of MeOH and quenched for 1 h. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 4/1). The pure product **163** is obtained as grey oil.

Yield 176 mg (86%).

TLC (CH/EE, 2/1, v/v): R_f (**163**) = 0.45.

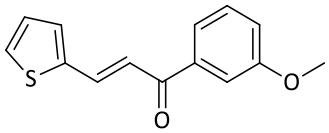
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.22 (dd, *J* = 0.9, 1.9 Hz, 1H), 7.21 – 7.14 (m, 1H), 6.84 (ddt, *J* = 0.8, 2.5, 5.1 Hz, 2H), 6.74 (ddd, *J* = 1.1, 2.5, 8.2 Hz, 1H), 6.20 (dd, *J* = 1.9, 3.2 Hz, 1H), 5.92 (dq, *J* = 0.9, 3.2 Hz, 1H), 4.60 (dd, *J* = 5.6, 7.6 Hz, 1H), 3.73 (s, 3H), 2.70 – 2.59 (m, 2H), 2.12 – 1.94 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 159.97, 155.67, 146.22, 141.08, 129.67, 118.32, 113.26, 111.53, 110.25, 105.16, 73.74, 55.37, 37.26, 24.52.

LC-MS (30-100% B, 19 min): t_R (**163**) = 8.78 min, m/z: calculated = 215.36 $[M-OH]^+$, found = 215.36 $[M-OH]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**163**) = 7.25 min (*er* = 95.31/4.69).

(E)-3-(thiophen-2-yl)-1-(3-methoxyphenyl)prop-2-en-1-one (MedChem19_CS_22)



Chemical Formula: $C_{14}H_{12}O_2S$
Exact Mass: 244,06
Molecular Weight: 244,31

164

Thiophen-2-carbaldehyde (5.00 g, 45 mmol, 1 eq) and 3'-methoxyacetophenon (6.70 g, 45 mmol, 1 eq) are dissolved in 150 mL EtOH and cooled to 0°C. KOH (10.00 g, 178 mmol, 4.0 eq) is dissolved in 100 mL H_2O, cooled and added slowly to the solution. The reaction is stirred overnight, then ice added and acidified with conc. HCl. 100 mL H_2O is added, then the mixture extracted with DCM (3×100 mL). The combined organic phases are dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The product **164** is obtained brown oil and used as crude in further reactions.

Yield 9.78 g (84%).

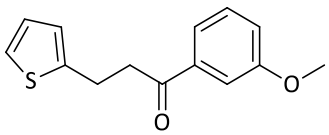
TLC (CH/EE, 2/1, v/v**):** R_f (**164**) = 0.58.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.92 (d, *J* = 15.3 Hz, 1H), 7.59 – 7.49 (m, 2H), 7.38 (d, *J* = 5.2 Hz, 2H), 7.35 – 7.28 (m, 2H), 7.15 – 7.00 (m, 2H), 3.84 (d, *J* = 1.3 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 189.52, 159.92, 140.40, 139.54, 137.19, 132.06, 129.60, 128.89, 128.39, 120.96, 120.84, 119.24, 112.87, 55.47.

LC-MS (0-100% B, 19 min): t_R (**164**) = 12.83 min, m/z: calculated = 245.31 $[M+H]^+$, found = 245.17 $[M+H]^+$.

3-(thiophen -2-yl)-1-(3-methoxyphenyl)propan-1-one (MedChem19_Zn_22)



Chemical Formula: $C_{14}H_{14}O_2S$
Exact Mass: 246,07
Molecular Weight: 246,32

165

Zn powder (13.10 g, 200 mmol, 10.0 eq) and NH_4Cl (10.70 g, 200 mmol, 10.0 eq) are added to a flask and suspended in 40 mL MeOH. **164** (3.10 g, 12 mmol, 1.0 eq) is dissolved in 40 mL MeOH, then added dropwise to the vigorously stirring suspension in 2 h. After complete addition, the mixture is filtered and washed with MeOH. The filtrate is diluted with 100 mL H_2O and extracted with DCM (3×100 mL). The combined organic layers are dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 15/1). The pure product **165** is obtained as a yellow oil.

Yield 2.13 g (45%).

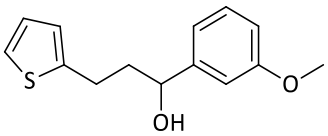
TLC (CH/EE, 10/1, v/v): R_f (**165**) = 0.27.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.55 (dt, *J* = 1.2, 7.7 Hz, 1H), 7.50 (t, *J* = 2.1 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.16 – 7.08 (m, 2H), 6.92 (dd, *J* = 3.4, 5.1 Hz, 1H), 6.86 (d, *J* = 3.0 Hz, 1H), 3.86 (s, 3H), 3.41 – 3.25 (m, 4H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 198.50, 160.02, 144.00, 138.27, 129.74, 126.98, 124.81, 123.51, 120.80, 119.80, 112.42, 55.59, 40.79, 24.42.

LC-MS (0-100% B, 19 min): t_R (**165**) = 10.93 min, m/z: calculated = 247.32 $[M+H]^+$, found = 247.23 $[M+H]^+$.

3-(thiophen -2-yl)-1-(3-methoxyphenyl)propan-1-ol (MedChem19_rac_22)



Chemical Formula: $C_{14}H_{16}O_2S$
Exact Mass: 248,09
Molecular Weight: 248,34

166

165 (100 mg, 0.41 mmol, 1.0 eq) is dissolved in 5 mL THF. $NaBH_4$ (31 mg, 0.82 mmol, 1.0 eq) is added and the reaction stirred at r.t. overnight. The mixture is diluted with 2 mL MeOH and quenched with a few drops conc. HCl. The mixture is extracted with DCM (3×20 mL) and the combined organic layers are dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 15/1). The pure product **166** is obtained as an orange oil.

Yield 100 mg (quant.).

TLC (CH/EE, 10/1): R_f (**166**) = 0.20.

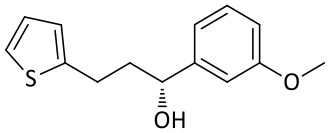
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.31 – 7.19 (m, 1H), 7.12 (dd, *J* = 1.2, 5.1 Hz, 1H), 6.97 – 6.88 (m, 3H), 6.87 – 6.80 (m, 2H), 4.71 (dd, *J* = 5.3, 7.8 Hz, 1H), 3.82 (s, 3H), 2.94 (dddd, *J* = 0.9, 3.2, 7.0, 8.1 Hz, 2H), 2.29 – 2.06 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 160.01, 146.25, 144.75, 129.72, 126.90, 124.45, 123.22, 118.33, 113.31, 111.55, 73.60, 55.39, 40.79, 26.35.

LC-MS (0-100% B, 19 min): t_R (**166**) = 9.44 min, m/z: calculated = 231.07 $[M-OH]^+$, found = 231.26 $[M-OH]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**166**) = 9.18 min, 9.49 min.

(R)-3-(thiophen -2-yl)-1-(3-methoxyphenyl)propan-1-ol (MedChem19_chiral_22)



Chemical Formula: $C_{14}H_{16}O_2S$
Exact Mass: 248,09
Molecular Weight: 248,34

167

S-CBS (23 mg, 0.10 mmol, 0.1 eq) is dissolved in 3.20 mL dry THF and added to a flask under argon atmosphere. 48 µL (0.1 eq) of a 2 M BH_3*SMe_2 solution in THF is added. **165** (200 mg, 0.81 mmol, 1.0 eq) is dissolved in 2.70 mL dry THF and added to the catalyst. Then 610 µL (1.5 eq) of a 2 M BH_3*SMe_2 solution in THF is added dropwise in 1.5 h. After complete addition, the reaction is further stirred for 2 h, then stopped by the addition of MeOH and quenched for 1 h. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 15/1). The pure product **167** is obtained as a colorless oil.

Yield 125 mg (63%).

TLC (CH/EE, 10/1, v/v): R_f (**167**) = 0.15.

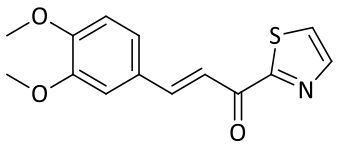
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.31 – 7.23 (m, 1H), 7.12 (dd, *J* = 1.2, 5.1 Hz, 1H), 6.96 – 6.90 (m, 3H), 6.88 – 6.79 (m, 2H), 4.72 (ddd, *J* = 2.5, 4.9, 7.9 Hz, 1H), 3.82 (s, 3H), 3.05 – 2.84 (m, 2H), 2.26 – 2.01 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 160.01, 146.25, 144.75, 129.73, 126.90, 124.46, 123.23, 118.33, 113.31, 111.55, 73.61, 55.40, 40.79, 26.35.

LC-MS (0-100% B, 19 min): t_R (**167**) = 9.51 min, m/z: calculated = 231.07 $[M-OH]^+$, found = 231.06 $[M-OH]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**167**) = 9.87 min (*er* = 95.49/4.51).

(E)-3-(3,4-dimethoxyphenyl)-1-(thiazol-2-yl)prop-2-en-1-one (AV578)



Chemical Formula: $C_{14}H_{13}NO_3S$
Exact Mass: 275,06
Molecular Weight: 275,32

168

3,4-Dimethoxybenzaldehyde (13.07 g, 78 mmol, 2 eq) is dissolved in 200 mL EtOH and cooled in an ice bath to 0°C. Cooled KOH (8.83 g, 156 mmol, 4.0 eq) dissolved in 100 mL H_2O is added. 2-Acetylthiazol (5.0 g, 39 mmol, 1 eq) is dissolved in 50 mL EtOH and added dropwise in 1 h. The reaction is checked by TLC (CH/EE, 2/1). After 6 h the mixture is acidified with 3 M HCl to pH = 3. The resulting precipitate is filtered and washed with H_2O, dissolved in EE, dried with $MgSO_4$, filtered and the solvent removed. The crude product is recrystallized in MeOH. Compound **168** is obtained as yellow crystals.

Yield 7.9 g (73%).

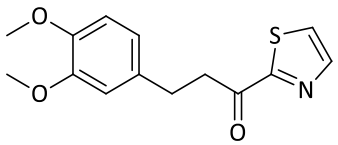
TLC (CH/EE, 2/1, v/v**):** R_f (**168**) = 0.35.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.08 (dd, *J* = 1.0, 3.0 Hz, 1H), 8.00 (d, *J* = 15.9 Hz, 1H), 7.82 (dd, *J* = 0.9, 15.9 Hz, 1H), 7.71 (dd, *J* = 0.9, 3.0 Hz, 1H), 7.34 – 7.24 (m, 3H), 6.92 (dd, *J* = 0.9, 8.3 Hz, 1H), 3.98 (d, *J* = 0.9 Hz, 3H), 3.95 (d, *J* = 0.9 Hz, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 181.63, 169.18, 152.09, 149.46, 144.72, 127.88, 126.33, 124.43, 118.39, 111.20, 110.25, 56.16.

LC-MS (30-100% B, 19 min): t_R (**168**) = 8.66 min, m/z: calculated = 276.32 $[M+H]^+$, found = 276.06 $[M+H]^+$.

3-(3,4-dimethoxyphenyl)-1-(thiazol-2-yl)propan-1-one (AV576/AV583/AV586/AV587/AV588)



Chemical Formula: $C_{14}H_{15}NO_3S$
Exact Mass: 277,08
Molecular Weight: 277,34

169

168 (240 mg, 0.87 mmol, 1.0 eq) is dissolved in 5 mL dry MeOH and added to a dried flask under argon atmosphere. 10 wt% Pd/C (46 mg, 0.04 mmol, 0.05 eq) is added and the solution sparged with H_2 for

5 min. The reaction is stirred at 1 bar H_2 for 1 h, then filtered and washed with DCM. The solvent is removed under reduced pressure and the crude product purified by column chromatography (CH/EE, 3/1). The pure product **169** is obtained as a white solid.

Yield 150 mg (62%).

TLC (CH/EE, 3/1, v/v**):** R_f (**169**) = 0.20.

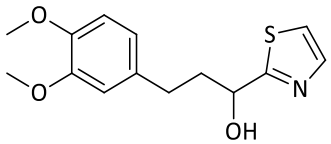
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.98 (d, *J* = 3.0 Hz, 1H), 7.66 (d, *J* = 3.0 Hz, 1H), 6.79 (d, *J* = 1.6 Hz, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.48 (t, *J* = 7.6 Hz, 2H), 3.04 (t, *J* = 7.6 Hz, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 193.18, 167.15, 149.01, 147.57, 144.82, 133.46, 126.33, 120.41, 111.97, 111.46, 56.05, 55.96, 40.39, 29.64.

LC-MS (30-100% B, 19 min): t_R (**169**) = 8.20 min, m/z: calculated = 278.08 $[M+H]^+$, found = 277.94 $[M+H]^+$.

RP-HPLC (30 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**169**) = 7.34 min (99% Purity).

(R)-3-(3,4-dimethoxyphenyl)-1-(thiazol-2-yl)propan-1-ol (AV592)



Chemical Formula: $C_{14}H_{17}NO_3S$
Exact Mass: 279,09
Molecular Weight: 279,35

170

169 (20 mg, 0.07 mmol, 1.0 eq) is dissolved in 5 mL THF. $NaBH_4$ (3 mg, 0.07 mmol, 1.0 eq) is added and the reaction stirred at r.t. overnight. The mixture is quenched with a few drops sat. NH_4Cl and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 2/1). The pure product **171** is obtained as a white oil.

Yield 17 mg (85%).

TLC (CH/EE, 2/1): R_f (**171**) = 0.15.

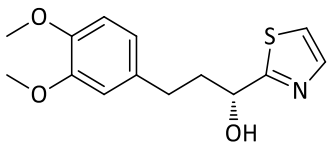
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 3.2 Hz, 1H), 7.29 (d, J = 3.2 Hz, 1H), 6.80 – 6.73 (m, 4H), 5.02 (dd, J = 4.3, 8.3 Hz, 1H), 3.86 (s, 2H), 3.84 (s, 2H), 2.84 – 2.69 (m, 2H), 2.32 – 2.11 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 175.18, 149.07, 147.49, 142.35, 133.97, 120.46, 119.09, 112.02, 111.53, 71.32, 56.08, 55.98, 40.09, 31.21.

LC-MS (30-100% B, 19 min): t_R (**171**) = 5.27 min, m/z: calculated = 280.09 $[M+H]^+$, found = 280.14 $[M+H]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**171**) = 19.05 min, 19.73 min.

3-(3,4-dimethoxyphenyl)-1-(thiazol-2-yl)propan-1-ol (AV591)



Chemical Formula: $C_{14}H_{17}NO_3S$
Exact Mass: 279,09
Molecular Weight: 279,35

171

169 (50 mg, 0.11 mmol, 1.0 eq) is dissolved in 5 mL iPrOH. Then KOtBu (20 mg, 0.18 mmol, 1.0 eq) is added and the solution is sparged with argon for 5 min. $RuCl_2$[(*S*)-(DM-SEGPHOS)][(*S*)-DAIPEN] (2.7 mg, 0.002 mmol, 0.02 eq) is added and the solution sparged with H_2 for 5 min, then the reaction stirred at 1 bar H_2 at r.t. overnight. After full conversion the solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 2/1). The pure product **171** is obtained as a white oil.

Yield 38 mg (76%).

TLC (CH/EE, 2/1, v/v): R_f (**171**) = 0.16.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.74 – 7.68 (m, 1H), 7.31 – 7.27 (m, 1H), 6.81 – 6.73 (m, 3H), 5.05 – 4.98 (m, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 2.85 – 2.68 (m, 2H), 2.35 – 2.06 (m, 2H).

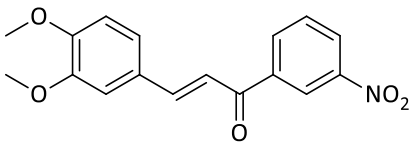
^{13}C-NMR (126 MHz, $CDCl_3$): δ 175.18, 149.07, 147.49, 142.35, 133.97, 120.46, 119.08, 112.03, 111.53, 71.33, 56.08, 55.98, 40.09, 31.21.

LC-MS (30-100% B, 19 min): t_R (**171**) = 5.29 min, m/z: calculated = 280.09 $[M+H]^+$, found = 280.11 $[M+H]^+$.

RP-HPLC (30 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**173**) = 3.82 min (99% Purity).

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**167**) = 19.02min (*er* = 76.07/23.93).

(E)-3-(3,4-dimethoxyphenyl)-1-(3-nitrophenyl)prop-2-en-1-one (AV480)



Chemical Formula: $C_{17}H_{15}NO_5$
Exact Mass: 313,10
Molecular Weight: 313,30

172

3,4-Dimethoxybenzaldehyde (5.00 g, 30 mmol, 1 eq) and 1-(3-nitrophenyl)ethanone (4.95 g, 30 mmol, 1 eq) are dissolved in 150 mL EtOH and cooled in an ice bath to 0°C. Cooled KOH (6.80 g, 120 mmol, 4.0 eq) dissolved in 100 mL H_2O is added slowly in 20 min. After 6 h the mixture is acidified with 3 M HCl to pH = 1. The resulting precipitate is filtered and washed with H_2O, dissolved in DCM, dried with $MgSO_4$, filtered and the solvent removed. The product is used as crude in further reactions. Compound **172** is obtained as brown solid.

Yield 6.47 g (69%).

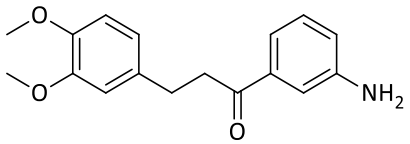
TLC (CH/EE, 1/1, v/v**):** R_f (**172**) = 0.54.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.80 (t, *J* = 2.0 Hz, 1H), 8.45 – 8.27 (m, 2H), 7.83 (d, *J* = 15.5 Hz, 1H), 7.69 (t, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 15.5 Hz, 1H), 7.30 – 7.21 (m, 1H), 7.17 (d, *J* = 2.0 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 188.08, 152.19, 149.51, 148.50, 147.07, 139.96, 134.17, 129.94, 127.44, 126.94, 123.93, 123.26, 118.63, 111.33, 110.43, 56.17.

LC-MS (30-100% B, 19 min): t_R (**172**) = 10.17 min, m/z: calculated = 314.30 $[M+H]^+$, found = 314.24 $[M+H]^+$.

1-(3-aminophenyl)-3-(3,4-dimethoxyphenyl)propan-1-one (AV503)



Chemical Formula: $C_{17}H_{19}NO_3$
Exact Mass: 285,14
Molecular Weight: 285,34

173

Zn powder (2.10 g, 32 mmol, 10.0 eq) and NH_4Cl (1.71 g, 32 mmol, 10.0 eq) are added to a flask and suspended in 20 mL MeOH. **172** (1.00 g, 3.2 mmol, 1.0 eq) is dissolved in 50 mL MeOH and 20 mL THF, then added dropwise to the vigorously stirring suspension in 1 h. After complete addition, the mixture

is filtered and washed with MeOH. The filtrate is concentrated under reduced pressure, then diluted with 100 mL H_2O and extracted with DCM (3×100 mL). The combined organic layers are dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 2/1 + 2% TEA). The pure product **173** is obtained as brown solid.

Yield 310 mg (34%).

TLC (CH/EE, 2/1, v/v + 2% TEA): R_f (**173**) = 0.15.

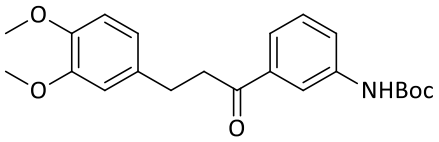
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.28 – 7.08 (m, 3H), 6.78 (ddd, *J* = 1.1, 2.5, 7.9 Hz, 1H), 6.70 (dd, *J* = 2.1, 4.6 Hz, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.15 (dd, *J* = 7.0, 8.5 Hz, 2H), 2.91 (dd, *J* = 6.8, 8.4 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 199.70, 149.02, 147.50, 146.78, 138.14, 134.12, 129.55, 120.28, 119.71, 118.56, 114.05, 112.02, 111.52, 56.06, 55.96, 40.84, 29.99.

LC-MS (30-100% B, 19 min): t_R (**173**) = 6.00 min, m/z: calculated = 286.14 $[M+H]^+$, found = 286.02 $[M+H]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**173**) = 8.55 min (99% Purity).

tert-butyl (3-(3-(3,4-dimethoxyphenyl)propanoyl)phenyl)carbamate (AV504/AV508)



Chemical Formula: $C_{22}H_{27}NO_5$
Exact Mass: 385,19
Molecular Weight: 385,45

174

173 (310 mg, 1 mmol, 1.0 eq) is dissolved in 20 mL dry DCM under argon atmosphere. Boc2O (1 mL, 4 mmol, 4.0 eq) is added and the reaction heated to 50°C for 2 h. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 3/1). The pure product **174** is obtained as brown solid.

Yield 140 mg (33%).

TLC (CH/EE, 3/1, v/v): R_f (**174**) = 0.35.

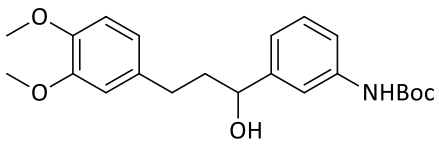
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.88 – 7.84 (m, 1H), 7.59 – 7.50 (m, 2H), 7.29 (t, J = 7.9 Hz, 1H), 6.71 (d, J = 2.0 Hz, 3H), 6.58 (s, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.24 – 3.16 (m, 2H), 2.99 – 2.87 (m, 2H), 1.45 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 199.12, 152.61, 148.92, 147.41, 138.92, 137.66, 133.88, 129.24, 122.92, 122.56, 120.22, 117.84, 111.92, 111.40, 55.95, 55.84, 40.79, 29.85, 28.30, 27.92.

LC-MS (50-100% B, 19 min): t_R (**174**) = 7.40 min, m/z: calculated = 286.14 $[M+H]^+$, found = 286.36 $[M+H]^+$.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**174**) = 7.37 min (92% Purity).

ert-butyl (3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenyl)carbamate (AV521)



Chemical Formula: $C_{22}H_{29}NO_5$
Exact Mass: 387,20
Molecular Weight: 387,47

175

174 (20 mg, 0.05 mmol, 1.0 eq) is dissolved in 1 mL iPrOH. $NaBH_4$ (2 mg, 0.05 mmol, 1.0 eq) is added and the reaction stirred at r.t. overnight. The mixture is diluted with 2 mL MeOH and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 4/1). The pure product **175** is obtained as a colorless oil.

Yield 15 mg (75%).

TLC (CH/EE, 3/1): R_f (**175**) = 0.14.

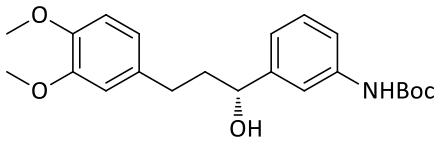
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.29 – 7.15 (m, 2H), 7.09 (dt, *J* = 1.7, 7.8 Hz, 1H), 7.00 (t, *J* = 1.9 Hz, 1H), 6.75 – 6.59 (m, 3H), 4.54 (dd, *J* = 5.2, 7.7 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 2.67 – 2.44 (m, 2H), 2.06 – 1.81 (m, 2H), 1.36 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 154.44, 152.16, 149.02, 147.37, 145.72, 138.93, 134.38, 128.98, 126.82, 125.56, 125.27, 120.35, 111.95, 111.46, 83.50, 73.42, 56.07, 55.96, 40.77, 31.70, 28.09.

LC-MS (50-100% B, 19 min): t_R (**175**) = 5.45 min, m/z: calculated = 410.19 $[M+Na]^+$, found = 410.14 $[M+Na]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**175**) = 19.54 min, 23.22 min.

(R)-tert-butyl (3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenyl)carbamate (AV530)



Chemical Formula: $C_{22}H_{29}NO_5$
Exact Mass: 387,20
Molecular Weight: 387,47

176

174 (30 mg, 0.08 mmol, 1.0 eq) is dissolved in 5 mL iPrOH. Then KO*t*Bu (80 µL, 0.08 mmol, 1 eq) is added and the solution is sparged with argon for 5 min. $RuCl_2$[(*S*)-(DM-SEGPHOS)][(*S*)-DAIPEN] (2.7 mg, 0.002 mmol, 0.03 eq) is added and the solution sparged with H_2 for 5 min, then the reaction stirred at 1 bar H_2 at r.t. overnight. After full conversion, the solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 4/1). The pure product **176** is obtained as a colorless oil.

Yield 23 mg (76%).

TLC (CH/EE, 3/1): R_f (**176**) = 0.14.

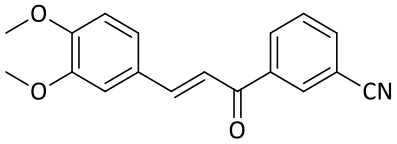
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.41 (s, 1H), 7.29 – 7.17 (m, 2H), 7.02 (dt, *J* = 1.4, 7.3 Hz, 1H), 6.78 (dd, *J* = 1.0, 8.0 Hz, 1H), 6.72 (dt, *J* = 1.8, 11.8 Hz, 2H), 6.55 (s, 1H), 4.66 (dd, *J* = 5.2, 7.9 Hz, 1H), 3.85 (s, 3H), 3.85 (s, 3H), 2.76 – 2.54 (m, 2H), 2.15 – 1.93 (m, 2H), 1.51 (s, 9H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 152.88, 148.99, 147.32, 145.89, 138.67, 134.55, 129.23, 120.66, 120.35, 117.86, 116.24, 111.96, 111.46, 80.71, 73.91, 56.07, 55.96, 40.74, 31.79, 29.83, 28.47.

LC-MS (30-100% B, 19 min): t_R (**176**) = 9.58 min, m/z: calculated = 410.19 $[M+Na]^+$, found = 410.10 $[M+Na]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**176**) = 23.60 min (*er* = 97.60/2.40).

(E)-3-(3-(3,4-dimethoxyphenyl)acryloyl)benzonitrile (MedChem19_17)



Chemical Formula: $C_{18}H_{15}NO_3$
Exact Mass: 293,11
Molecular Weight: 293,32

177

3,4-Dimethoxybenzaldehyde (4.67 g, 25 mmol, 1 eq) and 3-acetylbenzonitrile (4.95 g, 25 mmol, 1 eq) are dissolved in 120 mL EtOH and cooled in an ice bath to 0°C for 15 min. Cooled KOH (6.19 g, 100 mmol, 4.0 eq) dissolved in 80 mL H_2O is added slowly in 5 min. A yellow precipitate is observed. After 30 min the mixture is acidified with 3 M HCl to pH = 1. The resulting precipitate is filtered and washed with H_2O, dissolved in DCM, dried with $MgSO_4$, filtered and the solvent removed. The product recrystallized in MeOH. Compound **177** is obtained as an orange-yellow solid.

Yield 65.44 g (72%).

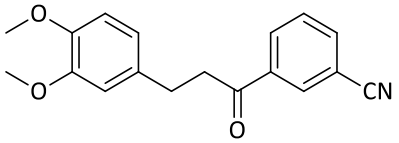
TLC (CH/EE, 1/5, v/v**):** R_f (**177**) = 0.45.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.26 – 8.09 (m, 2H), 7.80 – 7.66 (m, 2H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 15.5 Hz, 1H), 7.21 – 7.14 (m, 1H), 7.10 (d, *J* = 1.9 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 188.30, 152.12, 149.49, 146.82, 139.43, 135.49, 132.49, 132.12, 129.72, 127.45, 123.91, 118.70, 118.22, 113.11, 111.30, 110.24, 56.15.

LC-MS (0-100% B, 19 min): t_R (**177**) = 5.43 min, m/z: calculated = 294.31 $[M+H]^+$, found = 294.21 $[M+H]^+$.

3-(3-(3,4-dimethoxyphenyl)propanoyl)benzonitrile (AV500)



Chemical Formula: $C_{18}H_{17}NO_3$
Exact Mass: 295,12
Molecular Weight: 295,33

178

Zn powder (4.46 g, 70 mmol, 10.0 eq) and NH_4Cl (3.65 g, 70 mmol, 10.0 eq) are added to a flask and suspended in 25 mL MeOH. **177** (1.00 g, 3.2 mmol, 1.0 eq) is dissolved in 150 mL MeOH and 50 mL DMF, then added dropwise to the vigorously stirring suspension in 1 h. After complete addition, the mixture is filtered and washed with MeOH. The filtrate is concentrated under reduced pressure, then diluted with 100 mL H_2O and extracted with DCM (3×100 mL). The combined organic layers are dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 2/1 + 2% TEA). The pure product **178** is obtained as a white solid.

Yield 240 mg (12%).

TLC (CH/EE, 3/1, v/v): R_f (**178**) = 0.25.

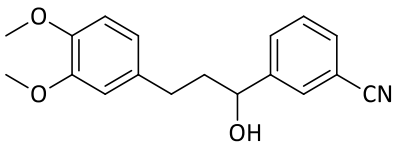
^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.14 (t, *J* = 1.7 Hz, 1H), 8.09 (dt, *J* = 1.5, 7.9 Hz, 1H), 7.75 (dt, *J* = 1.4, 7.7 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 6.78 – 6.62 (m, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.21 (dd, *J* = 6.9, 8.1 Hz, 2H), 2.96 (t, *J* = 7.5 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 197.21, 149.01, 147.61, 137.61, 135.90, 133.24, 131.91, 131.75, 129.66, 120.21, 117.87, 113.21, 111.88, 111.46, 55.95, 55.88, 40.75, 29.53.

LC-MS (30-100% B, 19 min): t_R (**178**) = 9.20 min, m/z: calculated = 296.12 $[M+H]^+$, found = 296.13 $[M+H]^+$.

RP-HPLC (30 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**178**) = 9.54 min (99% Purity).

3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)benzonitrile (AV517)



Chemical Formula: $C_{18}H_{19}NO_3$
Exact Mass: 297,14
Molecular Weight: 297,35

179

178 (20 mg, 0.07 mmol, 1.0 eq) is dissolved in 1 mL iPrOH. $NaBH_4$ (3 mg, 0.07 mmol, 1.0 eq) is added and the reaction stirred at r.t. overnight. The mixture is diluted with 2 mL MeOH and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 2/1). The pure product **179** is obtained as a white solid.

Yield 20 mg (quant.).

TLC (CH/EE, 2/1): R_f (**179**) = 0.43.

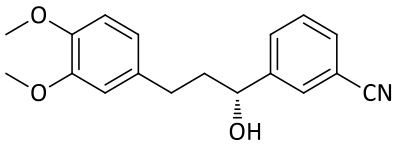
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.66 (t, *J* = 1.7 Hz, 1H), 7.57 (ddt, *J* = 1.5, 7.6, 9.1 Hz, 2H), 7.45 (t, *J* = 7.7 Hz, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 6.76 – 6.68 (m, 2H), 4.74 (dd, *J* = 4.9, 8.1 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.68 (dddd, *J* = 6.4, 9.1, 14.0, 23.0 Hz, 2H), 2.12 – 1.92 (m, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 149.15, 146.30, 133.81, 131.31, 130.43, 129.71, 129.40, 120.34, 118.92, 112.70, 111.89, 111.56, 72.94, 56.11, 56.02, 40.94, 31.60, 29.85.

LC-MS (30-100% B, 19 min): t_R (**179**) = 7.87 min, m/z: calculated = 298.14 $[M+H]^+$, found = 298.47 $[M+H]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**179**) = 15.15 min, 16.32 min.

(R)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)benzonitrile (AV532)



Chemical Formula: $C_{18}H_{19}NO_3$
Exact Mass: 297,14
Molecular Weight: 297,35

180

178 (60 mg, 0.20 mmol, 1.0 eq) is dissolved in 10 mL iPrOH. Then KO*t*Bu (200 µL, 0.20 mmol, 1 eq) is added and the solution is sparged with argon for 5 min. $RuCl_2$[(*S*)-(DM-SEGPHOS)][(*S*)-DAIPEN] (3 mg, 0.002 mmol, 0.03 eq) is added and the solution sparged with H_2 for 5 min, then the reaction stirred at

1 bar H_2 at r.t. overnight. After full conversion, the solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 3/1). The pure product **180** is obtained as a white solid.

Yield 34 mg (56%).

TLC (CH/EE, 2/1): R_f (**180**) = 0.23.

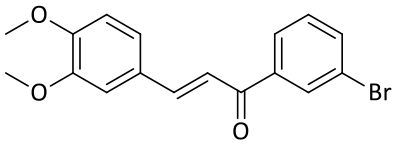
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.64 (q, *J* = 1.4 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.44 (t, *J* = 7.7 Hz, 1H), 6.79 (dd, *J* = 0.9, 8.1 Hz, 1H), 6.75 – 6.66 (m, 2H), 4.72 (dd, *J* = 4.8, 8.1 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 2.67 (dqd, *J* = 6.5, 14.2, 20.9 Hz, 2H), 2.12 – 1.87 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 149.07, 147.50, 146.35, 133.85, 131.21, 130.43, 129.66, 129.34, 120.32, 118.91, 112.55, 111.88, 111.54, 72.82, 56.06, 55.97, 40.90, 31.54, 29.80.

LC-MS (30-100% B, 19 min): t_R (**180**) = 7.83 min, m/z: calculated = 298.14 $[M+H]^+$, found = 298.17 $[M+H]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**180**) = 14.22 min (*er* = 86.59/13.41).

(E)-1-(3-bromophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (MedChem19_15)



Chemical Formula: $C_{17}H_{15}BrO_3$
Exact Mass: 346,02
Molecular Weight: 347,20

181

3,4-Dimethoxybenzaldehyde (820 mg, 5 mmol, 1 eq) and 1-(3-bromophenyl)ethanone (664 µL, 5 mmol, 1 eq) are dissolved in 30 mL EtOH and cooled in an ice bath to 0°C for 15 min. Cooled KOH (1.12 g, 20 mmol, 4.0 eq) dissolved in 20 mL H_2O is added slowly in 5 min. A yellow precipitate is observed. After 30 min the mixture is acidified with 3 M HCl to pH = 1. The resulting precipitate is filtered and washed with H_2O, dissolved in DCM, dried with $MgSO_4$, filtered and the solvent removed. Compound **181** is obtained as an orange-yellow solid.

Yield 1.52 g (87%).

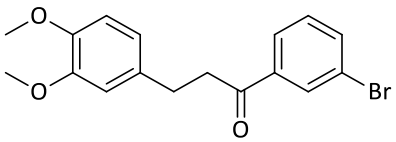
TLC (CH/EE, 2/1, v/v**):** R_f (**181**) = 0.33.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.04 (t, *J* = 1.8 Hz, 1H), 7.83 (ddd, *J* = 1.0, 1.6, 7.8 Hz, 1H), 7.68 (d, *J* = 15.6 Hz, 1H), 7.61 (ddd, *J* = 1.0, 2.0, 8.0 Hz, 1H), 7.33 – 7.17 (m, 2H), 7.17 – 7.12 (m, 1H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 189.15, 151.90, 149.50, 146.01, 140.49, 135.49, 131.53, 130.27, 127.78, 127.05, 123.57, 123.03, 119.52, 111.35, 110.42, 56.17.

LC-MS (0-100% B, 19 min): t_R (**181**) = 11.46 min, m/z: calculated = 347.02 $[M+H]^+$, found = 347.39 $[M+H]^+$.

1-(3-bromophenyl)-3-(3,4-dimethoxyphenyl)propan-1-one (MedChem19_Zn_15)



Chemical Formula: $C_{17}H_{17}BrO_3$
Exact Mass: 348,04
Molecular Weight: 349,22

182

Zn powder (2.28 g, 35 mmol, 10.0 eq) and NH_4Cl (1.90 g, 35 mmol, 10.0 eq) are added to a flask and suspended in 10 mL MeOH. **181** (1.20 g, 3.5 mmol, 1.0 eq) is dissolved in 15 mL MeOH and 15 mL DMF, then added dropwise to the vigorously stirring suspension in 2 h. After complete addition, the mixture is filtered and washed with MeOH. The filtrate is concentrated under reduced pressure. The product is then precipitated by the addition of 100 mL H_2O. The precipitate is filtered, dissolved in DCM, dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 2/1). The pure product **182** is obtained as a colorless oil.

Yield 590 mg (48%).

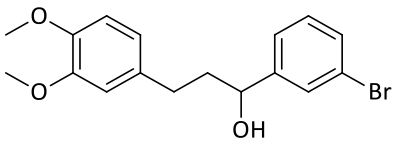
TLC (CH/EE, 2/1, v/v): R_f (**182**) = 0.39.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.07 (t, *J* = 1.8 Hz, 1H), 7.86 (ddd, *J* = 1.1, 1.6, 7.8 Hz, 1H), 7.68 (ddd, *J* = 1.1, 2.0, 7.9 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 6.84 – 6.73 (m, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.30 – 3.22 (m, 2H), 3.01 (dd, *J* = 6.9, 8.1 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 198.07, 149.18, 147.72, 138.83, 136.03, 133.75, 131.31, 130.34, 126.67, 123.13, 120.37, 112.10, 111.65, 56.13, 56.04, 40.92, 29.84.

LC-MS (0-100% B, 19 min): t_R (**182**) = 11.18 min, m/z: calculated = 349.04 $[M+H]^+$, found = 349.37 $[M+H]^+$.

1-(3-bromophenyl)-3-(3,4-dimethoxyphenyl)propan-1-ol (MedChem19_rac_15)



Chemical Formula: $C_{17}H_{19}BrO_3$
Exact Mass: 350,05
Molecular Weight: 351,23

183

182 (50 mg, 0.14 mmol, 1.0 eq) is dissolved in 3 mL THF. $NaBH_4$ (13 mg, 0.28 mmol, 2.0 eq) is added and the reaction stirred at r.t. overnight. The mixture is diluted with 2 mL MeOH and quenched with a few drops conc. HCl. The mixture is extracted with DCM (3×20 mL) and the combined organic layers are dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 3/1). The pure product **183** is obtained as black oil.

Yield 32 mg (64%).

TLC (CH/EE, 3/1): R_f (**183**) = 0.19.

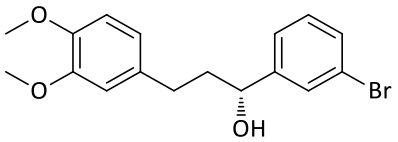
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.42 (t, *J* = 1.8 Hz, 1H), 7.32 (dt, *J* = 1.8, 7.5 Hz, 1H), 7.20 – 7.16 (m, 1H), 7.16 – 7.08 (m, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.65 (d, *J* = 2.0 Hz, 1H), 6.62 (t, *J* = 1.8 Hz, 1H), 4.57 (ddd, *J* = 2.8, 4.7, 8.0 Hz, 1H), 3.77 (s, 3H), 3.77 (s, 3H), 2.68 – 2.43 (m, 2H), 2.07 – 1.89 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 149.06, 147.45, 147.12, 134.16, 130.75, 130.21, 129.19, 124.63, 122.76, 120.34, 111.93, 111.51, 73.30, 56.09, 55.99, 40.77, 31.66, 27.06.

LC-MS (0-100% B, 19 min): t_R (**183**) = 9.93 min, m/z: calculated = 333.03 $[M-OH]^+$, found = 333.31 $[M-OH]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**183**) = 10.33 min, 11.77 min.

(R)-1-(3-bromophenyl)-3-(3,4-dimethoxyphenyl)propan-1-ol (MedChem19_chir_15)



Chemical Formula: $C_{17}H_{19}BrO_3$
Exact Mass: 350,05
Molecular Weight: 351,23

184

S-CBS (16 mg, 0.06 mmol, 0.1 eq) is dissolved in 2 mL dry THF and added to a flask under argon atmosphere. 30 µL (0.1 eq) of a 2 M BH_3*SMe_2 solution in THF is added. **182** (210 mg, 0.57 mmol,

1.0 eq) is dissolved in 2 mL dry THF and added to the catalyst. Then 430 µL (1.5 eq) of a 2 M BH_3*SMe_2 solution in THF is added dropwise in 1 h. After complete addition, the reaction is further stirred for 2 h, then stopped by the addition of MeOH and quenched for 1 h. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 3/1). The pure product **184** is obtained as a white solid.

Yield 210 mg (quant.).

TLC (CH/EE, 3/1, v/v): R_f (**184**) = 0.18.

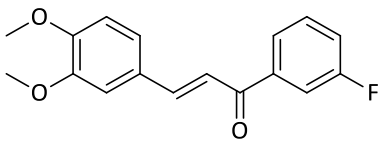
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.51 (q, *J* = 1.4 Hz, 1H), 7.40 (dt, *J* = 1.7, 7.5 Hz, 1H), 7.28 – 7.12 (m, 2H), 6.86 – 6.67 (m, 3H), 4.65 (ddd, *J* = 1.5, 5.2, 7.5 Hz, 1H), 3.86 (s, 4H), 3.85 (s, 3H), 2.76 – 2.55 (m, 2H), 2.19 – 1.89 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 149.08, 147.47, 147.15, 134.18, 130.73, 130.20, 129.19, 124.62, 122.75, 120.35, 111.98, 111.57, 73.29, 56.09, 55.99, 40.76, 31.65.

LC-MS (0-100% B, 19 min): t_R (**184**) = 9.86 min, m/z: calculated = 333.03 $[M-OH]^+$, found = 333.24 $[M-OH]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**184**) = 11.38 min (*er* = 91.21/8.79).

(E)-1-(3-fluorophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (MedChem19_CS_13)



Chemical Formula: $C_{17}H_{15}FO_3$
Exact Mass: 286,10
Molecular Weight: 286,30

185

3,4-Dimethoxybenzaldehyde (1.20 g, 7 mmol, 1 eq) and 3'-fluoro acetophenone (888 µL, 7 mmol, 1 eq) are dissolved in 30 mL EtOH and cooled in an ice bath to 0°C for 15 min. Cooled KOH (1.62 g, 28 mmol, 4.0 eq) dissolved in 20 mL H_2O is added slowly in 5 min. After 2 h the mixture is acidified with 3 M HCl to pH = 1. The mixture is extracted with DCM (3×20 mL). The combined organic phases are dried with $MgSO_4$, filtered and the solvent removed. Compound **185** is obtained as a yellow oil and used crude in further reactions.

Yield 1.69 g (95%).

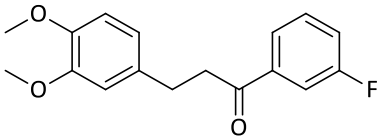
TLC (CH/EE, 2/1, v/v**):** R_f (**181**) = 0.27.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.69 – 7.65 (m, 1H), 7.63 – 7.46 (m, 2H), 7.38 – 7.27 (m, 2H), 7.23 – 6.99 (m, 3H), 6.80 (dd, *J* = 8.2, 23.1 Hz, 1H), 3.82 (d, *J* = 1.0 Hz, 3H), 3.79 (d, *J* = 0.6 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 190.67, 164.35, 161.07, 154.40, 151.61, 149.52, 149.22, 145.55, 140.55, 140.46, 130.19, 130.14, 130.09, 130.04, 127.55, 126.62, 124.00, 123.96, 123.32, 120.05, 119.77, 119.49, 119.25, 119.20, 115.18, 114.88, 114.58, 111.11, 110.37, 110.18, 108.95, 55.99, 55.83.

LC-MS (0-100% B, 19 min): t_R (**181**) = 10.55 min, m/z: calculated = 287.10 $[M+H]^+$, found = 287.21 $[M+H]^+$.

1-(3-fluorophenyl)-3-(3,4-dimethoxyphenyl)propan-1-one (MedChem19_Zn_13)



Chemical Formula: $C_{17}H_{17}FO_3$
Exact Mass: 288,12
Molecular Weight: 288,31

186

Zn powder (9.14 g, 140 mmol, 10.0 eq) and NH_4Cl (7.48 g, 140 mmol, 10.0 eq) are added to a flask and suspended in 40 mL MeOH. **185** (4.00 g, 14 mmol, 1.0 eq) is dissolved in 50 mL MeOH, then added dropwise to the vigorously stirring suspension in 30 min. After complete addition, the mixture is filtered and washed with MeOH. The filtrate is concentrated under reduced pressure. The product is then precipitated by the addition of 100 mL H_2O. The precipitate is filtered, dissolved in DCM, dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 2/1). The pure product **186** is obtained as a slightly yellow oil.

Yield 1.29 mg (32%).

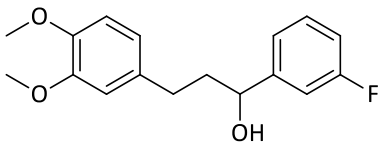
TLC (CH/EE, 2/1, v/v): R_f (**186**) = 0.29.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.72 (ddd, *J* = 1.0, 1.6, 7.7 Hz, 1H), 7.66 – 7.57 (m, 1H), 7.43 (dddd, *J* = 0.4, 5.6, 7.7, 8.2 Hz, 1H), 7.31 – 7.17 (m, 1H), 6.81 – 6.74 (m, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.30 – 3.23 (m, 2H), 3.04 – 2.98 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 198.16, 164.66, 161.37, 149.15, 147.69, 133.78, 130.44, 130.34, 123.90, 123.86, 120.34, 120.03, 115.07, 114.77, 112.09, 111.63, 56.11, 56.02, 40.96, 29.85.

LC-MS (0-100% B, 19 min): t_R (**186**) = 10.18 min, m/z: calculated = 289.12 $[M+H]^+$, found = 289.04 $[M+H]^+$.

1-(3-fluorophenyl)-3-(3,4-dimethoxyphenyl)propan-1-ol (MedChem19_rac_13)



Chemical Formula: $C_{17}H_{19}FO_3$
Exact Mass: 290,13
Molecular Weight: 290,33

187

186 (100 mg, 0.35 mmol, 1.0 eq) is dissolved in 5 mL THF. $NaBH_4$ (26 mg, 0.70 mmol, 2.0 eq) is added and the reaction stirred at r.t. overnight. The mixture is diluted with 2 mL MeOH and quenched with a few drops conc. HCl. The mixture is extracted with DCM (3×20 mL) and the combined organic layers are dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 2/1). The pure product **187** is obtained as a colorless oil.

Yield 80 mg (80%).

TLC (CH/EE, 2/1, v/v): R_f (**187**) = 0.18.

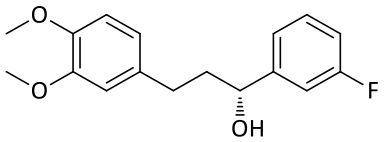
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.30 (td, *J* = 5.8, 8.0 Hz, 1H), 7.14 – 7.04 (m, 2H), 6.96 (tdd, *J* = 1.0, 2.6, 8.4 Hz, 1H), 6.82 – 6.69 (m, 3H), 4.69 (dd, *J* = 5.2, 7.8 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.78 – 2.55 (m, 2H), 2.14 – 1.87 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 164.77, 161.51, 149.09, 147.55, 147.47, 134.27, 130.16, 130.05, 121.59, 121.55, 120.36, 114.64, 114.36, 113.07, 112.78, 111.99, 111.56, 73.36, 56.10, 55.99, 40.78, 31.66.

LC-MS (0-100% B, 19 min): t_R (**187**) = 8.88 min, m/z: calculated = 273.11 $[M-OH]^+$, found = 273.21 $[M-OH]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**187**) = 9.51 min, 10.20 min.

(R)-1-(3-fluorophenyl)-3-(3,4-dimethoxyphenyl)propan-1-ol (MedChem19_chir_13)



Chemical Formula: $C_{17}H_{19}FO_3$
Exact Mass: 290,13
Molecular Weight: 290,33

188

S-CBS (19 mg, 0.07 mmol, 0.1 eq) is dissolved in 2.3 mL dry THF and added to a flask under argon atmosphere. 35 µL (0.1 eq) of a 2 M BH_3*SMe_2 solution in THF is added. **186** (200 mg, 0.69 mmol, 1.0 eq) is dissolved in 2.3 mL dry THF and added to the catalyst. Then 520 µL (1.5 eq) of a 2 M BH_3*SMe_2

solution in THF is added dropwise in 1 h. After complete addition, the reaction is further stirred for 2 h, then stopped by the addition of MeOH and quenched for 1 h. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 2/1). The pure product **188** is obtained as a colorless oil.

Yield 200 mg (quant.).

TLC (CH/EE, 2/1, v/v): R_f (**188**) = 0.24.

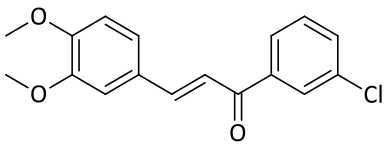
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.34 – 7.28 (m, 1H), 7.14 – 7.04 (m, 2H), 7.01 – 6.88 (m, 1H), 6.82 – 6.69 (m, 3H), 4.68 (dd, *J* = 5.3, 7.7 Hz, 1H), 3.86 – 3.84 (m, 6H), 2.75 – 2.56 (m, 2H), 2.15 – 1.94 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 164.75, 161.48, 149.05, 147.57, 147.48, 147.43, 134.25, 130.14, 130.03, 121.58, 121.54, 120.33, 114.61, 114.33, 113.06, 112.77, 111.93, 111.50, 73.32, 56.06, 55.95, 40.78, 31.65.

LC-MS (0-100% B, 19 min): t_R (**188**) = 8.84 min, m/z: calculated = 273.11 $[M-OH]^+$, found = 273.13 $[M-OH]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**188**) = 10.42 min (*er* = 96.65/3.35).

(E)-1-(3-chlorophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (MedChem19_CS_20)



Chemical Formula: $C_{17}H_{15}ClO_3$
Exact Mass: 302,07
Molecular Weight: 302,75

189

3,4-Dimethoxybenzaldehyde (5.34 g, 32 mmol, 1 eq) and 1-(3-chlorophenyl)ethanone (4.20 mL, 32 mmol, 1 eq) are dissolved in 150 mL EtOH and cooled in an ice bath to 0°C for 15 min. Cooled KOH (7.29 g, 128 mmol, 4.0 eq) dissolved in 100 mL H_2O is added slowly in 5 min. A yellow precipitate is observed. After reaction overnight the mixture is acidified with 3 M HCl to pH = 1. The resulting precipitate is filtered and washed with H_2O, dissolved in DCM, dried with $MgSO_4$, filtered and the solvent removed. Compound **189** is obtained as yellow solid.

Yield 7.90 g (76%).

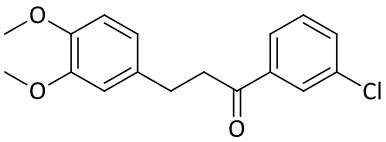
TLC (CH/EE, 1/1, v/v**):** R_f (**181**) = 0.46.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.89 (d, *J* = 2.2 Hz, 1H), 7.84 – 7.76 (m, 1H), 7.70 (d, *J* = 15.7 Hz, 1H), 7.52 – 7.32 (m, 2H), 7.27 – 7.13 (m, 2H), 7.08 (d, *J* = 2.2 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 189.24, 151.85, 149.45, 145.98, 140.24, 134.96, 132.57, 130.01, 128.60, 127.74, 126.60, 123.57, 119.51, 111.30, 110.32, 56.14.

LC-MS (0-100% B, 19 min): t_R (**181**) = 11.08 min, m/z: calculated = 303.07 $[M+H]^+$, found = 303.30 $[M+H]^+$.

1-(3-chlorophenyl)-3-(3,4-dimethoxyphenyl)propan-1-one (MedChem19_Zn_20)



Chemical Formula: $C_{17}H_{17}ClO_3$
Exact Mass: 304,09
Molecular Weight: 304,77

190

Zn powder (5.66 g, 90 mmol, 10.0 eq) and NH_4Cl (4.62 g, 90 mmol, 10.0 eq) are added to a flask and suspended in 40 mL MeOH. **189** (2.62 g, 9 mmol, 1.0 eq) is dissolved in 200 mL MeOH, then added dropwise to the vigorously stirring suspension in 30 min. After complete addition, the mixture is filtered and washed with MeOH. The filtrate is concentrated under reduced pressure. The product is then precipitated by the addition of 100 mL H_2O. The precipitate is filtered, dissolved in DCM, dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 5/1). The pure product **190** is obtained as slightly yellow resin.

Yield 1.25 g (48%).

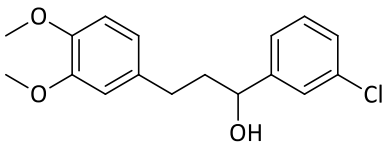
TLC (CH/EE, 5/1, v/v): R_f (**190**) = 0.35.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.91 (t, *J* = 1.9 Hz, 1H), 7.81 (dt, *J* = 1.3, 8.0 Hz, 1H), 7.52 (ddd, *J* = 1.1, 2.1, 7.9 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 6.85 – 6.75 (m, 4H), 3.87 (s, 3H), 3.85 (s, 3H), 3.25 (dd, *J* = 6.9, 8.2 Hz, 2H), 3.01 (t, *J* = 7.5 Hz, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 198.13, 149.14, 147.69, 138.60, 135.09, 133.73, 133.07, 130.06, 128.31, 126.20, 120.34, 112.07, 111.63, 56.10, 56.01, 40.91, 29.81.

LC-MS (0-100% B, 19 min): t_R (**190**) = 11.12 min, m/z: calculated = 305.09 $[M+H]^+$, found = 305.00 $[M+H]^+$.

1-(3-chlorophenyl)-3-(3,4-dimethoxyphenyl)propan-1-ol (MedChem19_rac_20)



Chemical Formula: $C_{17}H_{19}ClO_3$
Exact Mass: 306,10
Molecular Weight: 306,78

191

190 (100 mg, 0.3 mmol, 1.0 eq) is dissolved in 5 mL THF. $NaBH_4$ (25 mg, 0.6 mmol, 2.0 eq) is added and the reaction stirred at r.t. overnight. The mixture is diluted with 2 mL MeOH and quenched with a few drops conc. HCl. The mixture is extracted with DCM (3×20 mL) and the combined organic layers are dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 5/1). The pure product **191** is obtained as a colorless resin.

Yield 63 mg (63%).

TLC (CH/EE, 5/1): R_f (**191**) = 0.32.

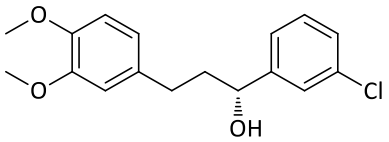
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.27 (q, *J* = 1.6 Hz, 1H), 7.24 – 7.11 (m, 3H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.67 – 6.60 (m, 2H), 4.59 (dd, *J* = 5.3, 7.8 Hz, 1H), 3.78 (s, 3H), 3.78 (s, 4H), 2.72 – 2.49 (m, 2H), 2.06 – 1.84 (m, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 149.06, 147.44, 146.87, 134.52, 134.19, 129.90, 127.81, 126.26, 124.16, 120.34, 111.94, 111.52, 73.34, 56.08, 55.98, 40.76, 31.65.

LC-MS (0-100% B, 19 min): t_R (**191**) = 9.67 min, m/z: calculated = 289.09 $[M-OH]^+$, found = 289.30 $[M-OH]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**191**) = 9.77 min, 10.55 min.

(R)-1-(3-chlorophenyl)-3-(3,4-dimethoxyphenyl)propan-1-ol (MedChem19_chir_20)



Chemical Formula: $C_{17}H_{19}ClO_3$
Exact Mass: 306,10
Molecular Weight: 306,78

192

S-CBS (18 mg, 0.07 mmol, 0.1 eq) is dissolved in 2.2 mL dry THF and added to a flask under argon atmosphere. 33 µL (0.1 eq) of a 2 M BH_3*SMe_2 solution in THF is added. **190** (200 mg, 0.70 mmol, 1.0 eq) is dissolved in 2.2 mL dry THF and added to the catalyst. Then 490 µL (1.5 eq) of a 2 M BH_3*SMe_2

solution in THF is added dropwise in 1 h. After complete addition, the reaction is further stirred for 2 h, then stopped by the addition of MeOH and quenched for 1 h. The solvent is removed under reduced pressure. The crude product is purified by column chromatography (CH/EE, 3/1). The pure product **192** is obtained as a yellow oil.

Yield 182 mg (91%).

TLC (CH/EE, 3/1, v/v): R_f (**192**) = 0.24.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.28 (d, *J* = 1.8 Hz, 1H), 7.23 – 7.09 (m, 3H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.68 – 6.58 (m, 2H), 4.59 (dd, *J* = 5.2, 7.8 Hz, 1H), 3.78 (s, 4H), 3.78 (s, 3H), 2.69 – 2.48 (m, 2H), 2.10 – 1.82 (m, 2H).

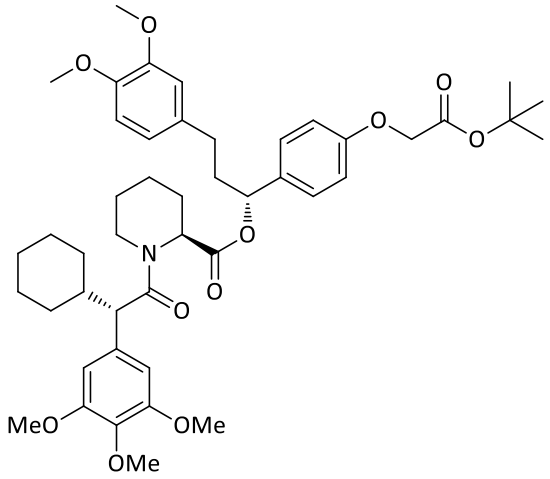
^{13}C-NMR (75 MHz, $CDCl_3$): δ 149.06, 147.44, 146.86, 134.52, 134.18, 129.90, 127.80, 126.25, 124.15, 120.33, 111.93, 111.51, 73.35, 56.08, 55.98, 40.76, 31.65.

LC-MS (0-100% B, 19 min): t_R (**192**) = 9.66 min, m/z: calculated = 289.09 $[M\text{-}OH]^+$, found = 289.20 $[M\text{-}OH]^+$.

Chiral-HPLC (20% iPrOH in n-Hexane, isocratic, 1.0 mL/min, 220 nm): t_R (**192**) = 10.49 min (*er* = 94.32/5.68).

6.4.2. Final compounds

(S)-(R)-1-(4-(2-(tert-butoxy)-2-oxoethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV585)



Chemical Formula: $C_{46}H_{61}NO_{11}$
Exact Mass: 803,42
Molecular Weight: 803,98

193

193 is synthesized according to general procedure 5.9.7. Reactants: **77** (20 mg), **226** (22 mg), DMAP (224 mg) and DIC (8 µL). The pure product is obtained as a white foam.

prep-HPLC (70 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**193**) = 5.61 min.

Yield 20 mg (52%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.33 – 7.27 (m, 1H), 6.93 – 6.87 (m, 1H), 6.82 – 6.75 (m, 2H), 6.74 – 6.70 (m, 1H), 6.69 – 6.55 (m, 2H), 6.52 (s, 1H), 6.50 – 6.39 (m, 1H), 5.57 (t, J = 7.0 Hz, 1H), 5.47 (d, J = 5.5 Hz, 1H), 4.55 – 4.46 (m, 2H), 4.02 – 3.93 (m, 5H), 3.87 – 3.81 (m, 9H), 3.78 (s, 2H), 3.75 (s, 4H), 3.39 (d, J = 10.2 Hz, 1H), 2.69 – 2.57 (m, 1H), 2.57 – 2.47 (m, 0H), 2.45 – 2.36 (m, 1H), 2.36 – 2.24 (m, 2H), 2.15 – 2.01 (m, 2H), 1.98 – 1.81 (m, 1H), 1.80 – 1.71 (m, 0H), 1.70 – 1.55 (m, 6H), 1.49 (s, 11H), 1.43 – 1.35 (m, 0H), 1.35 – 1.05 (m, 4H), 0.94 – 0.55 (m, 2H).

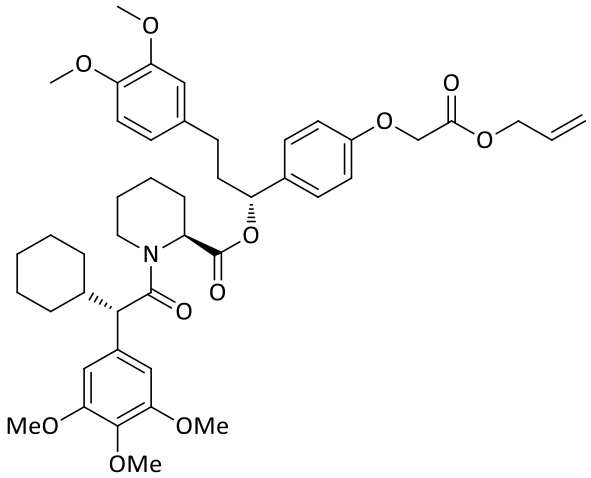
^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.12, 170.12, 168.34, 157.74, 153.50, 153.35, 148.93, 147.38, 137.11, 133.53, 133.40, 132.95, 128.52, 128.08, 120.40, 120.28, 114.86, 114.55, 111.94, 111.59, 111.53, 111.47, 105.84, 105.35, 82.87, 82.76, 75.75, 65.76, 61.04, 60.94, 56.45, 56.31, 56.23, 56.07, 56.07, 55.93, 55.16, 52.51, 44.19, 41.24, 41.14, 40.26, 37.57, 32.81, 31.14, 30.73, 28.17, 26.64, 26.24, 26.09, 25.64, 24.34, 20.87, 20.63.

LC-MS (50-100% B, 19 min): t_R (**193**) = 8.33 min, m/z: calculated = 804.42 $[M+H]^+$, found = 804.99 $[M+H]^+$.

HRMS (ESI): calculated = 804.43174 $[M+H]^+$, found = 804.43168 $[M+H]^+$, err [ppm] = 0.07.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**193**) = 13.40 min (95% Purity).

(S)-(R)-1-(4-(2-(allyloxy)-2-oxoethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV612)



Chemical Formula: $C_{45}H_{57}NO_{11}$
Exact Mass: 787,39
Molecular Weight: 787,93

194

194 is synthesized according to general procedure 5.9.7. Reactants: **77** (16 mg), **151** (15 mg), DMAP (19 mg) and DIC (7 µL). The pure product is obtained as a white foam.

prep-HPLC (75 – 90% B, 10 mL/min, 10 min, 254 nm): t_R (**194**) = 6.20 min.

Yield 16 mg (52%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.28 (m, 1H), 6.95 – 6.89 (m, 1H), 6.76 (qd, J = 2.3, 8.7 Hz, 4H), 6.67 – 6.58 (m, 2H), 6.53 (s, 1H), 5.99 – 5.87 (m, 1H), 5.59 (dd, J = 6.3, 7.6 Hz, 1H), 5.48 (d, J = 5.5 Hz, 1H), 5.38 – 5.24 (m, 2H), 4.71 (dt, J = 1.4, 5.8 Hz, 2H), 4.63 (s, 1H), 3.95 (d, J = 14.0 Hz, 1H), 3.89 – 3.69 (m, 15H), 3.38 (d, J = 10.0 Hz, 1H), 2.67 – 2.58 (m, 1H), 2.58 – 2.47 (m, 0H), 2.47 – 2.28 (m, 2H), 2.09 (dt, J = 12.4, 22.3 Hz, 1H), 1.98 – 1.83 (m, 3H), 1.80 – 1.50 (m, 6H), 1.43 (s, 2H), 1.22 (ddt, J = 12.6, 23.4, 59.2 Hz, 4H), 0.94 – 0.69 (m, 1H).

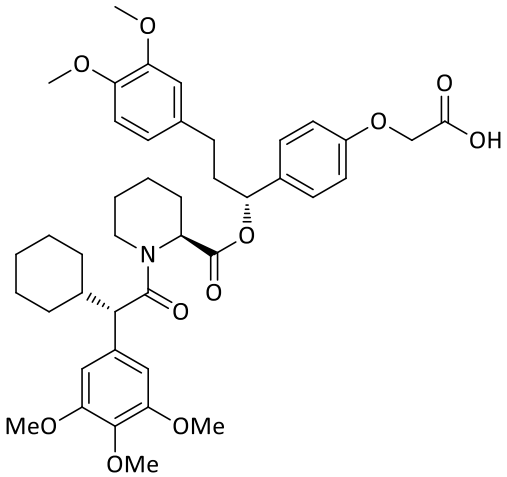
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.68, 170.35, 168.73, 157.62, 153.34, 148.98, 147.42, 137.14, 133.66, 133.34, 131.56, 128.56, 128.09, 120.40, 119.26, 114.94, 114.63, 111.94, 111.45, 105.89, 105.42, 75.57, 68.13, 66.03, 65.44, 60.95, 56.48, 56.25, 56.08, 55.96, 55.15, 52.32, 44.04, 41.39, 37.79, 32.87, 31.13, 30.76, 30.48, 26.70, 26.29, 26.18, 25.71, 21.00, 1.17.

LC-MS (50-100% B, 19 min): t_R (**194**) = 11.79 min, m/z: calculated = 810.38 $[M+Na]^+$, found = 810.41 $[M+Na]^+$.

HRMS (ESI): calculated = 788.40044 $[M+H]^+$, found = 788.40066 $[M+H]^+$, err [ppm] = 0.28.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**194**) = 12.16 min (98% Purity).

2-(4-((R)-1-(((S)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid (AV618)



Chemical Formula: $C_{42}H_{53}NO_{11}$
Exact Mass: 747,36
Molecular Weight: 747,87

195

194 (6 mg, 0.01 mmol, 1.0 eq) is dissolved in 1 mL dry THF. Then $Pd(OAc)_2$ (0.2 mg, 0.1 eq), PPh_3 (2 mg, 0.01 mmol, 1.0 eq) and morpholine (1 µL, 1.0 eq) are added. After 30 min the solvent is removed under airstream and the crude product purified by column chromatography (CH/EE, 2/1, then EE + 10% MeOH), then preparative HPLC.

prep-HPLC (80 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**195**) = 4.88 min.

TLC (CH/EE, 1/2): R_f (**195**) = 0.05.

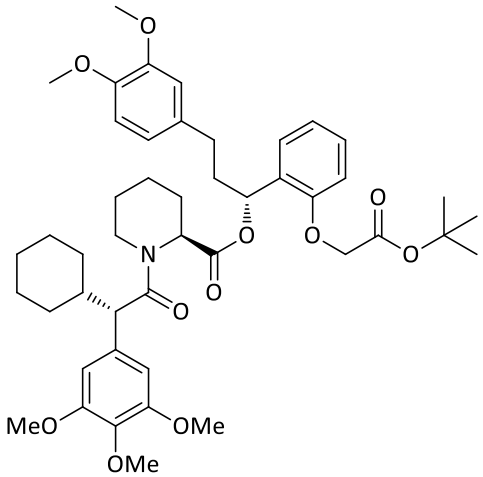
Yield 2 mg (33%).

LC-MS (50-100% B, 19 min): t_R (**195**) = 9.94 min, m/z: calculated = 765.39 $[M+NH_4]^+$, found = 765.52 $[M+NH_4]^+$.

HRMS (ESI): calculated = 748.36914 $[M+H]^+$, found = 748.36950 $[M+H]^+$, err [ppm] = 0.49.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**195**) = 8.68 min (98% Purity).

(S)-(R)-1-(2-(2-(tert-butoxy)-2-oxoethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV561)



Chemical Formula: $C_{46}H_{61}NO_{11}$
Exact Mass: 803,42
Molecular Weight: 803,98

196

196 is synthesized according to general procedure 5.9.7. Reactants: **77** (10 mg), **143** (10 mg), DMAP (12 mg) and DIC (4 µL). The pure product is obtained as a white foam.

prep-HPLC (75 – 90% B, 10 mL/min, 10 min, 254 nm): t_R (**196**) = 6.55 min.

Yield 5 mg (25%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.17 – 7.10 (m, 1H), 6.79 – 6.72 (m, 2H), 6.72 – 6.65 (m, 3H), 6.65 – 6.61 (m, 1H), 6.49 (s, 2H), 6.21 (dd, J = 5.0, 7.6 Hz, 1H), 5.53 (d, J = 5.4 Hz, 1H), 4.51 – 4.44 (m, 1H), 3.97 (d, J = 14.2 Hz, 1H), 3.85 – 3.84 (m, 6H), 3.84 (s, 3H), 3.73 (s, 2H), 3.68 (s, 4H), 3.38 (d, J = 9.9 Hz, 1H), 2.86 (td, J = 2.8, 13.2 Hz, 1H), 2.72 – 2.58 (m, 1H), 2.57 – 2.40 (m, 1H), 2.35 – 2.28 (m, 1H), 2.28 – 2.22 (m, 0H), 2.15 – 1.86 (m, 12H), 1.72 – 1.57 (m, 1H), 1.47 (s, 2H), 1.43 (s, 6H), 1.38 – 1.24 (m, 2H), 1.24 – 1.06 (m, 2H), 1.05 – 0.84 (m, 1H), 0.82 – 0.59 (m, 1H).

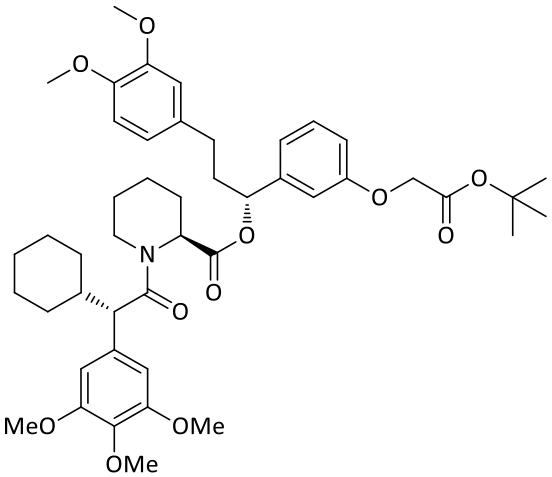
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.56, 170.40, 167.94, 154.30, 153.47, 153.22, 148.90, 147.26, 137.02, 134.37, 133.65, 129.51, 128.47, 126.78, 126.57, 121.75, 121.63, 120.42, 120.26, 112.02, 111.93, 111.77, 111.45, 111.34, 111.19, 105.84, 105.48, 82.35, 72.07, 70.73, 66.14, 66.03, 61.06, 60.89, 56.49, 56.16, 56.08, 55.96, 55.25, 52.29, 43.89, 41.53, 41.28, 39.84, 37.42, 37.19, 33.15, 33.01, 31.14, 30.82, 28.21, 28.17, 26.96, 26.74, 26.62, 26.35, 26.28, 25.80, 24.58, 21.07.

LC-MS (50-100% B, 19 min): t_R (**196**) = 13.29 min, m/z: calculated = 804.42 $[M+H]^+$, found = 804.49 $[M+H]^+$.

HRMS (ESI): calculated = 804.43174 $[M+H]^+$, found = 804.43169 $[M+H]^+$, err [ppm] = 0.06.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**196**) = 14.02 min (95% Purity).

(S)-(R)-1-(3-(2-(tert-butoxy)-2-oxoethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV603)



Chemical Formula: $C_{46}H_{61}NO_{11}$
Exact Mass: 803.42
Molecular Weight: 803.98

197

197 is synthesized according to general procedure 5.9.7. Reactants: **77** (24 mg), (R)-tert-butyl 2-(3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenoxy)acetate (23 mg) provided by Michael Bauder, DMAP (28 mg) and DIC (10 µL). The pure product is obtained as a white foam.

prep-HPLC (75 – 90% B, 10 mL/min, 10 min, 254 nm): t_R (**197**) = 8.02 min.

Yield 20 mg (43%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.10 (t, J = 7.9 Hz, 1H), 6.86 – 6.81 (m, 0H), 6.81 – 6.74 (m, 1H), 6.74 – 6.70 (m, 1H), 6.69 – 6.65 (m, 1H), 6.64 – 6.58 (m, 2H), 6.49 (s, 2H), 6.46 – 6.37 (m, 2H), 5.57 (dd, J = 5.8, 7.9 Hz, 1H), 5.50 – 5.45 (m, 1H), 4.48 (s, 2H), 4.00 – 3.94 (m, 1H), 3.85 – 3.84 (m, 6H), 3.77 (s, 3H), 3.72 (s, 6H), 3.39 (d, J = 9.9 Hz, 1H), 2.81 – 2.74 (m, 1H), 2.64 – 2.49 (m, 1H), 2.49 – 2.40 (m, 1H), 2.39 – 2.32 (m, 1H), 2.13 – 2.00 (m, 2H), 1.93 (ddd, J = 5.4, 9.6, 13.8 Hz, 1H), 1.86 (t, J = 9.2 Hz, 1H), 1.83 – 1.75 (m, 1H), 1.74 – 1.51 (m, 6H), 1.47 (d, J = 0.8 Hz, 8H), 1.38 – 1.23 (m, 3H), 1.14 (q, J = 12.4 Hz, 2H), 0.95 – 0.71 (m, 2H), 0.70 – 0.52 (m, 1H).

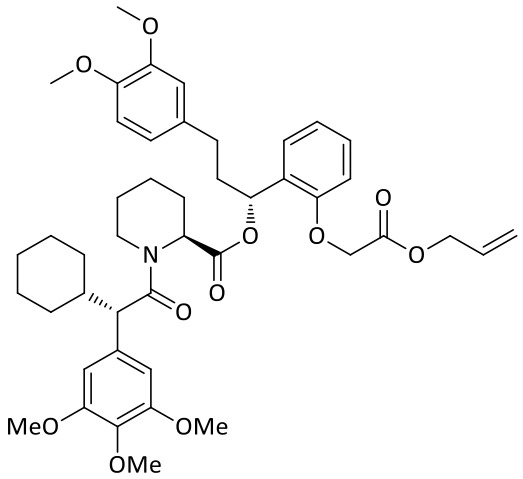
^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.03, 170.34, 168.24, 167.98, 158.28, 157.91, 153.49, 153.25, 149.12, 148.99, 147.43, 141.89, 141.55, 137.04, 134.03, 133.54, 133.44, 129.99, 129.73, 120.40, 120.27, 120.05, 119.42, 114.01, 113.91, 113.75, 113.65, 111.93, 111.85, 111.57, 111.47, 105.87, 105.39, 82.63, 75.83, 65.85, 65.80, 61.04, 60.93, 56.48, 56.20, 56.11, 56.07, 56.03, 55.96, 55.20, 52.44, 44.04, 41.35, 41.21, 40.02, 37.99, 37.85, 33.08, 32.90, 31.57, 31.12, 30.80, 30.62, 28.18, 26.83, 26.68, 26.56, 26.30, 26.19, 25.65, 24.41, 21.00, 20.79.

LC-MS (70-100% B, 19 min): t_R (**197**) = 8.32 min, m/z: calculated = 804.42 $[M+H]^+$, found = 804.52 $[M+H]^+$.

HRMS (ESI): calculated = 804.43174 $[M+H]^+$, found = 804.43215 $[M+H]^+$, err [ppm] = 0.51.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**197**) = 13.69 min (99% Purity).

(S)-(R)-1-(2-(2-(allyloxy)-2-oxoethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV644)



Chemical Formula: $C_{45}H_{57}NO_{11}$
Exact Mass: 787,39
Molecular Weight: 787,93

198

198 is synthesized according to general procedure 5.9.7. Reactants: **77** (24 mg), **144** (22 mg), DMAP (28 mg) and DIC (11 µL). The pure product is obtained as a white foam.

prep-HPLC (70 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**198**) = 6.59 min.

Yield 7 mg (16%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.84 – 6.74 (m, 2H), 6.72 – 6.68 (m, 2H), 6.66 (dd, J = 2.1, 10.1 Hz, 3H), 6.49 (s, 2H), 6.21 (dd, J = 5.2, 7.5 Hz, 1H), 5.95 – 5.81 (m, 1H), 5.53 (d, J = 5.4 Hz, 1H), 5.31 – 5.25 (m, 1H), 5.25 – 5.19 (m, 1H), 4.65 (dt, J = 1.4, 5.8 Hz, 2H), 3.97 (d, J = 14.0 Hz, 1H), 3.84 (d, J = 5.6 Hz, 10H), 3.68 (s, 4H), 3.38 (d, J = 9.8 Hz, 1H), 2.85 (t, J = 12.4 Hz, 1H), 2.72 – 2.50 (m, 1H), 2.50 – 2.41 (m, 1H), 2.35 – 2.22 (m, 10H), 2.09 (d, J = 12.2 Hz, 1H), 2.03 – 1.94 (m, 1H), 1.89 (d, J = 13.1 Hz, 1H), 1.75 – 1.50 (m, 7H), 1.46 (t, J = 12.9 Hz, 0H), 1.40 – 1.08 (m, 5H), 0.83 (dq, J = 11.4, 12.0, 72.6 Hz, 1H).

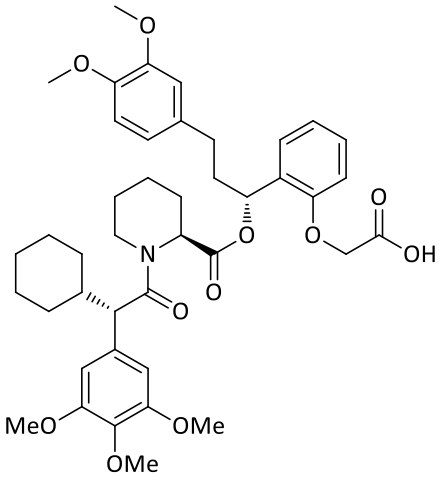
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.66, 170.37, 154.22, 153.24, 147.28, 134.31, 133.59, 131.57, 129.73, 128.62, 126.73, 121.98, 120.40, 119.11, 112.04, 111.94, 111.43, 111.35, 105.85, 105.49, 70.68, 65.89, 65.61, 61.06, 60.90, 56.50, 56.17, 55.97, 55.27, 52.33, 45.26, 43.93, 41.49, 41.25, 37.44, 33.16, 33.01, 31.18, 30.82, 26.97, 26.96, 26.73, 26.35, 26.27, 25.79, 21.06.

LC-MS (70-100% B, 19 min): t_R (**198**) = 7.65 min, m/z: calculated = 788.40 $[M+H]^+$, found = 788.84 $[M+H]^+$.

HRMS (ESI): calculated = 788.40044 $[M+H]^+$, found = 788.40046 $[M+H]^+$, err [ppm] = 0.03.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**198**) = 12.74 min (96% Purity).

2-(2-((R)-1-(((S)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)acetic acid (AV649)



Chemical Formula: $C_{42}H_{53}NO_{11}$
Exact Mass: 747,36
Molecular Weight: 747,87

199

198 (6 mg, 0.01 mmol, 1.0 eq) is dissolved in 1 mL dry THF. Then $Pd(OAc)_2$ (0.2 mg, 0.1 eq), PPh_3 (2 mg, 0.01 mmol, 1.0 eq) and morpholine (1 µL, 1.0 eq) are added. After 15 min the solvent is removed under airstream and the crude product purified by column chromatography (CH/EE, 1/3), then preparative HPLC.

prep-HPLC (70 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**199**) = 7.19 min.

Silica column chromatography: CH/EE, 1/3, v/v.

TLC (CH/EE, 1/3): R_f (**199**) = 0.25.

Yield 1.2 mg (20%).

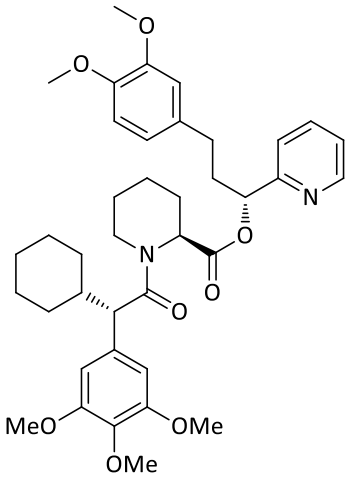
LC-MS (70-100% B, 19 min): t_R (**199**) = 4.72 min, m/z: calculated = 748.37 $[M+H]^+$,

found = 748.36924 $[M+H]^+$.

HRMS (ESI): calculated = 748.36914 $[M+H]^+$, found = 748.36924 $[M+H]^+$, err [ppm] = 0.14.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**199**) = 9.52 min (97% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(pyridin-2-yl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV548)



Chemical Formula: $C_{39}H_{50}N_2O_8$
Exact Mass: 674,36
Molecular Weight: 674,82

200

200 is synthesized according to general procedure 5.9.7. Reactants: **77** (21 mg), **102** (14 mg), DMAP (253 mg) and DIC (9 µL). The pure product is obtained as a white foam.

prep-HPLC (40 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**200**) = 6.04 min.

Yield 20 mg (59%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.79 (d, J = 5.5 Hz, 1H), 8.16 (t, J = 7.9 Hz, 1H), 7.72 (t, J = 6.6 Hz, 1H), 7.37 (d, 1H), 6.74 (d, J = 8.1 Hz, 1H), 6.66 – 6.56 (m, 2H), 6.41 (s, 2H), 6.03 (dd, J = 5.2, 7.9 Hz, 1H), 5.48 – 5.43 (m, 1H), 4.00 (d, J = 13.9 Hz, 1H), 3.85 – 3.84 (m, 2H), 3.84 – 3.81 (m, 6H), 3.80 (s, 3H), 3.70 (s, 5H), 3.44 (d, J = 10.0 Hz, 1H), 3.03 (td, J = 3.0, 13.2 Hz, 1H), 2.67 – 2.51 (m, 2H), 2.34 – 2.26 (m, 1H), 2.26 – 2.13 (m, 2H), 2.08 – 1.96 (m, 1H), 1.83 – 1.62 (m, 6H), 1.61 – 1.46 (m, 1H), 1.43 – 1.24 (m, 2H), 1.22 – 1.04 (m, 2H), 0.98 – 0.87 (m, 1H), 0.83 – 0.71 (m, 1H).

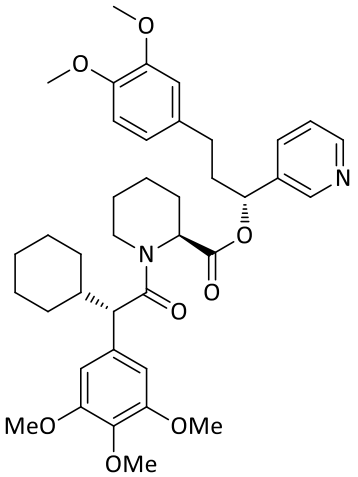
^{13}C-NMR (126 MHz, $CDCl_3$): δ 174.56, 169.97, 155.42, 153.22, 149.11, 147.73, 145.44, 142.47, 137.00, 133.02, 132.11, 125.71, 124.08, 120.44, 111.73, 111.61, 105.87, 105.40, 72.61, 61.01, 56.20, 56.07, 55.93, 55.16, 52.99, 44.28, 41.04, 36.91, 32.70, 30.89, 30.79, 26.67, 26.52, 26.18, 26.08, 25.27, 20.54.

LC-MS (70-100% B, 19 min): t_R (**200**) = 4.57 min, m/z: calculated = 675.36 $[M+H]^+$, found = 675.62 $[M+H]^+$.

HRMS (ESI): calculated = 675.36399 $[M+H]^+$, found = 675.36444 $[M+H]^+$, err [ppm] = 0.67.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**200**) = 6.91 min (97% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(pyridin-3-yl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV471/AV549)



Chemical Formula: $C_{39}H_{50}N_2O_8$
Exact Mass: 674,36
Molecular Weight: 674,82

201

201 is synthesized according to general procedure 5.9.7. Reactants: **77** (23 mg), **98** (12 mg), DMAP (27 mg) and DIC (9 µL). The pure product is obtained as a white foam.

prep-HPLC (30 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**201**) = 4.82 min.

Yield 14 mg (38%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.72 (s, 2H), 7.73 – 7.59 (m, 2H), 6.77 (d, J = 7.9 Hz, 1H), 6.68 – 6.59 (m, 2H), 6.50 (s, 2H), 5.76 (dd, J = 5.2, 8.4 Hz, 1H), 5.49 – 5.44 (m, 1H), 4.03 (d, J = 13.8 Hz, 1H), 3.85 (s, 6H), 3.80 (s, 3H), 3.74 (s, 5H), 3.42 (d, J = 10.0 Hz, 1H), 3.04 (s, 1H), 2.95 (s, 1H), 2.80 – 2.71 (m, 1H), 2.58 – 2.42 (m, 2H), 2.33 – 2.23 (m, 1H), 2.13 – 1.99 (m, 2H), 1.96 – 1.88 (m, 1H), 1.88 – 1.82 (m, 1H), 1.78 – 1.62 (m, 6H), 1.55 – 1.44 (m, 0H), 1.38 – 1.22 (m, 3H), 1.22 – 1.08 (m, 2H), 1.00 – 0.71 (m, 2H).

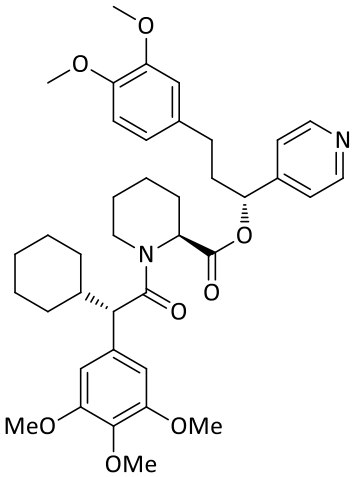
^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.43, 170.28, 153.32, 149.24, 147.85, 142.42, 141.89, 140.86, 140.61, 137.11, 133.60, 131.97, 126.75, 120.45, 111.74, 111.63, 105.99, 72.12, 61.01, 56.33, 56.08, 56.00, 55.09, 52.56, 44.30, 41.33, 37.68, 37.53, 32.75, 30.79, 30.73, 26.60, 26.53, 26.23, 26.14, 25.43, 20.86.

LC-MS (50-100% B, 19 min): t_R (**201**) = 7.19 min, m/z: calculated = 675.36 $[M+H]^+$, found = 675.59 $[M+H]^+$.

HRMS (ESI): calculated = 675.36399 $[M+H]^+$, found = 675.36394 $[M+H]^+$, err [ppm] = 0.09.

RP-HPLC (30 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**201**) = 9.54 min (97% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(pyridin-4-yl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV550)



Chemical Formula: $C_{39}H_{50}N_2O_8$
Exact Mass: 674,36
Molecular Weight: 674,82

202

202 is synthesized according to general procedure 5.9.7. Reactants: **77** (20 mg), **226** (13 mg), DMAP (23 mg) and DIC (8 µL). The pure product is obtained as a white foam.

prep-HPLC (30 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**202**) = 5.17 min.

Yield 18 mg (56%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.75 (d, J = 5.6 Hz, 2H), 7.35 (d, J = 5.1 Hz, 2H), 6.78 (d, J = 8.6 Hz, 1H), 6.62 (d, J = 6.5 Hz, 2H), 6.51 (s, 2H), 5.75 (dd, J = 4.8, 8.4 Hz, 1H), 5.58 – 5.52 (m, 1H), 4.09 (d, J = 13.8 Hz, 1H), 3.85 (d, J = 0.8 Hz, 6H), 3.78 (s, 3H), 3.72 (s, 6H), 3.45 (d, J = 10.1 Hz, 1H), 2.72 (td, J = 2.9, 13.3 Hz, 1H), 2.57 – 2.45 (m, 2H), 2.29 (d, J = 13.4 Hz, 1H), 2.15 – 2.04 (m, 1H), 2.04 – 1.89 (m, 1H), 1.89 – 1.82 (m, 1H), 1.80 – 1.61 (m, 4H), 1.58 – 1.46 (m, 1H), 1.40 – 1.23 (m, 6H), 1.22 – 1.07 (m, 2H), 0.97 – 0.72 (m, 2H).

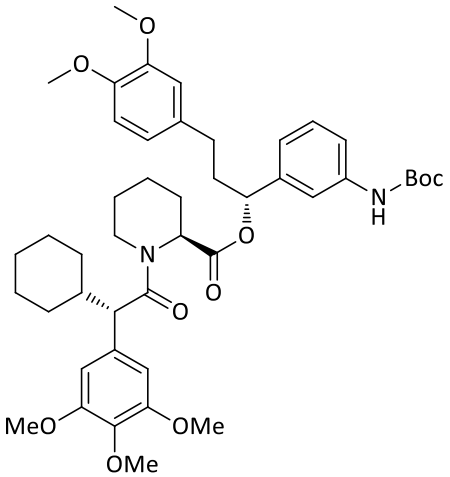
^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.81, 170.07, 160.35, 153.40, 149.27, 147.96, 142.29, 137.16, 133.32, 131.76, 124.18, 120.48, 111.78, 111.69, 106.02, 73.39, 61.02, 56.33, 56.09, 56.02, 55.23, 52.57, 44.48, 41.16, 37.63, 32.80, 30.69, 30.66, 26.55, 26.42, 26.17, 26.05, 25.39, 20.72.

LC-MS (50-100% B, 19 min): t_R (**202**) = 5.50 min, m/z: calculated = 675.36 $[M+H]^+$, found = 675.76 $[M+H]^+$.

HRMS (ESI): calculated = 675.6399$[M+H]^+$, found = 675.36446 $[M+H]^+$, err [ppm] = 0.70.

RP-HPLC (30 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**202**) = 9.38 min (98% Purity).

(S)-(R)-1-(3-((tert-butoxycarbonyl)amino)phenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV551)



Chemical Formula: $C_{45}H_{60}N_2O_{10}$
Exact Mass: 788,42
Molecular Weight: 788,97

203

233 is synthesized according to general procedure 5.9.7. Reactants: **77** (16 mg), **226** (15 mg), DMAP (19 mg) and DIC (7 µL). The pure product is obtained as a white foam.

prep-HPLC (70 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**203**) = 9.38 min.

Yield 17 mg (57%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.41 (d, J = 8.2 Hz, 1H), 7.12 (t, J = 7.9 Hz, 1H), 6.95 – 6.91 (m, 1H), 6.83 (s, 1H), 6.79 – 6.75 (m, 1H), 6.68 – 6.60 (m, 2H), 6.55 – 6.50 (m, 1H), 6.50 (s, 1H), 5.57 (dd, J = 5.7, 8.1 Hz, 1H), 5.47 (d, J = 5.3 Hz, 1H), 3.96 (d, J = 14.2 Hz, 1H), 3.90 – 3.82 (m, 11H), 3.79 (s, 2H), 3.70 (s, 5H), 3.40 (d, J = 10.0 Hz, 1H), 2.74 (td, J = 2.8, 13.3 Hz, 1H), 2.67 – 2.51 (m, 1H), 2.49 – 2.40 (m, 1H), 2.40 – 2.23 (m, 2H), 2.18 – 2.03 (m, 1H), 1.95 – 1.85 (m, 1H), 1.84 – 1.74 (m, 1H), 1.75 – 1.54 (m, 6H), 1.52 (s, 6H), 1.51 (s, 2H), 1.46 – 1.07 (m, 5H), 0.96 – 0.71 (m, 2H).

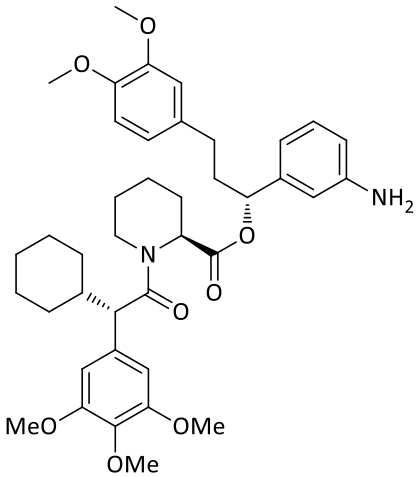
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.80, 170.59, 153.25, 148.99, 147.42, 145.79, 138.69, 133.68, 133.59, 129.26, 121.35, 120.44, 111.99, 111.46, 106.27, 75.77, 60.95, 56.37, 56.10, 55.97, 55.13, 52.35, 44.01, 41.20, 37.54, 32.89, 31.21, 28.54, 28.47, 26.82, 26.71, 26.33, 26.23, 25.65, 20.95.

LC-MS (70-100% B, 19 min): t_R (**203**) = 7.92 min, m/z: calculated = 789.42 $[M+H]^+$, found = 789.54 $[M+H]^+$.

HRMS (ESI): calculated = 789.43207 $[M+H]^+$, found = 789.43276 $[M+H]^+$, err [ppm] = 0.87.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**203**) = 13.28 min (92% Purity).

(S)-(R)-1-(3-aminophenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV602)



Chemical Formula: $C_{40}H_{52}N_2O_8$
Exact Mass: 688,37
Molecular Weight: 688,85

204

203 (10 mg, 0.013 mmol, 1 eq) is dissolved in 3 mL DCM and 150 µL TFA added. The reaction is stirred for 20 min, then diluted with 50 mL sat. $NaHCO_3$ solution and extracted with DCM (3x20 mL), the combined organic phases dried over $MgSO_4$, filtered and the solvent removed. The crude product is purified by silica column chromatography (CH/EE, 3/2 + 1% TEA) providing pure **204.**

TLC (CH/EE, 3/2 + 1% TEA**):** R_f (**204**) = 0.25.

Yield 6 mg (69%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.00 – 6.93 (m, 1H), 6.82 – 6.72 (m, 1H), 6.68 – 6.63 (m, 1H), 6.66 – 6.61 (m, 1H), 6.54 (s, 1H), 6.54 – 6.48 (m, 1H), 6.45 – 6.41 (m, 0H), 6.32 – 6.26 (m, 1H), 6.20 – 6.15 (m, 1H), 5.55 (dd, J = 6.0, 7.8 Hz, 1H), 5.49 (d, J = 5.5 Hz, 1H), 3.97 – 3.90 (m, 1H), 3.88 – 3.81 (m, 8H), 3.79 (s, 2H), 3.72 (s, 4H), 3.37 (d, J = 9.9 Hz, 1H), 2.71 (td, J = 2.8, 13.3 Hz, 1H), 2.66 – 2.51 (m, 1H), 2.51 – 2.32 (m, 2H), 2.32 – 2.22 (m, 1H), 2.19 – 2.02 (m, 1H), 1.98 – 1.87 (m, 2H), 1.85 – 1.74 (m, 1H), 1.73 – 1.54 (m, 10H), 1.46 – 1.22 (m, 4H), 1.24 – 1.06 (m, 2H), 0.95 – 0.70 (m, 2H).

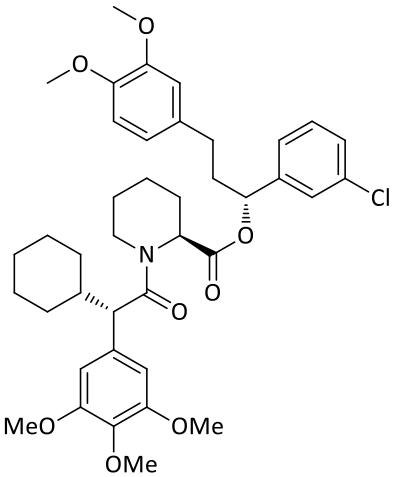
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.14, 170.75, 153.19, 148.97, 147.39, 146.70, 141.34, 137.07, 129.35, 122.31, 120.41, 116.90, 114.75, 112.90, 112.00, 111.42, 106.15, 105.50, 75.98, 60.94, 56.50, 56.32, 56.09, 55.99, 55.19, 52.13, 43.81, 41.54, 37.93, 32.97, 31.26, 30.80, 26.84, 26.76, 26.31, 25.77, 21.10.

LC-MS (50-100% B, 19 min): t_R (**204**) = 8.49 min, m/z: calculated = 689.37 $[M+H]^+$,
found = 689.32 $[M+H]^+$.

HRMS (ESI): calculated = 689.37964 $[M+H]^+$, found = 689.37987 $[M+H]^+$, err [ppm] = 0.32.

RP-HPLC (30 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**204**) = 9.86 min (95% Purity).

(S)-(R)-1-(3-chlorophenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV468)



Chemical Formula: $C_{40}H_{50}ClNO_8$
Exact Mass: 707,32
Molecular Weight: 708,28

205

205 is synthesized according to general procedure 5.9.7. Reactants: **77** (75 mg), **192** (50 mg), DMAP (80 mg) and DIC (28 µL). The pure product is obtained as a white foam.

prep-HPLC (70 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**205**) = 6.3 min.

TLC (CH/EE, 1/1): R_f (**205**) = 0.5.

Yield 20 mg (18%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.30 (m, 1H), 7.21 – 7.17 (m, 1H), 7.12 (t, J = 7.8 Hz, 1H), 7.03 – 7.00 (m, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.71 – 6.68 (m, 1H), 6.65 – 6.59 (m, 2H), 6.50 (s, 1H), 5.54 (dd, J = 5.8, 8.0 Hz, 1H), 5.48 (d, J = 5.5 Hz, 1H), 4.02 – 3.94 (m, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.78 (s, 3H), 3.73 (s, 6H), 3.39 (d, J = 9.9 Hz, 1H), 2.72 (td, J = 2.8, 13.3 Hz, 1H), 2.64 – 2.51 (m, 1H), 2.49 – 2.33 (m, 2H), 2.32 – 2.24 (m, 1H), 2.16 – 2.01 (m, 2H), 2.00 – 1.74 (m, 3H), 1.72 – 1.51 (m, 4H), 1.47 – 1.38 (m, 1H), 1.36 – 1.21 (m, 2H), 1.22 – 1.05 (m, 2H), 0.96 – 0.83 (m, 1H), 0.81 – 0.70 (m, 1H), 0.64 – 0.51 (m, 1H).

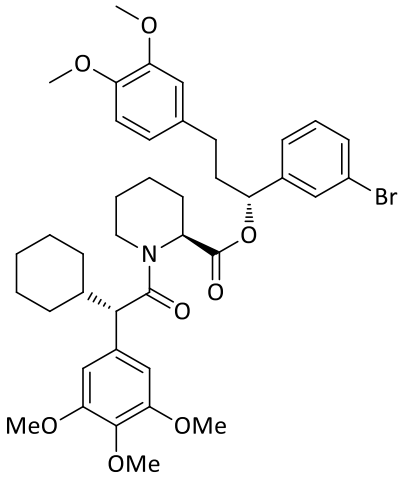
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.80, 170.34, 153.46, 153.24, 149.00, 147.48, 142.28, 137.04, 134.22, 133.47, 133.19, 130.18, 129.95, 128.79, 128.25, 126.90, 126.83, 125.16, 124.53, 120.38, 120.25, 111.90, 111.81, 111.58, 111.48, 105.84, 105.39, 76.35, 75.17, 61.01, 60.89, 56.46, 56.17, 56.09, 56.04, 56.00, 55.94, 55.17, 52.26, 43.96, 41.39, 41.18, 39.86, 37.87, 37.74, 33.11, 32.88, 31.50, 31.04, 30.75, 30.61, 26.93, 26.70, 26.66, 26.52, 26.28, 26.18, 25.63, 24.37, 20.98, 20.74.

LC-MS (50-100% B, 19 min): t_R (**205**) = 7.99 min, m/z: calculated = 708.32 $[M+H]^+$, found = 708.65 $[M+H]^+$.

HRMS (ESI): calculated = 708.32977 $[M+H]^+$, found = 708.33011 $[M+H]^+$, err [ppm] = 0.48.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**205**) = 13.38 min (99% Purity).

(S)-(R)-1-(3-bromophenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV467)



Chemical Formula: $C_{40}H_{50}BrNO_8$
Exact Mass: 751,27
Molecular Weight: 752,73

206

206 is synthesized according to general procedure 5.9.7. Reactants: **77** (66mg), **182** (50 mg), DMAP (70 mg) and DIC (24 µL). The pure product is obtained as a white foam.

prep-HPLC (70 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**206**) = 6.3 min.

TLC (CH/EE, 2/1): R_f (**206**) = 0.27.

Yield 18 mg (17%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.36 (ddd, J = 1.0, 2.0, 8.0 Hz, 1H), 7.20 (t, J = 1.8 Hz, 1H), 7.07 (t, J = 7.8 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 6.73 (dt, J = 1.3, 7.8 Hz, 1H), 6.64 – 6.58 (m, 2H), 6.50 (s, 2H), 5.53 (dd, J = 6.0, 8.0 Hz, 1H), 5.48 (d, J = 5.4 Hz, 1H), 4.02 – 3.98 (m, 1H), 3.87 – 3.86 (m, 2H), 3.85 – 3.85 (m, 5H), 3.79 (s, 2H), 3.73 (s, 5H), 3.40 (d, J = 10.0 Hz, 1H), 2.74 (td, J = 2.9, 13.4 Hz, 1H), 2.66 – 2.51 (m, 1H), 2.48 – 2.33 (m, 2H), 2.33 – 2.25 (m, 1H), 2.15 – 2.01 (m, 2H), 1.99 – 1.89 (m, 1H), 1.89 – 1.82 (m, 1H), 1.83 – 1.74 (m, 1H), 1.71 – 1.54 (m, 5H), 1.49 – 1.39 (m, 1H), 1.38 – 1.22 (m, 3H), 1.21 – 1.05 (m, 2H), 0.95 – 0.69 (m, 2H).

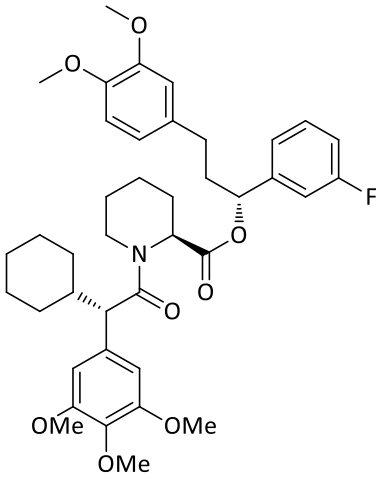
^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.40, 170.08, 153.54, 153.30, 149.15, 149.00, 147.72, 147.49, 142.44, 142.16, 137.22, 137.07, 133.72, 133.19, 133.16, 133.01, 131.83, 131.30, 130.52, 130.31, 129.88, 129.82, 125.67, 124.96, 122.95, 122.42, 120.42, 120.31, 111.91, 111.85, 111.64, 111.54, 105.84, 105.39, 76.51, 75.33, 61.07, 60.97, 56.51, 56.23, 56.12, 56.08, 56.05, 55.96, 55.28, 52.57, 44.19, 41.26, 41.12, 40.26, 37.82, 33.10, 32.89, 31.53, 31.06, 30.77, 30.63, 26.94, 26.71, 26.63, 26.50, 26.25, 26.10, 25.59, 24.31, 20.89, 20.65.

LC-MS (50-100% B, 19 min): t_R (**206**) = 8.42 min, m/z: calculated = 752.27 $[M+H]^+$, found = 752.77 $[M+H]^+$.

HRMS (ESI): calculated = 752.27926 $[M+H]^+$, found = 752.27940 $[M+H]^+$, err [ppm] = 0.20.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**206**) = 13.69 min (99% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-fluorophenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV466)



Chemical Formula: $C_{40}H_{50}FNO_8$
Exact Mass: 691,35
Molecular Weight: 691,83

207

207 is synthesized according to general procedure 5.9.7. Reactants: **77** (80 mg), **226** (50 mg), DMAP (84 mg) and DIC (30 µL). The pure product is obtained as a white foam.

prep-HPLC (70 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**207**) = 5.3 min.

TLC (CH/EE, 2/1): R_f (**207**) = 0.27.

Yield 42 mg (35%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.20 – 7.13 (m, 1H), 6.94 – 6.87 (m, 1H), 6.77 (d, J = 7.9 Hz, 1H), 6.67 – 6.63 (m, 1H), 6.63 – 6.58 (m, 3H), 6.51 (s, 2H), 5.58 (dd, J = 7.9, 6.0 Hz, 1H), 5.50 (d, J = 5.5 Hz, 1H), 4.01 (d, J = 14.0 Hz, 1H), 3.87 – 3.82 (m, 10H), 3.77 (s, 2H), 3.73 (s, 5H), 3.41 (d, J = 10.1 Hz, 1H), 2.75 – 2.67 (m, 1H), 2.66 – 2.52 (m, 1H), 2.47 – 2.33 (m, 2H), 2.33 – 2.22 (m, 1H), 2.15 – 1.99 (m, 2H), 1.97 – 1.89 (m, 1H), 1.88 – 1.82 (m, 1H), 1.82 – 1.73 (m, 1H), 1.73 – 1.53 (m, 3H), 1.49 – 1.38 (m, 1H), 1.35 – 1.21 (m, 2H), 1.20 – 1.04 (m, 2H), 1.02 – 0.70 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.64, 173.43, 170.20, 170.03, 163.75, 161.79, 158.93, 158.60, 158.27, 157.95, 153.52, 153.34, 149.12, 148.97, 147.69, 147.46, 142.64, 142.59, 137.18, 137.03, 133.65, 133.23, 133.15, 130.58, 130.52, 130.20, 130.14, 122.69, 122.21, 122.19, 120.43, 120.31, 115.76, 115.60, 115.18, 115.01, 113.80, 113.63, 113.49, 113.31, 111.91, 111.84, 111.63, 111.52, 105.73,

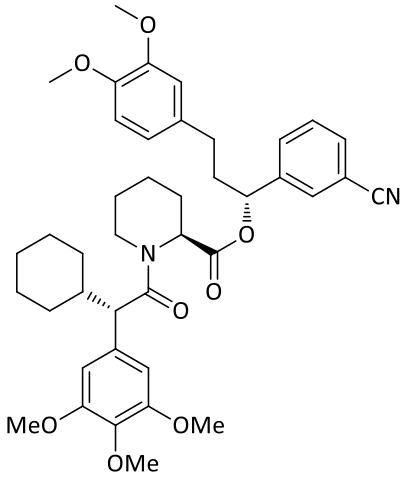
105.33, 76.61, 75.40, 61.05, 60.89, 56.44, 56.26, 56.15, 56.06, 55.93, 55.23, 52.55, 44.24, 41.24, 41.10, 40.30, 37.77, 33.07, 32.84, 31.50, 31.04, 30.72, 30.59, 26.89, 26.60, 26.47, 26.21, 26.05, 25.58, 24.27, 20.84, 20.61.

LC-MS (70-100% B, 19 min): t_R (**207**) = 7.16 min, m/z: calculated = 692.36 $[M+H]^+$, found = 692.52 $[M+H]^+$.

HRMS (ESI): calculated = 692.35932 $[M+H]^+$, found = 692.35983 $[M+H]^+$, err [ppm] = 0.73.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**207**) = 12.42 min (95% Purity).

(S)-(R)-1-(3-cyanophenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV552)



Chemical Formula: $C_{41}H_{50}N_2O_8$
Exact Mass: 698,36
Molecular Weight: 698,84

208

208 is synthesized according to general procedure 5.9.7. Reactants: **77** (21 mg), **180** (15 mg), DMAP (25 mg) and DIC (9 µL). The pure product is obtained as a white foam.

prep-HPLC (70 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**208**) = 6.88 min.

Yield 20 mg (57%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.55 – 7.51 (m, 1H), 7.38 – 7.36 (m, 1H), 7.31 (t, 1H), 7.05 – 6.98 (m, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.64 – 6.58 (m, 2H), 6.51 (s, 2H), 5.59 (dd, J = 5.8, 8.1 Hz, 1H), 5.49 (d, J = 5.1 Hz, 1H), 4.02 (d, J = 13.7 Hz, 1H), 3.89 – 3.83 (m, 8H), 3.79 (s, 3H), 3.74 (s, 5H), 3.41 (d, J = 10.0 Hz, 1H), 2.71 (td, J = 2.9, 13.4 Hz, 1H), 2.63 – 2.50 (m, 0H), 2.50 – 2.33 (m, 2H), 2.33 – 2.25 (m, 1H), 2.18 – 2.02 (m, 2H), 2.02 – 1.92 (m, 1H), 1.91 – 1.76 (m, 2H), 1.76 – 1.52 (m, 4H), 1.51 – 1.40 (m, 1H), 1.39 – 1.08 (m, 5H), 0.99 – 0.72 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.48, 170.06, 153.33, 149.07, 147.60, 141.74, 137.10, 133.24, 132.82, 131.92, 130.82, 130.29, 129.63, 120.42, 118.46, 112.61, 111.85, 111.57, 105.86, 105.40, 74.94, 60.99,

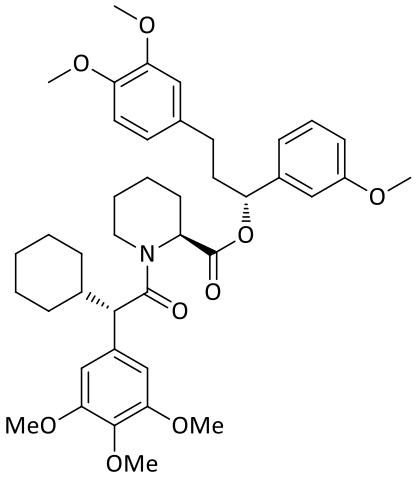
56.53, 56.27, 56.09, 55.98, 55.25, 52.58, 44.25, 41.27, 37.77, 32.86, 31.00, 30.75, 26.64, 26.62, 26.23, 26.10, 25.56, 20.90.

LC-MS (70-100% B, 19 min): t_R (**208**) = 6.16 min, m/z: calculated = 699.36 $[M+H]^+$, found = 699.64 $[M+H]^+$.

HRMS (ESI): calculated = 699.36399 $[M+H]^+$, found = 699.36414 $[M+H]^+$, err [ppm] = 0.22.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**208**) = 11.33 min (99% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-methoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV464/AV545)



Chemical Formula: $C_{41}H_{53}NO_9$
Exact Mass: 703,37
Molecular Weight: 703,86

209

209 is synthesized according to general procedure 5.9.7. Reactants: **77** (42 mg), **81** (30 mg), DMAP (50 mg) and DIC (17 µL). The pure product is obtained as a white foam.

prep-HPLC (70 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**209**) = 6.8 min.

Yield 26 mg (37%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.11 (t, J = 7.9 Hz, 1H), 6.97 – 6.87 (m, 1H), 6.83 – 6.74 (m, 2H), 6.64 – 6.58 (m, 2H), 6.50 (s, 2H), 6.41 – 6.36 (m, 1H), 5.57 (dd, J = 6.1, 7.7 Hz, 1H), 5.49 (d, J = 5.1 Hz, 1H), 4.05 – 3.98 (m, 1H), 3.87 – 3.84 (m, 9H), 3.82 (s, 1H), 3.79 (s, 2H), 3.76 (s, 2H), 3.73 (s, 4H), 3.42 (d, J = 10.1 Hz, 1H), 2.80 (td, J = 2.8, 13.4 Hz, 1H), 2.71 – 2.51 (m, 1H), 2.48 – 2.40 (m, 1H), 2.40 – 2.25 (m, 2H), 2.18 – 2.00 (m, 1H), 2.00 – 1.89 (m, 1H), 1.89 – 1.76 (m, 1H), 1.75 – 1.52 (m, 7H), 1.52 – 1.39 (m, 1H), 1.38 – 1.20 (m, 3H), 1.20 – 1.05 (m, 1H), 0.96 – 0.68 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.91, 170.16, 170.02, 159.58, 158.76, 158.43, 153.49, 153.26, 148.86, 147.31, 141.50, 136.85, 133.57, 133.07, 130.01, 129.71, 120.53, 120.41, 119.22, 118.55, 113.66, 113.23, 112.81, 111.98, 111.57, 105.78, 105.33, 76.40, 61.12, 60.99, 56.45, 56.17, 56.09, 56.04,

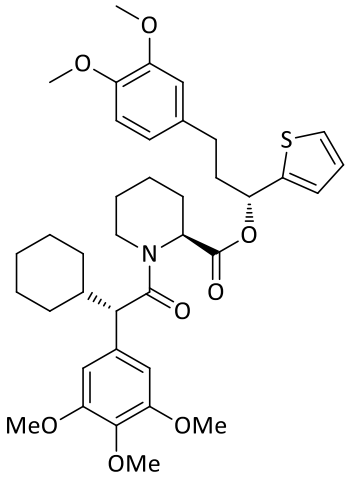
55.94, 55.31, 52.90, 44.37, 41.11, 40.61, 37.79, 32.99, 32.84, 31.60, 31.12, 30.75, 30.52, 26.75, 26.58, 26.42, 26.18, 25.99, 25.54, 24.20, 20.80, 20.51.

LC-MS (50-100% B, 19 min): t_R (**209**) = 6.85 min, m/z: calculated = 704.37 $[M+H]^+$, found = 704.45 $[M+H]^+$.

HRMS (ESI): calculated = 704.37931 $[M+H]^+$, found = 704.37956 $[M+H]^+$, err [ppm] = 0.36.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**209**) = 12.14 min (95% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(thiophen-2-yl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV469)



Chemical Formula: $C_{38}H_{49}NO_8S$
Exact Mass: 679,32
Molecular Weight: 679,86

210

210 is synthesized according to general procedure 5.9.7. Reactants: **77** (88 mg), **159** (50 mg), DMAP (93 mg) and DIC (25 µL). The pure product is obtained as a white foam.

prep-HPLC (70 – 100% B w/ TFA, 10 mL/min, 10 min, 220 nm,): t_R (**210**) = 7.60 min.

TLC (CH/EE, 2/1): R_f (**210**) = 0.24.

Yield 4 mg (3%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.20 – 7.15 (m, 1H), 6.87 (dd, J = 3.5, 5.1 Hz, 1H), 6.79 – 6.74 (m, 2H), 6.66 – 6.61 (m, 2H), 6.51 (s, 2H), 6.41 (s, 1H), 5.89 – 5.85 (m, 1H), 5.46 (d, J = 5.7 Hz, 1H), 3.97 (d, J = 13.8 Hz, 2H), 3.86 – 3.85 (m, 4H), 3.85 – 3.84 (m, 4H), 3.77 (s, 5H), 3.38 (d, J = 9.9 Hz, 1H), 2.80 – 2.73 (m, 1H), 2.68 – 2.56 (m, 2H), 2.48 – 2.33 (m, 2H), 2.32 – 2.27 (m, 1H), 2.17 – 2.02 (m, 1H), 2.01 – 1.92 (m, 1H), 1.92 – 1.85 (m, 2H), 1.73 – 1.58 (m, 2H), 1.46 – 1.38 (m, 2H), 1.37 – 1.21 (m, 3H), 1.22 – 1.05 (m, 3H), 0.94 – 0.84 (m, 1H), 0.79 – 0.70 (m, 1H).

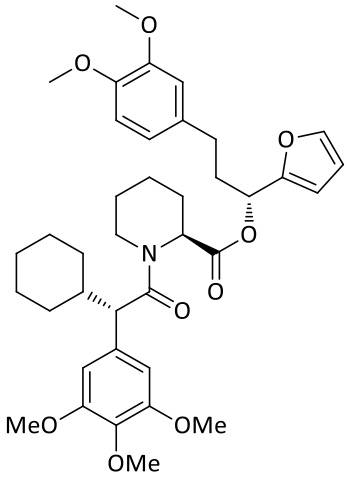
^{13}C-NMR (126 MHz, $CDCl_3$): δ 153.20, 149.02, 133.87, 130.40, 130.35, 126.90, 126.62, 125.89, 125.33, 120.50, 112.02, 111.95, 111.49, 106.03, 105.45, 70.88, 60.95, 56.49, 56.29, 56.08, 56.00, 55.00, 52.15, 43.85, 41.51, 37.97, 32.83, 31.06, 30.85, 26.94, 26.75, 26.41, 26.35, 26.30, 25.77, 24.48, 21.20.

LC-MS (70-100% B, 19 min): t_R (**210**) = 6.71 min, m/z: calculated = 680.33 $[M+H]^+$, found = 680.49 $[M+H]^+$.

HRMS (ESI): calculated = 680.32516 $[M+H]^+$, found = 680.32561 $[M+H]^+$, err [ppm] = 0.66.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**210**) = 11.92 min (95% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(furan-2-yl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV470)



Chemical Formula: $C_{38}H_{49}NO_9$
Exact Mass: 663,34
Molecular Weight: 663,80

211

211 is synthesized according to general procedure 5.9.7. Reactants: **77** (40 mg), **155** (22 mg), DMAP (45 mg) and DIC (12 µL). The pure product is obtained as a white foam.

prep-HPLC (70 – 100% B w/ TFA, 10 mL/min, 10 min, 254 nm): t_R (**211**) = 7.3 min.

TLC (CH/EE, 5/1 + 1% MeOH): R_f (**211**) = 0.22.

Yield 4 mg (6%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.29 (dd, J = 0.8, 1.9 Hz, 1H), 6.79 – 6.74 (m, 1H), 6.74 – 6.67 (m, 1H), 6.62 (s, 1H), 6.49 (s, 1H), 6.42 (s, 1H), 6.25 (dd, J = 1.8, 3.3 Hz, 1H), 6.10 – 6.07 (m, 1H), 5.69 (t, J = 7.1 Hz, 1H), 5.42 (d, J = 5.6 Hz, 1H), 3.97 – 3.91 (m, 1H), 3.86 – 3.85 (m, 2H), 3.85 – 3.84 (m, 2H), 3.83 (s, 6H), 3.78 (s, 5H), 3.37 (d, J = 9.9 Hz, 1H), 2.80 (td, J = 2.9, 13.3 Hz, 1H), 2.65 – 2.52 (m, 1H), 2.48 – 2.39 (m, 1H), 2.39 – 2.33 (m, 1H), 2.33 – 2.24 (m, 1H), 2.15 – 2.06 (m, 2H), 2.02 – 1.94 (m, 2H), 1.92 – 1.82 (m, 2H), 1.72 – 1.61 (m, 4H), 1.45 – 1.40 (m, 1H), 1.36 – 1.29 (m, 2H), 1.22 – 1.07 (m, 2H), 0.96 – 0.83 (m, 1H), 0.81 – 0.69 (m, 1H).

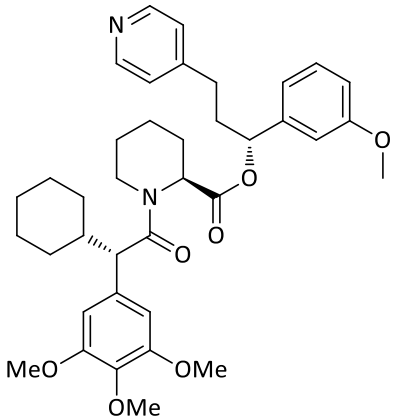
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.62, 170.61, 153.13, 142.41, 133.72, 133.41, 120.47, 120.34, 112.01, 111.90, 111.58, 111.48, 110.57, 110.31, 109.43, 108.43, 105.99, 105.46, 68.55, 60.93, 56.47, 56.26, 56.26, 56.08, 55.99, 55.06, 52.25, 43.72, 41.42, 34.23, 32.84, 31.47, 30.88, 30.86, 30.77, 27.03, 26.74, 26.36, 26.32, 25.74, 21.19.

LC-MS (70-100% B, 19 min): t_R (**211**) = 6.06 min, m/z: calculated = 664.34 $[M+H]^+$, found = 664.65 $[M+H]^+$.

HRMS (ESI): calculated = 664.34801 $[M+H]^+$, found = 664.34803 $[M+H]^+$, err [ppm] = 0.04.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**211**) = 11.29 min (96% Purity).

(S)-(R)-1-(3-methoxyphenyl)-3-(pyridin-4-yl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV451)



Chemical Formula: $C_{38}H_{48}N_2O_7$
Exact Mass: 644.35
Molecular Weight: 644.80

212

212 is synthesized according to general procedure 5.9.7. Reactants: **77** (86 mg), **106** (50 mg), DMAP (100 mg) and DIC (35 µL). The pure product is obtained as a white foam.

Silica column chromatography: DCM/Ac, 10/1 + 1% TEA, v/v.

TLC (DCM/Ac, 10/1 + 1% TEA): R_f (**212**) = 0.25.

Yield 50 mg (38%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.52 – 8.39 (m, 2H), 7.16 – 7.11 (m, 2H), 6.84 – 6.78 (m, 1H), 6.71 – 6.60 (m, 3H), 6.43 – 6.38 (m, 1H), 5.49 (dd, J = 5.0, 7.3 Hz, 3H), 4.22 (d, J = 13.6 Hz, 1H), 3.83 – 3.46 (m, 10H), 2.65 (ddd, J = 2.9, 10.4, 15.2 Hz, 1H), 2.48 – 2.31 (m, 1H), 2.23 – 1.92 (m, 2H), 1.88 – 1.81 (m, 1H), 1.75 (d, J = 12.5 Hz, 1H), 1.70 – 1.40 (m, 5H), 1.37 – 1.05 (m, 6H), 1.04 – 0.97 (m, 15H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 171.91, 170.13, 159.07, 156.76, 152.70, 152.51, 149.55, 149.51, 149.47, 141.49, 136.12, 133.80, 129.60, 129.40, 123.75, 123.66, 118.35, 117.82, 113.55, 113.10, 111.80,

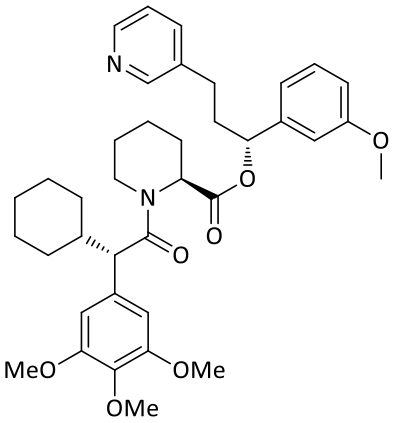
111.54, 105.81, 105.36, 75.69, 74.69, 59.96, 59.74, 55.93, 55.60, 55.32, 54.98, 54.93, 52.75, 51.47, 43.01, 36.00, 31.74, 30.00, 29.77, 26.25, 26.12, 25.57, 25.12, 23.26, 20.55.

LC-MS (50-100% B, 19 min): t_R (**212**) = 2.43 min, m/z: calculated = 645.35 $[M+H]^+$, found = 645.70 $[M+H]^+$.

HRMS (ESI): calculated = 654.35343 $[M+H]^+$, found = 654.35392 $[M+H]^+$, err [ppm] = 0.77

RP-HPLC (30 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**212**) = 10.89 min (95% Purity).

(S)-(R)-1-(3-methoxyphenyl)-3-(pyridin-3-yl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV547)



Chemical Formula: $C_{38}H_{48}N_2O_7$
Exact Mass: 644,35
Molecular Weight: 644,80

213

213 is synthesized according to general procedure 5.9.7. Reactants: **77** (52 mg), **114** (30 mg), DMAP (60 mg) and DIC (21 µL). The pure product is obtained as a white foam.

prep-HPLC (30 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**213**) = 6.68 min.

Yield 31 mg (39%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.70 (d, J = 5.7 Hz, 1H), 8.58 (s, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.79 (dd, J = 5.5, 8.0 Hz, 1H), 7.12 (t, J = 7.9 Hz, 1H), 6.79 – 6.73 (m, 1H), 6.60 – 6.52 (m, 3H), 6.42 – 6.36 (m, 1H), 5.57 (t, J = 6.8 Hz, 1H), 5.44 (d, J = 5.7 Hz, 1H), 4.07 (d, J = 13.6 Hz, 1H), 3.83 (d, J = 10.8 Hz, 2H), 3.76 (d, J = 0.8 Hz, 3H), 3.75 (d, J = 2.3 Hz, 8H), 3.47 (d, J = 10.2 Hz, 1H), 2.83 (td, J = 2.9, 13.3 Hz, 1H), 2.64 (ddd, J = 5.5, 9.4, 14.9 Hz, 1H), 2.51 (ddd, J = 6.9, 9.3, 15.2 Hz, 1H), 2.27 (d, J = 13.9 Hz, 1H), 2.11 (p, J = 9.2, 10.0 Hz, 1H), 1.98 – 1.88 (m, 1H), 1.88 – 1.76 (m, 2H), 1.74 – 1.53 (m, 4H), 1.50 – 1.38 (m, 1H), 1.34 (dd, J = 3.2, 13.1 Hz, 2H), 1.17 (dq, J = 12.2, 12.8, 19.9 Hz, 3H), 0.91 (qd, J = 3.3, 12.4 Hz, 1H), 0.82 – 0.66 (m, 1H).

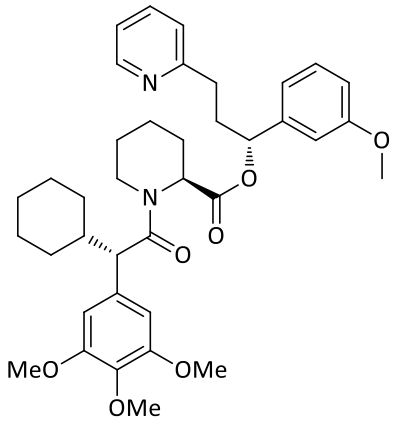
^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.38, 170.35, 161.20, 159.85, 153.26, 145.40, 141.68, 141.43, 140.27, 139.64, 137.21, 133.83, 130.02, 126.59, 118.43, 113.47, 112.91, 106.24, 105.36, 75.18, 60.93, 56.45, 56.33, 55.31, 54.83, 52.54, 44.29, 41.46, 36.01, 32.64, 30.80, 28.31, 26.62, 26.22, 26.12, 25.56, 20.91.

LC-MS (50-100% B, 19 min): t_R (**213**) = 8.13 min, m/z: calculated = 645.35 $[M+H]^+$, found = 645.68 $[M+H]^+$.

HRMS (ESI): calculated = 645.35343 $[M+H]^+$, found = 645.35379 $[M+H]^+$, err [ppm] = 0.57.

RP-HPLC (30 – 100% B, 1.5 mL/min, 15 min, 254 nm): t_R (**213**) = 9.45 min (95% Purity).

(S)-(R)-1-(3-methoxyphenyl)-3-(pyridin-2-yl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV546)



Chemical Formula: $C_{38}H_{48}N_2O_7$
Exact Mass: 644,35
Molecular Weight: 644,80

214

214 is synthesized according to general procedure 5.9.7. Reactants: **77** (52 mg), **110** (30 mg), DMAP (60 mg) and DIC (21 µL). The pure product is obtained as a white foam.

prep-HPLC (40 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**214**) = 6.71 min.

Yield 35 mg (44%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.76 (s, 1H), 8.22 (t, J = 7.8 Hz, 1H), 7.64 (t, J = 6.3 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.09 (t, J = 7.9 Hz, 1H), 6.73 (ddd, J = 0.8, 2.6, 8.2 Hz, 1H), 6.64 – 6.61 (m, 1H), 6.54 (s, 2H), 6.49 – 6.44 (m, 1H), 5.59 (dd, J = 5.8, 7.6 Hz, 1H), 5.41 (d, J = 5.5 Hz, 1H), 4.04 (d, J = 13.8 Hz, 1H), 3.85 – 3.81 (m, 3H), 3.74 (s, 9H), 3.46 (d, J = 10.0 Hz, 1H), 2.97 – 2.79 (m, 3H), 2.59 – 2.51 (m, 0H), 2.51 – 2.31 (m, 0H), 2.25 (d, J = 13.7 Hz, 1H), 2.18 – 1.94 (m, 3H), 1.89 – 1.78 (m, 1H), 1.76 – 1.58 (m, 6H), 1.58 – 1.50 (m, 1H), 1.50 – 1.37 (m, 1H), 1.38 – 1.27 (m, 2H), 1.27 – 1.03 (m, 2H), 0.98 – 0.83 (m, 1H), 0.82 – 0.71 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.29, 173.15, 170.36, 161.35, 161.04, 160.15, 159.81, 157.10, 156.91, 153.44, 153.15, 144.94, 144.68, 142.78, 142.28, 140.36, 137.08, 134.11, 133.81, 130.22, 129.90,

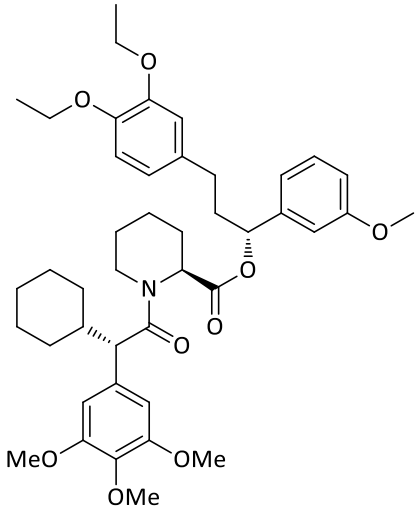
126.82, 126.23, 124.44, 124.20, 118.82, 118.25, 117.07, 114.76, 114.23, 113.87, 112.34, 112.21, 106.20, 105.31, 75.85, 75.10, 61.00, 60.89, 56.35, 56.29, 56.21, 55.54, 55.38, 55.27, 54.84, 52.55, 44.19, 41.57, 41.16, 40.02, 35.28, 35.05, 33.02, 32.68, 30.81, 30.41, 30.03, 29.44, 26.67, 26.61, 26.46, 26.26, 26.18, 25.54, 24.42, 20.89, 20.70.

LC-MS (30-100% B, 19 min): t_R (**214**) = 8.29 min, m/z: calculated = 645.35 $[M+H]^+$, found = 645.59 $[M+H]^+$.

HRMS (ESI): calculated = 645.35343 $[M+H]^+$, found = 645.35416 $[M+H]^+$, err [ppm] = 1.13.

RP-HPLC (30 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**214**) = 9.61 min (95% Purity).

(S)-(R)-3-(3,4-diethoxyphenyl)-1-(3-methoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV462)



Chemical Formula: $C_{43}H_{57}NO_9$
Exact Mass: 731,40
Molecular Weight: 731,91

215

215 is synthesized according to general procedure 5.9.7. Reactants: **77** (50 mg), **86** (40 mg), DMAP (50 mg) and DIC (30 µL). The pure product is obtained as a white foam.

Silica column chromatography: CH/EE, 3/1, v/v.

TLC (CH/EE,3/1): R_f (**215**) = 0.29.

Yield 47 mg (52%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.13 – 7.08 (m, 1H), 6.96 – 6.88 (m, 1H), 6.81 – 6.71 (m, 2H), 6.68 – 6.58 (m, 3H), 6.49 (s, 1H), 6.42 (s, 1H), 5.59 – 5.54 (m, 1H), 5.48 (d, J = 5.5 Hz, 1H), 4.10 – 4.01 (m, 5H), 3.94 (d, J = 14.0 Hz, 1H), 3.86 – 3.82 (m, 3H), 3.82 – 3.79 (m, 1H), 3.76 (s, 2H), 3.75 (s, 2H), 3.71 (s, 4H), 3.37 (d, J = 9.9 Hz, 1H), 2.78 (td, J = 2.9, 13.4 Hz, 1H), 2.71 – 2.49 (m, 1H), 2.49 – 2.32 (m, 1H), 2.32 – 2.22 (m, 1H), 2.16 – 2.01 (m, 1H), 2.01 – 1.78 (m, 2H), 1.76 – 1.50 (m, 5H), 1.46 – 1.37 (m, 8H), 1.37 – 1.06 (m, 5H), 0.96 – 0.66 (m, 2H).

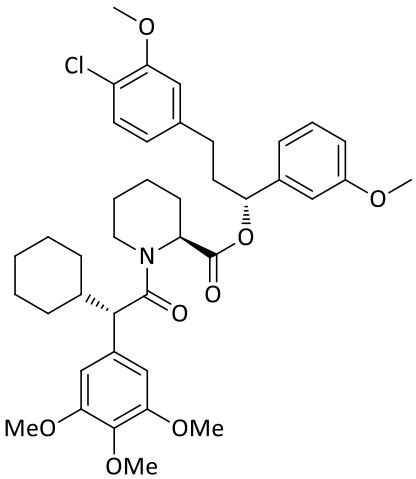
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.35, 170.73, 170.63, 159.93, 159.56, 153.39, 153.17, 148.94, 148.84, 147.39, 147.14, 141.94, 141.72, 136.98, 134.41, 133.80, 133.73, 133.59, 129.83, 129.60, 120.64, 120.60, 120.54, 119.09, 118.52, 118.35, 114.31, 114.27, 114.05, 114.01, 113.58, 113.18, 113.13, 112.54, 112.43, 111.54, 105.88, 105.63, 105.42, 75.84, 73.92, 64.85, 64.82, 64.66, 61.00, 60.86, 56.44, 56.37, 56.15, 55.94, 55.86, 55.35, 55.26, 55.15, 52.11, 43.75, 41.52, 41.28, 40.69, 39.58, 38.13, 37.98, 33.10, 32.94, 31.73, 31.58, 31.14, 30.79, 30.59, 26.87, 26.72, 26.55, 26.35, 26.30, 26.22, 25.71, 24.48, 21.10, 20.80, 15.05.

LC-MS (50-100% B, 19 min): t_R (**215**) = 11.96 min, m/z: calculated = 732.40 $[M+H]^+$, found = 732.04 $[M+H]^+$.

HRMS (ESI): calculated = 732.41061 $[M+H]^+$, found = 732.41037 $[M+H]^+$, err [ppm] = 0.33.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 254 nm): t_R (**215**) = 14.12 min (92% Purity).

(S)-(R)-3-(4-chloro-3-methoxyphenyl)-1-(3-methoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV461)



Chemical Formula: $C_{40}H_{50}ClNO_8$
Exact Mass: 707,32
Molecular Weight: 708,28

216

216 is synthesized according to general procedure 5.9.7. Reactants: **77** (100 mg), **90** (72 mg), DMAP (100 mg) and DIC (80 µL). The pure product is obtained as a white foam.

Silica column chromatography: CH/EE, 3/1, v/v.

TLC (CH/EE, 3/1): R_f (**216**) = 0.31.

Yield 49 mg (29%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.21 (d, J = 8.0 Hz, 1H), 7.10 (t, J = 7.9 Hz, 1H), 6.95 – 6.85 (m, 1H), 6.74 (ddd, J = 0.9, 2.6, 8.3 Hz, 1H), 6.70 – 6.65 (m, 1H), 6.64 – 6.58 (m, 2H), 6.51 (s, 1H), 6.39 (d, J = 1.1, 7.7 Hz, 1H), 5.58 – 5.51 (m, 1H), 5.49 – 5.45 (m, 1H), 3.97 (d, J = 13.8 Hz, 1H), 3.87 (s, 3H), 3.84 – 3.82 (m,

2H), 3.76 (s, 2H), 3.74 (s, 2H), 3.71 (s, 5H), 3.39 (d, J = 9.9 Hz, 1H), 2.78 (td, J = 2.9, 13.3 Hz, 1H), 2.67 – 2.52 (m, 1H), 2.51 – 2.33 (m, 2H), 2.32 – 2.23 (m, 1H), 2.16 – 2.01 (m, 2H), 1.97 – 1.75 (m, 3H), 1.75 – 1.49 (m, 6H), 1.46 – 1.05 (m, 5H), 0.95 – 0.70 (m, 2H).

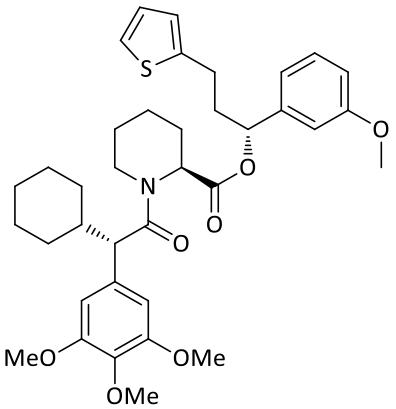
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.43, 172.36, 170.73, 170.64, 159.96, 159.57, 155.03, 154.91, 153.38, 153.18, 141.61, 141.37, 141.13, 140.93, 137.02, 134.33, 133.77, 130.20, 130.07, 129.90, 129.65, 121.31, 121.14, 120.33, 120.01, 119.06, 118.47, 113.60, 113.19, 112.63, 112.53, 112.42, 105.89, 105.40, 76.75, 75.55, 60.98, 60.83, 56.42, 56.18, 56.15, 55.93, 55.84, 55.34, 55.25, 55.04, 52.12, 43.79, 41.54, 41.24, 39.56, 37.72, 37.59, 33.11, 32.84, 31.87, 31.34, 30.75, 30.56, 26.89, 26.80, 26.68, 26.53, 26.31, 26.26, 26.19, 25.66, 24.43, 21.06, 20.80.

LC-MS (50-100% B, 19 min): t_R (**216**) = 12.07 min, m/z: calculated = 708.32 $[M+H]^+$, found = 708.07 $[M+H]^+$.

HRMS (ESI): calculated = 708.32977 $[M+H]^+$, found = 708.32966 $[M+H]^+$, err [ppm] = 0.16.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 254 nm): t_R (**216**) = 14.28 min (99% Purity).

(S)-(R)-1-(3-methoxyphenyl)-3-(thiophen-2-yl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV465)



Chemical Formula: $C_{37}H_{47}NO_7S$
Exact Mass: 649,31
Molecular Weight: 649,84

217

217 is synthesized according to general procedure 5.9.7. Reactants: **77** (93 mg), **167** (50 mg), DMAP (100 mg) and DIC (34 µL). The pure product is obtained as a white foam.

prep-HPLC (70 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**217**) = 6.5 min.

TLC (CH/EE, 3/1 + 1% HCOOH): R_f (**217**) = 0.15.

Yield 47 mg (33%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.13 – 7.08 (m, 1H), 6.96 – 6.92 (m, 1H), 6.92 – 6.86 (m, 2H), 6.80 – 6.75 (m, 1H), 6.74 – 6.71 (m, 1H), 6.64 – 6.60 (m, 1H), 6.49 (s, 1H), 6.44 – 6.41 (m, 1H), 5.61 (dd, J = 5.8,

8.1 Hz, 1H), 5.49 (d, J = 5.5 Hz, 1H), 4.03 – 3.97 (m, 1H), 3.85 (s, 3H), 3.82 (s, 1H), 3.78 (s, 2H), 3.76 (s, 2H), 3.74 (s, 4H), 3.42 (d, J = 10.0 Hz, 1H), 2.93 – 2.77 (m, 2H), 2.75 – 2.59 (m, 2H), 2.42 – 2.28 (m, 1H), 2.27 – 2.18 (m, 0H), 2.16 – 1.95 (m, 2H), 1.95 – 1.80 (m, 2H), 1.76 – 1.52 (m, 5H), 1.50 – 1.39 (m, 1H), 1.37 – 1.22 (m, 3H), 1.05 – 0.70 (m, 2H), 0.70 – 0.48 (m, 1H).

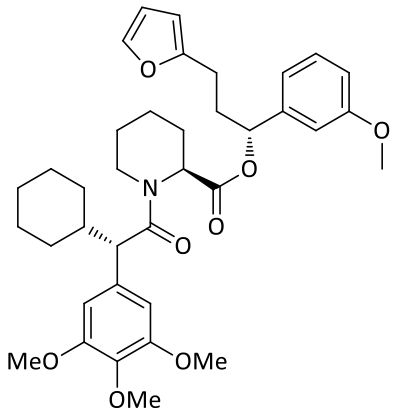
^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.96, 173.74, 170.06, 170.00, 160.00, 159.62, 158.56, 158.23, 153.51, 153.26, 143.36, 143.28, 141.40, 141.16, 137.06, 136.95, 133.64, 133.04, 130.04, 129.74, 127.07, 126.97, 124.75, 124.66, 123.58, 123.44, 119.05, 118.41, 116.13, 113.78, 113.32, 112.61, 112.56, 105.79, 105.53, 105.29, 75.90, 61.07, 60.96, 56.42, 56.35, 56.17, 56.04, 55.38, 55.29, 52.75, 44.28, 41.12, 40.51, 38.05, 37.94, 33.01, 32.85, 30.76, 30.53, 26.78, 26.59, 26.41, 26.20, 26.03, 25.99, 25.74, 25.56, 24.24, 20.82, 20.50.

LC-MS (50-100% B, 19 min): t_R (**217**) = 8.15 min, m/z: calculated = 650.31 $[M+H]^+$, found = 650.48 $[M+H]^+$.

HRMS (ESI): calculated = 650.31460 $[M+H]^+$, found = 650.31482 $[M+H]^+$, err [ppm] = 0.33.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**217**) = 13.40 min (99% Purity).

(S)-(R)-3-(furan-2-yl)-1-(3-methoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV463)



Chemical Formula: $C_{37}H_{47}NO_8$
Exact Mass: 633,33
Molecular Weight: 633,77

218

218 is synthesized according to general procedure 5.9.7. Reactants: **77** (100 mg), **163** (50 mg), DMAP (115 mg) and DIC (36 µL). The pure product is obtained as a white foam.

Silica column chromatography: CH/EE, 4/1, v/v.

TLC (CH/EE, 4/1): R_f (**218**) = 0.25.

Yield 71 mg (52%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.11 (t, J = 7.9 Hz, 1H), 6.74 (ddd, J = 1.0, 2.6, 8.2 Hz, 1H), 6.66 – 6.61 (m, 1H), 6.49 (s, 1H), 6.47 – 6.41 (m, 1H), 6.27 – 6.22 (m, 1H), 5.97 – 5.92 (m, 1H), 5.59 (dd, J = 5.7, 8.1 Hz, 1H), 5.49 – 5.43 (m, 1H), 3.97 – 3.89 (m, 1H), 3.83 (d, J = 4.2 Hz, 3H), 3.81 (s, 1H), 3.76 (d, J = 1.2 Hz, 4H), 3.74 (s, 4H), 3.37 (d, J = 9.8 Hz, 1H), 2.84 – 2.71 (m, 1H), 2.70 – 2.62 (m, 1H), 2.55 – 2.48 (m, 1H), 2.35 – 2.21 (m, 1H), 2.21 – 2.01 (m, 2H), 2.02 – 1.92 (m, 1H), 1.92 – 1.85 (m, 2H), 1.70 – 1.51 (m, 4H), 1.48 – 1.36 (m, 1H), 1.33 – 1.22 (m, 3H), 1.21 – 1.07 (m, 3H), 0.95 – 0.70 (m, 2H), 0.71 – 0.51 (m, 1H).

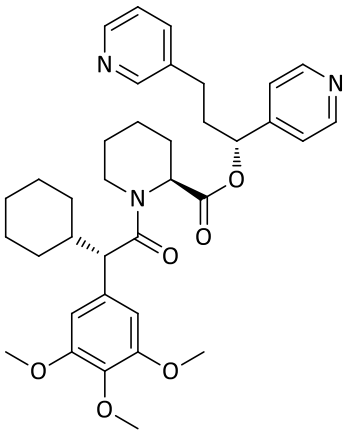
^{13}C-NMR (126 MHz, $CDCl_3$): 13C NMR (126 MHz, CDCl3) δ 172.38, 170.62, 159.96, 159.60, 154.61, 154.48, 153.39, 153.17, 141.71, 141.31, 141.16, 137.06, 136.98, 134.42, 133.72, 129.89, 129.64, 118.99, 118.44, 113.69, 113.28, 112.41, 112.33, 110.35, 110.25, 105.87, 105.63, 105.51, 105.45, 105.39, 76.59, 75.66, 61.00, 60.87, 56.43, 56.37, 56.16, 55.91, 55.87, 55.35, 55.27, 55.14, 52.08, 43.76, 41.49, 41.29, 39.60, 34.76, 34.67, 33.09, 32.94, 30.88, 30.80, 30.60, 26.85, 26.72, 26.54, 26.38, 26.35, 26.30, 26.21, 25.70, 24.48, 24.43, 24.04, 21.05, 20.75.

LC-MS (50-100% B, 19 min): t_R (**218**) = 12.17 min, m/z: calculated = 634.33 $[M+H]^+$, found = 634.49 $[M+H]^+$.

HRMS (ESI): calculated = 634.33744 $[M+H]^+$, found = 634.33777$[M+H]^+$, err [ppm] = 0.52.

RP-HPLC (60 – 80% B, 1.5 mL/min, 15 min, 220 nm): t_R (**218**) = 14.48 min (97% Purity).

(S)-(R)-3-(pyridin-3-yl)-1-(pyridin-4-yl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV773)



Chemical Formula: $C_{36}H_{45}N_3O_6$
Exact Mass: 615,33
Molecular Weight: 615,76

219

219 is synthesized according to general procedure 5.9.7. Reactants: **77** (14 mg), **131** (7 mg), DMAP (16 mg) and DIC (5 µL). The pure product is obtained as a white foam.

prep-HPLC (0 – 70% B, 10 mL/min, 10 min, 254 nm): t_R (**219**).

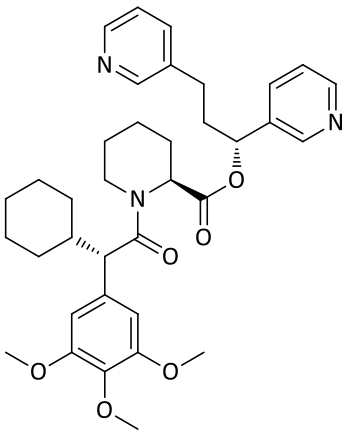
Yield 2 mg (10%).

LC-MS (0-100% B, 19 min): t_R (**219**) = 8.90 min, m/z: calculated = 616.34 $[M+H]^+$,

found = 616.33 $[M+H]^+$ (99% Purity, 93/7 dr).

HRMS (ESI): calculated = 618.33811 $[M+H]^+$, found = 618.33797 $[M+H]^+$, err [ppm] = 0.22.

(S)-(R)-1,3-di(pyridin-3-yl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV769)



Chemical Formula: $C_{36}H_{45}N_3O_6$
Exact Mass: 615,33
Molecular Weight: 615,76

220

220 is synthesized according to general procedure 5.9.7. Reactants: **77** (14 mg), **125** (7 mg), DMAP (16 mg) and DIC (5 µL). The pure product is obtained as a white foam.

prep-HPLC (0 – 70% B, 10 mL/min, 10 min, 254 nm): t_R (**220**).

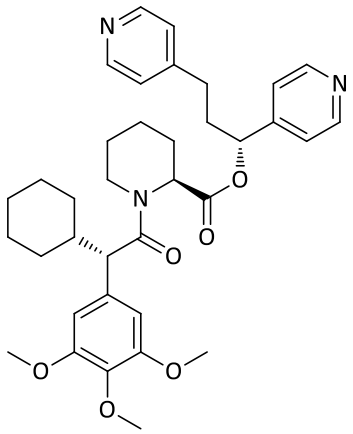
Yield 4 mg (20%).

LC-MS (0-100% B, 19 min): t_R (**220**) = 9.28 min, m/z: calculated = 616.34 $[M+H]^+$,

found = 616.47 $[M+H]^+$ (99% Purity, 96/4 dr).

HRMS (ESI): calculated = 618.33811 $[M+H]^+$, found = 618.33819 $[M+H]^+$, err [ppm] = 0.12.

(S)-(R)-1,3-di(pyridin-4-yl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV774)



Chemical Formula: $C_{36}H_{45}N_3O_6$
Exact Mass: 615,33
Molecular Weight: 615,76

221

221 is synthesized according to general procedure 5.9.7. Reactants: **77** (27 mg), **134** (14 mg), DMAP (32 mg) and DIC (9 µL). The pure product is obtained as a white foam.

prep-HPLC (0 – 70% B, 10 mL/min, 10 min, 254 nm): t_R (**221**).

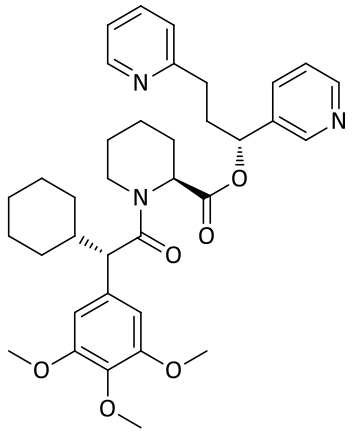
Yield 9 mg (23%).

LC-MS (0-100% B, 19 min): t_R (**221**) = 8.67 min, m/z: calculated = 616.34 $[M+H]^+$,

found = 616.35 $[M+H]^+$ (99% Purity, 95/5 dr).

HRMS (ESI): calculated = 618.33811 $[M+H]^+$, found = 618.33822 $[M+H]^+$, err [ppm] = 0.17.

(S)-(R)-3-(pyridin-2-yl)-1-(pyridin-3-yl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV770)



Chemical Formula: $C_{36}H_{45}N_3O_6$
Exact Mass: 615,33
Molecular Weight: 615,76

222

222 is synthesized according to general procedure 5.9.7. Reactants: **77** (16 mg), **128** (8 mg), DMAP (18 mg) and DIC (5 µL). The pure product is obtained as white foam.

prep-HPLC (0 – 70% B, 10 mL/min, 10 min, 254 nm): t_R (**222**).

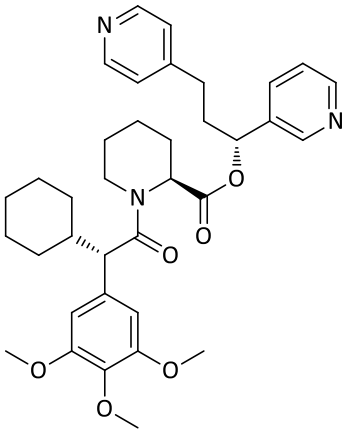
Yield 6 mg (26%).

LC-MS (0-100% B, 19 min): t_R (**222**) = 9.55 min, m/z: calculated = 616.34 $[M+H]^+$,

found = 616.42 $[M+H]^+$ (99% Purity, 89/11 dr).

HRMS (ESI): calculated = 618.33811 $[M+H]^+$, found = 618.33810 $[M+H]^+$, err [ppm] = 0.02.

((S)-(R)-1-(pyridin-3-yl)-3-(pyridin-4-yl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV772)



Chemical Formula: $C_{36}H_{45}N_3O_6$
Exact Mass: 615,33
Molecular Weight: 615,76

223

223 is synthesized according to general procedure 5.9.7. Reactants: **77** (20 mg), **137** (10 mg), DMAP (23 mg) and DIC (7 µL). The pure product is obtained as a white foam.

prep-HPLC (0 – 70% B, 10 mL/min, 10 min, 254 nm): t_R (**223**.

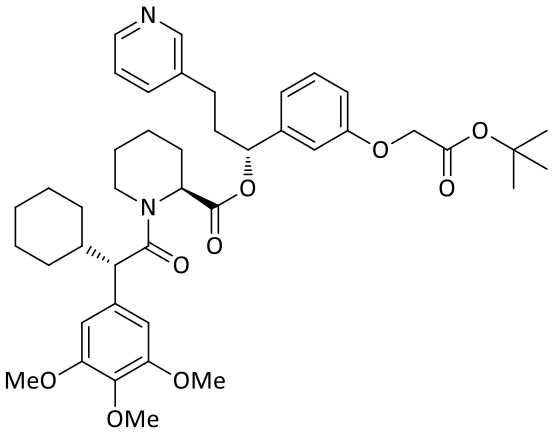
Yield 7 mg (25%).

LC-MS (0-100% B, 19 min): t_R (**223**) = 9.01 min, m/z: calculated = 616.34 $[M+H]^+$,

found = 616.44 $[M+H]^+$ (99% Purity, 92/8 dr).

HRMS (ESI): calculated = 618.33811 $[M+H]^+$, found = 618.33853 $[M+H]^+$, err [ppm] = 0.68.

(S)-(R)-1-(3-(2-(tert-butoxy)-2-oxoethoxy)phenyl)-3-(pyridin-3-yl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV737)



Chemical Formula: $C_{43}H_{56}N_2O_9$
Exact Mass: 744,40
Molecular Weight: 744,91

224

224 is synthesized according to general procedure 5.9.7. Reactants: **77** (61 mg), **119** (50 mg), DMAP (71 mg) and DIC (25 µL). The pure product is obtained as a white foam.

Silica column chromatography: CH/EE, 1/1, + 1% MeOH, v/v.

TLC (CH/EE, 1/1, + 1% MeOH, v/v): R_f (**224**) = 0.25.

Yield 73 mg (68%).

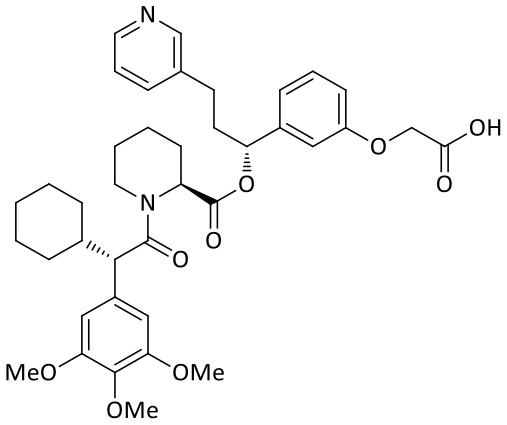
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.46 – 8.39 (m, 1H), 8.37 – 8.31 (m, 1H), 7.48 – 7.36 (m, 1H), 7.21 – 7.14 (m, 1H), 7.09 (t, J = 7.9 Hz, 1H), 6.75 – 6.70 (m, 1H), 6.68 – 6.64 (m, 1H), 6.49 (s, 2H), 6.43 – 6.35 (m, 1H), 5.56 (dd, J = 5.8, 7.8 Hz, 1H), 5.44 (d, J = 5.1 Hz, 1H), 4.55 (d, J = 14.2 Hz, 0H), 4.52 – 4.46 (m, 2H), 4.34 – 4.25 (m, 2H), 3.95 (d, J = 14.1 Hz, 1H), 3.84 – 3.78 (m, 3H), 3.75 (s, 2H), 3.70 (s, 4H), 3.37 (d, J = 9.9 Hz, 1H), 2.80 – 2.72 (m, 1H), 2.66 – 2.36 (m, 2H), 2.34 – 2.22 (m, 1H), 2.17 – 2.03 (m, 1H), 1.98 – 1.77 (m, 2H), 1.73 – 1.52 (m, 4H), 1.45 (s, 6H), 1.36 – 1.27 (m, 1H), 1.10 (d, J = 6.5 Hz, 9H), 0.94 – 0.69 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.49, 172.31, 170.54, 167.97, 167.77, 158.32, 157.99, 157.16, 153.38, 153.15, 149.94, 149.83, 147.90, 147.69, 141.42, 141.16, 137.01, 136.26, 135.96, 135.74, 134.32, 133.75, 130.04, 129.79, 123.54, 123.46, 119.88, 119.24, 114.12, 113.93, 113.75, 113.43, 105.95, 105.59, 105.36, 82.60, 82.42, 76.55, 75.34, 65.81, 65.75, 60.96, 60.85, 60.47, 56.42, 56.34, 56.18, 55.97, 55.80, 55.03, 52.14, 43.80, 42.12, 41.50, 41.26, 39.57, 37.46, 37.29, 33.12, 32.84, 30.75, 30.59, 29.09, 28.59, 28.13, 26.96, 26.80, 26.67, 26.54, 26.29, 26.25, 26.18, 25.62, 24.43, 23.60, 21.06, 20.86, 14.29.

LC-MS (50-100% B, 19 min): t_R (**224**) = 5.88 min, m/z: calculated = 745.41 $[M+H]^+$, found = 745.52 $[M+H]^+$.

HRMS (ESI): calculated = 745.40586 $[M+H]^+$, found = 745.40617 $[M+H]^+$, err [ppm] = 0.42.

2-(3-((R)-1-(((S)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(pyridin-3-yl)propyl)phenoxy)acetic acid (AV739)



Chemical Formula: $C_{39}H_{48}N_2O_9$
Exact Mass: 688,34
Molecular Weight: 688,81

225

225 (22 mg, 0.03 mmol, 1.0 eq) is dissolved in 1 mL dry THF. Then $Pd(OAc)_2$ (0.2 mg, 0.1 eq), PPh_3 (2 mg, 0.01 mmol, 1.0 eq) and morpholine (1 µL, 1.0 eq) are added. After 30 min the solvent is removed under airstream and the crude product purified by column chromatography (DCM + 5% MeOH).

TLC (DCM + 6% MeOH): R_f (**225**) = 0.26.

Yield 19 mg (95%).

^{1}H-NMR (500 MHz, DMSO-d_6): δ 8.63 – 8.41 (m, 2H), 7.88 – 7.78 (m, 1H), 7.58 – 7.45 (m, 1H), 7.11 (t, J = 7.9 Hz, 1H), 6.81 – 6.76 (m, 1H), 6.76 – 6.73 (m, 1H), 6.66 – 6.60 (m, 2H), 6.44 – 6.35 (m, 1H), 5.51 (t, J = 6.8 Hz, 1H), 5.30 – 5.25 (m, 1H), 4.71 – 4.62 (m, 2H), 4.21 (d, J = 13.5 Hz, 1H), 3.76 – 3.72 (m, 2H), 3.60 (s, 5H), 3.53 (s, 2H), 2.72 – 2.63 (m, 1H), 2.57 – 2.52 (m, 1H), 2.45 – 2.37 (m, 1H), 2.23 – 2.06 (m, 1H), 2.07 – 1.90 (m, 1H), 1.90 – 1.77 (m, 2H), 1.78 – 1.71 (m, 1H), 1.71 – 1.41 (m, 5H), 1.41 – 1.29 (m, 1H), 1.29 – 1.03 (m, 5H), 1.03 – 0.72 (m, 2H).

^{13}C-NMR (126 MHz, DMSO-d_6): δ 172.04, 171.73, 170.18, 170.10, 170.03, 169.96, 158.02, 157.85, 157.58, 152.69, 152.50, 146.79, 144.80, 141.51, 141.46, 139.01, 136.17, 136.10, 134.63, 133.80, 129.62, 129.41, 118.89, 118.24, 113.93, 113.56, 112.65, 112.57, 105.85, 105.41, 75.67, 74.56, 64.45, 59.99, 59.78, 55.96, 55.64, 52.74, 51.57, 43.04, 40.80, 40.57, 36.67, 36.55, 32.02, 31.73, 29.77, 28.95, 28.25, 27.74, 26.24, 26.11, 25.90, 25.56, 25.06, 20.53.

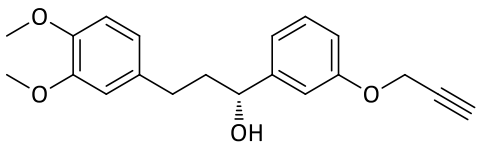
LC-MS (0-100% B, 19 min): t_R (**225**) = 10.36 min, m/z: calculated = 689.34 $[M+H]^+$, found = 689.47 $[M+H]^+$.

HRMS (ESI): calculated = 689.34326 $[M+H]^+$, found = 689.34358 $[M+H]^+$, err [ppm] = 0.47.

6.5. A/B ring derivatization through Click reaction

6.5.1. Building blocks

(R)-3-(3,4-dimethoxyphenyl)-1-(3-(prop-2-yn-1-yloxy)phenyl)propan-1-ol (AV563/AV648)



Chemical Formula: $C_{20}H_{22}O_4$
Exact Mass: 326,15
Molecular Weight: 326,39

226

7 (200 mg, 0.70 mmol, 1.0 eq) is dissolved in 20 mL dry MeCN. K_2CO_3 (550 g, 2.80 mmol, 4.0 eq) and propargyl bromide (80 wt% in toluene, 120 µL, 0.76 mmol, 1.1 eq) is added. The reaction is stirred at room temperature overnight. After complete conversion, the suspension is filtered, washed with MeCN and the solvent removed under reduced pressure. The crude product **226** is obtained as a colorless oil and used without further purification.

Yield 225 mg (quant.).

TLC (CH/EE, 3/1): R_f (**226**) = 0.20.

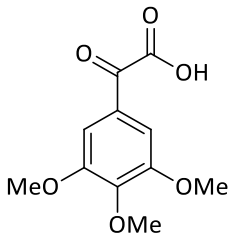
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.30 – 7.26 (m, 1H), 6.99 – 6.95 (m, 2H), 6.89 (dt, *J* = 1.7, 8.2 Hz, 1H), 6.81 – 6.69 (m, 3H), 4.71 – 4.64 (m, 3H), 3.85 (s, 3H), 3.85 (s, 3H), 2.65 (dddd, *J* = 6.1, 9.5, 14.0, 30.0 Hz, 2H), 2.51 (td, *J* = 0.7, 2.4 Hz, 1H), 2.18 – 1.93 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 157.86, 148.98, 147.33, 146.57, 134.46, 129.65, 120.31, 119.25, 113.98, 112.69, 111.93, 111.44, 78.67, 75.66, 73.79, 56.05, 55.94, 55.91, 40.67, 31.70.

LC-MS (50-100% B, 19 min): t_R (**226**) = 4.42 min, m/z: calculated = 344.18 $[M+NH_4]^+$, found = 344.17 $[M+NH_4]^+$.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 254 nm): t_R (**226**) = 4.08 min (98% Purity).

2-oxo-2-(3,4,5-trimethoxyphenyl)acetic acid (AV657/AV659)



Chemical Formula: $C_{11}H_{12}O_6$
Exact Mass: 240,06
Molecular Weight: 240,21

227

3, 4, 5-Trimethoxyacetophenone (2.93 g, 14 mmol, 1.0 eq) is dissolved in 30 mL dry pyridine. SeO_2 (2.32 g, 21 mmol, 1.5 eq) is added and the mixture heated to reflux overnight. The slurry is filtered over celite and washed with toluene. The solvent is removed under reduced pressure and co-evaporated with toluene (1x). The yellow solid is purified by silica column chromatography (EE + 1% acetic acid). Product **227** is obtained as a slight pink pyridine salt (~ 50% determined by NMR) and used as such in further reactions.

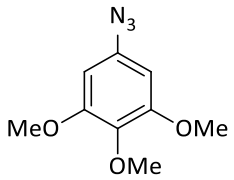
Yield 3.6 g (54%)

TLC (EE + 1% acetic acid, v/v): R_f(**227**) = 0.18

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 14.03 (s, 1H), 8.93 (dt, J = 1.6, 5.1 Hz, 1H), 8.28 – 8.20 (m, 0H), 7.85 – 7.74 (m, 1H), 7.41 (s, 2H), 3.92 (s, 3H), 3.88 (s, 6H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ = δ 188.40, 167.52, 153.20, 142.98, 127.92, 107.85, 61.09, 56.43.

5-azido-1,2,3-trimethoxybenzene (AV663)



Chemical Formula: $C_9H_{11}N_3O_3$
Exact Mass: 209,08
Molecular Weight: 209,20

228

3, 4, 5-trimethoxyaniline (100 mg, 0.55 mmol, 1.0 eq) is added into a flask and made into a slurry with 2 mL 50% HCl. The slurry is cooled to 0°C for 15 min, then a solution of $NaNO_2$ (56 mg, 0.82 mmol, 1.5 eq) in 1 mL H_2O added dropwise. After 30 min stirring to the yellow solution is added NaN_3 (42 mg, 0.66 mmol, 1.2 eq) dissolved in 1 mL H_2O slowly dropwise. After full addition of reactants, the ice bath

is removed and the reaction stirred for 3 h. The mixture is extracted with DCM (3x), the organic phases dried with $MgSO_4$, filtered and the solvent removed. The brown product **228** is used as crude in further reactions.

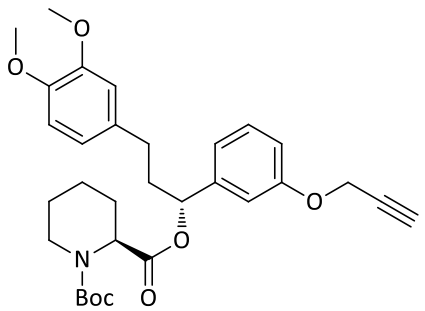
Yield 100 mg (crude)

TLC (CH/EE, 1/1, v/v): R_f (**228**) = 0.82

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 6.40 (s, 2H), 3.78 (s, 6H), 3.62 (s, 3H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ 153.77, 134.98, 134.91, 96.82, 60.14, 56.06.

(S)-1-tert-butyl 2-((R)-3-(3,4-dimethoxyphenyl)-1-(3-(prop-2-yn-1-yloxy)phenyl)propyl) piperidine-1,2-dicarboxylate (AV650)



Chemical Formula: $C_{31}H_{39}NO_7$
Exact Mass: 537,27
Molecular Weight: 537,64

229

226 (570 mg, 2.0 mmol, 1.0 eq) and Boc-*S*-pipecolate (440 mg, 2.2 mmol, 1.1 eq) are dissolved in 15 mL dry DCM and cooled to 0°C for 15 min. DMAP (40 mg, 0.4 mmol, 0.2 eq) is added and stirred until dissolved, then DCC (320 mg, 1.55 mmol, 1.1 eq) is added. The mixture is stirred for 15 min. Finally, the ice bath is removed and the reaction stirred overnight at r.t. The reaction mixture is filtered, washed with DCM and the solvent removed under reduced pressure. The crude product is purified by silica column chromatography (CH/EE, 3/1) and the pure product **229** is obtained as a colorless oil.

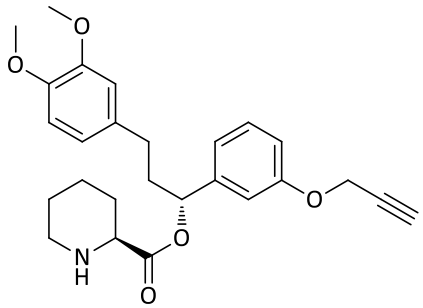
Yield 890 mg (95%).

TLC (CH/EE, 3/1, v/v): R_f (**229**) = 0.35.

LC-MS (50-100% B, 19 min): t_R (**229**) = 10.89 min, m/z: calculated = 560.26 $[M+Na]^+$, found = 560.32 $[M+Na]^+$.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**229**) = 10.76 min (98% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-(prop-2-yn-1-yloxy)phenyl)propyl piperidine-2-carboxylate (AV652)



Chemical Formula: $C_{26}H_{31}NO_5$
Exact Mass: 437,22
Molecular Weight: 437,53

230

229 (0.83 g, 2 mmol, 1.0 eq) is dissolved in 5 mL dry DCM and cooled to 0°C. TFA (600 µL, 8.0 mmol, 5.0 eq) is added and the reaction stirred for 1 h under rising temperature. The solution is quenched with sat. aqueous $NaHCO_3$ solution and extracted with DCM (3x50 mL). The combined organic phases are dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product **230** is used without further purification.

Yield 0.68 g (quant.).

TLC (CH/EE, 3/1, v/v): R_f (**230**) = 0.10.

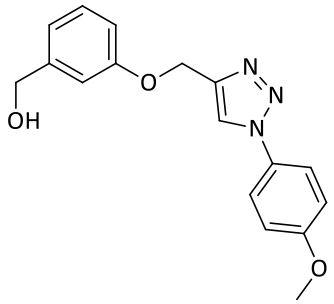
^{1}H-NMR (500 MHz, Chloroform-*d*): δ 7.24 (t, J = 8.0 Hz, 1H), 6.90 – 6.86 (m, 3H), 6.78 – 6.75 (m, 1H), 6.65 – 6.61 (m, 2H), 5.65 (dd, J = 6.0, 7.8 Hz, 1H), 5.28 (s, 1H), 4.67 (d, J = 2.4 Hz, 2H), 3.84 (d, J = 2.3 Hz, 6H), 3.69 (dd, J = 3.4, 11.5 Hz, 1H), 3.23 – 3.18 (m, 1H), 2.70 – 2.61 (m, 1H), 2.61 – 2.44 (m, 3H), 2.28 – 2.14 (m, 2H), 2.12 – 1.99 (m, 1H), 1.96 – 1.84 (m, 1H), 1.83 – 1.62 (m, 2H), 1.60 – 1.42 (m, 1H), 1.16 – 1.06 (m, 1H).

^{13}C-NMR (126 MHz, Chloroform-*d*): δ 168.80, 157.75, 149.04, 147.50, 140.97, 133.33, 129.85, 120.26, 119.55, 114.46, 113.41, 111.70, 111.43, 78.59, 77.61, 75.72, 57.23, 56.02, 55.94, 55.91, 44.01, 37.64, 31.21, 26.46, 22.67, 22.21.

LC-MS (0-100% B, 19 min): t_R (**230**) = 8.50 min, m/z: calculated = 438.22 $[M+H]^+$,
found = 438.26 $[M+H]^+$.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**230**) = 10.04 min (99% Purity).

(3-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)methanol (AV766)



Chemical Formula: $C_{17}H_{17}N_3O_3$
Exact Mass: 311,13
Molecular Weight: 311,34

231

3-Hydroxybenzaldehyde (50 mg, 0.41 mmol, 1.0 eq) is dissolved in 5 mL MeCN. Propargylbromide (80wt% in toluene, 30 µL, 0.49 mmol, 1.2 eq) and K_2CO_3 (68 mg, 0.49 mmol, 1.2 eq) are added and the slurry stirred at r.t. overnight. The mixture is filtered and the solvent removed. The crude is dissolved in 5 mL *t*BuOH and 5 mL H2O, then subsequently p-azido anisole (73 mg, 0.49 mmol, 1.2 eq), $CuSO_4$*5 H_2O (78 mg, 0.49 mmol, 1.2 eq) and sodium L-ascorbate (97 mg, 0.49 mmol, 1.2 eq) are added. The slurry is stirred at r.t. overnight. The mixture is diluted with 20 mL H_2O and extracted with DCM (3x10 mL). The combined organic phases are dried over $MgSO_4$, filtered and the solvent removed. The crude is dissolved in 5 mL THF, then $NaBH_4$ (16 mg, 0.41 mmol, 1.0 eq) is added and the reaction stirred at r.t. overnight. The mixture is diluted with 20 mL H_2O and 10 mL brine and extracted with DCM (3x10 mL). The combined organic phases are dried over $MgSO_4$, filtered and the solvent removed. The product **231** is used as crude in follow up reactions.

Yield 90 mg (71%).

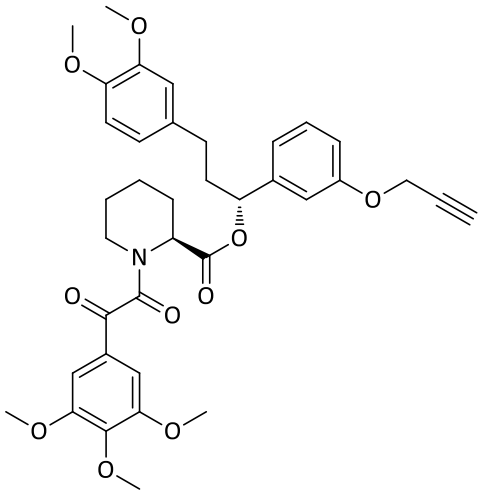
TLC (CH/EE, 1/1, v/v): R_f (**231**) = 0.30.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.65 – 7.58 (m, 2H), 7.29 – 7.22 (m, 1H), 7.05 (t, J = 2.0 Hz, 1H), 7.02 – 6.98 (m, 2H), 6.97 – 6.89 (m, 2H), 6.75 – 6.60 (m, 1H), 5.25 (s, 2H), 4.66 (s, 2H), 3.85 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 160.02, 158.55, 144.79, 143.04, 129.78, 122.34, 121.26, 119.84, 114.90, 114.06, 113.25, 68.06, 65.09, 62.05, 55.74, 25.71.

LC-MS (50-100% B, 19 min): t_R (**231**) = 3.22 min, m/z: calculated = 312.13 $[M+H]^+$, found = 312.37 $[M+H]^+$.

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-(prop-2-yn-1-yloxy)phenyl)propyl 1-(2-oxo-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV661)



Chemical Formula: $C_{37}H_{41}NO_{10}$
Exact Mass: 659,27
Molecular Weight: 659,72

232

227 (70 mg, 1.5 eq), HATU (80 mg, 1.1 eq), HOAt (20 mg, 1.1 eq) and DIPEA are dissolved in 3 ml dry DCM and 3 ml DMF and stirred for 10 min, Then **230** (80 mg, 1.0 eq) is added and the reaction is stirred overnight at r.t. The mixture is diluted with DCM and extracted with brine (3x). The organic phase is dried with MgSO4, filtered and the solvent removed under reduced pressure. The crude product is purified by silica column chromatography (CH/EE, 4/1 + 1% FA). Pure product **232** is obtained as a white solid.

Yield 80 mg (67%).

TLC (CH/EE, 4/1 +1% TEA + 1% FA, v/v): R_f (**232**) = 0.15.

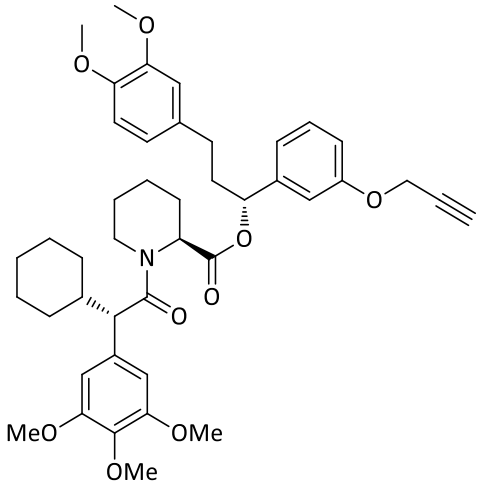
^{1}**H-NMR** (500 MHz, Chloroform-*d*): δ 7.31 – 7.27 (m, 1H), 7.16 – 7.07 (m, 1H), 6.99 – 6.95 (m, 2H), 6.95 – 6.90 (m, 1H), 6.82 – 6.79 (m, 1H), 6.76 – 6.63 (m, 3H), 5.75 (dd, J = 5.6, 8.0 Hz, 1H), 5.46 – 5.41 (m, 1H), 4.73 – 4.71 (m, 2H), 3.93 (s, 3H), 3.87 – 3.85 (m, 7H), 3.81 (s, 6H), 3.52 – 3.47 (m, 1H), 3.29 (td, J = 3.3, 13.0 Hz, 1H), 2.69 – 2.59 (m, 1H), 2.59 – 2.56 (m, 1H), 2.49 – 2.44 (m, 1H), 2.35 – 2.25 (m, 1H), 2.18 – 2.08 (m, 1H), 2.05 (s, 1H), 1.93 – 1.81 (m, 3H), 1.69 – 1.62 (m, 1H), 1.60 – 1.52 (m, 1H), 1.46 – 1.37 (m, 1H), 1.30 – 1.23 (m, 2H).

^{13}**C-NMR** (126 MHz, Chloroform-*d*): δ 190.89, 170.01, 167.88, 157.82, 153.58, 149.07, 147.56, 144.05, 141.56, 133.45, 129.78, 128.10, 120.26, 119.56, 114.56, 113.19, 111.84, 111.49, 107.07, 78.49, 75.96, 61.04, 56.38, 56.35, 56.22, 56.04, 55.97, 55.94, 51.88, 44.31, 38.22, 31.45, 26.53, 24.90, 21.35.

LC-MS (50-100% B, 19 min): t_R (**232**) = 10.25 min, m/z: calculated = 682.26 $[M+H]^+$, found = 682.55 $[M+H]^+$.

6.5.2. Final compounds

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-(prop-2-yn-1-yloxy)phenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV581/AV654)



Chemical Formula: $C_{43}H_{53}NO_9$
Exact Mass: 727,37
Molecular Weight: 727,88

233

233 is synthesized according to general procedure 5.9.7. Reactants: **77** (20 mg), **226** (17 mg), DMAP (23 mg) and DIC (8 µL). The pure product is obtained as a white foam.

prep-HPLC (70 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**233**) = 5.94 min.

Yield 20 mg (57%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.13 (t, *J* = 7.9 Hz, 1H), 7.03 – 6.95 (m, 1H), 6.84 (m, 1H), 6.78 (m, 1H), 6.73 – 6.69 (m, 1H), 6.65 (m, 1H), 6.62 (m, 1H), 6.49 (s, 2H), 6.47 (dd, *J* = 1.2, 7.7 Hz, 1H), 5.58 (dd, *J* = 5.7, 7.9 Hz, 1H), 5.49 – 5.44 (m, 1H), 4.67 – 4.65 (m, 2H), 3.96 (d, *J* = 14.0 Hz, 1H), 3.84 (m, 5H), 3.77 (m, 2H), 3.71 (m, 5H), 3.38 (d, *J* = 9.9 Hz, 1H), 2.79 (td, *J* = 2.9, 13.4 Hz, 1H), 2.63 – 2.54 (m, 1H), 2.52 (m, 1H), 2.49 – 2.33 (m, 2H), 2.32 – 2.25 (m, 1H), 2.16 – 2.01 (m, 2H), 2.01 – 1.76 (m, 4H), 1.74 – 1.48 (m, 3H), 1.48 – 1.38 (m, 1H), 1.38 – 1.05 (m, 6H), 0.98 – 0.70 (m, 2H), 0.68 – 0.52 (m, 1H).

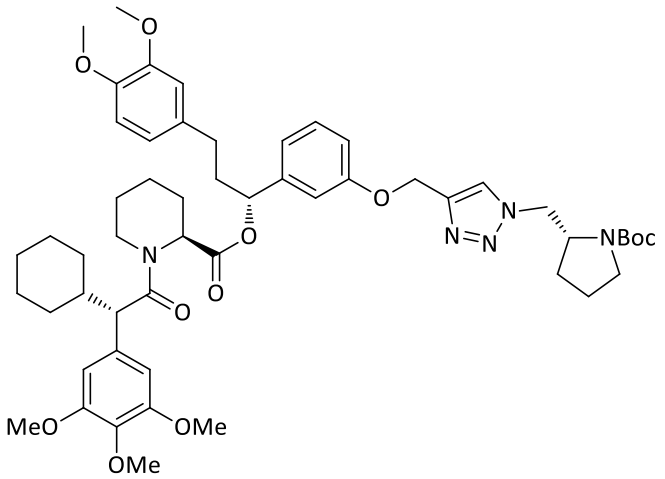
^{13}C-NMR (126 MHz, $CDCl_3$) δ 172.72, 170.52, 157.96, 157.60, 153.45, 153.22, 149.12, 148.99, 147.44, 141.96, 141.63, 137.02, 134.20, 133.56, 133.37, 129.92, 129.67, 120.39, 120.26, 120.11, 119.44, 114.49, 114.17, 113.74, 113.51, 111.94, 111.85, 111.56, 111.46, 105.87, 105.62, 105.41, 78.67, 75.89, 75.74, 75.70, 61.02, 60.90, 56.47, 56.38, 56.19, 56.10, 56.06, 56.02, 55.97, 55.93, 55.19, 52.30, 43.88, 41.44, 41.23, 39.81, 38.09, 37.90, 33.13, 32.93, 31.56, 31.12, 30.80, 30.63, 26.87, 26.71, 26.58, 26.33, 26.25, 26.20, 25.66, 24.44, 21.04, 20.79.

LC-MS (70-100% B, 19 min): t_R (**233**) = 6.40 min, m/z: calculated = 728.38 $[M+H]^+$, found = 728.34 $[M+H]^+$.

HRMS (ESI): calculated = 728.37888 $[M+H]^+$, found = 728.37931 $[M+H]^+$, err [ppm] = 0.58.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**233**) = 11.95 min (96% Purity).

(S)-(R)-1-(3-((1-(((R)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV383)



Chemical Formula: $C_{53}H_{71}N_5O_{11}$
Exact Mass: 953,52
Molecular Weight: 954,16

234

234 is synthesized according to general procedure 5.9.6. Starting material: **233** (30 mg) and (R)-2-azidoemthyl-1-boc-pyrrolidine (28 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/3, v/v.

TLC (CH/EE, 2/3): R_f (**234**) = 0.25.

Yield 25 mg (64%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.60 – 7.58 (m, 1H), 7.11 (t, J = 7.9 Hz, 1H), 7.01 – 6.96 (m, 1H), 6.89 – 6.82 (m, 1H), 6.78 – 6.74 (m, 2H), 6.63 – 6.61 (m, 1H), 6.50 (s, 2H), 6.42 (s, 1H), 5.58 (dd, J = 5.6, 8.0 Hz, 1H), 5.47 (d, J = 5.1 Hz, 1H), 5.16 (s, 2H), 4.63 – 4.56 (m, 2H), 4.15 – 4.03 (m, 2H), 4.01 – 3.93 (m, 1H), 3.87 – 3.83 (m, 6H), 3.83 (d, J = 2.9 Hz, 3H), 3.77 (s, 3H), 3.71 (s, 6H), 3.38 (d, J = 9.9 Hz, 1H), 3.27 – 3.19 (m, 1H), 3.10 (s, 1H), 2.79 (td, J = 2.9, 13.3 Hz, 1H), 2.64 – 2.49 (m, 1H), 2.50 – 2.33 (m, 2H), 2.33 – 2.24 (m, 1H), 2.16 – 2.04 (m, 2H), 2.02 – 1.78 (m, 6H), 1.76 – 1.61 (m, 1H), 1.48 (s, 9H), 1.36 – 1.20 (m, 4H), 1.21 – 1.04 (m, 2H), 0.95 – 0.82 (m, 2H), 0.80 – 0.70 (m, 1H), 0.69 – 0.52 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 171.27, 169.48, 157.10, 152.25, 152.03, 147.84, 146.28, 143.19, 140.85, 135.85, 132.63, 132.45, 128.83, 128.59, 122.51, 119.24, 119.10, 117.90, 112.87, 112.28, 110.80, 110.69, 110.39, 110.30, 104.79, 104.29, 74.56, 60.93, 59.86, 59.75, 56.15, 55.30, 55.05, 54.91, 54.84,

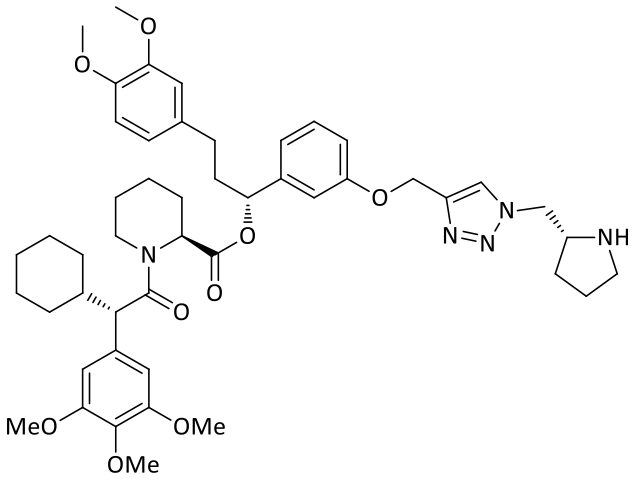
53.98, 51.02, 46.02, 42.65, 40.38, 37.01, 31.77, 29.99, 29.66, 27.48, 25.76, 25.58, 25.21, 25.15, 24.56, 22.33, 19.99.

LC-MS (50-100% B, 19 min): t_R (**234**) = 11.03 min, m/z: calculated = 954.52 $[M+H]^+$, found = 954.62 $[M+H]^+$.

HRMS (ESI): calculated = 954.52228 $[M+H]^+$, found = 954.52298 $[M+H]^+$, err [ppm] = 0.73.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**234**) = 15.18 min (99% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-((1-((R)-pyrrolidin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV478)



Chemical Formula: $C_{48}H_{63}N_5O_9$
Exact Mass: 853,46
Molecular Weight: 854,04

235

234 (5 mg) in 1 mL is dissolved in dry DCM and 0.5 mL TFA added. The reaction is stirred at RT for 30 min. The solvent is evaporated under airstream. The crude product is purified by silica column chromatography (DCM + 1% MeOH + 1% TEA). The pure product is obtained as a white solid.

TLC (DCM + 1% MeOH + 1% TEA**):** R_f (**235**) = 0.30.

Yield 4 mg (89%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.13 (t, J = 7.9 Hz, 1H), 6.88 – 6.82 (m, 1H), 6.80 – 6.73 (m, 1H), 6.72 – 6.69 (m, 1H), 6.67 – 6.60 (m, 2H), 6.55 (d, J = 7.6 Hz, 1H), 6.45 (s, 2H), 5.55 (dd, J = 5.5, 8.2 Hz, 1H), 5.44 (d, J = 5.5 Hz, 1H), 5.19 – 5.07 (m, 2H), 4.96 – 4.87 (m, 1H), 4.79 – 4.67 (m, 1H), 4.18 (s, 1H), 3.94 (d, J = 13.7 Hz, 1H), 3.89 – 3.62 (m, 15H), 3.38 (d, J = 9.8 Hz, 1H), 3.36 – 3.27 (m, 1H), 2.83 – 2.74 (m, 1H), 2.64 – 2.20 (m, 10H), 2.13 – 1.92 (m, 4H), 1.90 – 1.79 (m, 2H), 1.76 – 1.59 (m, 5H), 1.58 – 1.52 (m, 1H), 1.48 – 1.38 (m, 0H), 1.38 – 1.06 (m, 4H), 1.00 – 0.71 (m, 3H), 0.61 – 0.46 (m, 0H).

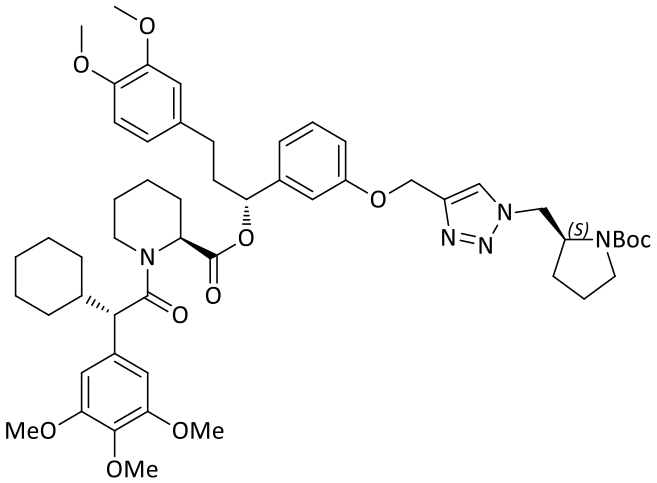
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.74, 170.69, 158.06, 153.03, 149.01, 147.47, 142.13, 136.75, 133.77, 133.58, 129.86, 124.78, 120.40, 119.32, 114.16, 113.49, 111.97, 111.50, 105.96, 75.93, 61.64, 60.98, 59.67, 56.47, 56.17, 56.09, 56.01, 55.15, 52.33, 50.22, 45.88, 43.86, 41.41, 38.13, 32.91, 31.27, 30.82, 28.13, 26.92, 26.69, 26.32, 25.64, 23.57, 21.10.

LC-MS (30-100% B, 19 min): t_R (**235**) = 7.18 min, m/z: calculated = 854.47 $[M+H]^+$, found = 854.89 $[M+H]^+$.

HRMS (ESI): calculated = 854.46986 $[M+H]^+$, found = 854.47097 $[M+H]^+$, err [ppm] = 1.30.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**235**) = 15.30 min (99% Purity).

(S)-(R)-1-(3-((1-(((S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV372)



Chemical Formula: $C_{53}H_{71}N_5O_{11}$
Exact Mass: 953,52
Molecular Weight: 954,16

236

236 is synthesized according to general procedure 5.9.6. Reactants: **233** (30 mg) and (S)-2-azidomethyl-1-boc-pyrrolidine (27 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/3, v/v.

TLC (CH/EE, 2/3): R_f (**236**) = 0.25.

Yield 10 mg (25%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.63 – 7.58 (m, 1H), 7.11 (t, J = 7.9 Hz, 1H), 7.02 – 6.94 (m, 1H), 6.84 (dd, J = 2.5, 8.1 Hz, 1H), 6.77 – 6.74 (m, 2H), 6.65 – 6.61 (m, 2H), 6.50 (s, 2H), 6.45 – 6.41 (m, 1H), 5.58 (dd, J = 5.7, 8.1 Hz, 1H), 5.47 (d, J = 5.1 Hz, 1H), 5.15 (s, 2H), 4.63 – 4.56 (m, 2H), 4.14 – 4.07 (m, 2H), 3.96 (d, J = 13.9 Hz, 1H), 3.87 – 3.85 (m, 5H), 3.84 (s, 3H), 3.83 – 3.82 (m, 3H), 3.77 (s, 3H), 3.71 (s, 6H), 3.38 (d, J = 9.9 Hz, 1H), 3.29 – 3.18 (m, 1H), 3.16 – 3.06 (m, 1H), 2.78 (td, J = 2.9, 13.4 Hz, 1H), 2.63 –

2.50 (m, 0H), 2.49 – 2.33 (m, 2H), 2.33 – 2.26 (m, 1H), 2.15 – 2.03 (m, 2H), 1.99 – 1.79 (m, 6H), 1.74 – 1.62 (m, 2H), 1.48 (s, 9H), 1.37 – 1.21 (m, 3H), 1.20 – 1.09 (m, 2H), 0.96 – 0.82 (m, 1H), 0.82 – 0.69 (m, 1H), 0.68 – 0.52 (m, 1H).

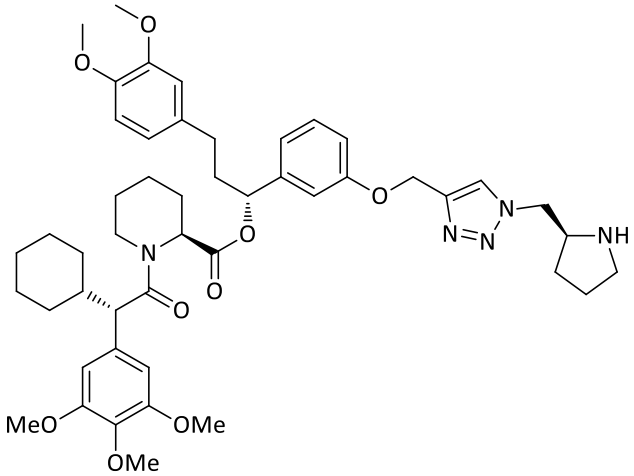
^{13}C-NMR (126 MHz, $CDCl_3$): δ 171.27, 169.48, 157.10, 152.25, 152.03, 147.84, 146.28, 140.86, 135.85, 132.64, 132.45, 128.83, 128.58, 122.50, 119.24, 119.10, 117.93, 112.88, 112.31, 110.81, 110.69, 110.39, 110.30, 104.79, 104.30, 74.55, 60.94, 59.86, 59.74, 56.15, 55.31, 55.05, 54.91, 54.84, 53.98, 51.02, 50.62, 46.02, 42.66, 40.38, 40.14, 38.46, 37.00, 36.82, 31.77, 30.44, 29.98, 29.65, 27.48, 27.20, 25.75, 25.58, 25.45, 25.20, 25.15, 24.56, 22.33, 20.00, 19.73.

LC-MS (50-100% B, 19 min): t_R (**233**) = 11.83 min, m/z: calculated = 954.52 $[M+H]^+$, found = 954.55 $[M+H]^+$.

HRMS (ESI): calculated = 954.52228 $[M+H]^+$, found = 954.52316 $[M+H]^+$, err [ppm] = 0.92.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**233**) = 15.16 min (99% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-((1-((S)-pyrrolidin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV474)



Chemical Formula: $C_{48}H_{63}N_5O_9$
Exact Mass: 853,46
Molecular Weight: 854,04

237

236 (6 mg) is dissolved in 1 mL dry DCM and 0.5 mL TFA added. The reaction is stirred at RT for 30 min. The solvent is evaporated under airstream. The crude product is purified by silica column chromatography (DCM + 1% MeOH + 1% TEA). The pure product is obtained as a white solid.

TLC (DCM + 1% MeOH + 1% TEA**):** R_f (**237**) = 0.30.

Yield 5 mg (93%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.15 (t, J = 7.9 Hz, 1H), 6.85 – 6.80 (m, 1H), 6.80 – 6.75 (m, 1H), 6.66 – 6.57 (m, 4H), 6.44 (s, 3H), 5.54 (dd, J = 5.7, 8.1 Hz, 1H), 5.44 (d, J = 5.5 Hz, 1H), 5.16 – 5.04 (m, 3H), 4.97 – 4.83 (m, 1H), 4.81 – 4.66 (m, 1H), 4.18 (s, 1H), 3.95 (d, J = 13.8 Hz, 1H), 3.86 – 3.80 (m, 11H), 3.78 (s, 3H), 3.63 (s, 5H), 3.47 – 3.41 (m, 2H), 3.38 (d, J = 9.9 Hz, 1H), 2.78 (t, J = 13.1 Hz, 1H), 2.68 – 2.45 (m, 2H), 2.45 – 2.35 (m, 1H), 2.35 – 2.19 (m, 2H), 2.17 – 1.94 (m, 4H), 1.93 – 1.81 (m, 4H), 1.75 – 1.59 (m, 7H), 1.59 – 1.39 (m, 1H), 1.35 – 1.19 (m, 4H), 1.19 – 1.05 (m, 2H), 0.98 – 0.70 (m, 2H).

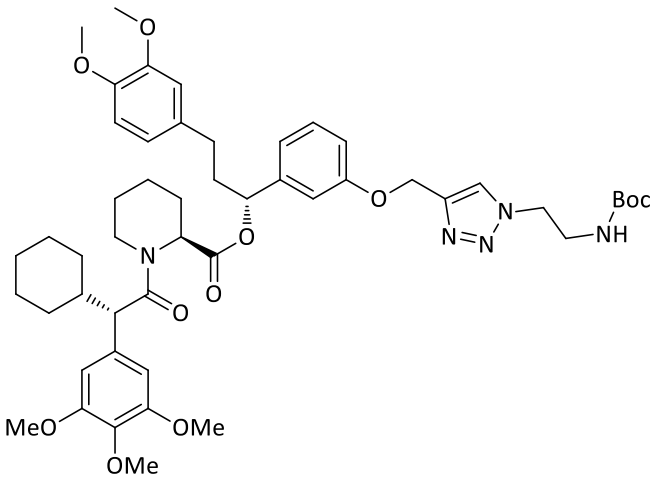
^{13}C-NMR (126 MHz, $CDCl_3$): δ 170.47, 152.97, 149.00, 142.14, 136.62, 133.57, 133.49, 129.91, 120.43, 119.57, 113.94, 113.34, 111.96, 111.52, 105.90, 76.05, 61.36, 61.00, 59.97, 56.21, 56.09, 55.99, 55.22, 52.50, 50.24, 46.14, 43.98, 41.25, 38.07, 32.89, 31.31, 30.80, 27.96, 26.85, 26.63, 26.28, 26.21, 25.56, 23.53, 20.97.

LC-MS (30-100% B, 19 min): t_R (**237**) = 7.12 min, m/z: calculated = 854.56 $[M+H]^+$, found = 855.00 $[M+H]^+$.

HRMS (ESI): calculated = 854.46986 $[M+H]^+$, found = 854.47064 $[M+H]^+$, err [ppm] = 0.91.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**237**) = 15.40 min (95% Purity).

(S)-(R)-1-(3-((1-(2-((tert-butoxycarbonyl)amino)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV378)



Chemical Formula: $C_{50}H_{67}N_5O_{11}$
Exact Mass: 913,48
Molecular Weight: 914,09

238

238 is synthesized according to general procedure 5.9.6. Starting material: **233** (30 mg) and 0.5 M *tert*-butyl (2-azidoethyl)carbamate solution in *t*BuOH (240 µL). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**238**) = 0.29.

Yield 37 mg (quant.).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.12 (t, J = 7.9 Hz, 1H), 7.01 – 6.94 (m, 1H), 6.85 (ddd, J = 0.9, 2.6, 8.3 Hz, 1H), 6.82 – 6.72 (m, 2H), 6.71 – 6.60 (m, 2H), 6.48 (s, 2H), 6.47 – 6.42 (m, 1H), 5.57 (dd, J = 5.6, 8.1 Hz, 1H), 5.46 (d, J = 5.1 Hz, 1H), 5.19 (d, J = 3.2 Hz, 0H), 5.15 (s, 1H), 5.03 – 4.91 (m, 1H), 4.50 – 4.43 (m, 2H), 3.98 – 3.91 (m, 1H), 3.86 – 3.81 (m, 8H), 3.76 (s, 2H), 3.69 (s, 4H), 3.65 – 3.60 (m, 2H), 3.37 (d, J = 9.8 Hz, 1H), 2.78 (td, J = 2.9, 13.4 Hz, 1H), 2.66 – 2.51 (m, 1H), 2.50 – 2.32 (m, 1H), 2.32 – 2.22 (m, 1H), 2.19 – 2.03 (m, 2H), 2.01 – 1.91 (m, 1H), 1.90 – 1.79 (m, 2H), 1.74 – 1.51 (m, 6H), 1.42 (s, 9H), 1.35 – 1.19 (m, 4H), 1.20 – 1.07 (m, 2H), 0.98 – 0.85 (m, 1H), 0.82 – 0.47 (m, 1H).

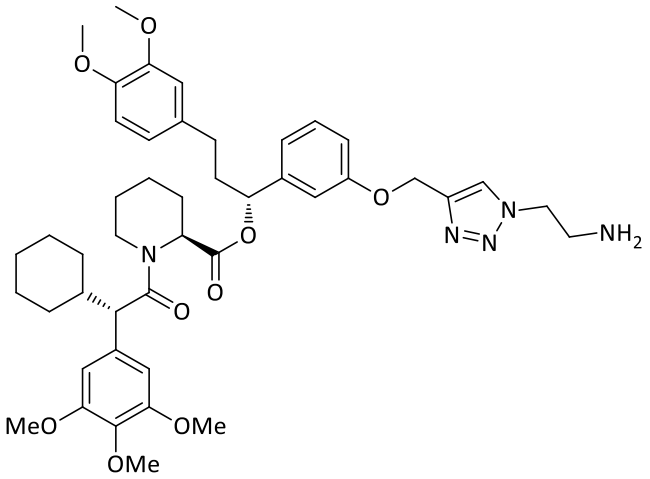
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.45, 170.66, 158.63, 158.25, 155.97, 153.40, 153.15, 149.12, 149.00, 147.64, 147.44, 144.24, 143.95, 142.06, 141.80, 136.95, 134.42, 133.75, 133.58, 133.39, 130.03, 129.77, 123.66, 120.39, 120.26, 119.67, 119.15, 114.29, 114.15, 113.71, 113.32, 111.96, 111.85, 111.56, 111.46, 105.92, 105.45, 75.76, 62.05, 61.01, 60.89, 56.44, 56.18, 56.10, 56.07, 56.03, 55.99, 55.84, 55.16, 52.18, 50.18, 43.79, 41.53, 41.29, 40.62, 39.62, 38.15, 37.94, 33.10, 32.94, 31.59, 31.18, 30.80, 30.61, 29.83, 28.45, 26.91, 26.71, 26.56, 26.36, 26.31, 26.22, 25.69, 24.47, 21.12, 20.82, 1.15.

LC-MS (50-100% B, 19 min): t_R (**238**) = 10.35 min, m/z: calculated = 914.48 $[M+H]^+$, found = 914.55 $[M+H]^+$.

HRMS (ESI): calculated = 914.49098 $[M+H]^+$, found = 914.49176 $[M+H]^+$, err [ppm] = 0.85.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**238**) = 12.84 min (99% Purity).

(S)-(R)-1-(3-((1-(2-aminoethyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV477)



Chemical Formula: $C_{45}H_{59}N_5O_9$
Exact Mass: 813,43
Molecular Weight: 813,98

239

238 (7 mg) is dissolved in 1 mL dry DCM and 0.5 mL TFA added. The reaction is stirred at RT for 30 min. The solvent is evaporated under airstream. The crude product is purified by semi-preparative HPLC. The pure product is obtained as a white solid.

prep-HPLC (30 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**239**) = 7.50 min.

Yield 6 mg (96%).

^{1}H-NMR (500 MHz, $CDCl_3$): 1H NMR (500 MHz, Chloroform-d) δ 7.14 (t, J = 7.9 Hz, 1H), 6.83 – 6.74 (m, 3H), 6.72 – 6.68 (m, 1H), 6.68 – 6.57 (m, 3H), 6.44 (s, 2H), 5.52 (dd, J = 5.5, 8.3 Hz, 1H), 5.43 (d, J = 5.6 Hz, 1H), 5.11 – 5.05 (m, 2H), 4.75 – 4.67 (m, 3H), 3.95 (d, J = 13.7 Hz, 1H), 3.87 – 3.82 (m, 8H), 3.75 (s, 3H), 3.64 (s, 6H), 3.60 – 3.53 (m, 2H), 3.40 (d, J = 9.7 Hz, 1H), 2.82 (t, J = 12.9 Hz, 1H), 2.58 – 2.37 (m, 2H), 2.34 – 2.25 (m, 2H), 2.13 – 1.93 (m, 3H), 1.93 – 1.76 (m, 2H), 1.74 – 1.53 (m, 7H), 1.49 – 1.39 (m, 1H), 1.35 – 1.23 (m, 5H), 1.20 – 1.06 (m, 2H), 0.98 – 0.68 (m, 2H).

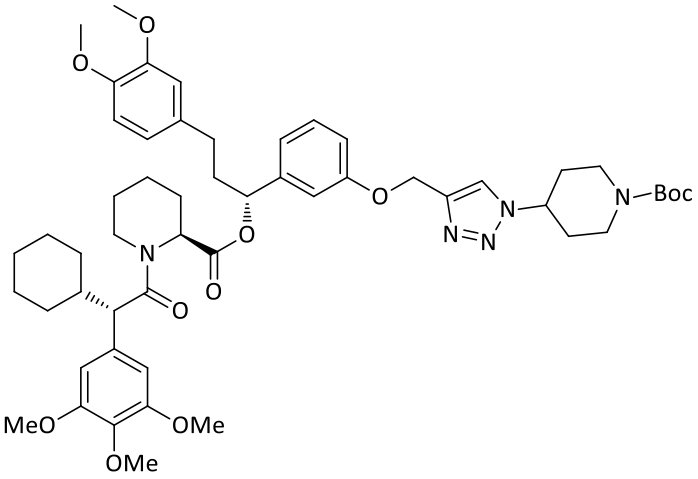
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.94, 170.79, 158.01, 152.96, 148.99, 147.47, 142.19, 136.58, 133.85, 133.56, 129.95, 120.44, 119.15, 114.14, 113.39, 112.00, 111.55, 105.93, 76.16, 61.40, 60.96, 56.46, 56.16, 56.09, 56.01, 55.07, 52.40, 47.42, 43.88, 41.36, 39.66, 38.20, 32.87, 31.31, 30.82, 26.94, 26.65, 26.28, 25.59, 21.05.

LC-MS (30-100% B, 19 min): t_R (**239**) = 7.00 min, m/z: calculated = 814.44 $[M+H]^+$, found = 814.87 $[M+H]^+$.

HRMS (ESI): calculated = 814.43855 $[M+H]^+$, found = 814.43920 $[M+H]^+$, err [ppm] = 0.79.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**239**) = 15.03min (99% Purity).

tert-butyl 4-(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)piperidine-1-carboxylate (AV374)



Chemical Formula: $C_{53}H_{71}N_5O_{11}$
Exact Mass: 953,52
Molecular Weight: 954,16

240

240 is synthesized according to general procedure 5.9.6. Starting material: **233** (30 mg) and *tert*-butyl 4-azidopiperidine-1-carboxylate (14 mg). The pure product is obtained as a colorless oil.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**240**) = 0.33.

Yield 33 mg (84%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.16 – 7.08 (m, 1H), 7.02 – 6.96 (m, 1H), 6.88 – 6.82 (m, 1H), 6.82 – 6.72 (m, 2H), 6.69 – 6.60 (m, 2H), 6.49 (s, 2H), 6.45 (d, J = 7.5 Hz, 1H), 5.57 (dd, J = 5.6, 8.1 Hz, 1H), 5.47 (d, J = 5.5 Hz, 1H), 5.16 (d, J = 1.8 Hz, 1H), 4.64 – 4.52 (m, 1H), 4.26 (s, 2H), 3.95 (d, J = 13.9 Hz, 1H), 3.88 – 3.81 (m, 8H), 3.77 (s, 3H), 3.70 (s, 5H), 3.38 (d, J = 9.8 Hz, 1H), 2.95 – 2.88 (m, 3H), 2.83 – 2.74 (m, 1H), 2.64 – 2.51 (m, 0H), 2.51 – 2.42 (m, 1H), 2.43 – 2.33 (m, 1H), 2.34 – 2.25 (m, 1H), 2.24 – 2.14 (m, 2H), 2.15 – 2.03 (m, 1H), 2.02 – 1.90 (m, 2H), 1.92 – 1.77 (m, 2H), 1.72 – 1.61 (m, 1H), 1.48 (s, 10H), 1.37 – 1.26 (m, 2H), 1.19 – 1.07 (m, 2H), 0.96 – 0.72 (m, 3H).

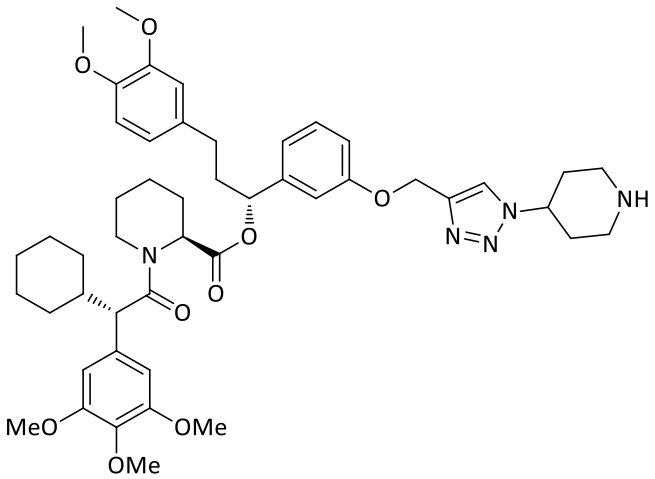
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.47, 170.69, 170.08, 158.30, 154.63, 153.43, 153.20, 147.47, 144.18, 144.08, 142.08, 133.78, 133.60, 129.79, 123.84, 120.76, 120.42, 119.13, 114.00, 113.43, 111.99, 111.48, 105.95, 105.47, 80.32, 75.73, 62.22, 60.92, 58.45, 56.47, 56.21, 56.09, 56.01, 55.18, 52.19, 43.81, 41.56, 38.16, 32.96, 32.54, 31.60, 31.18, 30.83, 29.85, 28.56, 26.92, 26.74, 26.39, 26.33, 26.25, 25.71, 21.14.

LC-MS (50-100% B, 19 min): t_R (**240**) = 11.64 min, m/z: calculated = 954.52 $[M+H]^+$, found = 954.91 $[M+H]^+$.

HRMS (ESI): calculated = 954.52228 $[M+H]^+$, found = 954.52322 $[M+H]^+$, err [ppm] = 0.98.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**240**) = 15.01 min (97% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-((1-(piperidin-4-yl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV475)



Chemical Formula: $C_{48}H_{63}N_5O_9$
Exact Mass: 853,46
Molecular Weight: 854,04

241

240 (5 mg, 0.01 mmol) is dissolved in 1.5 mL DCM/TFA - 2/1. After stirring for 30 min at r.t., the solvent is evaporated under airstream and the crude then purified by silica column chromatography (DCM + 1% MeOH + 1% TEA). Pure **241** is obtained in quantitative yield.

TLC (DCM + 1% MeOH + 1% TEA): R_f (**241**) = 0.21.

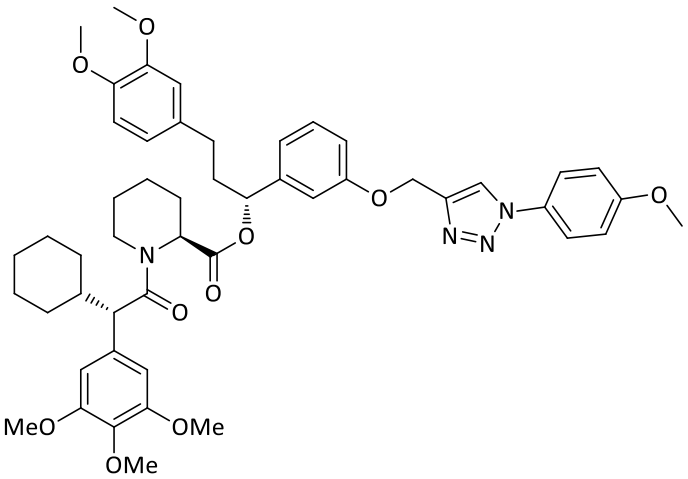
Yield 4.5 mg (quant.).

LC-MS (30-100% B, 19 min): t_R (**241**) = 7.65 min, m/z: calculated = 854.46 $[M+H]^+$, found = 854.89 $[M+H]^+$.

HRMS (ESI): calculated = 854.46986 $[M+H]^+$, found = 854.47012 $[M+H]^+$, err [ppm] = 0.30.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**241**) = 15.33 min (99% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV380/AV662)



Chemical Formula: $C_{50}H_{60}N_4O_{10}$
Exact Mass: 876,43
Molecular Weight: 877,03

242

242 is synthesized according to general procedure 5.9.6. Starting material: **233** (10 mg) and 4-azidoanisole (3 mg). The pure product is obtained as a colorless oil.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**242**) = 0.23.

Yield 11 mg (92%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.68 – 7.58 (m, 2H), 7.13 (t, J = 8.0 Hz, 1H), 7.04 – 6.97 (m, 3H), 6.88 (ddd, J = 0.9, 2.6, 8.3 Hz, 1H), 6.81 – 6.71 (m, 3H), 6.67 – 6.58 (m, 3H), 6.55 – 6.41 (m, 4H), 5.59 (dd, J = 5.7, 8.0 Hz, 1H), 5.48 (d, J = 5.7 Hz, 1H), 5.24 (d, J = 2.0 Hz, 2H), 3.88 – 3.81 (m, 17H), 3.77 (s, 3H), 3.70 (s, 5H), 3.38 (d, J = 9.7 Hz, 1H), 2.78 (td, J = 2.9, 13.4 Hz, 1H), 2.67 – 2.43 (m, 2H), 2.41 – 2.26 (m, 2H), 1.90 – 1.82 (m, 2H), 1.72 – 1.59 (m, 4H), 1.19 – 1.05 (m, 2H), 0.98 – 0.81 (m, 1H), 0.80 – 0.72 (m, 1H), 0.66 – 0.51 (m, 1H).

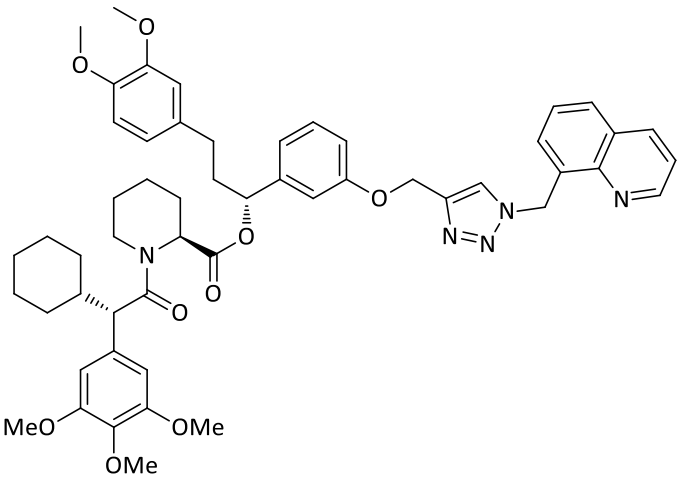
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.43, 170.71, 160.05, 158.27, 153.42, 153.20, 149.00, 147.45, 144.71, 142.06, 137.01, 133.80, 133.59, 130.61, 129.80, 122.40, 121.38, 120.41, 119.24, 114.94, 114.08, 113.46, 111.98, 111.47, 105.94, 105.49, 75.73, 62.12, 60.91, 56.48, 56.20, 56.08, 56.00, 55.78, 55.16, 52.19, 43.83, 41.56, 38.09, 32.94, 31.17, 30.82, 26.89, 26.74, 26.37, 26.32, 25.71, 21.13, 14.35.

LC-MS (50-100% B, 19 min): t_R (**242**) = 12.62 min, m/z: calculated = 877.44 $[M+H]^+$, found = 877.70 $[M+H]^+$.

HRMS (ESI): calculated = 877.43822 $[M+H]^+$, found = 877.43838 $[M+H]^+$, err [ppm] = 0.18

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**242**) = 12.36 min (98% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-((1-(quinolin-8-ylmethyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV376)



Chemical Formula: $C_{53}H_{61}N_5O_9$
Exact Mass: 911,45
Molecular Weight: 912,08

243

243 is synthesized according to general procedure 5.9.6. Starting material: **233** (30 mg) and 8-(azidomethyl)quinoline (23 mg). The pure product is obtained as a beige solid.

Silica column chromatography: CH/EE, 1/2, v/v.

TLC (CH/EE, 1/2): R_f (**243**) = 0.42.

Yield 30 mg (81%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.97 – 8.93 (m, 1H), 8.18 (dd, J = 1.8, 8.3 Hz, 1H), 7.86 (s, 1H), 7.85 – 7.77 (m, 1H), 7.67 – 7.58 (m, 1H), 7.54 – 7.42 (m, 2H), 7.09 (t, J = 7.9 Hz, 1H), 6.99 – 6.94 (m, 1H), 6.83 – 6.80 (m, 1H), 6.77 – 6.72 (m, 1H), 6.73 – 6.71 (m, 1H), 6.60 (s, 1H), 6.49 (s, 1H), 6.42 (s, 1H), 6.23 (s, 2H), 5.58 – 5.51 (m, 1H), 5.48 – 5.43 (m, 1H), 5.15 – 5.07 (m, 2H), 3.94 (d, J = 13.7 Hz, 1H), 3.85 – 3.83 (m, 6H), 3.81 (s, 2H), 3.75 (s, 2H), 3.69 (s, 4H), 3.37 (d, J = 9.8 Hz, 1H), 2.80 – 2.73 (m, 1H), 2.63 – 2.47 (m, 1H), 2.43 (t, J = 5.4, 9.3, 14.5 Hz, 1H), 2.39 – 2.23 (m, 2H), 2.13 – 1.99 (m, 1H), 1.98 – 1.84 (m, 1H), 1.84 – 1.74 (m, 1H), 1.72 – 1.46 (m, 7H), 1.45 – 1.35 (m, 0H), 1.34 – 1.18 (m, 3H), 1.18 – 1.03 (m, 2H), 0.99 – 0.82 (m, 1H), 0.81 – 0.69 (m, 1H), 0.63 – 0.50 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.41, 170.65, 158.35, 153.40, 153.18, 150.38, 148.98, 147.62, 147.42, 146.02, 143.90, 141.92, 141.63, 136.99, 136.53, 134.44, 133.79, 133.60, 133.38, 130.17, 130.06, 129.94, 129.69, 129.16, 129.09, 128.55, 126.60, 124.02, 121.81, 120.39, 120.25, 119.59, 119.06, 114.27, 114.00, 113.81, 113.49, 111.96, 111.84, 111.54, 111.45, 105.93, 105.44, 75.71, 62.18, 61.02, 60.89, 56.46, 56.19, 56.11, 56.07, 56.03, 55.98, 55.80, 55.12, 52.17, 50.05, 43.81, 41.54, 41.29, 39.59,

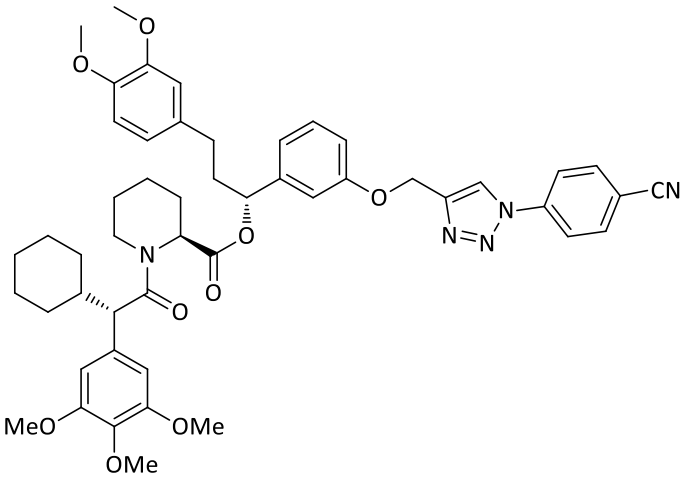
38.06, 37.92, 33.08, 32.92, 31.56, 31.11, 30.81, 30.63, 29.84, 27.01, 26.90, 26.73, 26.57, 26.35, 26.30, 25.70, 24.50, 21.13, 20.87, 1.16.

LC-MS (50-100% B, 19 min): t_R (**243**) = 11.12 min, m/z: calculated = 912.45 $[M+H]^+$, found = 912.57 $[M+H]^+$.

HRMS (ESI): calculated = 912.45421 $[M+H]^+$, found = 912.45515 $[M+H]^+$, err [ppm] = 1.04.

RP-HPLC (30 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**243**) = 17.22 min (99% Purity).

(S)-(R)-1-(3-((1-(4-cyanophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV708)



Chemical Formula: $C_{50}H_{57}N_5O_9$
Exact Mass: 871,42
Molecular Weight: 872,02

244

244 is synthesized according to general procedure 5.9.6. Starting material: **233** (20 mg) and 4-azidobenzonitrile (6 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**244**) = 0.21.

Yield 20 mg (87%).

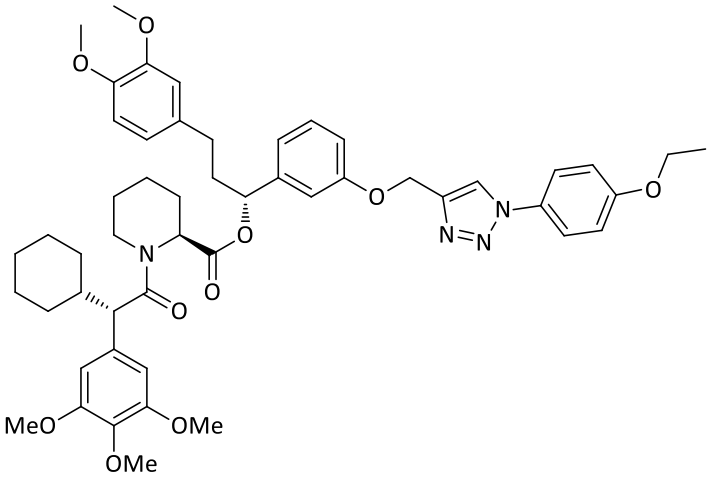
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.98 – 7.90 (m, 2H), 7.88 – 7.80 (m, 2H), 7.14 (t, J = 7.9 Hz, 1H), 7.06 – 6.96 (m, 1H), 6.86 (ddd, J = 0.9, 2.7, 8.3 Hz, 1H), 6.79 – 6.73 (m, 2H), 6.65 – 6.60 (m, 2H), 6.51 – 6.47 (m, 2H), 5.58 (dd, J = 5.5, 8.1 Hz, 1H), 5.49 – 5.43 (m, 1H), 5.26 (d, J = 5.0 Hz, 1H), 3.95 (d, J = 13.5 Hz, 1H), 3.88 – 3.81 (m, 9H), 3.76 (s, 3H), 3.69 (s, 5H), 3.38 (d, J = 9.9 Hz, 1H), 2.78 (td, J = 2.9, 13.3 Hz, 1H), 2.65 – 2.54 (m, 0H), 2.52 – 2.36 (m, 1H), 2.34 – 2.23 (m, 1H), 2.16 – 2.03 (m, 1H), 2.02 – 1.93 (m, 1H), 1.91 – 1.79 (m, 2H), 1.75 – 1.50 (m, 7H), 1.49 – 1.38 (m, 1H), 1.36 – 1.20 (m, 3H), 1.19 – 1.03 (m, 3H), 1.00 – 0.85 (m, 1H), 0.80 – 0.69 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.46, 170.82, 170.74, 158.42, 158.03, 153.44, 153.16, 149.14, 149.01, 147.69, 147.48, 145.82, 145.61, 142.18, 142.00, 139.90, 136.96, 134.39, 134.09, 134.04, 133.76, 133.51, 133.32, 130.15, 129.86, 120.94, 120.76, 120.40, 120.27, 119.91, 119.40, 117.80, 114.23, 114.06, 113.75, 113.41, 112.64, 111.98, 111.88, 111.56, 111.46, 105.93, 105.51, 75.68, 62.00, 61.93, 61.02, 60.90, 56.49, 56.17, 56.11, 56.07, 56.00, 55.89, 55.18, 52.18, 43.80, 41.55, 41.29, 39.64, 38.10, 37.94, 33.12, 32.94, 31.60, 31.19, 30.80, 30.59, 26.86, 26.71, 26.54, 26.36, 26.31, 26.21, 25.67, 24.46, 21.09, 20.77.

LC-MS (50-100% B, 19 min): t_R (**244**) = 12.08 min, m/z: calculated = 872.42 $[M+H]^+$, found = 872.49 $[M+H]^+$ (97% Purity).

HRMS (ESI): calculated = 872.42290 $[M+H]^+$, found = 872.42243 $[M+H]^+$, err [ppm] = 0.55.

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-((1-(4-ethoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV730)



Chemical Formula: $C_{51}H_{62}N_4O_{10}$
Exact Mass: 890,45
Molecular Weight: 891,06

245

245 is synthesized according to general procedure 5.9.6. Starting material: **233** (20 mg) and 1-azido-4-ethoxybenzene (7 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**245**) = 0.30.

Yield 23 mg (94%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.61 (t, J = 8.8 Hz, 2H), 7.13 (t, J = 8.0 Hz, 1H), 6.99 (dd, J = 1.2, 9.0 Hz, 2H), 6.88 (ddd, J = 0.9, 2.6, 8.4 Hz, 1H), 6.81 – 6.75 (m, 2H), 6.65 – 6.60 (m, 2H), 6.50 (s, 2H), 6.46 (dt, J = 1.1, 7.6 Hz, 1H), 5.58 (dd, J = 5.7, 8.0 Hz, 1H), 5.50 – 5.46 (m, 1H), 5.24 (d, J = 2.0 Hz,

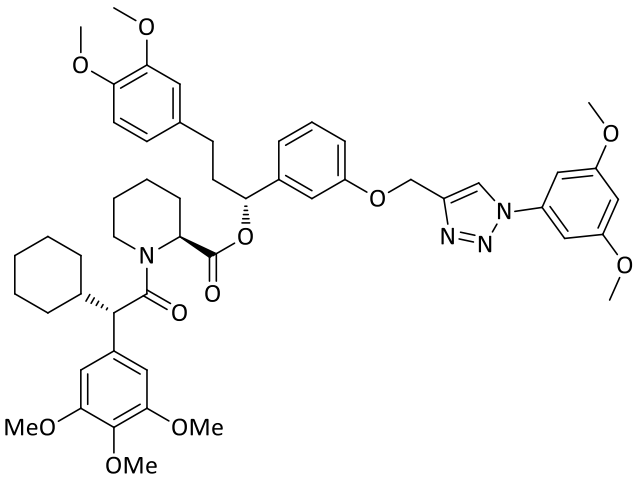
1H), 3.95 (d, J = 13.6 Hz, 1H), 3.86 – 3.81 (m, 10H), 3.76 (s, 2H), 3.70 (s, 5H), 3.38 (d, J = 9.8 Hz, 1H), 2.77 (td, J = 2.9, 13.3 Hz, 1H), 2.65 – 2.50 (m, 1H), 2.50 – 2.33 (m, 2H), 2.28 (dd, J = 4.7, 11.7 Hz, 1H), 2.17 – 2.01 (m, 2H), 1.96 (dtd, J = 5.5, 8.7, 13.8 Hz, 1H), 1.91 – 1.78 (m, 2H), 1.76 – 1.50 (m, 8H), 1.36 – 1.04 (m, 6H), 0.96 – 0.70 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.42, 170.78, 170.69, 159.43, 158.62, 158.26, 153.41, 153.19, 149.12, 148.99, 147.63, 147.43, 144.79, 144.66, 144.43, 142.04, 141.79, 136.99, 134.43, 133.79, 133.58, 133.40, 130.43, 130.05, 129.78, 122.36, 121.36, 121.30, 120.40, 120.26, 119.72, 119.22, 115.44, 115.42, 114.34, 114.07, 113.80, 113.45, 111.96, 111.85, 111.55, 111.45, 105.93, 105.47, 75.71, 64.07, 62.10, 62.10, 61.01, 60.90, 56.47, 56.19, 56.10, 56.06, 55.98, 55.84, 55.14, 52.17, 43.82, 41.55, 41.30, 39.61, 38.07, 37.94, 33.11, 32.92, 31.58, 31.15, 30.80, 30.63, 26.94, 26.87, 26.72, 26.58, 26.36, 26.30, 26.23, 25.70, 24.49, 21.12.

LC-MS (50-100% B, 19 min): t_R (**245**) = 13.09 min, m/z: calculated = 891.45 $[M+H]^+$, found = 891.92 $[M+H]^+$ (99% Purity).

HRMS (ESI): calculated = 891.45387 $[M+H]^+$, found = 891.45422 $[M+H]^+$, err [ppm] = 0.39.

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-((1-(3,5-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV677)



Chemical Formula: $C_{51}H_{62}N_4O_{11}$
Exact Mass: 906,44
Molecular Weight: 907,06

246

246 is synthesized according to general procedure 5.9.6. Starting material: **233** (10 mg) and 1-azido-3,5-dimethoxy-benzene (4 mg). The pure product is obtained as a colorless solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**246**) = 0.25.

Yield 5 mg (42%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.13 – 8.03 (m, 1H), 7.14 (t, J = 7.9 Hz, 1H), 7.05 – 6.98 (m, 1H), 6.95 – 6.84 (m, 3H), 6.80 – 6.74 (m, 2H), 6.68 – 6.60 (m, 2H), 6.53 – 6.50 (m, 2H), 6.49 – 6.41 (m, 1H), 5.59 (dd, J = 5.7, 7.9 Hz, 1H), 5.50 – 5.44 (m, 1H), 5.31 – 5.28 (m, 1H), 5.25 – 5.21 (m, 1H), 3.95 (d, J = 14.2 Hz, 1H), 3.87 – 3.83 (m, 12H), 3.83 – 3.82 (m, 2H), 3.77 (s, 2H), 3.70 (s, 4H), 3.38 (d, J = 9.8 Hz, 1H), 2.77 (td, J = 2.8, 13.4 Hz, 1H), 2.51 – 2.32 (m, 1H), 2.32 – 2.22 (m, 1H), 2.14 – 2.03 (m, 1H), 2.01 – 1.92 (m, 1H), 1.92 – 1.80 (m, 2H), 1.74 – 1.52 (m, 8H), 1.48 – 1.08 (m, 7H), 1.05 – 0.68 (m, 2H).

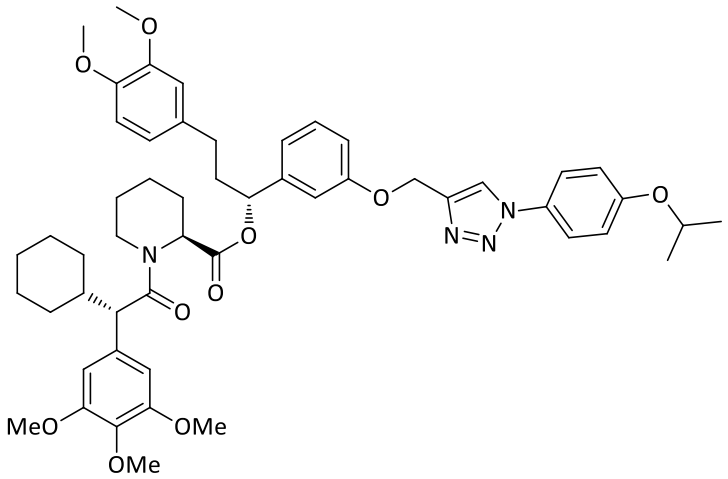
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.43, 170.72, 161.70, 158.25, 153.44, 153.22, 149.01, 147.46, 144.82, 142.08, 138.63, 137.03, 133.82, 133.59, 129.82, 121.34, 121.29, 120.42, 120.27, 119.77, 119.31, 114.39, 114.08, 113.85, 113.45, 111.98, 111.87, 111.56, 111.47, 105.96, 105.50, 100.84, 99.19, 75.72, 62.15, 62.07, 61.03, 60.92, 56.50, 56.21, 56.08, 56.00, 55.89, 55.17, 52.19, 43.84, 41.57, 41.30, 38.08, 37.95, 33.19, 32.95, 31.60, 31.17, 30.82, 30.69, 29.85, 26.88, 26.74, 26.38, 25.72, 24.52, 21.13, 20.87, 1.17.

LC-MS (50-100% B, 19 min): t_R (**246**) = 12.90 min, m/z: calculated = 907.44 $[M+H]^+$, found = 907.57 $[M+H]^+$.

HRMS (ESI): calculated = 907.44879 $[M+H]^+$, found = 907.44940 $[M+H]^+$, err [ppm] = 0.68.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**246**) = 13.08 min (97% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-((1-(4-isopropoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV678)



Chemical Formula: $C_{52}H_{64}N_4O_{10}$
Exact Mass: 904,46
Molecular Weight: 905,09

247

247 is synthesized according to general procedure 5.9.6. Starting material: **233** (10 mg) and 1-azido-4-isopropoxy-benzene (4 mg). The pure product is obtained as a colorless solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**247**) = 0.25.

Yield 10 mg (81%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.65 – 7.55 (m, 1H), 7.13 (t, J = 8.0 Hz, 1H), 7.05 – 6.97 (m, 2H), 6.90 – 6.85 (m, 1H), 6.80 – 6.72 (m, 2H), 6.63 (dd, J = 1.4, 6.9 Hz, 2H), 6.50 (s, 2H), 6.48 – 6.43 (m, 1H), 5.59 (dd, J = 5.7, 8.0 Hz, 1H), 5.52 – 5.45 (m, 1H), 5.30 (s, 3H), 5.24 (d, J = 1.9 Hz, 1H), 4.64 – 4.55 (m, 1H), 4.00 – 3.92 (m, 1H), 3.87 – 3.80 (m, 9H), 3.77 (s, 2H), 3.70 (s, 4H), 3.38 (d, J = 9.8 Hz, 1H), 2.78 (td, J = 2.9, 13.3 Hz, 1H), 2.66 – 2.52 (m, 1H), 2.49 – 2.33 (m, 1H), 2.32 – 2.24 (m, 1H), 2.15 – 2.06 (m, 1H), 2.01 – 1.94 (m, 1H), 1.90 – 1.77 (m, 2H), 1.71 – 1.51 (m, 9H), 1.37 (dd, J = 1.1, 6.1 Hz, 6H), 1.27 (d, 2H), 1.21 – 1.06 (m, 2H), 1.08 – 0.50 (m, 2H).

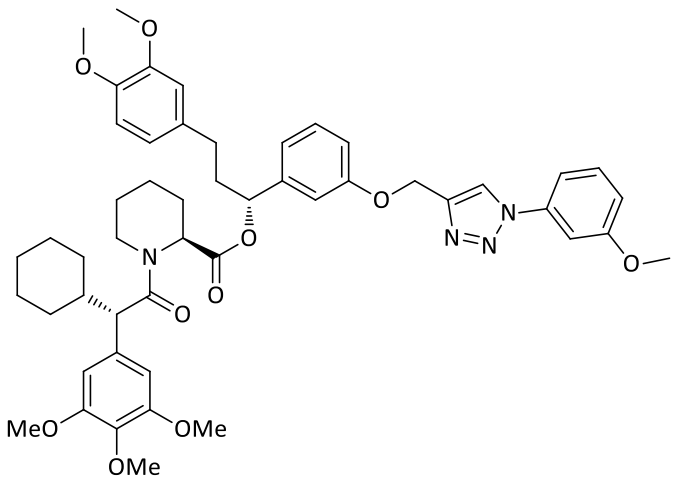
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.43, 170.80, 170.71, 158.45, 158.27, 153.42, 153.21, 149.01, 147.45, 144.66, 144.43, 142.06, 141.81, 137.01, 134.45, 133.80, 133.59, 130.30, 130.20, 130.07, 129.80, 122.42, 121.37, 120.42, 120.27, 119.74, 119.24, 116.70, 114.08, 113.82, 113.47, 111.98, 111.87, 111.56, 111.47, 105.95, 105.48, 75.73, 70.62, 62.19, 62.12, 61.03, 60.91, 56.48, 56.21, 56.08, 56.00, 55.16, 53.56, 52.19, 43.84, 41.56, 41.32, 38.09, 32.94, 31.60, 31.17, 30.82, 26.96, 26.89, 26.74, 26.60, 26.37, 26.32, 26.24, 25.72, 22.08, 21.13, 20.86.

LC-MS (50-100% B, 19 min): t_R (**247**) = 13.58 min, m/z: calculated = 905.46 $[M+H]^+$, found = 905.78 $[M+H]^+$.

HRMS (ESI): calculated = 905.46952 $[M+H]^+$, found = 905.47027 $[M+H]^+$, err [ppm] = 0.83.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**247**) = 14.05 min (98% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-((1-(3-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV728)



Chemical Formula: $C_{50}H_{60}N_4O_{10}$
Exact Mass: 876,43
Molecular Weight: 877,03

248

248 is synthesized according to general procedure 5.9.6. Starting material: **233** (20 mg) and 1-azido-3-methoxybenzene (6 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**248**) = 0.26.

Yield 18 mg (75%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.46 – 7.37 (m, 1H), 7.37 – 7.28 (m, 2H), 7.14 (t, J = 7.9 Hz, 1H), 7.06 – 6.94 (m, 2H), 6.88 (ddd, J = 0.9, 2.6, 8.3 Hz, 1H), 6.76 (d, J = 8.8 Hz, 2H), 6.67 – 6.60 (m, 2H), 6.50 (s, 2H), 6.47 (d, J = 7.9 Hz, 1H), 5.59 (dd, J = 5.7, 7.9 Hz, 1H), 5.48 (d, J = 5.0 Hz, 1H), 5.25 (s, 1H), 3.96 (d, J = 10.9 Hz, 1H), 3.88 (s, 3H), 3.87 – 3.82 (m, 9H), 3.77 (s, 2H), 3.70 (s, 5H), 3.38 (d, J = 9.8 Hz, 1H), 2.78 (t, J = 12.5 Hz, 1H), 2.66 – 2.51 (m, 0H), 2.51 – 2.34 (m, 1H), 2.28 (d, J = 13.9 Hz, 1H), 2.10 (q, J = 10.4, 10.9 Hz, 1H), 1.90 (ddd, J = 8.8, 14.5, 25.9 Hz, 2H), 1.61 (q, J = 7.8, 9.6 Hz, 9H), 1.48 – 1.03 (m, 3H), 0.76 (ddt, J = 12.1, 40.6, 64.2 Hz, 2H).

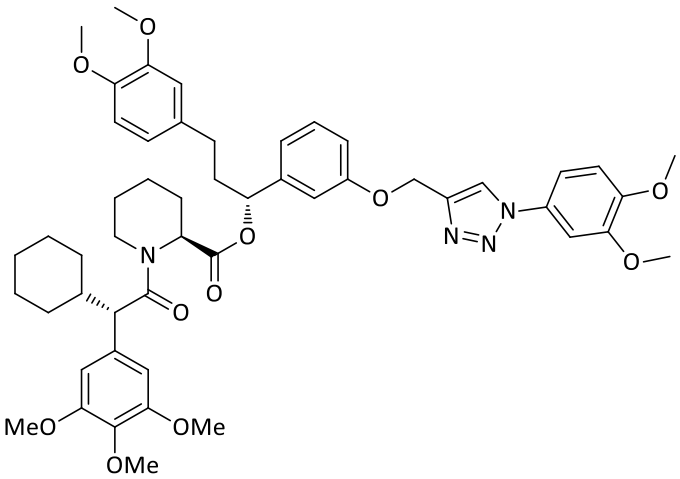
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.43, 170.71, 160.79, 158.24, 153.43, 153.21, 149.01, 147.45, 144.89, 143.04, 142.07, 138.17, 137.02, 136.35, 133.80, 133.58, 130.67, 129.80, 121.30, 120.41, 119.29, 114.89, 114.08, 113.83, 113.45, 112.60, 111.98, 111.57, 111.47, 106.62, 106.55, 105.96, 105.50, 75.71, 62.07, 60.91, 56.49, 56.20, 56.08, 56.04, 55.99, 55.79, 55.16, 52.19, 43.83, 43.32, 41.56, 41.30, 39.62, 38.08, 37.94, 33.15, 32.93, 31.16, 30.81, 26.87, 26.73, 26.36, 26.31, 26.25, 25.71, 21.12.

LC-MS (50-100% B, 19 min): t_R (**248**) = 12.61 min, m/z: calculated = 877.43 $[M+H]^+$, found = 877.66 $[M+H]^+$.

HRMS (ESI): calculated = 877.43822 $[M+H]^+$, found = 877.43869 $[M+H]^+$, err [ppm] = 0.54.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**248**) = 12.64 min (95% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-((1-(3,4-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV704)



Chemical Formula: $C_{51}H_{62}N_4O_{11}$
Exact Mass: 906,44
Molecular Weight: 907,06

249

249 is synthesized according to general procedure 5.9.6. Starting material: **233** (20 mg) and 4-azido-1,2-dimethoxybenzene (7 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**249**) = 0.25.

Yield 24 mg (96%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.37 – 7.33 (m, 1H), 7.21 – 7.08 (m, 2H), 7.06 – 6.98 (m, 1H), 6.93 (d, J = 8.7 Hz, 1H), 6.91 – 6.86 (m, 1H), 6.81 – 6.72 (m, 2H), 6.72 – 6.56 (m, 2H), 6.53 – 6.42 (m, 3H), 5.59 (dd, J = 5.7, 7.9 Hz, 1H), 5.53 – 5.38 (m, 1H), 5.24 (s, 2H), 3.97 – 3.92 (m, 7H), 3.88 – 3.81 (m, 9H), 3.77 (d, J = 1.8 Hz, 3H), 3.70 (s, 5H), 3.38 (d, J = 9.8 Hz, 1H), 2.78 (t, J = 13.0 Hz, 1H), 2.65 – 2.35 (m, 2H), 2.28 (d, J = 13.8 Hz, 1H), 2.18 – 2.02 (m, 1H), 1.94 – 1.73 (m, 1H), 1.60 (q, J = 11.0, 12.9 Hz, 8H), 1.44 – 1.08 (m, 3H), 1.04 – 0.52 (m, 2H).

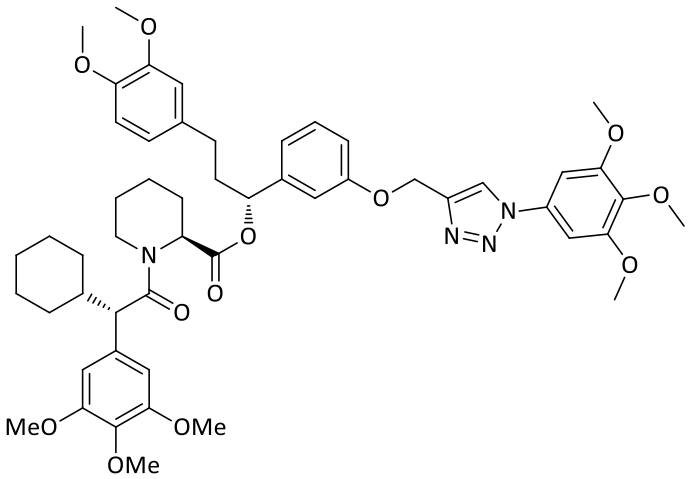
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.42, 170.70, 158.26, 153.18, 149.95, 149.00, 147.45, 144.75, 142.06, 136.99, 133.78, 133.57, 129.80, 121.41, 120.40, 119.24, 114.02, 113.46, 112.68, 111.98, 111.46, 111.37, 105.94, 105.49, 105.20, 75.70, 62.11, 60.89, 56.39, 56.35, 56.19, 56.06, 55.99, 55.15, 52.17, 43.81, 41.54, 38.08, 32.92, 31.16, 30.80, 26.72, 26.32, 25.69, 21.11.

LC-MS (50-100% B, 19 min): t_R (**249**) = 12.10 min, m/z: calculated = 907.44 $[M+H]^+$, found = 907.50 $[M+H]^+$.

HRMS (ESI): calculated = 907.44879 $[M+H]^+$, found = 907.44992 $[M+H]^+$, err [ppm] = 1.25.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 254 nm): t_R (**249**) = 11.57 min (98% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-((1-(3,4,5-trimethoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV666)



Chemical Formula: $C_{52}H_{64}N_4O_{12}$
Exact Mass: 936,45
Molecular Weight: 937,08

250

250 is synthesized according to general procedure 5.9.6. Starting material: **233** (10 mg) and **228** (4 mg). The pure product is obtained as a colorless solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 1/1): R_f (**250**) = 0.42.

Yield 10 mg (77%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.02 – 7.95 (m, 1H), 7.19 (s, 1H), 7.07 (t, J = 7.9 Hz, 1H), 6.94 – 6.88 (m, 2H), 6.86 – 6.80 (m, 1H), 6.76 – 6.63 (m, 2H), 6.65 – 6.54 (m, 2H), 6.46 – 6.34 (m, 3H), 5.52 (dd, J = 5.6, 8.0 Hz, 1H), 5.40 (d, J = 5.5 Hz, 1H), 5.17 (d, J = 3.4 Hz, 1H), 3.86 (s, 6H), 3.82 (s, 3H), 3.80 – 3.74 (m, 9H), 3.71 – 3.69 (m, 3H), 3.63 (s, 4H), 3.31 (d, J = 9.9 Hz, 1H), 2.76 – 2.65 (m, 1H), 2.57 – 2.44 (m, 0H), 2.44 – 2.28 (m, 1H), 2.24 – 2.16 (m, 1H), 2.07 – 1.97 (m, 2H), 1.95 – 1.70 (m, 2H), 1.64 – 1.43 (m, 8H), 1.41 – 1.31 (m, 0H), 1.31 – 1.17 (m, 2H), 1.15 – 1.00 (m, 2H), 0.88 – 0.63 (m, 2H).

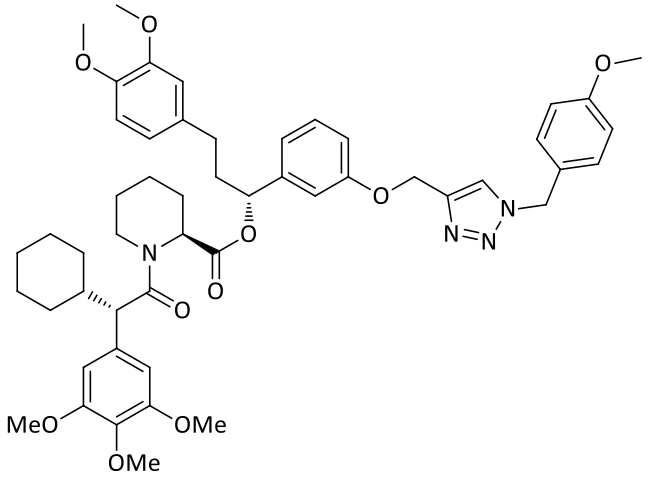
^{13}C-NMR (126 MHz, $CDCl_3$): δ 213.55, 211.82, 199.34, 195.19, 194.54, 194.29, 190.11, 188.56, 185.99, 183.20, 179.70, 178.08, 174.88, 174.65, 174.08, 171.19, 170.93, 162.57, 161.50, 161.36, 160.39, 155.40, 155.07, 154.94, 154.57, 153.08, 152.97, 152.66, 152.56, 147.04, 146.59, 139.90, 139.84, 116.80, 103.28, 103.21, 102.30, 102.12, 102.00, 101.63, 97.73, 97.59, 97.29, 97.17, 97.09, 96.28, 93.29, 84.92, 82.64, 79.18, 74.29, 74.04, 72.70, 72.27, 71.91, 67.99, 67.98, 67.82, 67.47, 67.41, 66.80, 62.28, 62.20, 61.94, 55.45.

LC-MS (50-100% B, 19 min): t_R (**250**) = 12.13 min, m/z: calculated = 937.45 $[M+H]^+$, found = 937.71 $[M+H]^+$.

HRMS (ESI): calculated = 937.45935 $[M+H]^+$, found = 937.45895 $[M+H]^+$, err [ppm] = 0.43.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**250**) = 12.12 min (98% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV702)



Chemical Formula: $C_{51}H_{62}N_4O_{10}$
Exact Mass: 890,45
Molecular Weight: 891,06

251

251 is synthesized according to general procedure 5.9.6. Starting material: **233** (20 mg) and 1-(azidomethyl)-4-methoxybenzene (7 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 1/1, v/v.

TLC (CH/EE, 1/1): R_f (**251**) = 0.30.

Yield 14 mg (58%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.23 (dd, J = 2.4, 8.8 Hz, 2H), 7.10 (t, J = 7.9 Hz, 1H), 7.00 – 6.93 (m, 1H), 6.88 (dd, J = 2.1, 8.7 Hz, 2H), 6.86 – 6.71 (m, 3H), 6.61 (d, J = 1.6 Hz, 1H), 6.49 (s, 2H), 6.47 – 6.41 (m, 1H), 5.56 (dd, J = 5.7, 8.0 Hz, 1H), 5.46 (s, 3H), 5.12 (s, 1H), 3.84 (q, J = 3.3 Hz, 8H), 3.80 (d, J = 9.8 Hz, 5H), 3.76 (s, 2H), 3.69 (s, 5H), 3.37 (d, J = 9.8 Hz, 1H), 2.78 (td, J = 2.8, 13.4 Hz, 1H), 2.63 – 2.49 (m, 1H), 2.49 – 2.32 (m, 2H), 2.32 – 2.22 (m, 1H), 2.14 – 2.02 (m, 2H), 1.98 – 1.91 (m, 1H), 1.91 – 1.76 (m, 2H), 1.72 – 1.61 (m, 2H), 1.55 (d, J = 11.3 Hz, 1H), 1.47 – 1.36 (m, 1H), 1.36 – 1.21 (m, 3H), 1.20 – 1.02 (m, 2H), 0.90 (qd, J = 3.3, 12.5 Hz, 1H), 0.75 (td, J = 9.1, 12.4 Hz, 1H), 0.64 – 0.49 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.44, 170.77, 170.65, 160.12, 158.28, 153.41, 153.18, 149.12, 149.00, 147.64, 147.44, 144.48, 144.23, 142.00, 141.71, 136.98, 134.44, 133.76, 133.59, 133.41, 129.99, 129.86, 129.73, 126.61, 122.58, 120.39, 120.26, 119.66, 119.09, 114.65, 114.21, 114.00, 113.80,

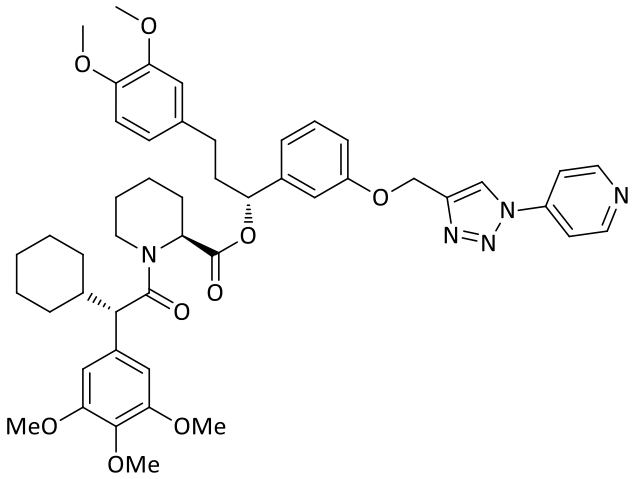
113.44, 111.96, 111.86, 111.55, 111.46, 105.94, 105.45, 75.71, 62.18, 61.02, 60.90, 56.46, 56.19, 56.07, 55.99, 55.83, 55.48, 55.15, 53.93, 52.17, 43.80, 41.53, 41.30, 39.60, 38.11, 37.92, 33.10, 32.94, 31.57, 31.14, 30.81, 30.63, 26.91, 26.73, 26.58, 26.36, 26.31, 26.22, 25.70, 24.49, 21.13, 20.86.

LC-MS (50-100% B, 19 min): t_R (**251**) = 11.98 min, m/z: calculated = 891.45 $[M+H]^+$, found = 891.69 $[M+H]^+$.

HRMS (ESI): calculated = 891.45387 $[M+H]^+$, found = 891.45475 $[M+H]^+$, err [ppm] = 0.98.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**251**) = 11.68 min (97% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-((1-(pyridin-4-yl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV714)



Chemical Formula: $C_{48}H_{57}N_5O_9$
Exact Mass: 847,42
Molecular Weight: 847,99

252

252 is synthesized according to general procedure 5.9.6. Starting material: **233** (20 mg) and 4-azidopyridine (5 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1 + 1% TEA, v/v.

TLC (CH/EE, 2/1 + 1% TEA): R_f (**252**) = 0.25.

Yield 23 mg (quant.).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.82 (s, 2H), 8.25 (s, 1H), 7.77 (s, 2H), 7.14 (t, J = 7.9 Hz, 1H), 7.06 – 6.94 (m, 1H), 6.92 – 6.82 (m, 1H), 6.80 – 6.70 (m, 2H), 6.70 – 6.57 (m, 2H), 6.49 (d, J = 2.6 Hz, 2H), 5.58 (dd, J = 5.6, 8.1 Hz, 1H), 5.52 – 5.40 (m, 1H), 5.26 (d, J = 1.8 Hz, 1H), 3.95 (d, J = 13.9 Hz, 1H), 3.84 (q, J = 2.4 Hz, 9H), 3.77 (s, 3H), 3.69 (s, 5H), 3.38 (d, J = 9.8 Hz, 1H), 2.77 (t, J = 12.8 Hz, 1H), 2.47 (dtq, J = 7.1, 7.8, 14.1, 34.6 Hz, 1H), 2.28 (d, J = 13.0 Hz, 1H), 2.19 – 2.01 (m, 1H), 1.98 – 1.77 (m, 2H), 1.76 – 1.47 (m, 13H), 1.47 – 1.06 (m, 2H), 0.82 (dq, J = 11.0, 45.5 Hz, 1H).

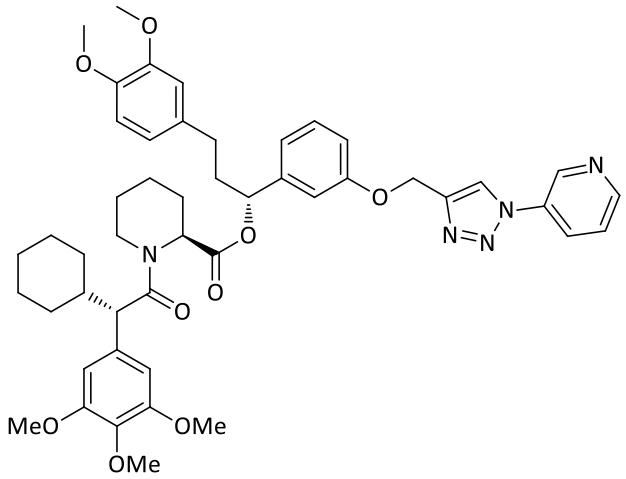
^{13}C-NMR (75 MHz, $CDCl_3$): δ 172.45, 170.74, 158.03, 153.44, 153.17, 151.85, 149.01, 147.47, 145.82, 143.09, 142.17, 136.98, 134.38, 133.77, 133.52, 129.85, 120.56, 120.40, 119.43, 114.07, 113.40, 111.98, 111.47, 105.94, 105.52, 75.68, 61.90, 60.90, 56.49, 56.17, 56.07, 55.99, 55.17, 52.19, 43.81, 41.55, 38.06, 37.93, 32.93, 31.18, 30.80, 26.85, 26.70, 26.34, 25.67, 21.08.

LC-MS (30-100% B, 19 min): t_R (**252**) = 13.08 min, m/z: calculated = 848.42 $[M+H]^+$, found = 848.51 $[M+H]^+$.

HRMS (ESI): calculated = 848.42290 $[M+H]^+$, found = 848.42336 $[M+H]^+$, err [ppm] = 0.53.

RP-HPLC (30 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**252**) = 11.29 min (97% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-((1-(pyridin-3-yl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV712)



Chemical Formula: $C_{48}H_{57}N_5O_9$
Exact Mass: 847,42
Molecular Weight: 847,99

253

253 is synthesized according to general procedure 5.9.6. Starting material: **233** (20 mg) and 3-azidopyridine (5 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1 + 1% TEA, v/v.

TLC (CH/EE, 2/1 + 1% TEA): R_f (**253**) = 0.25.

Yield 15 mg (65%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.10 – 8.88 (m, 1H), 8.71 (dd, J = 1.6, 4.8 Hz, 1H), 8.22 – 8.07 (m, 2H), 7.59 – 7.45 (m, 1H), 7.14 (t, J = 7.9 Hz, 1H), 7.06 – 6.97 (m, 1H), 6.92 – 6.84 (m, 1H), 6.81 – 6.70 (m, 2H), 6.72 – 6.59 (m, 2H), 6.50 (s, 2H), 5.59 (dd, J = 5.6, 8.1 Hz, 1H), 5.51 – 5.43 (m, 1H), 5.27 (s, 1H), 3.95 (d, J = 13.9 Hz, 1H), 3.88 – 3.81 (m, 8H), 3.77 (s, 3H), 3.69 (s, 4H), 3.38 (d, J = 9.8 Hz, 1H), 2.77 (t,

J = 12.8 Hz, 1H), 2.64 – 2.35 (m, 1H), 2.35 – 2.20 (m, 1H), 2.18 – 2.02 (m, 1H), 1.97 – 1.78 (m, 1H), 1.75 – 1.50 (m, 14H), 1.20 (d, J = 36.0 Hz, 3H), 1.03 – 0.49 (m, 1H).

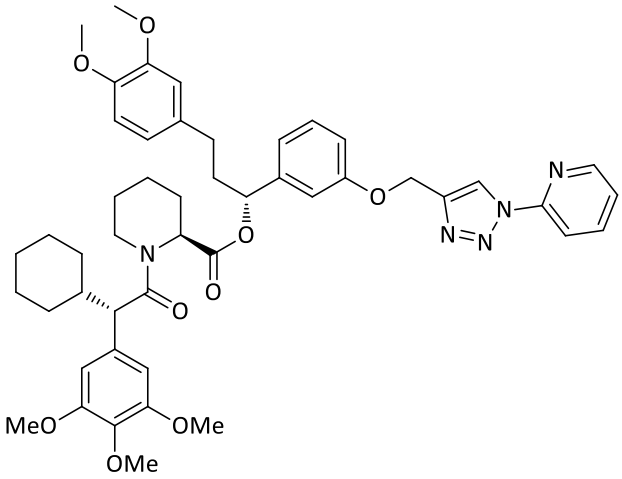
^{13}C-NMR (75 MHz, $CDCl_3$): δ 172.44, 172.37, 170.74, 158.13, 153.44, 153.19, 150.18, 149.02, 147.48, 145.57, 142.16, 141.84, 137.19, 137.01, 133.79, 133.55, 133.37, 129.83, 128.25, 124.37, 121.21, 120.42, 119.37, 114.10, 113.41, 111.99, 111.48, 105.96, 75.69, 61.95, 60.92, 56.50, 56.19, 56.08, 56.00, 55.19, 52.19, 43.82, 41.57, 38.09, 32.94, 31.19, 30.81, 26.87, 26.72, 26.36, 25.70, 21.11.

LC-MS (30-100% B, 19 min): t_R (**253**) = 13.34 min, m/z: calculated = 848.42 $[M+H]^+$, found = 848.42 $[M+H]^+$.

HRMS (ESI): calculated = 848.42290 $[M+H]^+$, found = 848.42363 $[M+H]^+$, err [ppm] = 0.86.

RP-HPLC (30 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**253**) = 12.93 min (98% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-((1-(pyridin-2-yl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV710)



Chemical Formula: $C_{48}H_{57}N_5O_9$
Exact Mass: 847,42
Molecular Weight: 847,99

254

254 is synthesized according to general procedure 5.9.6. Starting material: **233** (20 mg) and 2-azidopyridine (5 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 1/1 + 1% TEA, v/v.

TLC (CH/EE, 1/1 + 1% TEA): R_f (**254**) = 0.30.

Yield 8 mg (35%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.64 (d, J = 0.8 Hz, 1H), 8.48 (ddd, J = 0.9, 1.9, 4.9 Hz, 1H), 8.19 (dt, J = 1.0, 8.3 Hz, 1H), 7.91 (ddt, J = 2.1, 7.5, 8.3 Hz, 1H), 7.37 – 7.31 (m, 1H), 7.13 (t, J = 7.9 Hz, 1H), 7.06 – 6.97 (m, 1H), 6.89 (ddd, J = 0.9, 2.6, 8.2 Hz, 1H), 6.80 (q, J = 1.5 Hz, 1H), 6.77 – 6.74 (m, 1H), 6.72 –

6.63 (m, 1H), 6.62 (s, 1H), 6.51 (s, 1H), 6.44 (d, J = 10.7 Hz, 1H), 5.59 (dd, J = 5.7, 7.9 Hz, 1H), 5.48 (d, J = 5.1 Hz, 1H), 5.27 (d, J = 1.8 Hz, 2H), 3.96 (d, J = 13.7 Hz, 1H), 3.88 – 3.83 (m, 7H), 3.82 (d, J = 1.0 Hz, 2H), 3.77 (s, 2H), 3.71 (s, 5H), 3.38 (d, J = 9.9 Hz, 1H), 2.79 (td, J = 2.9, 13.4 Hz, 1H), 2.65 – 2.51 (m, 1H), 2.41 (dddd, J = 6.0, 9.1, 14.4, 44.6 Hz, 2H), 2.29 (d, J = 12.9 Hz, 1H), 2.10 (q, J = 11.9, 12.5 Hz, 2H), 2.01 – 1.77 (m, 3H), 1.71 – 1.58 (m, 2H), 1.48 – 1.37 (m, 1H), 1.37 – 1.22 (m, 2H), 1.22 – 1.04 (m, 2H), 1.00 – 0.79 (m, 1H), 0.75 (q, J = 10.5, 11.2 Hz, 1H), 0.67 – 0.52 (m, 1H).

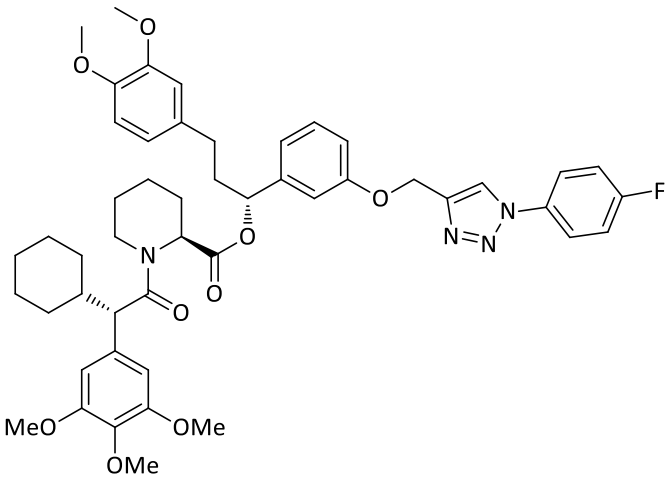
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.43, 170.68, 169.69, 158.27, 153.41, 153.22, 149.26, 149.00, 148.75, 147.43, 144.67, 144.44, 142.05, 139.28, 137.04, 133.80, 133.63, 129.79, 123.86, 123.80, 120.50, 120.41, 120.27, 119.22, 114.09, 113.97, 113.51, 111.97, 111.86, 111.55, 111.47, 105.96, 105.46, 75.72, 62.06, 62.00, 61.03, 60.92, 56.47, 56.22, 56.08, 56.00, 55.16, 52.19, 43.83, 41.56, 41.32, 38.11, 37.96, 33.13, 32.94, 31.58, 31.14, 30.83, 26.90, 26.75, 26.35, 25.72, 24.52, 21.14.

LC-MS (30-100% B, 19 min): t_R (**254**) = 14.29 min, m/z: calculated = 848.42 $[M+H]^+$, found = 848.64 $[M+H]^+$.

HRMS (ESI): calculated = 848.42290 $[M+H]^+$, found = 848.42233 $[M+H]^+$, err [ppm] = 0.67.

RP-HPLC (30 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**254**) = 14.66 min (97% Purity).

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV726)



Chemical Formula: $C_{49}H_{57}FN_4O_9$
Exact Mass: 864,41
Molecular Weight: 865,00

255

255 is synthesized according to general procedure 5.9.6. Starting material: **233** (10 mg) and 1-azido-4-fluorobenzene (6 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**255**) = 0.18.

Yield 24 mg (quant.).

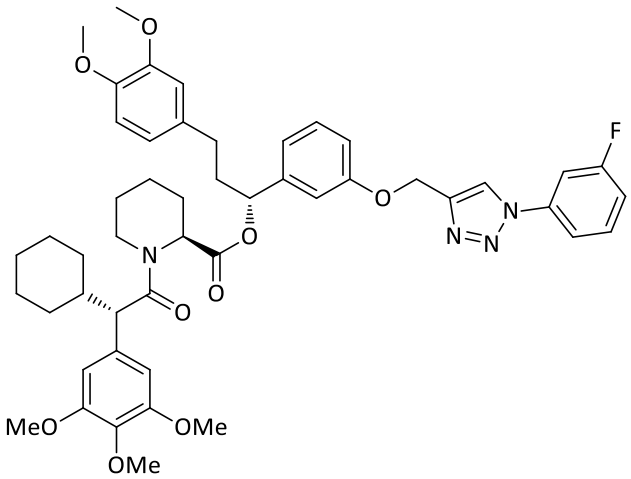
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.77 – 7.66 (m, 2H), 7.24 – 7.18 (m, 2H), 7.13 (t, J = 7.9 Hz, 1H), 6.87 (ddd, J = 1.0, 2.6, 8.2 Hz, 1H), 6.79 – 6.73 (m, 2H), 6.64 – 6.60 (m, 2H), 6.50 (s, 2H), 6.49 – 6.46 (m, 1H), 5.58 (dd, J = 5.6, 8.1 Hz, 1H), 5.50 – 5.45 (m, 1H), 5.25 (d, J = 3.1 Hz, 1H), 3.95 (d, J = 13.7 Hz, 1H), 3.84 – 3.82 (m, 6H), 3.76 (s, 3H), 3.69 (s, 5H), 3.38 (d, J = 9.9 Hz, 1H), 2.84 – 2.73 (m, 1H), 2.65 – 2.51 (m, 1H), 2.51 – 2.34 (m, 2H), 2.32 – 2.24 (m, 1H), 2.17 – 2.04 (m, 2H), 2.01 – 1.78 (m, 3H), 1.71 – 1.46 (m, 5H), 1.48 – 1.37 (m, 1H), 1.36 – 1.04 (m, 6H), 0.99 – 0.69 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): 13C NMR (126 MHz, CDCl3) δ 172.43, 170.70, 158.17, 153.42, 153.18, 149.00, 147.45, 145.09, 142.10, 136.98, 133.77, 133.55, 129.81, 122.76, 122.69, 121.38, 120.40, 120.26, 119.27, 116.95, 116.76, 114.06, 113.42, 111.97, 111.86, 111.45, 105.93, 105.48, 75.69, 62.02, 61.01, 60.89, 56.47, 56.17, 56.10, 56.06, 55.98, 55.16, 52.17, 43.80, 41.54, 38.09, 32.93, 31.17, 30.80, 26.86, 26.71, 26.35, 26.30, 25.68, 21.10.

LC-MS (50-100% B, 19 min): t_R (**255**) = 12.56 min, m/z: calculated = 865.42 $[M+H]^+$, found = 865.59 $[M+H]^+$ (99% Purity).

HRMS (ESI): calculated = 865.41823 $[M+H]^+$, found = 865.41948 $[M+H]^+$, err [ppm] = 1.44.

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-((1-(3-fluorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV724)



Chemical Formula: $C_{49}H_{57}FN_4O_9$
Exact Mass: 864,41
Molecular Weight: 865,00

256

256 is synthesized according to general procedure 5.9.6. Starting material: **233** (20 mg) and 1-azido-3-fluorobenzene (6 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**256**) = 0.30.

Yield 15 mg (62%).

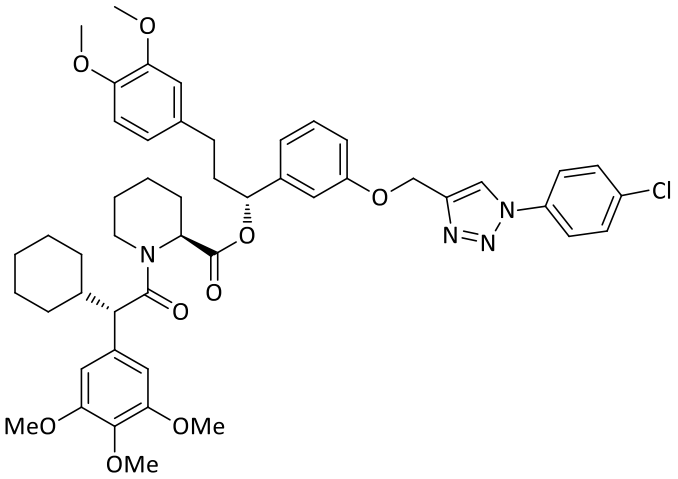
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.16 – 8.05 (m, 1H), 7.60 – 7.46 (m, 3H), 7.20 – 7.10 (m, 2H), 6.90 – 6.84 (m, 1H), 6.79 – 6.73 (m, 2H), 6.66 – 6.60 (m, 2H), 6.52 – 6.49 (m, 2H), 6.49 – 6.46 (m, 1H), 5.59 (dd, J = 5.7, 8.0 Hz, 1H), 5.53 – 5.43 (m, 1H), 5.27 – 5.22 (m, 2H), 3.95 (d, J = 14.2 Hz, 1H), 3.88 – 3.81 (m, 5H), 3.80 – 3.75 (m, 3H), 3.72 – 3.67 (m, 6H), 3.38 (d, J = 9.9 Hz, 1H), 2.77 (td, J = 2.8, 13.2 Hz, 1H), 2.68 – 2.50 (m, 1H), 2.52 – 2.34 (m, 2H), 2.32 – 2.24 (m, 1H), 2.16 – 2.03 (m, 2H), 2.02 – 1.91 (m, 1H), 1.92 – 1.78 (m, 2H), 1.74 – 1.50 (m, 11H), 1.49 – 1.35 (m, 1H), 1.37 – 1.02 (m, 8H), 1.01 – 0.82 (m, 1H), 0.82 – 0.66 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.43, 170.73, 164.23, 162.25, 158.15, 153.44, 153.20, 149.01, 147.46, 145.24, 142.11, 138.24, 137.00, 133.79, 133.56, 131.38, 131.31, 129.82, 121.16, 120.41, 119.34, 116.00, 115.79, 114.35, 114.09, 113.42, 111.98, 111.87, 111.47, 108.58, 108.37, 105.94, 105.50, 75.70, 61.99, 61.02, 60.90, 56.48, 56.19, 56.08, 55.99, 55.86, 55.18, 52.19, 43.83, 41.57, 38.08, 32.94, 31.59, 31.18, 30.81, 26.86, 26.72, 26.36, 26.31, 25.70, 21.11.

LC-MS (50-100% B, 19 min): t_R (**256**) = 12.96 min, m/z: calculated = 865.41 $[M+H]^+$, found = 865.49 $[M+H]^+$ (97% Purity).

HRMS (ESI): calculated = 865.41823 $[M+H]^+$, found = 865.41895 $[M+H]^+$, err [ppm] = 0.83.

(S)-(R)-1-(3-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV720)



Chemical Formula: $C_{49}H_{57}ClN_4O_9$
Exact Mass: 880,38
Molecular Weight: 881,45

257

257 is synthesized according to general procedure 5.9.6. Starting material: **233** (20 mg) and 1-azido-4-chlorobenzene (6 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**257**) = 0.26.

Yield 13 mg (54%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.73 – 7.63 (m, 2H), 7.58 – 7.43 (m, 2H), 7.14 (t, J = 7.9 Hz, 1H), 7.05 – 6.94 (m, 1H), 6.92 – 6.80 (m, 1H), 6.79 – 6.74 (m, 2H), 6.70 – 6.61 (m, 2H), 6.50 (s, 2H), 5.59 (dd, J = 5.7, 8.0 Hz, 1H), 5.47 (d, J = 5.2 Hz, 1H), 5.25 (s, 1H), 3.95 (d, J = 13.4 Hz, 1H), 3.89 – 3.82 (m, 9H), 3.77 (d, J = 1.8 Hz, 3H), 3.69 (s, 4H), 3.38 (d, J = 9.8 Hz, 1H), 2.78 (t, J = 13.0 Hz, 1H), 2.64 – 2.35 (m, 1H), 2.28 (d, J = 13.7 Hz, 1H), 2.19 – 2.02 (m, 0H), 1.96 – 1.77 (m, 1H), 1.61 (d, J = 8.4 Hz, 7H), 1.28 (t, J = 46.3 Hz, 5H), 0.99 – 0.50 (m, 1H).

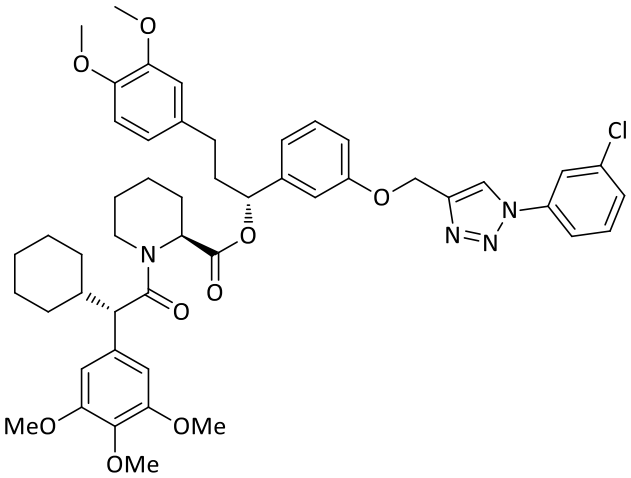
^{13}C-NMR (75 MHz, $CDCl_3$): δ 172.45, 170.72, 158.16, 153.19, 152.62, 142.12, 133.56, 130.09, 129.83, 121.88, 121.13, 120.41, 119.31, 114.09, 113.43, 111.99, 111.47, 105.95, 105.51, 75.71, 60.91, 60.91, 56.19, 56.00, 55.18, 52.19, 43.82, 41.56, 38.10, 32.95, 31.18, 26.36, 25.70.

LC-MS (50-100% B, 19 min): t_R (**257**) = 13.37 min, m/z: calculated = 881.38 $[M+H]^+$, found = 881.71 $[M+H]^+$.

HRMS (ESI): calculated = 881.38868 $[M+H]^+$, found = 881.38898 $[M+H]^+$, err [ppm] = 0.34.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**257**) = 13.55 min (98% Purity).

(S)-(R)-1-(3-((1-(3-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV722)



Chemical Formula: $C_{49}H_{57}ClN_4O_9$
Exact Mass: 880,38
Molecular Weight: 881,45

258

258 is synthesized according to general procedure 5.9.6. Starting material: **233** (20 mg) and 1-azido-3-chlorobenzene (6 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**258**) = 0.22.

Yield 24 mg (quant.).

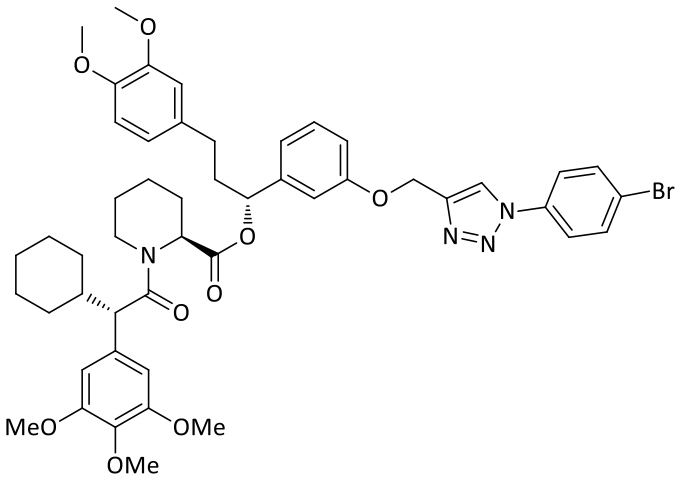
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.82 (t, J = 1.9 Hz, 1H), 7.69 – 7.64 (m, 1H), 7.48 – 7.39 (m, 2H), 7.13 (t, J = 7.9 Hz, 1H), 7.05 – 6.98 (m, 1H), 6.87 (ddd, J = 0.9, 2.6, 8.2 Hz, 1H), 6.78 – 6.74 (m, 2H), 6.65 – 6.60 (m, 2H), 6.50 (s, 1H), 6.49 – 6.46 (m, 1H), 5.61 – 5.54 (m, 1H), 5.50 – 5.46 (m, 1H), 5.24 (d, J = 4.0 Hz, 1H), 3.95 (d, J = 14.3 Hz, 1H), 3.87 – 3.81 (m, 10H), 3.77 (s, 3H), 3.70 (s, 4H), 3.38 (d, J = 9.9 Hz, 1H), 2.77 (td, J = 2.8, 13.4 Hz, 1H), 2.64 – 2.51 (m, 1H), 2.51 – 2.34 (m, 2H), 2.33 – 2.22 (m, 1H), 2.17 – 2.02 (m, 2H), 2.02 – 1.91 (m, 1H), 1.91 – 1.80 (m, 2H), 1.72 – 1.50 (m, 5H), 1.48 – 1.36 (m, 1H), 1.36 – 1.22 (m, 2H), 1.21 – 1.04 (m, 2H), 1.04 – 0.82 (m, 1H), 0.82 – 0.69 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.43, 170.72, 158.15, 153.43, 153.19, 149.00, 147.45, 145.26, 142.11, 137.98, 136.99, 135.76, 133.79, 133.56, 133.37, 130.98, 130.10, 129.81, 129.11, 129.03, 121.16, 120.95, 120.40, 120.26, 119.81, 119.33, 118.66, 114.34, 114.09, 113.40, 111.97, 111.46, 105.94, 105.50, 75.69, 62.09, 61.98, 61.02, 60.91, 56.49, 56.19, 56.07, 55.99, 55.86, 55.17, 52.19, 43.82, 41.57, 41.28, 38.09, 37.94, 33.17, 32.93, 31.59, 31.17, 30.80, 30.65, 26.87, 26.72, 26.36, 26.31, 25.69, 24.50, 21.11, 20.81.

LC-MS (50-100% B, 19 min): t_R (**258**) = 13.43 min, m/z: calculated = 881.38 $[M+H]^+$, found = 881.51 $[M+H]^+$ (94% Purity).

HRMS (ESI): calculated = 881.38868 $[M+H]^+$, found = 881.38941 $[M+H]^+$, err [ppm] = 0.82.

(S)-(R)-1-(3-((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV716)



Chemical Formula: $C_{49}H_{57}BrN_4O_9$
Exact Mass: 924,33
Molecular Weight: 925,90

259

259 is synthesized according to general procedure 5.9.6. Starting material: **233** (20 mg) and 1-azido-4-bromobenzene (8 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**259**) = 0.30.

Yield 25 mg (quant.).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.26 (s, 2H), 6.87 (s, 1H), 6.75 (t, J = 7.9 Hz, 1H), 6.68 – 6.56 (m, 1H), 6.48 (dd, J = 2.5, 7.9 Hz, 1H), 6.42 – 6.32 (m, 2H), 6.31 – 6.19 (m, 2H), 6.11 (s, 2H), 6.12 – 6.01 (m, 1H), 5.20 (dd, J = 5.6, 8.0 Hz, 1H), 5.13 – 5.04 (m, 1H), 4.86 (s, 1H), 3.56 (d, J = 13.4 Hz, 1H), 3.50 – 3.41 (m, 10H), 3.38 (s, 3H), 3.31 (s, 5H), 2.99 (d, J = 9.8 Hz, 1H), 2.39 (t, J = 12.4 Hz, 1H), 2.28 – 1.94 (m, 1H), 1.98 – 1.82 (m, 1H), 1.80 – 1.62 (m, 1H), 1.61 – 1.35 (m, 2H), 1.35 – 1.11 (m, 7H), 1.09 – 0.62 (m, 5H), 0.62 – 0.10 (m, 1H).

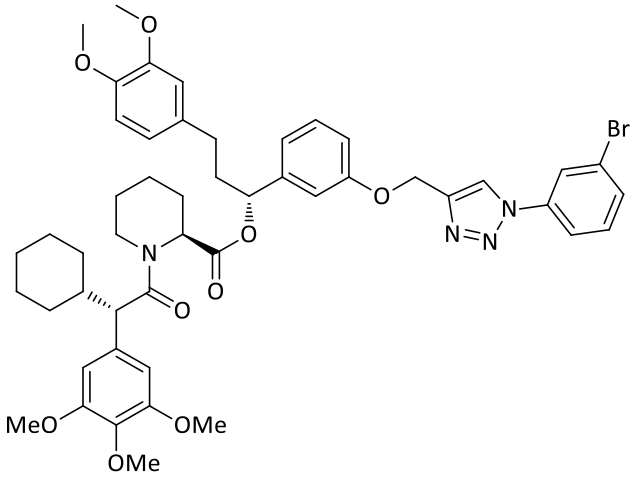
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.44, 170.70, 158.14, 153.42, 153.17, 149.00, 147.46, 145.25, 142.10, 136.98, 136.09, 134.40, 133.77, 133.55, 133.04, 129.81, 122.63, 122.09, 121.05, 120.40, 119.31, 114.08, 113.41, 111.97, 111.87, 111.56, 111.46, 105.94, 105.49, 75.69, 62.00, 61.02, 60.89, 56.48, 56.18, 56.07, 55.99, 55.17, 52.18, 43.81, 41.55, 38.09, 32.94, 31.17, 30.80, 26.87, 26.72, 26.35, 25.68, 21.11.

LC-MS (50-100% B, 19 min): t_R (**259**) = 13.64 min, m/z: calculated = 925.34 $[M+H]^+$, found = 925.60 $[M+H]^+$.

HRMS (ESI): calculated = 925.33817 $[M+H]^+$, found = 925.33817 $[M+H]^+$, err [ppm] = 0.0.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**259**) = 13.83 min (95% Purity).

(S)-(R)-1-(3-((1-(3-bromophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV718)



Chemical Formula: $C_{49}H_{57}BrN_4O_9$
Exact Mass: 924,33
Molecular Weight: 925,90

260

260 is synthesized according to general procedure 5.9.6. Starting material: **233** (20 mg) and 1-azido-3-bromobenzene (8 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**260**) = 0.25.

Yield 21 mg (83%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.97 (t, J = 2.0 Hz, 1H), 7.72 – 7.66 (m, 1H), 7.59 – 7.53 (m, 1H), 7.44 – 7.35 (m, 1H), 7.14 (t, J = 7.9 Hz, 1H), 7.05 – 6.95 (m, 1H), 6.89 – 6.84 (m, 1H), 6.78 – 6.74 (m, 2H), 6.66 – 6.60 (m, 2H), 6.50 (s, 1H), 6.49 – 6.45 (m, 1H), 5.59 (dd, J = 5.6, 8.1 Hz, 1H), 5.49 – 5.45 (m, 1H), 5.29 (d, J = 1.9 Hz, 0H), 5.24 (d, J = 4.0 Hz, 1H), 4.00 – 3.92 (m, 1H), 3.87 – 3.81 (m, 9H), 3.77 (s, 2H), 3.70 (s, 4H), 3.38 (d, J = 9.9 Hz, 1H), 2.77 (td, J = 2.8, 13.3 Hz, 1H), 2.66 – 2.52 (m, 1H), 2.51 – 2.36 (m, 1H), 2.32 – 2.22 (m, 1H), 2.15 – 2.03 (m, 1H), 2.02 – 1.92 (m, 1H), 1.92 – 1.80 (m, 2H), 1.73 – 1.50 (m, 7H), 1.48 – 1.37 (m, 1H), 1.37 – 1.22 (m, 2H), 1.21 – 1.05 (m, 2H), 0.95 – 0.84 (m, 1H), 0.83 – 0.68 (m, 1H).

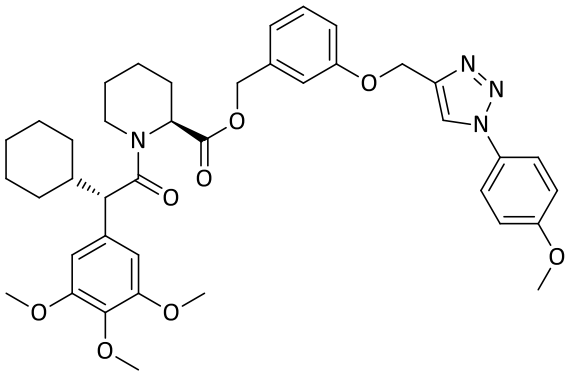
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.43, 170.72, 158.15, 153.43, 153.19, 149.01, 147.46, 145.27, 142.11, 141.85, 138.06, 137.00, 134.41, 133.79, 133.56, 133.38, 131.99, 131.21, 130.10, 129.82, 123.79, 123.48, 121.15, 120.41, 119.82, 119.34, 119.17, 114.36, 114.10, 113.82, 113.39, 111.97, 111.47, 105.94, 105.51, 75.69, 62.09, 61.99, 61.03, 60.92, 56.50, 56.19, 56.08, 55.99, 55.86, 55.18, 52.19,

43.82, 41.57, 41.28, 38.09, 33.18, 32.94, 31.59, 31.17, 30.81, 30.66, 26.88, 26.72, 26.60, 26.37, 26.31, 26.24, 25.70, 21.11, 20.82.

LC-MS (50-100% B, 19 min): t_R (**260**) = 13.61 min, m/z: calculated = 925.34 $[M+H]^+$, found = 925.44 $[M+H]^+$ (97% purity).

HRMS (ESI): calculated = 925.33817 $[M+H]^+$, found = 925.33864 $[M+H]^+$, err [ppm] = 0.51.

(S)-3-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)benzyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV778)



Chemical Formula: $C_{40}H_{48}N_4O_8$
Exact Mass: 712,35
Molecular Weight: 712,83

261

261 is synthesized according to general procedure 5.9.6. Starting material: **263** (12 mg) and 1-azido-4-fluorobenzene (5 mg). The pure product is obtained as a white solid.

prep-HPLC (80 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**261**).

Yield 20 mg (63%).

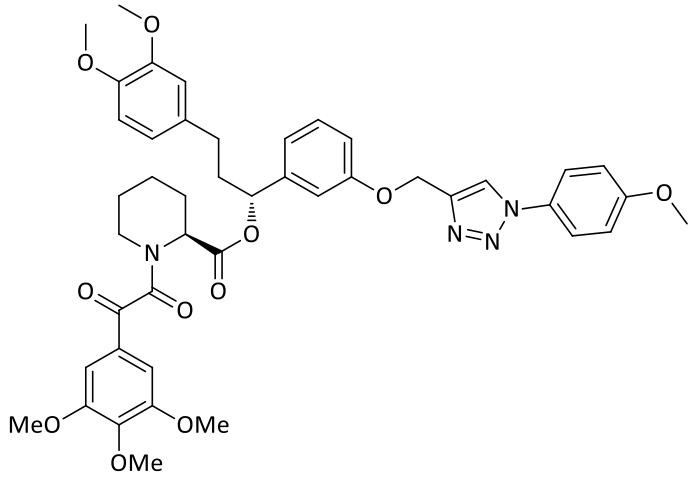
^{1}H-NMR (500 MHz, DMSO-d_6): δ 8.05 – 7.97 (m, 1H), 7.64 – 7.53 (m, 2H), 7.19 (s, 1H), 7.15 (t, J = 7.9 Hz, 1H), 7.00 – 6.91 (m, 3H), 6.76 – 6.66 (m, 1H), 6.48 – 6.24 (m, 2H), 5.38 – 5.30 (m, 1H), 5.29 – 5.11 (m, 3H), 5.01 (d, J = 12.4 Hz, 1H), 4.86 (d, J = 12.4 Hz, 1H), 3.91 (d, J = 14.3 Hz, 1H), 3.81 (s, 3H), 3.78 – 3.74 (m, 6H), 3.71 (s, 3H), 3.34 (d, J = 9.8 Hz, 1H), 2.87 (td, J = 2.9, 13.4 Hz, 1H), 2.72 (s, 2H), 2.22 (d, J = 13.7 Hz, 1H), 2.01 – 1.95 (m, 1H), 1.81 – 1.74 (m, 1H), 1.66 – 1.54 (m, 5H), 1.54 – 1.44 (m, 1H), 1.30 – 1.17 (m, 2H), 1.14 – 0.98 (m, 1H), 0.88 – 0.78 (m, 1H), 0.78 – 0.61 (m, 1H).

^{13}C-NMR (126 MHz, DMSO-d_6): δ 174.19, 170.54, 160.65, 159.30, 158.33, 158.11, 153.14, 137.42, 136.86, 133.66, 132.89, 130.21, 130.00, 122.60, 121.97, 121.16, 115.13, 114.60, 114.40, 105.89, 105.26, 67.48, 66.64, 61.24, 61.01, 56.42, 56.24, 55.85, 55.42, 53.12, 44.28, 41.10, 40.61, 39.38, 32.90, 30.83, 30.64, 26.89, 26.59, 26.24, 26.11, 25.42, 24.33, 22.90, 20.88, 20.61.

LC-MS (50-100% B, 19 min): t_R (**261**) = 10.86 min, m/z: calculated = 713.35 $[M+H]^+$, found = 713.54 $[M+H]^+$.

HRMS (ESI): calculated = 713.35449 $[M+H]^+$, found = 713.35490 $[M+H]^+$, err [ppm] = 0.57.

(S)-(R)-3-(3,4-dimethoxyphenyl)-1-(3-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)propyl 1-(2-oxo-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV664)



Chemical Formula: $C_{44}H_{48}N_4O_{11}$
Exact Mass: 808,33
Molecular Weight: 808,87

262

262 is synthesized according to general procedure 5.9.6. Starting material: **232** (20 mg) and 4-azidoanisole (7 mg). The pure product is obtained as a colorless solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**262**) = 0.25.

Yield 20 mg (82%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.64 – 7.60 (m, 2H), 7.37 – 7.28 (m, 2H), 7.12 – 7.03 (m, 1H), 7.03 – 6.95 (m, 4H), 6.87 – 6.80 (m, 1H), 6.75 – 6.66 (m, 2H), 5.77 (dd, J = 5.6, 8.0 Hz, 1H), 5.45 (d, J = 5.8 Hz, 1H), 5.32 (s, 2H), 5.26 – 5.17 (m, 0H), 3.93 (s, 2H), 3.89 – 3.87 (m, 9H), 3.81 (s, 5H), 3.55 – 3.47 (m, 1H), 3.34 – 3.26 (m, 1H), 2.70 – 2.55 (m, 2H), 2.48 (d, J = 13.6 Hz, 1H), 2.36 – 2.26 (m, 1H), 2.21 – 2.10 (m, 1H), 2.07 (s, 1H), 1.92 – 1.83 (m, 2H), 1.71 – 1.53 (m, 3H), 1.48 – 1.38 (m, 1H).

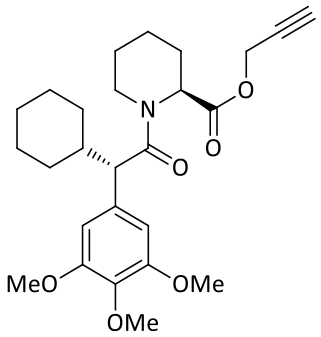
^{13}C-NMR (126 MHz, $CDCl_3$): δ 190.98, 170.11, 167.98, 160.01, 158.63, 153.61, 149.12, 147.61, 144.65, 144.08, 141.72, 133.50, 130.54, 129.90, 128.17, 122.34, 121.32, 120.29, 119.44, 114.95, 114.91, 114.41, 113.18, 111.88, 111.52, 107.10, 62.25, 61.09, 60.52, 56.43, 56.26, 56.10, 56.03, 55.75, 51.96, 44.36, 38.30, 31.51, 26.54, 24.94, 21.39, 14.35.

LC-MS (50-100% B, 19 min): t_R (**262**) = 10.33 min, m/z: calculated = 809.33 $[M+H]^+$, found = 809.52 $[M+H]^+$.

HRMS (ESI): calculated = 809.33923 $[M+H]^+$, found = 809.33952 $[M+H]^+$, err [ppm] = 0.36.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**262**) = 9.76 min (99% Purity).

(S)-prop-2-yn-1-yl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV562/AV564/AV575/AV577/AV698/AV740)



Chemical Formula: $C_{26}H_{35}NO_6$
Exact Mass: 457,25
Molecular Weight: 457,56

263

77 (20 mg, 0.05 mmol, 1.0 eq) is dissolved in 5 mL dry MeCN. DIPEA (9 µL, 0.05 mmol, 1.0 eq) and 80 wt% propargyl bromide in toluene (6 µL, 0.05 mmol, 1.0 eq) are added. The mixture is stirred overnight at room temperature. After complete conversion, the solvent is removed and the crude product filtered through a silica column (CH/EE, 4/1). The pure product **263** is obtained as a colorless oil.

TLC (CH/EE, 4/1): R_f (**263**) = 0.70.

Yield 19 mg (90%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.45 (d, *J* = 0.9 Hz, 2H), 5.39 – 5.30 (m, 1H), 4.83 – 4.75 (m, 1H), 4.61 – 4.49 (m, 2H), 3.96 – 3.87 (m, 1H), 3.84 (s, 6H), 3.83 (s, 3H), 3.37 (d, *J* = 9.6 Hz, 0.7H), 3.12 (d, *J* = 9.7 Hz, 0.3H), 2.94 (td, *J* = 3.1, 13.2 Hz, 0.7H), 2.63 (td, *J* = 3.0, 13.3 Hz, 0.3H), 2.51 (td, *J* = 0.9, 2.5 Hz, 0.3H), 2.38 (td, *J* = 0.9, 2.4 Hz, 0.7H), 2.25 (d, *J* = 13.9 Hz, 1H), 2.13 – 2.03 (m, 1H), 1.93 (d, *J* = 13.0 Hz, 0.3H), 1.88 (d, *J* = 12.6 Hz, 0.7H), 1.75 – 1.51 (m, 9H), 1.33 (m, 2H), 1.27 – 1.08 (m, 2H), 0.99 – 0.67 (m, 2H).

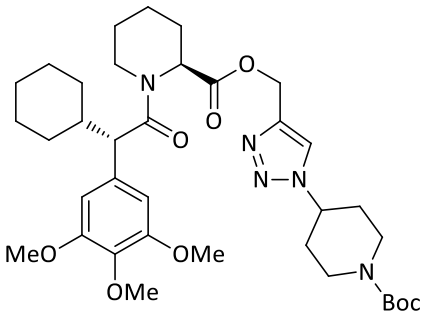
^{13}C-NMR (126 MHz, $CDCl_3$) δ 172.83, 170.68, 153.46, 153.09, 136.95, 134.40, 133.40, 106.03, 105.39, 75.59, 75.00, 60.97, 56.47, 56.33, 55.92, 55.70, 55.38, 52.95, 52.42, 52.31, 43.80, 41.26, 39.62, 33.00, 30.89, 30.79, 27.07, 26.96, 26.90, 26.74, 26.41, 26.38, 26.28, 25.57, 24.52, 21.10, 20.88.

LC-MS (50-100% B, 19 min): t_R (**263**) = 8.37 min, m/z: calculated = 458.25 $[M+H]^+$, found = 458.46 $[M+H]^+$.

HRMS (ESI): calculated = 458.2535 $[M+H]^+$, found = 458.2537 $[M+H]^+$, err [ppm] = 0.39.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 254 nm): t_R (**263**) = 7.90 min (97% Purity).

tert-butyl 4-(4-(((S)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-1H-1,2,3-triazol-1-yl)piperidine-1-carboxylate (AV484)



Chemical Formula: $C_{36}H_{53}N_5O_8$
Exact Mass: 683,39
Molecular Weight: 683,83

264

264 is synthesized according to general procedure 5.9.6. Starting material: **263** (30 mg) and *tert*-butyl 4-azidopiperidine-1-carboxylate (22 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 1/1, v/v.

TLC (CH/EE, 1/1): R_f (**264**) = 0.21.

Yield 27 mg (60%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.35 (s, 1H), 6.45 (s, 2H), 5.34 – 5.28 (m, 2H), 5.23 (d, J = 12.9 Hz, 1H), 5.05 (d, J = 12.9 Hz, 1H), 4.67 – 4.48 (m, 1H), 4.25 (s, 2H), 3.90 – 3.85 (m, 1H), 3.83 (s, 2H), 3.81 (s, 5H), 3.36 (d, J = 9.6 Hz, 1H), 3.11 – 3.03 (m, 1H), 2.99 – 2.85 (m, 3H), 2.25 – 2.01 (m, 4H), 2.01 – 1.89 (m, 2H), 1.88 – 1.77 (m, 1H), 1.72 – 1.52 (m, 6H), 1.47 (s, 9H), 1.37 – 1.04 (m, 3H), 0.93 – 0.60 (m, 4H).

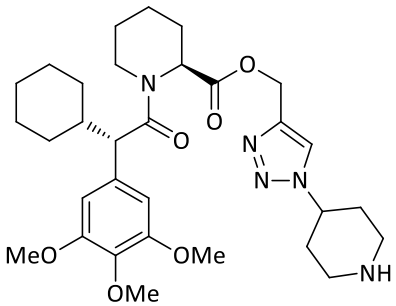
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.89, 172.29, 171.25, 154.63, 153.44, 153.07, 142.64, 142.31, 137.10, 136.84, 134.34, 133.63, 121.71, 121.48, 106.00, 105.36, 80.40, 80.23, 61.02, 60.95, 58.76, 58.53, 58.35, 57.73, 56.47, 56.29, 55.92, 55.56, 55.26, 52.55, 43.80, 41.40, 39.61, 33.07, 32.96, 32.55, 32.44, 30.88, 30.73, 29.84, 28.55, 26.96, 26.71, 26.40, 26.37, 25.54, 24.53, 21.06, 20.91.

LC-MS (50-100% B, 19 min): t_R (**264**) = 9.45 min, m/z: calculated = 684.40 $[M+H]^+$, found = 684.63 $[M+H]^+$.

HRMS (ESI): calculated = 684.39669 $[M+H]^+$, found = 684.39716 $[M+H]^+$, err [ppm] = 0.68.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**264**) = 10.33 min (98% Purity).

(S)-1-(piperidin-4-yl)-1H-1,2,3-triazol-4-yl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV488)



Chemical Formula: $C_{31}H_{45}N_5O_6$
Exact Mass: 583,34
Molecular Weight: 583,72

265

264 (5 mg, 0.01 mmol) is dissolved in 1.5 mL DCM/TFA - 2/1. After stirring for 30 min at r.t. the solvent is evaporated under airstream. The crude is purified by silica column chromatography (DCM + 3% MeOH + 2% TEA) and preparative HPLC and **265** obtained as a colorless solid.

prep-HPLC (30 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**265**) = 7.60 min.

TLC (DCM + 3% MeOH + 2% TEA): R_f (**265**) = 0.25.

Yield 6 mg (47%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.03 (s, 1H), 6.53 (s, 2H), 5.45 – 5.39 (m, 1H), 5.35 – 5.24 (m, 1H), 5.03 (d, J = 13.1 Hz, 1H), 4.70 – 4.61 (m, 1H), 3.95 (d, 1H), 3.83 (s, 9H), 3.64 – 3.53 (m, 2H), 3.39 (d, J = 9.8 Hz, 1H), 3.23 (s, 2H), 2.88 (ddd, J = 2.8, 12.9, 15.2 Hz, 1H), 2.41 – 2.24 (m, 3H), 2.25 – 1.98 (m, 6H), 1.85 (d, J = 12.6 Hz, 1H), 1.78 – 1.52 (m, 7H), 1.51 – 1.39 (m, 1H), 1.39 – 1.24 (m, 3H), 1.23 – 1.05 (m, 2H), 0.97 – 0.85 (m, 1H), 0.82 – 0.63 (m, 1H).

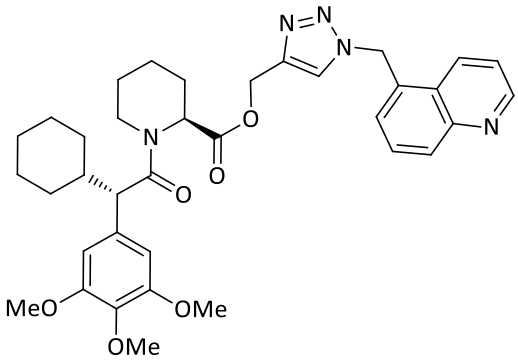
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.62, 171.20, 153.45, 152.98, 136.13, 134.69, 121.14, 105.92, 105.37, 61.17, 58.76, 56.34, 54.93, 54.70, 52.50, 44.03, 42.62, 41.70, 32.85, 30.88, 29.13, 28.90, 26.92, 26.65, 26.31, 26.28, 25.64, 21.08.

LC-MS (30-100% B, 19 min): t_R (**265**) = 4.95 min, m/z: calculated = 584.34 $[M+H]^+$,
found = 584.64 $[M+H]^+$.

HRMS (ESI): calculated = 584.34426 $[M+H]^+$, found = 584.34466 $[M+H]^+$, err [ppm] = 0.68.

RP-HPLC (30 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**265**) = 6.84 min (97% Purity).

(S)-1-(quinolin-5-ylmethyl)-1H-1,2,3-triazol-4-yl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV375)



Chemical Formula: $C_{36}H_{43}N_5O_6$
Exact Mass: 641,32
Molecular Weight: 641,76

266

266 is synthesized according to general procedure 5.9.6. Starting material: **263** (30 mg) and 8-(azidomethyl)quinoline (36 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 1/2, v/v.

TLC (CH/EE, 1/2): R_f (**266**) = 0.44.

Yield 35 mg (84%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.24 – 9.16 (m, 1H), 8.53 – 8.42 (m, 1H), 7.99 (d, 1H), 7.83 – 7.81 (m, 1H), 7.80 (s, 1H), 7.71 – 7.66 (m, 2H), 6.44 (s, 2H), 6.32 – 6.21 (m, 2H), 5.35 – 5.30 (m, 1H), 5.21 – 5.02 (m, 2H), 3.93 (d, J = 14.1 Hz, 1H), 3.84 – 3.79 (m, 9H), 3.39 (d, J = 9.8 Hz, 1H), 2.96 (td, J = 2.9, 13.2 Hz, 1H), 2.25 – 2.19 (m, 1H), 2.10 – 1.97 (m, 2H), 1.82 (d, J = 12.5 Hz, 1H), 1.74 – 1.53 (m, 5H), 1.53 – 1.37 (m, 1H), 1.35 – 1.24 (m, 1H), 1.24 – 0.98 (m, 2H), 0.95 – 0.83 (m, 1H), 0.80 – 0.71 (m, 1H), 0.70 – 0.53 (m, 1H).

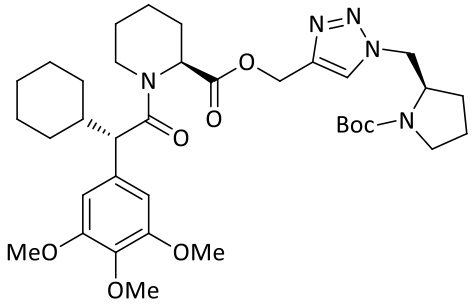
^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.63, 173.25, 170.69, 160.07, 159.75, 153.48, 153.06, 149.36, 148.86, 142.24, 142.12, 140.84, 139.97, 136.79, 133.94, 133.30, 133.23, 132.92, 130.82, 130.60, 129.96, 129.78, 129.12, 128.10, 127.79, 125.60, 125.09, 122.06, 121.96, 105.87, 105.23, 61.00, 57.89, 57.60, 56.38, 56.24, 56.12, 55.41, 55.24, 52.78, 50.29, 50.13, 44.04, 41.19, 41.12, 40.10, 32.86, 30.85, 30.54, 26.89, 26.76, 26.64, 26.56, 26.31, 26.22, 26.06, 25.45, 24.42, 20.88, 20.71.

LC-MS (50-100% B, 19 min): t_R (**266**) = 8.56 min, m/z: calculated = 642.32 $[M+H]^+$, found = 642.64 $[M+H]^+$.

HRMS (ESI): calculated = 642.32861 $[M+H]^+$, found = 642.32917 $[M+H]^+$, err [ppm] = 0.86.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**266**) = 7.56 min (98% Purity).

(S)-(R)-1-(3-((1-(((S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV371)



Chemical Formula: $C_{36}H_{53}N_5O_8$
Exact Mass: 683,39
Molecular Weight: 683,83

267

267 is synthesized according to general procedure 5.9.6. Reactants: **263** (30 mg) and (R)-2-azidoemthyl-1-boc-pyrrolidine (45 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/3, v/v.

TLC (CH/EE, 2/3): R_f (**267**) = 0.30.

Yield 12 mg (27%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.64 – 7.32 (m, 1H), 6.45 (d, J = 5.1 Hz, 2H), 5.36 – 5.29 (m, 2H), 5.13 (q, J = 13.5, 14.0 Hz, 1H), 4.56 (dd, J = 14.7, 29.1 Hz, 3H), 4.10 (dp, J = 4.3, 10.4 Hz, 1H), 3.88 (d, J = 15.5 Hz, 2H), 3.83 (d, J = 2.5 Hz, 9H), 3.36 (d, J = 9.5 Hz, 1H), 3.32 – 3.06 (m, 1H), 3.03 – 2.90 (m, 1H), 2.24 – 2.14 (m, 1H), 2.13 – 1.99 (m, 1H), 1.98 – 1.79 (m, 2H), 1.74 – 1.55 (m, 9H), 1.49 (s, 9H), 1.37 – 1.01 (m, 4H), 0.99 – 0.61 (m, 3H).

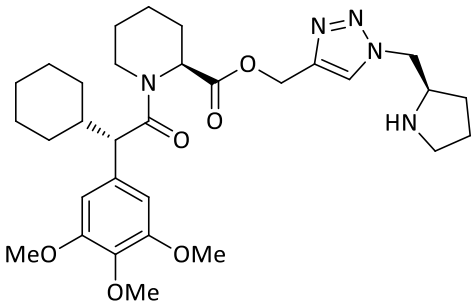
^{13}C-NMR (126 MHz, $CDCl_3$):) δ 172.93, 172.24, 171.16, 167.91, 153.43, 153.06, 142.86, 136.93, 133.53, 124.45, 106.02, 105.36, 61.03, 60.98, 58.13, 57.22, 56.47, 56.33, 55.95, 55.59, 55.27, 52.50, 47.17, 43.76, 41.39, 39.58, 33.03, 32.97, 30.91, 30.73, 28.64, 27.04, 26.96, 26.73, 26.41, 25.57, 24.53, 23.52, 21.13, 20.94.

LC-MS (50-100% B, 19 min): t_R (**267**) = 9.80 min, m/z: calculated = 684.39 $[M+H]^+$, found = 684.33 $[M+H]^+$.

HRMS (ESI): calculated = 628.33409 $[M+H]^+$, found = 628.33449 $[M+H]^+$, err [ppm] = 0.64.

RP-HPLC (30 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**267**) = 15.12 min (98% Purity).

(S)-1-((S)-pyrrolidin-2-ylmethyl)-1H-1,2,3-triazol-4-yl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV473)



Chemical Formula: $C_{31}H_{45}N_5O_6$
Exact Mass: 583,34
Molecular Weight: 583,72

268

267 (5 mg) is dissolved in 1 mL dry DCM and 0.5 mL TFA added. The reaction is stirred at RT for 30 min. The solvent is evaporated under airstream. The crude product is purified by silica column chromatography (DCM + 1% MeOH + 1% TEA). The pure product is obtained as a white solid.

TLC (DCM + 1% MeOH + 1% TEA**):** R_f (**268**) = 0.25.

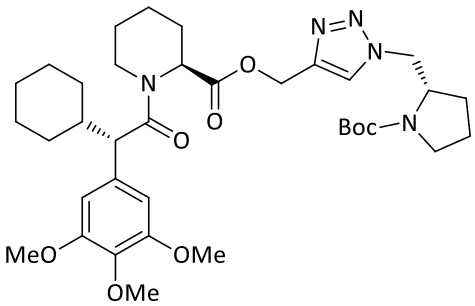
Yield 4 mg (93%).

LC-MS (30-100% B, 19 min): t_R (**268**) = 4.65 min, m/z: calculated = 584.34 $[M+H]^+$, found = 584.70 $[M+H]^+$.

HRMS (ESI): calculated = 584.34426 $[M+H]^+$, found = 584.34453 $[M+H]^+$, err [ppm] = 0.27.

RP-HPLC (0 – 100% B, 1.5 mL/min, 20 min, 220nm): t_R (**268**) = 12.51 min (95% Purity).

(S)-1-(((R)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl)methyl)-1H-1,2,3-triazol-4-yl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV580)



Chemical Formula: $C_{36}H_{53}N_5O_8$
Exact Mass: 683,39
Molecular Weight: 683,83

269

269 is synthesized according to general procedure 5.9.6. Starting material: **263** (10 mg) and (R)-2-azidomethyl-1-boc-pyrrolidine (7 mg). The pure product is obtained as a white solid.

prep-HPLC (50 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**269**) = 7.71 min.

Yield 10 mg (67%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.55 – 7.36 (m, 1H), 6.44 (s, 2H), 5.37 – 5.28 (m, 1H), 5.22 – 5.06 (m, 2H), 4.65 – 4.49 (m, 2H), 4.10 (s, 1H), 3.88 (d, J = 14.2 Hz, 1H), 3.84 – 3.82 (m, 9H), 3.36 (d, J = 9.6 Hz, 1H), 3.31 – 3.11 (m, 1H), 2.98 (t, J = 13.2 Hz, 1H), 2.29 (s, 6H), 2.20 (d, J = 13.8 Hz, 1H), 2.14 – 2.01 (m, 2H), 1.95 – 1.79 (m, 2H), 1.74 – 1.57 (m, 5H), 1.49 (s, 9H), 1.38 – 1.28 (m, 1H), 1.30 – 1.02 (m, 2H), 0.98 – 0.70 (m, 2H), 0.70 – 0.60 (m, 1H).

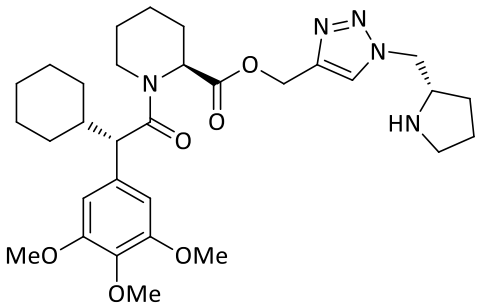
^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.06, 172.43, 171.07, 153.44, 153.07, 142.78, 136.92, 133.47, 106.00, 105.35, 61.03, 60.98, 58.43, 58.01, 57.24, 56.46, 56.32, 55.98, 55.55, 55.28, 52.55, 43.79, 41.35, 32.96, 30.91, 30.70, 28.61, 27.02, 26.71, 26.38, 26.29, 25.55, 24.52, 21.12, 20.93.

LC-MS (50-100% B, 19 min): t_R (**269**) = 9.50 min, m/z: calculated = 684.39 $[M+H]^+$, found = 684.52 $[M+H]^+$.

HRMS (ESI): calculated = 684.39669 $[M+H]^+$, found = 684.39699 $[M+H]^+$, err [ppm] = 0.44.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**269**) = 9.18 min (99% Purity).

(S)-1-((R)-pyrrolidin-2-ylmethyl)-1H-1,2,3-triazol-4-yl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV590)



Chemical Formula: $C_{31}H_{45}N_5O_6$
Exact Mass: 583,34
Molecular Weight: 583,72

270

269 (7 mg) is dissolved in 1 mL dry DCM and 0.5 mL TFA added. The reaction is stirred at RT for 30 min. The solvent is evaporated under airstream. The crude product is purified by semi-preparative HPLC. The pure product is obtained as a white solid.

prep-HPLC (30 – 100% B, 10 mL/min, 10 min, 254 nm): t_R (**270**) = 6.77 min.

Yield 4 mg (67%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.18 (s, 1H), 6.49 (s, 2H), 5.43 – 5.37 (m, 1H), 5.23 (d, J = 13.2 Hz, 1H), 4.94 (d, J = 13.1 Hz, 1H), 4.80 – 4.63 (m, 2H), 4.08 – 4.02 (m, 1H), 3.98 – 3.89 (m, 1H), 3.85 – 3.79 (m, 9H), 3.51 – 3.38 (m, 1H), 3.37 (d, J = 9.9 Hz, 1H), 2.85 (td, J = 2.8, 12.7, 13.3 Hz, 1H), 2.35 – 2.23 (m,

2H), 2.16 – 1.98 (m, 3H), 1.91 – 1.79 (m, 2H), 1.75 – 1.58 (m, 12H), 1.37 – 1.21 (m, 3H), 1.21 – 1.08 (m, 1H), 0.97 – 0.66 (m, 2H).

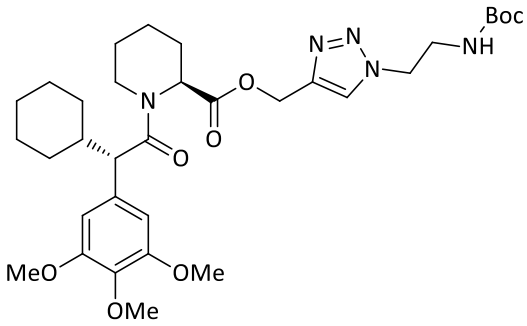
^{13}C-NMR (126 MHz, $CDCl_3$): δ 171.27, 152.92, 150.27, 136.13, 134.42, 131.10, 124.08, 105.83, 105.36, 61.12, 59.48, 58.29, 56.29, 55.01, 52.45, 50.06, 45.74, 43.99, 41.48, 32.86, 30.82, 28.22, 26.90, 26.67, 26.32, 26.26, 25.59, 23.67, 21.08.

LC-MS (30-100% B, 19 min): t_R (**270**) = 4.98 min, m/z: calculated = 584.34 $[M+H]^+$, found = 584.58 $[M+H]^+$.

HRMS (ESI): calculated = 584.34426 $[M+H]^+$, found = 584.34483 $[M+H]^+$, err [ppm] = 0.97.

RP-HPLC (0 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**270**) = 10.47 min (98% Purity).

(S)-1-(2-((tert-butoxycarbonyl)amino)ethyl)-1H-1,2,3-triazol-4-yl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV377)



Chemical Formula: $C_{33}H_{49}N_5O_8$
Exact Mass: 643,36
Molecular Weight: 643,77

271

271 is synthesized according to general procedure 5.9.6. Starting material: **263** (30 mg) and 0.5 M *tert*-butyl (2-azidoethyl)carbamate solution in *t*BuOH (400 µL). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**271**) = 0.25.

Yield 36 mg (85%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.63 (s, 0H), 7.25 (s, 1H), 6.45 (s, 2H), 5.35 – 5.29 (m, 1H), 5.25 (d, J = 12.9 Hz, 1H), 5.08 (s, 1H), 5.01 (d, J = 12.9 Hz, 1H), 4.41 (d, J = 5.9 Hz, 2H), 3.88 (d, J = 14.3 Hz, 1H), 3.85 – 3.80 (m, 4H), 3.81 (s, 5H), 3.68 – 3.51 (m, 2H), 3.35 (d, J = 9.8 Hz, 1H), 2.92 (t, J = 13.3 Hz, 1H), 2.23 (d, J = 13.8 Hz, 1H), 2.05 (td, J = 6.3, 10.7, 11.5 Hz, 2H), 1.85 (d, J = 12.6 Hz, 1H), 1.76 – 1.50 (m, 6H), 1.45 – 1.39 (m, 9H), 1.35 – 1.23 (m, 3H), 1.22 – 1.02 (m, 2H), 0.95 – 0.69 (m, 2H), 0.71 – 0.59 (m, 0H).

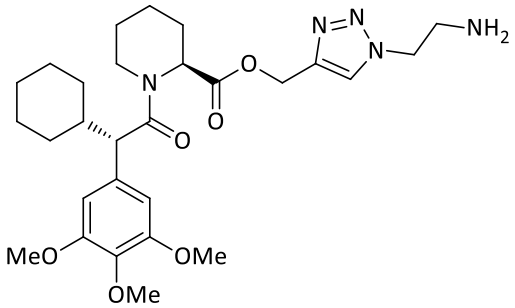
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.77, 171.21, 155.95, 153.03, 142.84, 142.45, 137.08, 136.72, 134.37, 133.74, 124.60, 123.71, 105.94, 105.36, 79.96, 61.02, 60.98, 58.60, 58.40, 56.46, 56.31, 55.93, 55.54, 55.21, 52.62, 50.17, 43.91, 41.40, 41.26, 40.61, 39.61, 33.05, 32.92, 30.86, 30.70, 28.46, 26.91, 26.88, 26.69, 26.36, 26.33, 26.30, 25.57, 24.52, 21.11, 20.91.

LC-MS (50-100% B, 19 min): t_R (**271**) = 8.75 min, m/z: calculated = 644.36 $[M+H]^+$, found = 644.31 $[M+H]^+$.

HRMS (ESI): calculated = 588.30279 $[M+H]^+$, found = 588.30282 $[M+H]^+$, err [ppm] = 0.05.

RP-HPLC (30 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**271**) = 13.23 min (99% Purity).

(S)-1-(2-aminoethyl)-1H-1,2,3-triazol-4-yl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV476)



Chemical Formula: $C_{28}H_{41}N_5O_6$
Exact Mass: 543,31
Molecular Weight: 543,66

272

271 (4 mg) is dissolved in 1 mL dry DCM and 0.5 mL TFA added. The reaction is stirred at RT for 30 min. The solvent is evaporated under airstream. The crude product is purified by silica column chromatography (DCM + 1% TEA + 1% MeOH). The pure product is obtained as a white solid.

Silica column chromatography: DCM + 1% TEA + 1% MeOH, v/v.

TLC (DCM + 1% TEA + 1% MeOH**):** R_f (**272**) = 0.25.

Yield 3 mg (quant.).

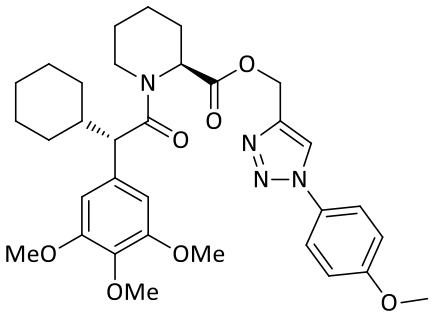
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.31 (s, 1H), 6.47 (s, 2H), 5.68 (s, 4H), 5.41 (d, J = 5.8 Hz, 1H), 5.26 (d, J = 13.0 Hz, 1H), 4.95 (d, J = 13.1 Hz, 1H), 4.84 – 4.69 (m, 1H), 3.92 (d, J = 14.0 Hz, 1H), 3.85 – 3.81 (m, 9H), 3.53 – 3.49 (m, 2H), 3.36 (d, J = 9.9 Hz, 1H), 2.90 (dd, J = 11.2, 13.5 Hz, 1H), 2.31 – 2.22 (m, 1H), 2.12 – 2.03 (m, 1H), 1.92 – 1.82 (m, 1H), 1.38 – 1.06 (m, 10H), 0.94 – 0.68 (m, 2H).

LC-MS (30-100% B, 19 min): t_R (**272**) = 4.37 min, m/z: calculated = 544.31 $[M+H]^+$, found = 544.44 $[M+H]^+$.

HRMS (ESI): calculated = 544.31296 $[M+H]^+$, found = 544.31332 $[M+H]^+$, err [ppm] = 0.36.

RP-HPLC (30 – 100% B, 1.5 mL/min, 20 min, 254 nm): t_R (**272**) = 7.00 min (97% Purity).

(S)-1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV379)



Chemical Formula: $C_{33}H_{42}N_4O_7$
Exact Mass: 606,31
Molecular Weight: 606,71

273

273 is synthesized according to general procedure 5.9.6. Starting material: **263** (30 mg) and 4-Azidoanisole (12 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 1/1, v/v.

TLC (CH/EE, 1/1): R_f (**273**) = 0.32.

Yield 31 mg (78%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.67 – 7.60 (m, 2H), 7.07 – 6.97 (m, 2H), 6.44 (s, 2H), 5.42 – 5.27 (m, 2H), 5.13 (d, J = 12.8 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.78 (s, 6H), 3.37 (d, J = 9.6 Hz, 1H), 2.97 (td, J = 3.1, 13.1 Hz, 1H), 2.10 – 2.03 (m, 2H), 1.72 – 1.62 (m, 9H), 1.58 – 1.50 (m, 1H), 1.49 – 1.38 (m, 1H), 1.37 – 1.22 (m, 3H), 1.22 – 1.06 (m, 2H), 1.03 – 0.82 (m, 1H), 0.81 – 0.71 (m, 1H), 0.70 – 0.55 (m, 1H).

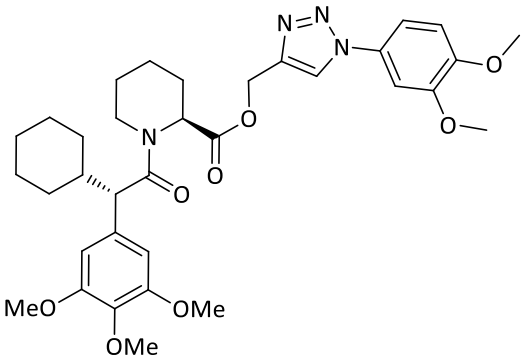
^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.13, 172.36, 171.34, 160.02, 153.43, 153.08, 143.51, 136.91, 133.46, 130.50, 122.26, 121.88, 115.03, 114.93, 106.02, 105.33, 60.97, 58.66, 58.14, 56.46, 56.27, 55.95, 55.78, 55.60, 55.36, 52.68, 43.82, 41.38, 41.29, 39.63, 33.10, 32.98, 30.89, 30.70, 26.91, 26.72, 26.61, 26.43, 26.35, 25.48, 24.53, 21.03, 20.92, 1.16.

LC-MS (50-100% B, 19 min): t_R (**273**) = 11.78 min, m/z: calculated = 607.31 $[M+H]^+$, found = 607.44 $[M+H]^+$.

HRMS (ESI): calculated = 607.31263 $[M+H]^+$, found = 607.31340 $[M+H]^+$, err [ppm] = 1.27.

RP-HPLC (30 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**273**) = 14.57 min (96% Purity).

(S)-(1-(3,4-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV703)



Chemical Formula: $C_{34}H_{44}N_4O_8$
Exact Mass: 636,32
Molecular Weight: 636,74

274

274 is synthesized according to general procedure 5.9.6. Starting material: **263** (12 mg) and 4-azido-1,2-dimethoxybenzene (7 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 3/1, v/v.

TLC (CH/EE, 3/1): R_f (**274**) = 0.37.

Yield 15 mg (71%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.37 (d, J = 2.5 Hz, 1H), 7.18 (dd, J = 2.5, 8.5 Hz, 1H), 6.95 (d, J = 8.6 Hz, 1H), 6.44 (s, 2H), 5.39 (s, 1H), 5.36 – 5.29 (m, 2H), 5.12 (d, J = 12.8 Hz, 1H), 3.97 (s, 4H), 3.94 (s, 4H), 3.83 (s, 5H), 3.78 (s, 5H), 3.37 (d, J = 9.6 Hz, 1H), 3.03 – 2.89 (m, 1H), 2.29 – 2.15 (m, 1H), 2.15 – 1.99 (m, 1H), 1.94 – 1.77 (m, 1H), 1.76 – 1.47 (m, 8H), 1.45 – 1.02 (m, 1H), 1.00 – 0.85 (m, 1H), 0.85 – 0.57 (m, 1H).

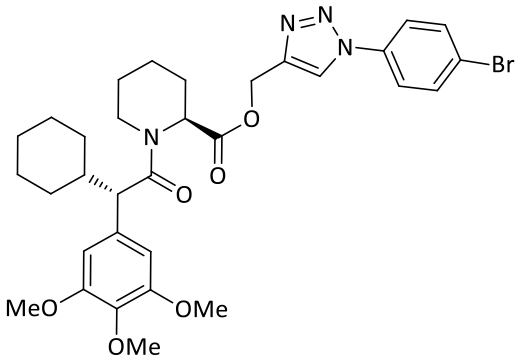
^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.14, 171.36, 153.10, 143.56, 133.46, 121.93, 112.60, 111.40, 106.05, 105.37, 105.08, 60.98, 58.09, 56.43, 56.36, 56.27, 55.62, 55.37, 52.69, 43.82, 41.37, 33.68, 32.98, 30.89, 26.92, 26.72, 26.42, 26.36, 25.49, 21.05.

LC-MS (50-100% B, 19 min): t_R (**274**) = 9.11 min, m/z: calculated = 637.32 $[M+H]^+$, found = 637.39 $[M+H]^+$.

HRMS (ESI): calculated = 637.32319 $[M+H]^+$, found = 637.32335 $[M+H]^+$, err [ppm] = 0.25.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**274**) = 7.75 min (96% Purity).

(S)-(1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV715)



Chemical Formula: $C_{32}H_{39}BrN_4O_6$
Exact Mass: 654,21
Molecular Weight: 655,58

275

275 is synthesized according to general procedure 5.9.6. Starting material: **263** (10 mg) and 1-azido-4-bromobenzene (8 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**275**) = 0.35.

Yield 14 mg (66%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.66 (s, 4H), 6.43 (s, 2H), 5.37 (d, J = 11.7 Hz, 1H), 5.31 (s, 1H), 5.10 (d, J = 12.9 Hz, 1H), 3.88 (d, J = 8.7 Hz, 1H), 3.82 (d, J = 2.6 Hz, 5H), 3.76 (s, 5H), 3.37 (d, J = 9.6 Hz, 1H), 2.94 (td, J = 3.0, 13.0 Hz, 1H), 2.23 (d, J = 13.0 Hz, 1H), 2.05 (t, J = 10.7 Hz, 1H), 1.87 (d, J = 13.0 Hz, 1H), 1.76 – 1.49 (m, 7H), 1.49 – 1.03 (m, 3H), 0.99 – 0.55 (m, 2H).

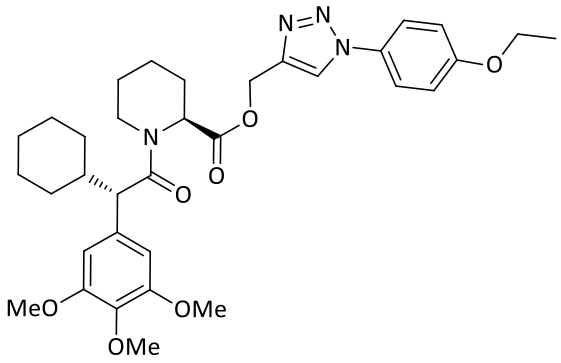
^{13}C-NMR (75 MHz, $CDCl_3$): δ 173.16, 171.36, 153.08, 144.02, 133.46, 133.19, 133.04, 122.02, 121.58, 106.03, 105.36, 60.97, 57.96, 56.26, 55.37, 52.72, 43.85, 41.35, 32.97, 30.88, 26.84, 26.71, 26.43, 25.45, 20.99.

LC-MS (50-100% B, 19 min): t_R (**275**) = 11.30 min, m/z: calculated = 655.21 $[M+H]^+$, found = 655.64 $[M+H]^+$.

HRMS (ESI): calculated = 655.212570 $[M+H]^+$, found = 655.21261 $[M+H]^+$, err [ppm] = 0.06.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**275**) = 10.41 min (97% Purity).

(S)-(1-(4-ethoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV729)



Chemical Formula: $C_{34}H_{44}N_4O_7$
Exact Mass: 620,32
Molecular Weight: 620,74

276

276 is synthesized according to general procedure 5.9.6. Starting material: **263** (12 mg) and 1-azido-4-ethoxybenzene (6 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**276**) = 0.35.

Yield 15 mg (76%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.62 (dd, J = 2.4, 9.1 Hz, 2H), 7.05 – 6.94 (m, 2H), 6.44 (d, J = 2.8 Hz, 2H), 5.42 – 5.30 (m, 2H), 5.14 (d, J = 12.8 Hz, 1H), 3.90 (s, 0H), 3.83 (d, J = 1.7 Hz, 5H), 3.78 (s, 4H), 3.37 (d, J = 9.6 Hz, 1H), 3.02 – 2.86 (m, 1H), 2.23 (d, J = 12.7 Hz, 1H), 2.06 (t, J = 11.0 Hz, 1H), 1.87 (d, J = 12.6 Hz, 1H), 1.61 (dd, J = 12.0, 25.3 Hz, 6H), 1.46 – 1.02 (m, 8H), 0.87 (q, J = 6.7 Hz, 6H).

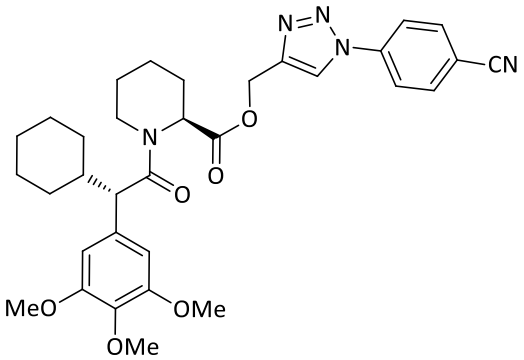
^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.14, 171.35, 169.36, 153.10, 133.47, 122.25, 121.88, 115.44, 106.05, 64.09, 60.98, 58.16, 56.28, 52.69, 41.39, 32.99, 29.85, 26.93, 26.45, 21.04, 14.88, 14.26, 1.17.

LC-MS (50-100% B, 19 min): t_R (**276**) = 10.76 min, m/z: calculated = 621.33 $[M+H]^+$, found = 621.65 $[M+H]^+$.

HRMS (ESI): calculated = 621.32828 $[M+H]^+$, found = 621.32890 $[M+H]^+$, err [ppm] = 1.0.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**276**) = 9.63 min (95% Purity).

(S)-(1-(4-cyanophenyl)-1H-1,2,3-triazol-4-yl)methyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV707)



Chemical Formula: $C_{33}H_{39}N_5O_6$
Exact Mass: 601,29
Molecular Weight: 601,69

277

277 is synthesized according to general procedure 5.9.6. Starting material: **263** (12 mg) and 4-azidobenzonitrile (6 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**277**) = 0.25.

Yield 15 mg (86%).

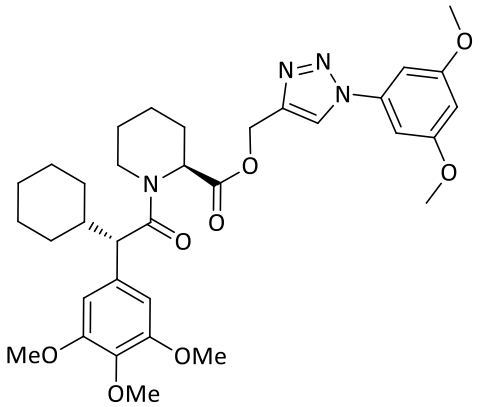
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.96 (d, J = 8.6 Hz, 2H), 7.84 (d, J = 8.8 Hz, 2H), 6.42 (d, J = 1.6 Hz, 2H), 5.44 – 5.35 (m, 1H), 5.33 – 5.28 (m, 1H), 5.07 (d, J = 13.0 Hz, 1H), 3.88 (d, J = 13.4 Hz, 1H), 3.83 (s, 2H), 3.81 (s, 2H), 3.75 (s, 5H), 3.37 (d, J = 9.6 Hz, 1H), 2.91 (td, J = 3.1, 13.1 Hz, 1H), 2.24 (d, J = 13.0 Hz, 1H), 2.07 (d, J = 11.3 Hz, 2H), 1.87 (d, J = 12.6 Hz, 1H), 1.74 – 1.59 (m, 4H), 1.51 – 1.39 (m, 1H), 1.38 – 1.21 (m, 3H), 1.15 (q, J = 12.4, 12.8 Hz, 2H), 0.98 – 0.83 (m, 1H), 0.76 (q, J = 12.4, 13.2 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.20, 171.40, 153.07, 144.53, 139.81, 136.84, 134.05, 133.48, 121.48, 120.72, 117.89, 112.60, 106.03, 105.37, 60.97, 58.37, 57.82, 56.49, 56.24, 55.67, 55.37, 52.77, 43.89, 41.35, 33.16, 32.96, 30.87, 30.72, 26.85, 26.76, 26.70, 26.62, 26.43, 26.31, 25.42, 24.50, 20.95.

LC-MS (50-100% B, 19 min): t_R (**277**) = 9.59 min, m/z: calculated = 602.30 $[M+H]^+$,
found = 602.56 $[M+H]^+$ (95% Purity)

HRMS (ESI): calculated = 602.29731 $[M+H]^+$, found = 602.29741 $[M+H]^+$, err [ppm] = 0.17.

(S)-(1-(3,5-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV741)



Chemical Formula: $C_{34}H_{44}N_4O_8$
Exact Mass: 636,32
Molecular Weight: 636,74

278

278 is synthesized according to general procedure 5.9.6. Starting material: **263** (15 mg) and 1-azido-3,5-dimethoxy-benzene (18 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**278**) = 0.23.

Yield 16 mg (76%).

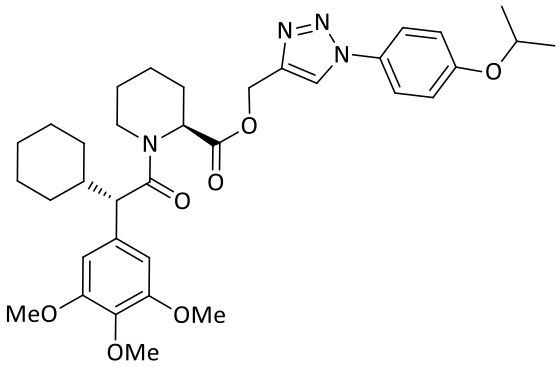
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.99 (s, 1H), 6.92 (d, J = 2.3 Hz, 1H), 6.50 (t, J = 2.2 Hz, 1H), 6.47 – 6.40 (m, 2H), 5.44 – 5.26 (m, 2H), 5.12 (d, J = 12.8 Hz, 1H), 4.79 (d, J = 5.5 Hz, 0H), 4.60 (d, J = 13.7 Hz, 0H), 3.86 (s, 7H), 3.85 – 3.81 (m, 5H), 3.77 (s, 4H), 3.37 (d, J = 9.6 Hz, 1H), 2.97 (td, J = 3.1, 13.1 Hz, 1H), 2.29 – 2.19 (m, 1H), 2.15 – 2.00 (m, 2H), 1.96 – 1.80 (m, 1H), 1.74 – 1.51 (m, 7H), 1.51 – 1.05 (m, 5H), 1.02 – 0.53 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.20, 172.34, 171.35, 161.77, 161.69, 153.43, 153.09, 143.67, 142.96, 138.51, 138.36, 136.92, 134.37, 133.40, 122.32, 121.87, 106.02, 105.34, 100.85, 99.10, 99.04, 61.02, 60.96, 58.54, 58.01, 56.47, 56.25, 55.94, 55.88, 55.63, 55.44, 52.73, 43.82, 41.31, 39.63, 33.09, 33.00, 30.89, 30.71, 26.89, 26.73, 26.62, 26.40, 26.36, 26.26, 25.46, 24.52, 21.02, 20.92.

LC-MS (50-100% B, 19 min): t_R (**278**) = 10.20 min, m/z: calculated = 637.32 $[M+H]^+$, found = 637.54 $[M+H]^+$ (99% Purity)

HRMS (ESI): calculated = 637.32319 $[M+H]^+$, found = 637.32335 $[M+H]^+$, err [ppm] = 0.25.

(S)-(1-(4-isopropoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV733)



Chemical Formula: $C_{35}H_{46}N_4O_7$
Exact Mass: 634,34
Molecular Weight: 634,76

279

279 is synthesized according to general procedure 5.9.6. Starting material: **263** (6 mg) and 1-azido-4-isopropoxy-benzene (4 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 3/1, v/v.

TLC (CH/EE, 3/1): R_f (**279**) = 0.22.

Yield 5 mg (60%).

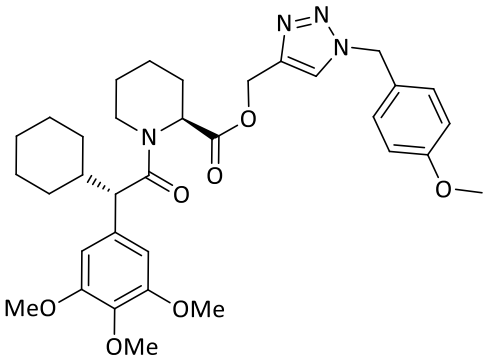
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.61 (dd, J = 3.5, 9.0 Hz, 2H), 7.03 – 6.96 (m, 2H), 6.44 (d, J = 5.7 Hz, 2H), 5.39 (s, 1H), 5.35 – 5.27 (m, 1H), 5.14 (d, J = 12.8 Hz, 1H), 4.60 (ddp, J = 2.9, 6.0, 9.0 Hz, 1H), 3.88 (d, J = 13.3 Hz, 1H), 3.85 – 3.80 (m, 5H), 3.79 (s, 4H), 3.37 (d, J = 9.6 Hz, 1H), 2.97 (td, J = 3.0, 13.0 Hz, 1H), 2.23 (d, J = 13.0 Hz, 1H), 2.07 (q, J = 10.3 Hz, 1H), 1.85 (t, J = 16.6 Hz, 1H), 1.73 – 1.58 (m, 4H), 1.56 (s, 4H), 1.37 (dd, J = 1.1, 6.1 Hz, 6H), 1.35 – 1.20 (m, 2H), 1.20 – 1.05 (m, 1H), 0.93 (tdd, J = 5.8, 9.2, 15.8 Hz, 1H), 0.76 (q, J = 12.8, 13.5 Hz, 1H), 0.70 – 0.54 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.13, 172.37, 171.34, 158.42, 153.44, 153.10, 143.48, 142.87, 134.38, 133.47, 130.20, 122.29, 121.88, 116.70, 106.04, 105.35, 70.67, 70.61, 61.03, 60.98, 58.69, 58.17, 56.47, 56.28, 55.95, 55.62, 55.37, 52.68, 43.82, 41.39, 41.31, 39.63, 33.12, 32.99, 30.91, 30.71, 26.93, 26.73, 26.62, 26.44, 26.37, 26.27, 25.50, 24.54, 22.08, 21.05, 20.92.

LC-MS (50-100% B, 19 min): t_R (**279**) = 11.53 min, m/z: calculated = 635.34 $[M+H]^+$, found = 635.77 $[M+H]^+$ (95% Purity).

HRMS (ESI): calculated = 635.34444 $[M+H]^+$, found = 635.34393 $[M+H]^+$, err [ppm] = 0.80.

(S)-(1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV701)



Chemical Formula: $C_{34}H_{44}N_4O_7$
Exact Mass: 620,32
Molecular Weight: 620,74

280

280 is synthesized according to general procedure 5.9.6. Starting material: **263** (12 mg) and 1-(azidomethyl)-4-methoxybenzene (6 mg). The pure product is obtained as a colorless solid.

Silica column chromatography: CH/EE, 1/1, v/v.

TLC (CH/EE, 1/1): R_f (**280**) = 0.28.

Yield 11 mg (69%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.31 (s, 1H), 7.24 – 7.19 (m, 2H), 6.90 – 6.85 (m, 2H), 6.44 – 6.40 (m, 2H), 5.47 – 5.40 (m, 2H), 5.33 – 5.28 (m, 1H), 5.18 (d, J = 12.8 Hz, 1H), 5.01 (d, J = 12.8 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.81 – 3.77 (m, 8H), 3.35 (d, J = 9.7 Hz, 1H), 2.90 (td, J = 2.9, 13.2 Hz, 1H), 2.22 – 2.13 (m, 1H), 2.10 – 2.01 (m, 1H), 1.89 – 1.78 (m, 1H), 1.73 – 1.47 (m, 8H), 1.37 – 1.24 (m, 2H), 1.23 – 1.03 (m, 3H), 0.98 – 0.85 (m, 1H), 0.81 – 0.62 (m, 1H).

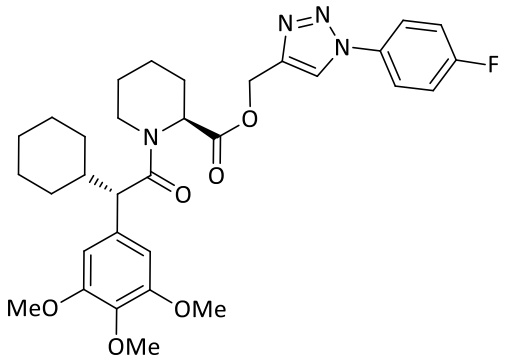
^{13}C-NMR (126 MHz, $CDCl_3$): δ 172.88, 172.29, 171.21, 160.22, 160.03, 153.42, 153.04, 143.11, 142.72, 136.84, 134.37, 133.55, 129.81, 129.76, 126.88, 126.38, 123.58, 123.18, 114.71, 114.57, 105.97, 105.35, 61.02, 60.97, 58.63, 58.21, 56.46, 56.27, 55.89, 55.46, 55.26, 54.00, 53.77, 52.49, 43.76, 41.35, 39.56, 32.97, 30.89, 30.70, 26.94, 26.71, 26.40, 26.37, 26.29, 25.53, 24.50, 21.03, 20.87.

LC-MS (50-100% B, 19 min): t_R (**280**) = 9.46 min, m/z: calculated = 621.32 $[M+H]^+$, found = 621.52 $[M+H]^+$.

HRMS (ESI): calculated = 621.32828 $[M+H]^+$, found = 621.32887 $[M+H]^+$, err [ppm] = 0.96.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**280**) = 8.07 min (96% Purity).

(S)-(1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV725)



Chemical Formula: $C_{32}H_{39}FN_4O_6$
Exact Mass: 594,29
Molecular Weight: 594,67

281

281 is synthesized according to general procedure 5.9.6. Starting material: **263** (12 mg) and 1-azido-4-fluorobenzene (5 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**281**) = 0.35.

Yield 9 mg (56%).

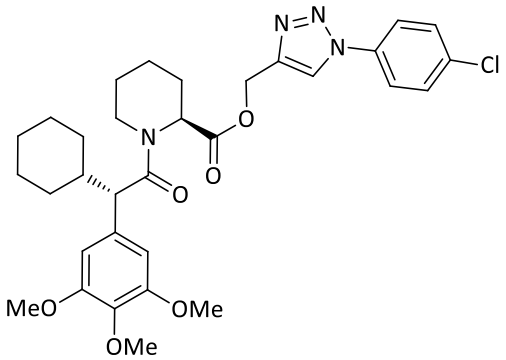
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.79 – 7.72 (m, 2H), 7.25 – 7.18 (m, 2H), 6.43 (s, 2H), 5.37 (d, J = 26.9 Hz, 1H), 5.34 – 5.29 (m, 2H), 5.12 (d, J = 12.9 Hz, 1H), 3.93 – 3.85 (m, 1H), 3.84 – 3.83 (m, 3H), 3.83 – 3.81 (m, 2H), 3.77 (s, 4H), 3.38 (d, J = 9.5 Hz, 1H), 2.95 (td, J = 3.1, 13.1 Hz, 1H), 2.23 (d, J = 13.0 Hz, 1H), 2.12 – 2.00 (m, 2H), 1.89 – 1.82 (m, 1H), 1.76 – 1.58 (m, 4H), 1.39 – 1.05 (m, 5H), 1.05 – 0.69 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.16, 171.37, 171.21, 163.61, 153.46, 153.09, 143.89, 136.90, 133.47, 122.67, 122.60, 122.34, 121.90, 117.13, 116.95, 116.77, 106.04, 105.36, 61.04, 60.97, 58.03, 56.48, 56.26, 55.95, 55.64, 55.38, 52.72, 43.85, 41.38, 41.27, 32.98, 30.89, 30.72, 26.87, 26.72, 26.62, 26.44, 25.47, 21.01.

LC-MS (50-100% B, 19 min): t_R (**281**) = 10.11 min, m/z: calculated = 595.29 $[M+H]^+$, found = 595.38 $[M+H]^+$ (95% Purity).

HRMS (ESI): calculated = 595.29264 $[M+H]^+$, found = 595.29306 $[M+H]^+$, err [ppm] = 0.71.

(S)-(1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV719)



Chemical Formula: $C_{32}H_{39}ClN_4O_6$
Exact Mass: 610,26
Molecular Weight: 611,13

282

282 is synthesized according to general procedure 5.9.6. Starting material: **263** (12 mg) and 1-azido-4-chlorobenzene (6 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**282**) = 0.30.

Yield 16 mg (81%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.77 – 7.64 (m, 2H), 7.57 – 7.45 (m, 2H), 6.43 (s, 2H), 5.38 (d, J = 11.8 Hz, 1H), 5.32 (s, 1H), 5.10 (d, J = 12.9 Hz, 1H), 3.88 (d, J = 14.3 Hz, 1H), 3.82 (d, J = 2.6 Hz, 5H), 3.77 (s, 5H), 3.37 (d, J = 9.6 Hz, 1H), 2.95 (td, J = 3.1, 12.9 Hz, 1H), 2.23 (d, J = 12.9 Hz, 1H), 2.16 – 1.96 (m, 2H), 1.93 – 1.77 (m, 2H), 1.68 (t, J = 11.8 Hz, 5H), 1.53 – 1.21 (m, 2H), 1.23 – 1.06 (m, 2H), 1.04 – 0.82 (m, 1H), 0.71 (dq, J = 11.0, 11.4, 34.3 Hz, 1H).

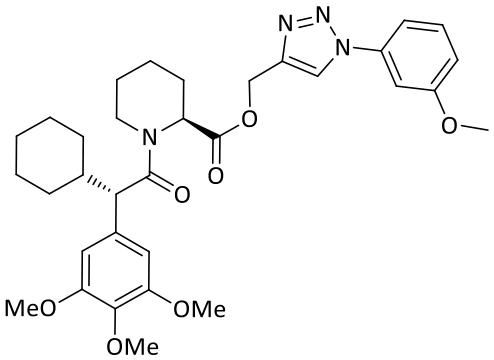
^{13}C-NMR (126 MHz, $CDCl_3$): δ 153.09, 133.46, 130.08, 121.79, 106.04, 60.97, 57.98, 56.26, 52.73, 43.85, 41.37, 32.98, 30.89, 26.86, 26.44, 21.01.

LC-MS (50-100% B, 19 min): t_R (**282**) = 11.10 min, m/z: calculated = 611.26 $[M+H]^+$, found = 611.52 $[M+H]^+$.

HRMS (ESI): calculated = 611.26309 $[M+H]^+$, found = 611.26336 $[M+H]^+$, err [ppm] = 0.44.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**282**) = 10.07 min (95% Purity).

(S)-(1-(3-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV727)



Chemical Formula: $C_{33}H_{42}N_4O_7$
Exact Mass: 606,31
Molecular Weight: 606,71

283

283 is synthesized according to general procedure 5.9.6. Starting material: **263** (12 mg) and 1-azido-3-methoxybenzene (6 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**283**) = 0.34.

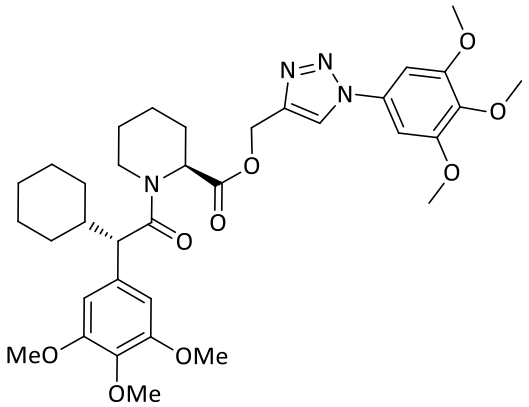
Yield 4 mg (23%).

LC-MS (50-100% B, 19 min): t_R (**283**) = 10.26 min, m/z: calculated = 607.31 $[M+H]^+$, found = 607.46 $[M+H]^+$.

HRMS (ESI): calculated = 607.31263 $[M+H]^+$, found = 607.31311 $[M+H]^+$, err [ppm] = 0.79.

RP-HPLC (50 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**283**) = 7.60 min (95% Purity).

(S)-(1-(3,4,5-trimethoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV731)



Chemical Formula: $C_{35}H_{46}N_4O_9$
Exact Mass: 666,33
Molecular Weight: 666,76

284

284 is synthesized according to general procedure 5.9.6. Starting material: **263** (6 mg) and **228** (4 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**284**) = 0.21.

Yield 5 mg (57%).

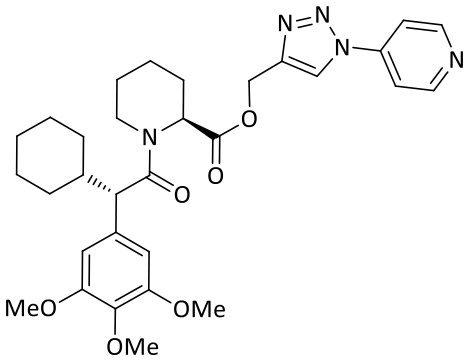
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.03 – 6.91 (m, 2H), 6.48 – 6.41 (m, 2H), 5.42 – 5.29 (m, 2H), 5.09 (d, J = 12.8 Hz, 1H), 3.97 – 3.93 (m, 6H), 3.89 (s, 3H), 3.83 (s, 3H), 3.82 (s, 2H), 3.78 (s, 4H), 3.37 (d, J = 9.7 Hz, 1H), 2.96 (td, J = 3.0, 13.1 Hz, 1H), 2.24 (d, J = 12.9 Hz, 1H), 2.11 – 2.03 (m, 2H), 1.96 – 1.75 (m, 1H), 1.74 – 1.59 (m, 3H), 1.56 (s, 5H), 1.48 – 1.38 (m, 0H), 1.37 – 1.23 (m, 2H), 1.22 – 1.06 (m, 1H), 1.03 – 0.82 (m, 1H), 0.83 – 0.56 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.19, 171.39, 154.09, 153.46, 153.11, 143.68, 138.56, 136.92, 134.33, 133.45, 132.88, 131.08, 121.96, 106.04, 105.38, 98.59, 61.21, 60.98, 58.55, 57.95, 56.66, 56.49, 56.27, 55.95, 55.42, 52.74, 43.84, 41.31, 39.66, 33.10, 32.98, 30.87, 30.71, 26.90, 26.71, 26.65, 26.39, 26.30, 25.49, 21.05, 20.91.

LC-MS (50-100% B, 19 min): t_R (**284**) = 9.70 min, m/z: calculated = 667.33 $[M+H]^+$, found = 667.60 $[M+H]^+$ (95% Purity).

HRMS (ESI): calculated = 667.33376 $[M+H]^+$, found = 667.33405 $[M+H]^+$, err [ppm] = 0.45.

(S)-(1-(pyridin-4-yl)-1H-1,2,3-triazol-4-yl)methyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV713)



Chemical Formula: $C_{31}H_{39}N_5O_6$
Exact Mass: 577,29
Molecular Weight: 577,67

285

285 is synthesized according to general procedure 5.9.6. Starting material: **263** (10 mg) and 4-azidopyridine (5 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 1/1 + 1% TEA, v/v.

TLC (CH/EE, 1/1 + 1% TEA): R_f (**285**) = 0.22.

Yield 15 mg (81%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.83 (s, 2H), 8.12 (s, 1H), 7.78 (s, 2H), 6.42 (d, J = 2.0 Hz, 2H), 5.40 (d, J = 4.0 Hz, 1H), 5.36 – 5.25 (m, 1H), 5.08 (d, J = 13.0 Hz, 1H), 3.90 (s, 1H), 3.82 (d, J = 4.7 Hz, 4H), 3.75 (s, 5H), 3.37 (d, J = 9.6 Hz, 1H), 3.01 – 2.85 (m, 1H), 2.23 (d, J = 12.9 Hz, 1H), 2.08 (d, J = 11.0 Hz, 1H), 1.88 (d, J = 13.1 Hz, 1H), 1.77 – 1.50 (m, 8H), 1.44 (d, J = 12.8 Hz, 0H), 1.40 – 1.04 (m, 4H), 0.79 (ddt, J = 10.9, 36.0, 59.0 Hz, 2H).

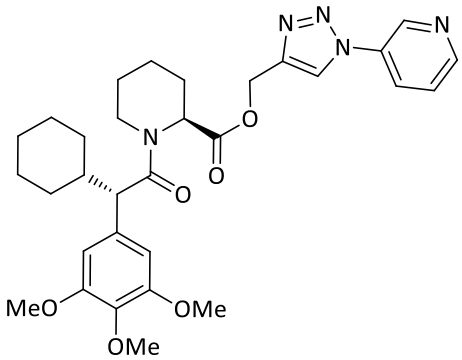
^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.24, 171.39, 153.08, 133.43, 121.18, 106.03, 60.96, 57.78, 56.49, 56.24, 55.39, 52.79, 43.89, 41.34, 32.97, 30.86, 26.75, 26.43, 25.41, 20.93.

LC-MS (30-100% B, 19 min): t_R (**285**) = 10.70 min, m/z: calculated = 578.30 $[M+H]^+$, found = 578.34 $[M+H]^+$.

HRMS (ESI): calculated = 578.29731 $[M+H]^+$, found = 578.29698 $[M+H]^+$, err [ppm] = 0.57.

RP-HPLC (30 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**285**) = 7.92 min (94% Purity).

(S)-(1-(pyridin-3-yl)-1H-1,2,3-triazol-4-yl)methyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV711)



Chemical Formula: $C_{31}H_{39}N_5O_6$
Exact Mass: 577,29
Molecular Weight: 577,67

286

286 is synthesized according to general procedure 5.9.6. Starting material: **263** (12 mg) and 3-azidopyridine (5 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1 +1% TEA, v/v.

TLC (CH/EE, 2/1 + 1% TEA): R_f (**286**) = 0.30.

Yield 9 mg (48%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.06 (d, J = 2.6 Hz, 1H), 8.71 (dd, J = 1.5, 4.8 Hz, 1H), 8.19 – 8.10 (m, 1H), 8.01 (s, 1H), 7.57 – 7.43 (m, 1H), 6.44 (s, 2H), 5.40 (d, J = 13.6 Hz, 1H), 5.33 (s, 1H), 5.10 (d, J = 12.9 Hz, 1H), 3.89 (d, J = 13.4 Hz, 1H), 3.83 (s, 2H), 3.81 (s, 2H), 3.77 (s, 5H), 3.37 (d, J = 9.7 Hz, 1H), 3.00 – 2.90 (m, 1H), 2.24 (d, J = 13.0 Hz, 1H), 2.08 (q, J = 10.6 Hz, 1H), 1.87 (d, J = 12.5 Hz, 1H), 1.69 (d, J = 16.6 Hz, 6H), 1.58 (s, 2H), 1.52 – 1.23 (m, 2H), 1.15 (q, J = 11.2 Hz, 2H), 1.00 – 0.67 (m, 1H), 0.68 – 0.51 (m, 1H).

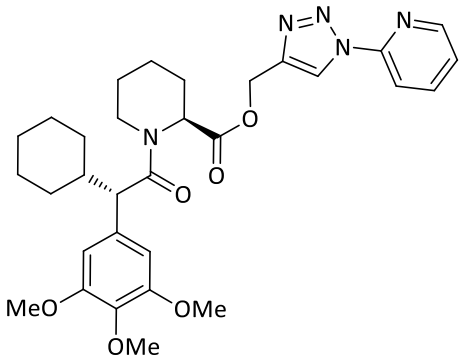
^{13}C-NMR (75 MHz, $CDCl_3$): δ 173.13, 171.35, 153.08, 150.14, 144.24, 141.87, 133.48, 128.17, 124.33, 121.72, 106.05, 105.37, 60.96, 57.82, 56.28, 55.36, 52.74, 43.89, 41.30, 32.97, 30.88, 26.85, 26.41, 25.48, 21.04.

LC-MS (30-100% B, 19 min): t_R (**286**) = 11.18 min, m/z: calculated = 578.30 $[M+H]^+$, found = 578.39 $[M+H]^+$.

HRMS (ESI): calculated = 578.29865 $[M+H]^+$, found = 579.29802 $[M+H]^+$, err [ppm] = 1.08.

RP-HPLC (30 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**286**) = 9.46 min (95% Purity).

(S)-(1-(pyridin-2-yl)-1H-1,2,3-triazol-4-yl)methyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV709)



Chemical Formula: $C_{31}H_{39}N_5O_6$
Exact Mass: 577,29
Molecular Weight: 577,67

287

287 is synthesized according to general procedure 5.9.6. Starting material: **263** (12 mg) and 2-azidopyridine (5 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 1/1 + 1% TEA.

TLC (CH/EE, 1/1 + 1% TEA): R_f (**287**) = 0.25.

Yield 5 mg (31%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.52 (s, 1H), 8.52 – 8.48 (m, 1H), 8.23 – 8.15 (m, 1H), 7.97 – 7.87 (m, 1H), 7.36 (dddd, J = 1.0, 4.9, 7.5, 12.3 Hz, 1H), 6.46 (s, 2H), 5.43 (s, 1H), 5.37 – 5.33 (m, 1H), 5.31 – 5.18 (m, 1H), 3.89 (d, J = 13.9 Hz, 1H), 3.85 – 3.78 (m, 9H), 3.37 (d, J = 9.5 Hz, 1H), 3.01 (td, J = 3.1, 13.4 Hz, 1H), 2.29 – 2.18 (m, 1H), 2.07 (td, J = 7.1, 13.6, 15.4 Hz, 2H), 1.90 – 1.79 (m, 1H), 1.74 – 1.57 (m, 6H), 1.48 – 1.23 (m, 3H), 1.23 – 1.06 (m, 1H), 1.02 – 0.84 (m, 1H), 0.84 – 0.56 (m, 2H).

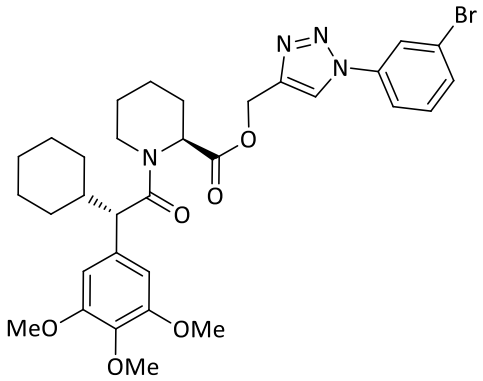
^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.01, 171.13, 153.42, 153.09, 149.20, 148.84, 148.77, 143.35, 139.37, 139.24, 136.97, 134.43, 133.46, 124.02, 123.83, 121.45, 121.07, 113.98, 106.05, 105.34, 61.03, 60.96, 58.55, 58.05, 56.46, 56.33, 55.96, 55.37, 52.57, 43.78, 41.37, 39.62, 33.07, 33.01, 30.92, 30.70, 27.02, 26.74, 26.60, 26.42, 26.23, 25.56, 24.54, 21.16, 20.92.

LC-MS (30-100% B, 19 min): t_R (**287**) = 12.30 min, m/z: calculated = 578.30 $[M+H]^+$, found = 578.62 $[M+H]^+$.

HRMS (ESI): calculated = 578.29731 $[M+H]^+$, found = 578.29643 $[M+H]^+$, err [ppm] = 1.53.

RP-HPLC (30 – 100% B, 1.5 mL/min, 15 min, 220 nm): t_R (**287**) = 11.51 min (95% Purity).

(S)-(1-(3-bromophenyl)-1H-1,2,3-triazol-4-yl)methyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV717)



Chemical Formula: $C_{32}H_{39}BrN_4O_6$
Exact Mass: 654,21
Molecular Weight: 655,58

288

288 is synthesized according to general procedure 5.9.6. Starting material: **263** (12 mg) and 1-azido-3-bromobenzene (8 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**288**) = 0.23.

Yield 12 mg (71%).

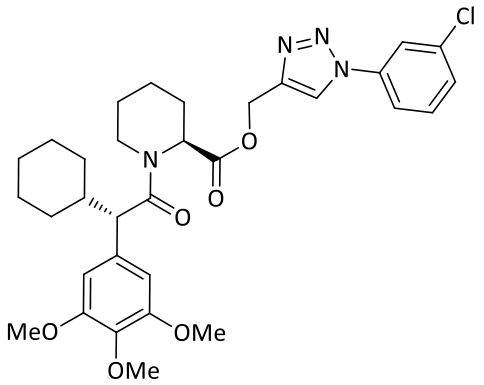
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.03 – 7.97 (m, 1H), 7.71 (dddd, J = 0.9, 2.1, 8.0, 13.1 Hz, 1H), 7.59 (dddd, J = 0.9, 1.9, 8.1, 14.2 Hz, 1H), 7.41 (q, J = 8.3 Hz, 1H), 6.43 (s, 2H), 5.42 – 5.33 (m, 1H), 5.31 (dd, J = 2.8, 6.5 Hz, 1H), 5.08 (d, J = 12.9 Hz, 1H), 3.86 (dd, J = 11.0, 14.4 Hz, 1H), 3.83 (d, J = 1.1 Hz, 5H), 3.76 (s, 4H), 3.37 (d, J = 9.6 Hz, 1H), 2.99 – 2.88 (m, 1H), 2.26 – 2.19 (m, 1H), 2.15 – 2.01 (m, 2H), 1.85 (dd, J = 12.2, 24.9 Hz, 1H), 1.74 – 1.61 (m, 6H), 1.57 (d, J = 15.3 Hz, 3H), 1.43 (ttd, J = 3.9, 7.8, 8.3, 11.5 Hz, 1H), 1.38 – 1.23 (m, 2H), 1.15 (ttd, J = 5.1, 9.2, 22.8 Hz, 2H), 0.92 (dtd, J = 7.9, 10.6, 11.6, 22.8 Hz, 1H), 0.76 (td, J = 9.0, 12.2 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.19, 171.36, 153.45, 153.09, 144.02, 137.96, 136.88, 133.43, 132.28, 131.95, 131.32, 131.20, 123.72, 123.46, 122.17, 121.69, 119.07, 106.03, 105.36, 60.99, 58.46, 57.87, 56.48, 56.26, 55.94, 55.66, 55.43, 52.77, 43.86, 41.28, 39.65, 32.99, 30.88, 26.83, 26.73, 26.63, 26.42, 26.38, 25.45, 21.00.

LC-MS (50-100% B, 19 min): t_R (**288**) = 11.33 min, m/z: calculated = 655.21 $[M+H]^+$, found = 655.70 $[M+H]^+$ (95% Purity).

HRMS (ESI): calculated = 655.21257 $[M+H]^+$, found = 655.21292 $[M+H]^+$, err [ppm] = 0.52.

(S)-(1-(3-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV721)



Chemical Formula: $C_{32}H_{39}ClN_4O_6$
Exact Mass: 610,26
Molecular Weight: 611,13

289

289 is synthesized according to general procedure 5.9.6. Starting material: **263** (12 mg) and 1-azido-3-chlorobenzene (6 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**289**) = 0.21.

Yield 13 mg (81%).

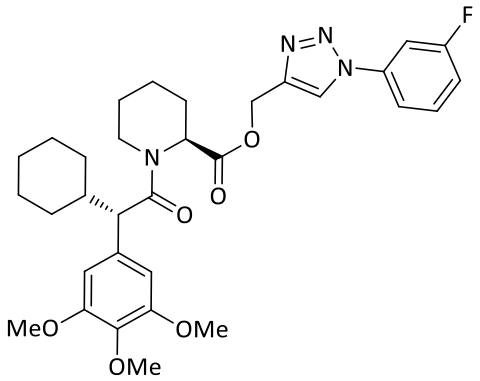
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.79 (t, J = 2.0 Hz, 1H), 7.63 – 7.56 (m, 1H), 7.43 – 7.33 (m, 2H), 7.19 (s, 1H), 6.36 (s, 2H), 5.35 – 5.26 (m, 1H), 5.25 – 5.18 (m, 1H), 5.01 (d, J = 12.9 Hz, 1H), 3.86 – 3.78 (m, 1H), 3.78 – 3.74 (m, 5H), 3.69 (s, 4H), 3.30 (d, J = 9.7 Hz, 1H), 2.88 (td, J = 3.1, 13.0 Hz, 1H), 2.20 – 2.12 (m, 1H), 2.07 – 1.95 (m, 1H), 1.86 – 1.73 (m, 1H), 1.66 – 1.43 (m, 8H), 1.31 – 1.14 (m, 3H), 1.13 – 0.99 (m, 2H), 0.95 – 0.77 (m, 1H), 0.75 – 0.49 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.20, 171.36, 153.45, 153.09, 144.03, 137.88, 136.88, 135.74, 134.32, 133.42, 131.10, 130.96, 129.32, 128.99, 122.15, 121.69, 120.89, 118.56, 106.02, 105.35, 61.03, 60.97, 58.46, 57.89, 56.47, 56.24, 55.94, 55.65, 55.43, 52.77, 43.85, 41.28, 39.65, 33.13, 32.99, 30.87, 30.72, 26.82, 26.72, 26.61, 26.41, 26.38, 25.44, 24.51, 20.99, 20.91.

LC-MS (50-100% B, 19 min): t_R (**289**) = 11.16 min, m/z: calculated = 611.26 $[M+H]^+$, found = 611.57 $[M+H]^+$ (95% Purity).

HRMS (ESI): calculated = 611.26309 $[M+H]^+$, found = 611.26298 $[M+H]^+$, err [ppm] = 0.18.

(S)-(1-(3-fluorophenyl)-1H-1,2,3-triazol-4-yl)methyl 1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (AV723)



Chemical Formula: $C_{32}H_{39}FN_4O_6$
Exact Mass: 594,29
Molecular Weight: 594,67

290

290 is synthesized according to general procedure 5.9.6. Starting material: **263** (12 mg) and 1-azido-3-fluorobenzene (5 mg). The pure product is obtained as a white solid.

Silica column chromatography: CH/EE, 2/1, v/v.

TLC (CH/EE, 2/1): R_f (**290**) = 0.31.

Yield 10 mg (67%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.59 (dt, J = 2.3, 9.4 Hz, 1H), 7.56 (ddd, J = 1.0, 2.0, 8.0 Hz, 1H), 7.53 – 7.47 (m, 1H), 7.21 – 7.02 (m, 1H), 6.43 (d, J = 1.7 Hz, 2H), 5.42 – 5.32 (m, 1H), 5.30 (dd, J = 2.7, 6.2 Hz, 1H), 5.10 (d, J = 12.9 Hz, 1H), 3.91 – 3.86 (m, 1H), 3.84 – 3.80 (m, 5H), 3.76 (s, 5H), 3.37 (d, J = 9.7 Hz, 1H), 3.03 – 2.86 (m, 1H), 2.26 – 2.19 (m, 1H), 2.13 – 2.00 (m, 2H), 1.85 (dd, J = 12.4, 25.2 Hz, 1H), 1.72 – 1.47 (m, 4H), 1.39 – 1.05 (m, 4H), 1.03 – 0.61 (m, 2H).

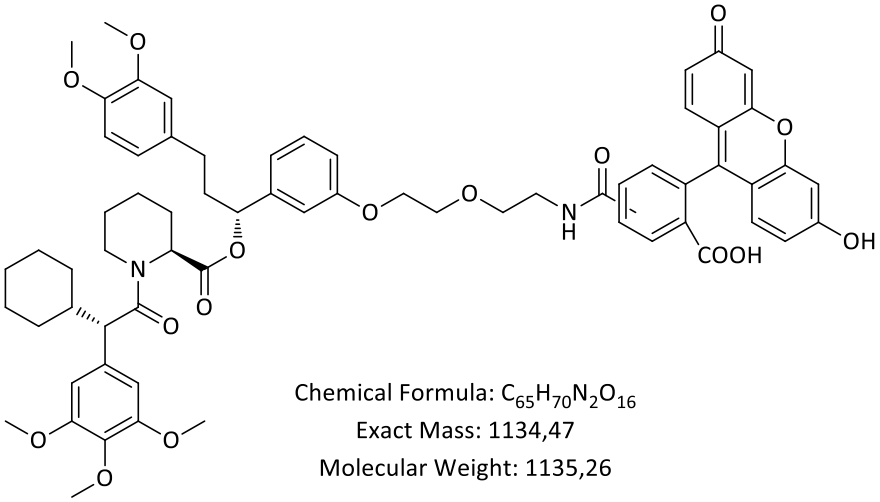
^{13}C-NMR (126 MHz, $CDCl_3$): δ 173.22, 171.38, 164.24, 162.27, 153.45, 153.09, 144.05, 143.39, 138.22, 136.90, 133.42, 131.37, 131.30, 122.15, 121.71, 115.92, 115.75, 108.51, 108.30, 106.03, 105.35, 60.95, 58.48, 57.94, 56.48, 56.24, 55.94, 55.66, 55.43, 52.77, 43.85, 41.33, 39.65, 33.14, 33.00, 30.89, 30.72, 26.82, 26.73, 26.61, 26.40, 25.44, 24.52, 20.98.

LC-MS (50-100% B, 19 min): t_R (**290**) = 10.37 min, m/z: calculated = 595.29 $[M+H]^+$, found = 595.63 $[M+H]^+$ (95% LCMS)

HRMS (ESI): calculated = 595.29264 $[M+H]^+$, found = 595.29247 $[M+H]^+$, err [ppm] = 0.28.

6.6. SAFit tracers (tool compounds)

4(5)-((2-(2-(3-((R)-1-(((S)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)ethoxy)ethyl)carbamoyl)-2-(6-hydroxy-3-oxo-3H-xanthen-9-yl)benzoic acid (AV155)



Chemical Formula: $C_{65}H_{70}N_2O_{16}$
Exact Mass: 1134,47
Molecular Weight: 1135,26

291

NG72 (7 mg, 0.01 mmol, 1.0 eq) is dissolved in 500 µL DMF and transferred to a dried flask under argon atmosphere. TEA (6 µL, 0.04 mmol, 5.0 eq) and 5(6)-NHS-fluoresceine (4 mg, 0.01 mmol, 1.0 eq) are added. The reaction is stirred for 2 h at r.t. then the solvent removed under reduced pressure. The crude product is purified by manual column chromatography (DCM + 10% MeOH).

Yield 9 mg (quant.).

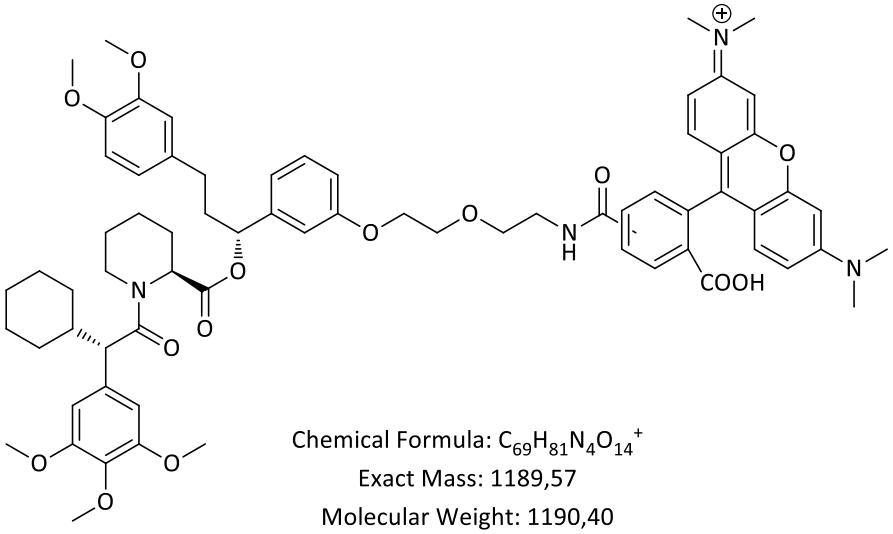
TLC (DCM + 10% MeOH): R_f (**291**) = 0.30.

LC-MS (0-100% B, 19 min): t_R (**291**) = 11.49 min, m/z: calculated = 1135.48 $[M+H]^+$, found = 1135.46 $[M+H]^+$.

HRMS (ESI): calculated = 1135.47981 $[M+H]^+$, found = 1135.48027 $[M+H]^+$, err [ppm] = 0.41.

RP-HPLC (50 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**291**) = 11.26 min (95% Purity).

N-(9-(2-carboxy-4(5)-((2-(2-(3-((R)-1-(((S)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)ethoxy)ethyl)carbamoyl)phenyl)-6-(dimethylamino)-3H-xanthen-3-ylidene)-N-methylmethanaminium (AV289)



Chemical Formula: $C_{69}H_{81}N_4O_{14}^+$
Exact Mass: 1189,57
Molecular Weight: 1190,40

292

NG72 (5 mg, 0.006 mmol, 1.0 eq) is dissolved in 500 µL DMF and transferred to a dried flask under argon atmosphere. TEA (4 µL, 0.03 mmol, 5.0 eq) and 5(6)-NHS-TAMRA (3 mg, 0.006 mmol, 1.0 eq) are added. The reaction is stirred overnight at r.t., then the solvent removed under reduced pressure. The crude product is purified by manual column chromatography (DCM + 10% MeOH).

Yield 2.5 mg (35%).

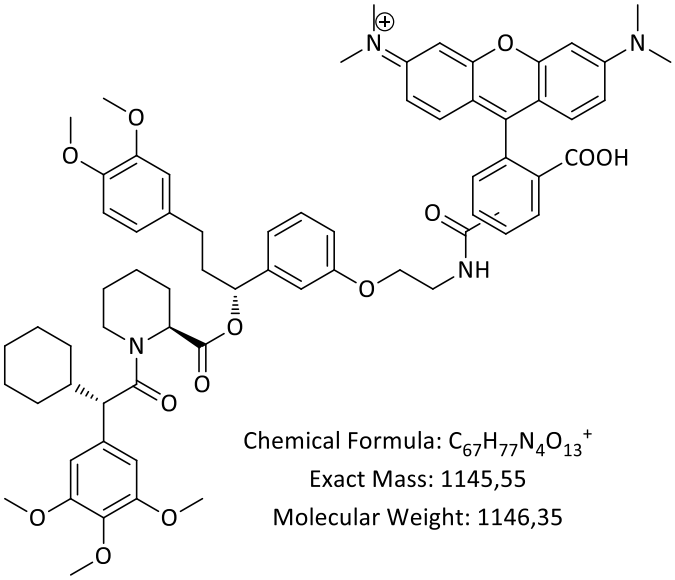
TLC (DCM + 20% MeOH): R_f (**292**) = 0.75.

LC-MS (50-100% B, 19 min): t_R (**292**) = 5.73 min, m/z: calculated = 1190.57 $[M+H]^+$, found = 1190.06 $[M+H]^+$.

HRMS (ESI): calculated = 1189.57438 $[M+H]^+$, found = 1189.57460 $[M+H]^+$, err [ppm] = 0.18.

RP-HPLC (30 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**292**) = 15.49 min (95% Purity).

N-(9-(2-carboxy-4(5)-((2-(3-((R)-1-(((S)-1-((S)-2-cyclohexyl-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carbonyl)oxy)-3-(3,4-dimethoxyphenyl)propyl)phenoxy)ethyl)carbamoyl)phenyl)-6-(dimethylamino)-3H-xanthen-3-ylidene)-N-methylmethanaminium (AV290)



293

NG67 (2 mg, 0.002 mmol, 1.0 eq) is dissolved in 500 µL DMF and transferred to a dried flask under argon atmosphere. TEA (2 µL, 0.01 mmol, 5.0 eq) and 5(6)-NHS-TAMRA (1 mg, 0.002 mmol, 1.0 eq) are added. The reaction is stirred overnight at r.t., then the solvent removed under reduced pressure. The crude product is purified by manual column chromatography (DCM + 10% MeOH).

Yield 2.7 mg (quant.).

TLC (DCM + 10% MeOH): R_f (**292**) = 0.25.

LC-MS (50-100% B, 19 min): t_R (**292**) = 5.58 min, m/z: calculated = 1145.55 $[M+H]^+$, found = 1145.98 $[M+H]^+$.

HRMS (ESI): calculated = 1145.54816 $[M+H]^+$, found = 1145.54844 $[M+H]^+$, err [ppm] = 0.24.

RP-HPLC (30 – 100% B, 1.5 mL/min, 20 min, 220 nm): t_R (**292**) = 15.63 min (95% Purity).

7. Supplement

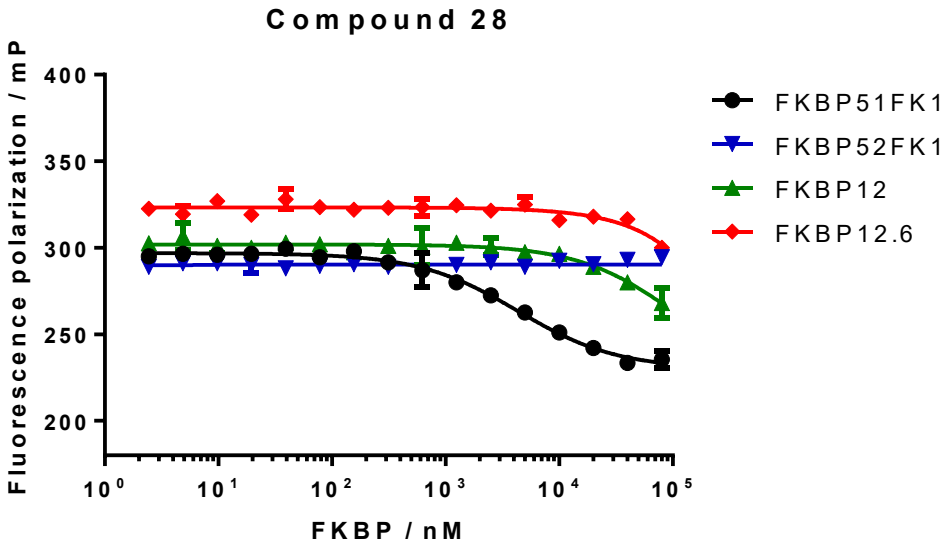


Figure 19. The FP-assay binding curves of macrocyclic compound **28**.

8. Curriculum Vitae

Personal information

Name: Andreas Voll

Date and place of birth: 26th November 1992, Munich

Citizenship: German

Education

1/2017 – 6/2020:

Doctoral thesis in medicinal chemistry: Design and synthesis of novel FKBP51 ligands, Technical University Darmstadt, Chemistry, Prof. Felix Hausch.

10/2014 – 10/2016:

Master thesis in organic and biological chemistry: Design and synthesis of selective FKBP51 inhibitors, Max Planck Institute for Psychiatry and Technical University Munich, Chemistry, Dr. Felix Hausch and Prof. Sieber.

10/2011 – 9/2014:

Bachelor thesis: Synthesis and biological evaluation of N-methylated cyclo-pentapeptides as integrin ligands, Technical University Munich, Chemistry, Prof. Kessler.

8/2003 – 7/2011:

A-Level, Gymnasium Gars am Inn.

Publications

Original research articles:

1. Tietze, D.; Kaufmann, D.; Tietze, A. A.; **Voll, A. M.**; Reher, R.; Konig, G.; Hausch, F., Structural and Dynamical Basis of G Protein Inhibition by YM-254890 and FR900359: An Inhibitor in Action. *J Chem Inf Model* **2019**, *59* (10), 4361-4373.
2. Konig, L.; Kalinichenko, L. S.; Huber, S. E.; **Voll, A. M.**; Bauder, M.; Kornhuber, J.; Hausch, F.; Muller, C. P., The selective FKBP51 inhibitor SAFit2 reduces alcohol consumption and reinstatement of conditioned alcohol effects in mice. *Addict Biol* **2019**, e12758.

Review:

3. Kolos, J. M.; **Voll, A. M.**; Bauder, M.; Hausch, F., FKBP Ligands-Where We Are and Where to Go? *Front Pharmacol* **2018**, *9*.

Poster and oral presentation:

4. Bauder, M.; **Voll, A. M.**; Feng X.; Gaali S.; Hausch F., The drug target FKBP51 - Selective inhibition and structure-based ligand optimization. *Frontiers in Medicinal Chemistry 2019* (Würzburg) **2019**.
5. **Voll, A. M.**; Heymann, T.; Knaup, F. H.; Hausch, F., PainStop - Pioneer Fund, *TU Startup + Innovation Day* (Darmstadt) **2019**.

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“Success is the ability to go from one failure to another with no loss of enthusiasm.”
- Winston Churchill

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