Synthesis of tailor-made bicyclic [4.3.1] aza-amides

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Dissertation

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Zweitgutachterin: Prof. Dr. Vera Krewald

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“I could never resist the temptation of having a look at something that doesn't exist.”

– Andrzej Sapkowski, The Last Wish

Erklärung laut Promotionsordnung

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Ich versichere hiermit, dass die elektronische Version meiner Dissertation mit der schriftlichen Version übereinstimmt und für die Durchführung des Promotionsverfahrens vorliegt.

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Die Arbeit hat bisher noch nicht zu Prüfungszwecken gedient.

Darmstadt, 14.12.2020 Unterschrift des Autors

Declaration of contributions

The synthesis of compound **[90]** was conducted by Michael Walz as part of his master thesis under my supervision. Details can be found in his master thesis.

The synthesis of compound **[93]** and **[94]** was conducted by Tianqi Mao. Details can be found in her dissertation.

The syntheses of compounds **[145]** – **[154]** were conducted by Robin Deutscher during an internship under my supervision.

Compounds **[169] – [171]**, used for molecular modelling, were synthesized by Sebastian Pomplun. Details can be found in his dissertation.

Parts of the introduction were previously published as: **Kolos, J.M.**, Voll, A.M., Bauder, M., & Hausch, F. (**2018**). FKBP Ligands – Where We Are and Where to Go?, Frontiers in pharmacology, 9, 1425. doi:10.3389/fphar.2018.01425

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

Co-crystallization of ligands with FKBPs and corresponding diffraction measurement were performed by Dr. Andreas Bracher. Crystal structures were solved by Andreas Voll.

Acknowledgments

First of all, I would like to thank Prof. Felix Hausch for giving me the opportunity to work in his group, be it in Munich or Darmstadt. I am grateful for your trust in my work, fruitful discussions during the 1v1 meetings and your professional and kind guidance throughout my PhD studies. I also thank you for the water provided, which quenched my thirst many times, for the free coffee that gave me the energy to get through the day and for the occasional ice cream on hot summer days that helped me keep a cool head!

Also, I want to thank Prof. Vera Krewald for supervising me during my molecular modelling studies. I appreciate your patience in introducing me to a new world for a synthetic chemist. Your welcoming attitude and your always open door for discussions helped me a lot during the project.

My special thanks go to Felix Roth for helping me with scripting. Your professional advice has helped me to save a lot of time!

Of course, I would also like to thank the NMR- and the MS-department for the countless samples they measured. Thank you, Alexander Schießer and Christiane Rudolph, for your kind support and the interesting discussions.

I especially appreciate the work and time Stefanie Merz has put into maintaining the FP-assay robot and measuring the FP assays. I know it was a tedious start after the move to Darmstadt, and it did cost you a lot of time for your own projects. For all your work I still owe you plenty of mead and Rittersport!

Moreover, I want to thank Christian Meyners for the time we worked together. I really enjoyed our discussions and cooperation even beyond the scope of this thesis.

I am really glad that I had Michael Bauder as my lab-mate in Darmstadt right from the start. The perfect teamwork when setting up the lab, the scientific discussions in front of the fuming hood and the ‘familiar silence’ are just some of the many good things I will remember.

I am truly happy that I met Andreas Voll during my PhD, whom I consider a close friend. I enjoyed the countless scientific discussions and the work on several scientific and non-scientific projects with you. I can still remember when we drove a four-meter-long board in my Seat Ibiza with open windows and open trunk across Darmstadt to install it in the kitchen to create a shelf for the coffee machine. And it's still standing!

I want to thank my three master students Patrick Purder, Michael Walz and Robin Deutscher for being talented students whose supervision was not too tedious.
Patrick, I want to thank you for making my everyday lab life better, especially for the many scientific discussions and the measuring of FP-assays, but also for the many funny moments and conversations. Meow!
Michael, thank you for providing me with one bicyclic compound and numerous pictures of Nicolas Cage. Every single one of them brought a contemptuous smile on my face!
Robin, thank you for the synthesis and purification of several compounds derived from Heck reaction. I am glad that the Prep-HPLC and you have become such good friends!
I am also grateful that all three of you did not injure yourselves or even die during HF-experiments under my supervision. I am proud that all three of you have been accepted as doctoral students in the research group! Carry on my will and take over the lab!

Thank you, Fabian Knaup, for all your entertaining buddy-stories. Not even Barnie Stinson has as many guys as you have buddies! If I ever need one, you are the first person I will call!

I want to thank you, Steffen Hartmann, for all the hilarious moments in pretty much every step of your scientific career! I think of you as a fluffy Abdelkarim and you have as much talent as he does as a comedian. “Too many cooks destroy the Brei!”

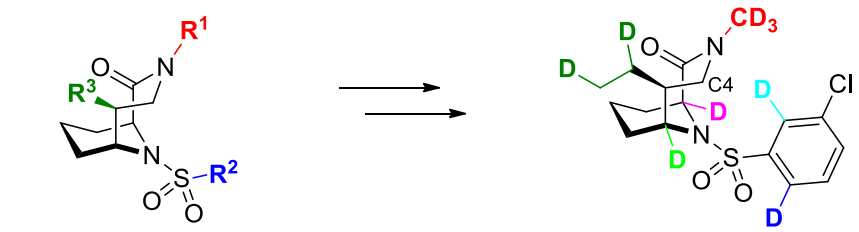
Many thanks go to my dear colleagues, Tim Heymann, Tianqi Mao, Sabine Schäfer, Asat Baischew, Anna Charalampidou, Thomas Geiger and Martha Taubert. We shared a lot of time in the lab – day and night – and without you it would not have been so motivating and delightful. Thank you for all the support and wonderful times we spent together!

Last but not least, my thanks go to my friends and family. It was a long road to become the man I am today, and you have always stood by my side. I thank you for all the moral support over the years! Knowing that I have family and friends like you, who believe in me and think of me even when we are far apart, has really helped me to give my personal best. My special thanks go to Sofia Milker, who more than anyone else showered me with moral and scientific support. Thank you, Annelies and Dieter, for all the love and support since my birth. I can’t express in words how grateful I am for everything you have done for me! I would also like to thank my grandparents, Elisabeth and Alfred, for all the support throughout the years. I will translate this for you when we meet again!

Abstract

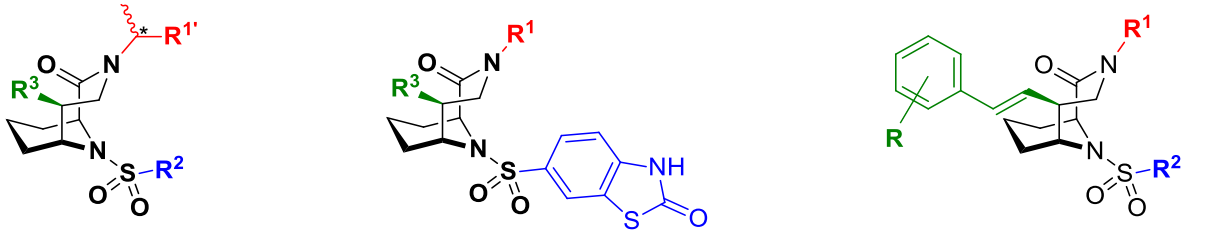
FK506-binding proteins (FKBPs) have emerged as a promising drug target due to their role in various diseases like psychiatric disorders, stress-related diseases, chronic pain and in microbial infections. Bicyclic [4.3.1.] aza-amides have proven to be a privileged scaffold for FKBPs and serve as valuable starting point for the development of potent FKBP inhibitors. The aim of this thesis was to further improve the affinity, selectivity and metabolic stability of this compound class.

The first part of the thesis was dedicated to the metabolic stability of these ligands. A series of deuterated derivatives was synthesized and a metabolite distribution analysis was conducted. This enabled the localization of metabolic soft spots and narrowed it down to two positions in the molecule. On the one hand, the *N*-alkyl-amide bond is readily cleaved by oxidative dealkylation. On the other hand, the carbon at the C4-position is prone to oxidation. In order to block the latter position, a novel tricyclic compound was synthesized, bridging the carbon C4 with the amide.



bicyclic [4.3.1] aza-amides **deuterated positions**

The second part of the thesis was dedicated to the effect of a methyl group at the *N*-α-position. Various pairs of compounds with a methyl group in *R*- and in *S*-configuration were synthesized and tested for their binding affinities to FKBPs. All *S*-isomers displayed an increase in binding affinity, while the *R*-isomers displayed a significant decrease in binding affinity to all tested FKBPs. Molecular modelling studies were performed for a series of *R*-methyl, no methyl and *S*-methyl compounds. Energy maps were created for each compound allowing to determine preferred conformations and studying the effect of pre-organization of the ligand on binding affinity. A compound with an additional rotational barrier was synthesized in order to lock the conformation that most closely resembles the conformation found in the crystal structure.



***S*- and *R*-methyl scaffold** **6-benzo[d]thiazol-2(3H)-one scaffold** **Modification by Heck-reaction**

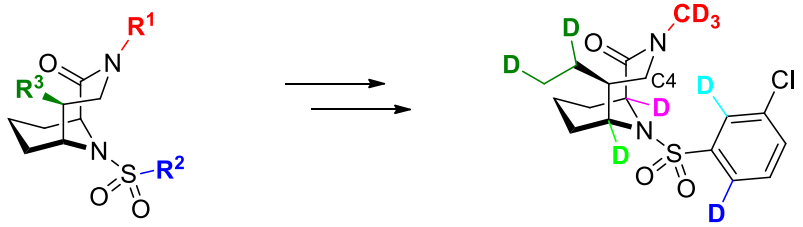
The third part of the thesis was dedicated to bicyclic [4.3.1] aza-amides with a 6-benzo[d]thiazol-2(3H)-one residue at the sulfone amide. This particular residue displayed sub-nanomolar binding affinity to FKBP12 and up to 1000-fold selectivity over FKBP51 and FKBP52. 45 derivatives were synthesized and tested for their binding affinities to FKBPs. Additionally, FP-assays were conducted with different FKBP12 constructs.

In the fourth part, a small library of bicyclic [4.3.1] aza-amides with a modification of the vinyl group by Heck-reaction was synthesized. Elucidation of the crystal structures illustrated a vast space for substituents at this position enabling further contacts to the binding pocket. One derivative with a benzonitrile displayed 100-fold improved binding affinity for FKBP12, thus serving as a starting point for crystal structures and future optimizations.

The fifth part was dedicated to modifications of different parts of the bicyclic [4.3.1] aza-amide scaffold in order to identify new positions for improvement. A novel series of sulfondiamides and sulfonamides as well as double-C5-substituted bicycles were synthesized and tested for their binding affinities.

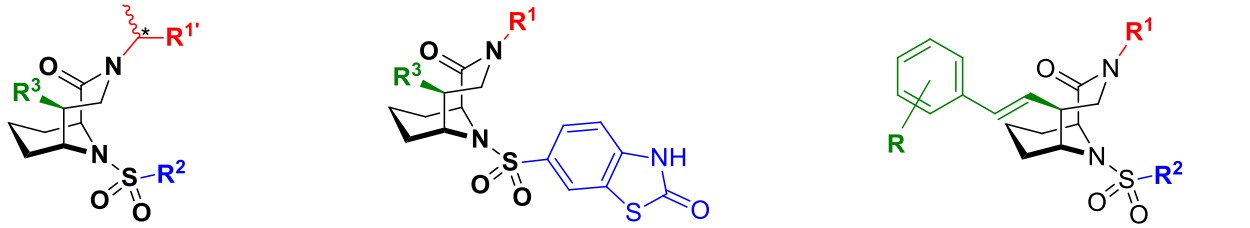
Zusammenfassung

FK506-bindende Proteine (FKBPs) haben sich aufgrund ihrer Rolle bei verschiedenen Krankheiten wie psychiatrischen Störungen, stressbedingten Erkrankungen, chronischen Schmerzen und bei mikrobiellen Infektionen als vielversprechender Ansatzpunkt für die Entwicklung von Medikamenten erwiesen. Bizyklische [4.3.1.] Aza-amide haben sich als ein privilegiertes Gerüst für FKBPs erwiesen und dienen als wertvoller Ausgangspunkt für die Entwicklung potenter FKBP-Inhibitoren. Das Ziel dieser Arbeit war es, die Affinität, Selektivität und metabolische Stabilität dieser Substanzklasse weiter zu verbessern.
Der erste Teil der Arbeit war der metabolischen Stabilität dieser Liganden gewidmet. Es wurden deuterierte Derivate synthetisiert und eine Metabolitenverteilungs-Analyse durchgeführt. Dies ermöglichte die Lokalisierung von metabolischen Schwachstellen und grenzte sie auf zwei Positionen im Molekül ein. Zum einen wird die *N*-Alkyl-Amid-Bindung durch oxidative Dealkylierung leicht gespalten, zum anderen ist der Kohlenstoff an der C4-Position anfällig für Oxidation. Um letztgenannte Position zu blockieren, wurde eine neuartige tricyclische Verbindung synthetisiert, die den Kohlenstoff C4 mit dem Amid verbrückt.



bizyklische [4.3.1] Aza-amide **deuterierte Positionen**

Der zweite Teil war der Wirkung einer Methylgruppe in der *N*-α-Position gewidmet. Verschiedene Paare von Verbindungen mit einer Methylgruppe in der *R*- und in der *S*-Konfiguration wurden synthetisiert und auf ihre Bindungsaffinitäten zu FKBPs getestet. Alle *S*-Isomere zeigten eine Zunahme der Bindungsaffinität, während die *R*-Isomere eine signifikante Abnahme der Bindungsaffinität zu allen getesteten FKBPs zeigten. Molekulare Modellierungsstudien wurden für eine Reihe von Verbindungen mit *R*-Methyl-, ohne Methyl bzw. *S*-Methyl- durchgeführt. Für jede Verbindung wurden Energiekarten erstellt, um bevorzugte Konformationen zu bestimmen und die Auswirkung der Pre-organisation des Liganden auf die Bindungsaffinität zu untersuchen. Eine Verbindung mit einer zusätzlichen Rotationsbarriere wurde synthetisiert, um die Konformation zu fixieren, die der in der Kristallstruktur gefundenen Konformation am ähnlichsten ist.



***S*- und *R*-Methyl Verbindungen** **6-Benzo[d]thiazol-2(3H)-one Verbindungen** **Modifikation durch Heck-Reaktion**

Der dritte Teil der Arbeit war den bizyklischen [4.3.1] Aza-amiden mit einem 6-Benzo[d]thiazol-2(3H)-one-Rest am Sulfonamid gewidmet. Dieser spezielle Rest zeigte eine subnanomolare Bindungsaffinität zu FKBP12 und eine bis zu 1000-fache Selektivität gegenüber FKBP51 und FKBP52. 45 Derivate wurden synthetisiert und auf ihre Bindungsaffinität zu FKBPs getestet. Zusätzlich wurden FP-Assays mit verschiedenen FKBP12-Konstrukten durchgeführt.
Im vierten Teil wurde eine kleine Bibliothek an bizyklischen [4.3.1] Aza-amiden mit einer Modifikation der Vinylgruppe durch die Heck-Reaktion synthetisiert. Die Analyse der Kristallstrukturen zeigte einen großen Raum für Substituenten an dieser Position, die weitere Kontakte zur Bindungstasche ermöglichen. Ein Derivat mit einem Benzonitril zeigte eine 100-fach verbesserte Bindungsaffinität für FKBP12 und kann somit als Ausgangspunkt für Kristallstrukturen und zukünftige Optimierungen dienen.
Der fünfte Teil war den Modifikationen verschiedener Teile des bizyklischen [4.3.1] Aza-amid-Gerüsts gewidmet, um neue Positionen für Verbesserungen zu identifizieren. Eine neuartige Serie von Sulfondiamiden und Sulfonamiden sowie doppelt C5-substituierte Bizyklen wurden synthetisiert und auf ihre Bindungsaffinitäten getestet.

Table of contents

1. Synthetic schemes

All prepared or used compounds in this thesis are numbered in bold Arabic numerals. Compounds unknown to literature are additionally underlined. Compounds that refer to the literature, not characterized intermediates as well as hypothetical compounds are numbered in bold Roman numerals. Compounds that are based on the scaffold depicted in **Fig. 1** are generally referred to as "bicyclic" and more specifically described by their residues in R^1, R^2 and R^3. Reaction conditions are abbreviated as letters and described in more detail below the scheme. Letters separated by a comma refer to reactions that have been performed consecutively; letters separated by a hyphen correspond to different reaction conditions.

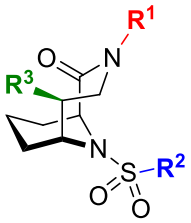
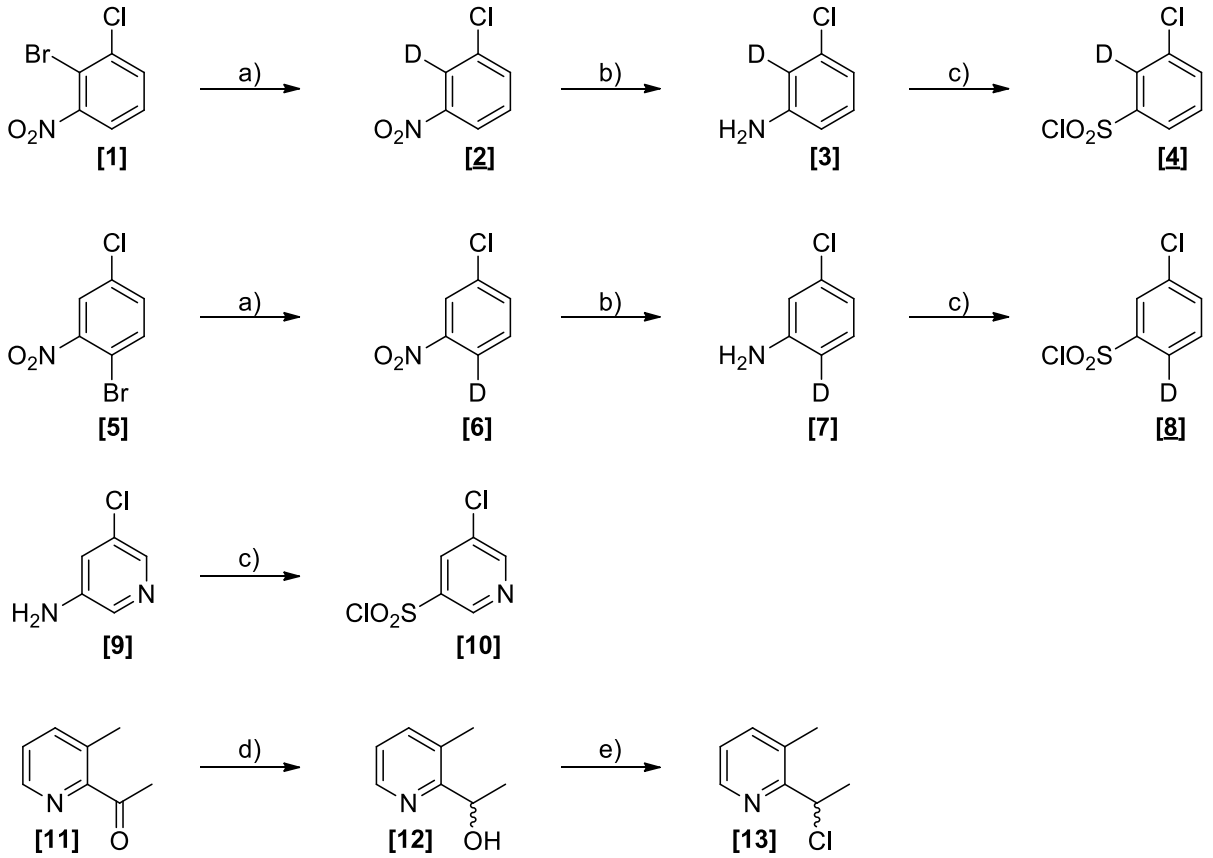
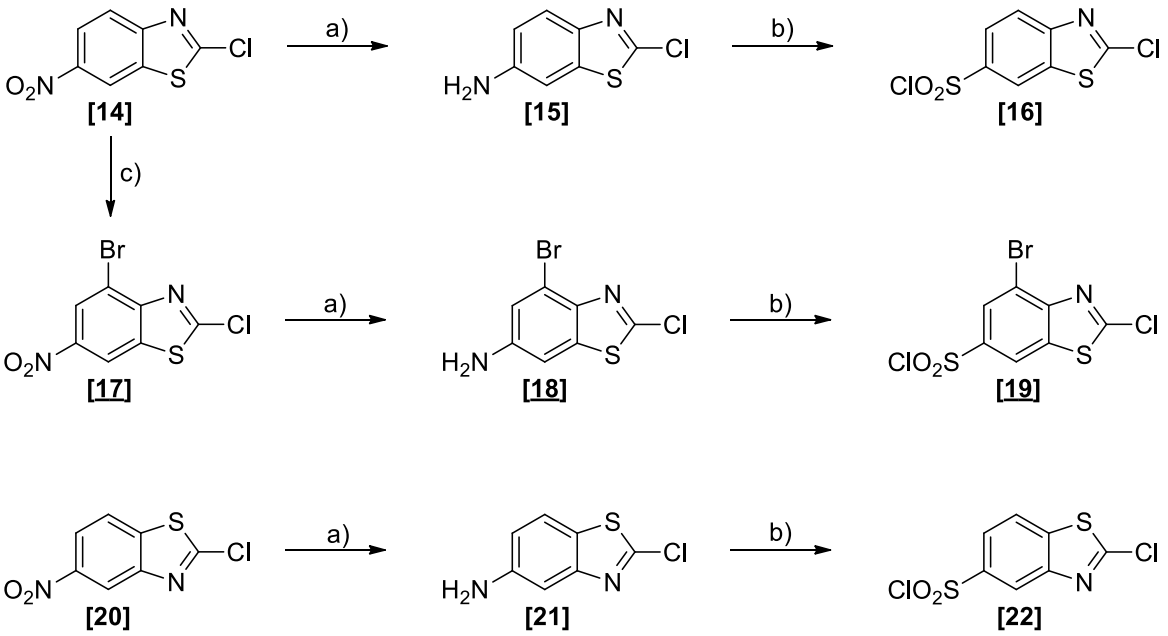


Figure 1. Basic scaffold of bicyclic [4.3.1] aza-amides.

1.1. Sulfonyl chlorides and chlorides

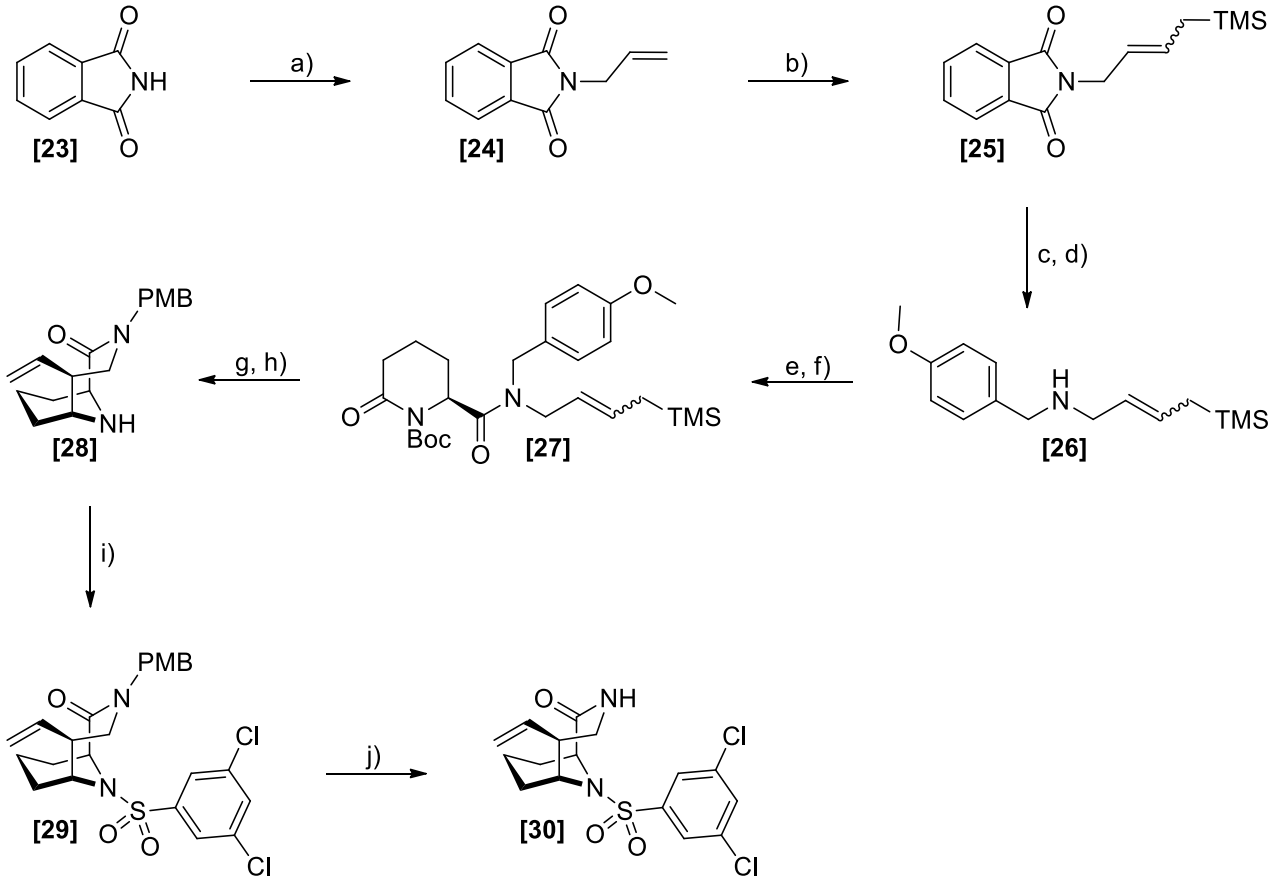


Scheme 1. Reagents and conditions: a) DCOONa, $Pd_2(dba)_3$, $P(Cy)_3$, DMSO, 80 °C, 16 h; b) Zn, NH_4Cl, EtOH, rt, 16 h; c) $NaNO_2$, MeCN, 0 °C, 15 min then SO_2/HCl, $CuCl_2$, rt, 16 h; d) $NaBH_4$, $CeCl_3$, EtOH, 0 °C, 30 min; e) $SOCl_2$, DCM, 0 °C, 2 h



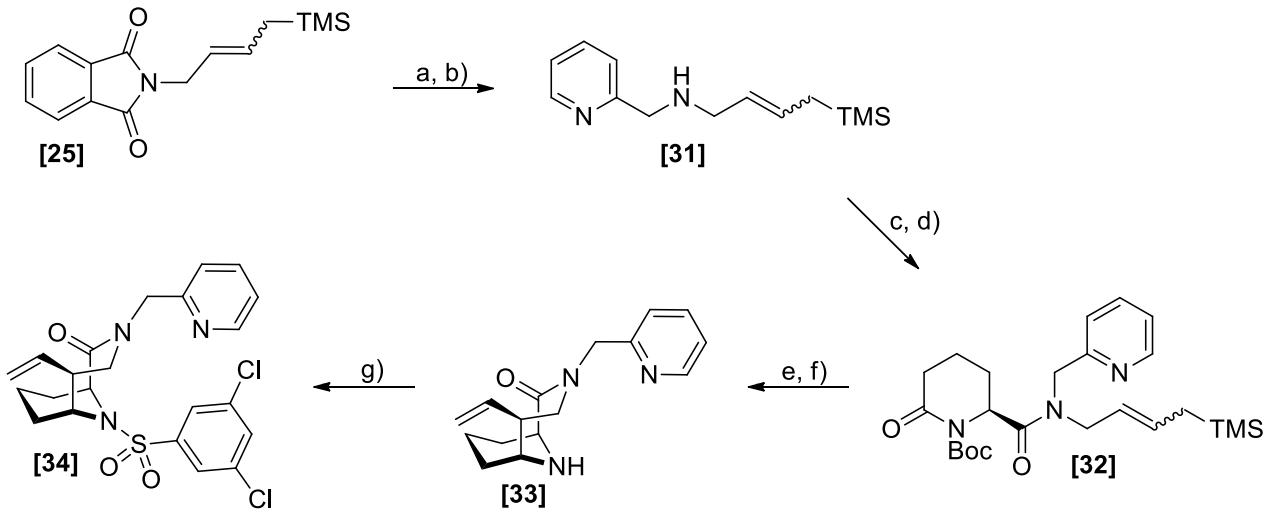
Scheme 2. Reagents and conditions: a) Zn, NH_4Cl, EtOH, rt, 16 h; b) $NaNO_2$, MeCN, 0 °C, 15 min then SO_2/HCl, $CuCl_2$, rt, 16 h; c) NBS, H_2SO_4, 60 °C, 16 h

1.2. PMB-protected building block [29] and PMB-deprotected compound [30]



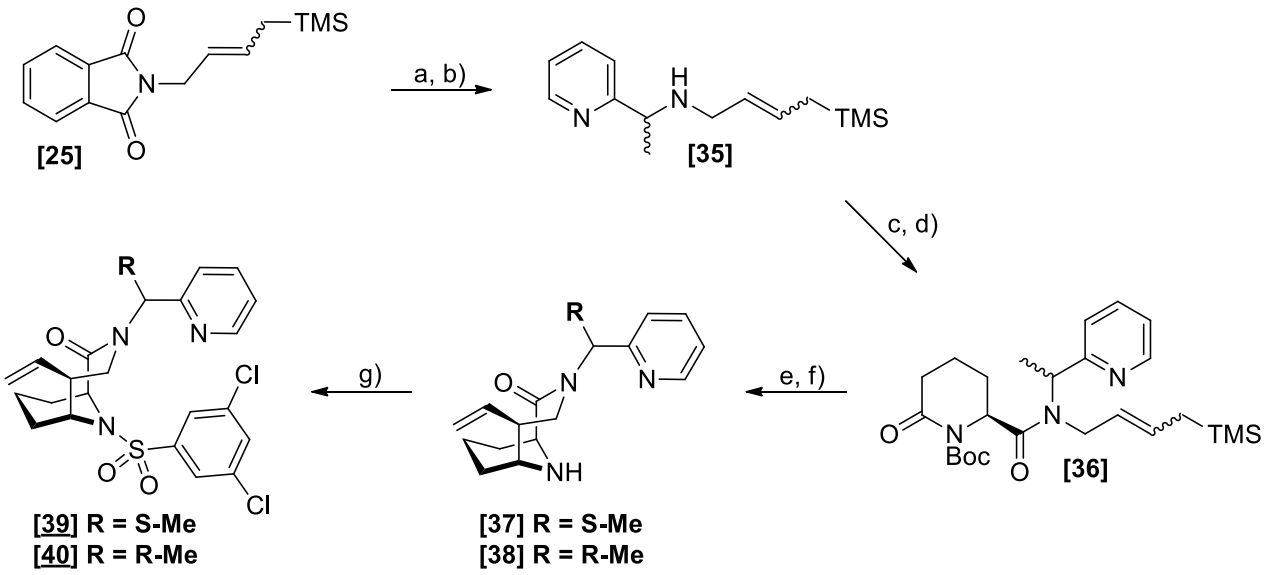
Scheme 3. Reagents and conditions: a) allyl bromide, K_2CO_3, DMF, rt, 5 h; b) allyltrimethylsilane, Grubbs I, DCM, 60 °C, 4 h; c) hydrazine, MeOH, 80 °C, 18 h; d) 4-methoxybenzaldehyde, $NaBH_4$, EtOH, rt, 2 h; e) (*S*)-6-oxopiperidine-2-carboxylic acid, HATU, DIPEA, DCM, rt, 16 h; f) Boc_2O, DMAP, DIPEA, DCM, rt, 72 h; g) DIBAL-H, THF, -78 °C, 1 h; h) HF-pyridine, DCM, -78 °C – 0 °C, 2 h; i) 3,5-Dichlorobenzenesulfonyl chloride, DIPEA, MeCN, rt, 20 h; j) CAN, MeCN/H_2O, rt, 4 h

1.3. Bicyclic building block with R^1 = (pyridine-2-ylmethyl)



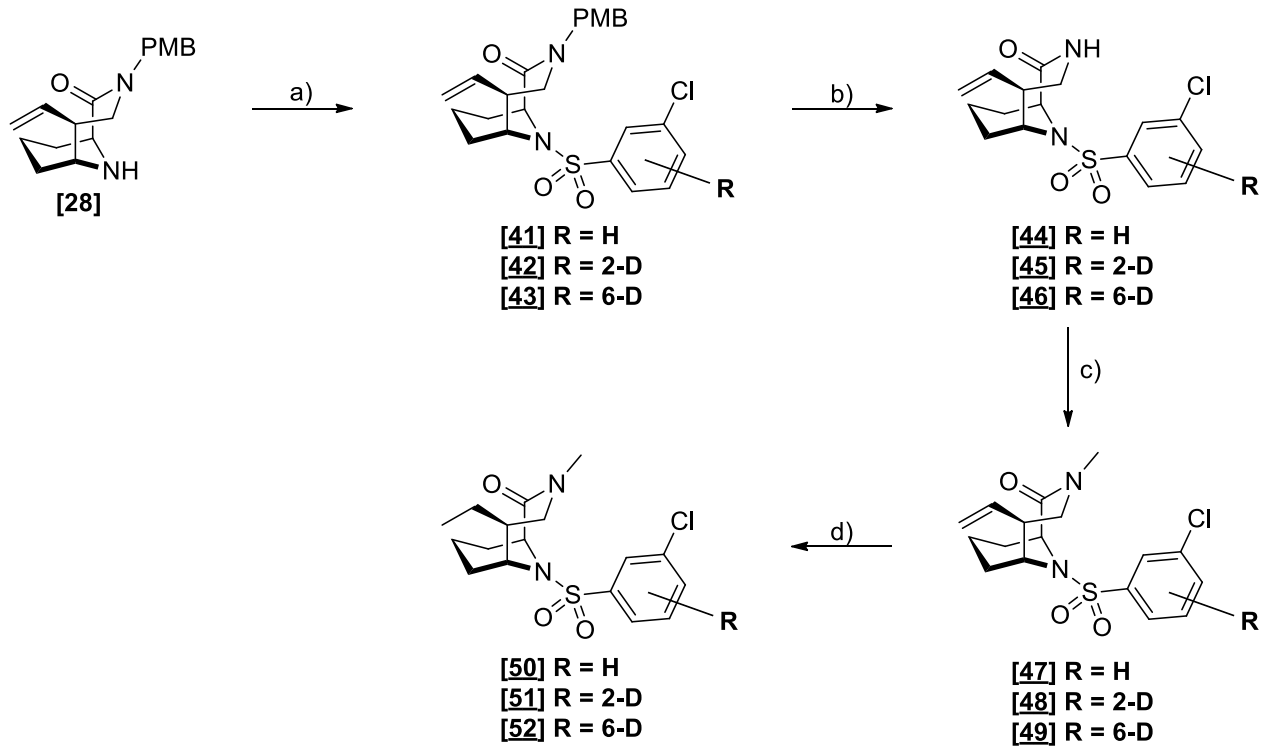
Scheme 4. Reagents and conditions: a) hydrazine, MeOH, 80 °C, 18 h; b) picolinaldehyde, $NaBH_4$, EtOH, rt, 2 h; c) (*S*)-6-oxopiperidine-2-carboxylic acid, HATU, DIPEA, DCM, rt, 16 h; d) Boc_2O, DMAP, DIPEA, DCM, rt, 72 h; e) DIBAL-H, THF, -78 °C, 1 h; f) HF-pyridine, DCM, -78 °C – 0 °C, 2 h; g) 3,5-Dichlorobenzenesulfonyl chloride, DIPEA, MeCN, rt, 20 h

1.4. Bicyclic building blocks with R^1 = (pyridine-2-ylethyl)

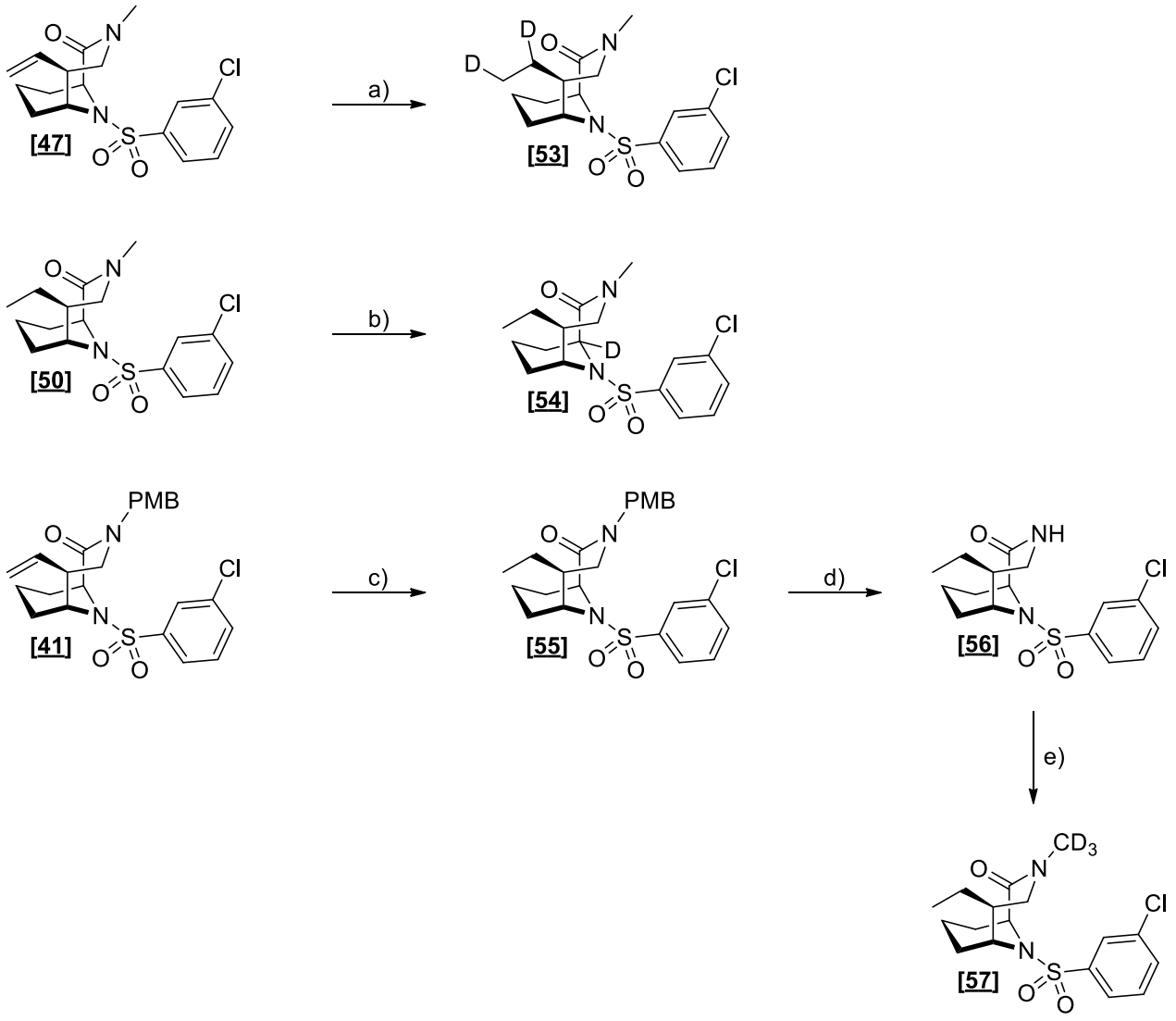


Scheme 5. Reagents and conditions: a) hydrazine, MeOH, 80 °C, 18 h; b) 1-(pyridine-2-yl)ethanone, $NaBH_4$, EtOH, rt, 2 h; c) (*S*)-6-oxopiperidine-2-carboxylic acid, HATU, DIPEA, DCM, rt, 16 h; d) Boc_2O, DMAP, DIPEA, DCM, rt, 72 h; e) DIBAL-H, THF, -78 °C, 1 h; f) HF-pyridine, DCM, -78 °C – 0 °C, 2 h; g) 3,5-Dichlorobenzenesulfonyl chloride, DIPEA, MeCN, rt, 20 h

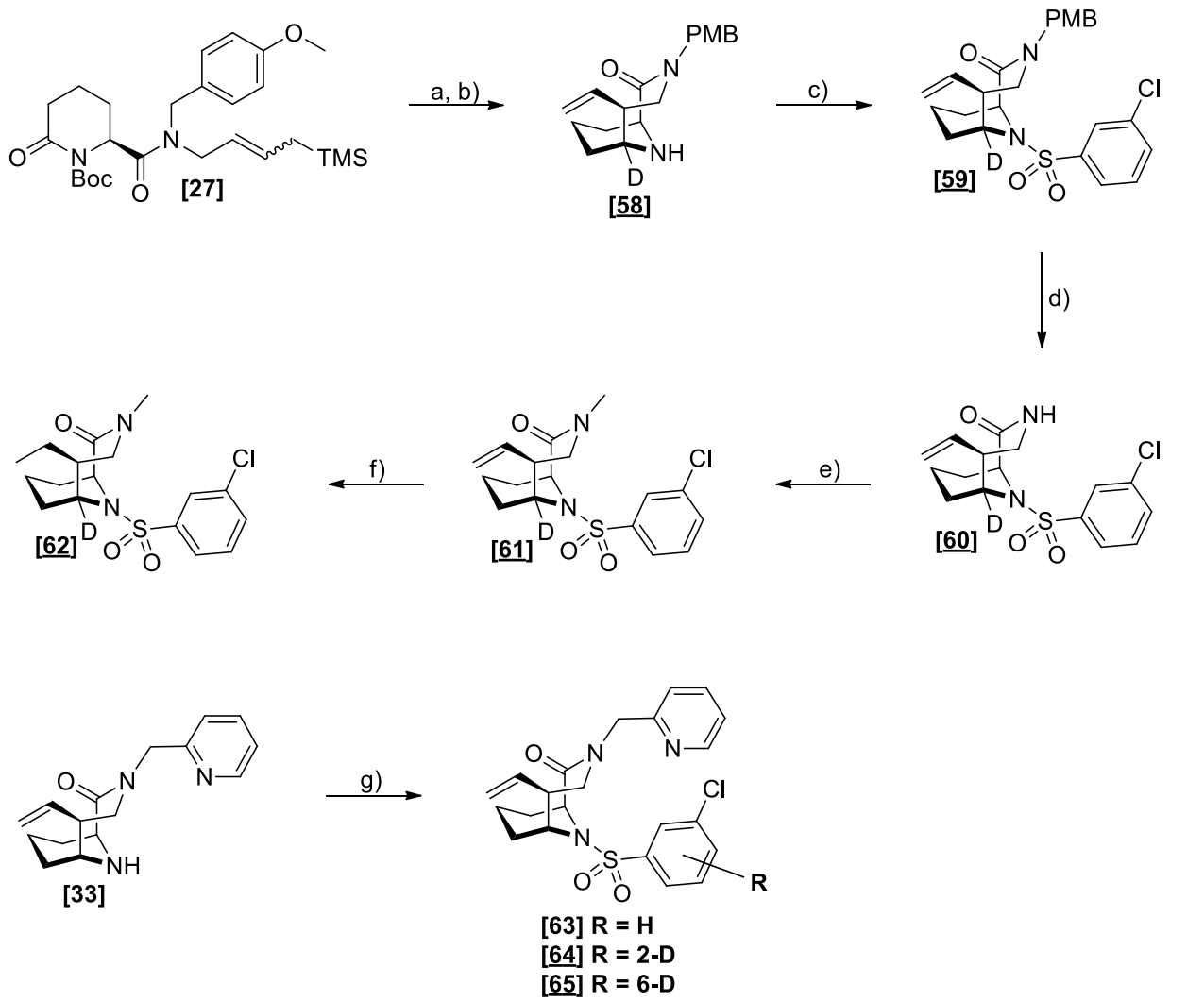
1.5. Deuterated derivatives and respective reference compounds [50] and [63]



Scheme 6. Reagents and conditions: a) **R**-3-chlorobenzenesulfonyl chloride, DIPEA, MeCN, rt, 20 h; b) CAN, MeCN/H_2O, rt, 4 h; c) MeI, NaH, MeCN, 40 °C, 4 h; d) H_2, Pt/C, MeOH, rt, 1 h

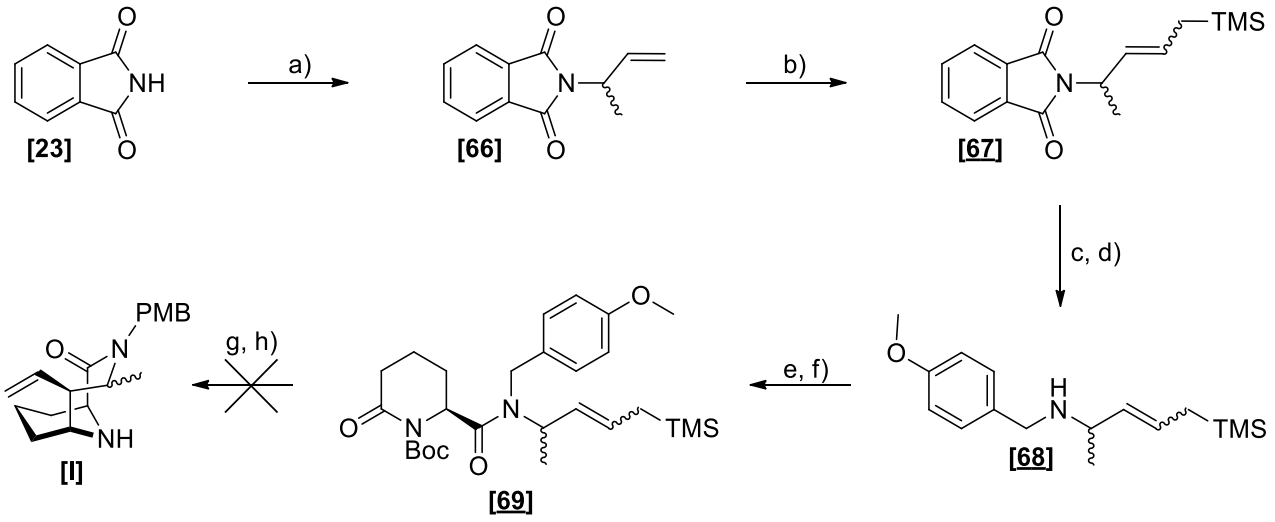


Scheme 7. Reagents and conditions: a) D_2, [$RhCl(PPh_3)_3$], toluene, rt, 16 h; b) KOD, MeOD, rt, 2 h; c) H_2, Pt/C, MeOH, rt, 1 h; d) CAN, $MeCN/H_2O$, rt, 4 h; e) MeI-d_3, NaH, DMF, 80 °C, 1h



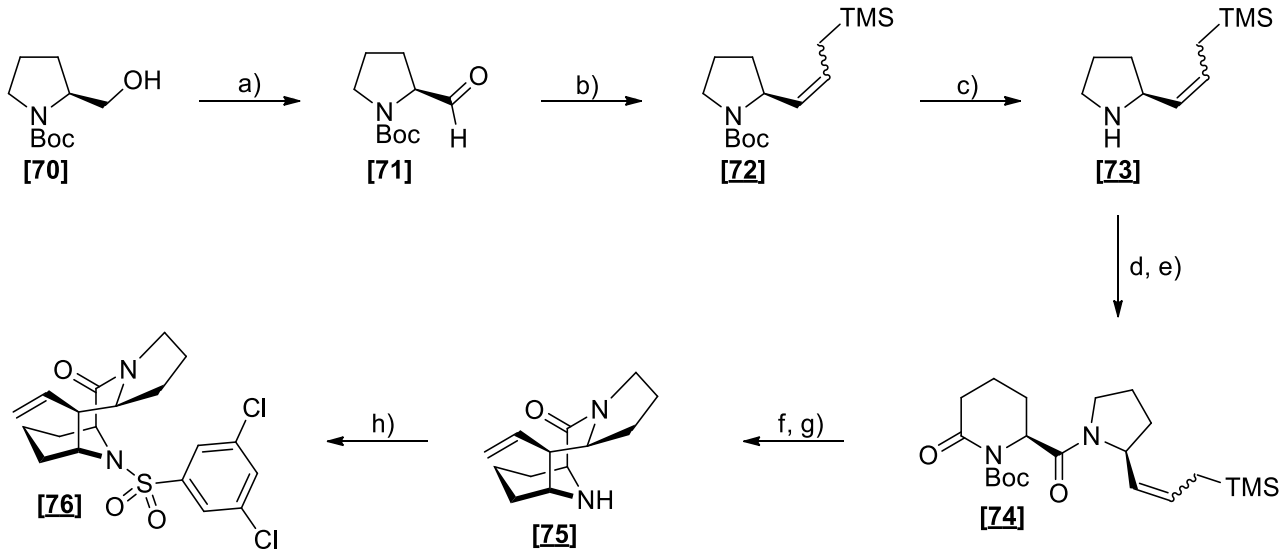
Scheme 8. Reagents and conditions: a) DIBAL-D, THF, -78 °C, 1 h; b) HF-pyridine, DCM, -78 °C – 0 °C, 2 h; c) 3-chlorobenzenesulfonyl chloride, DIPEA, MeCN, rt, 16 h; d) CAN, MeCN/H_2O, rt, 4 h; e) MeI, NaH, DMF, 80 °C, 1h; f) H_2, Pt/C, MeOH, rt, 1 h; g) **R**-3-chlorobenzenesulfonyl chloride, DIPEA, MeCN, rt, 16 h

1.6. Attempted synthesis of 4-methyl derivative [I]



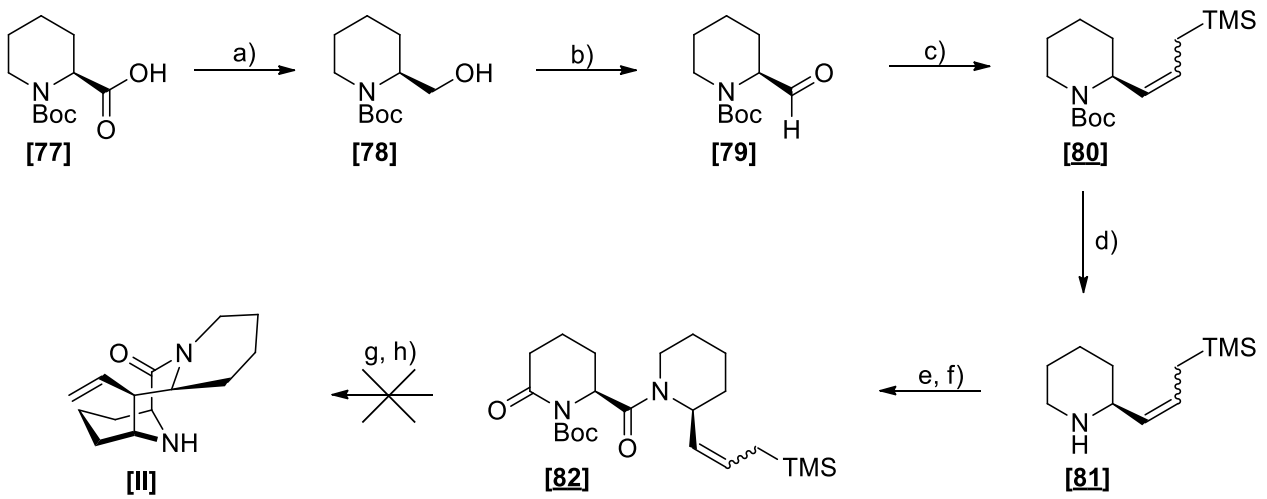
Scheme 9. Reagents and conditions: a) 3-chlorobut-1-ene, K_2CO_3, DMF, rt, 5 h; b) allyltrimethylsilane, Grubbs I, DCM, 60 °C, 4 h; c) hydrazine, MeOH, 80 °C, 18 h; d) 4-methoxybenzaldehyde, $NaBH_4$, EtOH, rt, 2 h; e) (*S*)-6-oxopiperidine-2-carboxylic acid, HATU, DIPEA, DCM, rt, 16 h; f) Boc_2O, DMAP, DIPEA, DCM, rt, 72 h; g) DIBAL-H, THF, -78 °C, 1 h; h) HF-pyridine, DCM, -78 °C – 0 °C, 2 h;

1.7. Tricyclic compound [76]



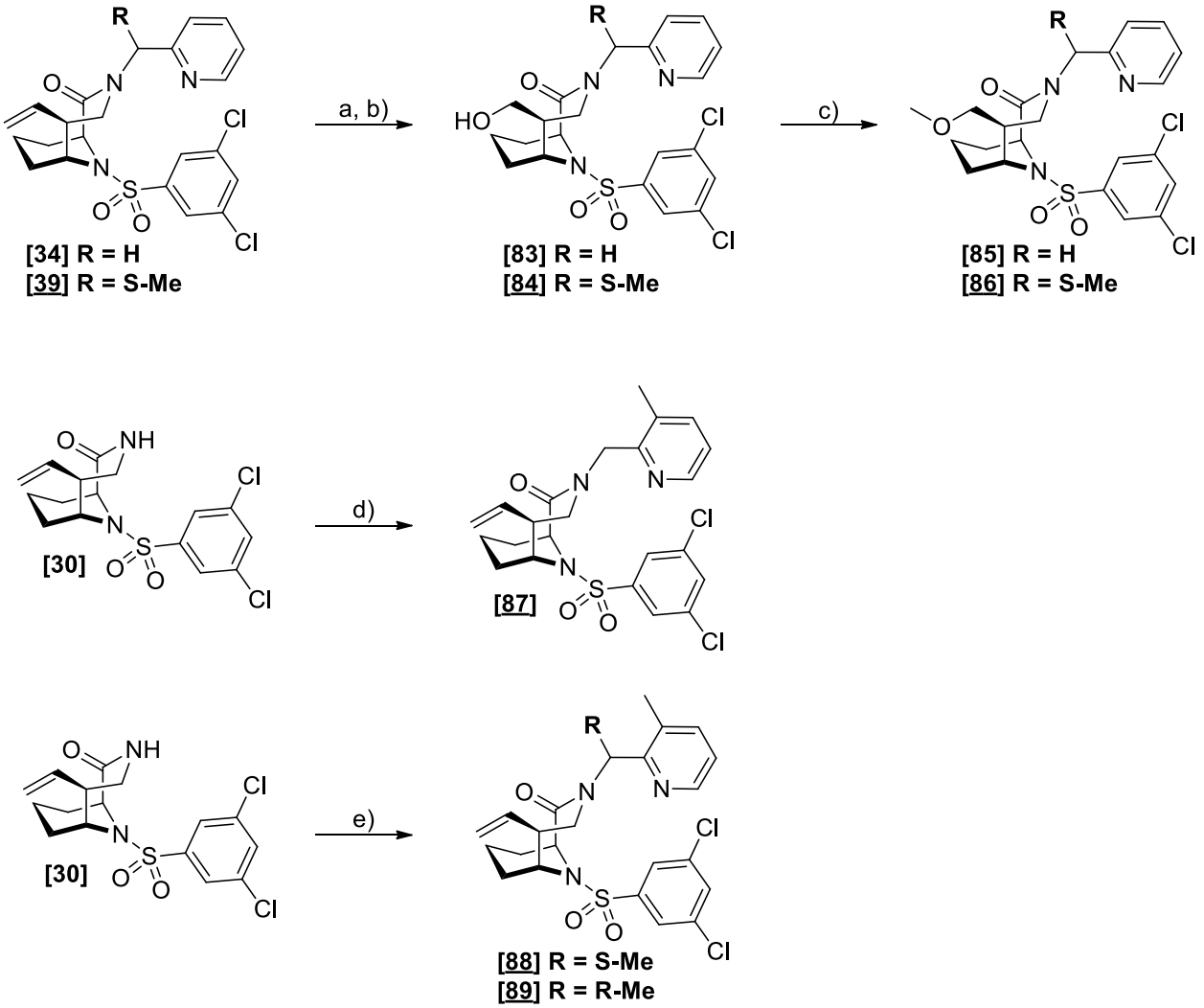
Scheme 10. Reagents and conditions: a) DMP, DCM, rt, 1 h; b) (2-Trimethylsilylethyl)triphenylphosphonium iodide, n-BuLi, THF, 0 °C, 2 h; c) $ZnBr_2$, DCM, rt, 16 h; d) (*S*)-6-oxopiperidine-2-carboxylic acid, HATU, DIPEA, DCM, rt, 16 h; e) Boc_2O, DMAP, DIPEA, DCM, rt, 72 h; f) DIBAL-H, THF, -78 °C, 1 h; g) HF-pyridine, DCM, -78 °C – 0 °C, 2 h; h) 3,5-Dichlorobenzenesulfonyl chloride, DIPEA, MeCN, rt, 16 h

1.8. Attempted synthesis of tricyclic compound [II]

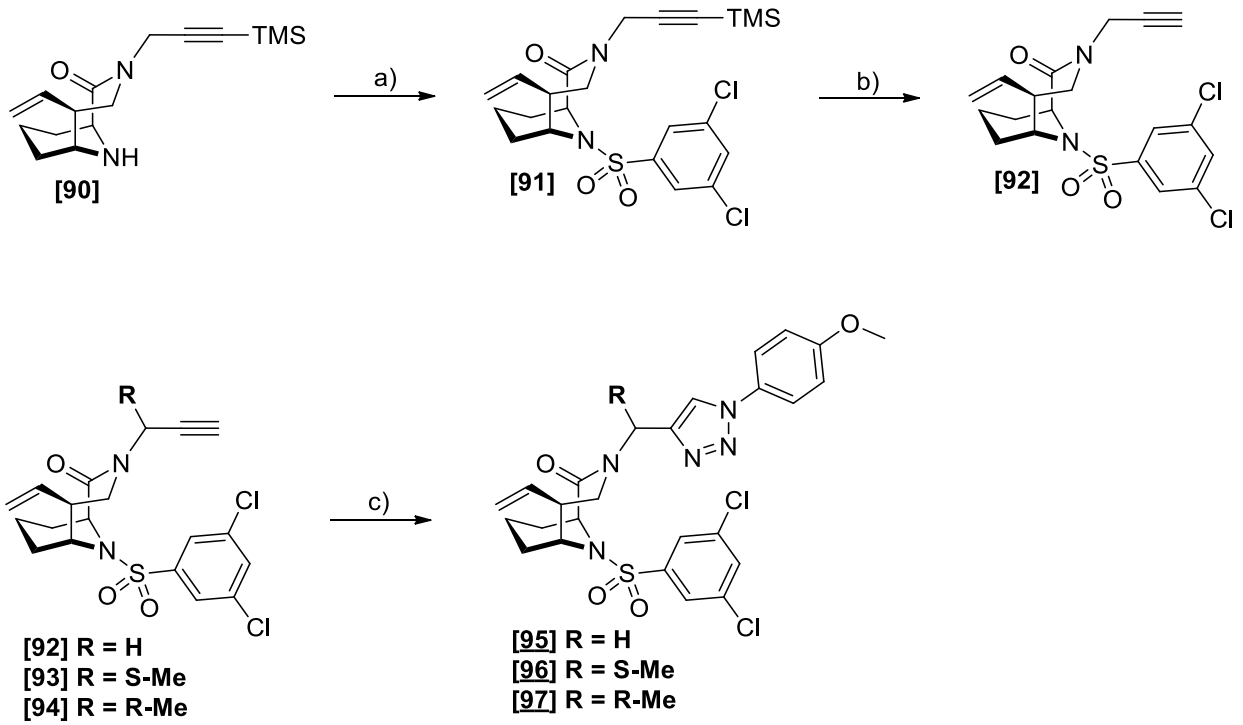


Scheme 11. Reagents and conditions: a) BH_3*SMe_2, THF, 0 °C, 16 h; b) DMP, DCM, rt, 1 h; c) (2-Trimethylsilylethyl)triphenylphosphonium iodide, n-BuLi, THF, 0 °C, 2 h; d) $ZnBr_2$, DCM, rt, 16 h; e) (*S*)-6-oxopiperidine-2-carboxylic acid, HATU, DIPEA, DCM, rt, 16 h; f) Boc_2O, DMAP, DIPEA, DCM, rt, 72 h; g) DIBAL-H, THF, -78 °C, 1 h; h) HF-pyridine, DCM, -78 °C – 0 °C, 2 h

1.9. *N*-α-methyl group in R^1 and R^2 = (3,5-dichlorophenyl) & respective compounds w/o methyl

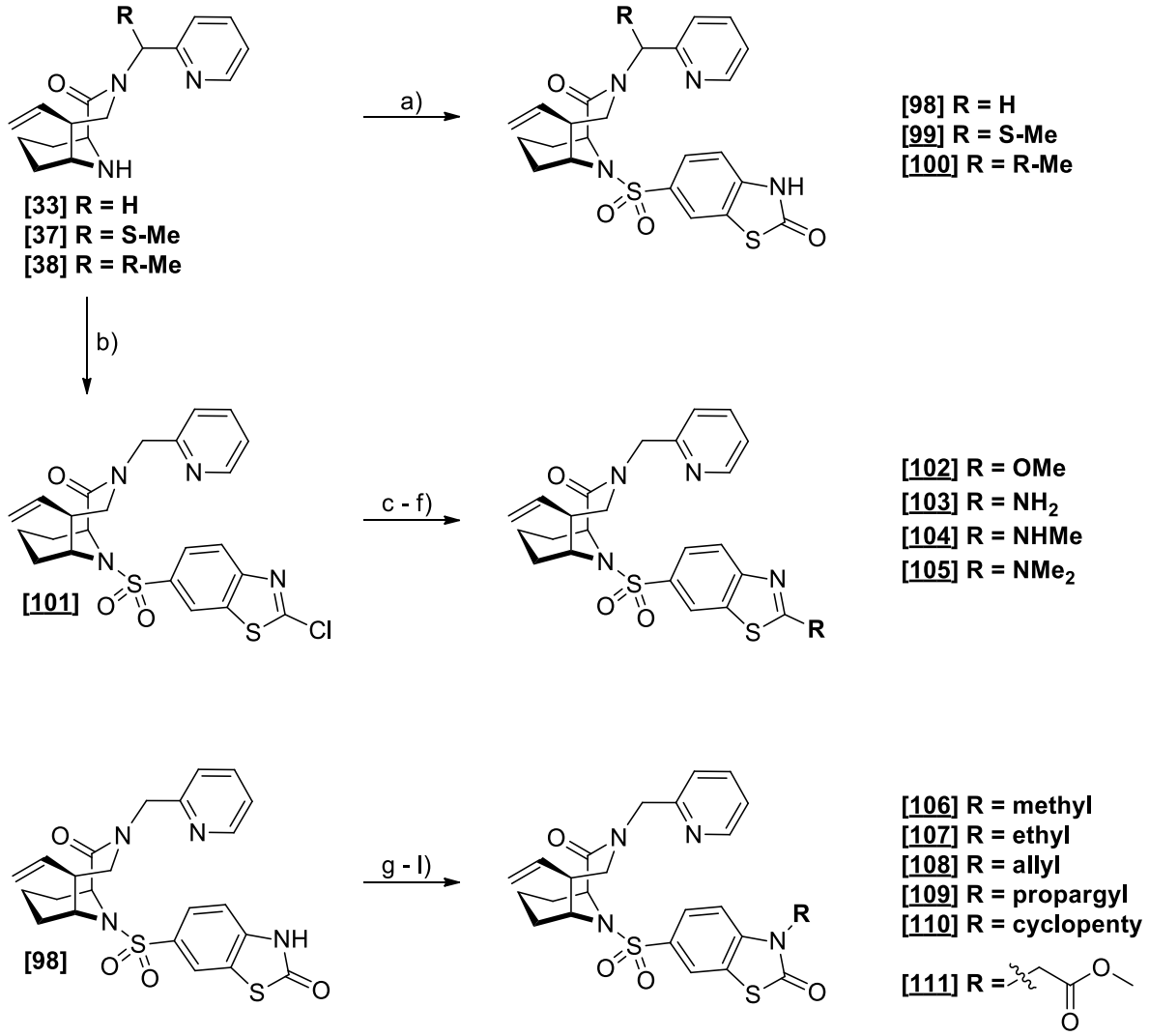


Scheme 12. Reagents and conditions: a) OsO_4, NMO, 2,6-lutidine, acetone/H_2O, 16 h then $PhI(OAc)_2$, 3 h; b) $NaBH_4$, EtOH, 0 °C, 1 h; c) MeI, NaH, DMF, 0 °C, 2 h; d) 2-(chloromethyl)-3-methylpyridine, NaH, DMF, 80 °C, 1 h; e) **[13]**, NaH, MeCN, 40 °C, 4 h;

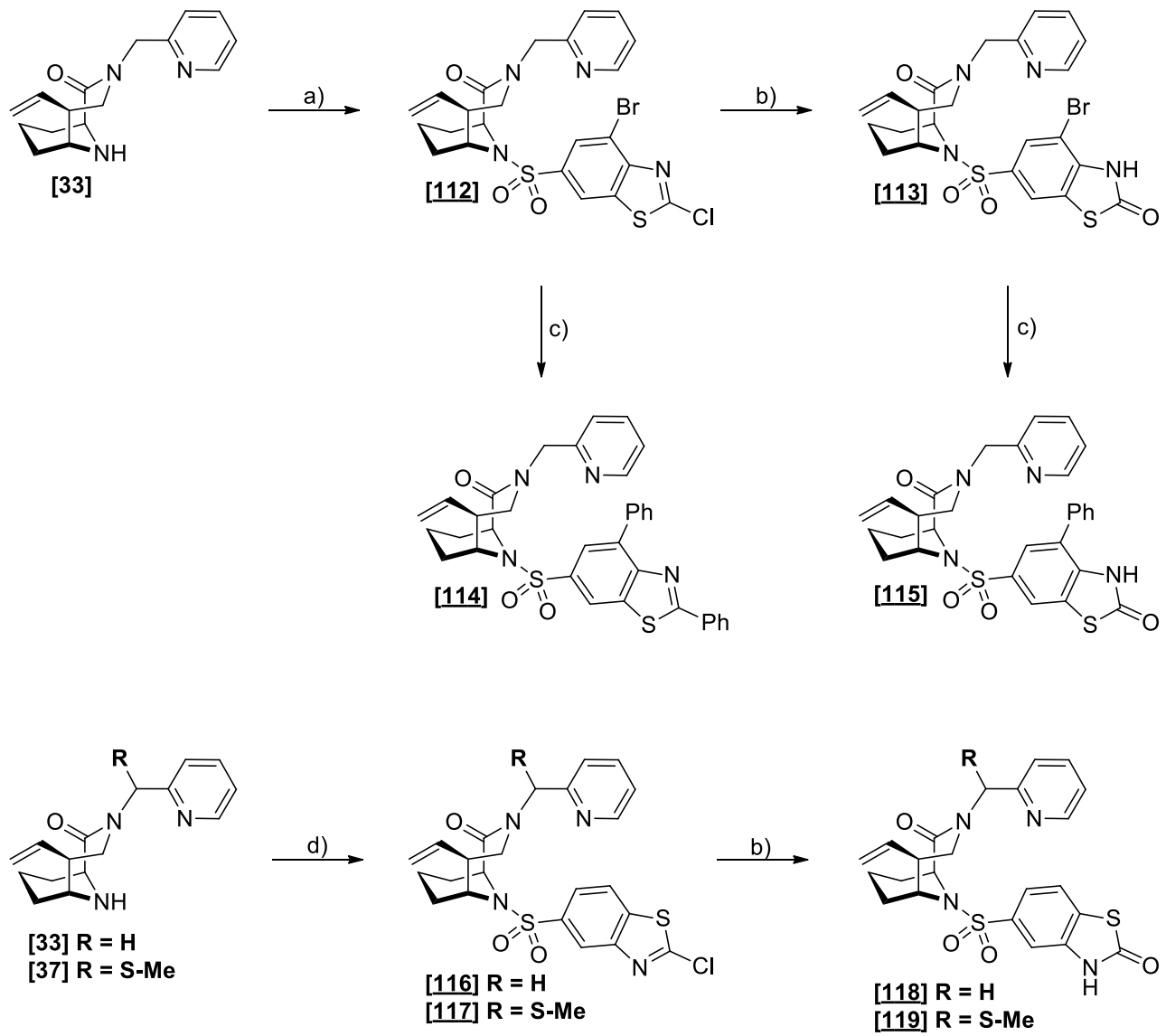


Scheme 13. Reagents and conditions: a) 3,5-Dichlorobenzenesulfonyl chloride, DIPEA, MeCN, rt, 16 h; b) 1M NaOH, THF, 80 °C, 16 h; c) 1-azido-4-methoxybenzene, $CuSO_4$, sodium ascorbate, t-BuOH/H_2O, 37 °C, 16 h

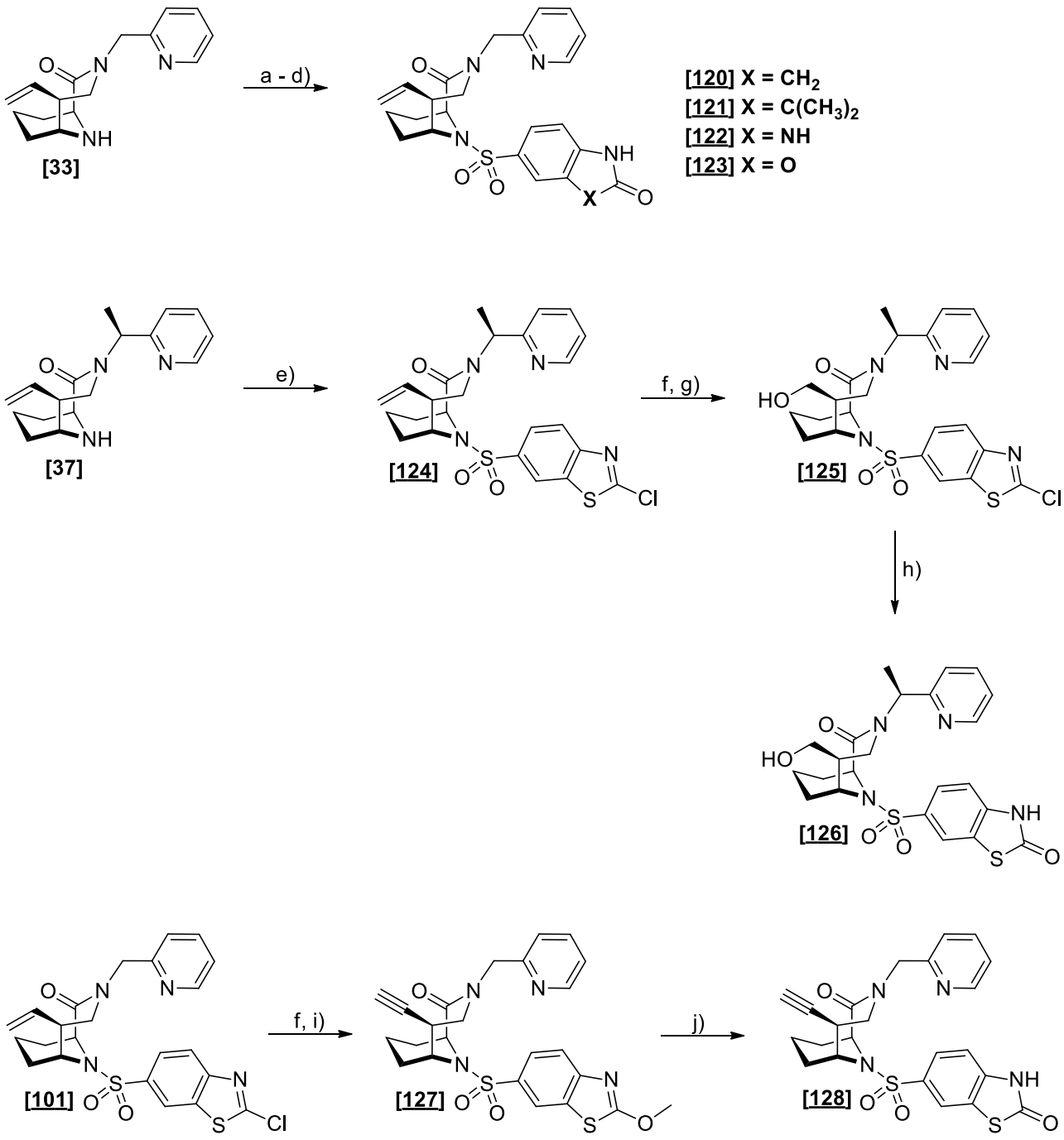
1.10. R^2 = 6- benzo[d]thiazol-2(3H)-one and derivatives thereof



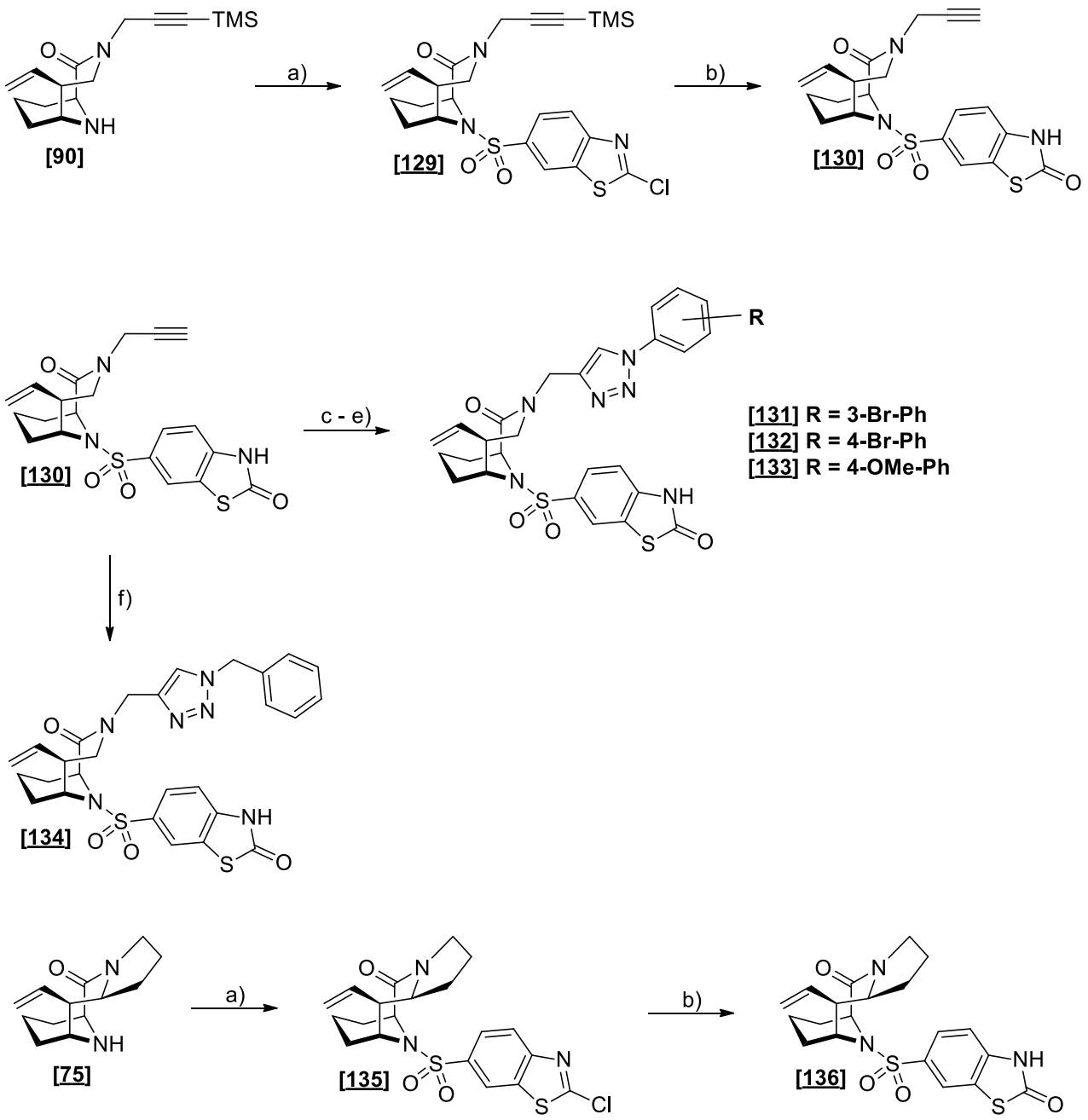
Scheme 14. Reagents and conditions: a) 2-Oxo-2,3-dihydro-1,3-benzothiazole-6-sulfonyl chloride, DIPEA, MeCN, rt, 16 h; b) 2-Chloro-1,3-benzothiazole-6-sulfonyl chloride, DIPEA, MeCN, rt, 16 h; c) MeONa, MeOH, 80 °C, 12 h; d) NH_3, dioxane, 80 °C, 8 h; e) $MeNH_2$*HCl, K_2CO_3, dioxane, 80 °C, 8 h; f) Me_2NH*HCl, K_2CO_3, dioxane, 80 °C, 8 h; g) MeI, NaH, DMF, rt, 1 h; h) EtI, NaH, DMF, rt, 1 h; i) allyl bromide, NaH, DMF, rt, 2 h; j) propargyl bromide, NaH, DMF, rt, 2 h; k) cyclopentyl iodide, NaH, DMF, rt, 16 h; methyl bromoacetate, NaH, DMF, rt, 2 h



Scheme 15. Reagents and conditions: a) **[19]**, DIPEA, MeCN, rt, 16 h; b) NaOH, dioxane, 80 °C, 16 h; c) phenylboronic acid, $Pd(PPH_3)_4$, K_2CO_3, toluene, ethanol, 90 °C, 14 h; d) 2-Chloro-1,3-benzothiazole-5-sulfonyl chloride, DIPEA, MeCN, rt, 16 h

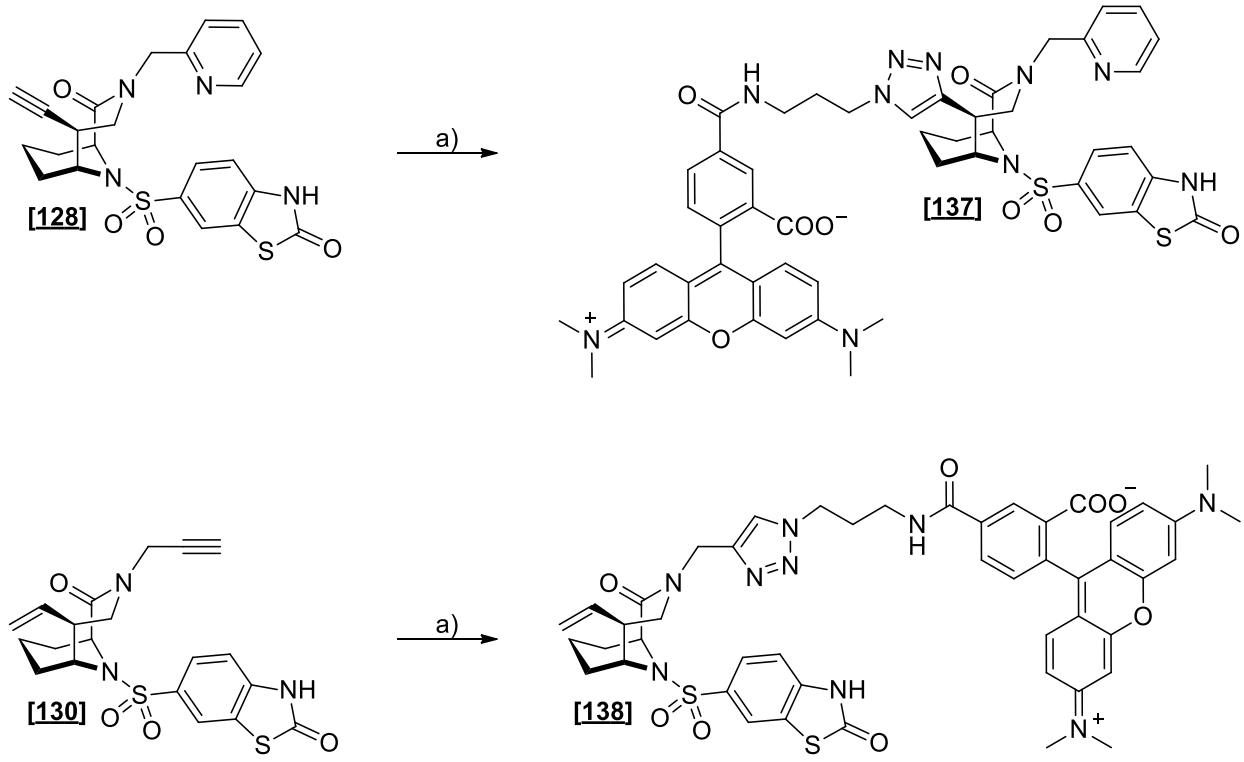


Scheme 16. Reagents and conditions: a) 2-oxoindoline-5-sulfonyl chloride, ZnO, MeCN, rt, 16 h; b) 3,3-dimethyl-2-oxoindoline-5-sulfonyl chloride, ZnO, MeCN, rt, 16 h; c) 2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-sulfonyl chloride, ZnO, MeCN, rt, 16 h; d) 2-oxo-2,3-dihydrobenzo[d]oxazole-6-sulfonyl chloride, ZnO, MeCN, rt, 16 h; e) 2-Chloro-1,3-benzothiazole-6-sulfonyl chloride, DIPEA, MeCN, rt, 16 h; f) OsO_4, NMO, 2,6-lutidine, acetone/H_2O, 16 h then $PhI(OAc)_2$, 3 h; g) $NaBH_4$, EtOH, 0 °C, 1 h; h) NaOH, dioxane, 80 °C, 16 h; i) Bestmann-Ohira reagent, K_2CO_3, MeOH, 0 °C, 16 h; j) HCl, dioxane, rt, 4 h



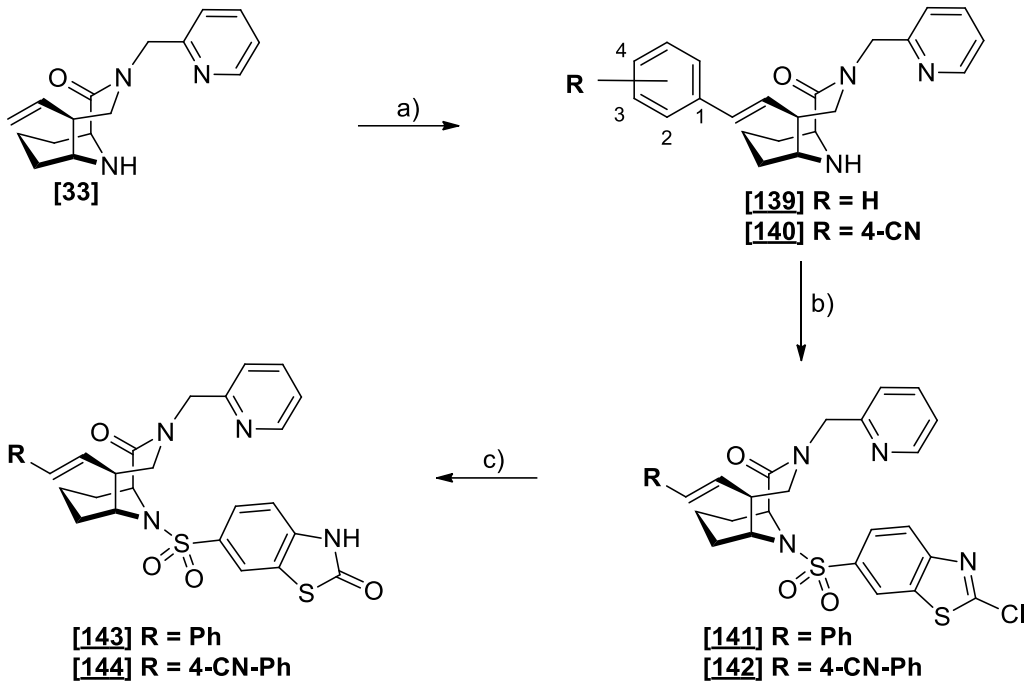
Scheme 17. Reagents and conditions: a) 2-Chloro-1,3-benzothiazole-6-sulfonyl chloride, DIPEA, MeCN, rt, 16 h; b) NaOH, dioxane, 80 °C, 16 h; c) 1-azido-4-bromobenzene, $CuSO_4$, sodium ascorbate, t-BuOH/H_2O, 37 °C, 16 h; d) 1-azido-3-bromobenzene, $CuSO_4$, sodium ascorbate, t-BuOH/H_2O, 37 °C, 16 h; e) 1-azido-4-methoxybenzene, $CuSO_4$, sodium ascorbate, t-BuOH/H_2O, 37 °C, 16 h; f) benzyl azide, $CuSO_4$, sodium ascorbate, t-BuOH/H_2O, 37 °C, 16 h;

1.11. Tracer

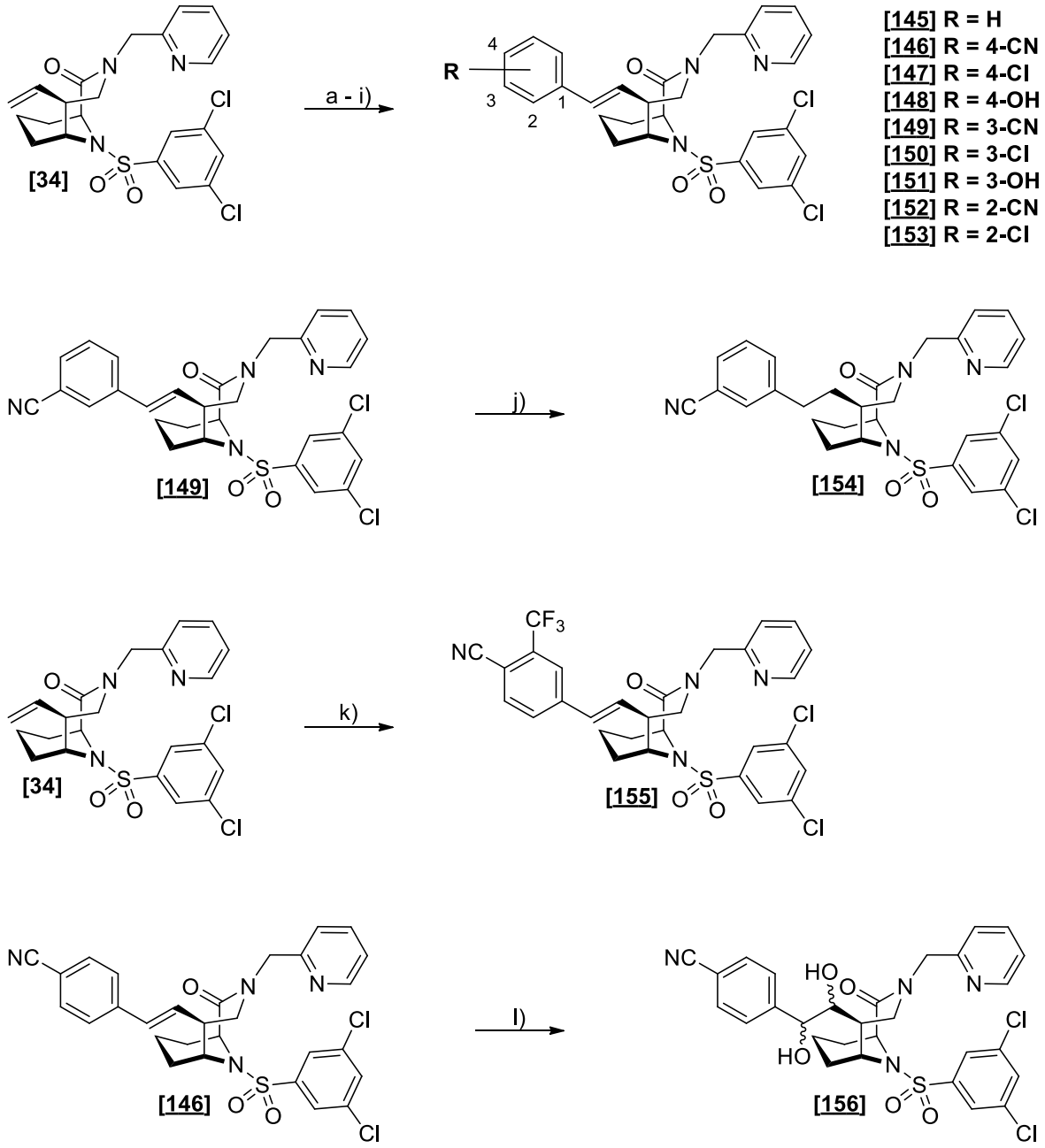


Scheme 18. Reagents and conditions: a) TAMRA-N_3, $CuSO_4$, sodium ascorbate, t-BuOH/H_2O, 37 °C, 16 h

1.12. Compounds derived from Heck-coupling at R^3

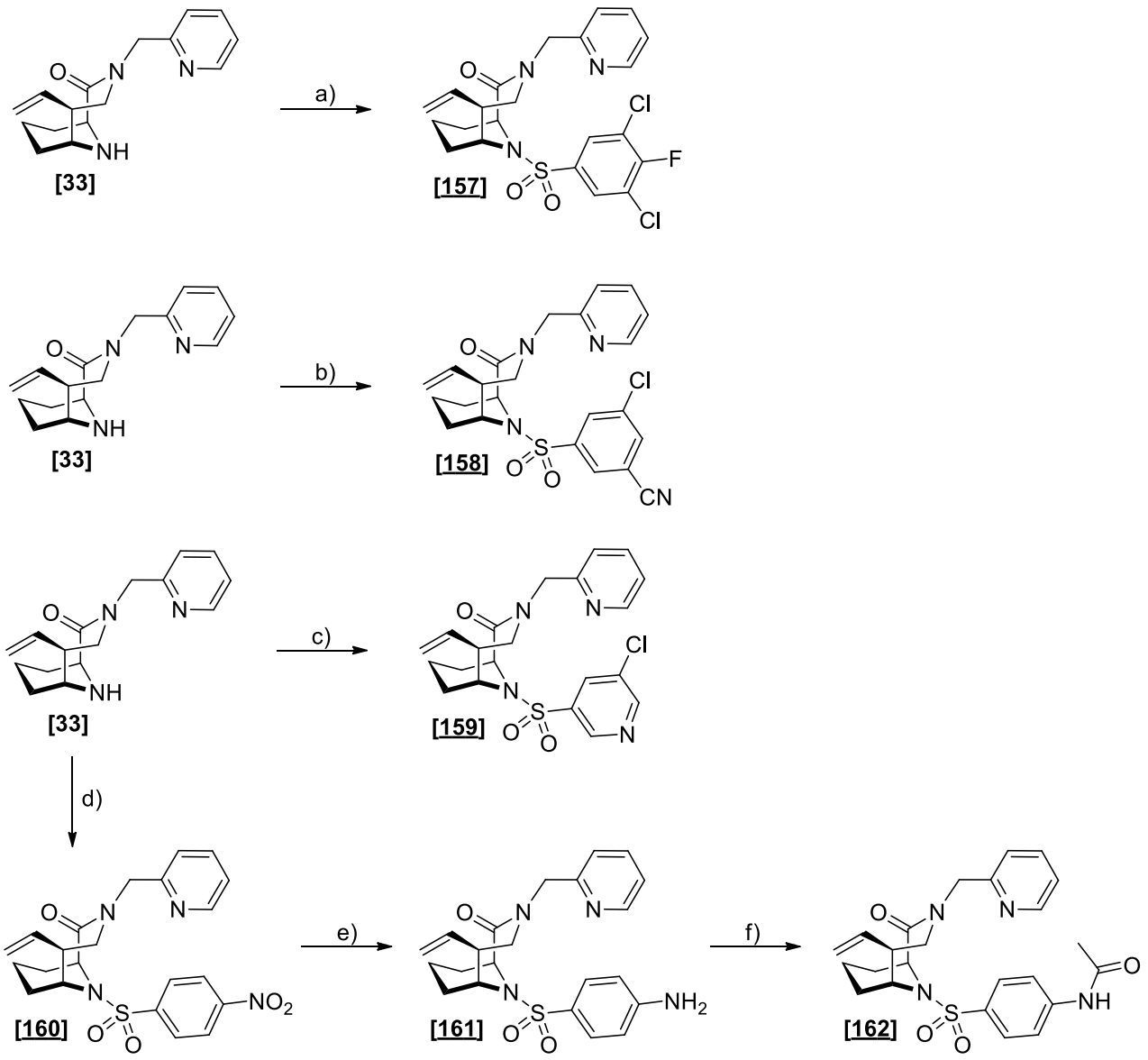


Scheme 19. Reagents and conditions: a) for **[139]** bromobenzene, for **[140]** 4-bromobenzonitrile, $Pd(PPh_3)_4$, K_2CO_3, DMF, 120 °C, 16 h; b) 2-Chloro-1,3-benzothiazole-6-sulfonyl chloride, DIPEA, MeCN, rt, 16 h; c) NaOH, dioxane, 80 °C, 16 h

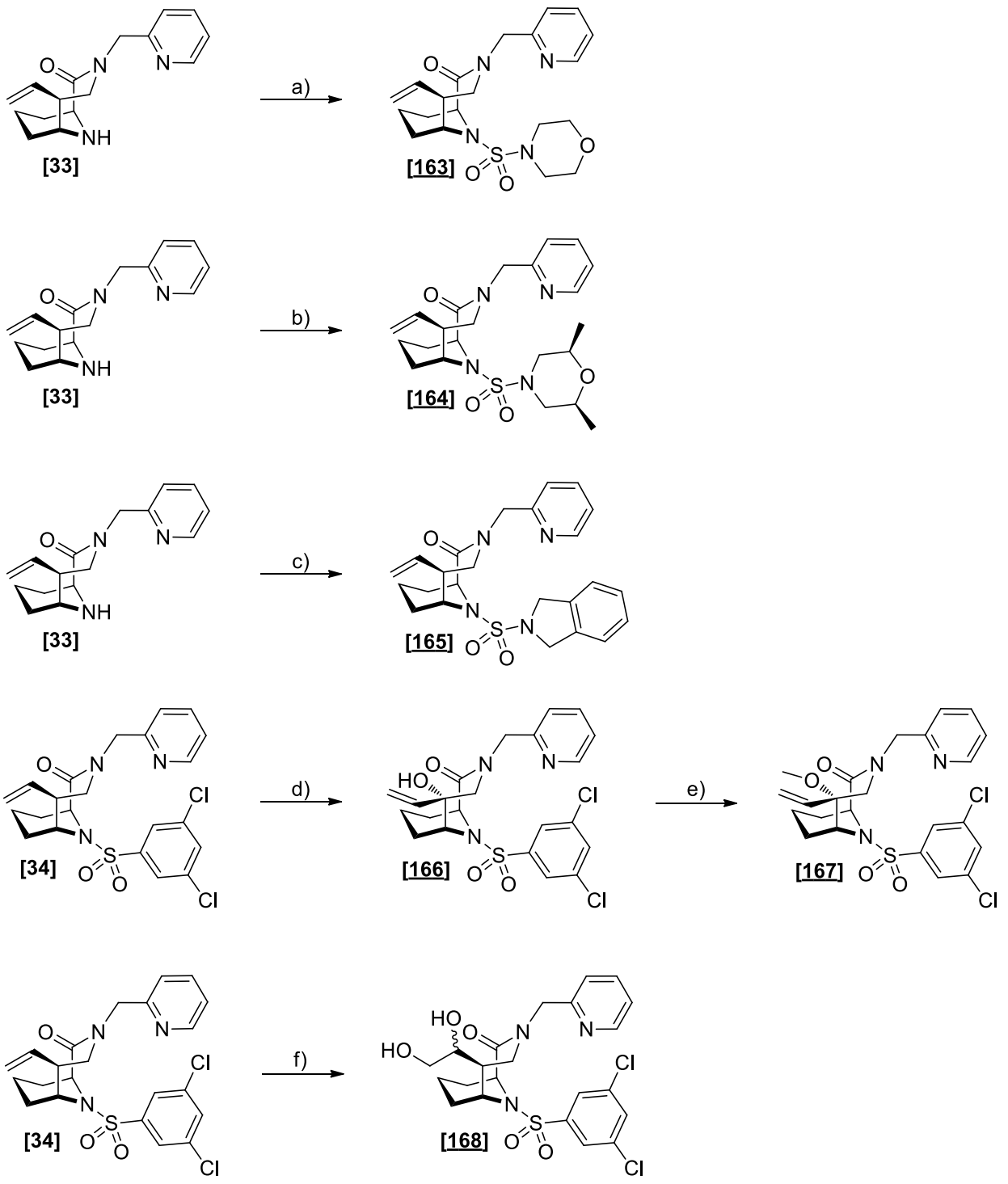


Scheme 20. Reagents and conditions: a) bromobenzene, $Pd(PPh_3)_4$, K_2CO_3, dioxane, 90 °C, 18 h; b) 4-bromobenzonitrile, $Pd(PPh_3)_4$, K_2CO_3, dioxane, 90 °C, 18 h; c) 1-bromo-4-chlorobenzene, $Pd(PPh_3)_4$, K_2CO_3, dioxane, 90 °C, 18 h; d) 4-bromophenol, $Pd(PPh_3)_4$, K_2CO_3, dioxane, 90 °C, 18 h; e) 3-bromobenzonitrile, $Pd(PPh_3)_4$, K_2CO_3, dioxane, 90 °C, 14 h; f) 1-bromo-3-chlorobenzene, $Pd(PPh_3)_4$, K_2CO_3, dioxane, 100 °C, 16 h; g) 3-bromophenol, $Pd(OAc)_2$, K_3PO_4, DMF, 100 °C, 15 h; h) 2-bromobenzonitrile, $Pd(OAc)_2$, K_3PO_4, DMF, 110 °C, 16 h; i) 1-bromo-2-chlorobenzene, $Pd(OAc)_2$, K_3PO_4, DMF, 110 °C, 16 h; j) H_2, Pt/C, rt, 19 h; k) 4-bromo-2-(trifluoromethyl)benzonitrile, $Pd(PPh_3)_4$, $Pd(OAc)_2$, K_3PO_4, dioxane, 80 °C, 16 h; l) OsO_4, NMO, 2,6-lutidine, acetone/H_2O, 16 h

1.13. Miscellaneous compounds with R^1 = (pyridine-2-ylmethyl)



Scheme 21. Reagents and conditions: a) 3,5-Dichloro-4-fluorobenzenesulfonyl chloride, DIPEA, DCM, rt, 16 h; b) 3-chloro-5-cyanobenzene-1-sulfonyl chloride, DIPEA, DCM, rt, 16 h; c) **[10]**, DIPEA, MeCN, rt, 16 h; d) 4-nitrobenzene-1-sulfonyl chloride, DIPEA, MeCN, rt, 16 h; e) Zn, NH_4Cl, EtOH, rt, 16 h; f) Ac_2O, DCM, 0 °C, 17 h



Scheme 22. Reagents and conditions: a) morpholine-4-sulfonyl chloride, ZnO, MeCN, rt, 16 h; b) (2R,6*S*)-2,6-dimethylmorpholine-4-sulfonyl chloride, ZnO, MeCN, rt, 16 h; c) isoindoline-2-sulfonyl chloride, ZnO, MeCN, rt, 16 h; d) SeO_2, dioxane, 100 °C, 10 h; e) MeI, NaH, DMF, rt, 16h; f) OsO_4, NMO, 2,6-lutidine, acetone/H_2O, 16 h

2. Introduction

2.1. FK506-Binding Proteins (FKBPs)

FK506-binding proteins (FKBPs) belong to the immunophilin family and most FKBPs possess a cis-trans peptidyl-prolyl isomerase (PPIase) activity. They are found in all eukaryotes and many prokaryotes[1] and are expressed in most tissues[2]. FKBPs can act as co-receptors for the natural products FK506 and Rapamycin. By binding these drugs, a complex is formed, which exhibits immunosuppressive effects via a gain-of-function mechanism. In the last three decades several homologs have been discovered and linked to pathological processes, thus making FKBPs a promising target for drug development.
Mammalian FKBPs can be subdivided into four groups: the cytoplasmic, endoplasmic reticulum, nuclear and tetratricopeptide repeats (TPR)-containing FKBPs. Until today, 15 human FKBPs have been identified (**Table 1**).[3] The best studied FKBPs are FKBP12 and FKBP51. Both FKBPs, as well as their respective closest homologs (FKBP12/FKBP12.6 and FKBP51/FKBP52), are discussed below.

Table 1. The 15 identified human FKBPs and their respective classes.

FKBP	Class
FKBP12	cytoplasmic
FKBP12.6	cytoplasmic
FKBP25	nuclear
FKBP135	nuclear
FKBP36	tetratricopeptide repeats
FKBP37	tetratricopeptide repeats
FKBP38	tetratricopeptide repeats
FKBP51	tetratricopeptide repeats
FKBP52	tetratricopeptide repeats
FKBP13	endoplasmic reticulum
FKBP19	endoplasmic reticulum
FKBP22	endoplasmic reticulum
FKBP23	endoplasmic reticulum
FKBP60	endoplasmic reticulum
FKBP65	endoplasmic reticulum

Besides human FKBPs, microbial FKBPs, so called macrophage infectivity potentiators (Mip) proteins, have become interesting drug targets. Mips belong to the FKBP subfamily of immunophilins due to their sequence homology to FKBPs and were identified in many human pathogens, including bacteria (e.g. *Salmonella*, *Chlamydia*, *Legionella pneumophila* (*Lp*Mip), *Burkholderia pseudomallei* (*Bp*Mip)) and parasites (e.g. *Trypanosoma cruzi* (*Tc*Mip), *Plasmodium falciparum* (*Pf*Mip)).[4-9]

2.1.1. FKBP12 and FKBP12.6

The first discovered FKBP was FKBP12, a 12 kDA variant encoded by the *FKBP1A* gene, which has been linked to T-cell activation due to its binding of the natural products FK506[10-11] and rapamycin[12]. Both compounds are potent immunosuppressive agents in complex with FKBPs in general, although the interactions are best described for FKBP12. The FKBP12-FK506 complex binds to calcineurin[13], a key enzyme in T-cell activation[14-15], while the FKBP12-Rapamycin complex binds to the FKBP Rapamycin binding (FRB) domain of the mammalian target of Rapamycin (mTOR)[16-17], a kinase involved in cell growth and cell proliferation.[18] Inhibition of either pathway leads to an immunosuppressive response which led to the application of FK506 and rapamycin as drugs to stop allograft rejection in post-transplantation patients.[19-25]
Besides the binding of these two natural products, two signaling pathways are well established to be modulated by FKBP12. On the one hand, ryanodine receptors (RyRs), on the other hand transforming growth factor β (TGFβ)/activin-like receptors. Both FKBP12 and its closest homolog FKBP12.6 bind to the glycine- and serine-rich sequence (GS domain) of TGFβRI[26] or activin receptor-like kinase-2 (ALK2)[27] and thereby stabilize these kinases in an inactive conformation leading to a blocked access of substrates. This is thought to prevent leaky signaling of the receptor kinases. Mutations in the GS region of ALK2 that abolish FKBP12 binding are associated

with the connective tissue disease fibrodysplasia ossificans progressiva (FOP), but with milder symptoms compared to other ALK mutations.[28] However, its role, as well as those of other FKBP homologs, on TGFβ/activin signaling is unknown. FKBP12 and FKBP12.6 are also well documented components of RyR complexes, which intracellularly amplify $Ca^{2\pm}$ signaling in myocytes to evoke muscle contraction. While the RyRs are important receptors in both skeletal muscle and heart muscle, the role of FKBP12 and FKBP12.6 on these receptors is controversially discussed in literature.[29-33]

2.1.2. FKBP51 and FKBP52

FKBP51, a 51 kDA variant encoded by the *FKBP5* gene, is an intracellular protein, which acts as a cochaperone for the heat shock protein 90 (Hsp90)[34] and is best known for the negative regulation of glucocorticoid and progesterone receptors.[35-38] It consists of two FK506 binding domains (FK1 and FK2) and a three-unit repeat of the tetratricopeptide (TPR) domain.[39] The N-terminal FK1 domain displays PPIase activity and binds FK506 and rapamycin[40], while the FK2 domain, although it adapts a typical FKBP-like fold, neither shows measurable isomerase activity in vitro, nor binds to FK506 and rapamycin.[38, 41] The C-terminal TPR domain is crucial for binding to Hsp90.[42] FKBP51 has been identified to play a role in the pathogenesis of psychiatric disorders and stress-related diseases. FKBP51-deficient mice displayed enhanced stress resistance and stress coping behavior[43-48], an improved sleep profile[45], resistance to diet-induced obesity[49] and protection from experimentally-induced forms of chronic pain[50].

FKBP52, a 52 kDA variant encoded by the *FKPB4* gene, is the closest homolog to FKBP51 with a sequence identity of 70% and a similar tertiary structure. Analogously to FKBP51, it possesses a N-terminal FK1 domain that displays PPIase activity and binds FK506 and rapamycin, a FK2 domain without isomerase activity and a C-terminal TPR domain.[41-42, 51] FKBP52 acts as positive regulator of glucocorticoid and progesterone receptors and is therefore antagonistic to FKBP51.[52-53] It is assumed, that the antagonistic behavior is due to the flexibility of a short hinge between the two FK domains and its modulation by phosphorylation.[54]

2.1.3. Microbial FKBPs – Macrophage Infectivity Potentiators (Mips)

Mips and Mip-like proteins are a group of virulence factors found in several human pathogens including bacteria and parasites. They belong to the FKBP subfamily of immunophilins and typically possess a peptidyl-prolyl cis/trans isomerase activity. Mips are inhibited by the natural products FK506 and rapamycin and are therefore classified as immunophilins.

The first Mip identified as virulence factor was *Lp*Mip found in *Legionella pneumophila*, a gram-negative bacterium which causes Legionnaiere's disease.[4] *Lp*Mip is considered to be essential for the pathogenicity of L. pneumophila. Intracellularly, genetic deletion of *mip* leads to reduced replication rates in human alveolar macrophages.[55] Extracellularly, Mip has been shown to contribute to the dissemination of the bacteria in the lungs and the spread of Legionella to the spleen in guinea pigs.[56]
The gram-negative bacteria *Burkholderia pseudomallei*, endemic in tropical regions, is the causative agent of melioidosis and classified as a potential biowarfare threat due to the high rate of infectivity and resistance to a broad range of antibiotics.[57-58] The genome of *B. pseudomallei* encodes for at least two FKPBs, one being the *Burkholderia pseudomallei* Mip-like protein 1 (*Bp*ML1), which consists mainly of a PPIase domain, the other being BPSL0918, which does not display any measurable PPIAse activity at all, but is important for full virulence.[59] BpML1 has been shown to positively affect intracellular replication and resistance to low pH (pH4). Inhibition of BpML1 by rapamycin or deletion of BpML1 lead to reduced protease production and swarming motility[9], which have been previously reported as important factors for pathogenesis in rat and mice models, respectively.[60-62]
Trypanosoma cruzi is a unicellular parasitic protozoon found in Central and South America and the cause of Chagas disease. It is spread by hematophagous triatomine bugs, commonly known as 'kissing bug' or 'assassin bug'. The disease is divided in two parts. In the initial acute phase, the parasites circulate in the bloodstream which is accompanied by mild symptoms, including fever, headache and enlarged lymph glands.[63] During the chronic phase, the parasite infests itself in heart and digestive muscle causing, after a dormant period of 10-30 years, heart diseases and digestive complications in 30-40% of infected people.[64] The parasites invasion of mammalian host cells is mediated by the *Trypanosoma cruzi* Mip-like protein (*Tc*Mip).[7] Interestingly, it was shown in an infectivity

assay that *Tc*Mip can be efficiently substituted by *Lp*Mip[65], suggesting that Mip has a conserved impact on infectivity in various pathogens.

2.2. Ligand Development

The first identified ligands for FKBPs were the two natural products FK506 and Rapamycin (**Figure 2**). Crystal structures revealed that rapamycin and FK506 bind to the pocket of FKBP12 via the pipecolate moiety, while the remaining part of the molecule faces outwards and enables ternary complexes.[66 67 68] Early development of FKBP12 ligands therefore focused on the improvement of these natural compounds by simplifying the structure and omitting the loop that leads to immunosuppression. Various groups developed synthetic cyclic and acyclic FK506 analogues by retaining the seemingly important pipecolinyl α-ketoamide function and modifying the residues.[69 70 71] The most potent inhibitor (2 nM) of this series had a t-pentyl residue on the diketo moiety and a diarylpropyl moiety on the ester (**Figure 2**). Notably, the stereochemistry highly effected the potency, since the *R*-isomer was approximately 40 times more active than the *S*-isomer.[72]

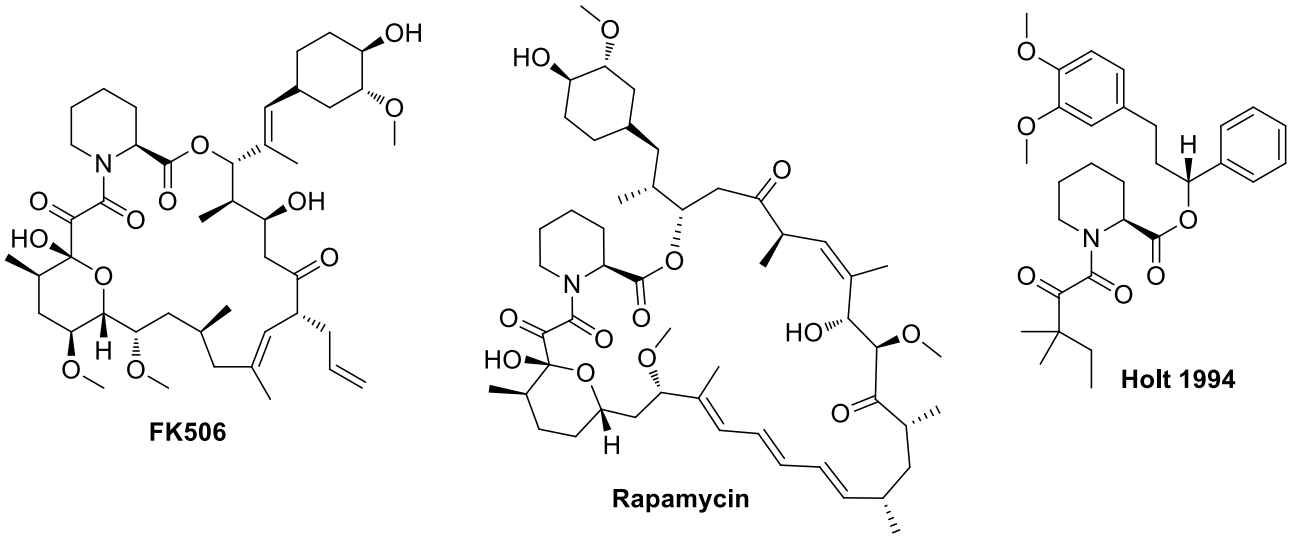


Figure 2. Structures of FK506, rapamycin and the derivative by Holt.

Further variation of the side chains resulted in synthetic ligands, which were reported to bind with similar affinities to FKBP12 as FK506. Examples are GPI-1485 and the prodrug thereof, GPI-1046 (Guilford Pharmaceuticals and Amgen)[73], V10367 (Vertex Pharmaceuticals)[70] and ElteN378[74]. (**Figure 3**)

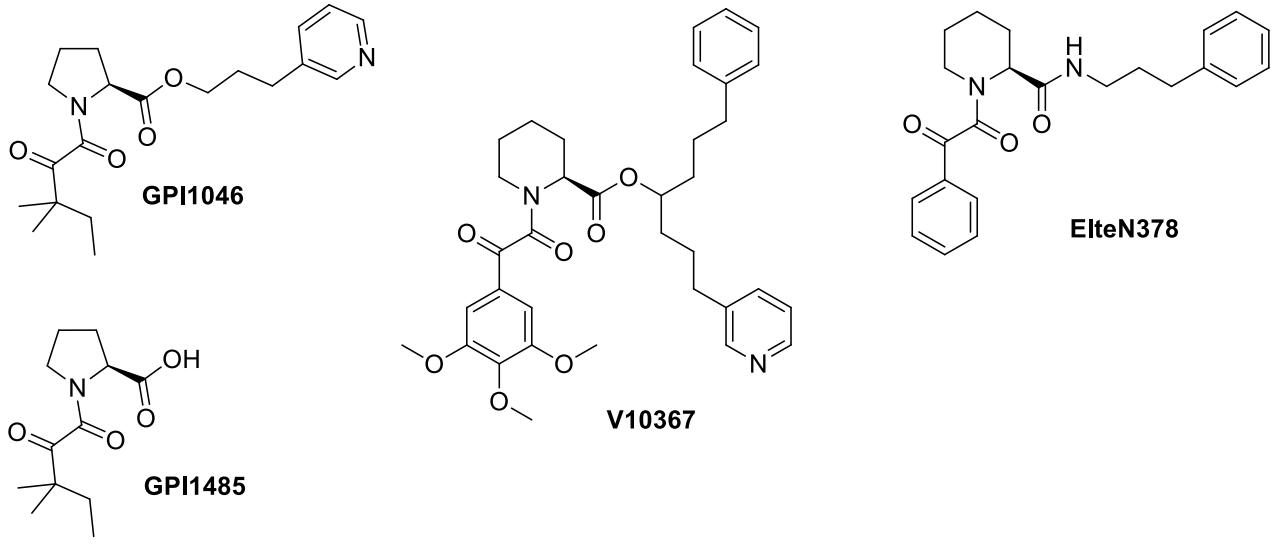


Figure 3. Synthetic derivatives based on pipecolate core.

By using computational modelling, Babine *et al.* found that bridged bicyclic structures fit the FKBP12 binding site well, as was further shown in crystal structures.[75] This led to the synthesis of many bicyclic scaffolds (**Figure 4)**, including [7.3.1] and [8.3.1] macrocycles[76], bicyclic diamides[77] and chiral bicyclic proline analogues[78]. Katoh *et al.* developed polycyclic aza-amides as inhibitors of isomerization activity.[79] Two compounds, AG5473 and AG5507, displayed high binding affinity for FKBP12, 84 nM and 54 nM, respectively.[80] Further derivatization of this scaffold by interconverting the α-keto amide to sulfonamides, sulfamides, ureas and α,α-difluoro amides resulted in no or only marginal improvements in affinity.[81]

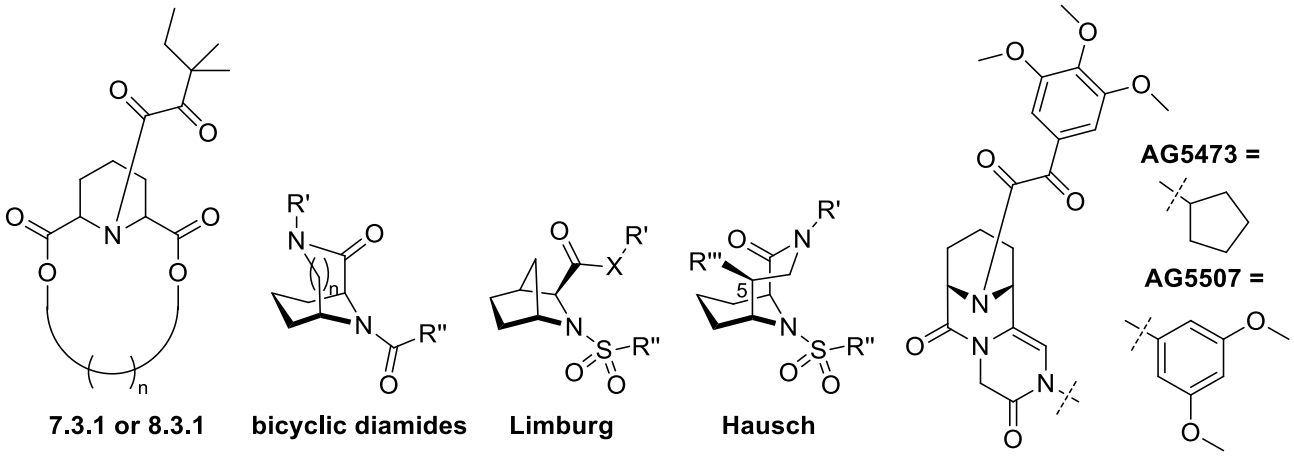


Figure 4. Novel scaffolds based on the pipecolate core.

Following the idea of rigidification and bridging the pipecolate core, Hausch et al. developed a new class of 3,10-diazabicyclo[4.3.1]-decan-2-one sulfonamides.[82] This very rigid structure closely mimics the active conformation of FK506, indicated by the dihedral $O{=}C^{2}\text{-}C^{1}\text{-}N^{3}$ angle, which strongly resemble the unconstrained FKBP ligands (both approximately 175°). Crystal structures elucidated the key interactions, some of which are the $C^{1}\text{-}O^{1}$ Ile^{87}-N hydrogen bond (FKBP51 numbering), a bifurcated hydrogen bond of Tyr^{113} to one of the S=O oxygens as well as to N^{10} and van der Waals contacts of the installed linker with Phe^{77} (**Figure 5**).[83] Further improvements were achieved by modifications of the C^{5} position, resulting in highly ligand-efficient FKBP inhibitors with neurotrophic activity.[84] [82] [85]

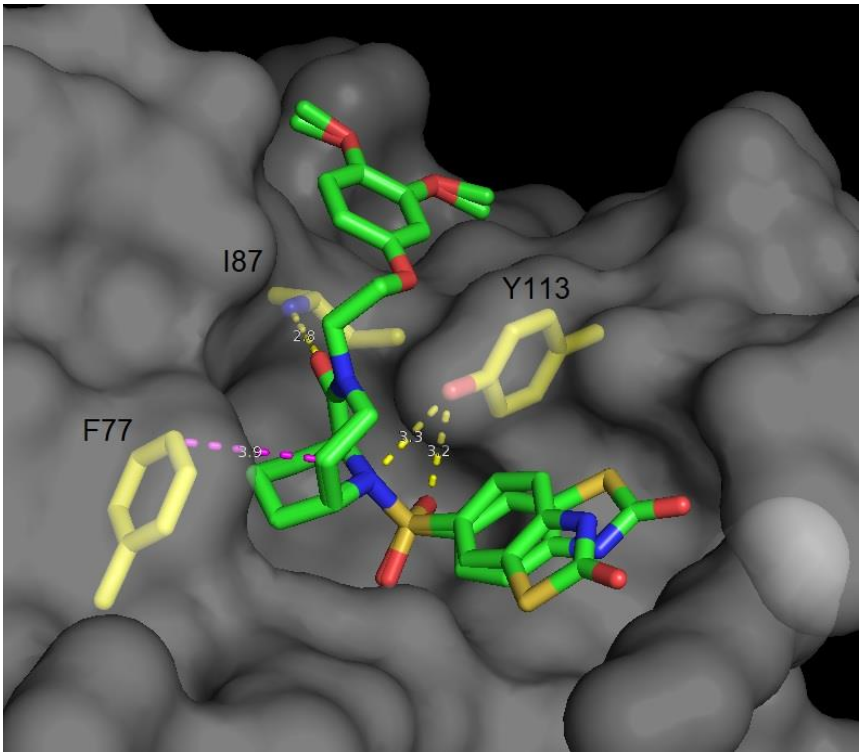


Figure 5. Cocrystal structure of a diazabicyclo[4.3.1]decan-2-one with the FK1 domain of FKBP51 (representative for FKBP12). The protein surface is depicted in grey, the key amino acids are highlighted as yellow sticks, the ligand is green. Blue atoms correspond to nitrogen, red atoms to oxygen. Hydrogen bonds are shown in yellow, van der Waals interactions in magenta. Lys121 is truncated for a better view of the structure. PDB code: 4JFJ

Although these ligands display high affinities towards FKBP12 it is noteworthy, that no selectivity between FKBP12 and its close homolog FKBP12.6 was observed. Furthermore, these ligands also display up two-digit nanomolar binding affinities towards other human FKBPs (FKBP51, FKBP52) and up to three-digit nanomolar binding affinities to the microbial FKBP-like LpMip. Besides the lack of selectivity between members of the FKBP family, these ligand class suffers from rapid degradation in metabolism phase I studies.

2.3. Aim of the Thesis

The overall aim of this thesis was to extend the scope and understanding of bicyclic [4.3.1] aza-amides as privileged FKBP ligands.
Firstly, the poor metabolic stability of this substance class needed to be addressed. In order to detect positions prone to metabolic degradation a measurement of metabolite distribution was envisioned. In order to distinguish the molecule fragments and assign the metabolized positions, strategic incorporation of deuterium at potential metabolic soft spots was conducted.
Secondly, the affinities of bicyclic [4.3.1] aza-amides should be increased. Based on the preliminary finding that a single methyl group in the *N*-α position of the amide either decreases (*R*-methyl, **Figure 6**) or increases (*S*-methyl, **Figure 6**) affinity to human FKBPs (12, 51, 52) by one order of magnitude, further derivatives were synthesized. To elucidate whether this effect is affected by specific groups in R^2, R^3 or R^4 (**Figure 6**) a broad library of compounds with variations in either of these positions was synthesized and tested.

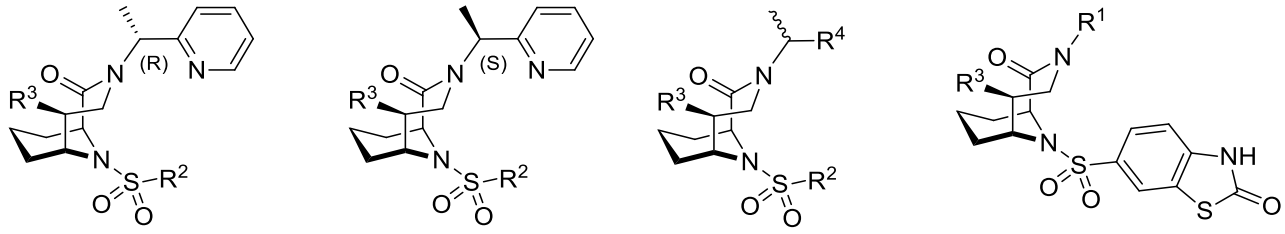


Figure 6. Bicyclic [4.3.1] aza-amide scaffolds

A subgoal was to better understand the molecular origin of the observed boost in affinity. A possible hypothesis was that the methyl group induces a rotational barrier by steric hindrance and thus locks the compounds in either a favorable (*S*-isomer) or unfavorable (*R*-isomer) conformation for binding to FKBPs. This was addressed by molecular modelling studies.

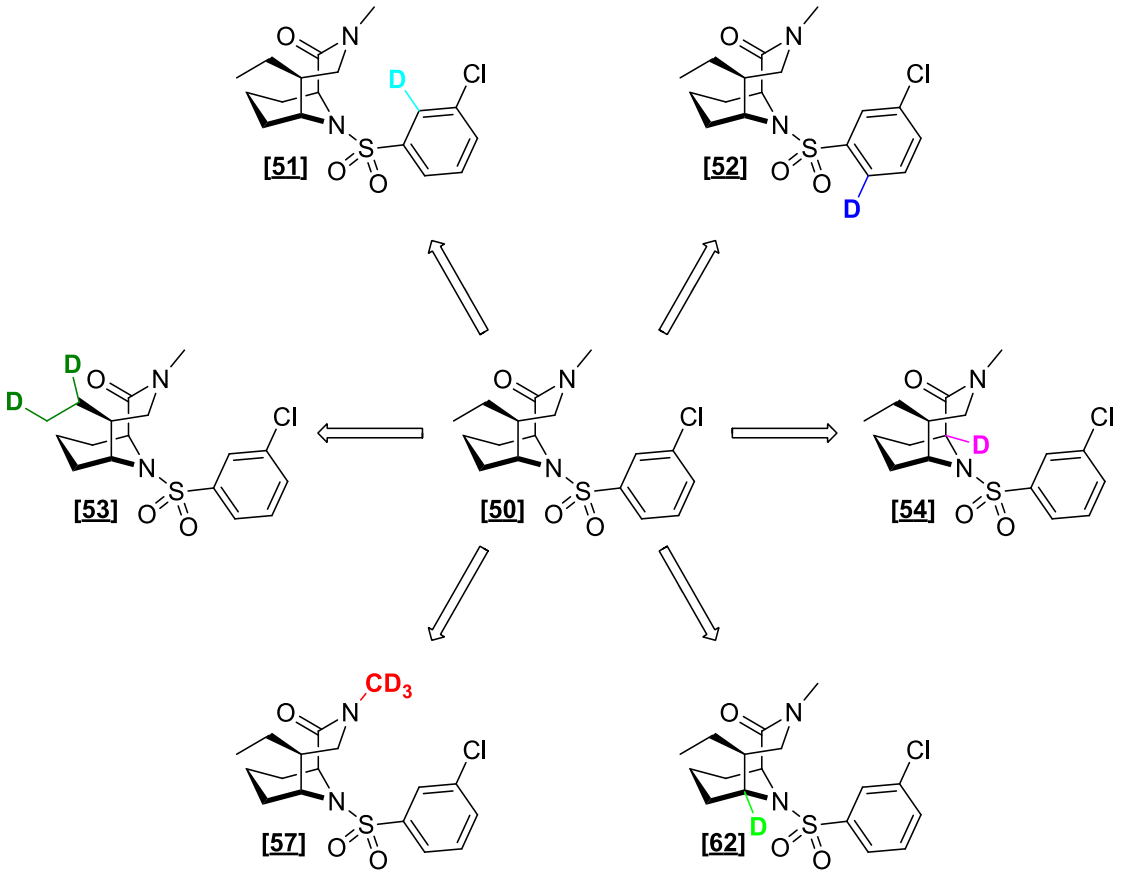
Thirdly, a series of bicyclic [4.3.1] aza-amides with a benzo[d]thiazol-2(3H)-one residue (**Figure 6**) at the sulfone amide as well as derivatives thereof were synthesized. This particular moiety was previously shown to impart sub-nanomolar binding affinity to FKBP12 and up to 1000-fold selectivity over FKBP51 and FKBP52.[86] A focused library provided the verification of this scaffold and enabled further insights into the important parts for high affinity and selectivity.

Lastly, derivatives of bicyclic [4.3.1] aza-amides with novel modifications were synthesized in order to screen for possible starting points for compounds with increased selectivity and/or affinity.

3. Results & Discussion

3.1. Overview of Project 1: Synthesis of Deuterated 3,10-Diazabicyclo[4.3.1] decan-2-ones

The aim of this project was the identification of metabolic soft spots in bicyclic [4.3.1] aza-amides. A series of deuterated derivatives on the basis of reference compound **[50]** were synthesized according to **Scheme 23**.



Scheme 23. Deuterated derivatives on the basis of reference compound **[50]**.

The compounds were subjected to phase I metabolite identification in mouse liver microsome incubations by the service provider Pharmacelsus and a metabolite analysis was conducted. Deuteration at C4 was considered, but rejected due to unavailability of respective precursors. Instead, the synthesis of a derivative with a methyl group at C4 (both isomers) as well as two tricyclic compounds with a bridge from C4 to the amide were intended (**Figure 7**).

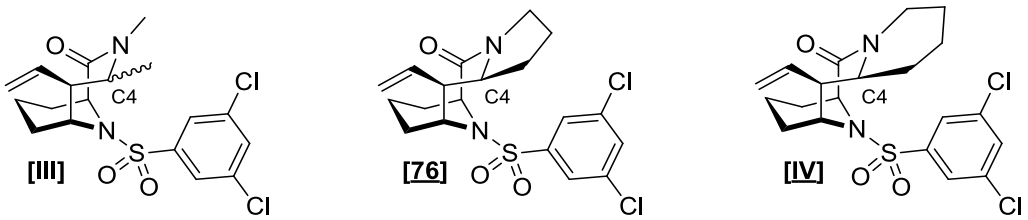
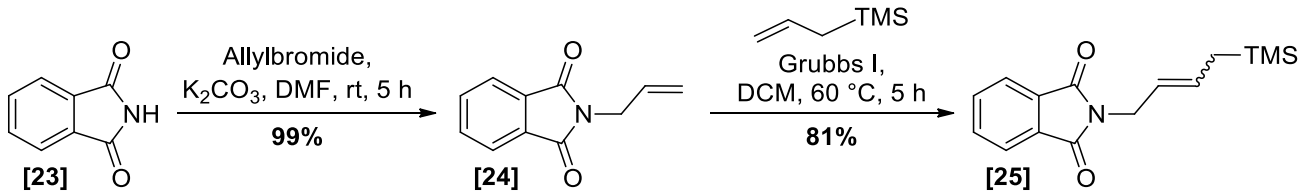


Figure 7. Bicyclic [4.3.1] aza-amides with modifications at C4.

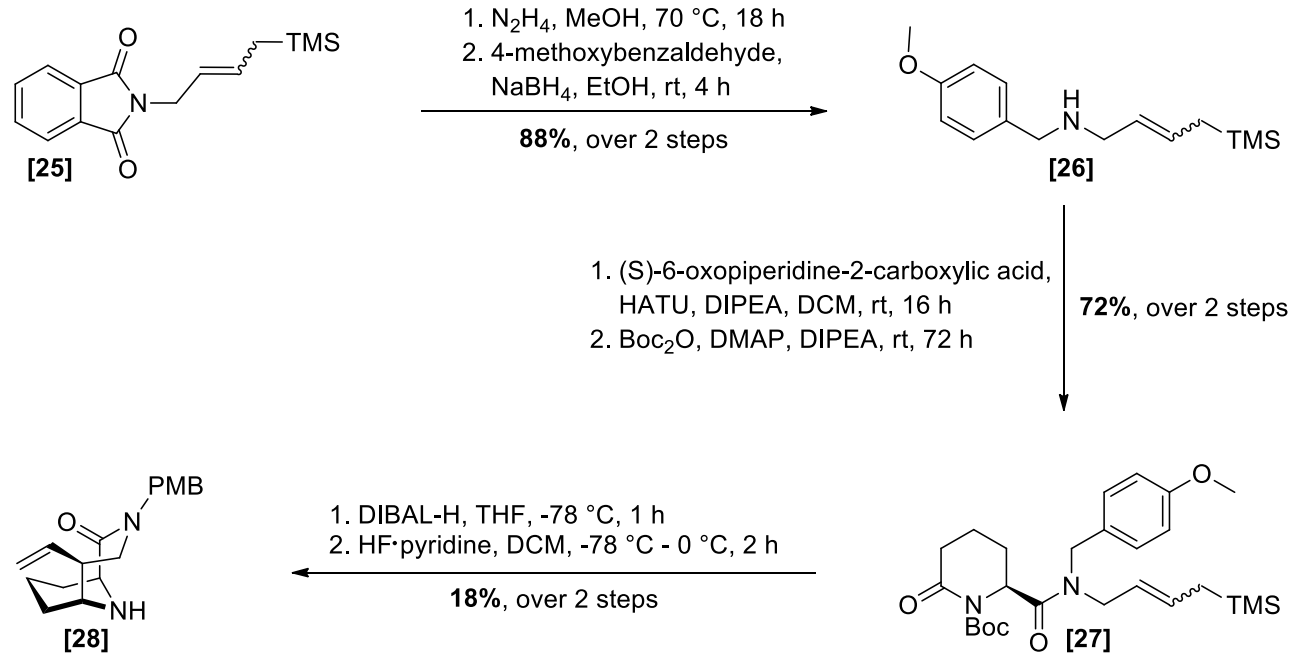
3.1.1. Synthesis of Reference Compound [50]

Reference compound **[50]** was synthesized analogously to a route previously published by Pomplun et al.[85] The synthesis commenced with commercially available phthalimide **[23]**, which was alkylated with allyl bromide in 99% yield (**Scheme 24**). Metathesis with Grubbs 1st generation catalyst yielded building block **[25]**, which was also used for other bicyclic [4.3.1] aza-amide building blocks.



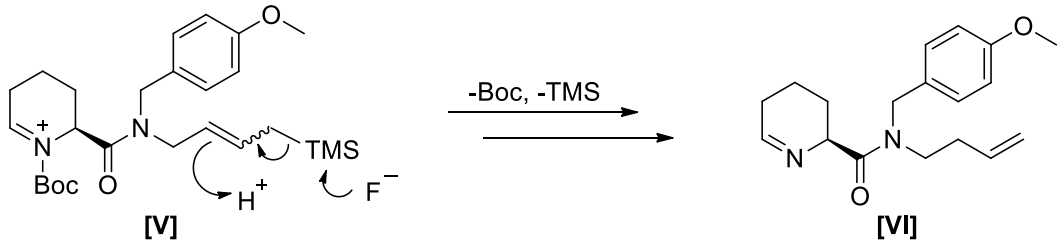
Scheme 24. Synthesis of compound **[24]** and compound **[25]**.

Compound **[25]** was treated with hydrazine to cleave the imide and obtain a primary amine which was successively subjected to reductive amination with 4-methoxybenzaldehyde yielding PMB-protected amine **[26]** with 88% over two steps (**Scheme 25**). HATU-mediated coupling to commercially available (*S*)-6-oxopiperidine-2-carboxylic acid followed by Boc-protection resulted in intermediate **[27]** in 72% yield over two steps. Reduction to the 6-hydroxypiperidine with DIBAL-H followed by treatment with HF·pyridine gave an intermediate iminium species which immediately underwent an acyliminium cyclization to afford bicyclic building block **[28]**.



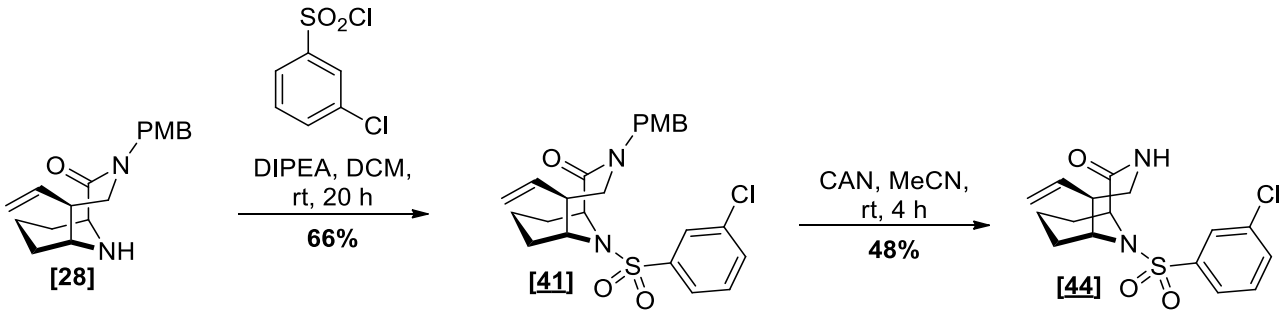
Scheme 25. Synthesis of PMB-protected bicyclic compound **[28]**.

The poor yield (18%) of the last sequence is attributed to various side products, especially dimerization and trimerization as well as the formation of a side product with the same mass as the product. This side product might result from loss of the Boc- and TMS-group but instead of intramolecular cyclization the intermediate is quenched by a proton (**Scheme 26**).



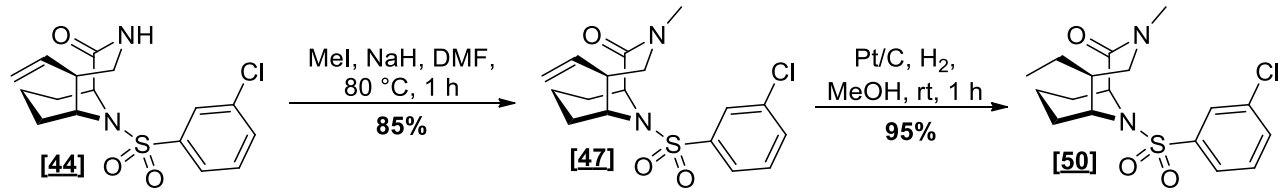
Scheme 26. Possible side product of the acyliminium cyclization step.

PMB-bicycle **[28]** was transformed to sulfonamide **[41]** with 3-chlorobenzenesulfonyl chloride with 66% yield and PMB-deprotected with cerium ammonium nitrate to afford amide **[44]** in 48% yield (**Scheme 27**).



Scheme 27. Synthesis of compound **[41]** and compound **[44]**.

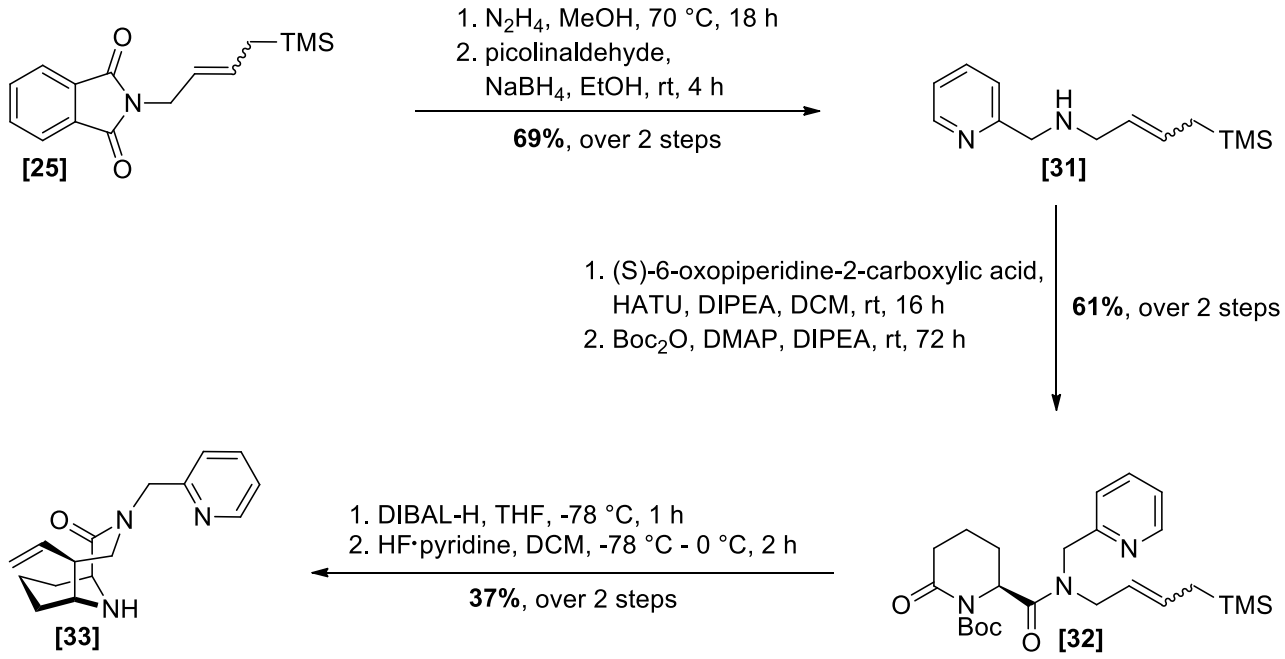
Methylation of **[44]** with methyl iodide afforded compound **[47]** in 85% yield. Hydrogenation with palladium on carbon as catalyst resulted in loss of the aromatic chlorine, therefore platinum on carbon was utilized. This resulted in far less dehalogenation and reference compound **[50]** was obtained in 95% yield (**Scheme 28**).



Scheme 28. Final steps towards reference compound **[50]**.

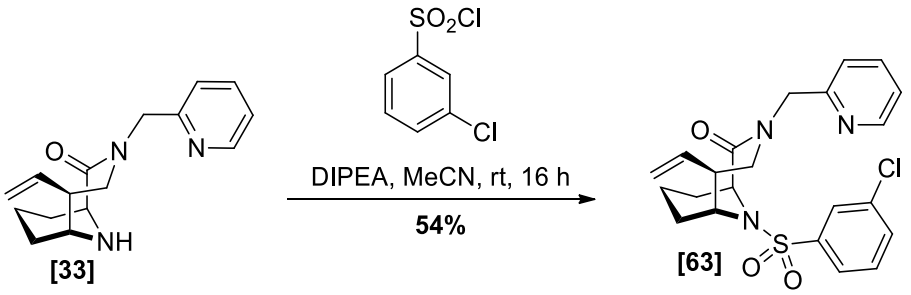
3.1.2. Synthesis of reference compound [63]

The synthesis of reference compound **[63]** is depicted in **Scheme 29**. It commenced with the deprotection of intermediate **[25]** to a primary amine, which was subjected to reductive amination to form the secondary amine **[31]** in 69% over two steps. HATU-mediated coupling to (*S*)-6-oxopiperidine-2-carboxylic acid followed by Boc-protection resulted in intermediate **[32]** in 61% yield over two steps. Reduction with DIBAL-H followed by treatment with HF-pyridine yielded building block **[33]** in 37% over two steps.



Scheme 29. Synthesis of bicyclic precursor with R^1= (pyridine-2-ylmethyl) **[33]**.

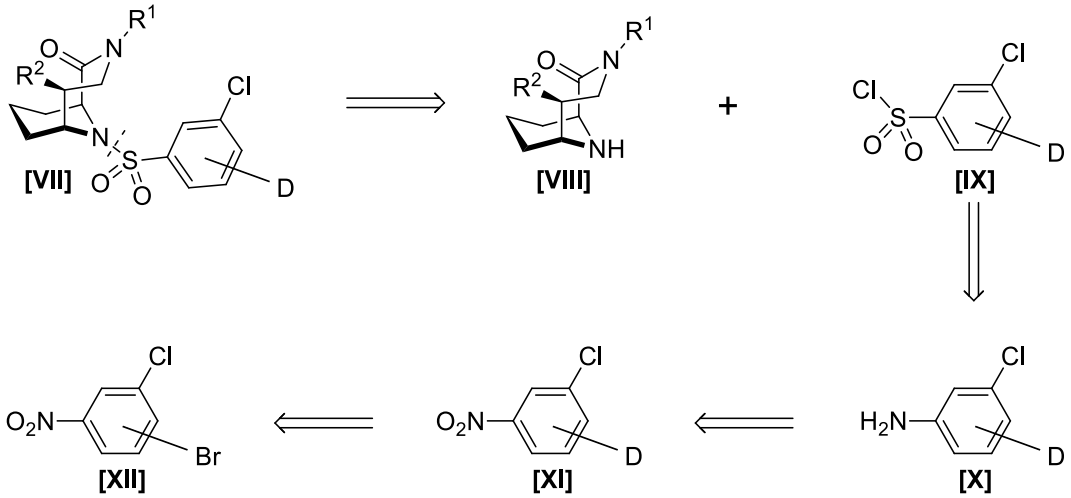
In the final step, building block **[33]** was converted to sulfonamide **[63]** with 54% yield, as depicted in **Scheme 30**.



Scheme 30. Final synthetic step towards reference compound **[63]**.

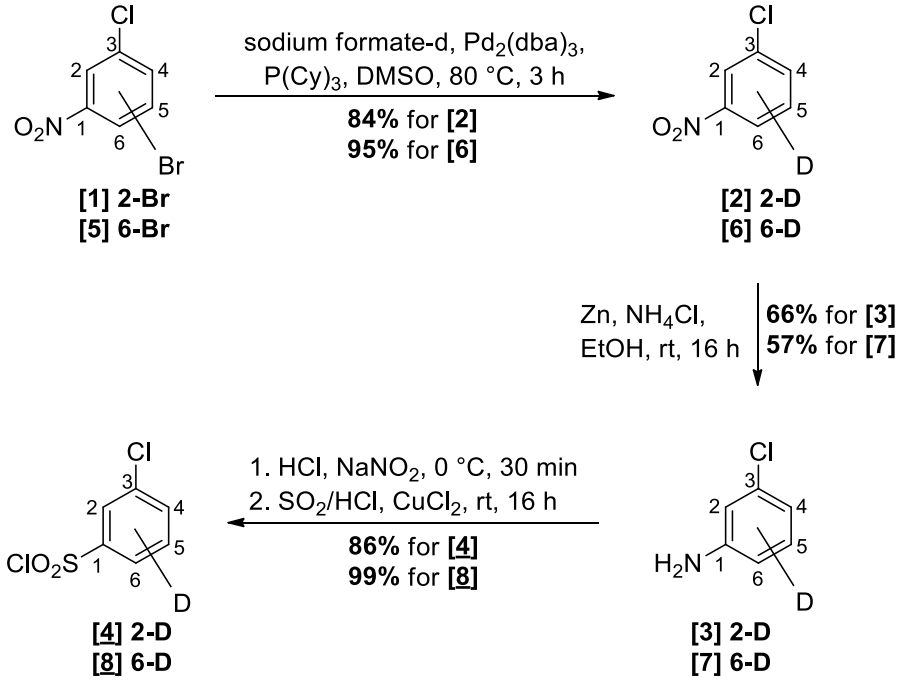
3.1.3. Synthesis of Deuterated Chlorobenzene Derivatives

Two ways of introducing deuterium into an aromatic ring were considered. On the one hand by hydrogen/deuterium (H/D) exchange on the other hand by halogen/deuterium (Hal/D) exchange. While H/D exchange enables late-stage modification, Hal/D exchange requires tailor-made aromatic rings. The downsides of the H/D exchange pathway are incomplete incorporation of deuterium and the indistinguishability of the two positions next to the sulfonyl group even by recent developed catalysts.[87-89] Therefore, a bromine/deuterium (Br/D) exchange was envisioned with the deuterium in the benzenesulfonyl chloride to avoid metal catalyzed side reactions with the vinyl group (**Scheme 31**).



Scheme 31. Retrosynthetic analysis of deuterium incorporation in aromatic position.

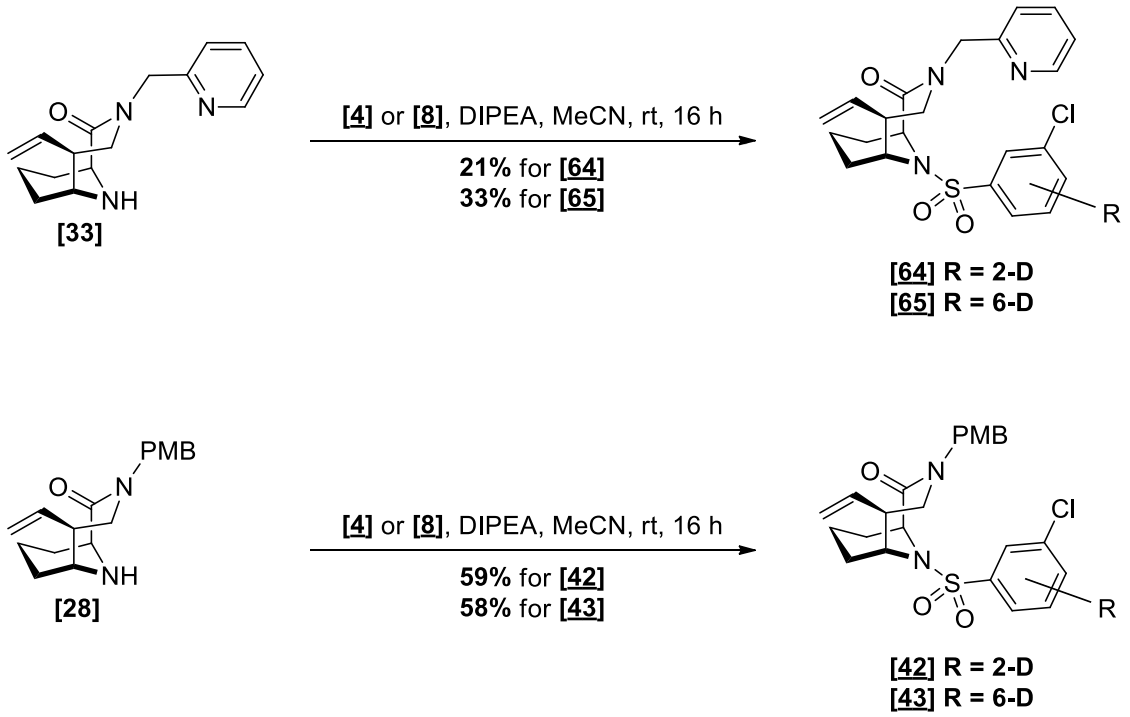
The deutero-3-chlorobenzenesulfonyl chloride **[IX]** is accessible via a radical copper catalyzed reaction of an aryl diazonium salt which can be generated from the respective amine **[X]**. The amine is derived from a nitro compound **[XI]** and the deuterium is incorporated by means of Br/D exchange which leads back to commercially available bromo-chloro-nitrobenzene **[XII]**.
The synthesis commenced with either 2-bromo-1-chloro-3-nitrobenzene **[1]** or 1-bromo-4-chloro-2-nitrobenzene **[5]** and is depicted in **Scheme 32**.



Scheme 32. Synthesis of 3-chlorobenzenesulfonyl chlorides with deuterium. Numbering corresponds to UIPAC nomenclature of **[4]** and **[8]**.

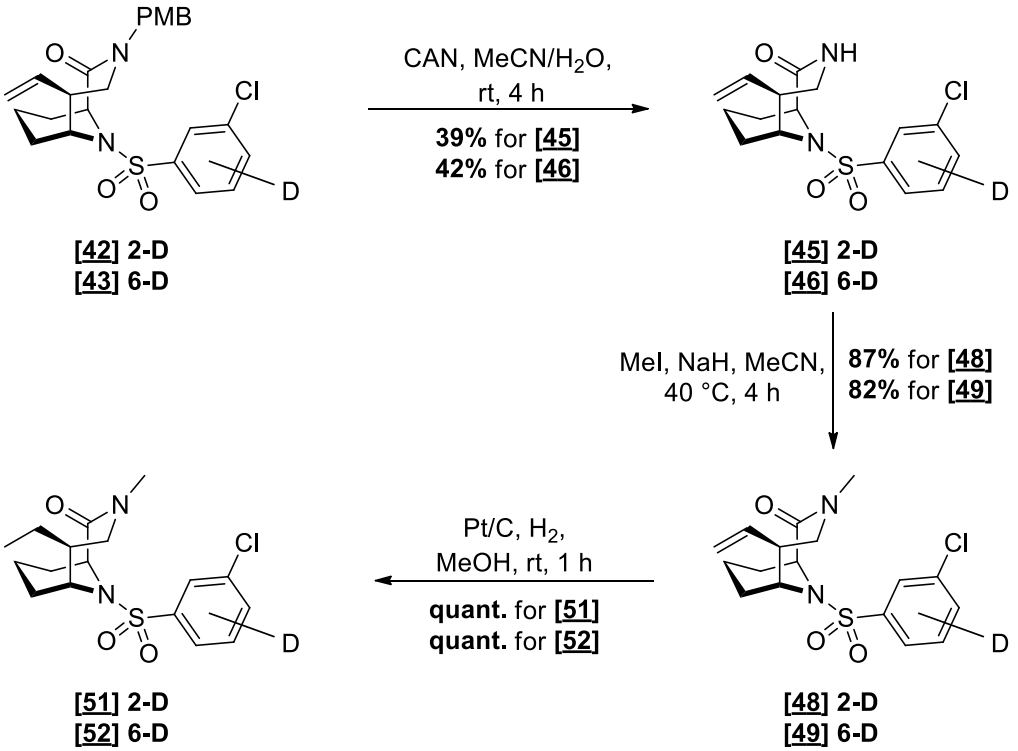
The Br/D exchange was performed according to a procedure described by Zhang et al.[90] The phosphine ligand was changed from tributylphosphin to tricyclohexylphosphin since the former ignites spontaneously if exposed to air and no glovebox was available. The reactions gave full conversion after 3 h. The isolated yields are 84% for **[2]** and 95% for **[6]**. The deuterium incorporation is >97% for **[2]** and >93% for **[6]** according to ^{1}H-NMR. With the deuterium in the desired position the compounds were reduced to the corresponding amines (66% yield for **[3]**, 57% for **[7]**) and transformed to the respective sulfonyl chlorides **[4]** and **[8]** in excellent yields of 86% and 99%, respectively.

The sulfonyl chlorides were reacted with bicyclic precursors **[28]** and **[33]** to give the two pyridine derivatives **[64]** and **[65]** in 21% and 33% yield, respectively, as well as the two PMB-protected derivatives **[42]** and **[43]** in 59% and 58% yield, respectively, depicted in **Scheme 33**.



Scheme 33. Synthesis of sulfonamides with deuterated 3-chlorobenzenesulfonyl chlorides.

The two PMB-protected compounds **[42]** and **[43]** were deprotected with cerium ammonium nitrate resulting in amides **[45]** and **[46]** in 39% and 42% yield, respectively (**Scheme 23**). Treatment with methyl iodide and sodium hydride in acetonitrile afforded methyl amides **[48]** in 87% and **[49]** in 82% yield. Hydrogenation with platinum on carbon as catalyst afforded the two final compounds **[51]** and **[52]** in quantitative yield.



Scheme 34. Final steps of the synthesis towards compounds **[51]** and **[52]**.

3.1.4. Synthesis of the (11,12-$^{2}H_1$)-derivative [53]

Deuteration of the vinyl group was initially attempted with gaseous deuterium and palladium on carbon as catalyst. This resulted in a deuterated compound with a deuterium pattern according to gaussian distribution. It is known in literature that hydrogenations on metal surfaces act via a mechanism which enables H/D scrambling.[91] The mechanism proposed by Horiuti and Polanyi is depicted in **Figure 8Figure 1**. First, the olefin is adsorbed on the metal surface. Then a hydrogen/deuterium migration to the β-carbon of the alkene occurs. In this step two events can take place, either reductive elimination to the free alkane or a highly reversible re-adsorption on the metal surface which eventually causes H/D scrambling.

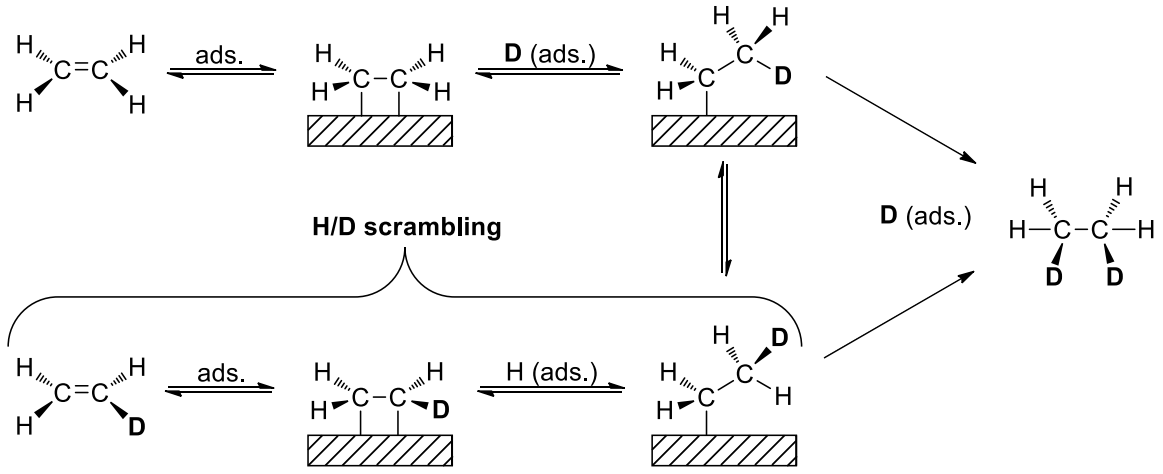


Figure 8. Horiuti-Polanyi mechanism for hydrogenation/deuteration on catalyst surfaces.

To avoid this problem a catalyst with a different mechanism was chosen, more precisely Wilkinson's catalyst.[92] The mechanism is depicted in **Figure 9**. Initial dissociation of one of the triphenylphosphine groups is followed by

oxidative addition of deuterium and π-complexation of the alkene. In the rate-determining step, one deuterium undergoes migratory insertion at the alkene. The successive reductive elimination is fast, and more importantly, irreversible. Therefore, no H/D scrambling is observed.

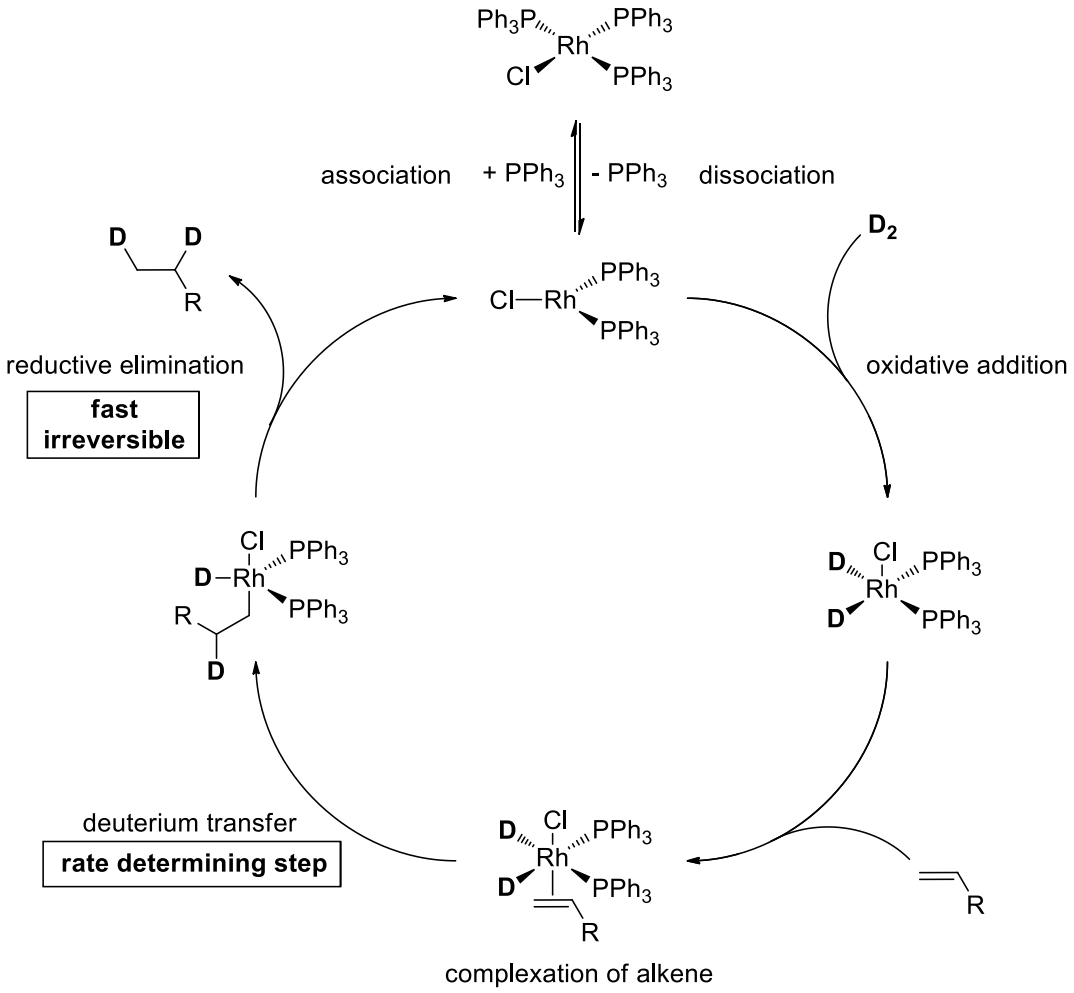
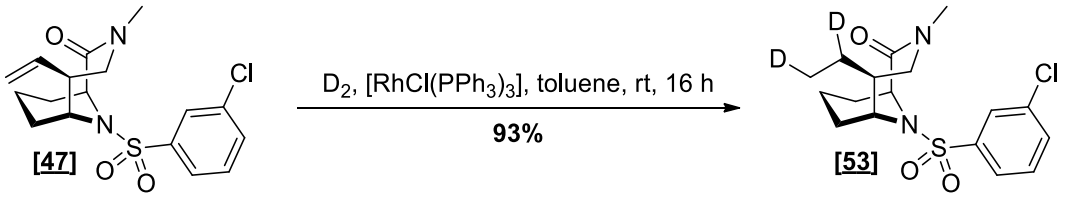


Figure 9. Mechanism of deuterogenation catalyzed by Wilkinson's catalysts.

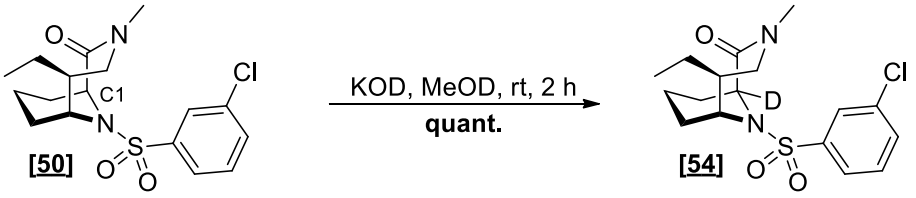
Reaction of **[47]** in toluene with Wilkinson's catalyst under deuterium atmosphere afforded desired compound **[53]** in 93% yield (**Scheme 35**).



Scheme 35. Deuteration of **[47]** with Wilkinson's catalyst to afford **[53]**.

3.1.5. Synthesis of the (1-^{2}H)-derivative [54]

Hydrogens at α-carbons are weakly acidic and can be deprotonated with strong bases. The only acidic proton in reference compound **[50]** is at C1 (**Scheme 36**), therefore a selective H/D exchange with a strong base was envisioned.

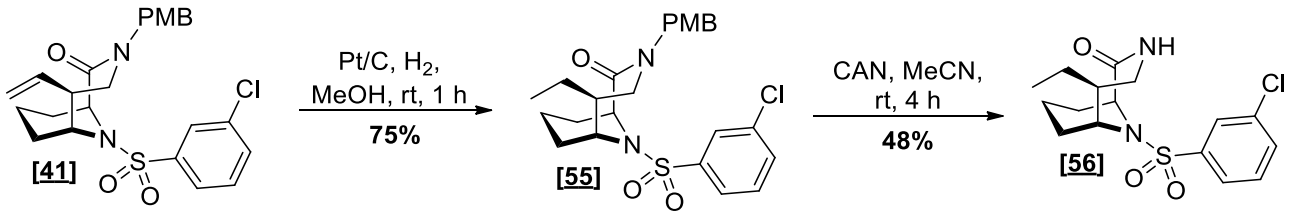


Scheme 36. Deuteration of **[50]** at position C1 to afford compound **[54]**.

As a test approach, compound **[50]** was dissolved in MeOD and placed in an NMR tube. Aqueous potassium deuteroxide (40 wt%) was added in excess and ^{1}H-NMR were recorded every 5 minutes. Satisfyingly, the integral corresponding to the α-hydrogen decreased during the course of the experiment and was no longer detectable after 2 h. The sample was neutralized with deuterium chloride before extraction to avoid possible H/D exchange. After removal of the solvents compound **[54]** was obtained in quantitative yield.

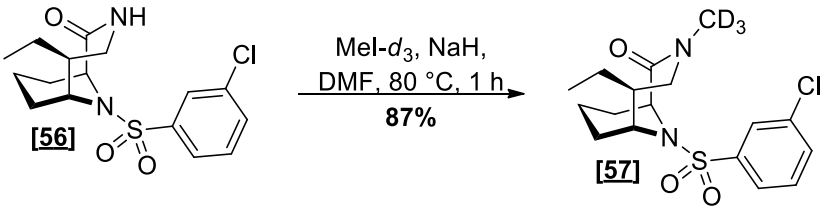
3.1.6. Synthesis of ($^{2}H_3$)methyl derivative [57]

The synthesis of the CD_3-derivative **[57]** commenced with PMB-protected compound **[41]** which was subjected to hydrogenation to afford **[55]** in 75% yield. Successive PMB-deprotection yielded amide **[56]** in 48% (**Scheme 37**).



Scheme 37. Synthesis of amide **[56]** via two steps from PMB-protected compound **[41]**.

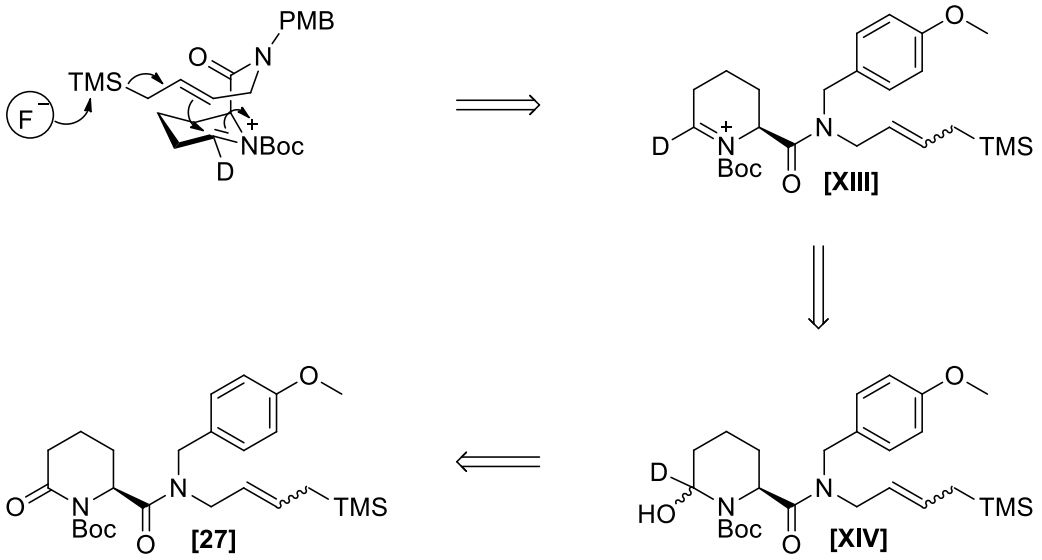
Methylation with methyl iodide-d_3 afforded the desired CD_3-derivative **[57]** in 87% yield depicted in **Scheme 38**.



Scheme 38. Methylation of amide **[56]** to afford CD_3-derivative **[57]**.

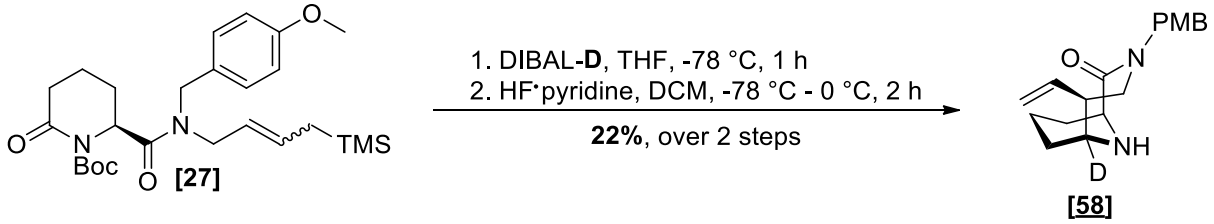
3.1.7. Synthesis of the (6-^{2}H)-derivative [62]

Late-stage modification at position 6 of the bicyclic [4.3.1] aza-amide scaffold is difficult to achieve since neither functional group modification nor the exploitation of directing groups is feasible. Therefore, an approach that inserts the deuterium in the cyclization step was envisioned. From a retrosynthetic point of view (**Scheme 39**), the mechanism of the cyclization involves the formation of an acyliminium species **[XIII]** which is generated from the 6-hydroxy pipecolate **[XIV]** in situ. The latter can be obtained by reduction with DIBAL-D of the respective 6-Oxopipecolate **[27]** which is an already synthesized building block (*vide supra*, **Scheme 25**).



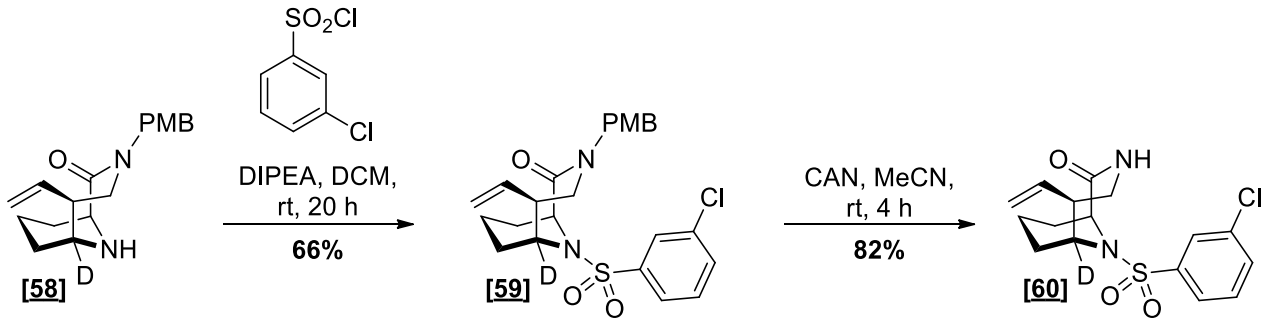
Scheme 39. Retrosynthetic analysis of the insertion of deuterium at position 6 of bicyclic [4.3.1] aza-amides.

The synthesis commenced with building block **[27]** which was reduced with DIBAL-D and subsequently subjected to HF·pyridine in dichloromethane to afford (6-^{2}H)bicyclic [4.3.1] aza-amide **[58]** in 22% over two steps (**Scheme 40**).



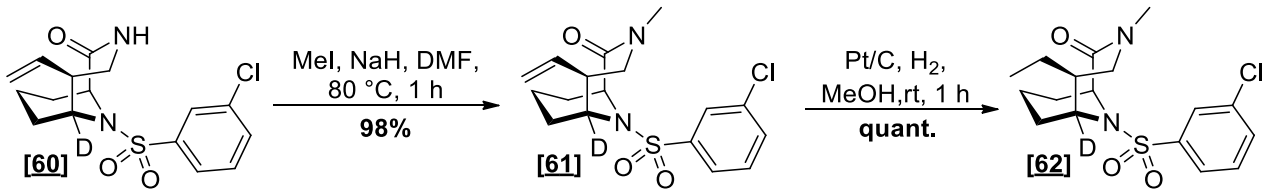
Scheme 40. Cyclization of oxopipecolate **[27]** to (6-^{2}H)bicyclic [4.3.1] aza-amide **[58]**.

With (6-^{2}H)bicyclic [4.3.1] aza-amide **[58]** in hand, the synthesis proceeded analogously to the reference compound **[50]**. The compound was transformed to sulfonamide **[59]** with 3-chlorobenzenesulfonyl chloride in 66% yield and PMB-deprotected with cerium ammonium nitrate to afford amide **[60]** in 82% yield (**Scheme 41Scheme 27**).



Scheme 41. Synthesis of compound **[59]** and compound **[60]**.

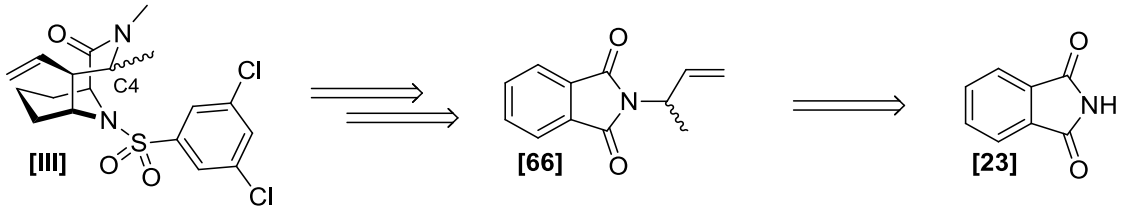
Methylation of **[60]** with methyl iodide afforded compound **[61]** in 98% yield. Hydrogenation with platinum on carbon as catalyst gave final compound **[62]** in quantitative yield (**Scheme 42**).



Scheme 42. Final synthetic steps towards (6-^{2}H)-derivative **[62]**.

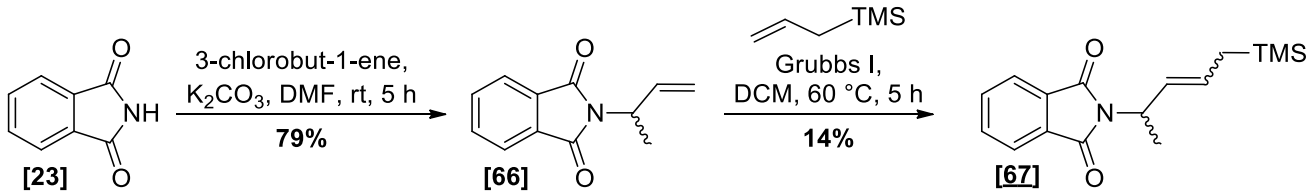
3.1.8. Attempted synthesis of 4-methyl derivative [III]

The two isomers of a 4-methylbicyclic [4.3.1] aza-amide **[III]** were intended to be synthesized instead of 4-deutero analog. The synthesis was intended to follow the synthesis pattern of the other bicyclic precursors described above (see chapter **3.1.1**) with the amendment that a methyl group is introduced in the allylisoindoline **[66]** as displayed in **Scheme 43**.



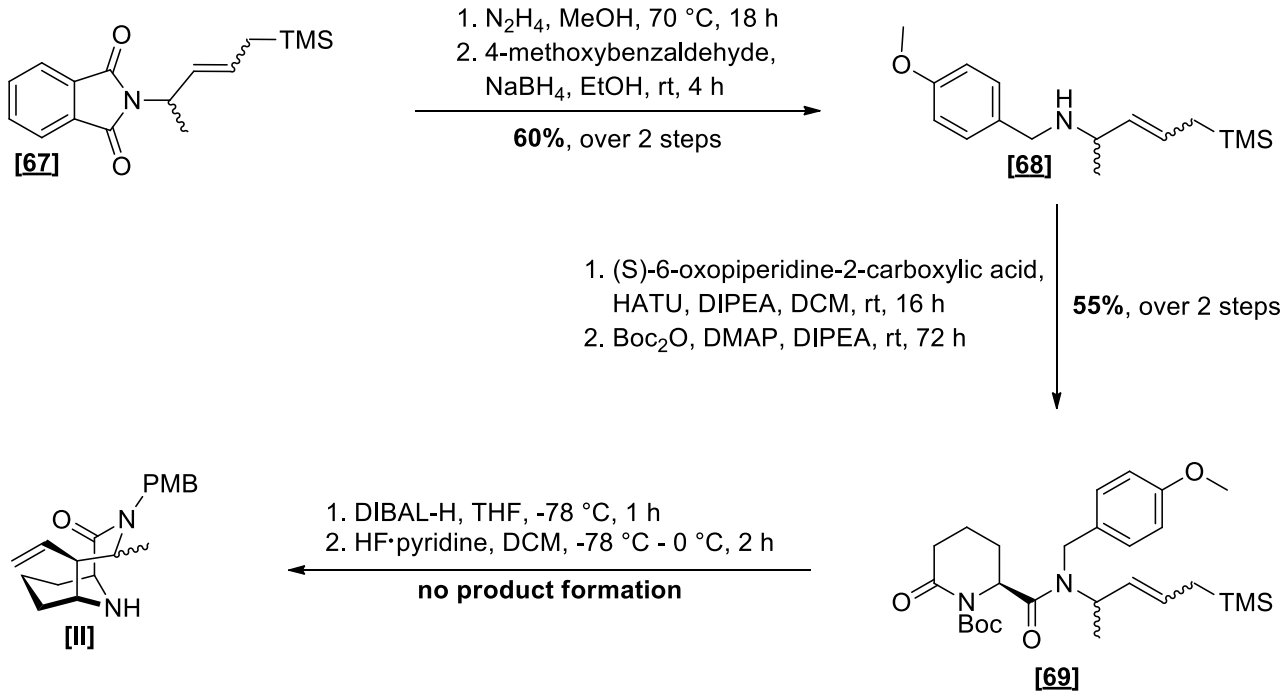
Scheme 43. Retrosynthetic analysis of 4-methyl derivative **[III]**.

The synthesis commenced with phthalimide **[23]** which was alkylated with 3-chlorobut-1-ene to afford alkylated isoindoline-1,3-dione **[66]** in 79% yield. The reaction afforded predominantly the desired product while allylic rearrangement was not observed. This was expected, due to the selected reaction conditions. A polar aprotic solvent (DMF), a good nucleophile (potassium phthalimide) and a low temperature were chosen, which favors S_N2 mechanism over S_N1. Regarding the probability of S_N2 versus S_N2', it was shown that the leaving group effects are decisive. Studies with 3-substituted-1-phenyl-1-butenes (representative of 3-chlorobut-1-ene) revealed, that the 3-chloro substrate favors S_N2 over S_N2' in a ratio of 96:4, while the 3-triphenylphosphonium bromide substrate gave exclusively (100:0) the S_N2'-product.[93]
Successive metathesis of alkylated isoindoline-1,3-dione **[66]** with Grubbs 1st generation catalyst afforded compound **[67]** in a poor yield of 14% (**Scheme 44**). No major side product was detectable and 55% starting material could be recovered. Probably the additional methyl group induces a steric hindrance, which decreases the yield of this step. Since the 14% yield gave enough material to proceed with the reaction scheme no optimizations were conducted.



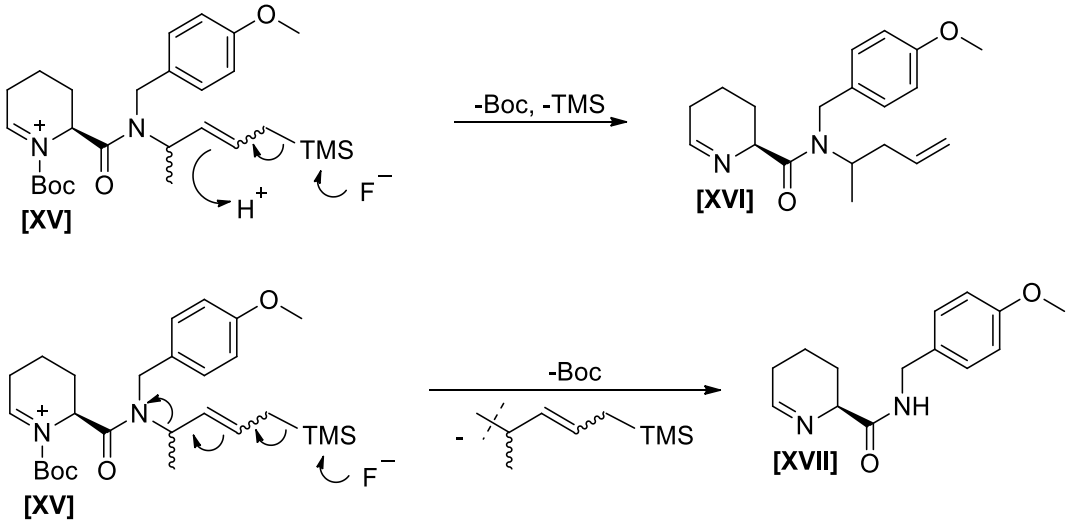
Scheme 44. Synthesis of compound **[66]** and compound **[67]**.

Compound **[67]** was treated with hydrazine to cleave the imide and obtain a primary amine which was successively subjected to reductive amination with 4-methoxybenzaldehyde yielding PMB-protected amine **[68]** with 60% yield over 2 steps (**Scheme 45**). HATU-mediated coupling to commercially available (*S*)-6-oxopiperidine-2-carboxylic acid followed by Boc-protection resulted in intermediate **[69]** in 55% yield over 2 steps.



Scheme 45. Attempted synthesis of 4-methylbicyclic [4.3.1] aza-amide **[II]**.

Reduction to the 6-hydroxypiperidine with DIBAL-H followed by treatment with HF·pyridine did not result in the desired compound **[II]**. Instead, a variety of new spots were detectable via thin layer chromatography (TLC). The two major spots were isolated by column chromatography and further analyzed by nuclear magnetic resonance (NMR) and mass spectroscopy (MS). The two proposed structures are depicted in **Scheme 46**.



Scheme 46. Identified side products of cyclization attempt of compound [71].

The side product **[XVI]** corresponds to the side product isolated in the same reaction step from the cyclization of **[27]** to **[28]** depicted in **Scheme 26**. The second side product **[XVII]** probably originates from a similar mechanism, where the TMS is cleaved and an electron shift cascade cleaves the pentenyl-residue from the amide nitrogen. Successive protonation results in side product **[XVII]**. Unfortunately, no product formation could be detected. This could be due to the additional methyl group introduced which sterically hinders the formation of the required conformation for cyclization and thus makes the compound more susceptible to decomposition. Since no traces of product were detectable this route was abolished.

3.1.9. Synthesis of the tricyclic compound [75]

The synthesis of the 4-methyl derivative probably failed due to a steric clash caused by the methyl group, which resulted in an unfavorable conformation for intramolecular cyclization. In order to overcome this problem, a tricyclic compound with a bridge from C4 to the amide was envisioned which would rigidify the molecule and lead to a more favorable transition state (**Figure 10**).

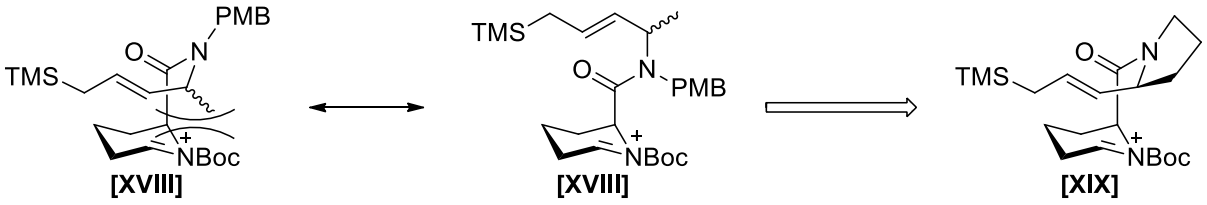
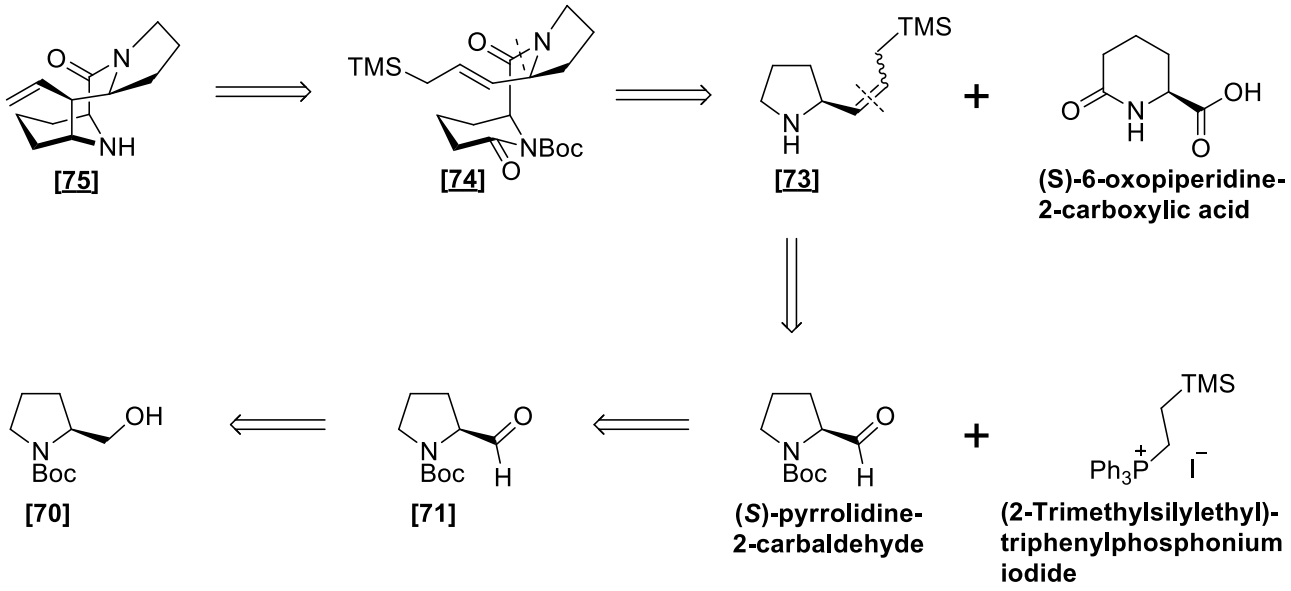


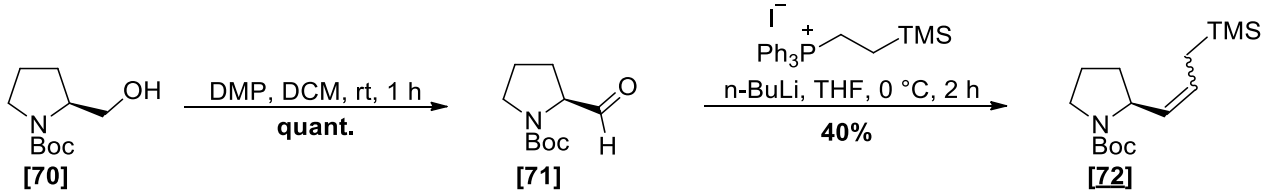
Figure 10. Possible clash of the C4-methyl group and envisioned work-around by cyclization.

The retrosynthetic analysis starting from tricyclic compound **[75]** is depicted in **Scheme 47**. With the HF-mediated cyclization in mind, the first retrosynthetic step leads back to compound **[74]**. Cleavage of the amide reveals (*S*)-6-oxopiperidine-2-carboxylic acid and amine **[73]**. The double bond can be obtained by a Wittig-reaction which leads back to (*S*)-pyrrolidine-2-carbaldehyde and commercially available (2-Trimethylsilylethyl)-triphenylphosphonium iodide. To avoid complications during the Wittig-reaction, a Boc-protection was envisioned. The aldehyde **[71]** can be obtained by oxidation of the respective alcohol which leads back to commercially available *N*-Boc-L-prolinol **[70]**.



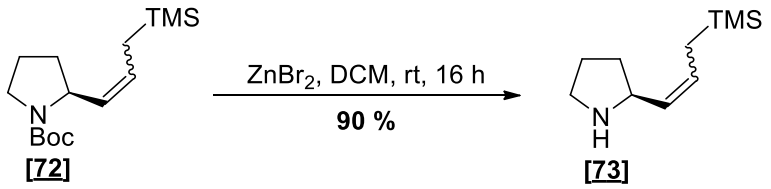
Scheme 47. Retrosynthetic analysis of tricyclic compound **[75]**.

The synthesis commenced with Boc-protected L-prolinol **[70]** which was oxidized to aldehyde **[71]** with Dess-Martin-Periodinane in dichloromethane in quantitative yield (**Scheme 48**). The product was directly used in the Wittig-reaction with (2-Trimethylsilylethyl)-triphenylphosphonium iodide to furnish intermediate **[72]** in 40% yield. According to ^{1}H-NMR the product is obtained as a ratio of *E/Z* = 1:4.



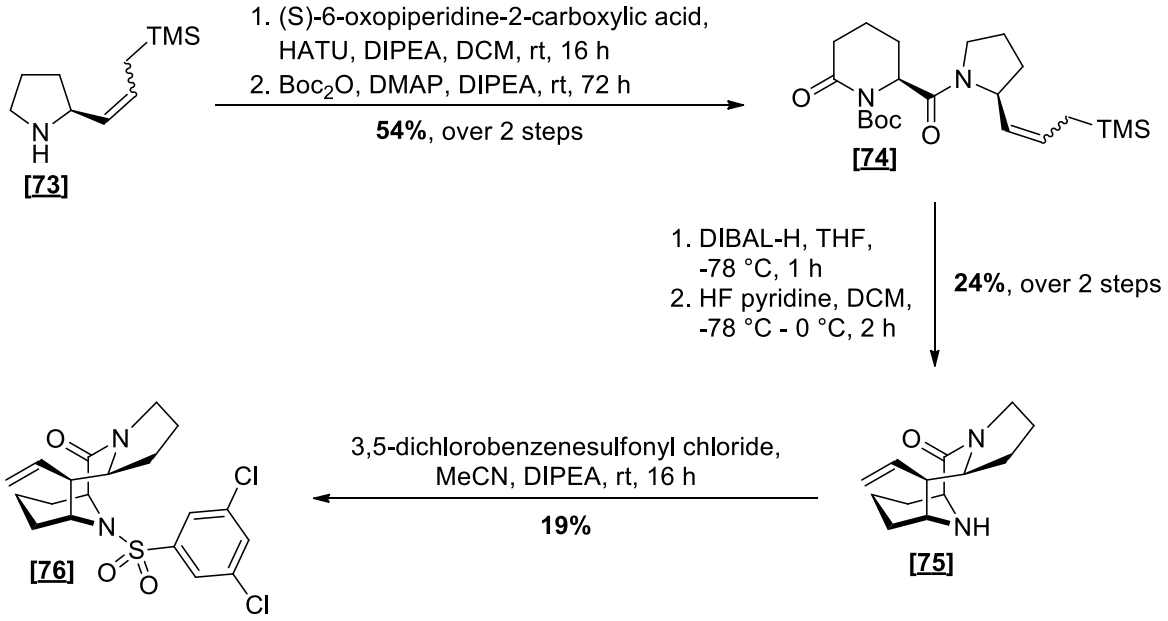
Scheme 48. Reaction of *N*-Boc-L-prolinol **[70]** to intermediate **[72]**.

The Boc-deprotection was initially attempted with trifluoroacetic acid in dichloromethane at 0 °C, which lead to complete decomposition. 1M HCl in tetrahydrofurane cleaved the Boc-group and the TMS group, while trimethylsilyl chloride in methanol, trimethylsilyl iodide in acetonitrile and boiling in water at 100 °C[94] did not give any conversion. Finally, a protocol by Nigam et al.[95], where $ZnBr_2$ in DCM is used, resulted in full cleavage of the Boc group. With this optimized procedure, a yield of 90% for amine **[73]** could be achieved as shown in **Scheme 49**.



Scheme 49. Boc-deprotection of **[72]** to afford amine **[73]**.

HATU-mediated coupling to commercially available (*S*)-6-oxopiperidine-2-carboxylic acid followed by Boc-protection resulted in intermediate **[74]** in 54% yield over 2 steps (**Scheme 50**). Reduction with DIBAL-H followed by treatment with HF-pyridine in dichloromethane yielded the novel tricyclic compound **[75]**. Reaction with 3,5-dichloro-benzenesulfonyl chloride afforded final compound **[76]** in 19% yield.



Scheme 50. Synthesis of tricyclic compound **[75]** and **[76]**.

To ensure the configuration of the stereocenter at C11a, a complete set of 2D-NMR spectra was recorded. All carbons and protons were assigned, and spatial proximity of protons was assigned by Nuclear Overhauser effect spectroscopy (NOESY) NMR (**Figure 11**).

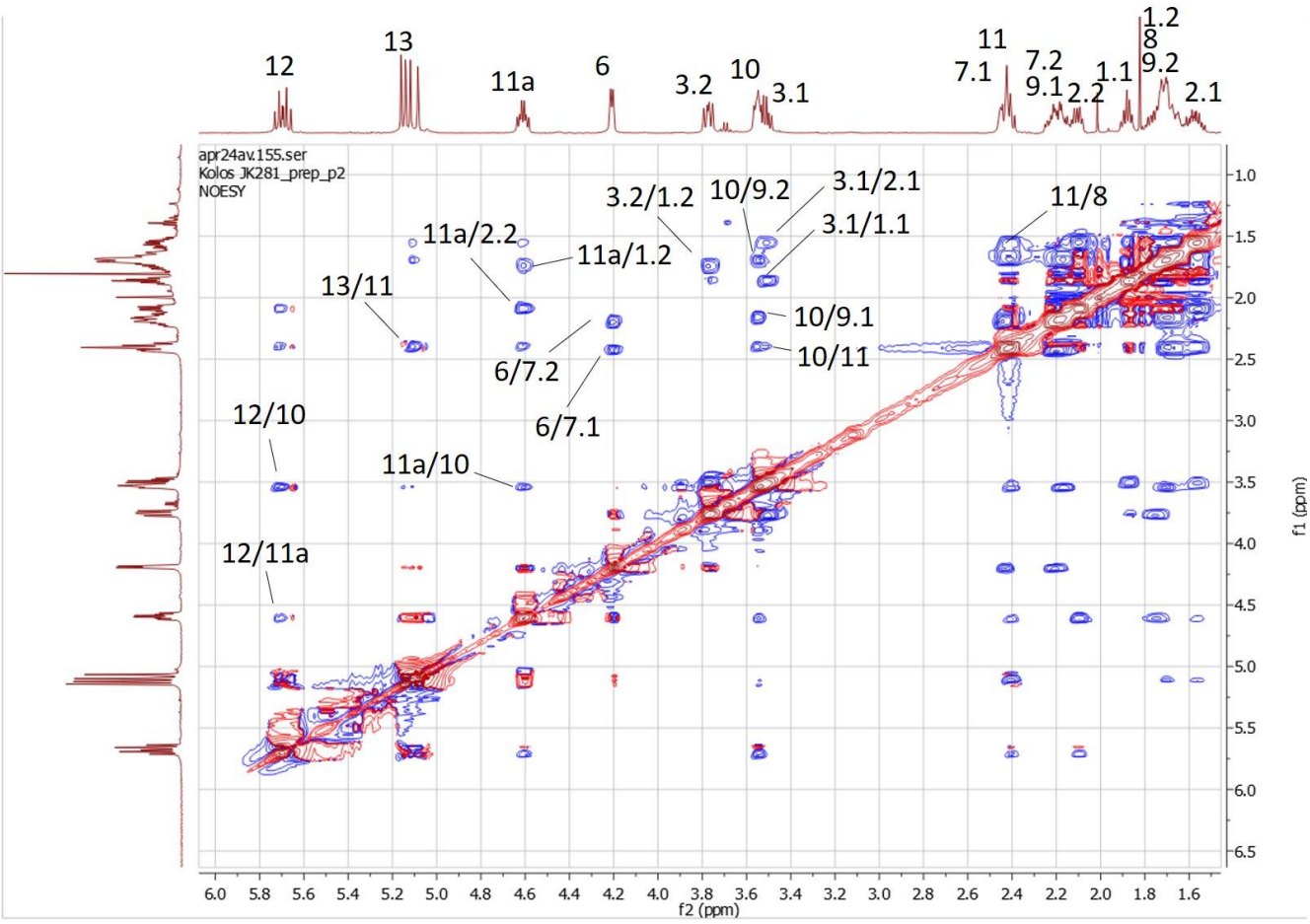


Figure 11. NOESY-spectrum of tricyclic compound **[75]**.

The numbering of the tricyclic compound **[75]** as well as the assigned protons in spatial proximity to each other are depicted in **Figure 12**.

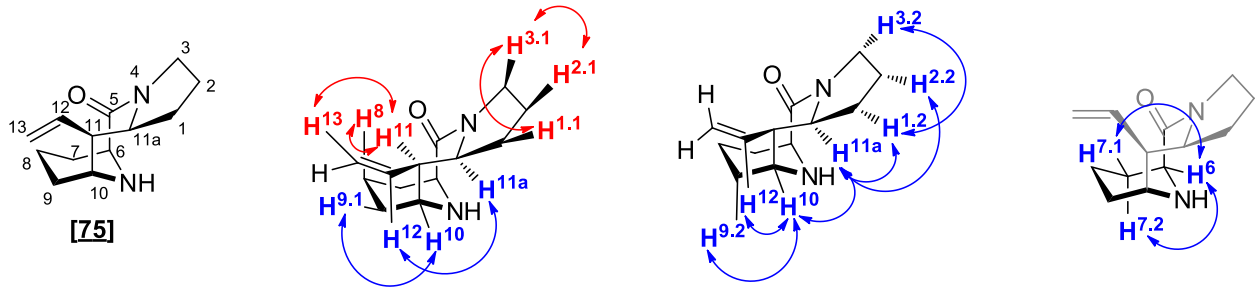
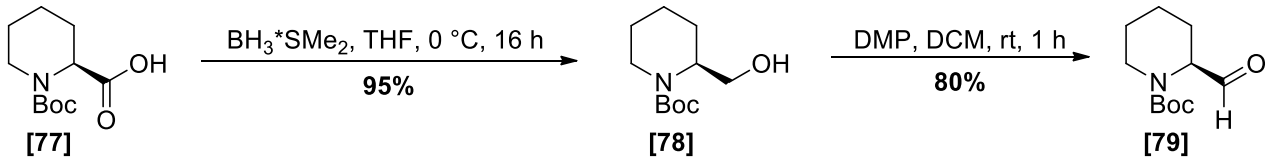


Figure 12. Numbering of tricycle **[75]** and the relevant spatial proximity hydrogen interactions assigned by NOESY-NMR. For the sake of clarity, the numbering of the hydrogens is superscript.

A clear indication that the configuration at C11a is as expected, is the interaction of H11a with H10. This spatial proximity can only be observed, if H11a faces downwards. Besides this interaction, all other hydrogens in spatial proximity to H11a could be found in either configuration. Another important point to consider, is the lacking interaction of H11a with either H11 or H8. If H11a would face upwards, these interactions should be visible to some extent.

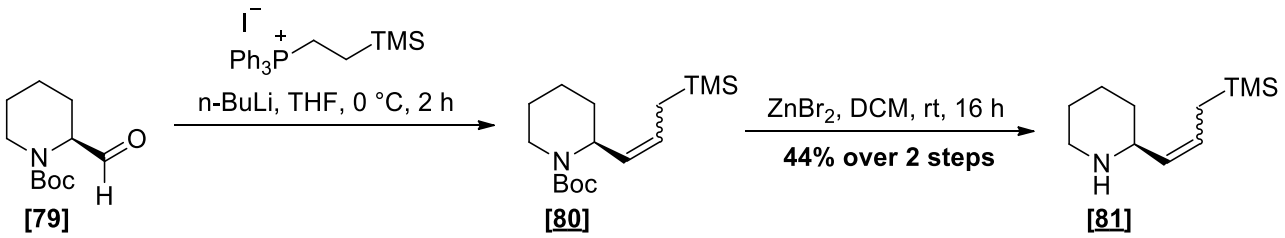
3.1.10. Attempted synthesis of tricyclic compound with 6-membered ring

In order to have a second tricyclic structure with a slightly deviating conformation of the new ring, compound **[IV]** (**Figure 7**) was envisioned with a 6-membered ring instead of a 5-membered ring. The synthesis commenced with commercially available (*S*)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid **[77]** which was reduced with borane to alcohol **[78]** in 95% yield and oxidized to aldehyde **[79]** in 80% yield (**Scheme 51**).



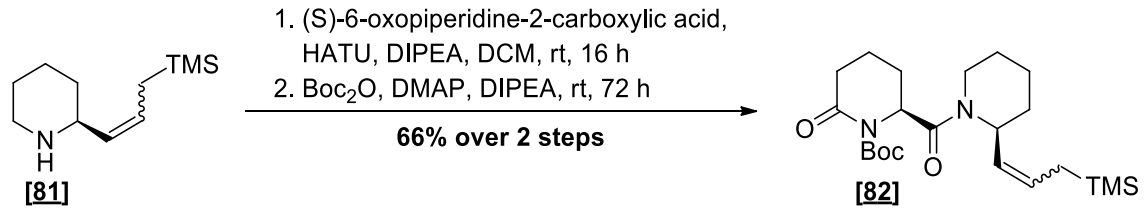
Scheme 51. Synthesis of compound **[78]** and compound **[79]**.

Aldehyde **[79]** was subjected to a Wittig reaction with (2-Trimethylsilylethyl)-triphenylphosphonium iodide to obtain alkene **[80]**. Since it was not possible to remove during the reaction formed triphenylphosphine oxide by column chromatography, the crude material was directly Boc-deprotected with zinc bromide to obtain amine **[81]** in 44% yield over two steps (**Scheme 52**). According to ^{1}H-NMR the product is obtained as a ratio of E/Z = 1:9.



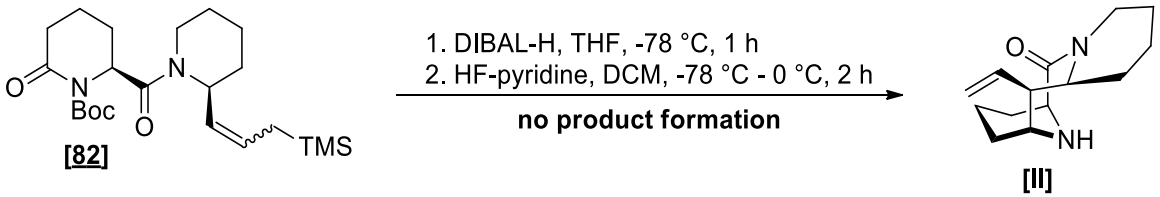
Scheme 52. Wittig-reaction of **[79]** to alkene **[80]** and Boc-deprotection to amine **[81]**.

HATU-mediated coupling to (*S*)-6-oxopiperidine-2-carboxylic acid followed by Boc-protection gave compound **[82]** in 66% over two steps (**Scheme 53**).



Scheme 53. Coupling and Boc-protection of compound **[81]**.

Reduction with DIBAL-H followed by treatment with HF-pyridine did not yield the desired product **[II]** as depicted in **Scheme 54**.



Scheme 54. Attempted cyclization of compound **[82]**.

Besides major decomposition, dimerization and previously described loss of the Boc- and the TMS-group without cyclization was observed by MS and NMR. Presumably, the slight change from the 5- to the 6-membered ring led to an unfavorable transition state. Since no product was detectable at all, this synthesis was aborted.

3.1.11. Binding Affinities

The deuterated compounds and their respective reference compounds as well as tricyclic compound **[76]** were measured in a fluorescence polarization (FP) assay for their binding affinities to various FKBPs (12, 12.6, 51, 52). The results are tabulated in **Table 2**.

Table 2. Binding affinities of deuterated compounds and tricyclic compound **[76]**.

#	Ki nM FKBP12	Ki nM FKBP12.6	Ki nM FKBP51	Ki nM FKBP52
[50]	67 ± 18	95 ± 4	1491 ± 227	1395 ± 186
[51]	93	132	1389	1679
[52]	67	117	1193	1598
[53]	56	92	1436	1387
[54]	53 ± 8	82 ± 2	1284 ± 134	1396 ± 154
[57]	79 ± 23	97 ± 10	1281 ± 22	1334 ± 140
[62]	60 ± 1	113 ± 4	1554 ± 120	1419 ± 50
[63]	8.9 ± 1.1	6.1 ± 1.1	297 ± 51	344 ± 28
[64]	5.8	12	320	342
[65]	7.3	13	248	267
[76]	146 ± 15	346 ± 50	3893	3853 ± 444

Compounds with a *N*-methyl amide (**[50]** – **[54]**, **[57]**, **[62]**) display similar affinity values for all tested FKBPs, with 56 – 93 nM for FKBP12, 82 – 132 nM for FKBP12.6, 1193 – 1554 nM for FKBP51 and 1334 – 1679 nM for FKBP52. Compounds with a (pyridine-2-ylmethyl) residue at the amide (**[63]** – **[65]**) bind slightly better due to an additional interaction of the pyridine nitrogen to Tyr113, with 5.8 – 8.9 nM for FKBP12, 6.1 – 13 nM for FKBP12.6, 248 – 320 nM for FKBP51 and 267 – 344 nM for FKBP52. Tricyclic compound **[76]** binds slightly weaker to all FKBPs compared to the reference compound **[50]**. The general trend of binding affinity is FKBP12 > FKBP12.6 > FKBP51 > FKBP52, which is consistent with the affinities of most bicyclic [4.3.1] aza-amides.

3.1.12. Metabolic stability

Compounds **[50]**, **[53]**, **[54]**, **[57]** and **[62]** were subjected to phase I metabolite identification in mouse liver microsomes incubations conducted by the external service provider Pharmacelsus. Briefly, the compounds were incubated with liver microsomal fractions from mice and samples were subjected to HPLC-HRMS metabolite analysis by means of accurate mass and MS/HRMS fragmentation for accurate mass structural analysis. and MS/HRMS fragmentation. All tested compounds displayed rapid degradation and were fully metabolized after ten minutes, as shown in **Figure 13**.

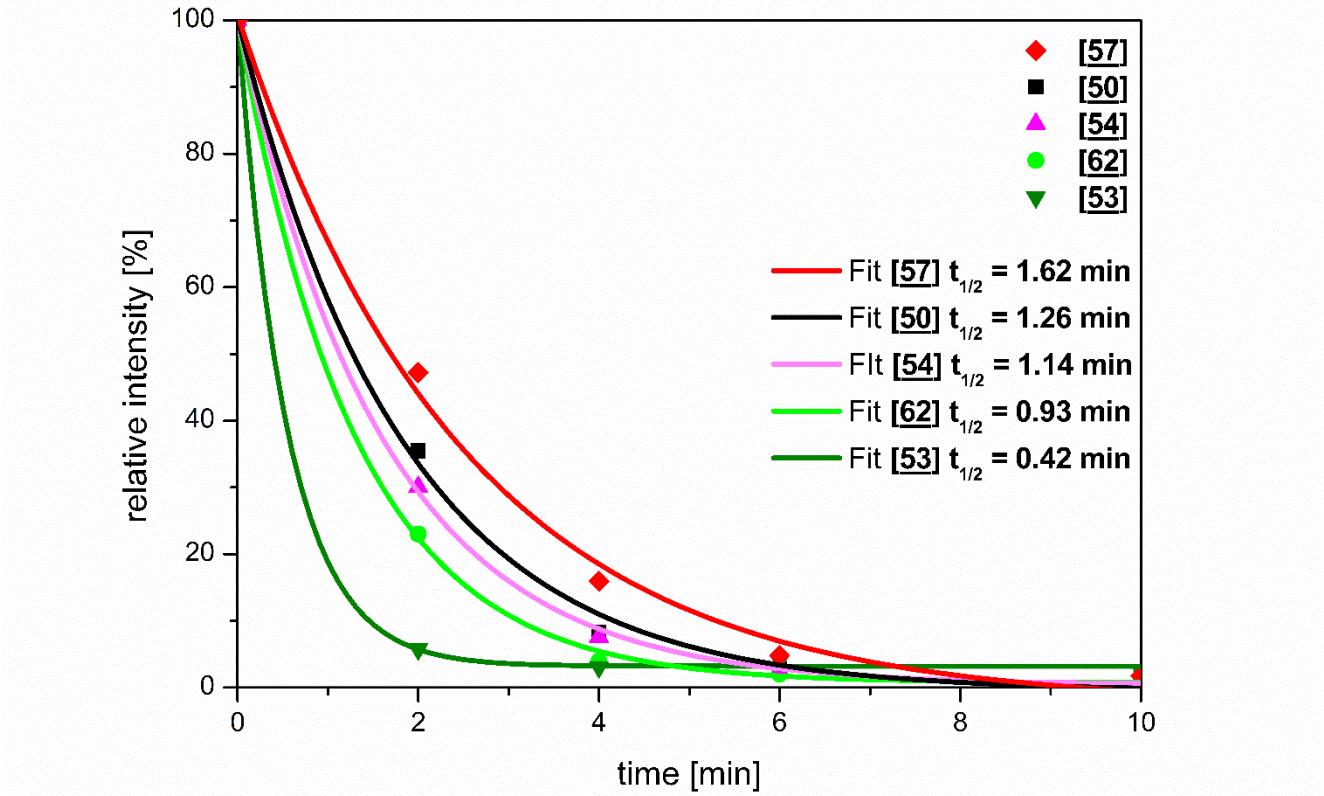
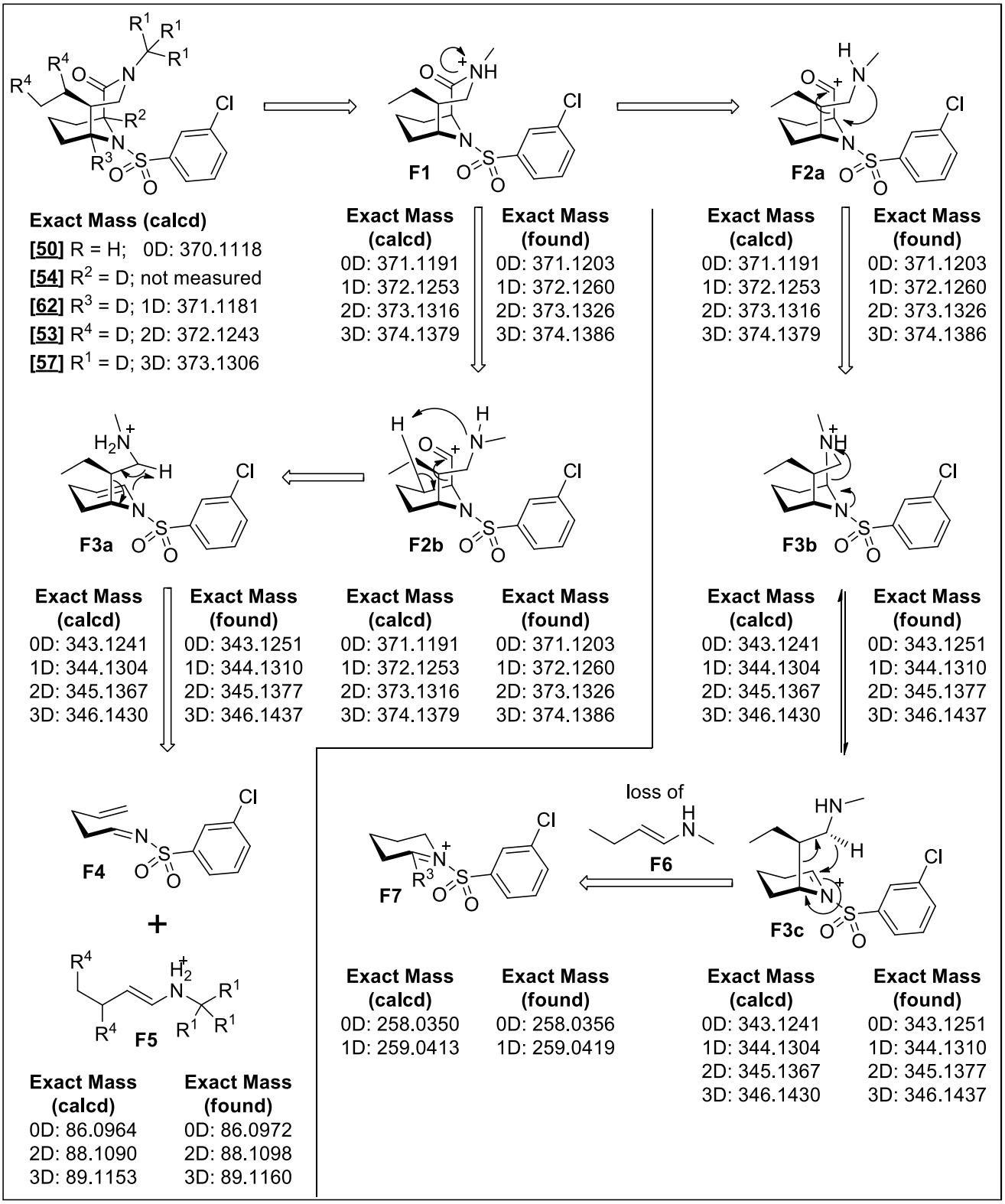


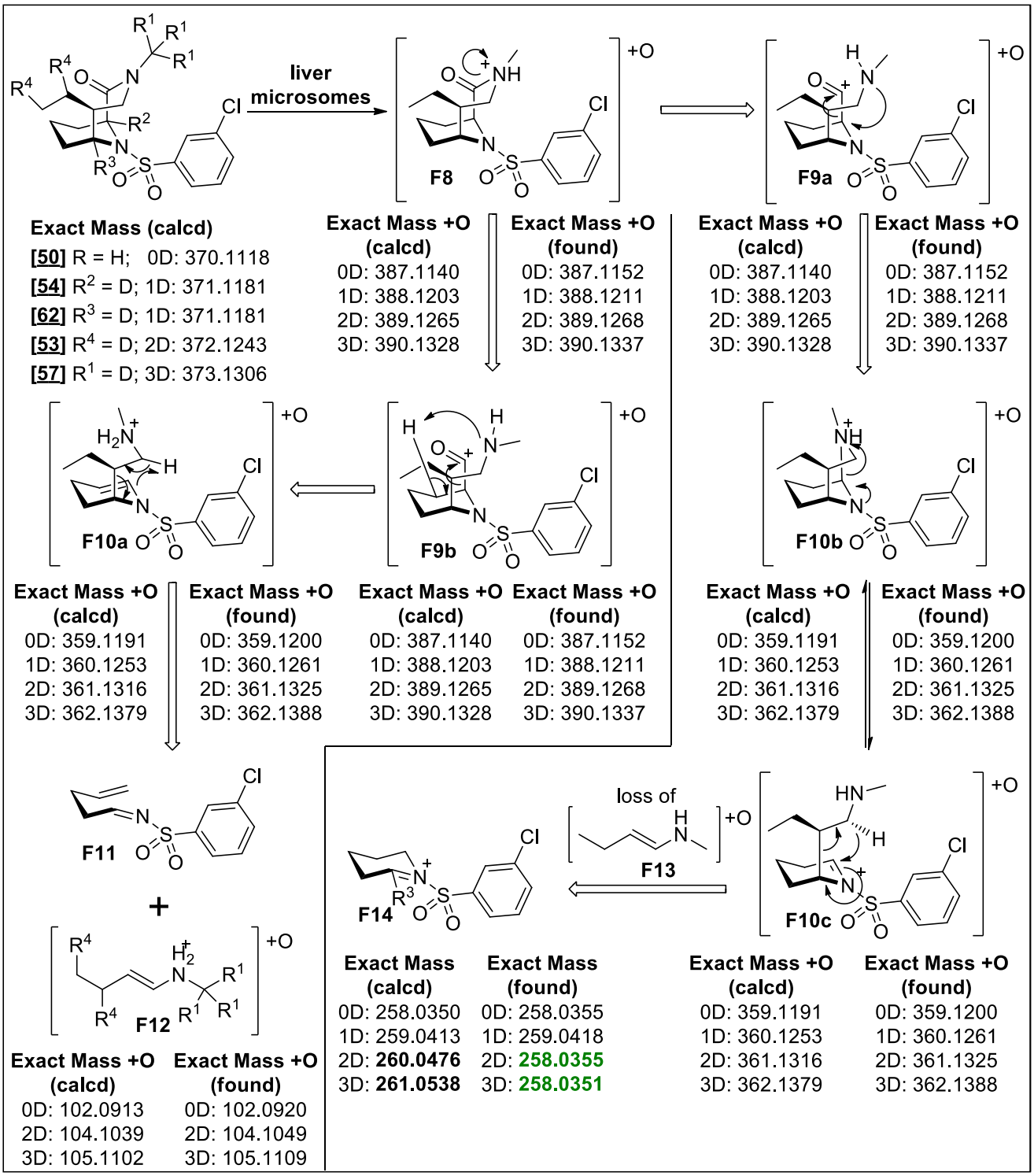
Figure 13. Metabolic degradation of compounds **[50]**, **[53]**, **[54]**, **[57]** and **[62]**.

Half-life times were calculated for all compounds. The only compound with increased half-life time compared to reference compound **[50]** was compound **[57]** with fully deuterated methyl group. This indicates that this position is important for metabolic degradation. Compounds **[54]** and **[62]** display a similar half-life time to **[50]**. Surprisingly, compound **[53]** displays a three times lower half-life time than **[50]**, although there is no apparent reason, why this compound should be metabolized faster. It might be due to an error in the experiment.
The fragmentation pattern of compounds **[50]**, **[53]**, **[57]** and **[62]** were further investigated. The proposed pathway is based on the detected fragments for each compound and is depicted in **Scheme 55**. After initial ionization, an amide bond break occurs followed by two possible scenarios for a loss of CO. Either, by a direct attack of the nitrogen lone pair at the α-carbon of the carbonyl moiety (**F2a**) or by a hydrogen abstraction of the nitrogen lone pair at C9 leading to desaturation of the piperdine ring (**F2b**). Subsequently, the loss of an alkyl amine occurs with two plausible fragmentations. In the first case, the positive charge remains on the secondary amine (**F3a**) and a 6-membered transition state leads to the loss of a charged secondary amine fragment (**F5**) and a neutral sulfonamide (**F4**). In the second case, the positive charge is located on the sulfonamide nitrogen (**F3c**) and a 6-membered transition state leads to a loss of a neutral secondary amine (**F6**) plus a charged sulfonamide (**F7**).



Scheme 55. Proposed fragmentation pathways of **[50]**, **[53]**, **[57]** and **[62]**.

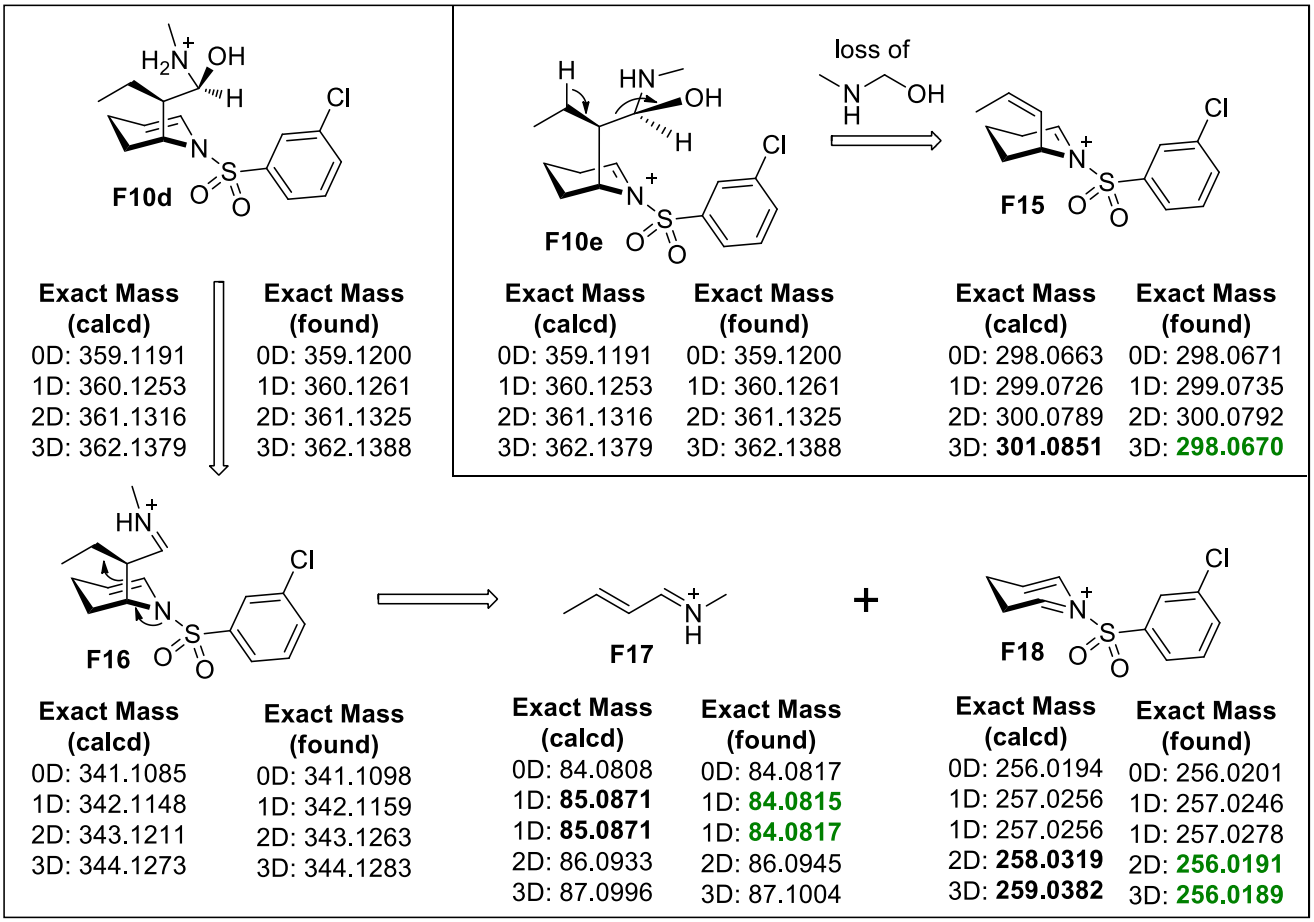
With the elucidated fragmentation pattern in hand, we looked at the metabolized fragments of compounds **[50]**, **[53]**, **[54]**, **[57]** and **[62]**. Neglecting follow-up metabolites, two major metabolites were identified. One, with oxidation at the amide-methyl group (further referred to as **[M2]**), as evident by the loss of fragment [-CH_3O], the other with oxidation at C4 of the bicyclic [4.3.1] aza-amide (henceforth referred to as **[M1]**). The fragments that lead to the identification of the oxygen at C4 are depicted in **Scheme 56**.



Scheme 56. Proposed fragmentation pathways of the metabolized fragment **[M1]** of [50], [53], [54], [57] and [62]. Numbers highlighted in bold black are calculated for the fragments with the respective number of deuterium, numbers in bold green emphasize the deviation compared to the calculated values due to absence of deuterium.

Firstly, the oxidation cannot happen at the amide methyl, otherwise the masses for the CD_3 derivatives (390, 362) would not be found in fragments **F8** – **F10**. Secondly, the oxidation cannot take place at the pipecolate core or the sulfonamide, due to the masses found for **F14** (258 or 259, for the monodeuterated pipecolates) instead of the masses with additional oxygen (274 or 275). Thirdly, fragments **F15** with the masses 298 – 300 were found

(**Scheme 57**), which probably originate from a cleavage at C5. These fragments were found for all compounds except the CD_3 derivative, where the mass 298 was found, which is in accordance with the proposed structure.



Scheme 57. Proposed fragmentation pathways of additional metabolized fragment **[M1]** of **[50]**, **[53]**, **[54]**, **[57]** and **[62]**. Numbers highlighted in bold black are calculated for the fragments with the respective number of deuterium, numbers in bold green emphasize the deviation compared to the calculated values due to absence of deuterium.

Therefore, the only possible position for oxidation is at C4. Another indication, that the oxidation takes place at C4 is **F16**. These masses probably originate from oxidation followed by loss of water. The eliminated fragment further follows a different fragmentation pathway, with fragmentations to **F17** (masses 84 – 87) and **F18** (masses 256 – 257).

The combination of the different fragmentation pattern allowed to narrow down the positions where metabolic events occur. The two proposed primary metabolite structures are depicted in **Figure 14**. For simplification only the primary metabolites are shown.

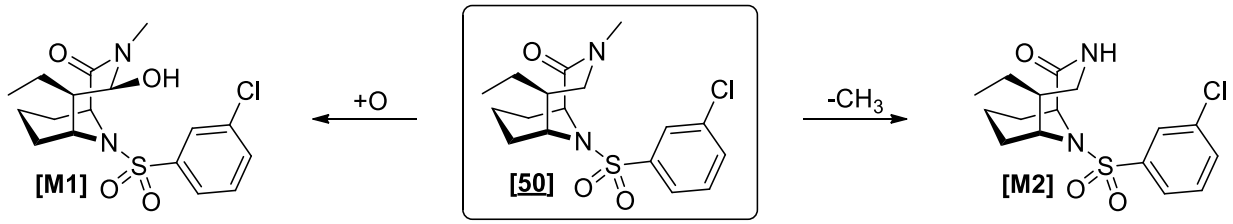


Figure 14. The two proposed main metabolites of **[50]**.

For each tested compound, pie charts were created which display the metabolite distribution after two minutes. For clarity, only metabolites with an initial relative percentage of >2% are plotted. For simplification only the primary metabolites are shown, follow-up metabolites and other metabolic events are combined as 'other'. It is

noteworthy, that the relative percentages are based on the intensity of the peaks in the mass spectra. It is assumed, that the ionization of the different deuterated iso-analogs is nearly identical, while the ionization of the different metabolic degradation products may vary. However, this was not taken into account in this study. The pie charts and the chemical structure of reference compound **[50]** are displayed in **Figure 15**.

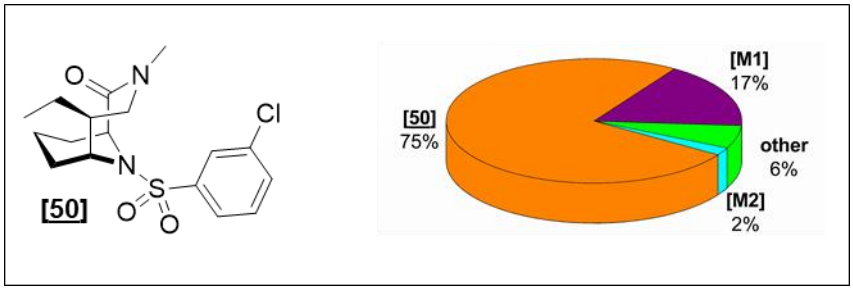


Figure 15. Structure (left) and metabolite distribution pattern after 2 min (right) of compound **[50]**.

The initial metabolites after two minutes are mainly (17%) due to oxidation of the alkyl bridge (**[M1]**) and to less extent (2%) due to oxidation of the *N*-methyl group (**[M2]**) and other events (6%).

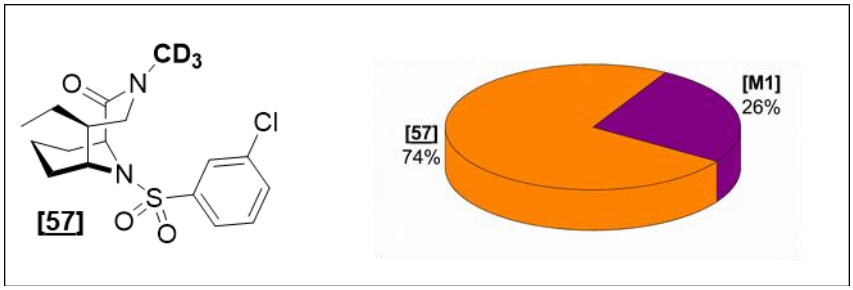


Figure 16. Structure (left) and metabolite distribution pattern after 2 min (right) of compound **[57]**.

Comparing **[50]** to derivative **[57]** with fully deuterated methyl group (**Figure 16**), a significant shift in metabolite distribution is observed. The only metabolite originates from oxidation of the alkyl chain (**[M1]**). It is apparent that the oxidative demethylation pathway is completely suppressed, while oxidation of the alkyl chain is now the main degradation pathway. This discloses the *N*-alkyl residue as one of the metabolic soft spots, however, when this position is chemically modified the metabolic degradation pathway switches to the alkyl bridge. This is further demonstrated by the metabolite distribution of **[53]** where two deuterium are introduced to the ethyl linker (**Figure 17**).

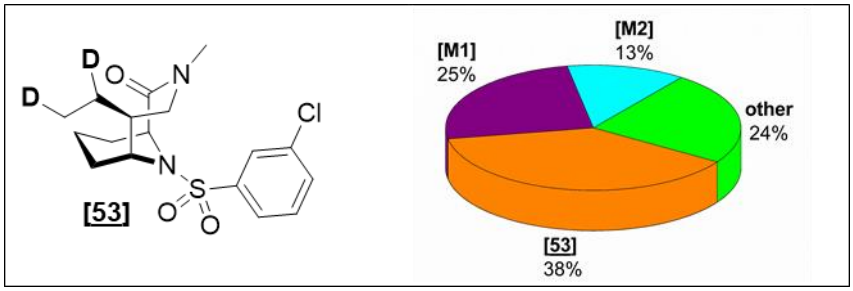


Figure 17. Structure (left) and metabolite distribution pattern after 2 min (right) of compound **[53]**.

The proportion of metabolites (13%) due to oxidative *N*-methyl cleavage (**[M2]**) and other events (24%) are increased, suggesting that another metabolic pathway is slowed down and therefore metabolism switches to another metabolic soft spot. However, this is in contrast to the finding that this compound has the lowest half-life time of the tested compounds and is therefore metabolized the fastest. It is assumed, that an experimental error occurred at some point, which limits the conclusions that can be drawn from the data for this compound.

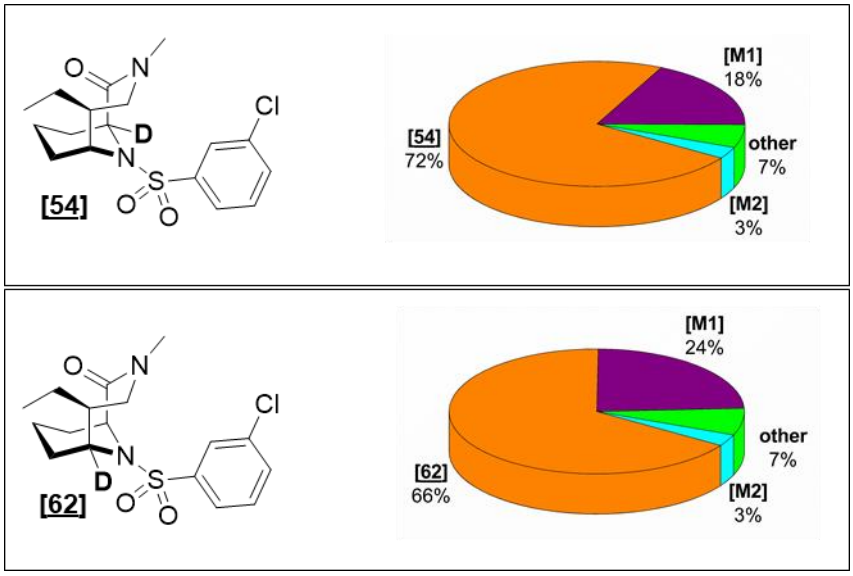


Figure 18. Structure (left) and metabolite distribution pattern after 2 min (right) of compound **[54]** and **[62]**.

Compounds **[54]** and **[62]** (**Figure 18**) display no significant differences compared to the reference compound **[50]**. This suggests, that those two positions play no role in the metabolism. Further examination of the proposed metabolic pathway reveals the absence of hydrolysis of the sulfonamide and reductive dehalogenation. Taken together, the rapid metabolic degradation is due to oxidation at the alkyl bridge (C4) and at the *N*-alkyl carbon.

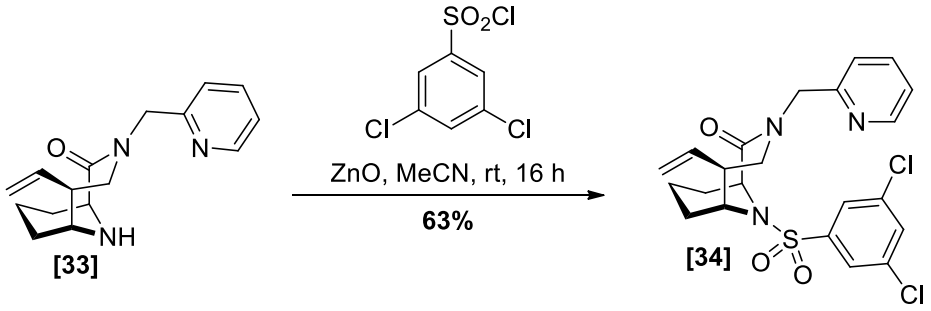
In order to improve the stability of the alkyl chain tricyclic compound **[76]** was synthesized. The compound was tested for its metabolic stability, however, it suffered from rapid degradation beyond measurability.

3.2. Overview of Project 2: Synthesis of α-Methyl Derivatives and Respective Reference Compounds

Bicyclic [4.3.1] aza-amides previously synthesized within our group have displayed varying binding affinities towards FKBPs with a methyl group located in the *N*-α-position of the amide. While the *S*-isomer displays enhanced binding affinity, the *R*-isomer displays decreased binding affinity. It was unclear, where this effect originates from and whether it is consistent for different residues in R^1, R^2 and R^3. To address the former question, a molecular modelling study was performed with previously (by Sebastian Pomplun) synthesized bicyclic compound **[169]** and its two methylated analogs **[170]** and **[171]** (**Figure 19**). To address the latter question, a small library of bicyclic [4.3.1] aza-amides with different residues in the three positions were synthesized and their binding affinities for FKBPs and Mips were measured.

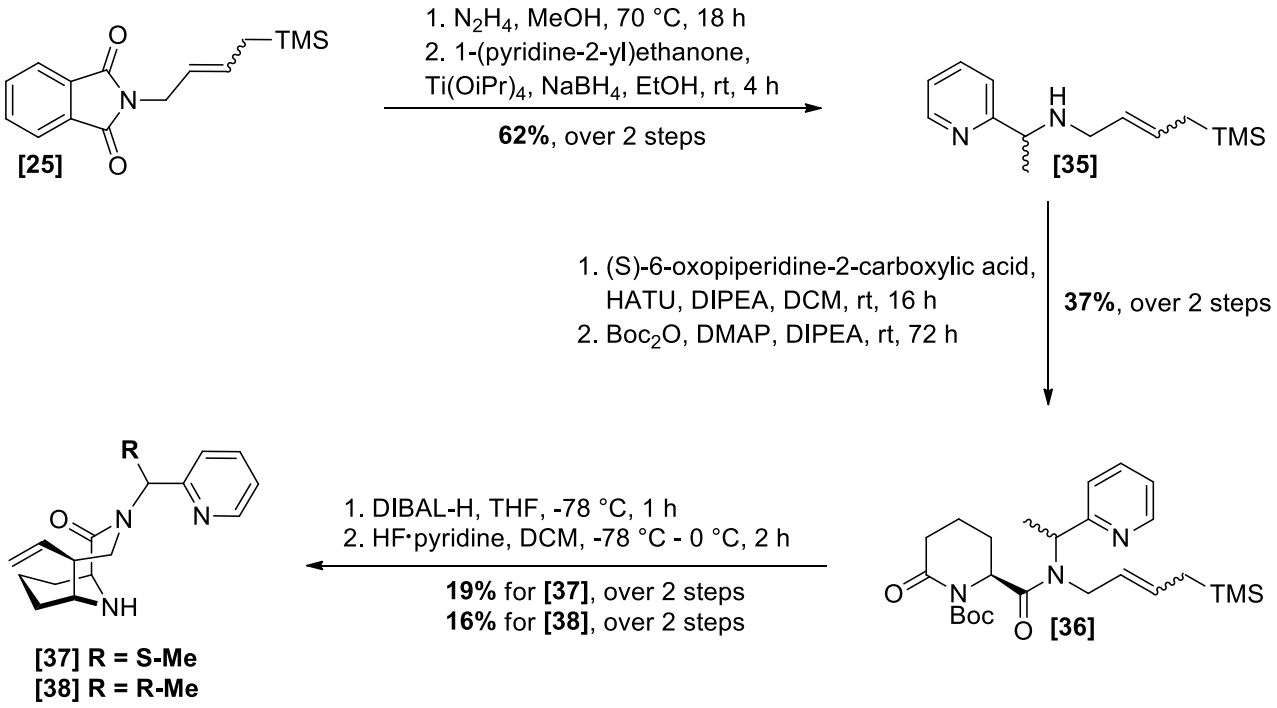
3.2.1. Synthesis of Derivatives with a Pyridine Moiety at R^1

Compound **[34]** was synthesized by reacting **[33]** (*vide supra*, **Scheme 29**) with 3,5-dichlorobenzenesulfonyl chloride as shown in **Scheme 58**. Here, zinc oxide was used instead of common organic bases according to a procedure by Meshram and Patil.[96] It it noteworthy, that the procedure using zinc oxide in acetonitrile gave better yields in comparison to Hünig's base in dichloromethane. However, it was found later that the boost in yield is attributed to acetonitrile as solvent. Control experiments with Hünig's base in acetonitrile displayed comparable yields to zinc oxide in acetonitrile.



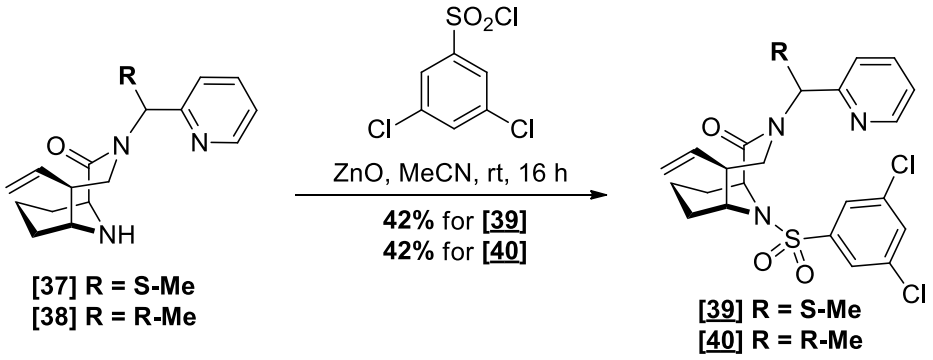
Scheme 58. Synthesis of compound **[34]**.

The synthesis of the two bicyclic precursors with R^1 = (pyridine-2-ylethyl) were synthesized accordingly to **[33]** as depicted in **Scheme 59**. The synthesis commenced with the deprotection of intermediate **[25]** to a primary amine, which was subjected to reductive amination with 1-(pyridine-2-yl)ethenone to yield a mixture of two stereoisomers **[35]** in 62% over two steps. HATU-mediated coupling to (*S*)-6-oxopiperidine-2-carboxylic acid followed by Boc-protection resulted in intermediate **[36]** in 37% yield over two steps. Reduction with DIBAL-H followed by treatment with HF-pyridine yielded two diastereomers, which were separated by column chromatography. The *S*-isomer **[37]** was obtained in 19% yield over two steps and the *R*-isomer **[38]** in 16% over two steps.



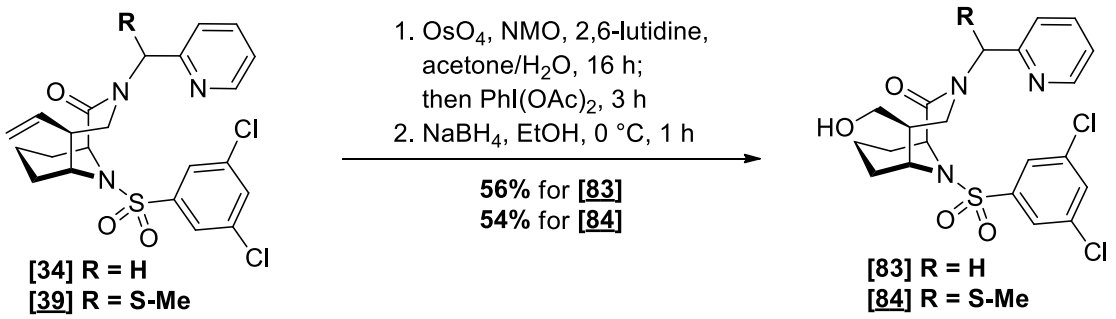
Scheme 59. Synthesis of building blocks **[37]** and **[38]**.

Both isomers were reacted to the respective sulfonamides with 3,5-dichlorobenzenesulfonyl chloride in acetonitrile to give the *S*-isomer **[39]** in 42% yield and the *R*-isomer **[40]** in 42% yield (**Scheme 60**).



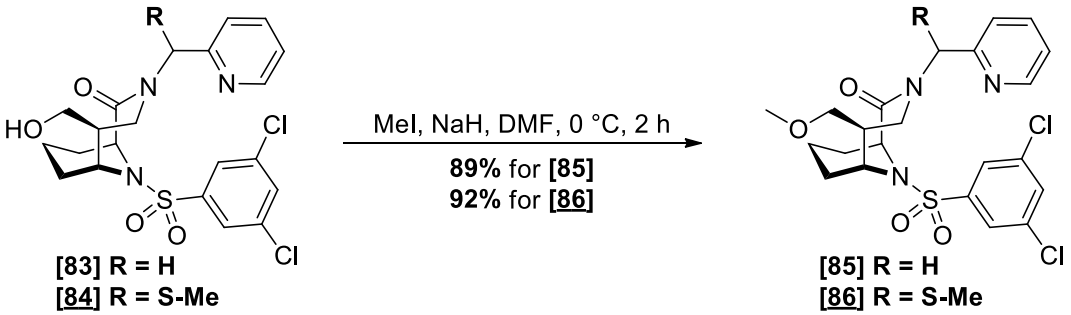
Scheme 60. Synthesis of compounds **[39]** and **[40]**.

Compound **[34]** without a *N*-α-methyl group and the *S*-isomer **[39]** were further subjected to derivatization at R^3. Dihydroxylation of the vinyl moiety with osmium tetroxide followed by oxidative cleavage to the aldehydes with (diacetoxyiodo)benzene and reduction with sodium borohydride furnished alcohols **[83]** and **[84]** in 56% and 54% yield, respectively (**Scheme 61**).



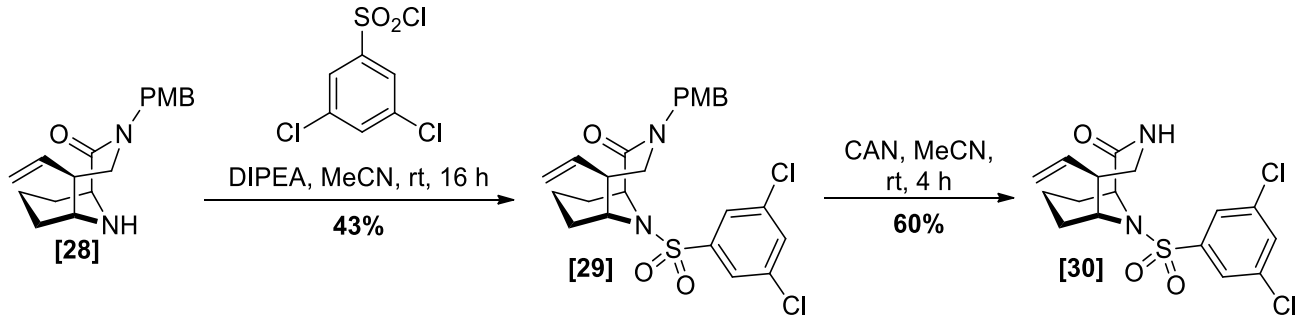
Scheme 61. Synthesis of alcohols **[83]** and **[84]**.

Methylation with methyl iodide gave methyl ethers **[85]** and **[86]** in 89% and 92% yield, respectively, as depicted in **Scheme 62**.



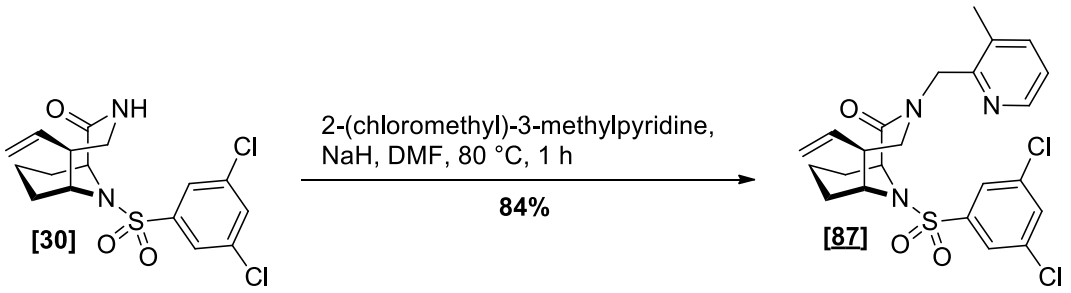
Scheme 62. Synthesis of methyl ethers **[85]** and **[86]**.

Derivatives with a modification in the pyridine ring were synthesized by introduction of the pyridine moiety as last step via alkylation of the free bicyclic amide. Therefore, PMB-protected compound **[28]** was transformed to sulfonamide **[29]** and PMB-deprotected to furnish the free amide **[30]** as depicted in **Scheme 63**.



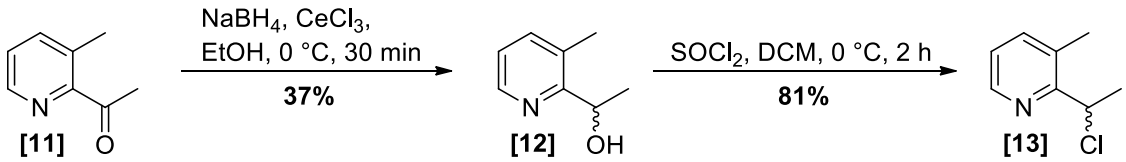
Scheme 63. Synthesis of PMB-deprotected compound **[30]**.

Compound **[30]** was alkylated with commercially available 2-(chloromethyl)-3-methylpyridine in 84% yield as shown in **Scheme 64**.



Scheme 64. Synthesis of compound **[87]**.

The precursor for *N*-α-methyl derivatives was not commercially available and was synthesized starting from commercially available 1-(3-methylpyridin-2-yl)ethenone **[11]** as shown in **Scheme 65**. Ketone **[11]** was reduced under Luche conditions to a racemic mixture of alcohols **[12]** in 37% yield. The poor yield is due to losses during aqueous work-up. Alcohols **[12]** were subjected to treatment with thionyl chloride in dichloromethane to give a racemic mixture of chloro-compound **[13]** in 81% yield.



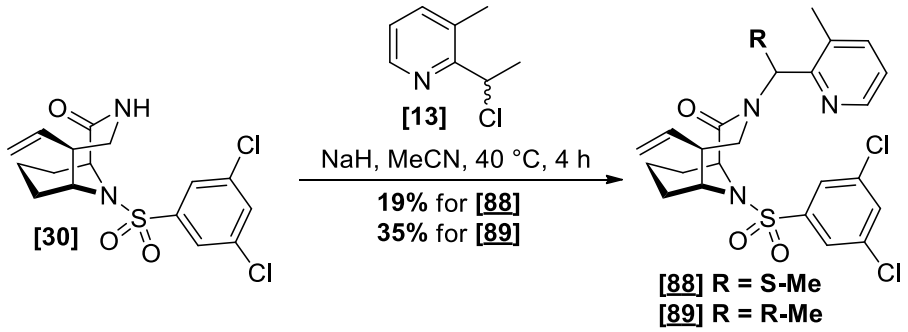
Scheme 65. Synthesis of precursor **[13]**.

The initial attempt to alkylate amide **[30]** with chloro-compound **[13]** and sodium hydride in dimethylformamide at 80 °C resulted in complete decomposition due to Truce-Smiles rearrangement (details to this side reaction can be found in the master thesis of Robin Deutscher). Different reaction conditions were screened and summarized in **Table 3**, with the best conditions found for entry 4, utilizing acetonitrile as solvent at 40 °C.

Table 3. Optimization of reaction of **[30]** with compound **[13]**.

#	[13] (eq.)	NaH (eq.)	Solvent	Temp.	Time (h)	Product [88] & [89]	Side product	Starting material
1	5	5	DMF	rt	1	0	100	0
2	5	5	MeCN	rt	1	8	0	92
	5	5	MeCN	rt	16	20	0	80
	5	30	MeCN	rt	72	79	21	0
3	5	5	THF	rt	1	0	0	100
	5	5	THF	rt	16	0	0	100
4	4	10	MeCN	40 °C	4	79	7	14
5	4	10	MeCN	60 °C	4	79	21	0

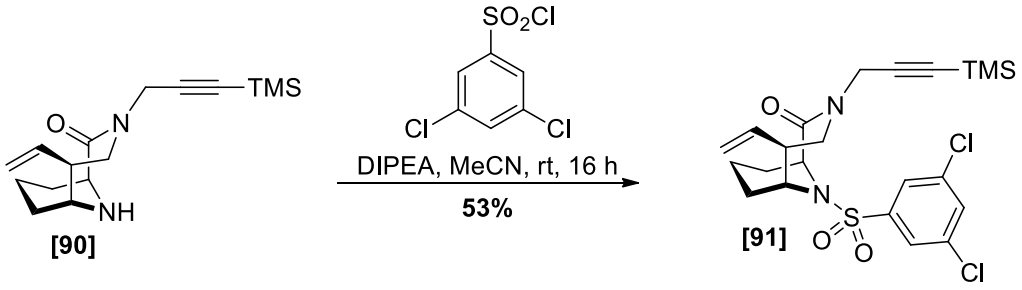
The optimized reaction conditions were applied on a larger scale as shown in **Scheme 66**. The reaction afforded two diastereomers which were separated by column chromatography. The *S*-isomer **[88]** was obtained in 19% and the *R*-isomer **[89]** in 35% yield.



Scheme 66. Synthesis of compounds **[88]** and **[89]**.

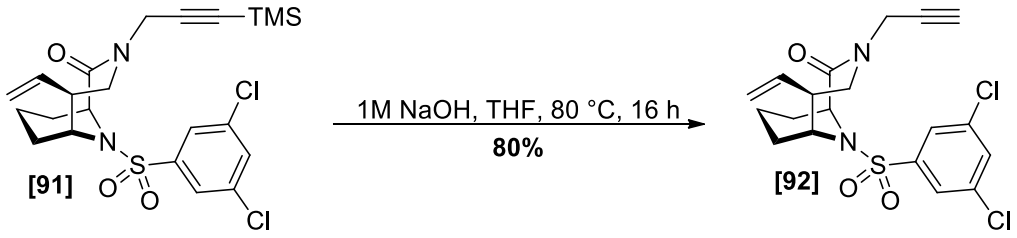
3.2.2. Synthesis of Derivatives with a Triazole Moiety at R^1

In order to obtain a building block for Click-type-reactions, a bicyclic [4.3.1] aza-amide with a propargyl linker at the amide was envisioned. The synthesis of the TMS-protected building block **[90]** was conducted by Michael Walz during the work for his master thesis under my supervision. Treatment with 3,5-dichlorobenzenesulfonyl chloride afforded compound **[91]** in 53% yield as depicted in Scheme 67. Synthesis of compound [91]**.**



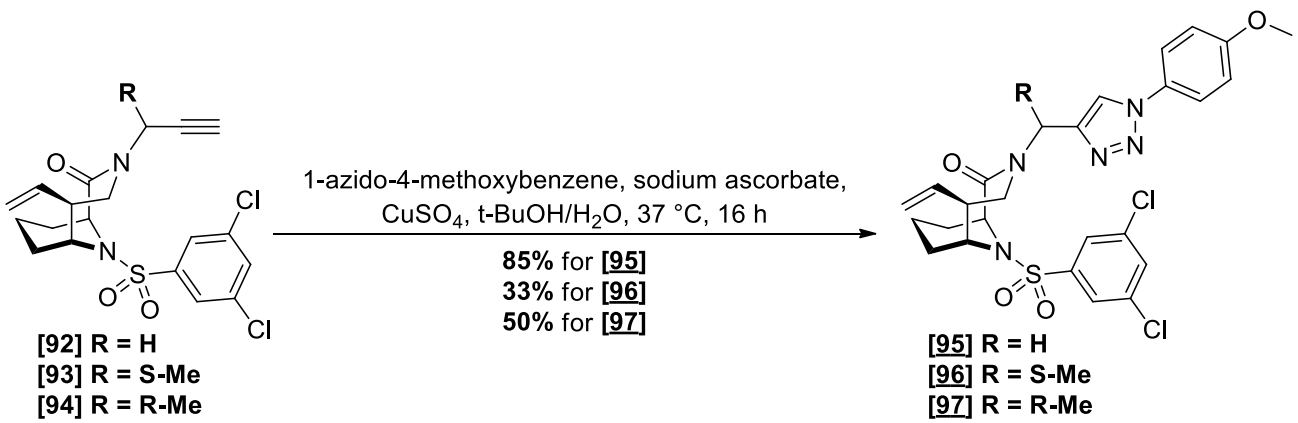
Scheme 67. Synthesis of compound **[91]**.

Compound **[91]** was TMS-deprotected in a biphasic system of aqueous sodium hydroxide and tetrahydrofuran to afford building block **[92]** in 80% yield as shown in **Scheme 68**.



Scheme 68. Synthesis of building block **[92]**.

The two *N*-α-methyl analogs of compound **[92]**, namely **[93]** and **[94]**, were provided by Dr. Tianqi Mao during her doctoral studies. All three compounds were subjected to Copper(I)-catalyzed Azide-Alkyne Cycloaddition (CuAAC) with 1-azido-4-methoxybenzene to afford triazoles **[95]** – **[97]** in 33 – 85% yield as depicted in **Scheme 69**.



Scheme 69. Synthesis of triazoles **[95]** – **[97]**.

3.2.3. FP-Assay Data

All synthesized compounds were tested for their binding affinity in a FP assay. The results are summarized in **Table 4**. Compounds that only differ in the *N*-*α* position were combined in one box and the configuration of the methyl group (*S*, *R*) or absence (-) is indicated in the second column.

Table 4. Binding affinities for *N*-α-methyl and respective reference compounds.

#	α-Me	Ki nM FKBP12	Ki nM FKBP12.6	Ki nM FKBP51	Ki nM FKBP52
[39]	*S*	0.15	0.41	2.6	2.2
[34]	-	1.7 ± 0.6	11.6 ± 3.8	142 ± 39	93 ± 28
[40]	*R*	130	812	>2000	>2000
[84]	*S*	0.06	0.31	1.9	1.2
[83]	-	0.6 ± 0.4	2.2 ± 1.1	29 ± 10	26 ± 7
[86]	*S*	0.04	0.41	0.83	0.35
[85]	-	0.5 ± 0.3	1.7	12 ± 0.5	10 ± 1
[96]	*S*	4.0 ± 0.4	16	n. d.	87 ± 4
[95]	-	15 ± 0.5	105	n. d.	370 ± 10
[97]	*R*	248 ± 15	390	n. d.	1177 ± 144
[88]	*S*	210	1640	>8000	>8000
[87]	-	4.2 ± 0.2	11.2 ± 1.5	154 ± 3	208 ± 19
[89]	*R*	n. b.	n. b.	n. b.	n. b.

n. d. = not determined, n. b. = no binding. Values without standard deviation were only measured as pseudo-duplicates. If a substance did not display binding in the assay, the value is reported as greater (>) than the highest measured concentration.

A distinctive trend in binding affinity is observable. The *S*-methyl compounds bind 4- to 10-fold better than the respective compounds without an *N*-α methyl group, while the *R*-methyl compounds bind up to three orders of magnitude worse than the *S*-isomers and up to two magnitudes worse than the not-methylated compounds. Interestingly, the effect of the *N*-α methyl group is stronger pronounced for the series with a pyridine in R^1 compared to a triazole. This might be due to the ring size, provided that a 6-membered ring occupies more space and thus increases the rotational barrier, ultimately leading to a higher occupation of a conformation favorable for binding. In regard to the tested FKBPs, the trend in binding affinity is decreasing in the order 12 > 12.6 >51 & 52, which is typical for bicyclic [4.3.1] aza-amides.

A very interesting exception is compound **[88]**. This compound was synthesized to lock the conformation of the pyridine ring by introducing a methyl group in position 3 of the pyridine ring, as this hinders the rotation of the aromatic ring. The methyl group in this position has no influence on the binding affinity, as the comparison of **[87]** with **[34]** shows. However, the combination of two methyl groups leads to a significant decrease in binding affinity for both **[88]** and **[89]**.

3.2.4. Molecular Modelling

In order to determine the conformational preferences of the *S*- and *R*-*N*-α methyl compounds, as well as the respective reference compound without a methyl group, a conformational landscape of the molecules was intended by molecular modelling. The project was supervised by Vera Krewald. Compound **[169]**, as well as its two methylated analogs **[170]** and **[171]** were chosen (**Figure 19**; previously synthesized by Sebastian Pomplun, unpublished data), due to the availability of crystal structures of **[169]** and **[170]**.

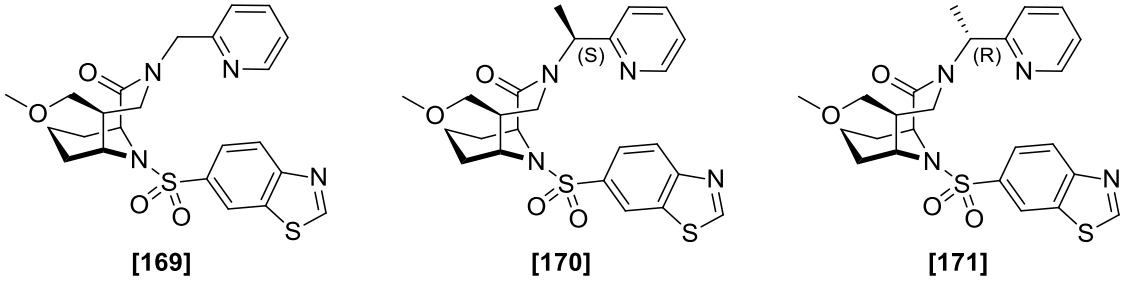


Figure 19. Compounds chosen for computational modelling.

The overlay of **[169]** and **[170]** in the binding pocket of FKBP51 is displayed in **Figure 20**.

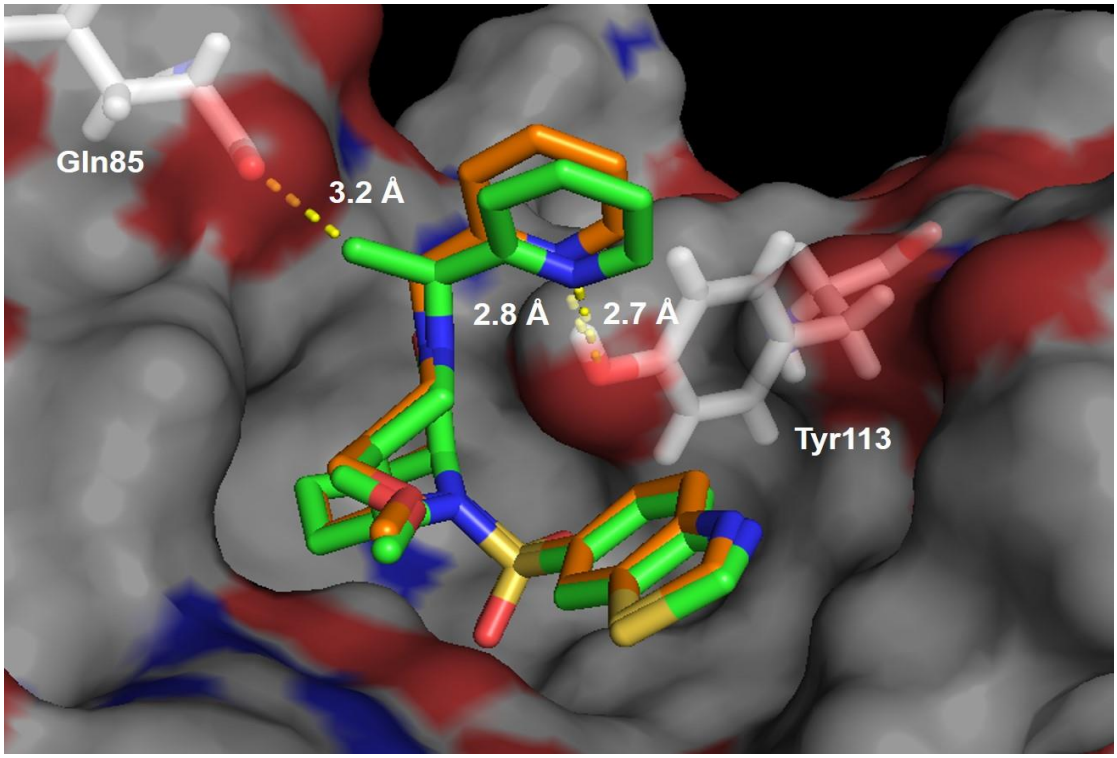


Figure 20. Overlay of crystal structures of **[169]** (in orange) and **[170]** (in green) in the binding pocket of FKBP51. Nitrogens are depicted in blue, oxygens in red, sulfur in yellow, the protein surface in grey. Gln85 and Tyr113 are highlighted as grey sticks. Hydrogen bonds to Gln85 and Tyr113 are shown as yellow doted lines.

The two structures display high convergence and only a small difference in the position of the pyridine ring is observable. The two dihedral angles, CNCC (amide-**C**=O, amide-**N**, α-**C**, Py-**C**2) and NCCN (amide-**N**, α-**C**, Py-**C**2, Py-**N**), that define the α-carbon of these two compounds, were measured for comparison of the conformation. The CNCC angle is -122.3° for the compound **[169]** and -131.0° for **[170]**; the NCCN angle is 37.1° for **[169]** and 48.2° for **[170]**. Both conformations enable a hydrogen bond between the pyridine nitrogen and Tyr113 with 2.8 Å for **[169]** and 2.7 Å for **[170]**. Surprisingly, the additional methyl group is largely solvent-exposed and displays only a single interaction (3.2 Å) with the backbone carbonyl of Gln85.

The key question of the molecular modelling studies was the preferred conformation of the pyridine ring of the molecules in solution. It was assumed, that preorganization of the conformation, which resembles the conformation found in the crystal structure, would lead to an increased binding affinity. The two dihedral angles that define the position of the pyridine ring and the position of the α-methyl group were varied to identify the most favorable conformation (**Figure 21A**). Theoretically, the pyridine ring is unlikely to be aligned with neither the carbonyl oxygen (due to clash of the pyridine with the oxygen of the amide) nor the bridge of the bicyclic compound (due to clash of the pyridine with the hydrogens in the *N*-α-position). This leaves two possible sides. Either, the pyridine is on the right-hand side (as in the crystal structure, favorable for binding) or on the left-hand side (facing the pipecolate ring, unfavorable for binding). Additionally, the position of the pyridine-nitrogen is not clear, since the pyridine ring can rotate freely. For each compound, **[169]**, **[170]** and **[171]**, the two dihedral angles were varied in 20° steps ranging from -180 – 0° and from 0 – 180°, and energies were calculated with density functional theory (DFT) calculations for each structure. The relative energies, referenced to the lowest energy found, were visualized in 2D plots as shown in **Figure 21**. Additionally, refined energies were calculated for selected minima as well as for the conformations observed in the crystal structure by applying thermodynamic corrections and substitution of the electronic energies by B2PLYP electronic energies. The Gibbs free energies are discussed below simultaneously with the 2D-plots.

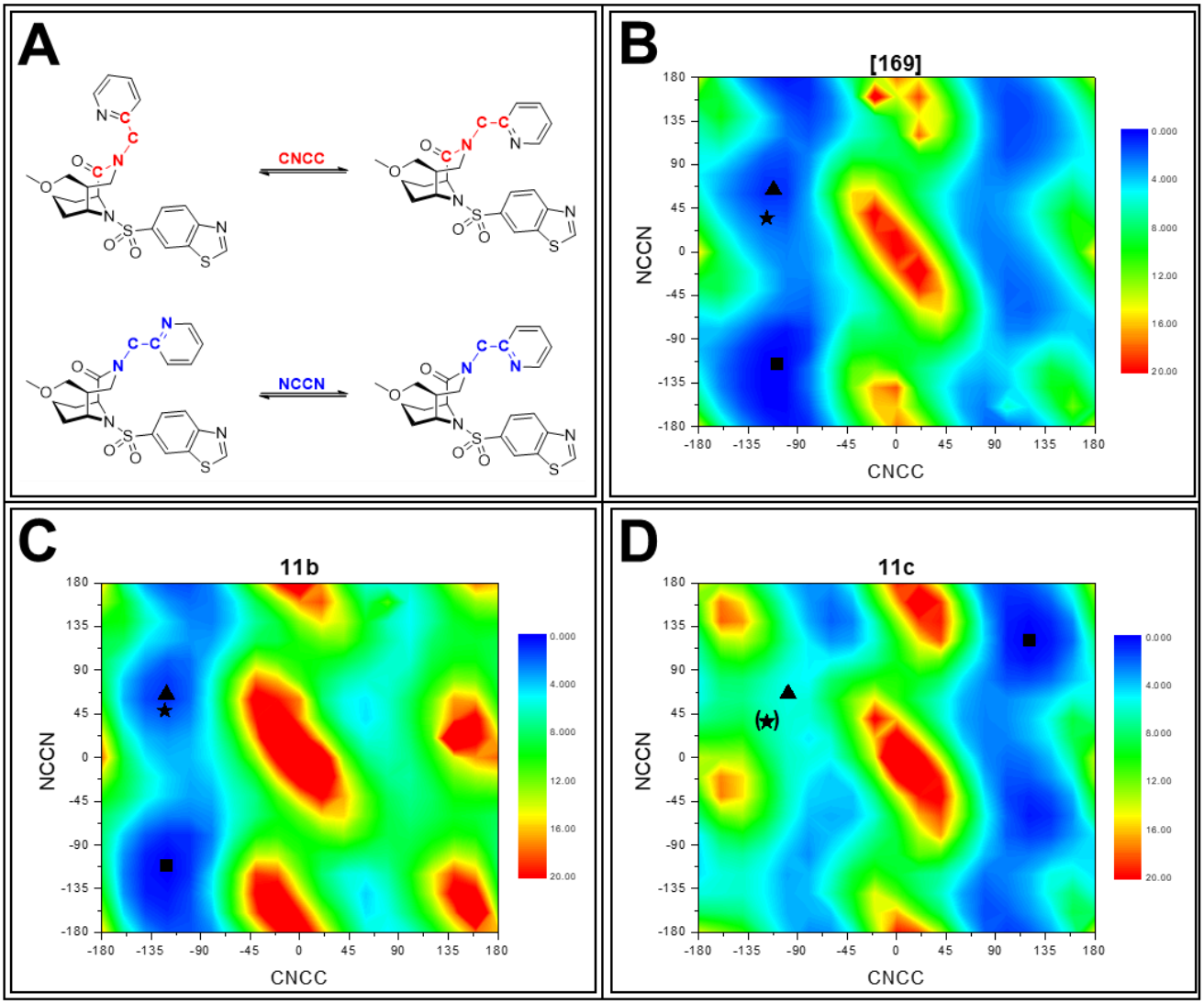


Figure 21. **A**: Rotation of the two dihedral angles CNCC and NCCN. **B, C, D**: Energy maps of **[169]**, **[170]** and **[171]**, respectively. Blue areas represent low energy, red areas high energy. A black asterisk indicates the conformation found in the respective crystal structure; in the case of **[171]** the asterisk in brackets corresponds to the conformation of the crystal structure found for **[169]**. A black triangle indicates the nearest local minimum, a black square indicates the global minimum.

The energy map of the structure without a methyl group **[169]** (**Figure 21**, **B**) displays two areas of low energy along the CNCC rotation, one with the pyridine ring at approximately -90° (pyridine on the right-hand side), the other with the pyridine ring at approximately +90° (pyridine on the left-hand side). The rotation around the NCCN bond is free in either case. The conformation of the crystal structure, with a CNCC angle of -117.8° and a NCCN angle of 37.1°, is found in an area of low energy, almost isoenergetic (ΔΔG = 0.2 kcal/mol) to the closest local minimum at CNNC -112.38° and NCCN +64.75°. The global minimum was found at a slightly lower energy (ΔΔG = 2.8 kcal/mol) at CNNC -108.35 and NCCN -115.18, which correspond to the conformation of the crystal structure but with the pyridine ring rotated approximately 180°, causing the pyridine-nitrogen to face upwards.
In the case of **[170]**, a low-energy area along the CNCC rotation was detected at a CNCC angle of approximately -100°. This is in accordance with the not methylated compound **[169]**. In this conformation the rotation around the NCCN bond is unhindered, suggesting that the methyl group does not influence on the rotatability of this bond. In contrast to **[169]**, no low-energy area at a CNCC angle of approximately +90° was found for **[170]**. This result was expected, since the rotation of the pyridine ring to a positive CNCC angle leads to a conformation where the α-methyl group is aligned with the oxygen of the carbonyl group and thus resulting in a steric clash of those two groups. The conformation of the crystal structure, with a CNCC angle of -123.5° and a NCCN angle of +48.2° lies within the found low-energy area, almost isoenergetic (ΔΔG = 0.5 kcal/mol) to the local minimum at CNCC -121.38 and NCCN +65.96°. The global minimum was found at CNCC -121.20 and NCCN -111.05 with a slightly

lower energy (ΔΔG = -2.9 kcal/mol). As for **[169]**, this conformation corresponds to the conformation of the crystal structure with the pyridine-nitrogen flipped approximately 180°.
The energy map of **[171]** displays the opposite behavior of **[170]**. A low energy area is found at a CNCC angle of around +100°, while no low-energy area is found at around -100°. This again results from a clash of the methyl group with the carbonyl oxygen. For **[171]**, no crystal structure was available. The expected conformation for high affinity binding to the binding pocket of FKBPs would require similar CNCC and NCCN angles as for **[169]** and **[170]**, however, this area is highly unfavorable. The closest local minimum was detected at CNCC -97.66° and NCCN 65.03°, with a fairly higher energy (ΔΔG = 5.7 kcal/mol) compared to the global minimum.

Boltzmann-distributions were calculated and distribution maps, analogously to the energy maps, were created. The plots are displayed in **Figure 22**. For **[169]** and **[170]** the highest occupancy is naturally located in the area of the lowest energy found in the energy maps. For both structures a flip of the pyridine ring is sufficient for adopting a crystal-structure-like conformation, which is also occupied to some extent. In comparison to **[169]**, **[170]** displays a narrower occupancy. **[171]** displays occupancy only in conformations, where the entire pyridinyl residue is shifted to the left side of the molecule This conformation is far from the conformation necessary for binding, since the pyridine ring is on the wrong side of the molecule and rotation is sterically hindered by collision with either the carbonyl oxygen or the alkyl bridge (see **Figure 21**, A).

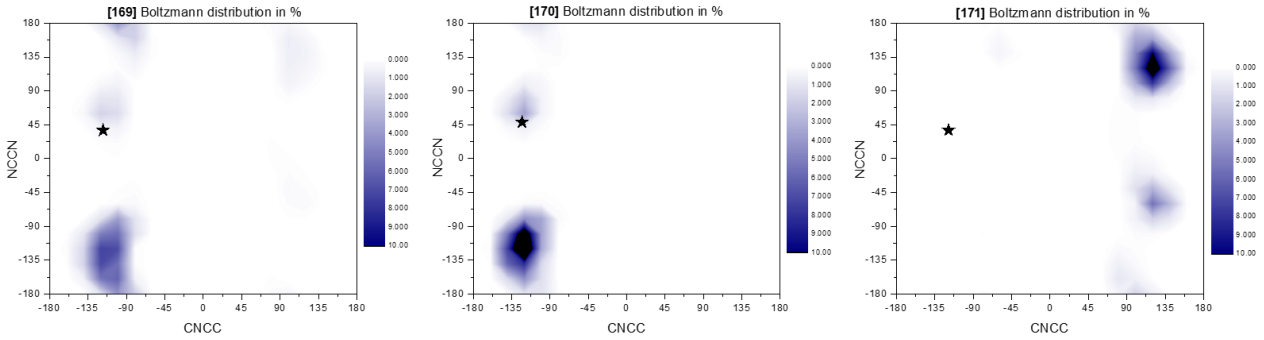


Figure 22. Boltzmann distributions of **[169]**, **[170]** and **[171]**, respectively. Blue indicates areas of high occupancy; white indicates areas of low occupancy. A black asterisk indicates the conformation of the crystal structure; in the case of **[171]** the asterisk corresponds to the conformation of the crystal structure found for **[169]**.

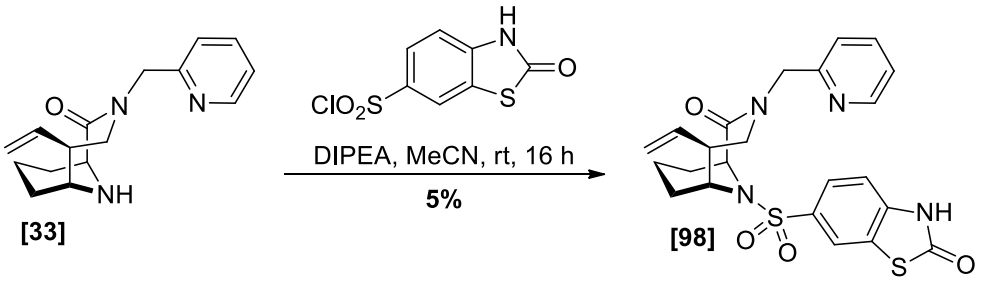
Taken together, it is clear why the structure **[171]** is unfavorable for binding. The molecule only adopts conformations with the pyridinyl moiety on the wrong side for binding. **[169]** and **[170]** both adopt conformations with the pyridinyl moiety on the compatible side for binding. While the conformation, which is found in the crystal structure, is occupied, the majority of molecules adopt a conformation with the pyridine-nitrogen facing in the wrong direction. This is not surprising since the conformational preferences of 2-substituted pyridines are well studied in literature and it was shown for bipyridinyl systems[97], as well as 2-alkoxypyridines and 2-acyl pyridines[98], that the lone pairs of the pyridine-nitrogens are repulsive, and therefore adopt an *anti* conformation[97]. However, due the localization of the amide-nitrogen lone pair within the amide bond the repulsion is less pronounced than for two pyridine-nitrogen lone pairs, which results in a lower energetic barrier for rotation around the NCCN bond and a lower energy for the *syn* conformation. Due to the highly stabilizing hydrogen bond of the pyridine-nitrogen to Tyr113, this conformation is adopted in the crystal structure. Although it appears that the energy map of **[170]** has less possible conformations than the energy map of **[169]**, the Boltzmann distribution illustrates similar occupancies for **[169]** and **[170]**. Careful examination reveals that the area of the crystal structure (CNCC -140 – -80, NCCN 40 – 100) has an occupancy of 7.7% for **[169]** and 11.2% for **[170]**, and the area with the flipped pyridine (CNCC -140 – -80, NCCN -180 – -60) has an occupancy of 70.0% for **[169]** and 84.0% for **[170]**. The slightly more occupied crystal-structure-like conformation, together with the higher occupied conformation, which requires only a rotation of the pyridine ring, does explain a better affinity for the *S*-Me isomer to some extent, however, there must be additional effects beyond the rigidification of the conformation that cause the boost in affinity.

3.3. Project 3: Synthesis of Benzo[d]thiazol-2(3H)-one Derivatives

Previously within our group, a benzo[d]thiazol-2(3H)-one moiety displayed high binding affinity towards FKBP12 and 700-fold selectivity over other FKBPs.[86] In order to verify the effect of this moiety, a focused library around this scaffold was synthesized.

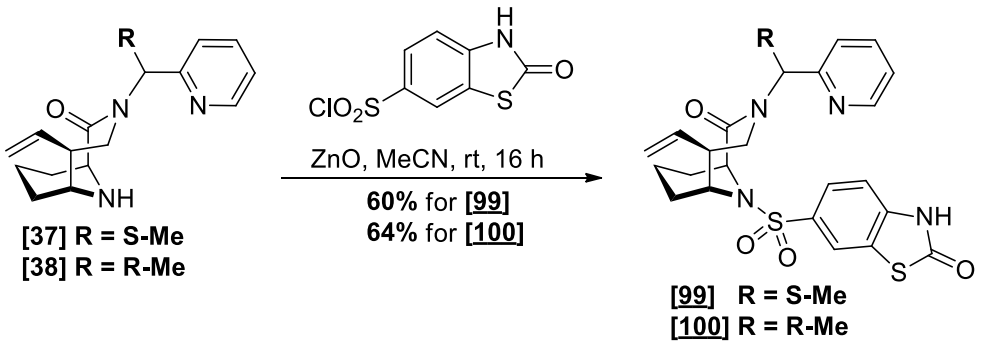
3.3.1. Synthesis of first compounds with R^2 = 6-benzo[d]thiazol-2(3H)-one

In order to verify the effect of the benzo[d]thiazol-2(3H)-one moiety, a series with compound **[98]** and its two *N*-α-methyl derivatives **[99]** and **[100]** were synthesized. Initially, the synthesis of **[98]** was conducted with Hünig's base in acetonitrile as shown in **Scheme 70**. This resulted in a poor yield of 5% after multiple chromatographic purification steps. The main issue was the reactivity of the thiazolone-nitrogen, which reacted as a nucleophile and attacked the sulfonyl chloride. This led to multimerization of the starting material and the desired product. Attempts to purify the compound by column chromatography gave only partial success, due to the side product with one additional benzothiazolone. Finally, purification via reversed-phase HPLC resulted in pure product.



Scheme 70. Synthesis of compound **[98]**.

It was hypothesized, that the Hünig' base is too strong a base for this reaction. Therefore, it was substituted by zinc oxide, which previously resulted in improved yields (*vide supra*, **Scheme 58**). Satisfyingly, this procedure gave good yields for the two compounds **[99]** and **[100]** (60 and 64%, respectively) as shown in **Scheme 71**.

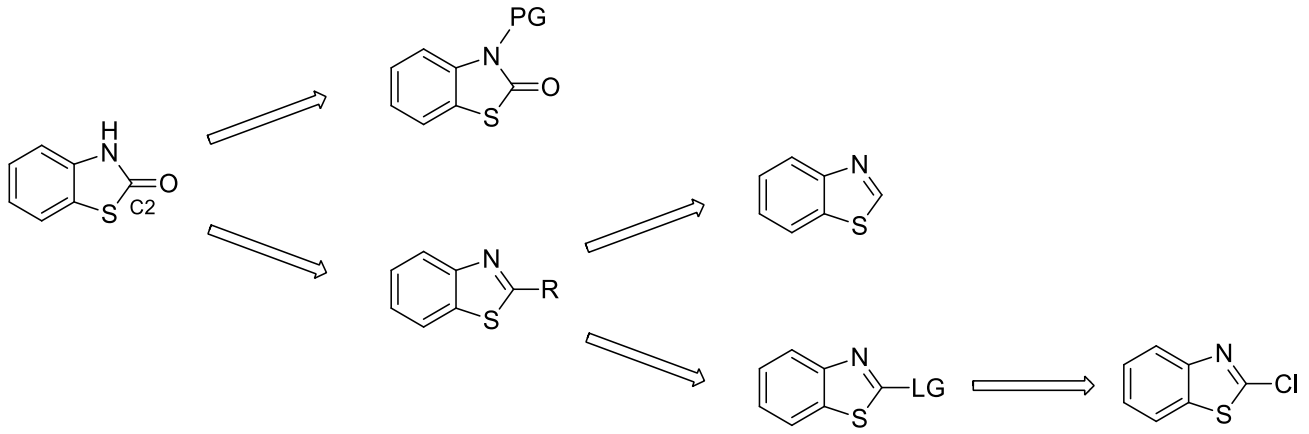


Scheme 71. Synthesis of compounds **[99]** and **[100]**.

3.3.2. Synthesis of derivatives with modifications at C2 of 6-benzo[d]thiazol-2(3H)-one

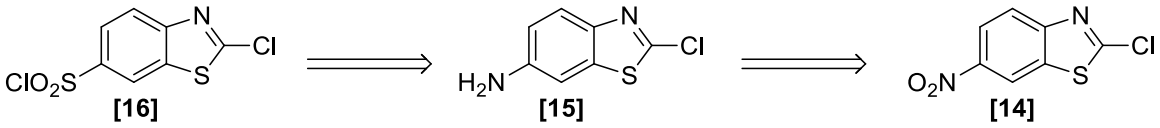
A series of derivatives with modifications of the C2 position (**Scheme 72**) of the benzothiazolone scaffold was envisioned. Since the nitrogen has increased reactivity compared to the oxygen in the benzothiazolone, it was necessary to hinder the nitrogen from participation in reactions. The two possibilities are introduction of a protective group (PG) or the formation of a double bond to C2. Instead of a protective group, which would only avoid participation of the nitrogen in the reaction but not improve the reactivity of the C2 position, a double bond between the nitrogen and C2 was chosen. This leaves two options, either starting from benzothiazole or installing a leaving group (LG). The former approach would require either C-H activation or metal-catalyzed oxidation procedures for derivatization, while the latter would give the opportunity of nucleophilic substitution. Since the

typical bicyclic scaffold contains a double bond which would cause problem during metal-catalyzed derivatization, nucleophilic substitution was chosen as the way to go. Chlorine was envisioned as leaving group, since it is a fairly good leaving group in aromatic nucleophilic substitutions and benzothiazole derivatives with a chlorine at C2 are cheap, commercially available compounds.



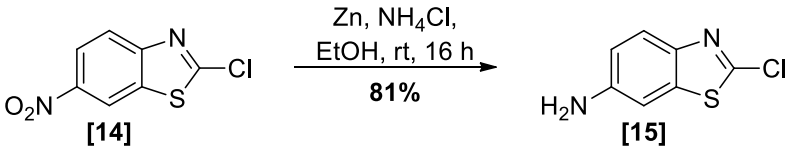
Scheme 72. Modification possibilities at the C2 position of the benzothiazolone scaffold.

Retrosynthetic analysis of the required sulfonyl chloride **[16]** leads back to amine **[15]** with the above discussed diazotation/radical sulfonation procedure in mind (**Scheme 73**). The amine is easily accessible by reduction of commercially available nitro-compound **[14]**.



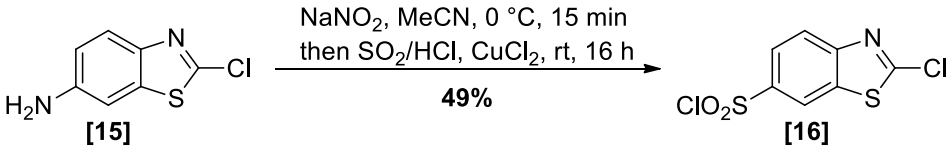
Scheme 73. Retrosynthetic analysis of compound **[16]**.

The forward synthesis commenced with reduction of **[14]** with zinc and ammonium chloride to amine **[15]** in 81% yield as displayed in **Scheme 74**.



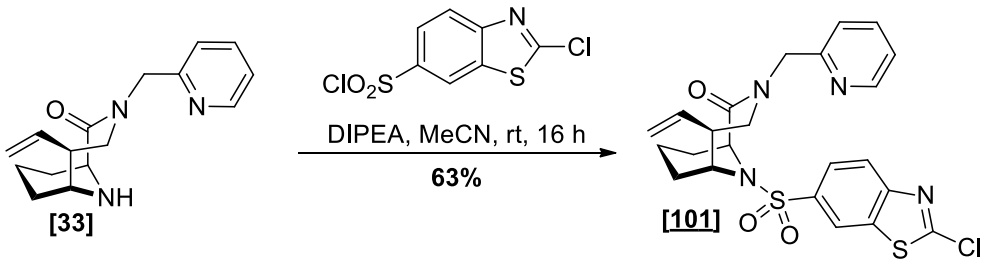
Scheme 74. Synthesis of amine **[15]**.

Diazotation of **[15]** followed by treatment with sulfur dioxide under copper-catalysis afforded sulfonyl chloride **[16]** in 49% yield as shown in **Scheme 75**.



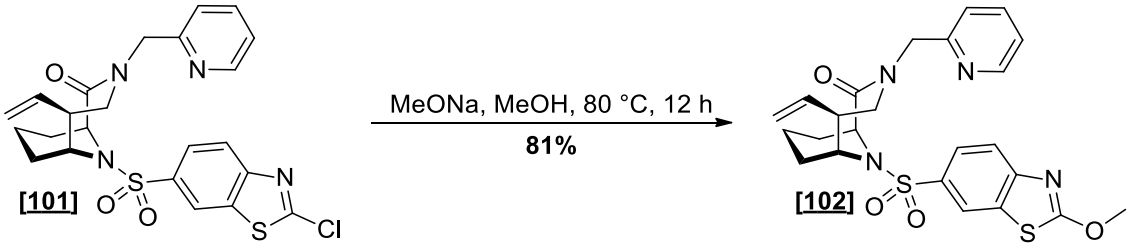
Scheme 75. Synthesis of sulfonyl chloride **[16]**.

Sulfonyl chloride **[16]** was reacted with bicycle **[33]** to afford building block **[101]** in 63% yield as shown in **Scheme 76**.



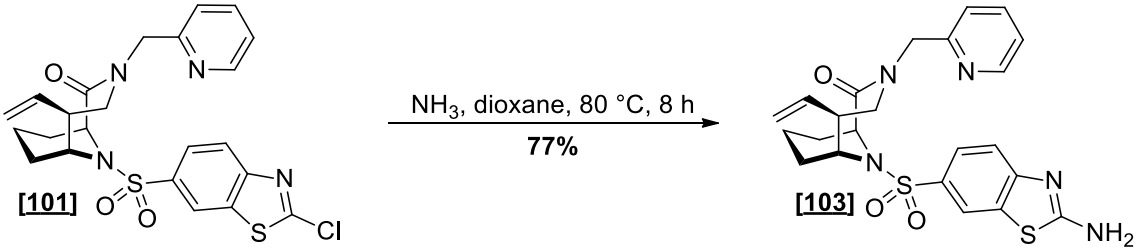
Scheme 76. Synthesis of building block **[101]**.

With building block **[101]** in hand, different nucleophilic substitutions were performed. Reaction with sodium methoxide in methanol resulted in methoxy-derivative **[102]** in 81% yield as displayed in **Scheme 77**.



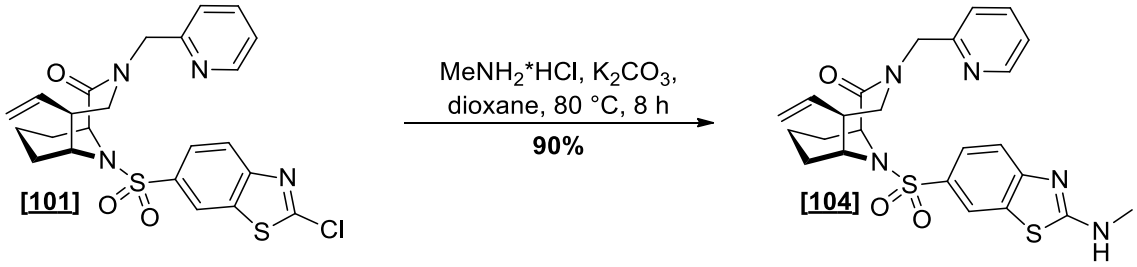
Scheme 77. Synthesis of compound **[102]**.

Reaction with aqueous ammonia afforded compound **[102]** in 77% yield as shown in **Scheme 78**.



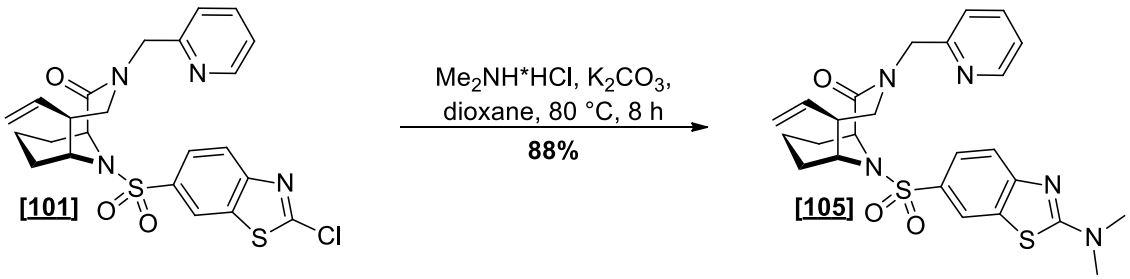
Scheme 78. Synthesis of compound **[103]**.

Reaction of with methylamine hydrochloride afforded compound **[104]** in 90% yield as shown in **Scheme 79**.



Scheme 79. Synthesis of compound **[104]**.

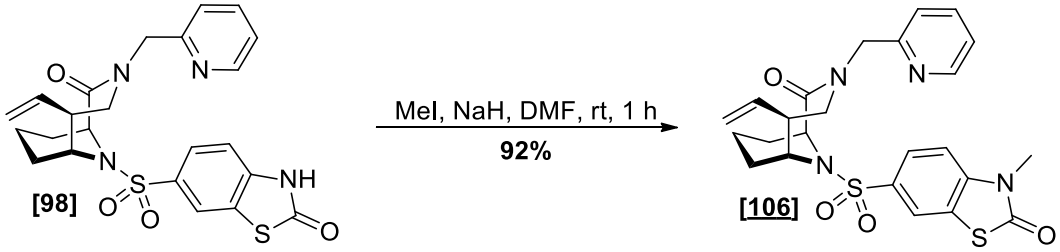
Reaction of with dimethylamine hydrochloride afforded compound **[105]** in 88% yield as shown in **Scheme 80**.



Scheme 80. Synthesis of compound **[105]**.

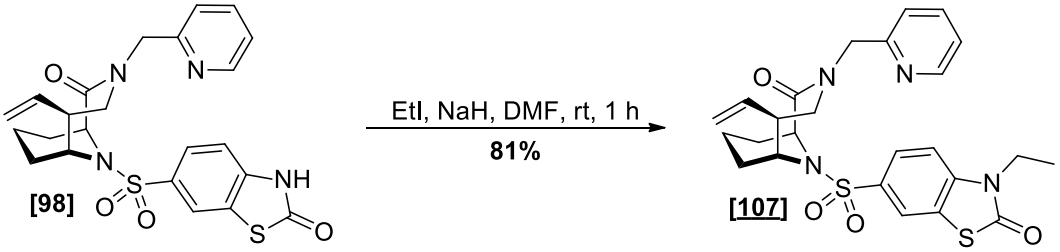
3.3.3. Synthesis of derivatives at the nitrogen of 6-benzo[d]thiazol-2(3H)-one

A series of different residues at the nitrogen of the benzothiazolone was envisioned. Due to the lack of competing nucleophilic positions, alkylations was straight forward. Reaction of **[98]** with methyl iodide gave compound **[106]** in 92% yield as shown in **Scheme 81**.



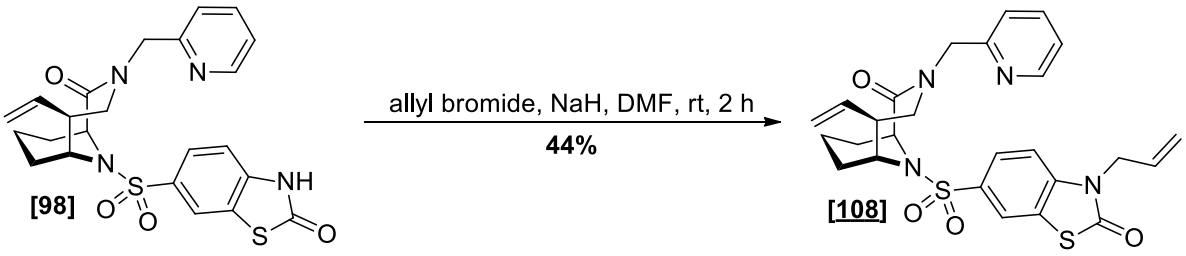
Scheme 81. Synthesis of compound **[106]**.

Reaction of **[98]** with ethyl iodide gave compound **[107]** in 81% yield as shown in **Scheme 82**.



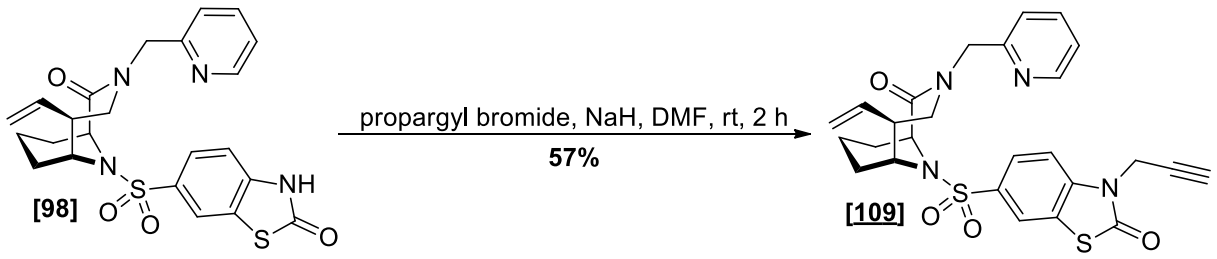
Scheme 82. Synthesis of compound **[107]**.

Reaction of **[98]** with allyl bromide gave compound **[108]** in 44% yield as shown in **Scheme 83**.



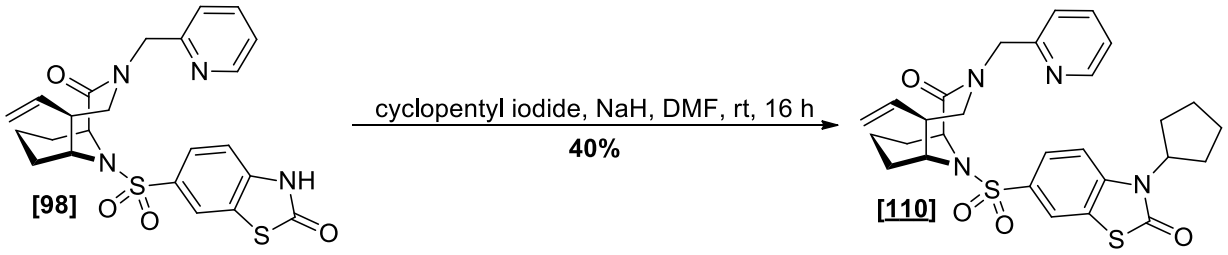
Scheme 83. Synthesis of compound **[108]**.

Reaction of **[98]** with propargyl bromide gave compound **[109]** in 57% yield as shown in **Scheme 84**.



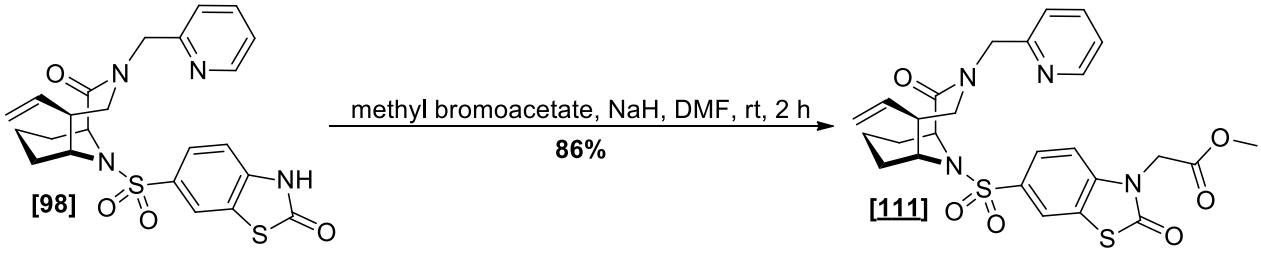
Scheme 84. Synthesis of compound **[109]**.

Reaction of **[98]** with cyclopentyl iodide gave compound **[110]** in 40% yield as shown in **Scheme 85**.



Scheme 85. Synthesis of compound **[110]**.

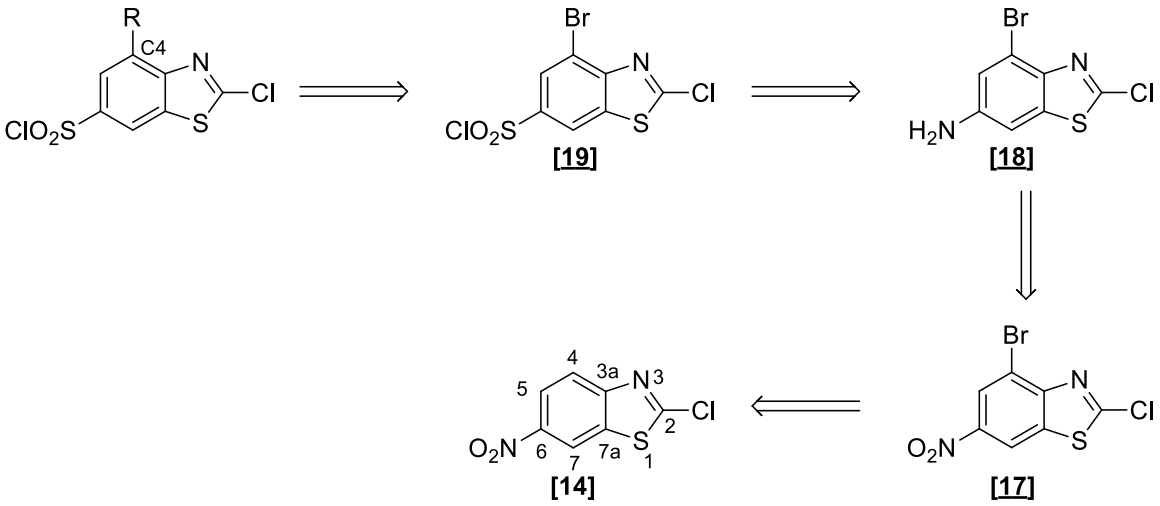
Reaction of **[98]** with methyl bromoacetate gave compound **[111]** in 86% yield as shown in **Scheme 86**.



Scheme 86. Synthesis of compound **[111]**.

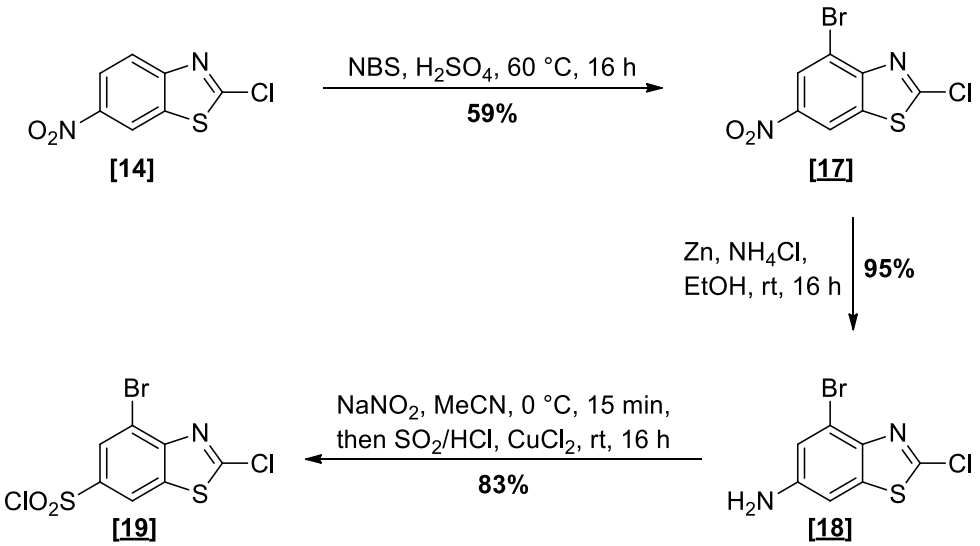
3.3.4. Synthesis of derivatives with modifications at C4 of 6-benzo[d]thiazol-2(3H)-one

A series of compounds with different residues at C4 of the benzothiazolone scaffold was envisioned. Retrosynthetic analysis of the required sulfonyl chloride is depicted in **Scheme 87**. A versatile functional group for several modifications at C4 was required. Ideally, this would be a halogen, since it is fairly easy to install by electrophilic halogenation and enables modifications by means of metal-catalyzed reactions. Bromine was chosen, as brominations are the most practical and reliable halogenation methods known to literature. To avoid complications with the sulfonyl chloride, it was envisioned to install the bromine in an earlier step. Furthermore, the thiazolone moiety was substituted by a 2-chlorothiazole moiety, which acts as a protective group of the benzothiazolone moiety, as it can be hydrolyzed later on. Bromination of the amine is not feasible, since the amine would direct the bromine in positions 5 and 7 (see **[14]**, **Scheme 87**), thus yielding wrong regioisomers. On the contrary, the nitro group deactivates positions 5 and 7 for electrophilic substitution. Additionally, the N3 has a stronger activating effect compared to S1, again favoring position 4. From a retrosynthetic perspective, sulfonyl chloride **[19]** can be obtained by the above discussed diazotation of the respective amine **[18]** followed by copper-catalyzed chlorosulfonation. The amine can be obtained by reduction of nitro-compound **[17]**, which might originate from bromination of compound **[14]**.



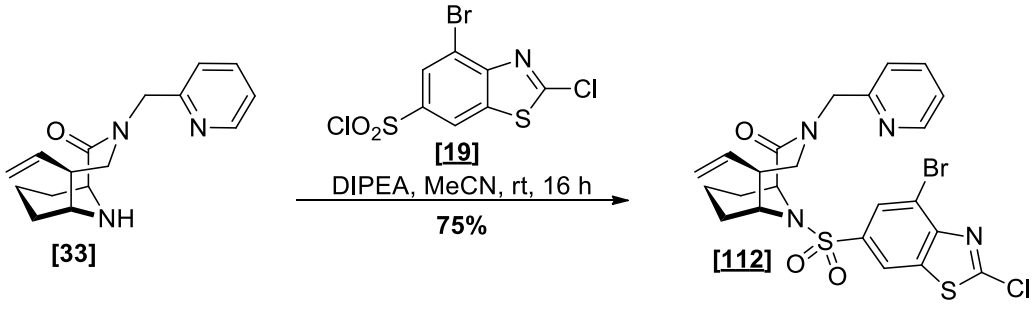
Scheme 87. Retrosynthetic analysis of the benzothiazolone scaffold with modification at C4.

The synthesis is displayed in **Scheme 88**. Bromination with *N*-bromosuccinimide in concentrated sulfuric acid at 60 °C resulted in a reasonable yield of 59% of compound **[17]**. Reduction with zinc and ammonium chloride gave amine **[18]** in 95% yield. Diazotation followed by copper-catalyzed sulfonation yielded the desired sulfonyl chloride **[19]** in 83%.



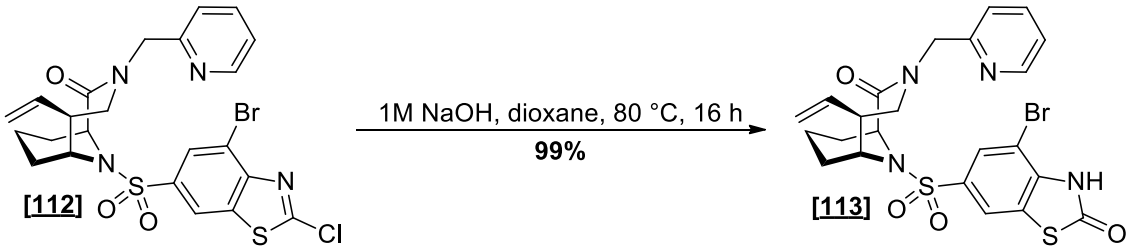
Scheme 88. Synthesis of sulfonyl chloride **[19]**.

Sulfonyl chloride **[19]** was reacted with bicyclic precursor **[33]** to afford intermediate **[112]** in 75% yield as shown in **Scheme 89**.



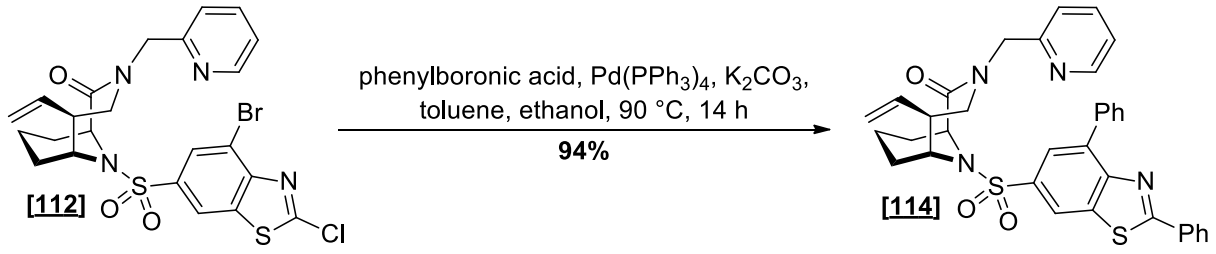
Scheme 89. Synthesis of intermediate **[112]**.

Hydrolysis with a biphasic system of sodium hydroxide and tetrahydrofurane afforded compound **[113]** in 99% yield as displayed in **Scheme 90**.



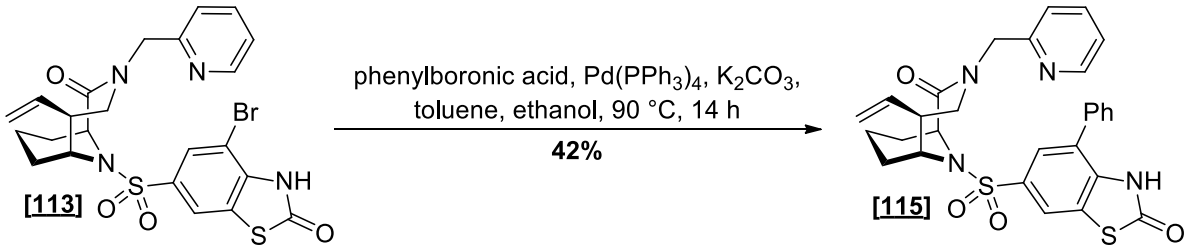
Scheme 90. Synthesis of compound **[113]**.

The first envisioned modification was the substitution of bromine with a benzene via Suzuki reaction with phenylboronic acid. Initially, a test reaction with compound **[112]** was performed, which did not result in the desired product but gave the double-substituted compound **[114]** in 94% yield as shown in **Scheme 91**.



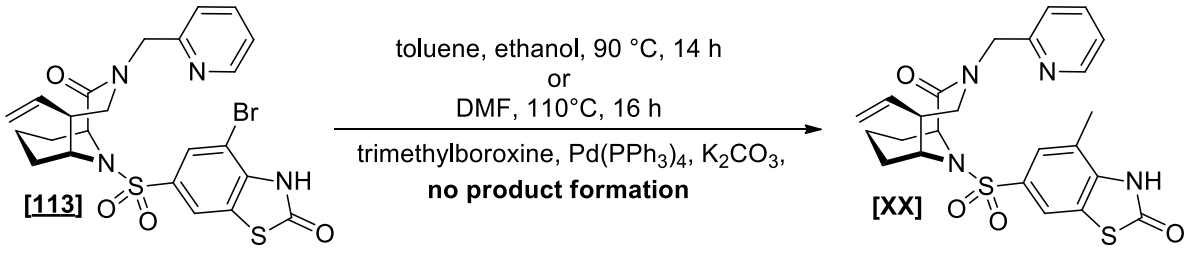
Scheme 91. Synthesis of compound **[114]**.

With the same conditions, compound **[113]** was transformed to the phenyl substituted compound **[115]** in 42% yield as shown in **Scheme 92**.



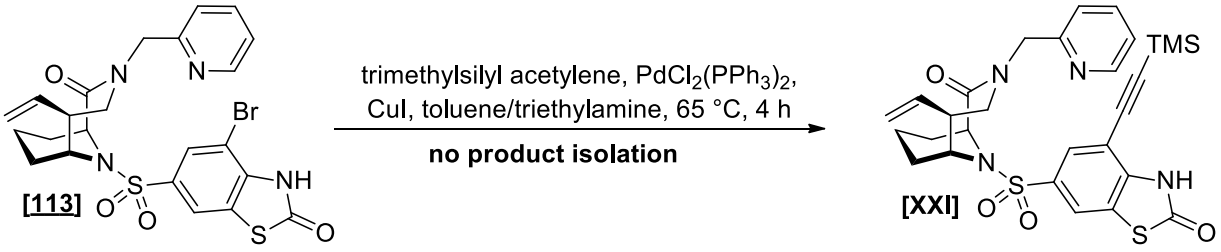
Scheme 92. Synthesis of compound **[115]**.

Substitution of the bromine by a methyl group (**Scheme 93**) with trimethylboroxine in either a mixture of toluene/ethanol or in DMF resulted in no detectable product formation by means of LC-MS. It might be, that the used trimethylboroxine was already decomposed.



Scheme 93. Attempted synthesis of [III].

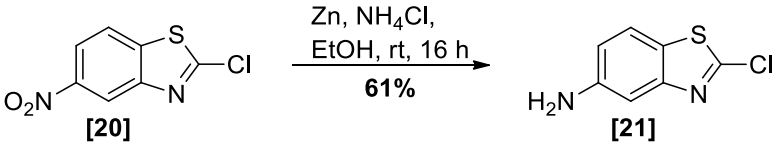
Substitution of the bromine by an alkyne was attempted twice via Sonogashira-coupling as shown in **Scheme 94**. The reaction displayed initial conversion to the product on LC-MS after two hours at 65 °C (up to 22% according to UV-peak area), but eventually decomposed after one additional hour. Due to the complex mixture of side products and the low amount of starting material, no purification attempts were conducted with this conversion rate.



Scheme 94. Attempted synthesis of compound [IV].

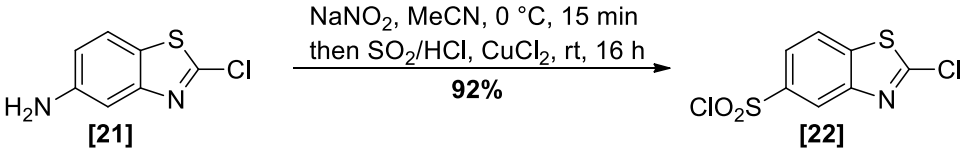
3.3.5. Synthesis of analogs with R^2 = 5-benzo[d]thiazol-2(3H)-one

A derivative with the sulfonyl moiety at C5 instead of C6 was envisioned. This would slightly adjust the orientation of the benzothiazolone in the FKBP binding pocket and therefore serve as valuable negative control. First, the required sulfonyl chloride had to be synthesized. The synthesis commenced with commercially available 2-chloro-5-nitrobenzo[d]thiazole **[20]** which was reduced to amine **[21]** with zinc and ammonium chloride in 61% yield as shown in **Scheme 95**.



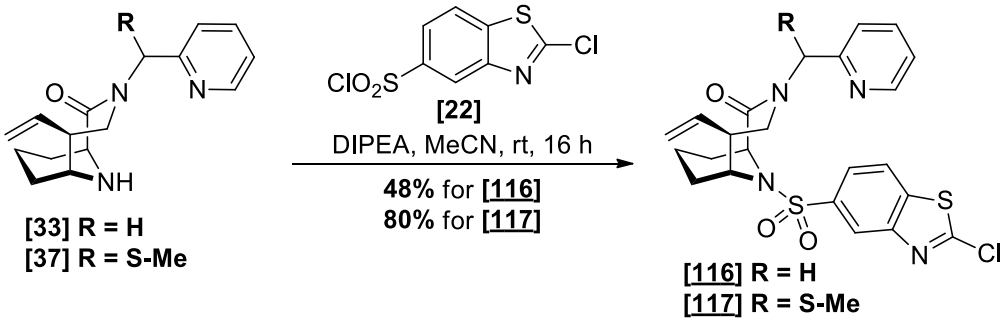
Scheme 95. Synthesis of amine **[21]**.

The amine was transformed to the sulfonyl chloride via diazotation followed by copper-catalyzed sulfonation in 93% yield as shown in **Scheme 96**.



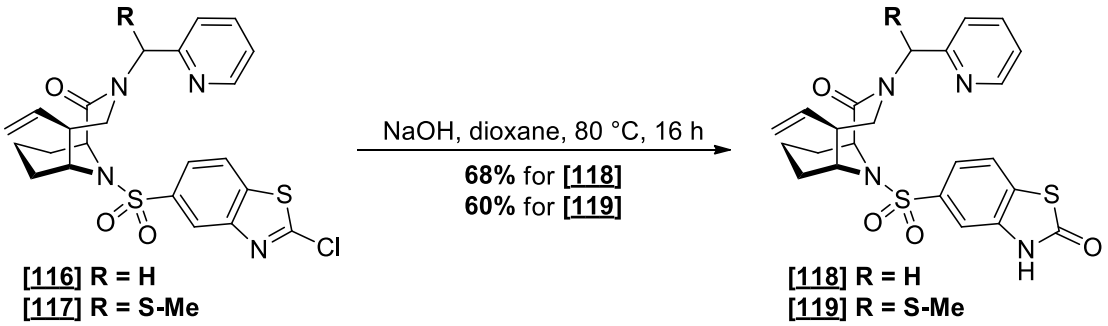
Scheme 96. Synthesis of sulfonyl chloride **[22]**.

Sulfonyl chloride **[22]** was coupled with the two bicyclic precursors **[33]** and **[37]** to give the two sulfonamides **[116]** and **[117]** in 48% and 80% yield, respectively, as shown in **Scheme 97**.



Scheme 97. Synthesis of compounds and **[116]** and **[117]**.

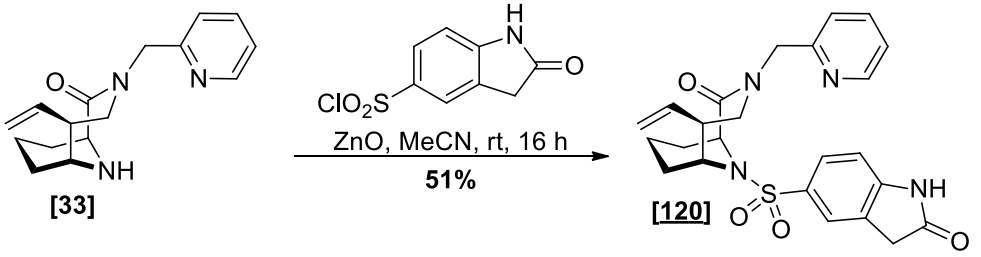
Hydrolysis in a biphasic system of aqueous sodium hydroxide and tetrahydrofurane afforded the two C5-linked benzothiazolones **[118]** and **[119]** in 68% and 60% yield, respectively, as shown in **Scheme 98**.



Scheme 98. Synthesis of the two C5-linked benzothiazolones **[118]** and **[119]**.

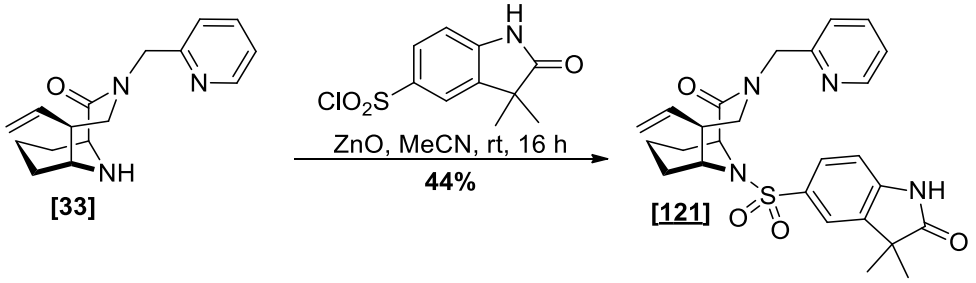
3.3.6. Synthesis of 6-benzo[d]thiazol-2(3H)-one analogs with substituted sulfur

In order to study the importance of the sulfur atom within the benzothiazolone scaffold, compounds with other heteroatoms (N, O), a carbon, and a demethylated carbon, which acts as a bioisoster for sulfur, were envisioned. The respective sulfonyl chlorides were commercially available and directly reacted with bicyclic building block **[33]**. The synthesis of the carbon analog afforded 51% yield of **[120]** and is depicted in **Scheme 99**.



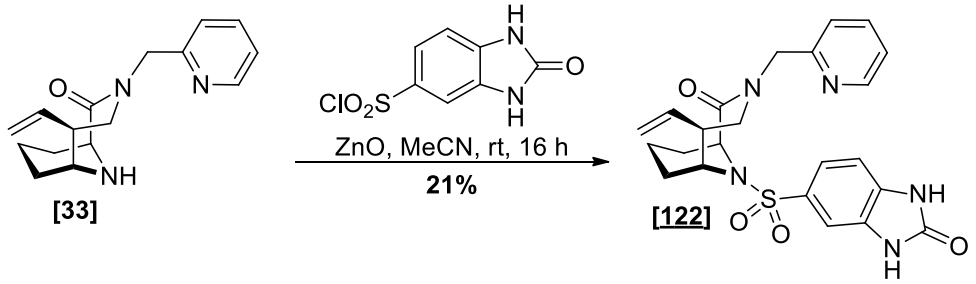
Scheme 99. Synthesis of compound **[120]**.

The bioisoster **[121]** was afforded in 44% yield as shown in **Scheme 100**.



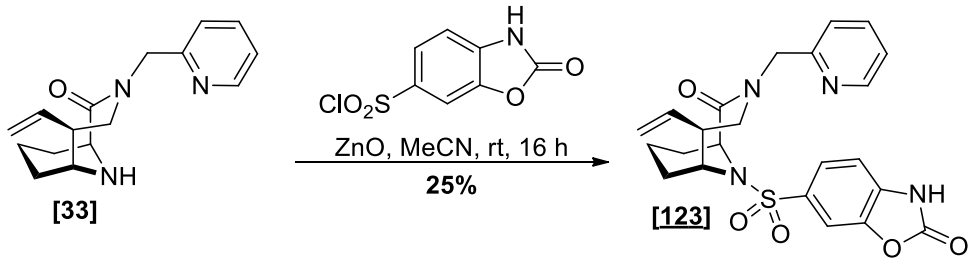
Scheme 100. Synthesis of compound **[121]**.

The analog **[122]** with nitrogen instead of sulfur was obtained in 21% yield as displayed in **Scheme 101**.



Scheme 101. Synthesis of compound **[122]**.

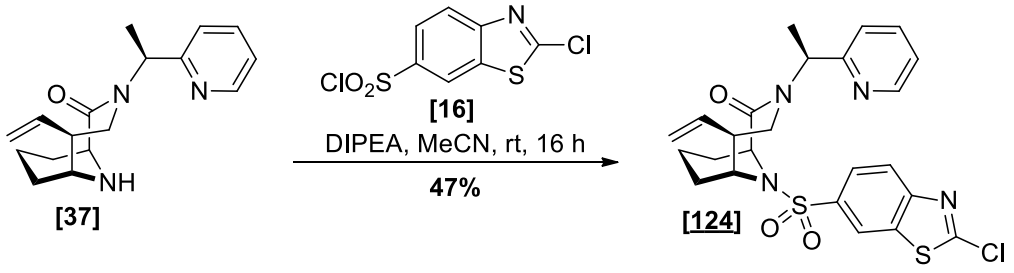
The analog **[123]** with oxygen instead of sulfur was obtained in 25% yield as displayed in **Scheme 102**.



Scheme 102. Synthesis of compound **[123]**.

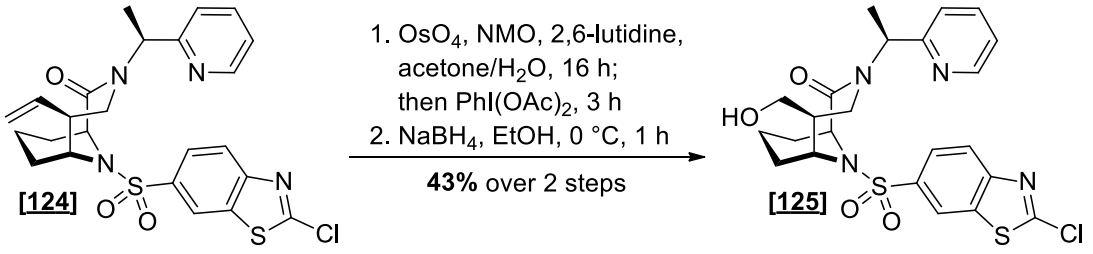
3.3.7. Synthesis of a 6-benzo[d]thiazol-2(3H)-one analog with optimized residues at R^1 and R^3

A benzothiazolone derivative with optimized residues at R^1 and R^3 was synthesized. The synthesis commenced with bicyclic precursor **[37]**, which was reacted with sulfonyl chloride **[16]** to afford compound **[124]** in 47% yield as shown in **Scheme 103**.



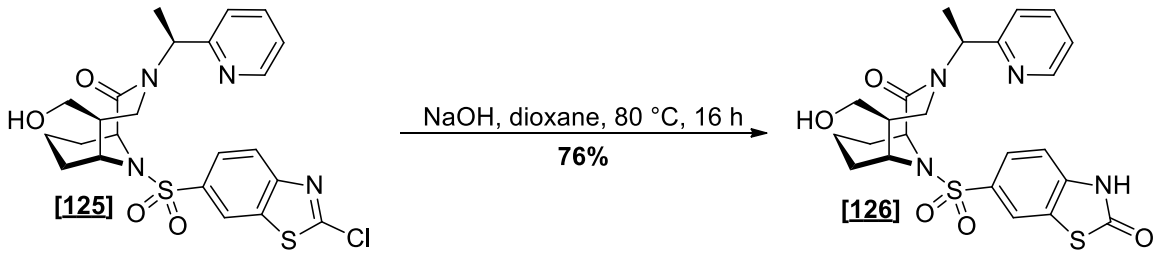
Scheme 103. Synthesis of compound **[124]**.

Dihydroxylation with osmium tetroxide followed by oxidative cleavage with (diacetoxyiodo)benzene and reduction with sodium borohydride yielded alcohol **[125]** in 43% as displayed in **Scheme 104**.



Scheme 104. Synthesis of compound **[125]**.

Hydrolysis in a biphasic system of aqueous sodium hydride and dioxane afforded compound **[126]** in 76% yield as shown in **Scheme 105**.



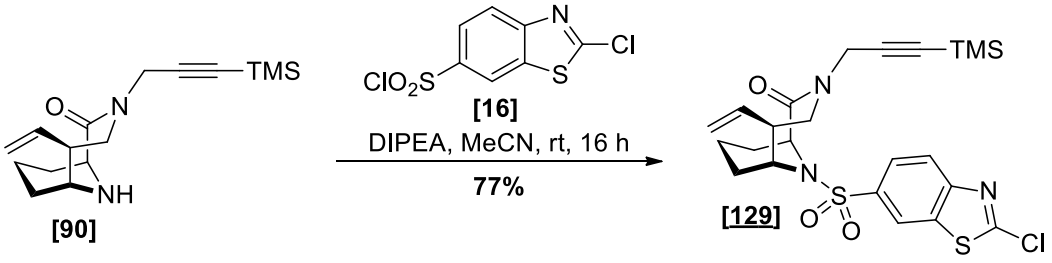
Scheme 105. Synthesis of compound **[126]**.

A methyl ester derivative of **[126]** was attempted, but without success. Direct methylation of **[126]** failed due to preferred methylation at the nitrogen of the benzothiazolone. Methylation of **[125]** was attempted with several

bases (NaH, K_2CO_3, Et_3N) at different temperatures (0 – 40 °C) in dimethylformamide, but no product formation was detectable by LC-MS. Low temperature (0 °C) and weak bases (K_2CO_3, Et_3N) did not display any product formation, while decomposition to a complex mixture of side products occurred at higher temperatures (>20 °C) and with a stronger base (NaH). This finding was somewhat surprising, since methylation at this position usually resulted in high yields without a detectable side product (e.g., methylation of **[83]** and **[84]**). Since none of the masses of the side products could be allocated, the reason why this reaction failed is unclear.

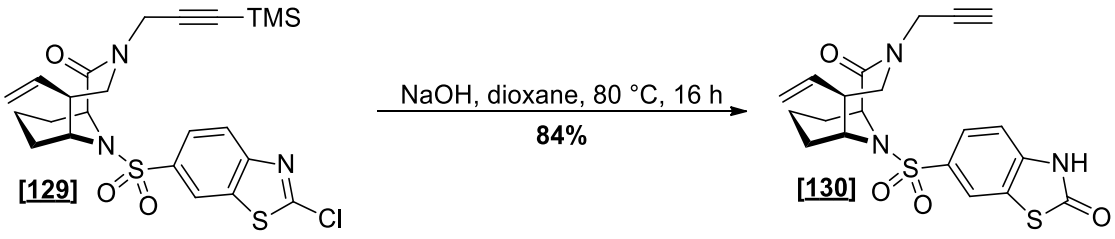
3.3.8. Synthesis of 6-benzo[d]thiazol-2(3H)-one analogs with modifications at R^1

In order to prove that the observed affinity boost by the benzothiazolone moiety is independent of the residue at R^1, compounds with a different substituent at this position were envisioned. More precisely, an alkyne at R^1 was intended with modifications by Click-chemistry in mind. The synthesis commenced with building block **[90]** which was reacted with sulfonyl chloride **[16]** to afford compound **[129]** in 77% yield as shown in **Scheme 106**.



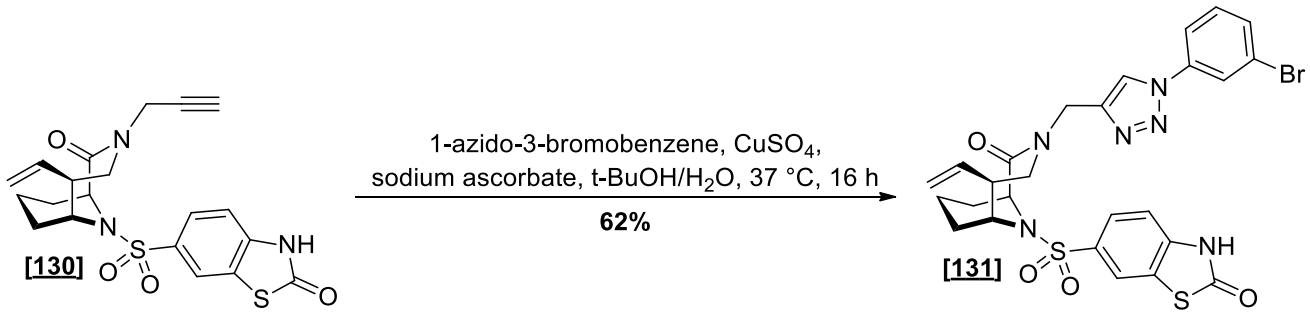
Scheme 106. Synthesis of intermediate **[129]**.

Hydrolysis to the benzothiazolone and cleavage of the TMS-group were performed in one step in a biphasic system of aqueous sodium hydroxide and tetrahydrofurane. Building block **[130]** was afforded in 84% yield as shown in **Scheme 107**.



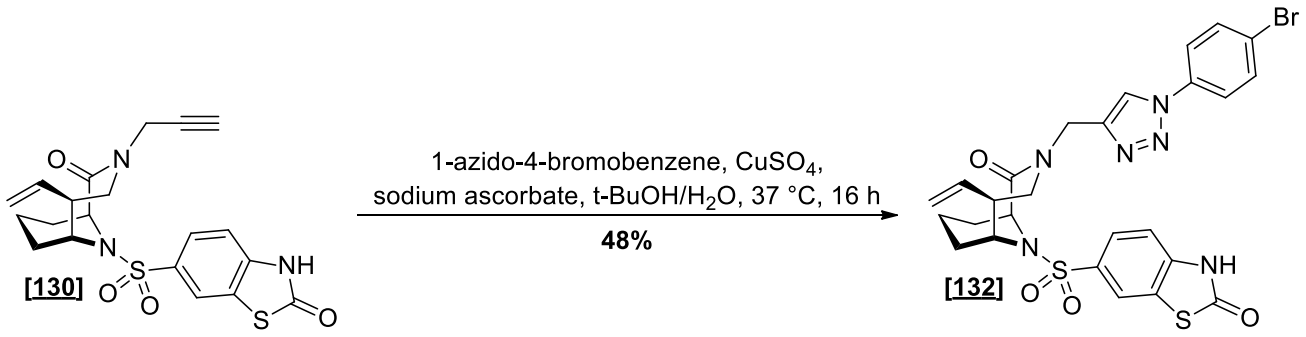
Scheme 107. Synthesis of building block **[130]**.

With building block **[130]** in hand, Copper(I)-catalyzed Azide-Alkyne Cycloaddition (CuAAC) was performed with different azides. Reaction with 1-azido-3-bromobenzene afforded compound **[131]** in 62% yield as shown in **Scheme 108**.



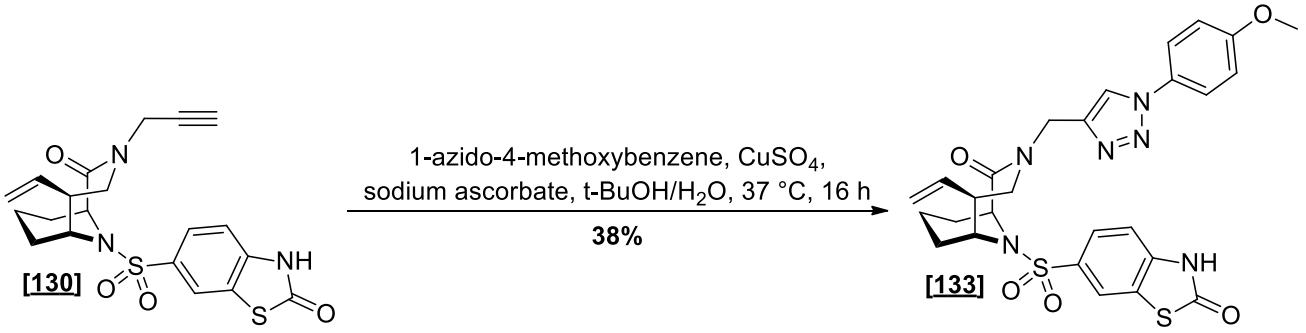
Scheme 108. Synthesis of compound **[131]**.

Treatment of **[130]** with 1-azido-4-bromobenzene afforded compound **[132]** in 48% yield as displayed in **Scheme 109**.



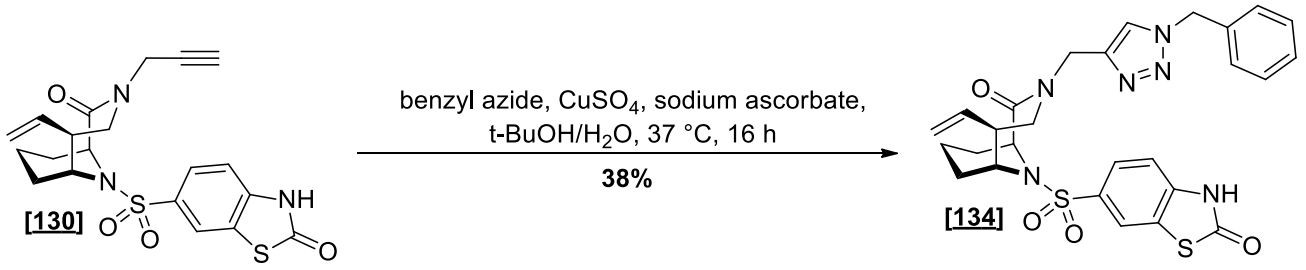
Scheme 109. Synthesis of compound **[132]**.

Reaction of **[130]** with 1-azido-4-methoxybenzene yielded 38% of compound **[133]** as shown in **Scheme 110**.



Scheme 110. Synthesis of compound **[133]**.

Treatment with benzyl azide gave 69% yield of **[134]** as depicted in **Scheme 111**.

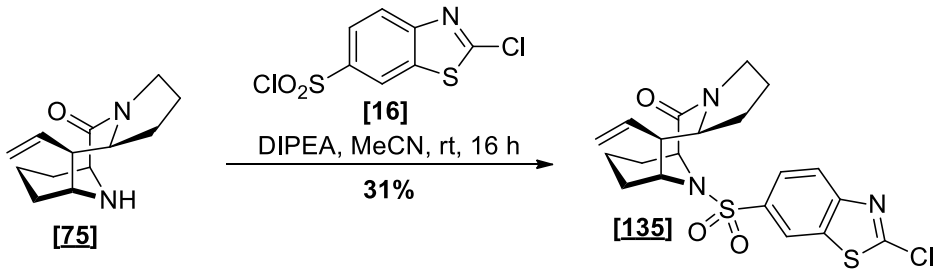


Scheme 111. Synthesis of compound **[134]**.

Deprotection of the benzyl protective group to furnish the free triazole was attempted by hydrogenation. Applying ambient pressure of gaseous hydrogen with either palladium on charcoal or palladium hydroxide on carbon did not display any conversion on LC-MS. Performing the reaction in an autoclave at 7 bar resulted in complete decomposition. Direct conversion of **[130]** with trimethylsilyl azide and copper(I) iodide was attempted, but the reaction did not display any significant conversion after 12 hours at room temperature. Successive heating to 60 °C did not improve product formation but caused steady decomposition of the starting material.

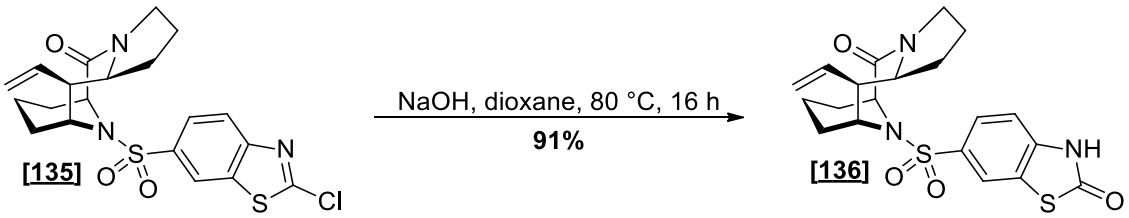
3.3.9. Synthesis of a tricyclic 6-benzo[d]thiazol-2(3H)-one analog

A tricyclic benzothiazolone derivative was synthesized starting from tricycle **[75]**. Reaction with sulfonyl chloride **[16]** gave tricyclic intermediate **[135]** in 31% yield as depicted in **Scheme 112**.



Scheme 112. Synthesis of tricyclic intermediate **[135]**.

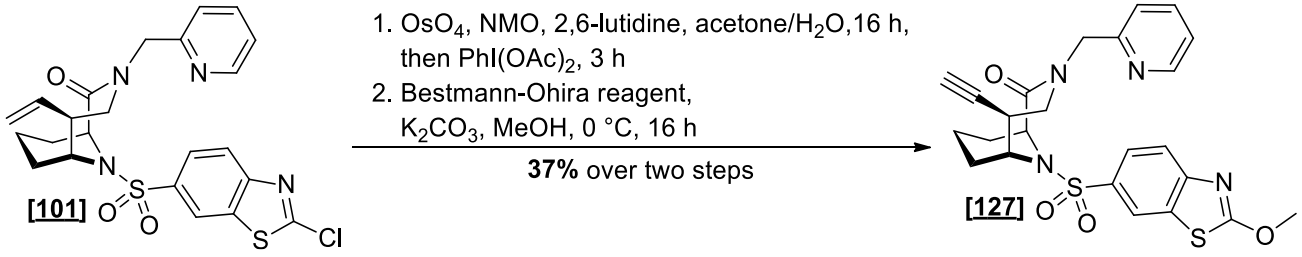
Hydrolysis was performed in a biphasic system of aqueous sodium hydroxide and dioxane to yield tricyclic benzothiazolone **[136]** in 91% yield as shown in **Scheme 113**.



Scheme 113. Synthesis of tricyclic benzothiazolone **[136]**.

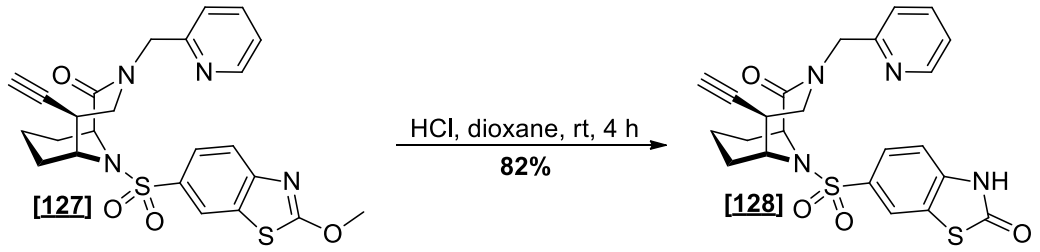
3.3.10. Synthesis of 6-benzo[d]thiazol-2(3H)-one tracers

In order to better understand the behavior of the 6-benzo[d]thiazol-2(3H)-one moiety and be able to track the compound by means of fluorescence, a fluorophore-labeled benzothiazolone derivative was envisioned. Since it was not clear, whether the position of the attachment would influence the binding affinity, two derivatives were synthesized. One with the fluorophore attached at R^1, the other with the fluorophore at R^3.
To install the fluorophore at R^3 utilizing CuAAC, a benzothiazolone with an alkyne at R^3 had to be synthesized. Starting from precursor **[101]**, the vinyl group was first transformed to the respective aldehyde by dihydroxylation with osmium tetroxide followed by oxidative cleavage with (diacetoxyiodo)benzene. Successive treatment with Bestmann-Ohira reagent resulted in intermediate **[127]** with a yield of 37% over two steps as depicted in **Scheme 114**.



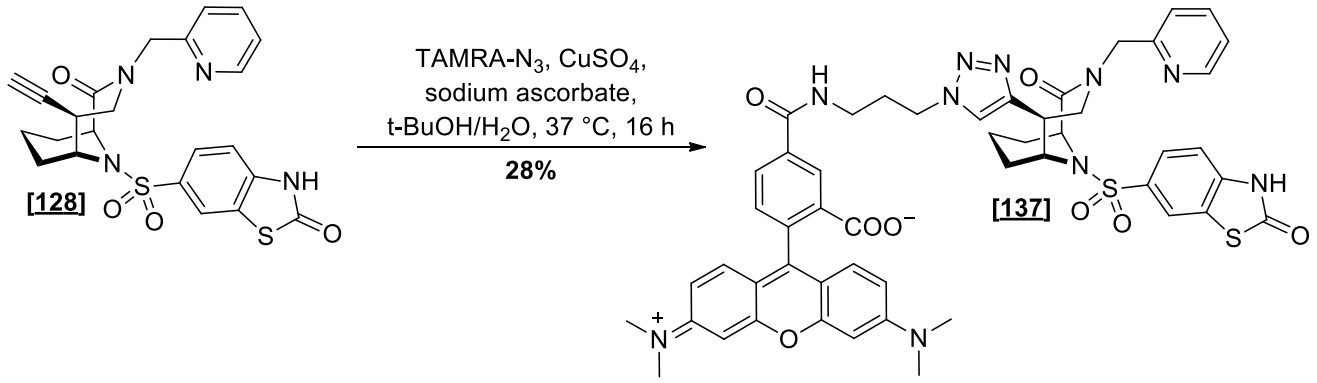
Scheme 114. Synthesis of intermediate **[127]**.

Unexpectedly, the 2-chlorobenzothiazole reacted to the 2-methoxybenzothiazole. Apparently, the basic conditions in methanol lead to an attack of methanol at C2 of the benzothiazole. Although compound **[127]** was not the desired product of this reaction, it is evident that it is convertible to the desired compound by demethylation. Therefore, a small screening was conducted. The Lewis acid boron trichloride in dichloromethane did not display any conversion on LC-MS. A mixture of tetrahydrofuran and aqueous sodium hydroxide resulted in a mixture of starting material, product and side product in a ratio of approximately 1:1:1. Hydrochloric acid in dioxane resulted in complete conversion to the product without any detectable side product. The reaction was repeated on a preparative scale yielding compound **[128]** in 82% as shown in **Scheme 115**.



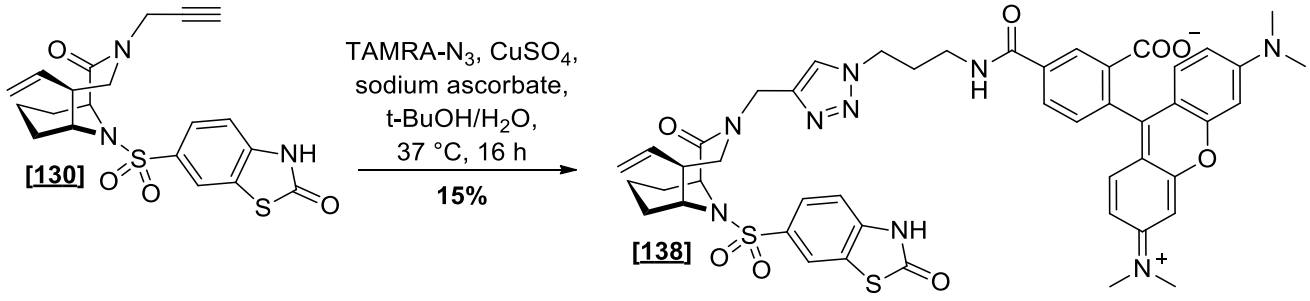
Scheme 115. Demethylation of compound **[127]** to afford compound **[128]**.

Copper-catalyzed cycloaddition with 5-TAMRA-azide yielded tracer **[137]** in 28% yield as displayed in **Scheme 116**.



Scheme 116. Synthesis of tracer **[137]**.

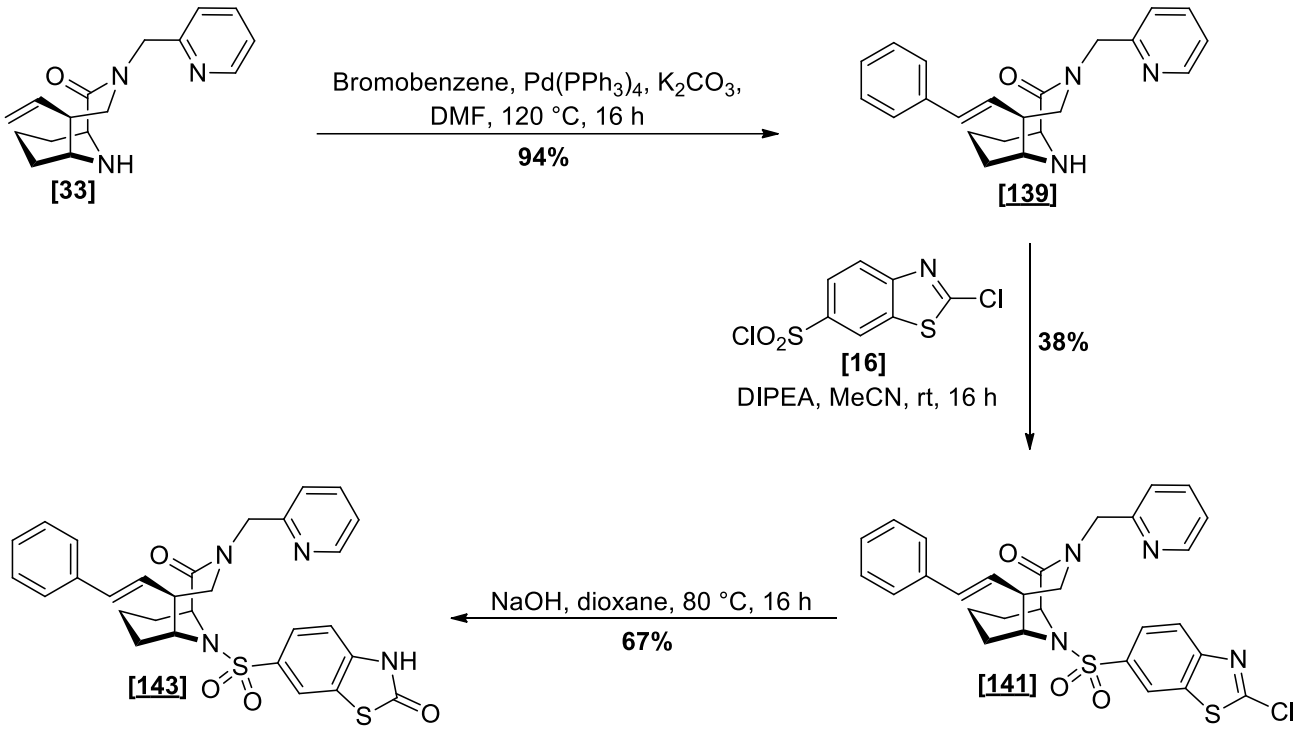
Copper-catalyzed cycloaddition of compound **[130]** with 5-TAMRA-azide yielded tracer **[138]** in 15% yield as displayed in **Scheme 117**.



Scheme 117. Synthesis of tracer **[138]**.

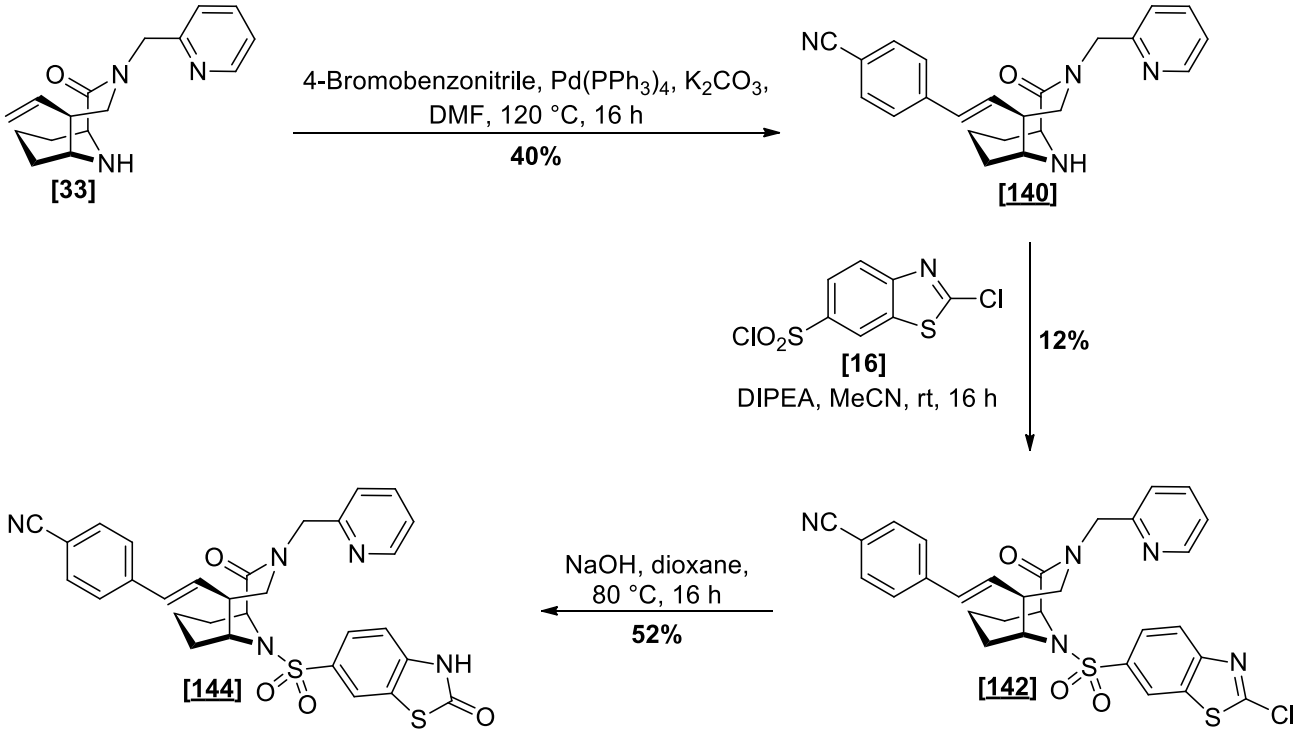
3.3.11. Synthesis of benzothiazolones derived from Heck-reaction at position R^3

Benzothiazolones with a extended substituents at R^3 were envisioned. The chosen method for this approach was a Heck-reaction, as discussed in more detail in chapter **3.4.** To avoid complications with the benzothiazolone (N-arylation) and its precursor 2-chlorobenzothiazole (coupling to C2 of benzothiazole), the Heck-reaction was performed as the first step. The synthesis commenced with bicyclic precursor **[33]** as shown in **Scheme 118**. Heck-reaction with bromobenzene afforded compound **[139]** in 94% yield. Formation of the sulfonamide **[141]** with sulfonyl chloride **[16]** in 38% yield followed by hydrolysis of the 2-chlorobenzothiazole in 67% yield afforded desired compound **[143]**.



Scheme 118. Synthesis of compound **[143]**.

A second derivative with an additional nitrile-group in position 4 of the aromatic ring was synthesized accordingly. The synthesis is displayed in **Scheme 119** and commenced with bicyclic precursor **[33]**, which was subjected to Heck reaction conditions with 4-bromobenzonitrile to afford compound **[140]** in 40% yield. Treatment with sulfonyl chloride **[16]** gave sulfonamide **[140]** in 12% yield. The low yield of the last two steps is due to several chromatographic purification steps, which were necessary to remove various side products and impurities originating from the Heck-reaction. Hydrolysis in a biphasic system of aqueous sodium hydroxide and dioxane yielded the desired compound **[142]** in 52% yield.



Scheme 119. Synthesis of compound [144].

3.3.12. FP-Assay Data

All final compounds were tested for their binding affinities for various FKBPs (12, 12.6, 51, 52) and for a different FKBP12 construct (tag-free), which resembles the native FKBP more closely. The results are tabulated in **Table 1**.

Table 5. FP-Assay data of benzothiazolones and derivatives.

#	Ki nM FKBP12 (HG21)	Ki nM FKBP12 tag-free (HG825)	Ki nM FKBP12.6	Ki nM FKBP51	Ki nM FKBP52
[98]	0.40 ± 0.21	8.0	0.57	196 ± 60	283 ± 116
[99]	0.11 ± 0.073	5.8	0.42	8.0 ± 2.4	14 ± 6.2
[100]	26 ± 1.5	704	n.d.	>1000	194
[101]	21	n.d.	n.d.	450	221
[102]	7.9	7.8	n.d.	235	59
[103]	22 ± 5	14	n.d.	154	93
[104]	7.8	4.8	n.d.	235	59
[105]	25	n.d.	n.d.	403	188
[106]	15 ± 4.5	7.7	n.d.	481	380
[107]	12 ± 5.9	8.5	n.d.	422	193
[108]	20	n.d.	n.d.	356	306
[109]	12	n.d.	n.d.	972	506
[110]	30	n.d.	n.d.	661	321
[111]	17	n.d.	n.d.	714	439
[112]	4.0	n.d.	n.d.	64	60
[113]	4.9 ± 2.2	5.0	n.d.	36	14
[114]	141	n.d.	n.d.	>1000	>1000
[115]	17	n.d.	n.d.	671	1282
[116]	75	n.d.	n.d.	>1000	>1000
[117]	21	n.d.	n.d.	295	156
[118]	27 ± 21	4.4	n.d.	1116 ± 595	1068 ± 931
[119]	8.0	10	n.d.	157	265
[120]	12	n.d.	57	>80	>80
[121]	5.0	n.d.	20	>80	>80
[122]	5.0	n.d.	17	>80	>80
[123]	0.28 ± 0.16	82	1.52	75	>80
[126]	0.13 ± 0.09	3.6	1.0	3.0	5.0
[127]	4.2	n.d.	7.4	126	121
[128]	0.07	7.6	n.d.	n.d.	n.d.
[130]	7.0	108	n.d.	n.d.	n.d.

[131]	2.0 ± 0.61	106	6.0	102	>80
[132]	2.2 ± 1.3	98	8.0	>80	>80
[133]	0.29 ± 0.14	n.d.	1.7	486	538
[134]	0.47 ± 0.10	23	2.5	260	319
[135]	249	n.d.	323	4632	7274
[136]	11	478	n.d.	n.d.	n.d.
[143]	0.12	1.0	n.d.	n.d.	n.d.
[144]	0.03 ± 0.02	0.24	0.05	5.88	2.59

n. d. = not determined. Values without standard deviation were only measured as pseudo-duplicates. If a substance did not display binding in the assay, the value is reported as greater (>) than the highest measured concentration.

In general, the trend in binding affinity is decreasing in the order 12 > 12.6 >51 & 52, which is typical for bicyclic [4.3.1.] aza-amides. The most important difference is apparent, when comparing the binding affinities for FKBP12 (HG21) with the tag-free construct HG825. The binding affinities of most 6-benzothiazolones are in the sub-nanomolar range when measured with the HG21 construct, but all 6-benzothiazolones display a drop in affinity by a factor of 50 – 100 when measured with HG825. This effect is not observed for any other moiety, e.g. the 5-benzothiazolone derivative **[118]**, the *N*-methylated 6-benzothiazolone **[106]**, or the O-methylated derivative **[102]**. It appears, that this specific scaffold has additional protein contacts with parts of the His-tag still present. This finding is currently under investigation and beyond the scope of this thesis.

In the series **[98]** – **[100]**, the effect of the α-methyl group is decisive, with the *S*-methylated analog **[99]** displaying the best binding affinities while the *R*-methylated analog **[100]** displays the poorest binding affinity.
The 2-chlorobenzothiazole precursor **[101]** displays poorer binding affinities than the respective benzothiazolone **[98]**. Derivatives thereof, which substitute the oxygen of the benzothiazolone with -OMe (**[102]**), -NH_2 (**[103]**), NHMe (**[104]**) or NMe_2 (**[105]**), display comparable to slightly worse binding affinities compared to **[98]**. Derivatives with substituents at the benzothiazolone-nitrogen **[106]** – **[111]** display similar binding affinities to each other with double-digit nanomolar binding to FKBP12 and triple-digit nanomolar binding to FKBP51 and FKBP52, therefore suggesting that modifications at this position do not have contacts with the protein.
Derivative **[113]**, with an additional bromine at position 4 of the benzothiazolone, displays similar binding affinities to the tag-free FKBP12 compared to benzothiazolone **[98].** Interestingly, it displays a comparable binding affinity with the HG21 construct (no loss in binding affinity), although it has a 6-benzothiazolone moiety. This suggests, that it binds in a different conformation, probably by a flip of the benzothiazolone. The same effect is observed for the 5-benzothiazolones **[118]** and **[119]**, which display nanomolar to double-digit nanomolar binding to both FKBP12 constructs.
In the series **[120]** – **[123]**, where the benzothiazolone sulfur is substituted, the substitutes CH_2 (**[120]**), $C(CH_3)_2$ (**[121]**) and NH (**[122]**) display worse binding affinities than reference **[98]**, while the substitute O (**[123]**) displays comparable binding affinities and additional displays a difference when comparing the two FKBP12 constructs.
Within the triazole series **[131]** – **[134]**, compounds **[133]** and **[134]** display equal binding affinities compared to reference **[98]**. Furthermore, they display the loss in binding affinity regarding the two FKBP12 constructs.
The tricyclic derivative **[136]** displays double-digit nanomolar binding to HG21 and triple-digit nanomolar affinity to HG825, which is poorer compared to reference compound **[98]**.
The Heck-reaction-derived compound **[144]** display the best binding affinity of all measured benzothiazolones. Although it displays the same drop in affinity in regard to the two FKBP12 constructs, it is still a sub-nanomolar binder to HG825 (and FKBP12.6).
Taken together, no variation of the benzothiazolone scaffold yielded improved binding affinities. Observed improvements in binding affinity are due to different residues in R_1 and R_3, thus proving the independence of the different positions. The most interesting finding is, that the increased binding affinity to FKBP12 seems to be influenced by remains of the His-tag, although it is not obvious how.

3.4. Bicyclic Compounds derived from Heck-reaction at R^2

Analysis of crystal structures of bicyclic [4.3.1] aza-amides in the FKBP binding pocket (*vide supra*, **Figure 24**) revealed that there is plenty of space for chemical residues at C5. The vinyl linker in this position offers various possible means for modifications, out of which the Heck-reaction was chosen for a small library. The Heck-reaction requires no modification of the vinyl group and a vast variety of arene bromides is commercially available. Compound **[34]** was chosen as scaffold for the Heck-reaction-derived small library. Initially, the synthesis was performed by Robin Deutscher during an internship under my supervision. The idea was to generate a small library with substituents in the 2,3 and 4 position of the aromatic ring and find possible interactions within the binding pocket of FKBPs. The desired residues in R^3 are displayed in **Figure 23**.

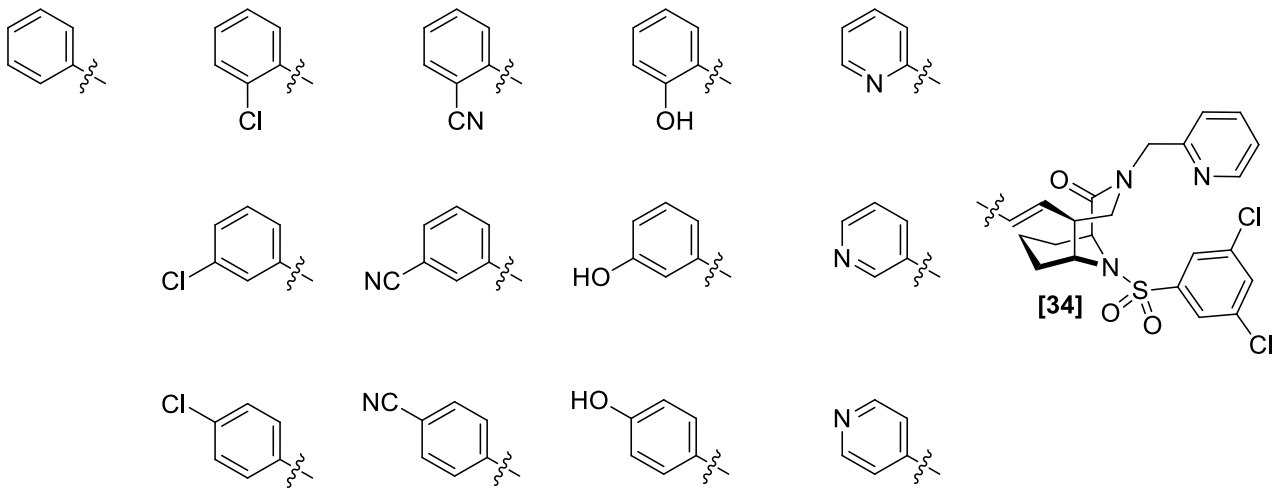
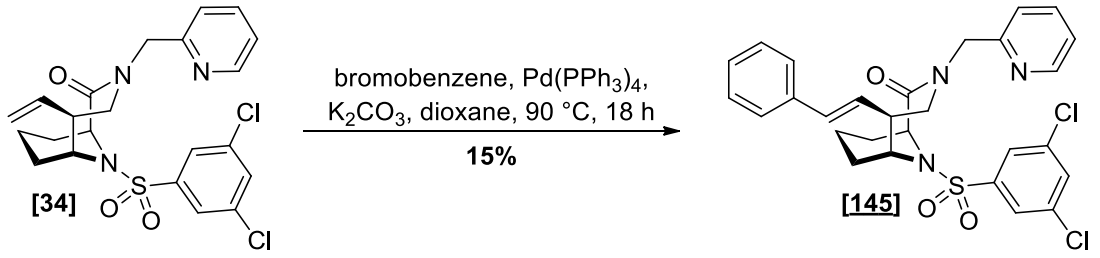


Figure 23. Envisioned residues for Heck-reaction-derived small library.

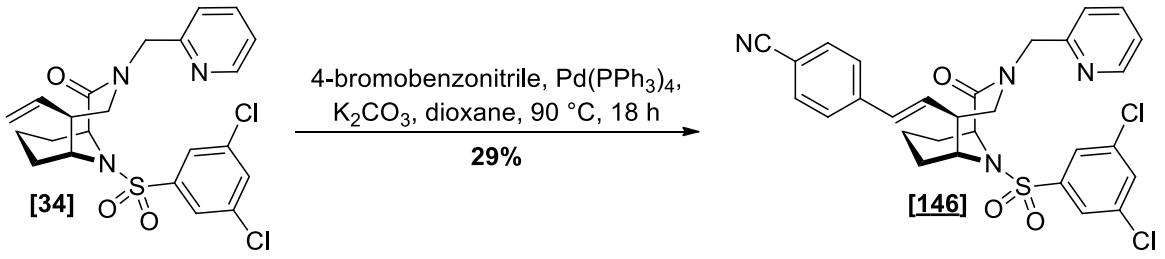
3.4.1. Synthesis

The synthesis of compounds **[145]** – **[154]** were conducted by Robin Deutscher during an internship under my supervision. To validate this synthetic approach and to test whether the two chlorine atoms of the sulfonamide are stable at elevated temperatures and metal-catalysts, compound **[34]** was reacted with bromobenzene and tetrakis(triphenylphosphane)palladium(0) in dioxane at 90 °C as depicted in **Scheme 120**.



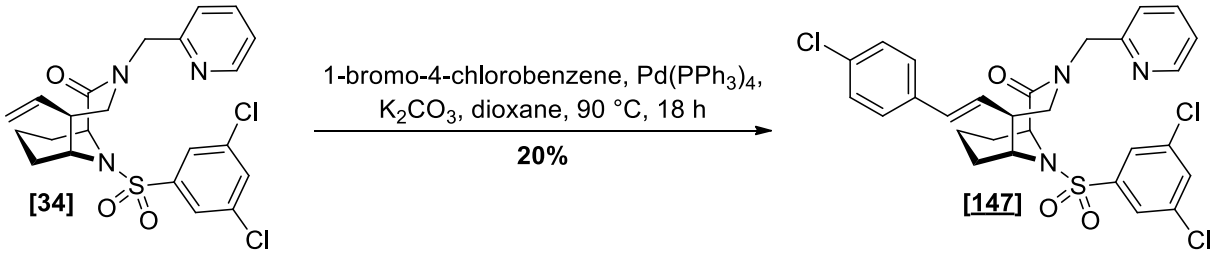
Scheme 120. Synthesis of compound **[145]**.

The reaction gave full conversion after 16 hours, but the isolated yield of compound **[145]** is only 15% due to problematic chromatographic purification. The reaction mixture was first purified by column chromatography over silica and afterwards by utilizing a semi-preparative HPLC. This is in general true for all following Heck-reaction-derived compounds (compounds **[145]** – **[153]**).
With a working procedure in hand, we prioritized to synthesize more derivatives instead of optimizing the reaction conditions. We decided to begin with simpler substrates, in terms of reactivity and steric properties, and therefore postponed the pyridines and started with para-substituted bromobenzenes. The reaction of compound **[34]** with 4-bromobenzonitrile yielded 29% of compound **[146]**, as shown in **Scheme 121**.



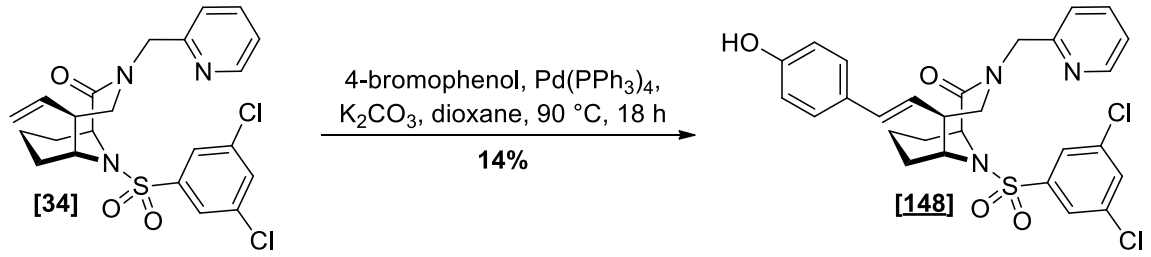
Scheme 121. Synthesis of compound **[146]**.

Reacting **[34]** with 1-bromo-4-chlorobenzene yielded 20% of compound **[147]**, as displayed in **Scheme 122**.



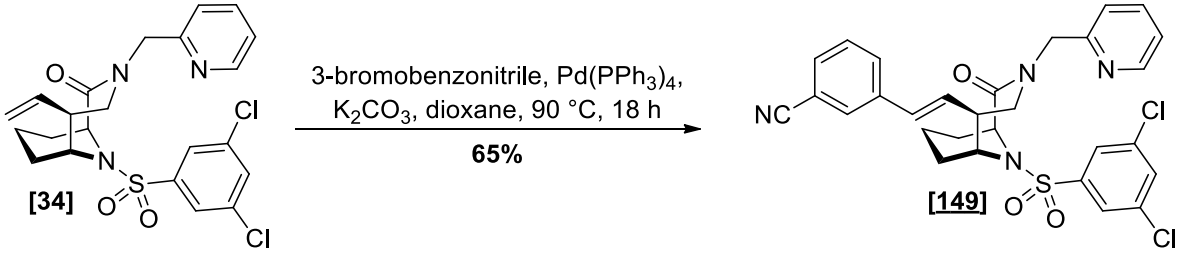
Scheme 122. Synthesis of compound **[147]**.

Treatment of **[34]** with 1-bromo-4-hydroxybenzene afforded compound **[148]** in 14% yield, as depicted in **Scheme 123**.



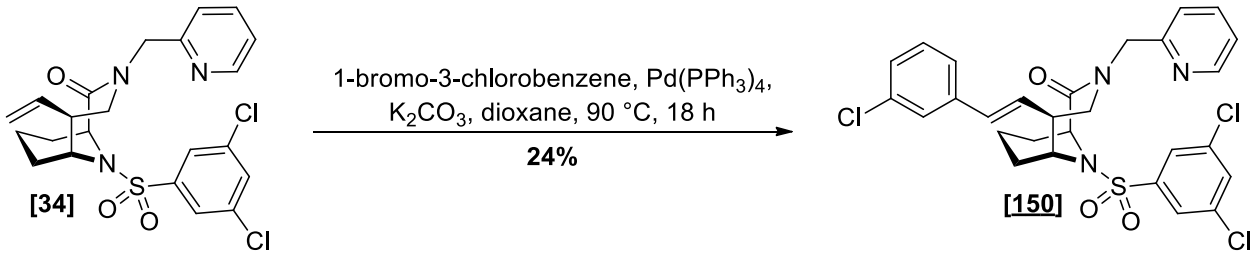
Scheme 123. Synthesis of compound **[148]**.

With the para-substituted derivatives in hand, we continued with the meta-substituted derivatives. Synthesis of **[34]** with 3-bromobenzonitrile yielded 65% of compound **[149]**, as shown in **Scheme 124**.



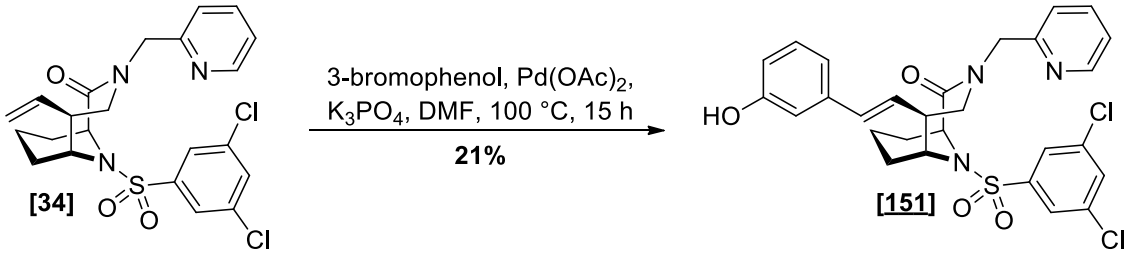
Scheme 124. Synthesis of compound **[149]**.

Reaction of compound **[34]** with 1-bromo-3-chlorobenzene yielded 24% of compound **[150]**, as shown in **Scheme 125**.



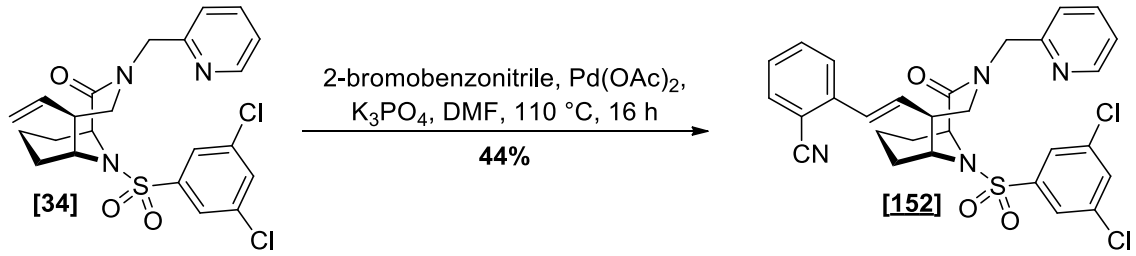
Scheme 125. Synthesis of compound **[150]**.

The same reaction conditions were applied with 3-bromophenol, but the yield dropped below a practicable work-up. Therefore, the reaction conditions were changed to palladium(II) acetate in dimethylformamide. With these conditions, a yield of 21% of compound **[151]** was achieved, as shown in **Scheme 126**.



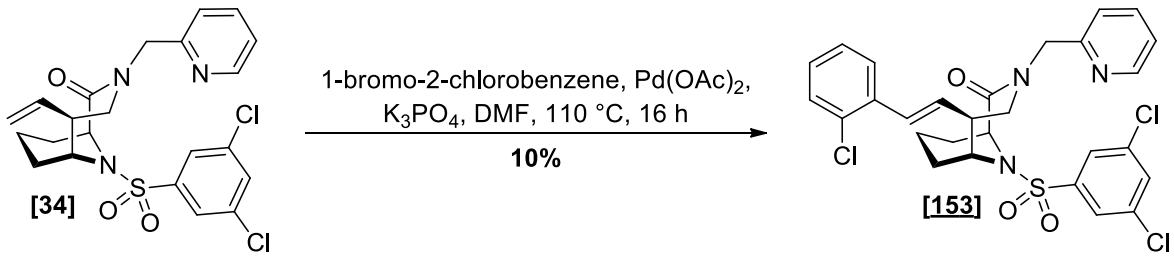
Scheme 126. Synthesis of compound **[151]**.

For the ortho-substituted derivatives, the most sterically demanding in this series, the procedure with tetrakis(triphenylphosphane)palladium(0) in dioxane resulted in no significant conversion. The procedure with palladium(II) acetate in dimethylformamide gave reasonable conversions with 2-bromobenzonitrile and 1-chloro-2-bromobenzene, although no product was detectable in the case of 2-bromophenol. The reaction of compound **[34]** with 2-bromobenzonitrile yielded 44% of compound **[152]**, as shown in **Scheme 127**.



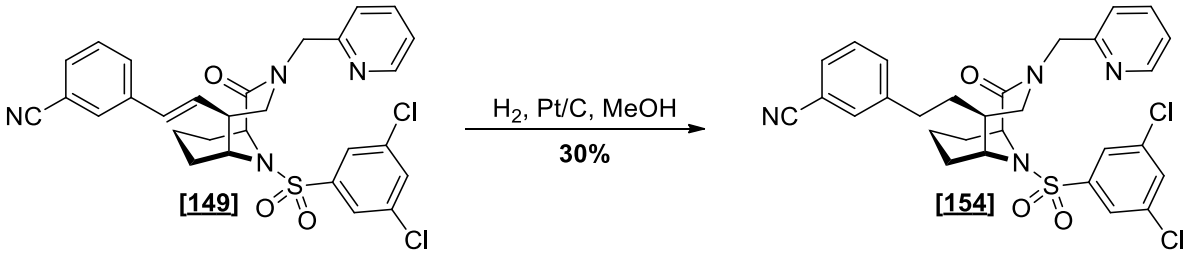
Scheme 127. Synthesis of compound **[152]**.

Reaction of compound **[34]** with 1-bromo-2-chlorobenzene gave compound **[153]** in 10% yield, as displayed in **Scheme 128**.



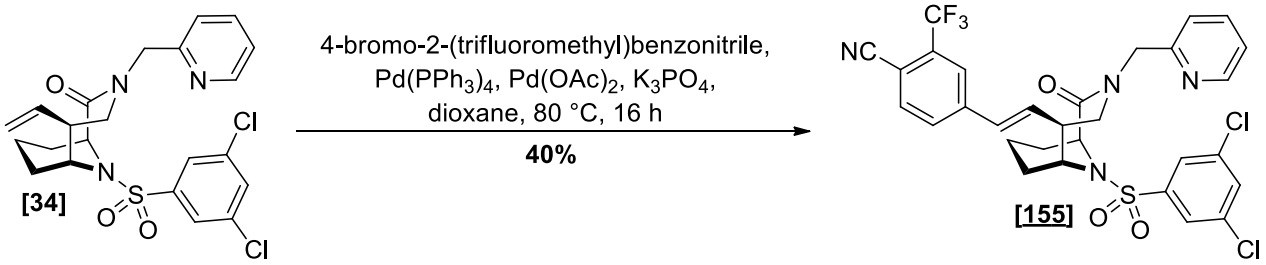
Scheme 128. Synthesis of compound **[153]**.

In order to see, whether the double bond affects the binding affinity, compound **[149]** was subjected to hydrogenation, as shown in **Scheme 129**. This afforded compound **[154]** in 30% yield.



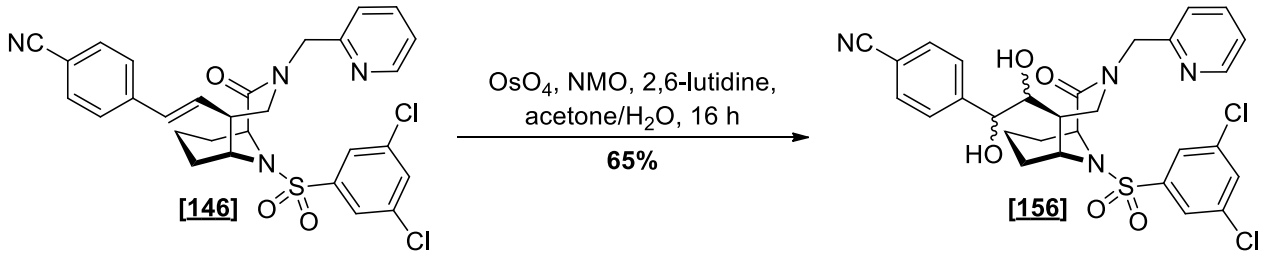
Scheme 129. Synthesis of compound **[154]**.

After evaluation of the binding affinities of these compounds (discussed in the following chapter), two additional compounds were synthesized. Reaction of **[34]** with 4-bromo-2-(trifluoromethyl)benzonitrile afforded compound **[155]** in 40% yield.



Scheme 130. Synthesis of compound **[155]**.

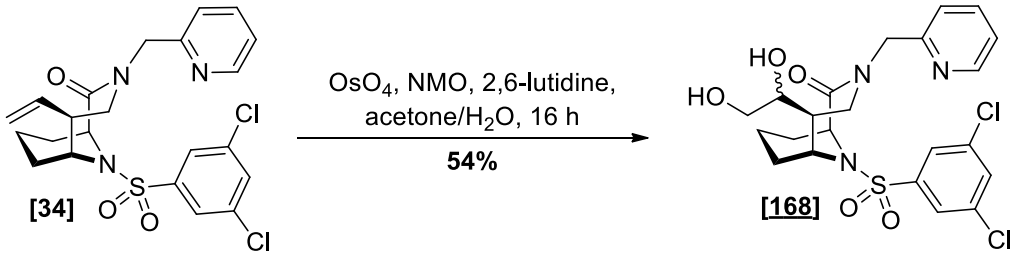
A dehydroxylated derivative of compound **[146]** was envisioned, since dihydroxylation of the vinyl group resulted in improved binding affinity for other bicyclic [4.3.1] aza-amides.[82] Utilizing osmium tetroxide yielded compound **[156]** in 65% yield, as displayed in **Scheme 131**.



Scheme 131. Synthesis of compound **[156]**.

It was attempted to separate the two diastereomers (dihydroxylation with osmium tetroxide gives only *cis*-product due to concerted oxidation mechanism), but without success. However, different fractions were collected (**[156a]** = 89:11, **[156b]** = 50:50, **[156c]** = 32:68) and measured in a FP-Assay for their binding affinity.

As reference, compound **[168]** was synthesized with the same reaction conditions in 54% yield as depicted in **Scheme 132**.



Scheme 132. Synthesis of compound **[168]**.

3.4.2. FP-Assay Data

All Heck-reaction-derived compounds, as well as the reference compound **[34]** with just a vinyl group, were tested for their binding affinities to FKBPs (12, 12.6, 51, 52) in a FP-assay. The values are tabulated in **Table 6**.

Table 6. Binding affinities of Heck-reaction-derived compounds.

#	Ki nM FKBP12	Ki nM FKBP12.6	Ki nM FKBP51	Ki nM FKBP52
[34]	1.7 ± 0.6	12 ± 4	142 ± 39	93 ± 28
[145]	1.2	8.7	157	63
[146]	0.07 ± 0.03	0.55 ± 0.17	57 ± 14	16 ± 5.5
[147]	1.2	6.8	156	41
[148]	0.40	4.0	37	22
[149]	0.40	2.7	50	14
[150]	5.6	15	49	32
[151]	1.3	9.5	82	32
[152]	0.80	4.0	67	16
[153]	6.0	41	544	174
[154]	0.30	1.0	31	14
[155]	0.63	5.1	42	25
[156a]	1.2	12	138	122
[156b]	0.65	5.7	63	40
[156c]	0.19	2.5	30	15
[168]	0.51	7.0	52	30

Values without standard deviation were only measured as pseudo-duplicates.

Comparing the reference compound **[34]** to the Heck-reaction product **[145]** with an unsubstituted benzene ring, reveals almost identical binding affinities. This suggests, that the benzene ring does not have any beneficial interactions with the protein, but, on the other hand, does not have disadvantageous interactions, e.g. a steric clash. Comparison of the different functional groups identifies the nitrile moiety as a favorable group in any of the three positions, with binding affinities decreasing in the order 4-CN (**[146]**) > 3-CN (**[149]**) > 2-CN (**[152]**). It is assumed, that the nitrile group interacts with Arg73 (**Figure 24**), as arginine has been identified as nitrile interaction partner in several crystal structures.[99] The second best compound was **[148]** with a hydrxy group in para position. This hydroxy group might also interact with Arg73 via a hydrogen bond (network). A hydroxy group in the meta positon (**[151]**) does not effect the binding affinity, compared to **[34]**. A chlorine does not improve the binding affinity in any position (**[147]**, **[150]**, **[153]**), on the contrary, the binding affinity seems to decrease for the 2-Cl and 3-Cl. Compound **[154]**, the analog of **[149]** with a saturated linker, displays comparable bindign affinities to **[149]**, thus suggesting that the rigidity of the linker is not important for binding affinity. Compound **[155]**, the derivative of **[146]** with an additional trifluoromethyl group in meta position, displays poorer binding

affinity than **[146]**. It was assumed, that the electron withdrawing effect of the trifuloromethyl group would strengthen the hydrogen bond acceptor properties of the nitrile group. Additionally, the fluorine atoms could form multipolar fluorine–backbone interactions. The poorer binding affinity is somewhat surprising and might result from a steric clash. Comparison of the 5-vinyl compound **[34]** with its dihydroxylated derivative **[168]**, demonstrates the increased binding affinity of the dihydroxylated compound **[168]**. This effect is not detectable, when comparing the 4-CN compound **[146]** with its dihydroxylated derivative **[156]**. While the orientation of the two hydroxy groups effect binding affinity, as evident by comparison of **[156a]** and **[156c]**, the overall binding affinity is worse compared to **[146]**. Apparently, the increase in binding affinity by dihydroxylation is not synergistic with the Heck-reaction derived compounds. This suggests, that the hydroxy groups influence the conformation of the linker and force the aryl ring, especially the nitrile group, in a less favorable position for interactions with the protein.

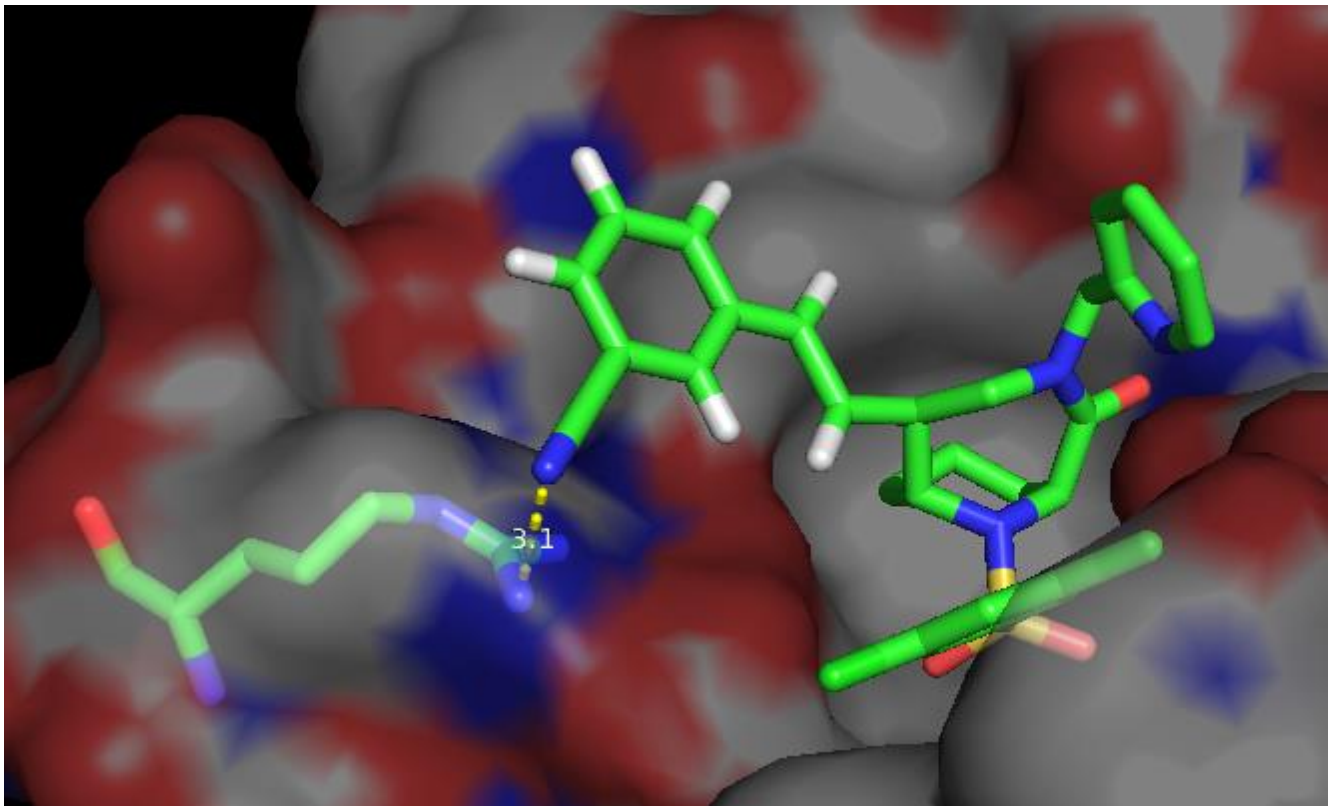


Figure 24. Compound **[148]** in the binding pocket of FKBP51 and it's possible interaction with Arg73. This is the crystal structure 5OBK with a 5-CH_2OH residue. The structure of **[148]** is drawn in PyMOL.

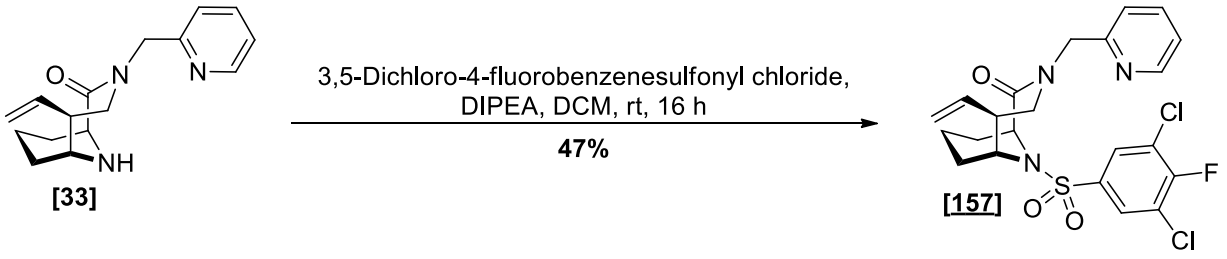
Taken together, the screening of Heck-derived-compounds resulted in a double-digit picomolar binder **[146]**, possibly by a novel interaction with Arg73. The aromatic ring itself does not influence the binding properties, thus could be rendered obsolete. The combination of the 4-CN Heck-product with dihydroxylation did not result in improved binding affinity. The major drawback of this compound class is the increase in molecular weight, which is not justified by the increase in binding affinity. Future optimizations should focus on the replacement of the aryl ring with an alkxyl chain. This would not only reduce the molecular weight of the compounds but also enable the possibility of hydroxylation of the linker. A crystal structure of **[146]** could give further insights in the binding mode and thus assist in future optimizations.

3.5. Miscellaneous 3,10-Diazabicyclo[4.3.1]decan-2-ones

During the course of the dissertation a few tailormade bicyclic [4.3.1] aza-amides were synthesized, which are beyond the scope of the previous chapters. These compounds are described here and their binding affinities towards FKBPs are discussed.

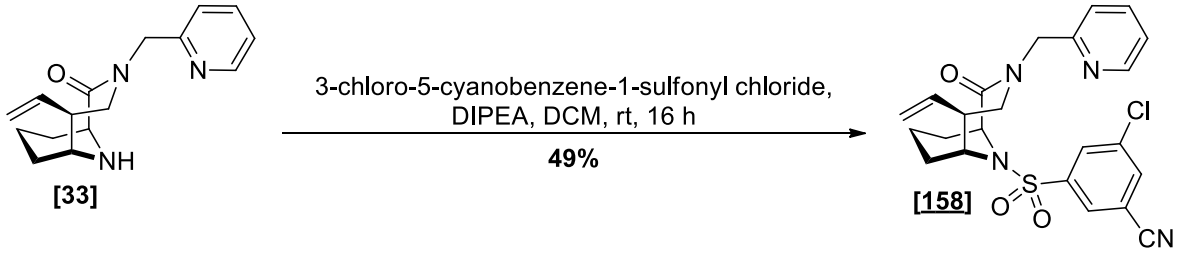
3.5.1. Synthesis of 3,5-dichlorosulfonamide derivatives

A small series of derivatives of the 3,5-dichlorosulfonamide scaffold were envisioned. A derivative of **[34]** with an additional fluorine in position 4 of the dichlorobenzene was synthesized according to **Scheme 133**. The reaction was performed with commercially available 3,5-dichloro-4-fluorobenzenesulfonyl yielding 47% of compound **[157]**.



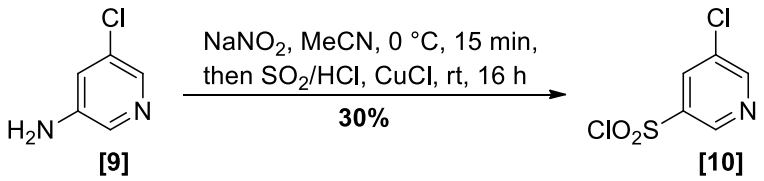
Scheme 133. Synthesis of compound **[157]**.

Another derivative of **[34]** with one of the chlorines substituted by a nitrile group was synthesized. The reaction was performed with commercially available 3-chloro-5-cyanobenzene-1-sulfonyl chloride in 49% yield as shown in **Scheme 134**.



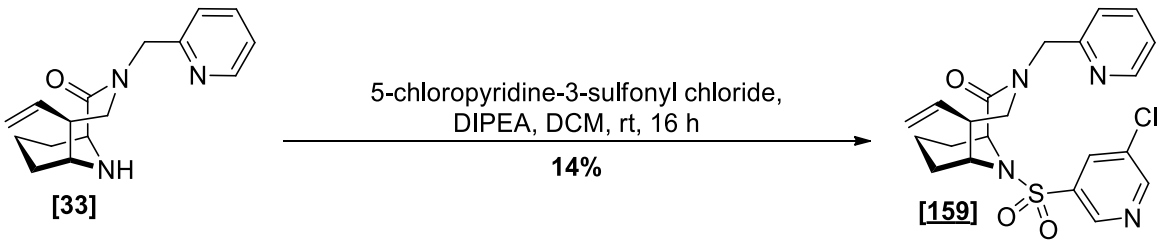
Scheme 134. Synthesis of compound **[158]**.

A further derivative of **[34]** with a pyridine nitrogen in position 3 and a chlorine in position 5 was envisioned. The required sulfonyl chloride was synthesized from the respective amine **[9]** in 30% yield as depicted in **Scheme 135**.



Scheme 135. Synthesis of sulfonyl chloride **[10]**.

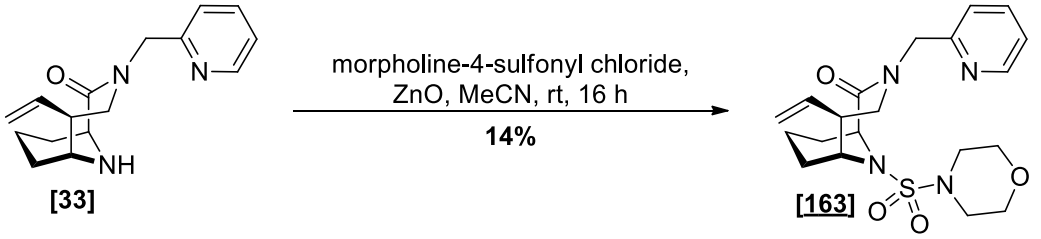
Reaction of sulfonyl chloride **[10]** with bicycle **[33]** afforded compound **[159]** in 14% yield as shown in **Scheme 136**.



Scheme 136. Synthesis of compound **[159]**.

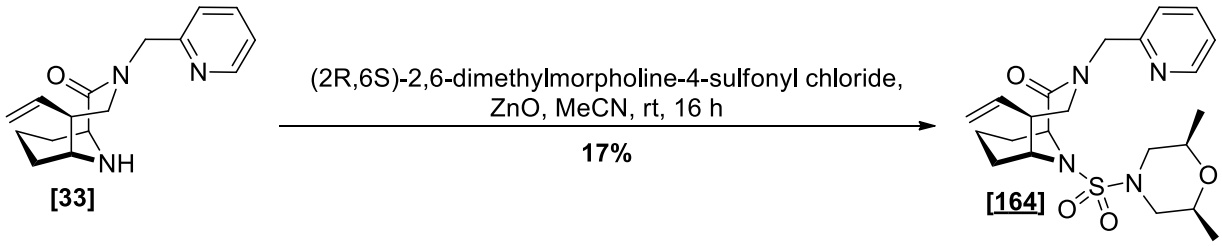
3.5.2. Synthesis of sulfondiamides

A small series of sulfondiamides was synthesized with commercially available sulfonyl chlorides. Compound **[33]** was reacted with morpholine-4-sulfonyl chloride to give compound **[163]** in 14% yield as shown in **Scheme 137**.



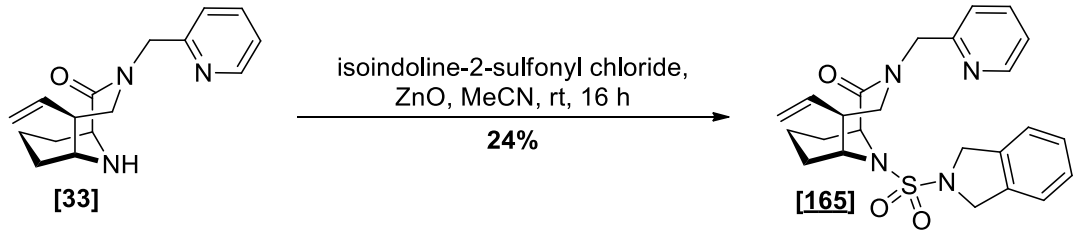
Scheme 137. Synthesis of compound **[163]**.

Reaction of **[33]** with (2R,6S)-2,6-dimethylmorpholine-4-sulfonyl chloride yielded compound **[164]** in 17% yield as displayed in **Scheme 138**.



Scheme 138. Synthesis of compound **[164]**.

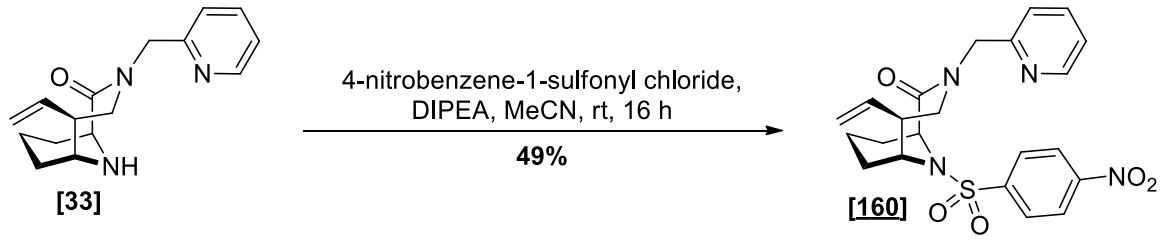
Treatment of **[33]** with isoindoline-2-sulfonyl chloride afforded compound **[165]** in 24% yield as depicted in **Scheme 139**.



Scheme 139. Synthesis of compound **[165]**.

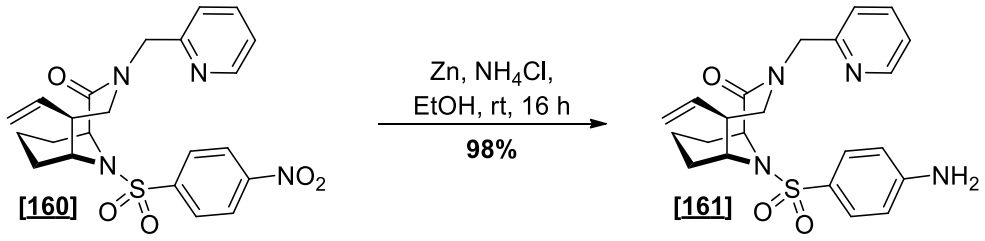
3.5.3. Synthesis of other sulfonamides

Reaction of **[33]** with 4-nitrobenzene-1-sulfonyl chloride afforded compound **[160]** in 49% yield as shown in **Scheme 140**.



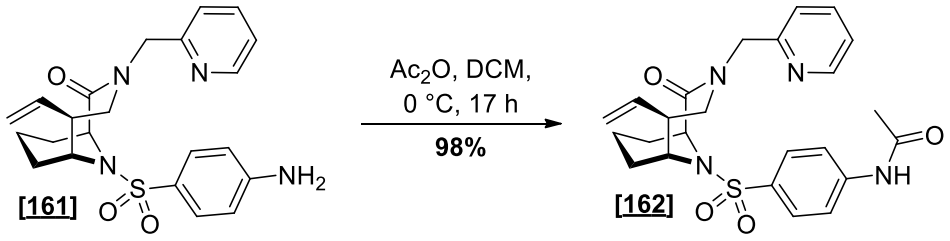
Scheme 140. Synthesis of compound **[160]**.

Reduction of the nitro group with zinc and ammonium chloride afforded compound **[161]** in 98% yield as displayed in **Scheme 141**.



Scheme 141. Synthesis of compound **[161]**.

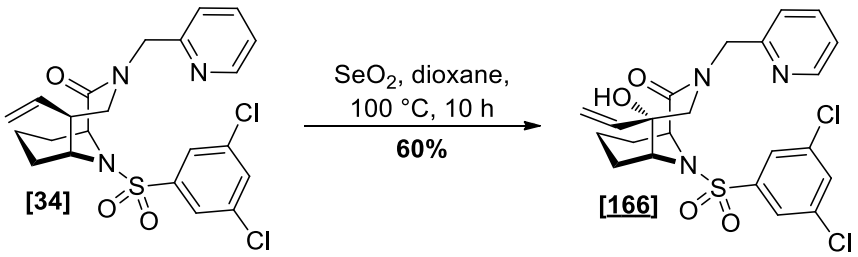
Acetylation of the aniline resulted in a yield of 98% of compound **[162]** as depicted in **Scheme 142**.



Scheme 142. Synthesis of compound **[162]**.

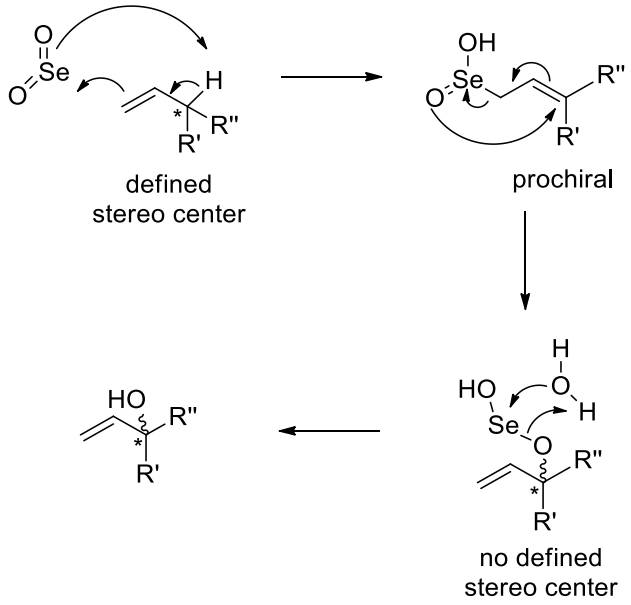
3.5.4. Synthesis of 5,5-substituted bicyclic [4.3.1] aza-amides

A synthetic mean to further modify position 5 of bicyclic [4.3.1] aza-amides was envisioned. Riley-oxidation was chosen, utilizing selenium dioxide to oxidize in allylic position. The reaction yielded 60% of compound **[166]** as shown in **Scheme 143**.



Scheme 143. Synthesis of compound **[166]**.

Surprisingly, only one stereoisomer was isolated. This was unexpected, since the mechanism of the allylic oxidation, depicted in **Scheme 144**, involves sp^2 hybridization at the carbon with a stereo center which results in a prochiral carbon that can be attacked by oxygen from two sites.



Scheme 144. Mechanism of allylic oxidation with selenium dioxide.

The identity of the structure was verified by 1D- and 2D-NMR spectra and the configuration was assigned by NOESY NMR (**Figure 25**).

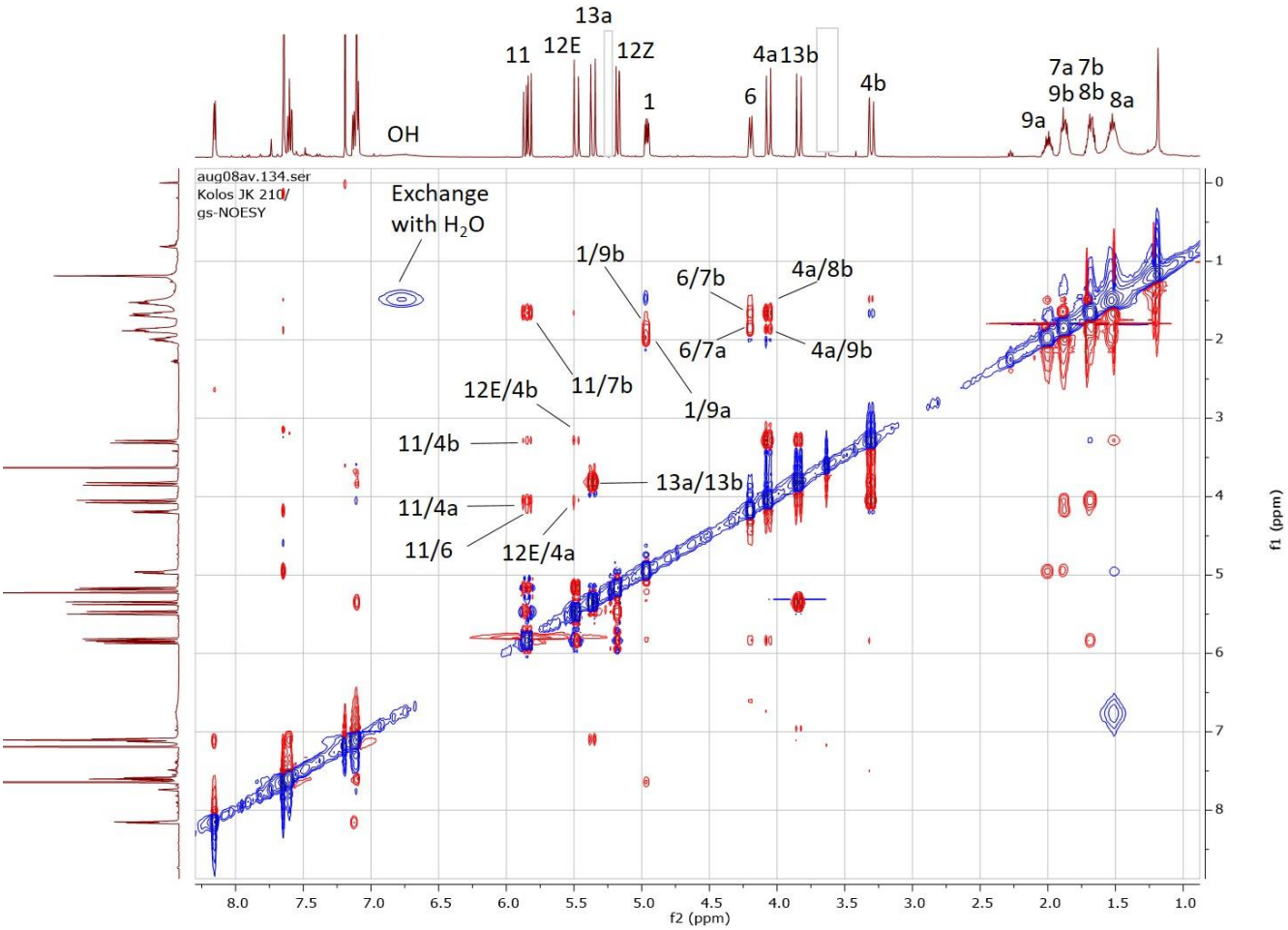


Figure 25. NOESY-NMR of compound **[166]**.

The key NOESY interactions are displayed in **Figure 26**. The most important finding is, that H^{11} has interactions to H^{4a}, H^{4b}, H^{6} and H^{7b}, while no interactions to 8^{b} or 9^{b} were found. This is only possible, if the vinyl group is facing away from the molecule and the hydroxyl group facing towards the pipecolate core. An interesting finding are the contacts of H^{8b} and H^{9b} to H^{4a}. This is only possible, if the alkyl bridge twists, as shown on the right side of **Figure 26**.

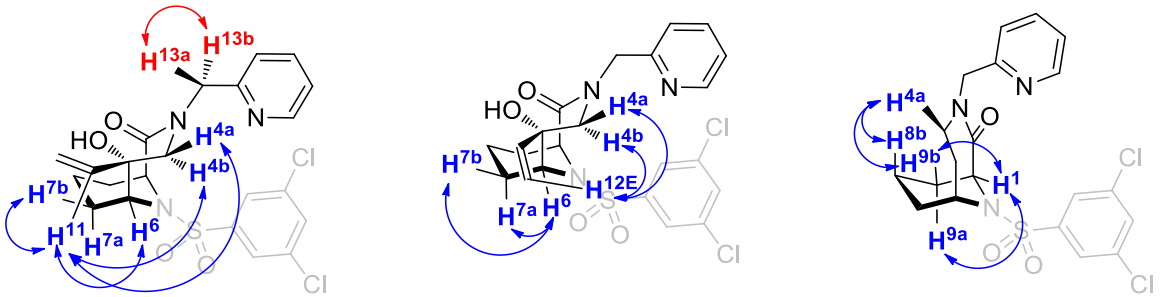
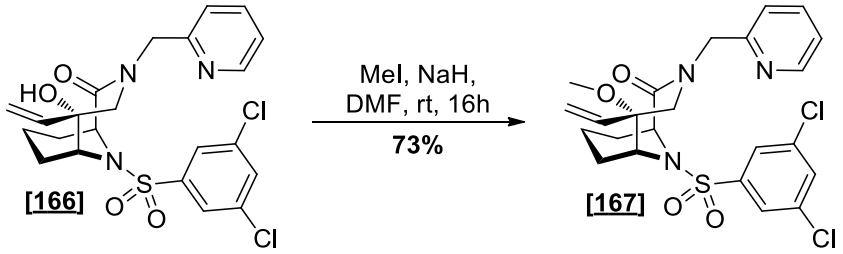


Figure 26. Key spatial proximities of the hydrogens of compound **[166]**.

Methylation of **[166]** with methyl iodide afforded compound **[167]** in 73% yield as shown in **Scheme 145**.



Scheme 145. Synthesis of compound **[167]**.

3.5.5. Binding affinities

All compounds were tested for their binding affinities towards FKBPs (12, 12.6, 51, 52). The values are tabulated in **Table 7**.

Table 7. Binding affinities of miscellaneous compounds.

#	Ki nM FKBP12	Ki nM FKBP12.6	Ki nM FKBP51	Ki nM FKBP52
[34]	1.7 ± 0.6	12 ± 4	142 ± 39	93 ± 28
[157]	11	n.d.	258	170
[158]	7.0	n.d.	183	135
[159]	6.0	31	268	132
[163]	817	n.d.	>1000	>1000
[164]	176	n.d.	>1000	>1000
[165]	67	n.d.	>200	184
[160]	64	n.d.	>1000	>1000
[161]	118	n.d.	>1000	>1000
[162]	179	n.d.	>1000	636
[166]	22	240	159	602
[167]	10 ± 1.4	64 ± 19	310 ± 64	358 ± 8.5

n. d. = not determined. Values without standard deviation were only measured as pseudo-duplicates. If a substance did not display binding in the assay, the value is reported as greater (>) than the highest measured concentration.

Compound **[157]**, with an additional fluorine in position 4 of the aromatic ring in comparison to **[34]**, displays slightly poorer binding affinities to all FKBPs compared to **[34]**. The two compounds **[158]** and **[159]**, where one of the chlorines is substituted compared to reference **[34]**, also display slightly poorer binding affinity compared to reference **[34]**. It appears, that neither the fluorine in position 4, nor the nitrile group or pyridine-nitrogen in position 3 undergo interactions with the protein. The slightly poorer binding affinity might be due to the removal of one of the chlorines. At least one of the chlorines engages in halogen interactions with the protein, and by depleting the number of chlorines, the probability of a chlorine in the favorable conformation is also depleted. Additionally, this decrease in binding affinity is also detectable when comparing the two-chlorines derivative **[34]** with the one-chlorine derivatives **[63]** – **[65]** (see **Table 2**).
In the sulfondiamide series **[163]**– **[165]**, a significant drop in binding affinity compared to reference compound **[34]** is observed. While the two morpholine derivatives **[163]** and **[164]** decrease the binding affinity by two orders of magnitude, the isoindoline derivative **[165]** displays only a loss of one order of magnitude. This might be due to the aromatic ring, which appears to be of essence in this position.
Nitro compound **[160]**, the aniline derivative **[161]** and its acetylated analog **[162]** all display poorer binding affinities (double- to triple-digit nanomolar) compared to reference **[34]**.

The two 5,5-disubstituted bicyclic compounds **[166]** and **[167]** display a decrease in binding affinity by one order of magnitude. Presumably, the additional substituent leads to increased tension of the ring system and causes subtle shifts that eventually lead to poorer interactions with the protein.

4. Conclusion & Outlook

In summary, 86 novel, tailor-made bicyclic compounds and 3 tailor-made tricyclic compounds based on the bicyclic [4.3.1] aza-amide scaffold have been synthesized and tested for their binding affinities. These compounds enabled a deeper understanding of this scaffold and its requirements for enhanced binding affinity and metabolic stability. The key findings will be discussed in the following.

The first part was dedicated to the metabolic stability of the compounds. A series of deuterium-labeled derivatives enabled the unravelling of the fragmentation pattern in an MS/MS setting. This allowed the identification of metabolites in a metabolic stability phase I study and the localization of metabolic soft spots in the bicyclic [4.3.1] aza-amide scaffold. The first of the two identified positions prone to oxidation is the residue at the amide. This is not a surprising finding, since metabolic N-dealkylation is commonly described in literature. A simple methyl group is rapidly metabolized, while the fully deuterated analog displayed a slowed-down degradation. Future optimizations should focus on either a sterically demanding residue to block this position to hinder the degradation. The second identified metabolic weakness was located within the bicycle. Careful examination of the fragmentation patterns allowed the localization at C4, the carbon at the bridge next to the amide-nitrogen. This position might be considered the second *N*-alkyl residue and therefore prone to oxidation. Additionally, ring tension might be an issue. From the gathered data, it is not clear, whether stereospecific position at C4 is affected, but it is assumed that the metabolic attack happens from the top of the molecule, since it is less sterically shielded. A tricyclic derivative with a bridge from the amide to the top site of C4 was synthesized, to avoid metabolic degradation at this position, however, this compound was also rapidly metabolized. Presumably, the metabolic degradation happens via N-dealkylation, but it is not clear if the modification blocked one pathway or even created a new metabolic weakness.
It is noteworthy, that no further metabolic soft spot was detected to a significant extent, including hydrolysis of the sulfonamide and degradation at the two bridgehead carbons.

The second part was dedicated to a preliminary finding, that a single methyl group in *N*-α-position either boosted (for the *S*-isomer) or decreased (for the *R*-isomer) binding affinity to FKBPs by one order of magnitude. 5 series of compounds with methylated analogs were synthesized and verified the observed finding. To elucidate the origin of the effect, a molecular modelling study was performed with one series. The hypothesis was, that the methyl group induces a steric hindrance regarding rotation of the *N*-residue, and therefore causes a pre-organization of the molecule in either a favorable (for the *S*-isomer) or unfavorable (for the *R*-isomer) conformation for binding. Energy maps for all three compounds with variation of the two dihedral angles which define the *N*-residue were created. These maps demonstrate, that the preferred conformation of the *R*-isomer is incompatible with binding, while the preferred conformation of the *S*-isomer is close to the binding mode. While these findings clarify the decreased binding affinity of the *R*-isomer, the increase in binding affinity for the *S*-isomer cannot be fully explained. Although the *S*-isomer roughly occupies half the conformations compared to the not methylated analogs, this does not explain the observed boost by one order of magnitude. It is likely, that an additional effect, besides the pre-organized conformation, is responsible for the improved binding affinity.

The third part was dedicated to the benzothiazolone moiety. A preliminary finding, that this particular residue displays sub-nanomolar binding to FKBP12 and selectivity to other FKBPs by three orders of magnitude, was further investigated. 21 variations of this scaffold were synthesized and tested for their binding affinity to various FKBPs. In general, all tested derivatives with a modified benzothiazolone moiety displayed decreased binding affinity to FKBP12. Any modification of the N-H position causes a drop in binding affinity to FKBP12 by three orders of magnitude, demonstrating the importance of this hydrogen donor. Substitution of the sulfur by oxygen doesn't affect the binding affinity, while substitution by nitrogen or the $C(CH_3)_2$ group decreases binding affinity to FKBP12 by three orders of magnitude. All other tested derivatives caused a drop in affinity by one or two orders of magnitude. This unique behavior was remarkable, and therefore the FP-assays were conducted with different constructs of FKBP12. When testing these compounds with a His-tag free version of FKBP12, the observed boost in affinity for FKBP12 was not observed anymore. Interestingly, the difference in binding affinity for FKBP12 with parts of the His-tag still attached compared to the His-tag free FKBP12, is only observed for derivatives with the free N-H moiety, while all other derivatives display no significant difference in binding affinity for the two protein versions. It appears, that the observed boost in binding affinity is either a His-tag artefact or a complex His-tag mediated effect. If the latter is true, the understanding of the origin of this effect might be utilized in the future to synthesize compounds, which are able to evoke the boost in affinity without mediation by the His-tag.

The fourth part was dedicated to a small library of bicyclic [4.3.1] aza-amides with aryl rings at the terminal alkene derived from Heck reaction. Examination of crystal structures of the bicyclic scaffold revealed a vast space in the binding pocket next to the vinyl group. A focused library with different functional groups in different positions of the aryl ring were synthesized in order to find novel interactions within the binding pocket. A simple benzene ring in this position did not affect binding affinity to any FKBP, thus verifying that an aryl ring in this position doesn't cause a steric clash. The most interesting functional group was a nitrile group in para-position, which boosted the binding affinity by two orders of magnitude. By examination of the crystal structure, it was hypothesized that the nitrile group acts as a hydrogen acceptor for Arg73, thus resulting in improved binding. Further modifications, either by a CF_3 group in meta-position or by dihydroxylation of the alkene caused a drop in binding affinity, although these derivatives are still better binder than the respective vinyl derivative without an aryl ring. A crystal structure of this compound will give further insights and a starting point for future optimizations of this scaffold.

The fifth and last part summarized additional synthesized bicyclic [4.3.1] aza-amides. Three derivatives of the sulfonamide with a 3,5-dichlorobenzene residue were synthesized, one with an additional fluor in position 4, one with a chlorine substituted by nitrile and one with 3-chloropyridine. Additionally, a small series of sulfondiamides and a derivative with an additional hydroxy group in position 5 to enable further modifications were synthesized. All of the above-mentioned derivatives displayed 2-100 times poorer binding affinity to the tested FKBPs and are therefore not considered as valuable starting points for future optimizations.

Taken together, this work has enabled a better understanding of the bicyclic [4.3.1] aza-amide scaffold, more precisely, its metabolic soft spots and its residues mandatory for improved binding affinity. It will serve as a guideline for further improvements on metabolic stability and binding affinity and as a starting point for the still pending issue of the selectivity of these compounds regarding different FKBPs.

5. Experimental Part

5.1. General

In general, reactions were performed in round bottom flasks. Air and/or water sensitive reactions were performed under argon atmosphere.

Purchased reagents from commercial sources were used directly without further purification.

The removal of solvents under reduced pressure was conducted at 40 °C, if not stated otherwise.

5.1.1. Nuclear Magnetic Resonance (NMR)

NMR measurements were performed by the NMR department of TU Darmstadt. Spectra were recorded on a 300 MHz Avance III NMR spectrometer or a 500 Mhz NMR spectrometer DRX 500, both from Bruker BioSpin GmbH. Chemical shifts are given in parts per million, referenced to the residual solvent peak. Coupling constants are given in Hertz and peak multiplicities are assigned as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), doublet of doublets (dd), doublet of triplets (dt), triplet of doublets (td) or multiplet (m).

5.1.2. Mass Spectrometry (MS) and High Resolution Mass Spectrometry (HRMS)

Mass measurements were performed on a LC-MS system with a Beckman Coulter System Gold solvent module, Beckman Coulter System Gold 508 autosampler, Beckman Coulter System 166 Detector and a Thermo Finnigan LCQ Deca XP Plus. Eluents were 0.1% formic acid (Eluent A) in water and 0.1% formic acid in acetonitrile (Eluent B). The usual method was 5 – 95% B in 19 minutes.

HR-MS measurements were conducted by the MS department of TU Darmstadt. Spectra were recorded on an Impact II, quadrupole-time-of-flight spectrometer from Bruker Daltonics.

5.1.3. High-Performance Liquid Chromatography (HPLC)

Analytical HPLC was conducted with a Dionex P580 pump, Dionex ASI-100 automated sample injector and Dionex UCD 340U Photodiode Array Detector. The column was a Phemomenex Kinetex 5 μm C18 100 Å, 250 x 4.6 mm. Eluents were 0.1% TFA (Eluent A) in water and 0.1% TFA in acetonitrile (Eluent B). The measurement time was 20 minutes with a gradient from 0 – 100% Eluent B. If not stated otherwise, the flowrate was 1.5 ml min^{-1}.

5.1.4. Semi-Preparative HPLC

Reverse-phase purifications were performed with a Beckman System Gold 126 NMP Programmable Solvent Module and Beckman System Gold 166 Programmable Detector Module. The column was a Phenomenex Jupiter 4μ Proteo 90Å, 250 * 10 mm, 4 micron. Eluents were 0.1% TFA (Eluent A) in water and 0.1% TFA in acetonitrile (Eluent B).

5.1.5. Column Chromatography

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

5.1.6. Thin Layer Chromatography (TLC)

Thin layer chromatography (TLC) was performed using TLC plates from Merck (TLC Silica gel 60 F_{254}). Substances were detected by UV (λ = 254/366 nm) and by using the following stains:

Ninhydrin
1.5 g ninhydrin in 100 ml of ethanol (abs.) and 3.0 ml acetic acid

Potassium Permanganate
1.5 g of $KMnO_4$, 10 g K_2CO_3 and 1.25 ml 10% NaOH in 200 ml water (dest.)

Phosphomolybdic Acid (PMA)
10 g of phosphomolybdic acid in 100 ml ethanol (abs.)

Cerium Molybdate (Hanessian's stain)
5 g ammonium molybdate, 1 g ceric sulfate and 10 ml concentrated sulfuric acid in 90 ml water (dest.)

5.1.7. Lyophilization

All compounds were subjected to lyophilization before measurement of HRMS and NMRs, HPLCs and before preparation of DMSO stocks. Therefore, the compounds were dissolved in acetonitrile to water ratio of 2 to 1. The solution was frozen in liquid nitrogen and solvents were removed under reduced pressure.

5.1.8. Determination of Purity

Purity of final compounds was determined by reversed phase HPLC and was > 95%. For all intermediates (which were not tested in an FP-assay or by ITC) purity was determined by ^{1}H-NMR.

5.1.9. Metabolic Stability Studies

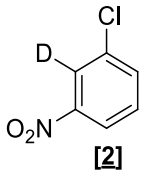
Metabolic stability studies were conducted by the external service provider Pharmacelsus. Test items were incubated with liver microsomal fractions (0.25 mg/ml) from mice (CD-1, male) in 96-deep-well-plates.
Incubation medium: phosphate buffer, pH 7.4, NADPH
Test concentration: 1 μM
Positive control: verapamil (1 μM)
Negative control: liver microsomes without NADPH
Replicates: 2
Analysis: HPLC-HRMS (Q-Orbitrap, positive and/or negative mode) and MS/HRMS fragmentation

5.1.10. Molecular Modelling

All calculation experiments were performed on the Lichtenberg cluster of TU Darmstadt utilizing ORCA. Geometry optimizations were performed using the BP functional utilizing the resolution of the identity (RI) approximation. The employed basis set was the valence triple-zeta basis set def2-TZVP of the Karlsruhe group. The applied auxiliary basis set for coulomb fitting was def2/j. CPCM (water) was used as conductor-like polarizable continuum model with water as solvent. SlowConv was used as convergence strategy and the threshold was set to TIGHTSCF. An increased grid size (GRID6) was utilized and final grid was turned off (nofinalgrid). Frequency calculations were performed at the same level of theory as the geometry optimizations to afford thermodynamic corrections. Selected conformations were calculated with the double hybrid basis set B2PLYP. Gibbs-free energies discussed in this thesis are based on thermodynamic corrections and substitution of the electronic energies by B2PLYP electronic energies.

5.2. Synthesis

5.2.1. Compound [2]: (2-2H)-1-chloro-3-nitrobenzene



[2]

2-bromo-1-chloro-3-nitrobenzene **[1]** (1.0 g, 4.23 mmol, 1 eq.), sodium formate-d (583 mg, 8.46 mmol, 2.0 eq., 99 atom% D), $Pd_2(dba)_3$ (77 mg, 0.09 mmol, 0.02 eq.) and $P(Cy)_3$ (71 mg, 0.25 mmol, 0.06 eq.) were dissolved in DMSO (10 ml) and stirred at 80 °C for 3 h. The mixture was diluted with DCM (100 ml) and washed with brine (2 x 50 ml). Solvents were removed under reduced pressure and the crude product was purified by column chromatography (25 g silica; cycH/EA = 50:1) to afford the title compound as slightly yellow liquid.

Yield: 84% (560 mg, 3.55 mmol)

Appearance: slightly yellow liquid

TLC: R_f = 0.20 (cycH/EA = 50:1; UV)

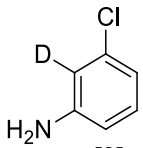
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52 (t, *J* = 8.1 Hz, 1H), 7.70 (dd, *J* = 8.0, 1.0 Hz, 1H), 8.14 (dd, *J* = 8.2, 1.1 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 121.7, 123.6, 130.3, 134.7, 135.3, 148.7.

Mass (EI): $[M^{+\bullet}]$ = 158

Lab book number(s): JK394

5.2.2. Compound [3]: (2-^{2}H)-3-chloroaniline



[3]

Compound **[2]** (560 mg, 3.53 mmol, 1 eq.) was dissolved in EtOH (100 ml). Sat. aq. NH_4Cl (4.0 ml, 28.25 mmol, 8 eq.) and Zn (1.85 g, 28.25 mmol, 8 eq.) were added and the mixture was stirred at rt for 16 h. The mixture was filtered over diatomaceous earth and solvents were removed under reduced pressure. The crude product was purified by column chromatography (50 g silica; cycH/EA = 9:1 → 4:1).

Yield: 66% (296 mg, 2.33 mmol)

Appearance: slightly yellow liquid

TLC: R_f = 0.34 (cycH/EA = 4:1; UV)

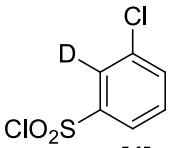
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.73 (s, 2H), 6.56 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.74 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.07 (t, *J* = 8.0 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 113.2, 114.6, 118.4, 130.3, 134.8, 147.6.

Mass (EI): $[M^{+\cdot}]$ = 128

Lab book number(s): JK398

5.2.3. Compound [4]: (2-^{2}H)-3-chlorobenzene-1-sulfonyl chloride



[4]

Compound **[3]** (296 mg, 2.30 mmol, 1 eq.) was dissolved in MeCN (70 ml). HCl (1.0 ml, 37%) was added and the mixture was cooled to 0 °C with an ice bath. $NaNO_2$ (190 mg, 2.76 mmol, 1.2 eq.) was added and the mixture was stirred for 15 min. A mixture of SO_2Cl in H_2O [SO_2Cl (13 ml, 179 mmol, 78 eq.) in H_2O (26 ml, 1444 mmol, 627 eq.)] was added and the mixture was stirred for 15 min. $CuCl_2$ (155 mg, 1.15 mmol, 0.5 eq.) was added, the ice bath was removed and the mixture was stirred for 16 h at rt. The mixture was diluted with EA (150 ml) and washed with brine (50 ml). Solvents were removed under reduced pressure and the residue was dissolved in cycH. Filtration over silica (1 g) afforded the title compound as slightly yellow liquid.

Yield: 86% (420 mg, 1.98 mmol)

Appearance: slightly yellow liquid

TLC: R_f = 0.48 (cycH/EA = 5:1; UV)

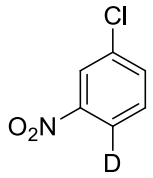
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (t, *J* = 8.0 Hz, 1H), 7.74 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.96 (dd, *J* = 7.9, 1.1 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 125.0, 127.0, 130.9, 135.4, 135.8, 145.4.

Mass (EI): $[M^{+\cdot}]$ = 211

Lab book number(s): JK400

5.2.4. Compound [6]: (4-^{2}H)-1-chloro-3-nitrobenzene



[6]

1-bromo-4-chloro-2-nitrobenzene **[5]** (1.55 g, 6.61 mmol, 1 eq.), sodium formate-d (912 mg, 13.22 mmol, 2.0 eq., 99 atom% D), $Pd_2(dba)_3$ (121 mg, 0.13 mmol, 0.02 eq.) and $P(Cy)_3$ (111 mg, 0.40 mmol, 0.06 eq.) were dissolved in DMSO (10 ml) and stirred at 80 °C for 3 h. The mixture was diluted with DCM (100 ml) and washed with brine (2 x 50 ml). Solvents were removed under reduced pressure and the crude product was purified by column chromatography (8 g silica; cycH) to afford the title compound as slightly yellow liquid.

Yield: 95% (1.0 g, 6.28 mmol)

Appearance: slightly yellow liquid

TLC: R_f = 0.10 (cycH; UV)

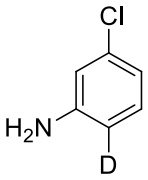
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 (m, 1H), 7.61 – 7.78 (m, 1H), 8.23 (t, *J* = 2.0 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 121.4, 123.8, 130.3, 134.7, 135.4, 148.7.

Mass (EI): $[M^{+\cdot}]$ = 158

Lab book number(s): JK390, JK391, JK392, JK393

5.2.5. Compound [7]: (6-^{2}H)-3-chloroaniline



[7]

Compound **[6]** (1.0 g, 6.31 mmol, 1 eq.) was dissolved in EtOH (100 ml). Sat. aq. NH_4Cl (7.2 ml, 50.45 mmol, 8 eq.) and Zn (3.30 g, 50.45 mmol, 8 eq.) were added and the mixture was stirred at rt for 16 h. The mixture was filtered over diatomaceous earth and solvents were removed under reduced pressure. The crude product was purified by column chromatography (90 g silica; cycH/EA = 9:1 ⟶ 4:1).

Yield: 57% (456 mg, 3.60 mmol)

Appearance: slightly yellow liquid

TLC: R_f = 0.34 (cycH/EA = 4:1; UV)

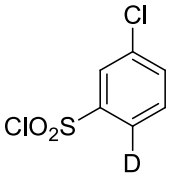
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.73 (s, 2H), 6.60 – 6.83 (m, 2H), 7.07 (dt, *J* = 7.9, 1.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 112.9, 114.9, 118.4, 130.2, 134.8, 147.6.

Mass (EI): $[M^{+\bullet}]$ = 128

Lab book number(s): JK397

5.2.6. Compound [8]: (6-^{2}H)-3-chlorobenzene-1-sulfonyl chloride



[8]

Compound **[7]** (456 mg, 3.55 mmol, 1 eq.) was dissolved in MeCN (70 ml). HCl (1.5 ml, 37%) was added and the mixture was cooled to 0 °C with an ice bath. $NaNO_2$ (293 mg, 4.26 mmol, 1.2 eq.) was added and the mixture stirred for 15 min. A mixture of SO_2Cl in H_2O [SO_2Cl (20 ml, 275 mmol, 77 eq.) in H_2O (40 ml, 2222 mmol, 626 eq.)] was added and the mixture was stirred for 15 min. $CuCl_2$ (238 mg, 1.77 mmol, 0.5 eq.) was added, the ice bath was removed and the mixture was stirred for 16 h at rt. The mixture was diluted with EA (150 ml) and washed with brine (50 ml). Solvents were removed under reduced pressure and the residue was dissolved in cycH. Filtration over silica (1 g) afforded the title compound as slightly orange liquid.

Yield: 99% (750 mg, 3.51 mmol)

Appearance: slightly orange liquid

TLC: R_f = 0.48 (cycH/EA = 5:1; UV)

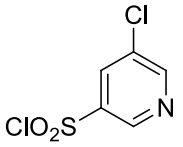
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.1 Hz, 1H), 7.74 (dd, *J* = 8.1, 2.0 Hz, 1H), 8.05 (d, *J* = 2.0 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 124.8, 127.0, 130.8, 135.4, 135.9, 145.4.

Mass (EI): $[M^{+\cdot}]$ = 211

Lab book number(s): JK399

5.2.7. Compound [10]: 5-cyanopyridine-3-sulfonyl chloride



[10]

3-Amino-5-chloropyridine (100 mg, 0.78 mmol, 1 eq.) was dissolved in MeCN (50 ml). HCl (2.0 ml, 37%) was added and the mixture was cooled to 0 °C with an ice bath. $NaNO_2$ (64 mg, 0.93 mmol, 1.2 eq.) was added and the mixture stirred for 15 min. A mixture of SO_2Cl in H_2O [SO_2Cl (3 ml, 41 mmol, 53 eq.) in H_2O (6 ml, 333 mmol, 428 eq.)] was added and the mixture was stirred for 15 min. $CuCl_2$ (52 mg, 0.39 mmol, 0.5 eq.) was added, the ice bath was removed and the mixture was stirred for 16 h at rt. The mixture was diluted with EA (150 ml) and washed with brine (50 ml). Solvents were removed under reduced pressure and the residue was dissolved in cycH. Filtration over silica (1 g) afforded the title compound as orange solids.

Yield: 30% (50 mg, 0.24 mmol)

Appearance: orange solids

TLC: R_f = 0.44 (cycH/EA = 5:1; UV)

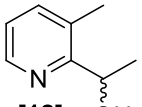
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22 (t, *J* = 2.2 Hz, 1H), 8.85 (d, *J* = 2.2 Hz, 1H), 9.06 (d, *J* = 2.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 134.0, 135.6, 145.1, 146.7, 154.6.

Mass (ESI): $[M + H]^+$ = 211.93

Lab book number(s): JK253

5.2.8. Compound [12]: 1-(3-methylpyridin-2-yl)ethanol



[12]

1-(3-methylpyridin-2-yl)ethanone **[11]** (530 mg, 3.92 mmol, 1 eq.) was dissolved in EtOH (50 ml) and cooled to 0 °C with an ice-bath. $CeCl_3$ (97 mg, 0.39 mmol, 0.1 eq.) and $NaBH_4$ (222 mg, 5.88 mmol, 1.5 eq.) were added successively and the mixture was stirred for 30 min at 0 °C. The mixture was quenched with sat. aq. $NaHCO_3$ (10 ml) and extracted with EA (2 x 50 ml). The organic phase was washed with brine (20 ml), dried over $MgSO_4$ and solvents were removed under reduced pressure. The product was obtained as slightly yellow liquid and was used in the next step without further purification. No impurities were detectable in the ^1H and ^{13}C NMR.

Yield: 37% (200 mg, 1.45 mmol)

Appearance: slightly yellow liquid

TLC: R_f = 0.33 (cycH/EA = 1:1; UV)

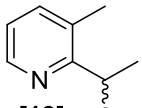
^1H NMR (300 MHz, $CDCl_3$): δ = 1.40 (d, *J* = 6.4 Hz, 3H), 2.29 (d, *J* = 0.7 Hz, 3H), 4.84 (s, 1H), 4.97 (q, *J* = 6.4 Hz, 1H), 7.12 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.45 (m, 1H), 8.38 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.5, 23.6, 66.0, 122.2, 128.9, 138.3, 145.5, 160.7.

Mass (ESI): $[M + H]^+$ = 138

Lab book number(s): JK401

5.2.9. Compound [13]: 2-(1-chloroethyl)-3-methylpyridine



[13]

Compound **[12]** (200 mg, 1.46 mmol, 1 eq.) was dissolved in DCM (10 ml) and cooled to 0 °C with an ice-bath. $SOCl_2$ (212 μl, 2.92 mmol, 2.0 eq.) was added and the mixture was stirred for 2 h at 0 °C. The mixture was basified with 1 M NaOH (30 ml) and extracted with DCM (2 x 40 ml). The organic phase was washed with brine (20 ml), dried over $MgSO_4$ and solvents were removed under reduced pressure. The product was obtained as colorless liquid and was used in the next step without further purification. No impurities were detectable in the ^{1}H and ^{13}C NMR.

Yield: 81% (183 mg, 1.18 mmol)

Appearance: colorless liquid

TLC: R_f = 0.73 (cycH/EA = 1:1; UV)

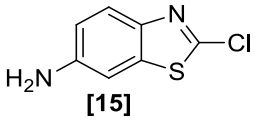
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.86 – 2.10 (m, 3H), 2.45 (s, 3H), 5.36 (q, *J* = 6.7 Hz, 1H), 7.16 (dd, *J* = 7.7, 4.7 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 8.49 (d, *J* = 4.7 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2, 22.7, 55.0, 123.2, 131.0, 138.5, 147.0, 157.4.

Mass (ESI): $[M + H]^+$ = 156

Lab book number(s): JK406

5.2.10. Compound [15]: 2-chlorobenzo[d]thiazol-6-amine



[15]

2-chloro-6-nitrobenzo[d]thiazole **[14]** (430 mg, 2.00 mmol, 1 eq.) was dissolved in EtOH (150 ml). Sat. aq. NH_4Cl (2.9 ml, 20 mmol, 10 eq.) and Zn (1.30 g, 20 mmol, 10 eq.) were added and the mixture was stirred at rt for 16 h. The mixture was filtered over silica and solvents were removed. The residue was dissolved in EA (100 ml) and washed with brine (50 ml). Solvents were removed under reduced pressure and the crude product was purified by column chromatography (40 g silica; cycH/EA = 2:1).

Yield: 81% (301 mg, 1.62 mmol)

Appearance: yellow solids

TLC: R_f = 0.35 (cycH/EA = 2:1; UV)

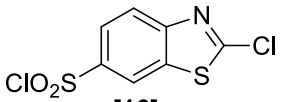
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 2H), 6.80 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.98 (dd, *J* = 2.4, 0.4 Hz, 1H), 7.69 (dd, *J* = 8.7, 0.4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 105.1, 115.7, 123.4, 137.8, 144.1, 144.9.

Mass (ESI): $[M + H]^+$ = 185.25

Lab book number(s): JK165, JK168

5.2.11. Compound [16]: 2-chlorobenzo[d]thiazole-6-sulfonyl chloride



[16]

Compound **[15]** (300 mg, 1.62 mmol, 1 eq.) was dissolved in MeCN (50 ml). HCl (2.0 ml, 37%) was added and the mixture was cooled to 0 °C with an ice bath. $NaNO_2$ (134 mg, 1.95 mmol, 1.2 eq.) was added and the mixture stirred for 15 min. A mixture of SO_2Cl in H_2O [SO_2Cl (9 ml, 124 mmol, 76 eq.) in H_2O (18 ml, 1000 mmol, 615 eq.)] was added and the mixture was stirred for 15 min. $CuCl_2$ (109 mg, 0.81 mmol, 0.5 eq.) was added, the ice bath was removed and the mixture was stirred for 2 h at rt. The mixture was diluted with EA (150 ml) and washed with brine (50 ml). Solvents were removed under reduced pressure and the residue was dissolved in cycH. Filtration over silica (1 g) afforded the title compound as yellow solids.

Yield: 49% (214 mg, 0.79 mmol)

Appearance: yellow solids

TLC: R_f = 0.85 (EA; UV)

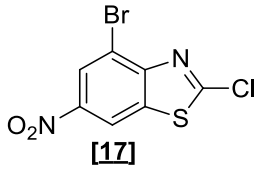
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.76 (d, *J* = 2.1 Hz, 1H), 7.86 (d, *J* = 8.7 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 120.8, 123.7, 127.6, 131.9, 137.2, 149.6, 153.6.

Mass (EI): $[M^{+\cdot}]$ = 267

Lab book number(s): JK166, JK171

5.2.12. Compound [17]: 4-Bromo-2-chloro-6-nitrobenzothiazole



[17]

2-chloro-6-nitrobenzo[d]thiazole **[14]** (900 mg, 4.19 mmol, 1 eq.) was dissolved in H_2SO_4 (20 ml) and NBS (1120 mg, 6.29 mmol, 1.5 eq.) was added. The mixture was heated to 60 °C and kept at this temperature for 16 h. The reaction was cooled to 0 °C and quenched with aq. Sat. $NaHCO_3$. Solids precipitated and were filtered off and washed with water. Column chromatography (100 g silica; DCM/cycH = 1:1) afforded the title compound as yellow solids.

Yield: 59% (535 mg, 2.47 mmol)

Appearance: yellow solids

TLC: R_f = 0.58 (cycH/EA = 3:1; UV)

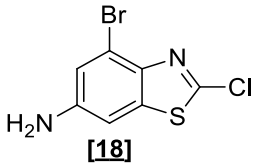
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.58 (d, *J* = 2.1 Hz, 1H), 8.68 (d, *J* = 2.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 116.5, 116.8, 125.6, 136.5, 145.4, 153.2, 159.4.

Mass (EI): $[M^{+\cdot}]$ = 294

Lab book number(s): JK125, JK127, JK133, JK140

5.2.13. Compound [18]: 4-bromo-2-chlorobenzo[d]thiazol-6-amine



[18]

Compound **[17]** (270 mg, 1.26 mmol, 1 eq.) was dissolved in EtOH (120 ml). Sat. aq. NH_4Cl (1.8 ml, 12.58 mmol, 10 eq.) and Zn (822 mg, 12.58 mmol, 10 eq.) were added and the mixture was stirred at rt for 16 h. The mixture was filtered over silica and solvents were removed. The residue was dissolved in EA (100 ml) and washed with brine (40 ml). Solvents were removed and the crude product was used in the next step without further purification.

Yield: 95% (230 mg, 1.20 mmol)

Appearance: yellow solids

TLC: R_f = 0.54 (cycH/EA = 1:1; UV)

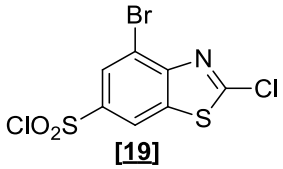
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.41 – 4.31 (m, 2H), 6.91 (d, *J* = 2.2 Hz, 1H), 7.03 (d, *J* = 2.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 104.3, 116.4, 118.7, 138.2, 142.5, 145.6, 149.1.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_7H_4BrClN_2S$ 262.9040; Found 262.9042

Lab book number(s): JK134, JK142, JK144, JK145, JK148

5.2.14. Compound [19]: 4-bromo-2-chlorobenzo[d]thiazole-6-sulfonyl chloride



[19]

Compound **[18]** (230 mg, 0.87 mmol, 1 eq.) was dissolved in MeCN (25 ml). HCl (1.2 ml, 37%) was added and the mixture was cooled to 0 °C with an ice bath. $NaNO_2$ (79 mg, 1.15 mmol, 1.3 eq.) was added and the mixture stirred for 15 min. A mixture of SO_2Cl in H_2O [SO_2Cl (7 ml, 96 mmol, 110 eq.) in H_2O (14 ml, 777 mmol, 893 eq.)] was added and the mixture was stirred for 15 min. $CuCl_2$ (64 mg, 0.47 mmol, 0.5 eq.) was added, the ice bath was removed and the mixture was stirred for 6 h at rt. The mixture was diluted with EA (100 ml) and washed with brine (40 ml). Solvents were removed under reduced pressure and the residue was dissolved in cycH. Filtration over silica (1 g) afforded the title compound as yellow solids.

Yield: 83% (250 mg, 0.72 mmol)

Appearance: yellow solids

TLC: R_f = 0.79 (cycH/EA = 3:1; UV)

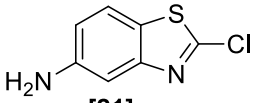
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 1.4 Hz, 1H), 8.46 (d, *J* = 1.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 117.7, 120.1, 128.1, 136.8, 141.8, 153.4, 160.1.

Mass (EI): $[M^{+\cdot}]$ = 347

Lab book number(s): JK149, JK151

5.2.15. Compound [21]: 2-chlorobenzo[d]thiazol-5-amine



[21]

2-chlorobenzo[d]thiazole-5-sulfonyl chloride **[20]** (210 mg, 0.98 mmol, 1 eq.) was dissolved in EtOH (100 ml). Sat. aq. NH_4Cl (1.1 ml, 7.83 mmol, 8 eq.) and Zn (511 mg, 7.83 mmol, 8 eq.) were added and the mixture was stirred at rt for 16 h. The mixture was filtered over silica and solvents were removed. The residue was dissolved in EA (100 ml) and washed with brine (50 ml). Solvents were removed at reduced pressure and the crude product was purified by column chromatography (20 g silica; cycH/EA = 1:2).

Yield: 61% (110 mg, 0.60 mmol)

Appearance: yellow solids

TLC: R_f = 0.29 (cycH/EA = 1:2; UV)

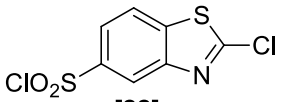
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.84 (s, 2H), 6.80 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.22 (d, *J* = 2.3 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 107.8, 115.3, 121.4, 125.6, 145.9, 152.4, 153.7.

Mass (ESI): $[M + H]^+$ = 185.25

Lab book number(s): JK173

5.2.16. Compound [22]: 2-Chlorobenzo[d]thiazole-5-sulfonyl chloride



[22]

Compound **[21]** (100 mg, 0.54 mmol, 1 eq.) was dissolved in MeCN (25 ml). HCl (0.5 ml, 37%) was added and the mixture was cooled to 0 °C with an ice bath. $NaNO_2$ (45 mg, 0.65 mmol, 1.2 eq.) was added and the mixture stirred for 15 min. A mixture of SO_2Cl in H_2O [SO_2Cl (4 ml, 55 mmol, 101 eq.) in H_2O (8 ml, 444 mmol, 820 eq.)] was added and the mixture was stirred for 15 min. $CuCl_2$ (36 mg, 0.27 mmol, 0.5 eq.) was added, the ice bath was removed and the mixture was stirred for 16 h at rt. The mixture was diluted with EA (100 ml) and washed with brine (50 ml). Solvents were removed under reduced pressure and the residue was dissolved in cycH. Filtration over silica (1 g) afforded the title compound as yellow solids.

Yield: 92% (133 mg, 0.50 mmol)

Appearance: yellow solids

TLC: R_f = 0.58 (cycH/EA = 3:1; UV)

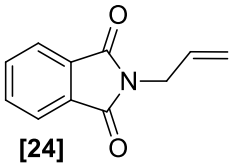
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.04 (dd, *J* = 8.6, 0.6 Hz, 1H), 8.08 (dd, *J* = 8.6, 1.9 Hz, 1H), 8.62 (dd, *J* = 1.9, 0.6 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 122.0, 122.6, 123.1, 143.1, 143.2, 150.6, 157.2.

Mass (ESI): $[M + H]^+$ = 267.91

Lab book number(s): JK175

5.2.17. Compound [24]: 2-Allylisoindoline-1,3-dione



[24]

Phthalimide **[23]** (60.0 g, 408 mmol, 1 eq.) and potassium carbonate (73.3 g, 530 mmol, 1.3 eq.) were dissolved in DMF (400 ml) in a 1000 ml flask. After stirring for 15 min allylbromide (45.9 ml, 530 mmol, 1.3 eq.) was added over 15 min and the reaction mixture was stirred at rt for 5 h. The reaction mixture was diluted with Et_2O (1000 ml) and filtered through a glass frit. The filtrate was washed with brine (3 x 300 ml) dried over $MgSO_4$ and solvents were removed under reduced pressure.

Yield: 99% (75.09 g, 404 mmol)

Appearance: white solids

TLC: R_f = 0.42 (cycH/EA = 4:1; UV)

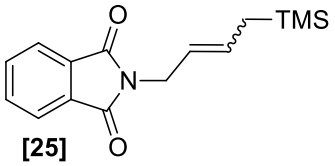
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.29 (dt, J = 5.7, 1.5 Hz, 2H), 5.16 – 5.28 (m, 2H), 5.82 – 5.94 (m, 1H), 7.68 – 7.74 (m, 2H), 7.82 – 7.88 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 40.0, 117.7, 123.3 (2C), 131.5, 132.0, 133.9 (2C), 167.9.

Mass (ESI): $[M + H]^+$ = 188.05

Lab book number(s): JK008

5.2.18. Compound [25]: 2-(4-(trimethylsilyl)but-2-en1-yl)isoindoline-1,3-dione



[25]

Compound **[24]** (28.5 g, 152.25 mmol, 1 eq.) and allyltrimethylsilane (174.0g, 1523 mmol, 10 eq.) were dissolved in DCM (1500 ml). Grubbs I catalyst (11.5 g, 13.7 mmol, 9% loading) was added and the mixture refluxed for 5 h (60 °C, oil bath). Tris(hydroxymethyl) phosphine (152 ml, 152 mmol, 1 eq., 1 M solution in *i*-PrOH) was added and the mixture refluxed for 12 h. Washing with brine (1 x 1000 ml), drying over $MgSO_4$ and removing solvents under reduced pressure resulted in an orange oil. Column chromatography (800 g SiO_2, cycH/EA = 19:1) afforded the title compound as pale-yellow oil which solidified at 4 °C resulting in white solids.

Yield: 81% (33.71 g, 123.32 mmol)

Appearance: white solids

TLC: R_f = 0.60 (cycH/EA = 4:1; UV)

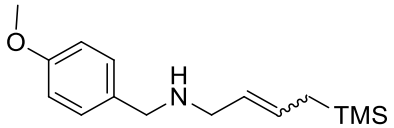
^{1}H-NMR (300 MHz, $CDCl_3$): δ = -0.03 (s, 7H), 0.04 (s, 2H), 1.44 (d, *J* = 8.5 Hz, 1.6H), 1.73 (d, *J* = 8.5 Hz, 0.4H), 4.21 (d, *J* = 6.6 Hz, 1.6H), 4.27 (d, *J* = 6.6 Hz, 0.4H), 5.29 – 5.44 (m, 1H), 5.59 – 5.68 (m, 0.2H), 5.72 – 5.84 (m, 0.8H), 7.66 – 7.72 (m, 2H), 7.80 – 7.86 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = -2.0, 19.0, 22.8, 27.0, 34.8, 39.9, 120.5, 121.3, 123.2, 130.8, 132.3, 133.8, 168.0.

Mass (ESI): $[M + H]^+$ = 274.13

Lab book number(s): JK018

5.2.19. Compound [26]: *N*-(4-Methoxybenzyl)-4-(trimethylsilyl)but-2-en-1-amine



[26]

Compound **[25]** (20.0 g, 73.15 mmol, 1 eq.) was dissolved in MeOH (350 ml) and hydrazine (7 ml, 146.3 mmol, 2 eq., 50-60% solution) was added. The mixture was refluxed for 18 h. 1 M NaOH (200 ml) and DCM (200 ml) were added and the organic phase was separated. The aqueous phase was extracted with DCM (2 x 200 ml). Both organic phases were combined, dried over $MgSO_4$ and solvents were removed under reduced pressure (700 mbar, 40 °C). The residue was diluted with EtOH (125 ml) and 4-methoxybenzaldehyde (9.3 ml, 76.8 mmol, 1.05 eq.) was added. The mixture was stirred at rt for 2 h. After adding $NaBH_4$ (3.32 g, 76.8 mmol, 1.2 eq.) stirring was continued until no more gas formation was observed (2 h). Sat. aq. $NaHCO_3$ (150 ml) was added carefully and the mixture was extracted with DCM (3 x 200 ml). The combined organic phases were dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (640 g SiO_2, EA + 3% TEA) afforded the title compound as pale-yellow oil.

Yield: 88% (16.96 g, 64.37 mmol, over 2 steps)

Appearance: pale-yellow oil

TLC: R_f = 0.33 (EA + 3% TEA; UV, ninhydrin)

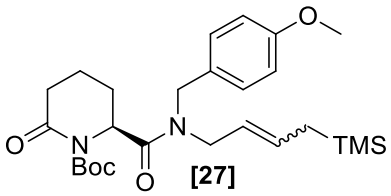
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 9H), 1.38 (s, 1H), 1.42 – 1.52 (m, 2H), 3.16 – 3.26 (m, 2H), 3.69 – 3.74 (m, 2H), 3.79 (s, 3H), 5.30 – 5.47 (m, 1H), 5.48 – 5.65 (m, 1H), 6.82 – 6.89 (m, 2H), 7.20 - 7.27 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = -2.0, 19.0, 22.7, 45.6, 51.3, 52.5, 53.0, 55.2, 113.7, 125.6, 126.8, 128.0, 129.1, 129.3, 132.6, 158.5.

Mass (EI): $[M^{+\bullet}]$ = 263

Lab book number(s): JK053

5.2.20. Compound [27]: (*S*)-tert-butyl-2-[(4-methoxybenzyl)(4-(trimethylsilyl)but-2-en-1-yl) carbomyl]piperidine-1-carboxylate



[27]

HATU (8.66 g, 22.77 mmol, 1.2 eq.) and (*S*)-6-oxopiperidine-2-carboxylic acid (2.99 g, 20.9 mmol, 1.1 eq.) were placed in a flask and stirred for 10 min in DCM (200 ml). DIPEA (6.63 ml, 37.96 mmol, 2 eq.) was added and the mixture stirred for 5 min. Compound **[26]** (5.0 g, 18.98 mmol, 1 eq.) was dissolved in DCM (20 ml) and added to the mixture which was stirred for 16 h at rt. The organic phase was washed twice with sat. aq. $NaHCO_3$ (200 ml) and solvents were removed under reduced pressure. The residue was dissolved in Et_2O (200 ml) and washed with brine (3 x 100 ml). The organic phase was dried over $MgSO_4$ and solvents were removed in vacuo. The resulting reddish oil (10.2 g) was dissolved in DCM (50 ml) and DIPEA (12 ml, 5 eq.) was added. The mixture was stirred for 15 min before Boc_2O (16.57 g, 75.92 mmol, 4 eq.) and DMAP (0.35 g, 2.85 mmol, 0.15 eq.) were added. Stirring was continued at rt for 72 h. The reaction mixture was washed with brine (2 x 200 ml), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography (390 g SiO_2, cycH/EA = 2:1 + 3% TEA → EA + 3% TEA) afforded the desired product as yellow oil.

Yield: 72% (6.68 g, 16.39 mmol, over 2 steps)

Appearance: yellow oil

TLC: R_f = 0.46 (cycH/EA = 4:1; UV, $KMnO_4$)

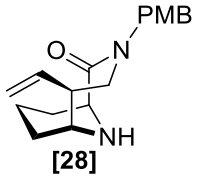
^{1}H-NMR (300 MHz, $CDCl_3$): δ = -0.01 – 0.06 (m, 9H), 1.40 – 1.55 (m, 11H), 1.65 – 1.80 (m, 1H), 1.85 – 2.07 (m, 3H), 2.35 – 2.70 (m, 2H), 3.70 – 3.95 (m, 5H), 4.95 – 5.10 (m, 1H), 5.15 – 5.40 (m, 1H), 5.45 – 5.70 (m, 1H), 6.75 – 6.95 (m, 2H), 7.10 - 7.30 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = -1.9, 18.3, 19.2, 22.9, 25.8, 26.0, 26.9, 27.8, 28.0, 34.5, 47.0, 47.5, 48.3, 48.9, 55.2, 55.6, 55.8, 83.0, 113.9, 114.2, 122.3, 122.4, 128.3, 128.4, 129.4, 129.5, 130.2, 131.6, 131.9, 153.4, 153.8, 158.9, 159.2, 170.9, 171.3.

Mass (ESI): $[M + H]^+$ = 489.28

Lab book number(s): JK059

5.2.21. Compound [28]: (1*S*,5*S*,6*R*)-3-(4-methoxybenzyl)-5-vinyl-3,10-diazabicyclo[4.3.1] decan-2-one



[28]

Compound **[27]** (6.68 g, 13.67 mmol, 1 eq.) was dissolved in THF (200 ml, dry) and the reaction mixture was cooled to -78 °C. DIBAL-H (15 ml, 15.04 mmol, 1.1 eq., 1 M in DCM) was added over 1 h after which no more starting material was detectable by TLC. The reaction was quenched with Glauber's salt and was allowed to warm to rt. Solids were filtered off over celite and the solvent was removed under reduced pressure. The resulting yellow oil (6.89 g) was dissolved in DCM (700 ml) in a fluorinated HDPE bottle and cooled to -78 °C. HF (39 ml, 1366 mmol, 100 eq., 70% in pyridine) was added and the mixture stirred for 15 min. The bottle was transferred to an ice-bath and stirred for 2 h. The reaction was quenched with sat. aq. $CaCO_3$ solution (300 ml) and 10 M NaOH (150 ml). The phases were separated and the aqueous phase was extracted with DCM (3 x 200 ml). The combined organic phases were dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (300 g SiO_2, EA + 3% TEA + 2% MeOH) afforded the desired product a yellow resin.

Yield: 18% (0.74 g, 10.12 mmol, over 2 steps)

Appearance: yellow resin

TLC: R_f = 0.19 (EA + 3% TEA + 2% MeOH; UV, ninhydrin)

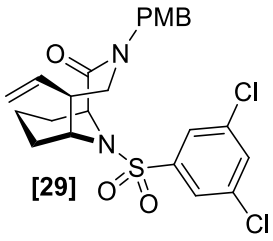
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 – 1.82 (m, 5H), 2.11 – 2.40 (m, 2H), 2.41 – 2.58 (m, 1H), 2.83 (dd, *J* = 7.4, 3.8 Hz, 1H), 2.95 (dd, *J* = 13.8, 2.0 Hz, 1H), 3.83 (s, 4H), 3.85 – 4.01 (m, 2H), 4.47 (d, *J* = 14.3 Hz, 1H), 4.71 – 4.98 (m, 3H), 5.58 (m, 1H), 6.84 – 6.93 (m, 2H), 7.21 – 7.29 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.8, 28.1, 29.4, 49.5, 50.2, 52.5, 53.0, 55.3, 57.8, 113.9, 115.1, 129.4, 129.9, 139.1, 158.9, 174.5.

Mass (ESI): $[M + H]^+$ = 301.01

Lab book number(s): JK070, JK211

5.2.22. Compound [29]: (1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-3-(4-methoxybenzyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[29]

Compound **[28]** (350 mg, 1.17 mmol, 1 eq.) was dissolved in MeCN (90 ml). 3,5-Dichlorobenzenesulfonyl chloride (568 mg, 2.33 mmol, 2 eq.) and DIPEA (670 µl, 2.33 mmol, 2 eq.) were added and the mixture was stirred for 20 h at rt. Sat. aq. $NaHCO_3$ (5 ml) was added and the mixture was extracted with EA (3 x 40 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (100 g SiO_2, cycH/EA = 4:1) afforded the title compound as colorless resin.

Yield: 43% (255 mg, 0.50 mmol)

Appearance: colorless resin

TLC: R_f = 0.29 (cycH/EA = 3:1; UV)

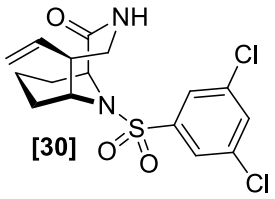
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.18 – 1.35 (m, 1H), 1.43 – 1.57 (m, 2H), 2.31 – 2.41 (m, 2H), 2.91 (dd, *J* = 14.3, 2.1 Hz, 1H), 3.80 (s, 3H), 3.90 (dd, *J* = 14.3, 10.8 Hz, 1H), 3.94 – 3.98 (m, 1H), 4.38 (d, *J* = 14.4 Hz, 1H), 4.75 (dt, *J* = 6.1, 1.9 Hz, 1H), 4.82 (d, *J* = 14.4 Hz, 1H), 4.88 (m, 1H), 5.00 (dd, *J* = 10.1, 1.1 Hz, 1H), 5.61 – 5.72 (m, 1H), 6.84 – 6.89 (m, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.55 (td, *J* = 1.9, 0.7 Hz, 1H), 7.69 (dd, *J* = 1.9, 0.7 Hz, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 14.0, 24.8, 26.1, 47.8, 49.2, 51.8, 53.3, 53.7, 55.4, 75.2, 75.5, 75.7, 112.5 (2C), 115.3, 123.3 (2C), 127.5, 127.8 (2C), 131.1, 134.8 (2C), 135.7, 142.6, 157.6, 168.5.

Mass (ESI): $[M + H]^+$ = 509.12

Lab book number(s): JK315

5.2.23. Compound [30]: (1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-5-vinyl-3,10-diazabicyclo [4.3.1]decan-2-one



[30]

Compound **[29]** (250 mg, 0.49 mmol, 1 eq.) was dissolved in MeCN/H_2O (30 ml, 21:9) and CAN (670 mg, 1.22 mmol, 2.5 eq.) was added. The mixture was stirred for 4 h at rt. Brine (20 ml) was added and the mixture was extracted with DCM (4 x 50 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (30 g SiO_2, cycH/EA = 2:3) afforded the title compound as colorless solids.

Yield: 60% (115 mg, 0.30 mmol)

Appearance: colorless resin

TLC: R_f = 0.39 (cycH/EA = 2:3; UV)

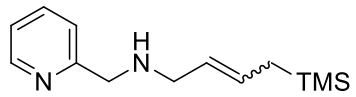
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 – 1.41 (m, 2H), 1.53 – 1.75 (m, 4H), 2.25 (d, *J* = 13.7 Hz, 1H), 2.71 (m, 1H), 2.94 (m, 1H), 3.79 (m, 1H), 4.07 (t, *J* = 5.9 Hz, 1H), 4.70 (d, *J* = 6.0 Hz, 1H), 5.02 – 5.35 (m, 2H), 5.71 – 5.94 (m, 1H), 6.62 (d, *J* = 8.2 Hz, 1H), 7.47 – 7.69 (m, 1H), 7.69 – 7.89 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 15.4, 26.5, 27.0, 45.1, 50.1, 55.5, 56.3, 117.1, 124.9, 132.8, 136.4, 137.0, 144.0, 172.9.

Mass (ESI): $[M + H]^+$ = 389.30

Lab book number(s): JK317

5.2.24. Compound [31]: *N*-(Pyridin-2-ylmethyl)-4-(trimethylsilyl)but-2-en-1-amine



[31]

Compound **[25]** (33.7 g, 123.26 mmol, 1 eq.) was dissolved in MeOH (500 ml) and hydrazine (8 ml, 255 mmol, 2 eq., 50-60% solution) was added. The mixture was refluxed for 20 h. 1 M NaOH (300 ml) and DCM (500 ml) were added and the organic phase was separated. The aqueous phase was extracted with DCM (1 x 100 ml). Both organic phases were combined, dried over $MgSO_4$ and solvents were removed under reduced pressure (700 mbar). The residue was diluted with EtOH (150 ml) and picolinaldehyde (11.8 ml, 123 mmol, 1 eq.) was added. The mixture was stirred at rt for 3 h. After adding $NaBH_4$ (7 g, 185 mmol, 1.5 eq.) stirring was continued until no more gas formation was observed (4 h). Sat. aq. $NaHCO_3$ (200 ml) was added carefully and the mixture was extracted with DCM (3 x 300 ml). The combined organic phases were dried over $MgSO_4$ and solvents were reduced under reduced pressure. Column chromatography (1000 g SiO_2, EA + 3% TEA) afforded the title compound as yellow oil.

Yield: 69% (31.20 g, 84.05 mmol, over 2 steps)

Appearance: yellow oil

TLC: R_f = 0.30 (EA + 3% TEA; UV, ninhydrin)

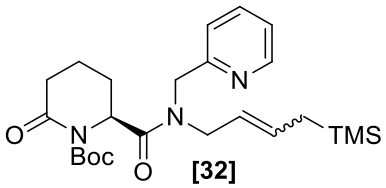
^{1}H-NMR (300 MHz, $CDCl_3$): δ = -0.04 – 0.00 (m, 9H), 1.42 – 1.48 (m, 2H), 2.32 (s, 1H), 3.20 – 3.30 (m, 2H), 3.87 – 3.91 (m, 2H), 5.34 – 5.46 (m, 1H), 5.49 – 5.62 (m, 1H), 7.11 – 7.16 (m, 1H), 7.27 – 7.32 (m, 1H), 7.58 – 7.65 (m, 1H), 8.52 – 8.55 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = -2.0, 1.0, 19.0, 22.7, 51.6, 54.2, 54.6, 121.8, 122.3, 125.2, 126.3, 128.3, 129.6, 136.4, 149.3, 159.7.

Mass (ESI): $[M + H]^+$ = 235.02

Lab book number(s): JK022, JK024

5.2.25. Compound [32]: (*S*)-tert-butyl-2-[(pyridine-2-ylmethyl)(4-(trimethylsilyl)but-2-en-1-yl)carbomyl]piperidine-1-carboxylate



[32]

Compound **[31]** (5.0 g, 21.3 mmol, 1 eq.) and (*S*)-6-oxopiperidine-2-carboxylic acid (3.05 g, 21.3 mmol, 1 eq.) were dissolved in DMF (50 ml). After stirring for 30 min at rt a mixture of EDC-HCl (4.91 g, 25.6 mmol, 1.2 eq) and HOBt (3.92 g, 25.6 mmol, 1.2 eq.) was added and the reaction mixture was stirred at rt for 3 h. Et_2O (400 ml) was added and the mixture was washed with brine (1 x 100 ml, 3 x 20 ml) dried over $MgSO_4$ and concentrated in vacuo. The resulting brown oil (10.9 g) was dissolved in DCM (5 ml) and DIPEA (20 ml, 6 eq.) was added. The mixture was stirred for 15 min before Boc_2O (23.3 g, 107.0 mmol, 5 eq.) and DMAP (0.25 g, 2.0 mmol, 0.1 eq.) were added. Stirring was continued at rt for 2 h. The reaction mixture was washed with brine (2 x 100 ml), dried over $MgSO_4$ and concentrated in vacuo. Column chromatography (400 g SiO_2, cycH/EA = 2:3 → EA) afforded the desired product as yellow oil.

Yield: 61% (6.01 g, 13.0 mmol, over 2 steps)

Appearance: yellow oil

TLC: R_f = 0.47 (EA; UV)

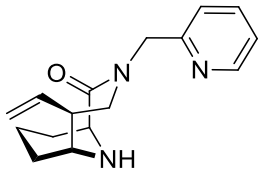
^{1}H-NMR (300 MHz, $CDCl_3$): δ = -0.04 – 0.00 (m, 9H), 1.47 – 1.51 (m, 11H), 1.65 – 1.75 (m, 1H), 1.80 – 1.95 (m, 2H), 2.00 – 2.08 (m, 1H), 2.40 – 2.50 (m, 1H), 2.57 – 2.62 (m, 1H), 3.90 – 4.30 (m, 2H), 4.45 – 4.85 (m, 1H), 4.90 – 5.10 (m, 2H), 5.20 – 5.40 (m, 1H), 5.50 – 6.00 (m, 1H), 7.18 – 7.25 (m, 1H), 7.36 – 7.42 (m, 1H), 7.64 – 7.74 (m, 1H), 8.48 – 8.58 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = -1.9, -1.5, 18.2, 22.8, 23.0, 25.7, 25.9, 34.4, 34.5, 48.6, 50.2, 50.4, 51.5, 55.7, 55.9, 83.1, 121.6, 122.0, 122.4, 122.7, 132.0, 132.4, 137.1, 139.5, 149.5, 153.7, 156.8, 157.0, 171.3, 171.4.

Mass (ESI): $[M + H]^+$ = 460.01

Lab book number(s): JK026

5.2.26. Compound [33]: (1*S*,5*S*,6*R*)-3-(pyridine-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1] decan-2-one



[33]

Compound **[32]** (15.0 g, 32.6 mmol, 1 eq.) was dissolved in THF (200 ml, dry) and the reaction mixture was cooled to -78 °C. DIBAL-H (42.4 ml, 42.4 mmol, 1.3 eq., 1 M in DCM) was added over 1 h after which no more starting material was detectable by TLC. The reaction was quenched with Glauber's salt and was allowed to warm to rt. Solids were filtered off over celite and the solvent was removed under reduced pressure. The resulting yellow oil (13.6 g) was dissolved in 1800 ml DCM in a fluorinated HDPE bottle and cooled to -78 °C. HF (74 ml, 4061 mmol, 125 eq., 70% in pyridine) was added and the mixture stirred for 15 min. The bottle was transferred to an ice-bath and stirred for 2 h. The reaction was quenched with sat. aq. $CaCO_3$ solution (500 ml) and 10 M NaOH (600 ml). The phases were separated and the aqueous phase was extracted with DCM (5 x 300 ml). The combined organic phases were dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (500 g SiO_2, EA + 3% TEA + 5% MeOH) afforded the desired product as an orange resin.

Yield: 37% (3.31 g, 12.1 mmol, over 2 steps)

Appearance: orange resin

TLC: R_f = 0.11 (EA + 3% TEA + 5% MeOH; UV, ninhydrin)

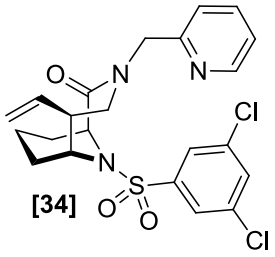
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.44 – 1.74 (m, 5H), 2.07 (s, 1H), 2.20 – 2.40 (m, 1H), 2.55 – 2.70 (m, 1H), 2.75 – 2.90 (m, 1H), 3.05 – 3.15 (m, 1H), 3.80 – 3.88 (m, 1H), 3.96 – 4.10 (m, 1H), 4.67 – 4.96 (m, 1H), 4.81 – 4.95 (m, 3H), 5.50 – 5.66 (m, 1H), 7.10 – 7.23 (m, 1H), 7.29 – 7.38 (m, 1H), 7.60 – 7.70 (m, 1H), 8.46 – 8.58 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 16.9, 28.1, 29.4, 49.5, 51.2, 52.6, 55.9, 57.8, 115.0, 122.3 (2C), 136.7, 139.0, 149.1, 157.8, 174.9.

Mass (ESI): $[M + H]^+$ = 272.11

Lab book number(s): JK037

5.2.27. Compound [34]: (1*S*,5*S*,6*R*)-10-[(3,5-dichlorophenyl)sulfonyl]3-(pyridine-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[34]

Compound **[33]** (280 mg, 1.03 mmol, 1 eq.), 3,5-dichlorobenzenesulfonyl chloride (330 mg, 1.34 mmol, 1.3 eq.) and ZnO (168 mg, 2.07 mmol, 2 eq.) were placed in a flask under argon atmosphere. MeCN (30 ml) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with DCM (80 ml) and washed with brine (20 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (25 g SiO_2, cycH/EA = 1:1) afforded the title compound as colorless resin.

Yield: 63% (301 mg, 0.65 mmol)

Appearance: colorless solids

TLC: R_f = 0.27 (cycH/EA = 1:1; UV, PMA)

HPLC: R_t = 13.46 min (0 – 100% B in 20 min)

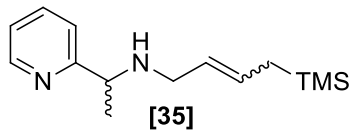
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.01 – 1.44 (m, 2H), 1.44 – 1.73 (m, 3H), 2.31 (dt, *J* = 15.2, 2.7 Hz, 1H), 2.62 – 2.83 (m, 1H), 3.12 (dd, *J* = 14.3, 2.0 Hz, 1H), 3.90 – 4.12 (m, 2H), 4.62 – 5.19 (m, 5H), 5.71 (m, 1H), 7.20 (dd, *J* = 7.5, 5.0 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 1.9 Hz, 1H), 7.63 – 7.81 (m, 3H), 8.43 – 8.59 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.5, 26.4, 27.6, 49.1, 52.1, 54.9, 56.1, 56.9, 116.9, 122.1, 122.5, 124.9, 132.7, 136.3, 137.2, 144.1, 149.0, 156.8, 170.4.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{23}Cl_2N_3O_3S$ 480.0910; Found 480.0916

Lab book number(s): JK091

5.2.28. Compound [35]: *N*-(1-(pyridin-2-yl)ethyl)-4-(trimethylsilyl)but-2-en-1-amine



[35]

Compound **[25]** (5.0 g, 18.29 mmol, 1 eq.) was dissolved in MeOH (70 ml) and hydrazine (1.2 ml, 36.6 mmol, 2 eq., 50-60% solution) was added. The mixture was refluxed for 24 h. 1 M NaOH (15 ml) and DCM (50 ml) were added and the organic phase was separated. The aqueous phase was extracted with DCM (1 x 50 ml). Both organic phases were combined, dried over $MgSO_4$ and solvents were removed under reduced pressure (700 mbar). The residue was diluted with MeOH (10 ml). 1-(pyridine-2-yl)ethanone (2.2 ml, 18.3 mmol, 1 eq.) and titanium(IV)isopropoxide (5.4 ml, 18.3 mmol, 1 eq.) were added and the mixture was stirred at rt for 4 h. After adding $NaBH_4$ (1.0 g, 27.4 mmol, 1.5 eq.) stirring was continued until no more gas formation was observed (2 h). Sat. aq. $NaHCO_3$ (100 ml) was added carefully and the mixture was extracted with DCM (3 x 100 ml). The combined organic phases were dried over $MgSO_4$ and solvents were reduced under reduced pressure. Column chromatography (150 g SiO_2, EA + 3% TEA) afforded the title compound as yellow oil.

Yield: 62% (2.85 g, 11.47 mmol, over 2 steps)

Appearance: yellow oil

TLC: R_f = 0.30 (EA + 3% TEA; UV, ninhydrin)

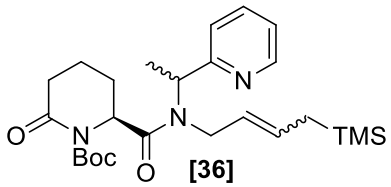
^{1}H-NMR (300 MHz, $CDCl_3$): δ = -0.05 (d, *J* = 12.4 Hz, 9H), 1.28 – 1.51 (m, 5H), 1.76 (s, 2H), 2.91 – 3.14 (m, 2H), 3.88 (q, *J* = 6.7 Hz, 1H), 5.19 – 5.60 (m, 2H), 6.98 – 7.20 (m, 1H), 7.20 – 7.39 (m, 1H), 7.63 (m, 1H), 8.55 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = -0.0, 0.1, 20.8, 24.6, 46.2, 51.9, 60.4, 61.0, 123.2, 123.7, 127.6, 128.9, 129.9, 130.9, 138.3, 151.3, 166.7.

Mass (ESI): $[M + H]^+$ = 248.99

Lab book number(s): JK030, JK218

5.2.29. Compound [36]: (6*S*)-tert-butyl 2-oxo-6-((1-(pyridin-2-yl)ethyl)(4-(trimethylsilyl)but-2-en-1-yl)carbamoyl)piperidine-1-carboxylate



[36]

(*S*)-6-oxopiperidine-2-carboxylic acid (1.32 g, 9.2 mmol, 1.1 eq.) was dissolved in DMF (15 ml) and HATU (3.8 g, 10.0 mmol, 1.2 eq.) was added. After adding DIPEA (3.0 ml, 16.8 mmol, 2 eq.) the mixture was stirred for 15 min. Compound **[35]** (2.1 g, 8.4 mmol, 1 eq.) was added and the reaction was stirred for 3 h at rt. The reaction was diluted with Et_2O (70 ml) and washed with brine (50 ml). Solvents were evaporated and the residue was dissolved in DCM (20 ml). Boc2O (7.33 g, 33.6 mmol, 4 eq.), DIPEA (4.0 ml, 42.0 mmol, 5 eq.) and DMAP (210 mg, 1.7 mmol, 0.2 eq.) were added and the mixture was stirred for 14 h at rt. DCM (100 ml) was added and the mixture was washed with brine. Solvents were removed under reduced pressure and the crude material was purified by column chromatography (250 g silica, cycH/EA = 1:1).

Yield: 37% (1.45 g, 3.4 mmol, over 2 steps)

Appearance: yellow oil

TLC: R_f = 0.56 (EA; UV)

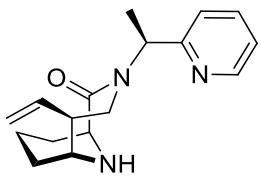
^{1}H-NMR (300 MHz, $CDCl_3$): δ = -0.17 – 0.07 (m, 9H), 1.19 – 1.78 (m, 18H), 1.86 – 2.05 (m, 2H), 2.37 – 2.51 (m, 1H), 2.51 – 2.68 (m, 1H), 3.48 – 4.29 (m, 3H), 4.74 – 4.96 (m, 1H), 5.03 – 5.42 (m, 1H), 5.43 – 5.64 (m, 1H), 5.75 – 5.93 (m, 1H), 7.06 – 7.23 (m, 1H), 7.32 – 7.42 (m, 1H), 7.49 – 7.75 (m, 1H), 8.46 – 8.64 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = -0.0, 0.1, 16.1, 18.1, 18.3, 20.1, 20.2, 20.3, 21.1, 22.9, 24.5, 24.7, 27.8, 28.2, 29.9, 29.9, 30.0, 36.3, 36.6, 43.5, 47.3, 48.9, 55.8, 56.1, 57.8, 59.6, 62.3, 84.9, 123.0, 124.0, 124.1, 124.5, 124.9, 125.1, 126.3, 127.0, 127.4, 130.1, 131.0, 132.2, 138.2, 138.3, 138.5, 150.4, 151.5, 155.8, 162.0, 173.4, 174.2, 174.4.

Mass (APCI): $[M + H]^+$ = 474.28

Lab book number(s): JK049, JK219

5.2.30. Compound [37]: (1*S*,5*S*,6*R*)-3-((*S*)-1-(pyridin-2-yl)ethyl)-5-vinyl-3,10-diazabicyclo[4.3.1] decan-2-one



[37]

Compound **[36]** (1.45 g, 3.07 mmol, 1 eq.) was dissolved in THF (35 ml, dry) and the reaction mixture was cooled to -78 °C. DIBAL-H (3.4 ml, 3.37 mmol, 1.1 eq., 1 M in DCM) was added over 1 h after which no more starting material was detectable by TLC. The reaction was quenched with Glauber's salt and was allowed to warm to rt. Solids were filtered off over celite and solvents were removed under reduced pressure. The resulting yellow oil was dissolved in 150 ml DCM in a HDPE bottle and cooled to -78 °C. HF (6.5 ml, 306 mmol, 100 eq., 70% in pyridine) was added and the mixture stirred for 15 min. The bottle was transferred to an ice-bath and stirred for 2 h. The reaction was quenched with sat. aq. $CaCO_3$ solution (50 ml) and 10 M NaOH (60 ml). The phases were separated and the aqueous phase was extracted with DCM (5 x 100 ml). The combined organic phases were dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (50 g SiO_2, EA + 3% TEA + 5% MeOH) afforded the desired product as a yellow resin.

Yield: 19% (166 mg, 0.58 mmol, over 2 steps)

Appearance: yellow resin

TLC: R_f = 0.15 (EA + 3% TEA + 5% MeOH; UV, ninhydrin)

HPLC: R_t = 8.27 min (0 – 100% B in 20 min)

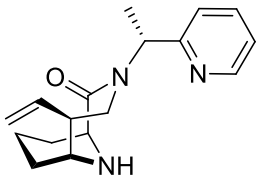
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.45 – 1.73 (m, 8H), 2.13 – 2.41 (m, 2H), 2.42 – 2.61 (m, 1H), 2.79 (dd, *J* = 7.0, 4.0 Hz, 1H), 2.90 (dd, *J* = 14.3, 1.9 Hz, 1H), 3.46 (dd, *J* = 14.3, 10.7 Hz, 1H), 3.87 (q, *J* = 2.1 Hz, 1H), 4.84 – 5.08 (m, 2H), 5.58 (m, 1H), 6.18 (q, *J* = 6.9 Hz, 1H), 7.15 (m, 1H), 7.23 – 7.34 (m, 1H), 7.62 (td, *J* = 7.7, 1.8 Hz, 1H), 8.55 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.2, 16.9, 28.1, 29.8, 45.3, 50.6, 52.8, 54.3, 58.0, 115.0, 122.1, 122.9, 136.4, 139.0, 148.9, 160.0, 174.3.

Mass (ESI): $[M + H]^+$ = 286.19

Lab book number(s): JK062, JK226

5.2.31. Compound [38]: (1*S*,5*S*,6*R*)-3-((*R*)-1-(pyridin-2-yl)ethyl)-5-vinyl-3,10-diazabicyclo[4.3.1] decan-2-one



[38]

Compound **[38]** was obtained in the previous reaction and was isolated by column chromatography.

Yield: 16% (140 mg, 0.49 mmol, over 2 steps)

Appearance: yellow resin

TLC: R_f = 0.29 (EA + 3% TEA + 5% MeOH; UV, ninhydrin)

HPLC: R_t = 8.33 min (0 – 100% B in 20 min)

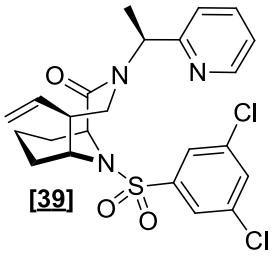
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.30 – 1.73 (m, 8H), 2.09 (m, 2H), 2.29 – 2.40 (m, 1H), 2.74 (t, *J* = 4.7 Hz, 1H), 3.02 (dd, *J* = 13.9, 1.9 Hz, 1H), 3.72 (dd, *J* = 13.8, 10.5 Hz, 1H), 3.78 – 3.90 (m, 1H), 4.52 (d, *J* = 17.1 Hz, 1H), 4.76 (d, *J* = 10.2 Hz, 1H), 5.43 (m, 1H), 6.19 (q, *J* = 7.0 Hz, 1H), 7.16 (dd, *J* = 7.4, 5.0 Hz, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.64 (td, *J* = 7.7, 1.8 Hz, 1H), 8.53 (d, *J* = 4.9 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.5, 16.9, 28.0, 29.7, 44.9, 49.7, 52.6, 54.0, 58.0, 114.8, 122.3, 122.9, 136.4, 139.1, 148.7, 160.2, 174.4.

Mass (ESI): $[M + H]^+$ = 286.20

Lab book number(s): JK062

5.2.32. Compound [39]: (((1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-3-((*S*)-1-(pyridin-2-yl) ethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[39]

Compound **[37]** (150 mg, 0.55 mmol, 1 eq.), 3,5-dichlorobenzene-1-sulfonyl chloride (203 mg, 0.83 mmol, 1.5 eq.) and DIPEA (290 μl, 1.66 mmol, 3 eq.) were placed in a flask under argon atmosphere. MeCN (50 ml) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with EA (150 ml) and washed with brine (50 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (50 g SiO_2, cycH/EA = 1:1) afforded the title compound as colorless resin.

Yield: 42% (110 mg, 0.23 mmol)

Appearance: white solids

TLC: R_f = 0.50 (cycH/EA = 1:1; UV, Hanessian)

HPLC: R_t = 14.10 min (0 – 100% B in 20 min)

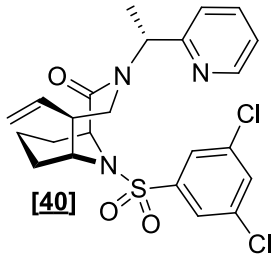
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.15 – 1.25 (m, 2H), 1.31 (tt, *J* = 13.1, 5.3 Hz, 1H), 1.42 – 1.58 (m, 6H), 2.23 – 2.35 (m, 1H), 2.40 – 2.53 (m, 1H), 2.82 (dd, *J* = 14.8, 1.9 Hz, 1H), 3.32 (dd, *J* = 14.8, 10.7 Hz, 1H), 3.93 (m, 1H), 4.69 (dt, *J* = 6.0, 1.9 Hz, 1H), 4.94 – 5.09 (m, 2H), 5.63 (m, 1H), 6.08 (q, *J* = 6.9 Hz, 1H), 7.10 – 7.14 (m, 1H), 7.21 (m, 1H), 7.48 (t, *J* = 1.9 Hz, 1H), 7.56 – 7.66 (m, 3H), 8.49 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.0, 15.6, 26.5, 27.9, 46.0, 50.2, 55.0, 55.1, 57.1, 116.8, 122.4, 122.9, 124.9, 132.7, 136.3, 136.8, 137.1, 144.1, 148.9, 159.0, 169.9.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{25}Cl_2N_3O_3S$ 494.1066; Found 494.1069

Lab book number(s): JK229

5.2.33. Compound [40]: (((1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-3-((*R*)-1-(pyridin-2-yl) ethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[40]

Compound **[38]** (90 mg, 0.32 mmol, 1 eq.), 3,5-dichlorobenzene-1-sulfonyl chloride (116 mg, 0.47 mmol, 1.5 eq.) and DIPEA (165 μl, 0.95 mmol, 3 eq.) were placed in a flask under argon atmosphere. MeCN (30 ml) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with DCM (150 ml) and washed with brine (50 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (50 g SiO_2, cycH/EA = 1:1) afforded the title compound as colorless resin.

Yield: 42% (65 mg, 0.13 mmol)

Appearance: white solids

TLC: R_f = 0.48 (cycH/EA = 1:1; UV, Hanessian)

HPLC: R_t = 14.38 min (0 – 100% B in 20 min)

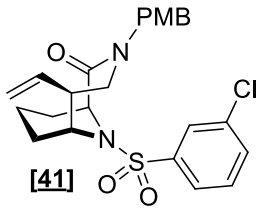
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.28 – 1.35 (m, 2H), 1.39 – 1.47 (m, 1H), 1.52 m, 2H), 1.59 (d, *J* = 7.0 Hz, 3H), 2.20 (q, *J* = 8.6 Hz, 1H), 2.29 – 2.45 (m, 1H), 3.12 (dd, *J* = 14.2, 1.9 Hz, 1H), 3.70 (dd, *J* = 14.3, 10.5 Hz, 1H), 3.95 (m, 1H), 4.69 (dt, *J* = 16.9, 1.1 Hz, 1H), 4.79 (dt, *J* = 6.1, 1.9 Hz, 1H), 4.94 (dd, *J* = 10.1, 1.3 Hz, 1H), 5.61 (m, 1H), 6.15 (q, *J* = 7.1 Hz, 1H), 7.16 – 7.28 (m, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 1.8 Hz, 1H), 7.67 – 7.80 (m, 3H), 8.50 – 8.69 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.6, 15.8, 26.3, 27.8, 45.8, 49.2, 54.8, 54.9, 57.1, 116.5, 122.6, 122.8, 124.9, 132.6, 136.3, 137.0, 137.3, 144.2, 148.6, 159.6, 170.0.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{25}Cl_2N_3O_3S$ 494.1066; Found 494.1068

Lab book number(s): JK297

5.2.34. Compound [41]: (1*S*,5*S*,6*R*)-10-((3-chlorophenyl)sulfonyl)-3-(4-methoxybenzyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[41]

Compound **[28]** (500 mg, 0.66 mmol, 1 eq.) was dissolved in DCM (15 ml). 3-Chlorobenzenesulfonyl chloride (583 mg, 2.77 mmol, 1.5 eq.) and DIPEA (740 µl, 3.69 mmol, 2 eq.) were added and the mixture was stirred for 20 h at rt. Sat. aq. $NaHCO_3$ (5 ml) was added and the mixture was extracted with DCM (3 x 10 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (100 g SiO_2, cycH/EA = 3:1 → 3:2) afforded the title compound as colorless resin.

Yield: 66% (580 mg, 0.44 mmol)

Appearance: colorless resin

TLC: R_f = 0.55 (cycH/EA = 1:1; UV, PMA)

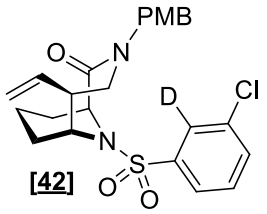
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14 – 1.36 (m, 3H), 1.40 – 1,56 (m, 3H), 2.25 – 2.42 (m, 2H), 2.89 (dd, *J* = 14.3, 2.0 Hz, 1H), 3.80 (s, 3H), 3.84 – 4.01 (m, 2H), 4.38 (d, *J* = 14.4 Hz, 1H), 4.74 – 4.94 (m, 3H), 4.99 (dd, *J* = 10.1, 1.3 Hz, 1H), 5.67 (m, 1H), 6.82 – 6.90 (m, 2H), 7.16 – 7.23 (m, 2H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.55 (m, 1H), 7.70 (m, 1H), 7.82 (t, *J* = 1.9 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.6, 26.2, 27.5, 49.4, 50.8, 53.3, 54.6, 55.3, 56.9, 114.1, 116.7, 124.6, 126.7, 129.1, 129.3, 130.6, 132.8, 135.5, 137.4, 143.0, 159.1, 170.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{28}ClN_2O_4S$ 475.1453; Found 475.1451

Lab book number(s): JK063, JK073

5.2.35. Compound [42]: (1*S*,5*S*,6*R*)-10-((3-chloro(2-^{2}H)phenyl)sulfonyl)-3-(4-methoxybenzyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[42]

Compound **[28]** (245 mg, 0.82 mmol, 1 eq.) was dissolved in MeCN (150 ml). Compound **[4]** (172 μl, 1.22 mmol, 1.5 eq.) and DIPEA (277 μl, 1.63 mmol, 2.0 eq.) were added successively and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with EA (200 ml) and washed with brine (100 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (75 g SiO_2, cycH/EA = 4:1 → 2:1) afforded the title compound as slightly yellow solids.

Yield: 58% (227 mg, 0.48 mmol)

Appearance: slightly yellow solids

TLC: R_f = 0.38 (cycH/EA = 2:1; UV, PMA)

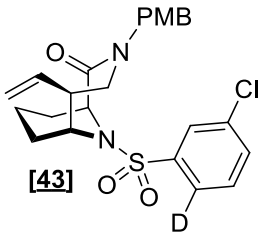
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 – 1.62 (m, 5H), 2.37 (m, 2H), 2.92 (dd, *J* = 14.2, 1.9 Hz, 1H), 3.83 (d, *J* = 1.0 Hz, 3H), 3.88 – 4.04 (m, 2H), 4.41 (d, *J* = 14.4 Hz, 1H), 4.72 – 4.96 (m, 3H), 5.02 (dd, *J* = 10.1, 1.2 Hz, 1H), 5.69 (m, 1H), 6.84 – 6.94 (m, 2H), 7.18 – 7.27 (m, 2H), 7.48 (td, *J* = 8.0, 0.9 Hz, 1H), 7.58 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.73 (dt, *J* = 7.8, 1.0 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.6, 26.2, 27.5, 49.4, 50.8, 53.3, 54.6, 55.3, 56.9, 114.1, 116.7, 124.6, 126.7, 129.1, 129.3, 130.6, 132.8, 135.5, 137.4, 142.9, 159.1, 170.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{27}ClDN_2O_4S$ 476.1516; Found 476.1514

Lab book number(s): JK405

5.2.36. Compound [43]: (1*S*,5*S*,6*R*)-10-((3-chloro(6-^{2}H)phenyl)sulfonyl)-3-(4-methoxybenzyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[43]

Compound **[28]** (240 mg, 0.80 mmol, 1 eq.) was dissolved in MeCN (150 ml). Compound **[8]** (170 μl, 1.20 mmol, 1.5 eq.) and DIPEA (272 μl, 1.60 mmol, 2.0 eq.) were added successively and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with EA (200 ml) and washed with brine (100 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (70 g SiO_2, cycH/EA = 4:1 → 2:1) afforded the title compound as slightly yellow solids.

Yield: 58% (220 mg, 0.46 mmol)

Appearance: slightly yellow solids

TLC: R_f = 0.38 (cycH/EA = 2:1; UV, PMA)

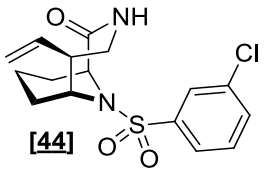
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 – 1.58 (m, 5H), 2.25 – 2.44 (m, 2H), 2.92 (dd, *J* = 14.2, 2.0 Hz, 1H), 3.83 (s, 3H), 3.89 – 4.03 (m, 2H), 4.41 (d, *J* = 14.4 Hz, 1H), 4.74 – 4.97 (m, 3H), 5.02 (dd, *J* = 10.3, 1.2 Hz, 1H), 5.69 (m, 1H), 6.85 – 6.93 (m, 2H), 7.19 – 7.27 (m, 2H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.58 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.84 (d, *J* = 2.0 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.6, 26.2, 27.5, 49.4, 50.8, 53.3, 54.6, 55.3, 56.9, 114.1, 116.7, 124.4, 126.7, 129.1, 129.3, 130.5, 132.8, 135.6, 137.4, 142.9, 159.1, 170.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{27}ClDN_2O_4S$ 476.1516; Found 476.1517

Lab book number(s): JK404

5.2.37. Compound [44]: (1*S*,5*S*,6*R*)-10-((3-chlorophenyl)sulfonyl)-5-vinyl-3,10-diazabicyclo [4.3.1]decan-2-one



[44]

Compound **[41]** (150 mg, 0.32 mmol, 1 eq.) was dissolved in MeCN/H_2O (14 ml, 2:1) and CAN (433 mg, 0.79 mmol, 2.5 eq.) was added. The mixture was stirred for 4 h at rt. Brine (5 ml) was added and the mixture was extracted with DCM (3 x 40 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (12 g SiO_2, cycH/EA = 2:1 → EA) afforded the title compound as colorless solids.

Yield: 48% (54 mg, 0.15 mmol)

Appearance: colorless solids

TLC: R_f = 0.18 (cycH/EA = 1:1; UV, PMA)

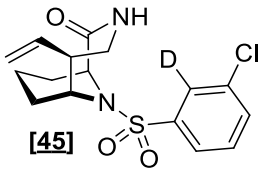
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (m, 3H), 1.43 – 1.69 (m, 3H), 2.17 (d, *J* = 13.6 Hz, 1H), 2.65 (m, 1H), 2.87 (dd, *J* = 14.0, 8.4 Hz, 1H), 3.60 – 3.81 (m, 1H), 4.04 (d, *J* = 5.7 Hz, 1H), 4.67 (d, *J* = 5.9 Hz, 1H), 4.98 – 5.19 (m, 2H), 5.77 (m, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.81 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4, 26.3, 26.8, 44.9, 50.0, 55.2, 56.2, 116.7, 124.6, 126.6, 130.6, 132.8, 135.5, 137.2, 142.8, 173.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{19}ClN_2O_3S$ 355.0878; Found 355.0876

Lab book number(s): JK066, JK076

5.2.38. Compound [45]: (1*S*,5*S*,6*R*)-10-(((2-^{2}H)-3-chlorophenyl)sulfonyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[45]

Compound **[42]** (200 mg, 0.42 mmol, 1 eq.) was dissolved in MeCN/H_2O (14 ml, 2:1) and CAN (576 mg, 1.05 mmol, 2.5 eq.) was added. The mixture was stirred for 4 h at rt. Brine (5 ml) was added and the mixture was extracted with DCM (3 x 40 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (25 g SiO_2, cycH/EA = 1:1 → EA) afforded the title compound as colorless solids.

Yield: 39% (59 mg, 0.16 mmol)

Appearance: colorless solids

TLC: R_f = 0.51 (EA; UV, PMA)

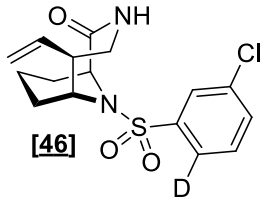
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 – 1.71 (m, 5H), 2.12 – 2.27 (m, 1H), 2.67 (m, 1H), 2.87 (m, 1H), 3.76 (m, 1H), 4.05 (t, *J* = 6.0 Hz, 1H), 4.68 (dt, *J* = 6.2, 1.9 Hz, 1H), 5.04 – 5.21 (m, 2H), 5.79 (m, 1H), 6.36 (d, *J* = 7.5 Hz, 1H), 7.48 (td, *J* = 7.9, 0.8 Hz, 1H), 7.56 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.71 (dd, *J* = 7.8, 1.1 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4, 26.4, 26.9, 45.1, 50.1, 55.2, 56.3, 116.9, 124.6, 126.7, 130.7, 132.9, 135.5, 137.2, 142.8, 173.0.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{19}DClN_2O_3S$ 356.0940; Found 356.0940

Lab book number(s): JK408

5.2.39. Compound [46]: (1*S*,5*S*,6*R*)-10-(((6-^{2}H)-3-chlorophenyl)sulfonyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[46]

Compound **[43]** (200 mg, 0.42 mmol, 1 eq.) was dissolved in MeCN/H_2O (14 ml, 2:1) and CAN (576 mg, 1.05 mmol, 2.5 eq.) was added. The mixture was stirred for 4 h at rt. Brine (5 ml) was added and the mixture was extracted with DCM (3 x 40 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (25 g SiO_2, cycH/EA = 1:1 → EA) afforded the title compound as colorless solids.

Yield: 42% (62 mg, 0.18 mmol)

Appearance: colorless solids

TLC: R_f = 0.51 (EA; UV, PMA)

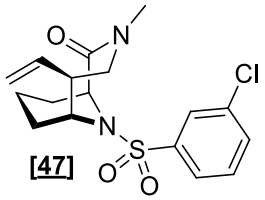
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 – 1.72 (m, 5H), 2.14 – 2.27 (m, 1H), 2.66 (m, 1H), 2.87 (m, 1H), 3.76 (m, 1H), 4.05 (t, *J* = 6.0 Hz, 1H), 4.68 (dd, *J* = 6.2, 1.8 Hz, 1H), 5.02 – 5.20 (m, 2H), 5.79 (m, 1H), 6.24 – 6.50 (m, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.56 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.72 (d, *J* = 7.7 Hz, 0H), 7.82 (d, *J* = 2.0 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4, 26.4, 26.9, 45.1, 50.1, 55.2, 56.3, 116.9, 124.2, 126.7, 130.6, 132.9, 135.6, 137.2, 142.8, 173.0.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{19}DClN_2O_3S$ 356.0940; Found 356.0941

Lab book number(s): JK407

5.2.40. Compound [47]: (1*S*,5*S*,6*R*)-10-((3-chlorophenyl)sulfonyl)-3-methyl-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[47]

Compound **[44]** (50 mg, 0.14 mmol, 1 eq.) was dissolved in dry DMF (2 ml) and NaH (12 mg, 0.28 mmol, 2 eq.) was added. The mixture was stirred for 15 min at rt. MeI (55 µl, 0.85 mmol, 6 eq.) was added and the mixture was heated to 80 °C and stirred for 1 h. Et_2O (80 ml) was added and the organic phase was washed with brine (3 x 10 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (10 g SiO_2, cycH/EA = 2:1) afforded the title compound as colorless crystals.

Yield: 85% (44 mg, 0.12 mmol)

Appearance: colorless crystals

TLC: R_f = 0.31 (cycH/EA = 1:1; UV, Hanessian)

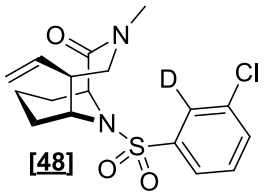
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 – 1.34 (m, 3H), 1.40 – 1.60 (m, 2H), 2.15 – 2.28 (m, 1H), 2.65 (m, 1H), 2.89 (dd, *J* = 14.2, 2.0 Hz, 1H), 3.06 (s, 3H), 3.93 – 4.01 (m, 1H), 4.08 (m, 1H), 4.68 (m, 1H), 5.08 – 5.18 (m, 2H), 5.69 – 5.87 (m, 1H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.51 – 7.58 (m, 1H), 7.69 (dt, *J* = 7.9, 1.6 Hz, 1H), 7.80 (t, *J* = 1.9 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4, 26.0, 26.9, 27.1, 39.3, 48.9, 53.3, 54.5, 56.7, 116.7, 124.6, 126.6, 130.6, 132.8, 135.5, 137.4, 142.9, 170.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{21}ClN_2O_3S$ 369.1034; Found 369.1036

Lab book number(s): JK068, JK077

5.2.41. Compound [48]: (1*S*,5*S*,6*R*)-10-(((2-^{2}H)-3-chlorophenyl)sulfonyl)-3-methyl-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[48]

Compound **[45]** (20 mg, 0.06 mmol, 1 eq.) was dissolved in dry MeCN (8 ml) and MeI (21 µl, 0.34 mmol, 6 eq.) and NaH (7 mg, 0.18 mmol, 2 eq.) were added. The mixture was stirred for 4 h at 40 °C. The reaction was quenched with water (2 ml) and extracted with EA (2 x 40 ml). The organic phase was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (8 g SiO_2, cycH/EA = 3:1) afforded the title compound as colorless solids.

Yield: 87% (18 mg, 0.05 mmol)

Appearance: colorless solids

TLC: R_f = 0.23 (cycH/EA = 2:1; UV)

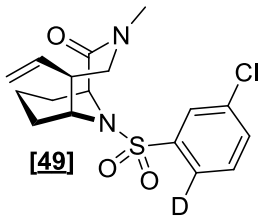
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 – 1.33 (m, 3H), 1.42 – 1.65 (m, 2H), 2.24 – 2.30 (m, 1H), 2.68 (m, 1H), 2.92 (dd, *J* = 14.1, 2.0 Hz, 1H), 3.10 (s, 3H), 4.00 (td, *J* = 6.0, 5.2, 1.9 Hz, 1H), 4.12 (dd, *J* = 14.2, 10.9 Hz, 1H), 4.71 (dt, *J* = 6.2, 1.9 Hz, 1H), 5.03 – 5.22 (m, 2H), 5.82 (m, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.58 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.72 (dd, *J* = 7.7, 1.1 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.5, 26.1, 27.1, 39.3, 49.0, 53.4, 54.6, 56.8, 116.7, 124.6, 126.2, 126.4, 126.7, 130.6, 132.8, 135.5, 137.5, 142.9, 170.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{21}ClDN_2O_3S$ 370.1097; Found 370.1097

Lab book number(s): JK416

5.2.42. Compound [49]: (1*S*,5*S*,6*R*)-10-(((6-^{2}H)-3-chlorophenyl)sulfonyl)-3-methyl-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[49]

Compound **[46]** (20 mg, 0.06 mmol, 1 eq.) was dissolved in dry MeCN (8 ml) and MeI (21 µl, 0.34 mmol, 6 eq.) and NaH (7 mg, 0.18 mmol, 2 eq.) were added. The mixture was stirred for 4 h at 40 °C. The reaction was quenched with water (2 ml) and extracted with EA (2 x 40 ml). The organic phase was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (8 g SiO_2, cycH/EA = 2:1) afforded the title compound as colorless solids.

Yield: 82% (17 mg, 0.05 mmol)

Appearance: colorless solids

TLC: R_f = 0.23 (cycH/EA = 2:1; UV)

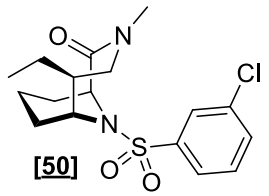
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 – 1.60 (m, 5H), 2.19 – 2.29 (m, 1H), 2.68 (m, 1H), 2.87 – 2.99 (m, 1H), 3.10 (s, 3H), 3.93 – 4.05 (m, 1H), 4.12 (dd, *J* = 14.1, 10.9 Hz, 1H), 4.71 (dd, *J* = 6.2, 1.8 Hz, 1H), 5.03 – 5.24 (m, 2H), 5.82 (m, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.58 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.83 (d, *J* = 2.1 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.5, 26.1, 27.1, 39.3, 49.0, 53.4, 54.6, 56.8, 116.7, 124.2, 124.4, 124.6, 126.7, 130.5, 132.8, 135.6, 137.5, 142.9, 170.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{21}ClDN_2O_3S$ 370.1097; Found 370.1096

Lab book number(s): JK415

5.2.43. Compound [50]: (1*S*,5*S*,6*R*)-10-((3-chlorophenyl)sulfonyl)-5-ethyl-3-methyl-3,10-diazabicyclo[4.3.1]decan-2-one



[50]

Compound **[47]** (21.0 mg, 0.059 mmol, 1 eq.) was dissolved in MeOH (10 ml) and Pt/C (1 mg, 0.001 mmol, 0.01 eq., 10% loading) was added. H_2 was bubbled through for 2 min and the reaction mixture was stirred for 1 h under hydrogen atmosphere. Filtration through Celite, washing with EA and removing of the solvents under reduced pressure afforded the product in 99% purity as white solids.

Yield: 95% (20 mg, 0.054 mmol)

Appearance: white solids

TLC: R_f = 0.29 (cycH/EA = 1:1; UV)

HPLC: R_t = 17.41 min (0 – 100% B in 20 min)

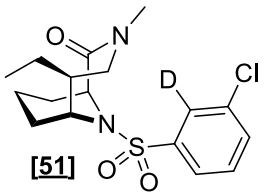
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.4 Hz, 3H), 1.17 – 1.59 (m, 7H), 1.92 (m, 1H), 2.15 – 2.26 (m, 1H), 2.87 (dd, *J* = 14.3, 2.0 Hz, 1H), 3.06 (s, 3H), 3.76 – 3.97 (m, 2H), 4.68 (dt, *J* = 6.2, 2.0 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.55 (m, 1H), 7.71 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.82 (t, *J* = 1.9 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 11.7, 15.7, 26.5, 27.4, 27.5, 39.2, 45.5, 52.9, 55.2, 57.0, 124.7, 126.8, 130.7, 132.8, 135.6, 143.2, 170.4.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{24}ClN_2O_3S$ 371.1191; Found 371.1190

Lab book number(s): JK080

5.2.44. Compound [51]: (1*S*,5*S*,6*R*)-10-(((2-^{2}H)-3-chlorophenyl)sulfonyl)-5-ethyl-3-methyl-3,10-diazabicyclo[4.3.1]decan-2-one



[51]

Compound **[48]** (19 mg, 0.05 mmol, 1 eq.) was dissolved in MeOH (10 ml) and Pt/C (1 mg, 0.001 mmol, 0.01 eq., 10% loading) was added. H_2 was bubbled through for 2 min and the reaction mixture was stirred for 1 h under hydrogen atmosphere. Filtration through Celite, washing with EA and removing of the solvents under reduced pressure afforded the product as white solids.

Yield: quant. (19 mg, 0.05 mmol)

Appearance: white solids

TLC: R_f = 0.26 (cycH/EA = 1:1; UV)

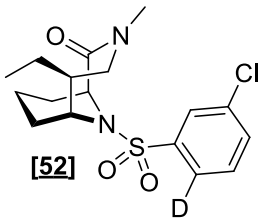
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.4 Hz, 3H), 1.05 – 1.38 (m, 7H), 1.86 (m, 1H), 2.04 – 2.23 (m, 1H), 2.82 (dd, *J* = 14.3, 1.9 Hz, 1H), 3.00 (d, *J* = 1.3 Hz, 3H), 3.65 – 3.93 (m, 2H), 4.62 (dd, *J* = 6.0, 2.0 Hz, 1H), 7.40 (td, *J* = 7.9, 1.3 Hz, 1H), 7.49 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.64 (dt, *J* = 7.8, 1.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 11.6, 15.6, 26.4, 27.3, 27.4, 39.1, 45.4, 52.8, 55.1, 56.8, 124.6, 126.7, 130.6, 132.7, 135.4, 143.0, 170.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{23}ClDN_2O_3S$ 372.1253; Found 372.1253

Lab book number(s): JK421

5.2.45. Compound [52]: (1*S*,5*S*,6*R*)-10-(((6-^{2}H)-3-chlorophenyl)sulfonyl)-5-ethyl-3-methyl-3,10-diazabicyclo[4.3.1]decan-2-one



[52]

Compound **[49]** (19 mg, 0.05 mmol, 1 eq.) was dissolved in MeOH (10 ml) and Pt/C (1 mg, 0.001 mmol, 0.01 eq., 10% loading) was added. H_2 was bubbled through for 2 min and the reaction mixture was stirred for 1 h under hydrogen atmosphere. Filtration through Celite, washing with EA and removing of the solvents under reduced pressure afforded the product as white solids.

Yield: quant. (19 mg, 0.05 mmol)

Appearance: white solids

TLC: R_f = 0.26 (cycH/EA = 1:1; UV)

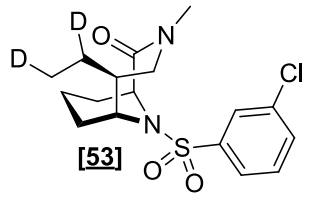
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.4 Hz, 3H), 1.13 – 1.47 (m, 7H), 1.85 (m, 1H), 2.12 – 2.20 (m, 1H), 2.82 (dd, *J* = 14.2, 1.9 Hz, 1H), 3.00 (s, 3H), 3.64 – 3.91 (m, 2H), 4.62 (dd, *J* = 5.9, 2.0 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.49 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.75 (d, *J* = 2.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 11.6, 15.6, 26.4, 27.3, 27.4, 39.1, 45.4, 52.8, 55.1, 56.8, 124.4, 126.7, 130.5, 132.7, 135.5, 143.0, 170.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{22}ClDN_2NaO_3S$ 394.1073; Found 394.1076

Lab book number(s): JK419

5.2.46. Compound [53]: (1*S*,5*S*,6*R*)-(11,12-$^{2}H_1$)-10-((3-chlorophenyl)sulfonyl)-5-ethyl-3-methyl-3,10-diazabicyclo[4.3.1]decan-2-one



[53]

Compound **[47]** (15.0 mg, 0.041 mmol, 1 eq.) was dissolved in dry toluene (4 ml) and Wilkinson's catalyst (18.81 mg, 0.02 mmol, 0.5 eq.) was added. A D_2 balloon was attached and D_2 was bubbled through for 5 min and afterwards the mixture was stirred overnight. The mixture was diluted with EA and filtered over silica. Solvents were removed under reduced pressure and the product was purified by column chromatography (10 g silica, cycH/EA = 1:1).

Yield: 93% (14 mg, 0.038 mmol)

Appearance: colorless solid

TLC: R_f = 0.29 (cycH/EA = 1:1; UV)

HPLC: R_t = 14.34 min (0 – 100% B in 20 min)

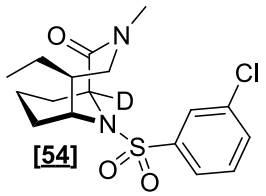
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (dt, *J* = 7.5, 1.9 Hz, 2H), 1.17 (m, 1H), 1.28 – 1.40 (m, 1H), 1.40 – 1.48 (m, 3H), 1.52 (m, 1H), 1.84 – 1.97 (m, 1H), 2.17 – 2.27 (m, 1H), 2.88 (dd, *J* = 14.2, 1.9 Hz, 1H), 3.07 (s, 3H), 3.80 – 3.97 (m, 2H), 4.68 (dt, *J* = 6.2, 1.9 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.55 (m, 1H), 7.71 (m, 1H), 7.82 (t, *J* = 1.9 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 10.5, 10.6, 10.8, 15.0, 25.2, 25.4, 26.8, 26.8, 38.5, 44.8, 52.2, 54.5, 56.3, 124.1, 126.1, 130.0, 132.1, 134.9, 142.5, 169.7.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{22}ClD_2N_2O_3S$ 373.1316; Found 373.1315

Lab book number(s): JK164

5.2.47. Compound [54]: (1*S*,5*S*,6*R*)-(1-^{2}H)-10-((3-chlorophenyl)sulfonyl)-5-ethyl-3-methyl-3,10-diazabicyclo[4.3.1]decan-2-one



[54]

Compound **[50]** (5.0 mg, 0.013 mmol, 1 eq.) was dissolved in MeOD (600 μl) in an NMR tube and KOD (100 μl, 0.990 mmol, 76 eq., 40 wt.% in D_2O) was added. The mixture was measured by NMR and after 2 h the hydrogen at position C1 was completely substituted by deuterium. The mixture was neutralized with DCl, extracted with EA (10 ml) and solvents were removed under reduced pressure. The product was obtained as white solids.

Yield: quant. (5.0 mg, 0.013 mmol)

Appearance: white solid

TLC: R_f = 0.29 (cycH/EA = 1:1; UV)

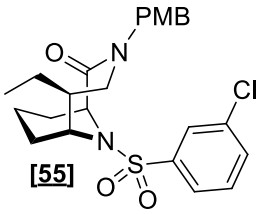
^{1}H NMR (600 MHz, MeOD) δ = 0.99 (t, *J* = 7.4 Hz, 3H), 1.16 – 1.36 (m, 3H), 1.36 – 1.60 (m, 5H), 2.02 (t, *J* = 8.9 Hz, 1H), 2.12 (d, *J* = 13.7 Hz, 1H), 3.08 (s, 4H), 3.81 (dd, *J* = 27.2, 13.5 Hz, 2H), 7.68 (t, *J* = 7.9 Hz, 1H), 7.73 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.85 (d, *J* = 2.2 Hz, 1H).

^{13}C NMR (151 MHz, MeOD) δ = 10.4, 15.0, 26.0, 26.8, 26.9, 38.3, 44.9, 52.8, 55.0, 100.0, 124.8, 126.1, 131.3, 133.0, 135.2, 142.7, 171.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{23}ClDN_2O_3S$ 372.1253; Found 372.1257

Lab book number(s): JK101

5.2.48. Compound [55]: (1*S*,5*S*,6*R*)-10-((3-chlorophenyl)sulfonyl)-3-(4-methoxybenzyl)-5-ethyl-3,10-diazabicyclo[4.3.1]decan-2-one



[55]

Compound **[41]** (40 mg, 0.08 mmol, 1 eq.) was dissolved in MeOH (2 ml) and Pd/C (8 mg, 0.008 mmol, 0.1 eq., 10% loading) was added. The mixture was stirred for 10 min at rt before H_2 was bubbled through for 5 min. The reaction mixture was stirred for 2 h under hydrogen atmosphere and filtered through Celite. Solvents were removed under reduced pressure affording the product in 90% purity as yellow resin, which was used in the next step without further purification.

Yield: 75% (28 mg, 0.06 mmol)

Appearance: yellow resin

TLC: R_f = 0.62 (cycH/EA = 1:1; UV, Hanessian)

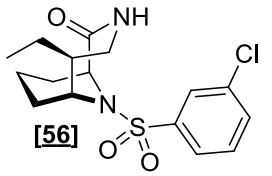
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.70 (t, *J* = 7.4 Hz, 3H), 0.89 (m, 1H), 1.12 – 1.67 (m, 5H), 2.29 (d, *J* = 13.5 Hz, 1H), 2.92 (dd, *J* = 14.3, 1.8 Hz, 1H), 3.47 (m, 2H), 3.79 (m, 5H), 4.23 (d, *J* = 14.4 Hz, 1H), 4.76 (m, 1H), 4.95 (d, *J* = 14.4 Hz, 1H), 6.81 – 6.91 (m, 2H), 7.15 – 7.23 (m, 2H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.54 (m, 1H), 7.70 (m, 1H), 7.81 (t, *J* = 1.9 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.4, 15.7, 26.2, 27.2, 27.6, 45.8, 49.5, 53.0, 55.3 (2C), 56.9, 114.0, 124.6, 126.7, 129.2, 129.4, 130.6, 132.7, 135.5, 143.1, 159.1, 170.4.

Mass (ESI): $[M + H]^+$ = 477.30

Lab book number(s): JK065

5.2.49. Compound [56]: (1*S*,5*S*,6*R*)-10-((3-chlorophenyl)sulfonyl)-5-ethyl-3,10-diazabicyclo [4.3.1]decan-2-one



[56]

Compound **[55]** (28 mg, 0.06 mmol, 1 eq.) was dissolved in MeCN/H_2O (6 ml, 2:1) and CAN (80 mg, 0.15 mmol, 2.5 eq.) was added. The mixture was stirred for 4 h at rt. Brine (2 ml) was added and the mixture was extracted with DCM (4 x 5 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (4 g SiO_2, cycH/EA = 2:1 → EA) afforded the title compound as colorless solids.

Yield: 48% (10 mg, 0.03 mmol)

Appearance: colorless solid

TLC: R_f = 0.21 (cycH/EA = 1:1; UV, PMA)

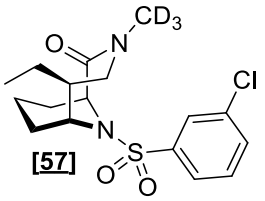
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.4 Hz, 3H), 1.24 (d, *J* = 6.4 Hz, 1H), 1.46 (m, 4H), 1.57 – 1.73 (m, 2H), 1.94 (m, 1H), 2.10 – 2.24 (m, 1H), 2.90 (m, 1H), 3.55 (m, 1H), 3.82 – 3.96 (m, 1H), 4.68 (m, 1H), 6.48 (s, 1H), 7.47 (t, *J* = 7.9 Hz, 1H), 7.56 (m, 1H), 7.72 (m, 1H), 7.83 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.6, 15.5, 26.3, 27.0, 27.7, 44.5, 46.5, 55.8, 56.3, 124.7, 126.7, 130.6, 132.8, 135.6, 143.0, 173.2.

Mass (ESI): $[M + H]^+$ = 357.14

Lab book number(s): JK067, JK078

5.2.50. Compound [57]: (1*S*,5*S*,6*R*)-10-((3-chlorophenyl)sulfonyl)-5-ethyl-3-($^2H_3$)methyl-3,10-diazabicyclo[4.3.1]decan-2-one



[57]

Compound **[56]** (9.0 mg, 0.025 mmol, 1 eq.) was dissolved in dry DMF (2 ml) and NaH (1.95 mg, 0.05 mmol, 2 eq.) was added. After addition of MeI (9 µl, 0.15 mmol, 6 eq.) the mixture was stirred for 1 h at 80 °C. Brine (2 ml) was added and the mixture was extracted with Et_2O (4 x 30 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (1.2 g SiO_2, cycH/EA = 2:1) afforded the title compound as colorless crystals.

Yield: 87% (8.2 mg, 0.022 mmol)

Appearance: colorless solid

TLC: R_f = 0.29 (cycH/EA = 1:1; UV)

HPLC: R_t = 17.55 min (0 – 100% B in 20 min)

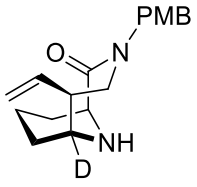
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.4 Hz, 3H), 1.17 (m, 1H), 1.22 – 1.59 (m, 6H), 1.92 (m, 1H), 2.15 – 2.26 (m, 1H), 2.87 (dd, *J* = 14.3, 2.0 Hz, 1H), 3.76 – 3.97 (m, 2H), 4.68 (dt, *J* = 6.2, 2.0 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.55 (m, 1H), 7.71 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.82 (t, *J* = 1.9 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 11.6, 15.6, 26.4, 27.3, 27.4, 38.4, 45.4, 52.7, 55.1, 56.8, 124.7, 126.7, 130.6, 132.7, 135.5, 143.1, 170.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{21}ClD_3N_2O_3S$ 374.1379; Found 374.1376

Lab book number(s): JK071

5.2.51. Compound [58]: (1*S*,5*S*,6*R*)-(6-^{2}H)-3-(4-methoxybenzyl)-5-vinyl-3,10-diazabicyclo [4.3.1]decan-2-one



[58]

Compound **[27]** (1.40 g, 3.07 mmol, 1 eq.) was dissolved in THF (40 ml, dry) and the reaction mixture was cooled to -78 °C. DIBAL-D (5.2 ml, 3.68 mmol, 1.2 eq., 1 M in toluene) was added over 15 min after which no more starting material was detectable by TLC. The reaction was quenched with Glauber's salt and was allowed to warm to rt. Solids were filtered off over celite and the solvent was removed under reduced pressure. The resulting yellow oil (1.42 g) was dissolved in DCM (150 ml) in a fluorinated HDPE bottle and cooled to -78 °C. HF (7 ml, 300 mmol, 100 eq., 70% in pyridine) was added and the mixture stirred for 15 min. The bottle was transferred to an ice-bath and stirred for 1 h. The reaction was quenched with sat. aq. $CaCO_3$ solution (100 ml) and 10 M NaOH (50 ml). The phases were separated and the aqueous phase was extracted with DCM (3 x 200 ml). The combined organic phases were dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (70 g SiO_2, EA + 3% TEA + 2% MeOH) afforded the desired product a yellow resin.

Yield: 22% (187 mg, over 2 steps)

Appearance: yellow resin

TLC: R_f = 0.19 (EA + 3% TEA + 2% MeOH; UV, ninhydrin)

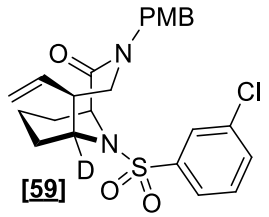
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.37 – 1.65 (m, 5H), 2.11 (s, 1H), 2.21 – 2.30 (m, 1H), 2.38 (t, *J* = 9.6 Hz, 1H), 2.85 (dd, *J* = 13.8, 2.0 Hz, 1H), 3.73 (d, *J* = 0.8 Hz, 3H), 3.75 – 3.89 (m, 2H), 4.37 (d, *J* = 14.3 Hz, 1H), 4.68 (d, *J* = 14.3 Hz, 1H), 4.75 (dt, *J* = 17.1, 1.3 Hz, 1H), 4.83 (m, 1H), 5.48 m, 1H), 6.69 – 6.86 (m, 2H), 7.06 – 7.28 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 16.8, 28.0, 29.4, 49.5, 50.2, 52.1, 53.0, 55.3, 57.8, 113.9, 115.1, 129.4, 129.9, 139.1, 158.9, 174.5.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{23}DN_2O_2$ 302.1973; Found 302.1974

Lab book number(s): JK108

5.2.52. Compound [59]: (1*S*,5*S*,6*R*)-(6-^{2}H)-10-((3-chlorophenyl)sulfonyl)-3-(4-methoxybenzyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[59]

Compound **[58]** (180 mg, 0.60 mmol, 1 eq.) was dissolved in MeCN (2 ml). 3-Chlorobenzenesulfonyl chloride (163 mg, 0.78 mmol, 1.3 eq.) and ZnO (121 mg, 0.90 mmol, 1.5 eq.) were added and the mixture was stirred for 16 h at rt. The mixture was filtered over celite, dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (25 g SiO_2, cycH/EA = 7:3) afforded the title compound as colorless resin.

Yield: 66% (190 mg, 0.40 mmol)

Appearance: colorless resin

TLC: R_f = 0.30 (cycH/EA = 7:3; UV, PMA)

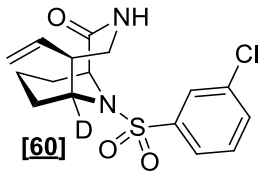
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 – 1.71 (m, 5H), 2.14 – 2.38 (m, 2H), 2.82 (dd, *J* = 14.3, 2.0 Hz, 1H), 3.73 (s, 3H), 3.84 (dd, *J* = 14.2, 10.8 Hz, 1H), 4.31 (d, *J* = 14.4 Hz, 1H), 4.63 – 4.87 (m, 3H), 4.92 (dd, *J* = 10.1, 1.3 Hz, 1H), 5.60 (m, 1H), 6.73 – 6.89 (m, 2H), 7.07 – 7.17 (m, 2H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.48 (m, 1H), 7.63 (m, 1H), 7.75 (t, *J* = 1.9 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.6, 26.2, 27.5, 49.4, 50.8, 52.3, 53.3, 55.3, 56.9, 114.1, 116.7, 124.6, 126.7, 129.1, 129.3, 130.6, 132.8, 135.5, 137.4, 143.0, 159.1, 170.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{26}ClDN_2O_4S$ 476.1516; Found 476.1515

Lab book number(s): JK109

5.2.53. Compound [60]: (1*S*,5*S*,6*R*)-(6-^{2}H)-10-((3-chlorophenyl)sulfonyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[60]

Compound **[59]** (180 mg, 0.38 mmol, 1 eq.) was dissolved in MeCN (7 ml) and CAN (433 mg, 0.79 mmol, 2.5 eq.) in H_2O (3 ml) was added. The mixture was stirred for 3 h at rt. Brine (5 ml) was added and the mixture was extracted with DCM (3 x 40 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (15 g SiO_2, cycH/EA = 7:3 → EA) afforded the title compound as colorless solids.

Yield: 82% (110 mg, 0.31 mmol)

Appearance: colorless solids

TLC: R_f = 0.50 (EA; UV, PMA)

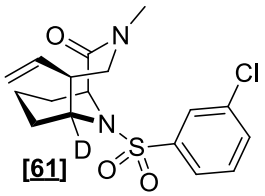
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.07 – 1.30 (m, 3H), 1.39 – 1.54 (m, 2H), 2.04 – 2.20 (m, 1H), 2.51 – 2.65 (m, 1H), 2.80 (m, 1H), 3.69 (m, 1H), 4.61 (dd, *J* = 6.4, 1.9 Hz, 1H), 4.95 – 5.12 (m, 2H), 5.72 (m, 1H), 6.37 (d, *J* = 8.1 Hz, 1H), 7.41 (td, *J* = 7.9, 1.0 Hz, 1H), 7.49 (m, 1H), 7.65 (m, 1H), 7.76 (q, *J* = 1.7 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 15.4, 26.3, 26.9, 45.1, 50.0, 54.7, 56.2, 116.8, 124.6, 126.7, 130.7, 132.9, 135.6, 137.2, 142.9, 173.0.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{18}ClDN_2O_3S$ 356.0940; Found 356.0942

Lab book number(s): JK110

5.2.54. Compound [61]: (1*S*,5*S*,6*R*)-(6-^{2}H)-10-((3-chlorophenyl)sulfonyl)-3-methyl-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[61]

Compound **[60]** (70 mg, 0.20 mmol, 1 eq.) was dissolved in dry DMF (2 ml) and NaH (16 mg, 0.39 mmol, 2 eq.) was added. The mixture was stirred for 15 min at rt. MeI (61 µl, 0.98 mmol, 5 eq.) was added and the mixture was heated to 80 °C and stirred for 1 h. The mixture was quenched with sat. aq. NH_4Cl solution and extracted with DCM (3 x 20 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (15 g SiO_2, cycH/EA = 2:1) afforded the title compound as colorless crystals.

Yield: 98% (71 mg, 0.19 mmol)

Appearance: colorless crystals

TLC: R_f = 0.31 (cycH/EA = 1:1; UV, Hanessian)

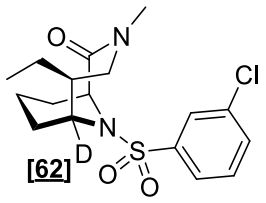
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.05 – 1.25 (m, 2H), 1.34 – 1.55 (m, 3H), 2.11 – 2.21 (m, 1H), 2.59 (m, 1H), 2.83 (dd, *J* = 14.2, 2.1 Hz, 1H), 3.01 (s, 3H), 4.03 (dd, *J* = 14.1, 10.9 Hz, 1H), 4.62 (dd, *J* = 6.1, 2.1 Hz, 1H), 4.98 – 5.10 (m, 2H), 5.73 (m, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.49 (m, 1H), 7.64 (m, 1H), 7.74 (t, *J* = 1.9 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 15.5, 26.0, 27.2, 39.3, 48.9, 53.4, 54.4, 56.8, 116.7, 124.6, 126.7, 130.6, 132.8, 135.6, 137.4, 143.0, 170.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{20}ClDN_2O_3S$ 370.1097; Found 370.1099

Lab book number(s): JK112

5.2.55. Compound [62]: (1*S*,5*S*,6*R*)-(6-^{2}H)-10-((3-chlorophenyl)sulfonyl)-5-ethyl-3-methyl-3,10-diazabicyclo[4.3.1]decan-2-one



[62]

Compound **[61]** (24.0 mg, 0.07 mmol, 1 eq.) was dissolved in MeOH (4 ml) and Pt/C (1 mg, 0.001 mmol, 0.01 eq., 10% loading) was added. H_2 was bubbled through for 2 min and the reaction mixture was stirred for 1 h under hydrogen atmosphere. Filtration through Celite, washing with EA and removing of the solvents under reduced pressure afforded the product in 99% purity as white crystals.

Yield: quant. (25 mg, 0.07 mmol)

Appearance: white solid

TLC: R_f = 0.29 (cycH/EA = 1:1; UV)

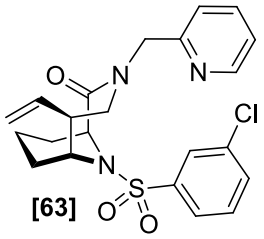
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.4 Hz, 3H), 1.02 – 1.52 (m, 7H), 1.77 – 1.90 (m, 1H), 2.08 – 2.20 (m, 1H), 2.81 (dd, *J* = 14.2, 1.9 Hz, 1H), 3.00 (s, 3H), 3.82 (dd, *J* = 14.2, 10.7 Hz, 1H), 4.61 (dd, *J* = 6.1, 2.0 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.48 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.56 – 7.69 (m, 1H), 7.75 (d, *J* = 1.9 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 11.6, 15.6, 26.3, 27.3, 27.3, 39.1, 45.4, 52.8, 54.9, 56.8, 124.7, 126.7, 130.6, 132.7, 135.5, 143.1, 170.3.

Mass (ESI): $[M + H]^+$ = 372.31

Lab book number(s): JK113

5.2.56. Compound [63]: (1*S*,5*S*,6*R*)-10-[(3-chlorophenyl)sulfonyl]3-(pyridine-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[63]

Compound **[33]** (40 mg, 0.15 mmol, 1 eq.), 3-chlorobenzenesulfonyl chloride (47 mg, 0.22 mmol, 1.5 eq.) and DIPEA (50 μl, 0.29 mmol, 2 eq.) were placed in a flask under argon atmosphere. MeCN (30 ml) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with EA (80 ml) and washed with brine (20 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (25 g SiO_2, cycH/EA = 1:1) afforded the title compound as colorless resin.

Yield: 53% (35 mg, 0.08 mmol)

Appearance: colorless resin

TLC: R_f = 0.16 (cycH/EA = 1:2; UV)

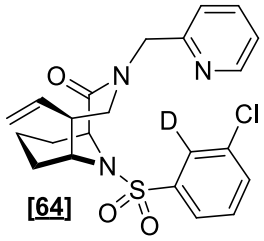
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.16 – 1.37 (m, 2H), 1.46 – 1.55 (m, 2H), 1.54 – 1.67 (m, 1H), 2.19 – 2.36 (m, 1H), 2.61 – 2.79 (m, 1H), 3.10 (dd, *J* = 14.2, 1.9 Hz, 1H), 3.96 – 4.13 (m, 2H), 4.71 – 4.91 (m, 3H), 4.90 – 5.11 (m, 2H), 5.57 – 5.84 (m, 1H), 7.20 (m, 1H), 7.33 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.48 (td, *J* = 8.0, 1.2 Hz, 1H), 7.57 (m, 1H), 7.63 – 7.78 (m, 2H), 7.84 (t, *J* = 1.9 Hz, 1H), 8.54 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.6, 26.3, 27.4, 49.1, 52.1, 54.7, 56.2, 56.8, 116.7, 122.0, 122.4, 124.6, 126.7, 130.6, 132.8, 135.6, 136.9, 137.3, 143.0, 149.2, 157.0, 170.7.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{25}ClN_3O_3S$ 446.1300; Found 446.1300

Lab book number(s): JK396

5.2.57. Compound [64]: (1*S*,5*S*,6*R*)-10-[((2-^{2}H)-3-chlorophenyl)sulfonyl]3-(pyridine-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[64]

Compound **[33]** (97 mg, 0.36 mmol, 1 eq.) was dissolved in MeCN (75 ml). Compound **[4]** (75 μl, 0.54 mmol, 1.5 eq.) and DIPEA (122 μl, 0.71 mmol, 2.0 eq.) were added successively and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with EA (200 ml) and washed with brine (100 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (75 g SiO_2, cycH/EA = 1:2) afforded the title compound as slightly yellow solids.

Yield: 21% (33 mg, 0.08 mmol)

Appearance: slightly yellow solids

TLC: R_f = 0.19 (cycH/EA = 1:2; UV)

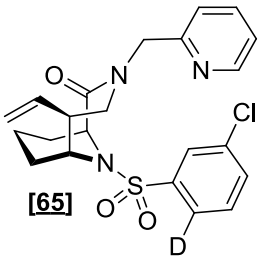
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.12 – 1.39 (m, 1H), 1.38 – 1.81 (m, 3H), 2.19 – 2.42 (m, 1H), 2.69 (m, 1H), 3.10 (dd, *J* = 14.1, 2.0 Hz, 1H), 3.92 – 4.14 (m, 2H), 4.64 – 4.90 (m, 3H), 4.90 – 5.10 (m, 2H), 5.71 (m, 1H), 7.20 (m, 1H), 7.32 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.47 (td, *J* = 7.9, 1.3 Hz, 1H), 7.56 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.63 – 7.77 (m, 2H), 8.53 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.6, 26.3, 27.4, 49.1, 52.1, 54.7, 56.2, 56.8, 116.7, 122.0, 122.4, 124.6, 126.4, 130.6, 132.8, 135.5, 136.9, 137.3, 142.9, 149.2, 157.0, 170.7.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{24}ClDN_3O_3S$ 447.1362; Found 447.1361

Lab book number(s): JK403

5.2.58. Compound [65]: (1*S*,5*S*,6*R*)-10-[((6-^{2}H)-3-chlorophenyl)sulfonyl]3-(pyridine-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[65]

Compound **[33]** (89 mg, 0.33 mmol, 1 eq.) was dissolved in MeCN (75 ml). Compound **[8]** (69 μl, 0.49 mmol, 1.5 eq.) and DIPEA (112 μl, 0.66 mmol, 2.0 eq.) were added successively and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with EA (200 ml) and washed with brine (100 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (75 g SiO_2, cycH/EA = 1:2) afforded the title compound as slightly yellow solids.

Yield: 36% (53 mg, 0.12 mmol)

Appearance: slightly yellow resin

TLC: R_f = 0.19 (cycH/EA = 1:2; UV)

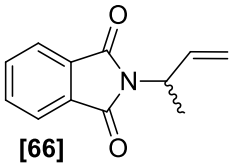
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.10 – 1.38 (m, 2H), 1.43 – 1.78 (m, 3H), 2.27 – 2.38 (m, 1H), 2.52 – 2.78 (m, 1H), 3.10 (dd, *J* = 14.2, 2.0 Hz, 1H), 3.89 – 4.16 (m, 2H), 4.66 – 4.90 (m, 3H), 4.90 – 5.10 (m, 2H), 5.72 (m, 1H), 7.20 (m, 1H), 7.24 – 7.37 (m, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.57 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.69 (td, *J* = 7.7, 1.8 Hz, 1H), 7.84 (d, *J* = 2.0 Hz, 1H), 8.53 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.6, 26.3, 27.4, 49.1, 52.1, 54.7, 56.2, 56.8, 116.7, 122.0, 122.4, 124.4, 126.6, 130.5, 132.8, 135.5, 136.9, 137.3, 142.9, 149.2, 157.0, 170.6.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{24}ClDN_3O_3S$ 447.1362; Found 447.1365

Lab book number(s): JK402

5.2.59. Compound [66]: 2-(but-3-en-2-yl)isoindoline-1,3-dione



[66]

Phthalimide **[23]** (12.0 g, 81.6 mmol, 1 eq.) and potassium carbonate (22.5 g, 162.8 mmol, 12.0 eq.) were dissolved in DMF (250 ml) in a 1000 ml flask. After stirring for 15 min 3-chlorobutene (9.9 ml, 97.8 mmol, 1.2 eq.) was added over 15 min and the reaction mixture was stirred at rt for 5 h. The reaction mixture was diluted with water (800 ml) and solids were collected by filtration.

Yield: 79% (13.0 g, 64.5 mmol)

Appearance: white solids

TLC: R_f = 0.38 (cycH/EA = 5:1; UV)

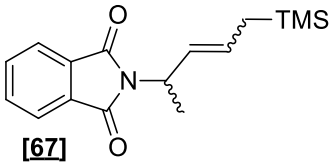
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.57 (d, *J* = 7.2 Hz, 3H), 4.92 (m, 1H), 5.14 (dt, *J* = 10.4, 1.1 Hz, 1H), 5.22 (dt, *J* = 17.3, 1.2 Hz, 1H), 6.18 (m, 1H), 7.62 – 7.73 (m, 2H), 7.73 – 7.87 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 18.2, 48.9, 116.3, 123.1, 132.1, 133.8, 136.8, 167.9.

Mass (ESI): $[M + H]^+$ = 202.27

Lab book number(s): JK248

5.2.60. Compound [67]: 2-(5-(trimethylsilyl)pent-3-en-2-yl)isoindoline-1,3-dione



[67]

Compound **[66]** (13.0 g, 64.5 mmol, 1 eq.) and allyltrimethylsilane (73.8g, 646.1 mmol, 10 eq.) were dissolved in DCM (1500 ml). Grubbs I catalyst (4.8 g, 5.8 mmol, 9% loading) was added and the mixture refluxed for 5 h (60 °C, oil bath). Tris(hydroxymethyl) phosphine (65 ml, 64.6 mmol, 1 eq., 1 M solution in *i*-PrOH) was added and the mixture refluxed for 16 h. Washing with brine (1 x 1000 ml), drying over $MgSO_4$ and removing solvents under reduced pressure resulted in an orange oil. Column chromatography (800 g SiO_2, cycH/EA = 5:1) afforded the title compound as pale-yellow oil which solidified at 4 °C resulting in white solids.

Yield: 14% (2.6 g, 9.0 mmol)

Appearance: white solids

TLC: R_f = 0.52 (cycH/EA = 5:1; UV)

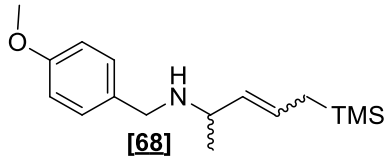
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.00 (d, *J* = 2.9 Hz, 9H), 1.36 – 1.51 (m, 2H), 1.56 (dd, *J* = 15.9, 7.0 Hz, 3H), 4.92 (m, 1H), 5.62 – 5.81 (m, 2H), 7.72 (m, 2H), 7.78 – 7.92 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 0.0, 21.3, 24.5, 51.2, 125.0, 129.1, 131.8, 134.2, 135.7, 170.0.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{22}NO_2Si$ 288.1414; Found 288.1415

Lab book number(s): JK251

5.2.61. Compound [68]: *N*-(4-methoxybenzyl)-5-(trimethylsilyl)pent-3-en-2-amine



[68]

Compound **[67]** (2.6 g, 9.05 mmol, 1 eq.) was dissolved in MeOH (50 ml) and hydrazine (0.4 ml, 18.1 mmol, 2 eq., 50-60% solution) was added. The mixture was refluxed for 18 h. 1 M NaOH (40 ml) and DCM (100 ml) were added and the organic phase was separated. The aqueous phase was extracted with DCM (2 x 100 ml). Both organic phases were combined, dried over $MgSO_4$ and solvents were removed under reduced pressure (700 mbar). The residue was diluted with EtOH (75 ml) and 4-methoxybenzaldehyde (1.2 ml, 10.0 mmol, 1.1 eq.) was added. The mixture was stirred at rt for 2 h. After adding $NaBH_4$ (0.41 g, 10.9 mmol, 1.2 eq.) stirring was continued until no more gas formation was observed (2 h). Sat. aq. $NaHCO_3$ (100 ml) was added carefully and the mixture was extracted with DCM (3 x 100 ml). The combined organic phases were dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (200 g SiO_2, EA + 3% TEA) afforded the title compound as pale-yellow oil.

Yield: 60% (1.5 g, 5.43 mmol, over 2 steps)

Appearance: pale-yellow oil

TLC: R_f = 0.33 (cycH/EA = 2:1 + 3% TEA; UV, ninhydrin)

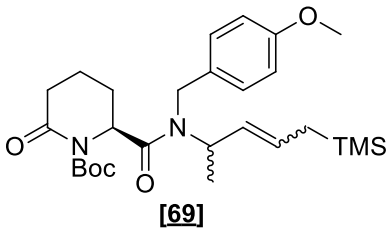
^{1}H-NMR (300 MHz, $CDCl_3$): δ = -0.08 – 0.11 (m, 9H), 1.11 (t, *J* = 6.8 Hz, 3H), 1.28 – 1.49 (m, 2H), 3.05 – 3.20 (m, 1H), 3.48 – 3.75 (m, 2H), 3.77 (s, 3H), 5.14 (m, 1H), 5.49 (m, 1H), 6.66 – 6.94 (m, 2H), 7.12 – 7.30 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 0.0, 24.5, 52.7, 57.2, 57.5, 115.7, 129.3, 131.2, 134.9, 160.4.

Mass (EI): $[M^{+\bullet}]$ = 278.05

Lab book number(s): JK258

5.2.62. Compound [69]: (2*S*)-tert-butyl 2-((4-methoxybenzyl)(5-(trimethylsilyl)pent-3-en-2-yl)carbamoyl)-6-oxopiperidine-1-carboxylate



[69]

HATU (2.26 g, 5.95 mmol, 1.1 eq.) and (*S*)-6-oxopiperidine-2-carboxylic acid (0.85 g, 5.95 mmol, 1.1 eq.) were placed in a flask and stirred for 10 min in DCM (50 ml). DIPEA (1.9 ml, 10.81 mmol, 2 eq.) was added and the mixture stirred for 5 min. Compound **[68]** (1.5 g, 5.41 mmol, 1 eq.) was dissolved in DCM (10 ml) and added to the mixture which was stirred for 16 h at rt. The organic phase was washed twice with sat. aq. $NaHCO_3$ (100 ml) and solvents were removed under reduced pressure. The residue was dissolved in Et_2O (100 ml) and washed with brine (3 x 50 ml). The organic phase was dried over $MgSO_4$ and solvents were removed in vacuo. The resulting reddish oil was dissolved in DCM (50 ml) and DIPEA (4.6 ml, 27.03 mmol, 5 eq.) was added. The mixture was stirred for 15 min before Boc_2O (4.72 g, 21.62 mmol, 4 eq.) and DMAP (0.10 g, 0.81 mmol, 0.15 eq.) were added. Stirring was continued at rt for 72 h. The reaction mixture was washed with brine (2 x 50 ml), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography (200 g SiO_2, cycH/EA = 2:1) afforded the desired product as yellow oil.

Yield: 55% (1.5 g, 3.27 mmol, over 2 steps)

Appearance: yellow oil

TLC: R_f = 0.42 (cycH/EA = 2:1; UV, PMA)

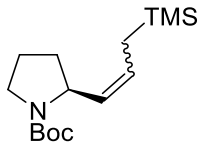
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.24 – 0.12 (m, 9H), 1.17 – 1.26 (m, 2H), 1.36 – 1.56 (m, 12H), 1.59 – 2.69 (m, 6H), 3.63 – 3.88 (m, 3H), 4.15 – 5.83 (m, 6H), 6.73 – 6.80 (m, 1H), 6.83 – 6.91 (m, 1H), 7.12 – 7.18 (m, 1H), 7.25 (d, *J* = 7.8 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = -0.0, 0.0, 0.1, 16.1, 19.7, 20.2, 20.3, 21.3, 21.5, 21.6, 22.9, 24.6, 24.8, 27.5, 27.8, 28.1, 29.9, 30.0, 36.3, 36.4, 46.7, 46.8, 48.6, 49.7, 54.9, 55.3, 55.6, 56.4, 57.1, 57.2, 57.8, 57.9, 58.1, 58.3, 62.2, 84.9, 84.9, 115.4, 115.5, 115.9, 116.0, 129.6, 129.9, 130.1, 130.2, 130.3, 130.3, 130.5, 130.8, 131.4, 131.9, 132.1, 132.4, 133.3, 160.2, 160.8, 172.8, 173.1, 173.5, 174.2.

Mass (ESI): $[M + Na]^+$ = 525.29

Lab book number(s): JK261

5.2.63. Compound [72]: (*S,Z*)-tert-butyl 2-(3-(trimethylsilyl)prop-1-en-1-yl)pyrrolidine-1-carboxylate



[72]

N-Boc-L-prolinol (5.00 g, 24.84 mmol, 1 eq.) was dissolved in DCM (150 ml) and DMP (10.54 mg, 24.84 mmol, 1.0 eq.) was added portionwise. After 1 h the mixture was filtered over silica to remove the formed precipitate and solvents were removed under reduced pressure. 4 g (20.08 mmol) of the afforded *N*-Boc-L-prolinal **[71]** (4.95 g, quant.) were used directly in the next step.
(2-Trimethylsilylethyl)triphenylphosphonium iodide (9.85 g, 20.08 mmol, 1eq.) was dissolved in dry THF (120 ml). The mixture was cooled to 0 °C with an ice bath and n-butyllithium (8.0 ml, 20.08 mmol, 1.0 eq., 2.5 M in hexanes) was added dropwise. The clear deep-red solution was stirred for 90 min at room temperature before *N*-Boc-L-prolinal **[71]** (4 g, 20.08 mmol, 1 eq.) was added dropwise. Upon addition the reaction mixture turned from red to slightly yellow. After full addition of the starting material the reaction was quenched with sat. aq. NH_4Cl solution (50 ml) and extracted with EA (3 x 100 ml). The organic phase was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (30 g silica, cycH/EA = 9:1) afforded the product as slightly yellow oil.

Yield: 40% (2.30 g, 8.03 mmol, over 2 steps)

Appearance: slightly yellow oil

TLC: R_f = 0.54 (cycH/EA = 5:1; Hanessian)

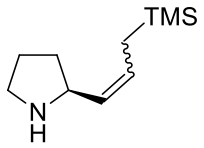
^{1}H NMR (500 MHz, $CDCl_3$): δ = -0.01 (d, *J* = 13.8 Hz, 9H), 1.42 (d, *J* = 2.2 Hz, 11H), 1.55 – 2.10 (m, 4H), 3.20 – 3.49 (m, 2H), 4.35 (m, *J* = 113.8 Hz, 1H), 5.06 – 5.25 (m, 1H), 5.38 (td, *J* = 10.6, 6.6 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = -0.0, 20.5, 24.1, 30.3, 47.8, 48.1, 55.5, 80.6, 128.0, 131.2, 156.3.

Mass (ESI): $[M + H]^+$ = 283.99

Lab book number(s): JK257, JK264, JK288

5.2.64. Compound [73]: (*S*)-2-(3-(trimethylsilyl)prop-1-en-1-yl)pyrrolidine



[73]

Compound **[72]** (2.30 g, 11.54 mmol, 1 eq.) was dissolved in DCM (200 ml) and $ZnBr_2$ (7.80 g, 34.63 mmol, 3.0 eq.) was added portionwise. After 16 h the mixture was filtered over cotton and washed with aq. Sat. $NaHCO_3$ solution (100 ml). Solvents were removed under reduced pressure and the residue was purified by column chromatography (200 g silica, EA + 3% TEA + 5% MeOH) to yield colorless oil. According to ^{1}H-NMR the product is obtained as a ratio of *E/Z* = 1:4, which was not distinguishable in the NMR of the Boc-protected precursor.

Yield: 90% (1.9 g, 10.36 mmol)

Appearance: colorless oil

TLC: R_f = 0.20 (EA + 3% TEA + 5% MeOH; Ninhydrin)

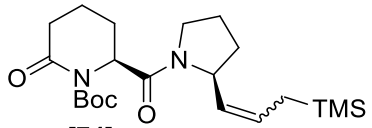
^{1}H NMR (500 MHz, $CDCl_3$, **major**): δ = -0.01 (d, *J* = 12.5 Hz, 9H), 1.35 (m, 1H), 1.53 (m, 2H), 1.68 – 1.80 (m, 2H), 1.83 – 1.96 (m, 1H), 2.75 – 2.90 (m, 1H), 3.04 (m, 1H), 3.71 – 3.81 (m, 1H), 5.25 (m, 1H), 5.43 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$, **major**): δ = -0.1, 0.0, 20.8, 27.4, 34.6, 48.4, 57.0, 128.8, 132.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{21}NSi$ 184.1516; Found 184.1517

Lab book number(s): JK269, JK273, JK293

5.2.65. Compound [73]: (*S*)-tert-butyl 2-oxo-6-((*S*)-2-(3-(trimethylsilyl)prop-1-en-1-yl) pyrrolidine-1-carbonyl)piperidine-1-carboxylate



[74]

HATU (4.30 g, 11.40 mmol, 1.1 eq.) and (*S*)-6-oxopiperidine-2-carboxylic acid (1.63 g, 11.40 mmol, 1.1 eq.) were placed in a flask and stirred for 10 min in DCM (50 ml). DIPEA (3.62 ml, 20.72 mmol, 2 eq.) was added and the mixture stirred for 5 min. Compound **[73]** (1.9 g, 10.36 mmol, 1 eq.) was dissolved in DCM (20 ml) and added to the mixture which was stirred for 16 h at rt. The organic phase was washed twice with sat. aq. $NaHCO_3$ (100 ml) and solvents were removed under reduced pressure. The residue was dissolved in Et_2O (200 ml) and washed with brine (3 x 100 ml). The organic phase was dried over $MgSO_4$ and solvents were removed in vacuo. The resulting reddish oil (3.2 g) was dissolved in DCM (50 ml) and DIPEA (8.82 ml, 51.87 mmol, 5 eq.) was added. The mixture was stirred for 15 min before Boc_2O (9.06 g, 41.49 mmol, 4 eq.) and DMAP (1.27 g, 10.37 mmol, 1.0 eq.) were added. Stirring was continued at rt for 72 h. The reaction mixture was diluted with DCM (200 ml), washed with brine (2 x 100 ml), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography (300 g SiO_2, cycH/EA = 2:1) afforded the desired product as slightly yellow oil.

Yield: 54% (2.54 g, 6.21 mmol, over 2 steps)

Appearance: slightly yellow oil

TLC: R_f = 0.28 (cycH/EA = 1:1; Hanessian)

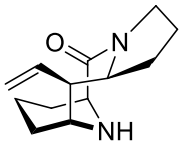
^{1}H NMR (500 MHz, $CDCl_3$): δ = -0.16 – 0.22 (m, 9H), 1.21 – 2.22 (m, 20H), 2.41 (m, 1H), 2.50 – 2.70 (m, 1H), 3.37 – 3.76 (m, 2H), 4.19 – 5.70 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = -0.3, 0.0, 15.9, 19.7, 20.2, 20.4, 20.6, 22.7, 24.2, 25.9, 26.5, 27.1, 29.8, 32.3, 33.3, 36.0, 36.2, 36.7, 47.8, 47.9, 48.8, 55.8, 55.9, 58.6, 58.7, 59.9, 62.0, 84.4, 84.5, 128.9, 129.0, 129.1, 129.4, 130.4, 154.8, 170.6, 171.2, 172.7, 172.9.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{36}N_2O_4Si$ 409.2571; Found 409.2520

Lab book number(s): JK274, JK276, JK277, JK295, JK296

5.2.66. Compound [75]: (6*S*,10*R*,11*R*,11a*S*)-11-vinyloctahydro-1H-6,10-epiminopyrrolo[1,2-a] azonin-5(6H)-one



[75]

Compound **[74]** (1.40 g, 3.43 mmol, 1 eq.) was dissolved in THF (80 ml, dry) and the reaction mixture was cooled to -78 °C. DIBAL-H (3.77 ml, 3.77 mmol, 1.1 eq., 1 M in DCM) was added over 1 h after which no more starting material was detectable by TLC. The reaction was quenched with Glauber's salt and was allowed to warm to rt. Solids were filtered off over celite and the solvent was removed under reduced pressure. The resulting yellow oil (1.40 g) was dissolved in DCM (160 ml) in a fluorinated HDPE bottle and cooled to -78 °C. HF (8 ml, 280 mmol, 82 eq., 70% in pyridine) was added and the mixture stirred for 15 min. The bottle was transferred to an ice-bath and stirred for 2 h. The reaction was quenched with sat. aq. $CaCO_3$ solution (200 ml) and 10 M NaOH (100 ml). The phases were separated and the aqueous phase was extracted with DCM (3 x 200 ml). The combined organic phases were dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (175 g SiO_2, DCM + 2% TEA + 2% MeOH) afforded the desired product a yellow resin.

Yield: 24% (180 mg, 0.82 mmol, over 2 steps)

Appearance: yellow resin

TLC: R_f = 0.45 (DCM + 2% TEA + 2% MeOH)

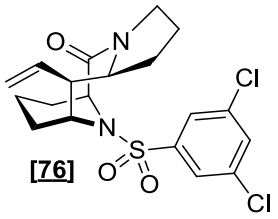
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.50 – 2.28 (m, 10H), 2.34 – 2.51 (m, 2H), 3.44 – 3.59 (m, 2H), 3.75 (dd, *J* = 12.2, 7.9 Hz, 1H), 4.19 (d, *J* = 5.8 Hz, 1H), 4.59 (td, *J* = 10.0, 5.7 Hz, 1H), 5.00 – 5.21 (m, 2H), 5.68 (dt, *J* = 16.7, 9.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.8, 22.0, 24.3, 25.5, 34.2, 49.9, 52.6, 53.0, 54.4, 56.8, 118.8, 135.6, 165.5.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{20}N_2O$ 221.1648; Found 221.1647

Lab book number(s): JK281, JK299, JK339

5.2.67. Compound [76]: (6*S*,10*R*,11*R*,11a*S*)-12-((3,5-dichlorophenyl)sulfonyl)-11-vinyloctahydro-1H-6,10-epiminopyrrolo[1,2-a]azonin-5(6H)-one



[76]

Compound **[75]** (40 mg, 0.18 mmol, 1 eq.), 3,5-dichlorobenzenesulfonyl chloride (67 mg, 0.27 mmol, 1.5 eq.) and DIPEA (106 μl, 0.36 mmol, 2 eq.) were placed in a flask under argon atmosphere. MeCN (15 ml) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with EA (80 ml) and washed with brine (20 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (10 g SiO_2, cycH/EA = 2:1) afforded the title compound as colorless resin.

Yield: 19% (15 mg, 0.035 mmol)

Appearance: colorless resin

TLC: R_f = 0.39 (cycH/EA = 1:1)

HPLC: R_t = 16.77 min (0 – 100% B in 20 min)

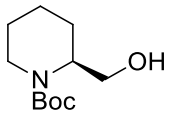
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.18 – 1.27 (m, 2H), 1.56 (m, 3H), 1.64 (m, 1H), 1.73 (m, 1H), 1.89 (dt, *J* = 12.3, 6.3 Hz, 1H), 2.05 (dt, *J* = 12.1, 5.8 Hz, 1H), 2.25 – 2.39 (m, 2H), 3.47 (td, *J* = 11.6, 6.4 Hz, 1H), 3.82 (dd, *J* = 12.1, 7.7 Hz, 1H), 3.91 – 4.04 (m, 1H), 4.12 (td, *J* = 9.9, 6.0 Hz, 1H), 4.70 (d, *J* = 6.1 Hz, 1H), 4.99 – 5.25 (m, 2H), 5.77 (dt, *J* = 16.8, 9.8 Hz, 1H), 7.59 (dt, *J* = 2.3, 1.2 Hz, 1H), 7.72 (dd, *J* = 1.9, 0.7 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 15.4, 22.3, 25.5, 26.7, 33.5, 49.5, 54.7, 55.3, 56.3, 58.5, 117.4, 124.9, 132.7, 136.3, 136.9, 144.2, 169.0.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{22}Cl_2N_2O_3S$ 420.0801; Found 429.0803

Lab book number(s): JK345

5.2.68. Compound [78]: (*S*)-tert-butyl 2-(hydroxymethyl)piperidine-1-carboxylate



[78]

(*S*)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid **[77]** (4.95 g, 21.59 mmol, 1 eq) was dissolved in THF (50 ml) and cooled to 0 °C. BH_3*SMe_2 (8.6 ml, 43.19 mmol, 2.0 eq) was added and the mixture was stirred for 15 min at 0 °C followed by 16 h at rt. The reaction mixture was cooled to 0 °C and carefully quenched with water. The mixture was diluted with EA (150 ml) and washed with brine (2 x 50 ml). Solvents were removed under reduced pressure to afford the desired compound as colorless liquid.

Yield: 95% (4.4 g, 20.51 mmol)

Appearance: colorless liquid

TLC: R_f = 0.45 (cycH/EA = 1:1; Hanessian)

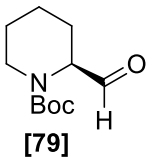
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.39 (s, 9H), 1.41 – 1.73 (m, 6H), 2.70 (s, 1H), 2.75 – 2.86 (m, 1H), 3.54 (dd, *J* = 11.0, 6.4 Hz, 1H), 3.70 (dd, *J* = 11.0, 8.6 Hz, 1H), 3.80 – 3.94 (m, 1H), 4.20 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 19.5, 25.1, 25.2, 28.4, 39.9, 52.4, 61.3, 79.7, 156.1.

Mass (ESI): $[M + H]^+$ = 216.05

Lab book number(s): JK321, JK322

5.2.69. Compound [79]: (*S*)-tert-butyl 2-formylpiperidine-1-carboxylate



[79]

Compound **[78]** (4.40 g, 19.19 mmol, 1 eq.) was dissolved in DCM (150 ml) and DMP (8.95 mg, 21.10 mmol, 1.0 eq.) was added portionwise. After 1 h the mixture was washed with sat. aq. $NaHCO_3$ (2 x 50 ml) and solvents were removed under reduced pressure. Column chromatography (70 g silica, cycH/EA = 3:1) afforded the desired compound as colorless liquid.

Yield: 40% (2.30 g, 8.03 mmol, over 2 steps)

Appearance: colorless liquid

TLC: R_f = 0.60 (cycH/EA = 3:1; Hanessian)

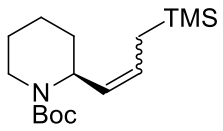
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01 – 1.92 (m, 14H), 2.07 – 2.30 (m, 1H), 2.66 – 3.17 (m, 1H), 3.97 (m, 1H), 4.60 (t, *J* = 36.5 Hz, 1H), 9.60 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 20.9, 23.6, 24.7, 28.3, 43.1, 60.3, 80.4, 155.6, 201.3.

Mass (ESI): $[M + H]^+$ = 214.11

Lab book number(s): JK323

5.2.70. Compound [80]: (*S*)-tert-butyl 2-(3-(trimethylsilyl)prop-1-en-1-yl)piperidine-1-carboxylate



[80]

(2-Trimethylsilylethyl)triphenylphosphonium iodide (8.05 g, 16.41 mmol, 1eq.) was dissolved in dry THF (250 ml). The mixture was cooled to 0 °C with an ice bath and n-butyllithium (7.0 ml, 16.41 mmol, 1.0 eq., 2.5 M in hexanes) was added dropwise. The clear deep-red solution was stirred for 90 min at room temperature before compound **[79]** (3.5 g, 16.41 mmol, 1 eq.) was added dropwise. Upon addition the reaction mixture turned from red to slightly yellow. After full addition of the starting material the reaction was quenched with sat. aq. NH_4Cl solution (50 ml) and extracted with EA (3 x 100 ml). The organic phase was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (200 g silica, cycH/EA = 9:1) afforded the product as slightly yellow oil with impurities of triphenylphosphine which were not seperable by column chromatography. Therefore, the crude material (5.5 g, 113%) was used directly in the next step.

Yield: 113% (5.5 g, crude)

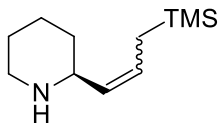
Appearance: slightly yellow oil

TLC: R_f = 0.42 (cycH/EA = 9:1; Hanessian)

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{32}NO_2Si$ 298.2197; Found 298.2196

Lab book number(s): JK324

5.2.71. Compound [81]: (*S*)-2-(3-(trimethylsilyl)prop-1-en-1-yl)piperidine



[81]

Compound **[80]** (5.5 g, crude, assumed 4.9 g actual product, 16.41 mmol, 1 eq.) was dissolved in DCM (200 ml) and $ZnBr_2$ (15.0 g, 70.33 mmol, 4.3 eq.) was added portionwise. After 16 h the mixture was filtered over cotton and washed with aq. Sat. $NaHCO_3$ solution (100 ml). Solvents were removed under reduced pressure and the residue was purified by column chromatography (200 g silica, EA + 2.5% TEA + 2.5% MeOH) to yield colorless oil. According to ^{1}H-NMR the product is obtained as a ratio of *E/Z* = 1:9, which was not distinguishable in the NMR of the Boc-protected precursor.

Yield: 44% (1.4 g, 7.22 mmol, over 2 steps)

Appearance: colorless oil

TLC: R_f = 0.32 (EA + 2.5% TEA + 2.5% MeOH; Ninhydrin)

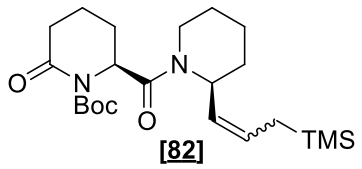
^{1}H NMR (500 MHz, $CDCl_3$, **major**): δ = -0.08 – 0.07 (m, 9H), 1.18 – 1.83 (m, 8H), 2.18 (s, 1H), 2.67 (m, 1H), 3.06 (m, 1H), 3.24 – 3.33 (m, 1H), 5.17 – 5.32 (m, 1H), 5.40 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$, **major**): δ = 0.0, 20.8, 26.5, 27.5, 34.4, 48.7, 55.9, 128.5, 132.6.

Mass (ESI): $[M + H]^+$ = 198.23

Lab book number(s): JK331

5.2.72. Compound [82]: (*S*)-tert-butyl 2-oxo-6-((*S*)-2-(3-(trimethylsilyl)prop-1-en-1-yl) piperidine-1-carbonyl)piperidine-1-carboxylate



[82]

HATU (3.2 g, 8.51 mmol, 1.2 eq.) and (*S*)-6-oxopiperidine-2-carboxylic acid (1.22 g, 8.51 mmol, 1.2 eq.) were placed in a flask and stirred for 10 min in DCM (100 ml). DIPEA (2.48 ml, 14.19 mmol, 2 eq.) was added and the mixture stirred for 5 min. Compound **[81]** (1.4 g, 7.09 mmol, 1 eq.) was dissolved in DCM (20 ml) and added to the mixture which was stirred for 16 h at rt. The organic phase was washed twice with sat. aq. $NaHCO_3$ (100 ml) and solvents were removed under reduced pressure. The residue was dissolved in Et_2O (200 ml) and washed with brine (3 x 100 ml). The organic phase was dried over $MgSO_4$ and solvents were removed in vacuo. The resulting reddish oil (3.2 g) was dissolved in DCM (50 ml) and DIPEA (6.06 ml, 4.61 mmol, 5 eq.) was added. The mixture was stirred for 15 min before Boc_2O (6.23 g, 28.53 mmol, 4 eq.) and DMAP (0.87 g, 7.13 mmol, 1.0 eq.) were added. Stirring was continued at rt for 72 h. The reaction mixture was diluted with DCM (200 ml), washed with brine (2 x 100 ml), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography (200 g SiO_2, cycH/EA = 3:1) afforded the desired product as slightly yellow solids.

Yield: 65% (1.95 g, 4.61 mmol, over 2 steps)

Appearance: slightly yellow solids

TLC: R_f = 0.50 (cycH/EA = 1:1; Hanessian)

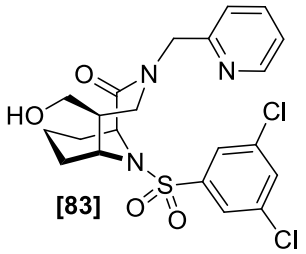
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.01 (d, *J* = 12.7 Hz, 9H), 1.14 – 2.20 (m, 21H), 2.41 (m, 1H), 2.58 (m, 1H), 3.26 (dt, *J* = 14.5, 7.5 Hz, 1H), 3.58 (d, *J* = 13.7 Hz, 1H), 4.78 – 5.13 (m, 1H), 5.23 – 5.78 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 0.0, 20.1, 21.3, 21.3, 26.9, 28.1, 29.9, 31.7, 36.2, 43.7, 47.8, 57.5, 84.6, 125.3, 132.1, 155.2, 170.3, 173.3.

Mass (ESI): $[M + Na]^+$ = 445.25

Lab book number(s): JK334, JK335

5.2.73. Compound [83]: (1*S*,5*S*,6*R*))-10-((3,5-dichlorophenyl)sulfonyl)-5-(hydroxymethyl)-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



[83]

Compound **[34]** (230 mg, 0.48 mmol, 1 eq.) was dissolved in aceton (9 ml) and water (1 ml), 2,6-lutidine (110 μl, 0.96 mmol, 2 eq.), NMO (84 mg, 0.96 mmol, 2 eq.) and OsO_4 (120 µL, 0.0096 mmol, 0.02 eq., 2.5% in t-BuOH) were added successively. After full conversion (2 h, monitored by TLC) $PhI(OAc)_2$ (308 mg, 0.96 mmol, 2 eq.) was added and the mixture stirred for 3 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ solution (0 ml), extracted with EA (50 ml), washed with sat. aq. $CuSO_4$ solution, dried over $MgSO_4$ and filtered over silica. Solvents were removed under reduced pressure and the residue was dissolved in EtOH (15 ml). After cooling to 0 °C $NaBH_4$ (15 mg, 0.40 mmol, 1.5 eq.) was added, the mixture stirred for 15 min at 0 °C and 1 h at rt. The reaction was quenched with sat. aq. $NaHCO_3$ solution, extracted with DCM, dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (EA) afforded the title compound as white solids.

Yield: 56% (130 mg, 0.27 mmolover 2 steps)

Appearance: white solids

TLC: R_f = 0.14 (EA; UV)

HPLC: R_t = 10.72 min (0 – 100% B in 20 min)

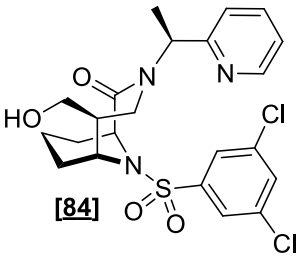
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.11 – 1.58 (m, 5H), 2.10 – 2.34 (m, 2H), 2.55 (bs, 1H), 3.32 (dd, *J* = 14.4, 1.9 Hz, 1H), 3.47 (d, *J* = 6.4 Hz, 2H), 3.78 (dd, *J* = 14.4, 10.6 Hz, 1H), 3.88 (td, *J* = 5.2, 2.6 Hz, 1H), 4.61 – 4.81 (m, 3H), 7.14 (dd, *J* = 7.5, 4.9 Hz, 1H), 7.26 (d, *J* = 7.9 Hz, 1H), 7.49 (t, *J* = 1.9 Hz, 1H), 7.63 (dd, *J* = 4.6, 1.8 Hz, 3H), 8.43 (d, *J* = 4.9 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.5, 27.9, 27.9, 46.8, 49.5, 52.4, 56.0, 57.1, 63.3, 122.6, 124.9, 132.7, 136.3, 137.2, 144.0, 149.0, 156.9, 170.4.

Mass (ESI): $[M + H]^+$ = 484.54

Lab book number(s): JK095

5.2.74. Compound [84]: (((1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-5-(hydroxymethyl)-3-((*S*)-1-(pyridin-2-yl)ethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



[84]

Compound **[39]** (100 mg, 0.20 mmol, 1 eq.) was dissolved in aceton (5.5ml) and water (0.5 ml), 2,6-lutidine (47 μl, 0.40 mmol, 2 eq.), NMO (48 mg, 0.40 mmol, 2 eq.) and OsO_4 (50 µL, 0.0040 mmol, 0.02 eq., 2.5% in t-BuOH) were added successively. After full conversion (2 h, monitored by TLC) $PhI(OAc)_2$ (130 mg, 0.40 mmol, 2 eq.) was added and the mixture stirred for 3 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ solution, extracted with EA, washed with sat. aq. $CuSO_4$ solution, dried over $MgSO_4$ and filtered over silica. Solvents were removed under reduced pressure and the residue was dissolved in EtOH (10 ml). After cooling to 0 °C $NaBH_4$ (7.5 mg, 0.20 mmol, 1.0 eq.) was added, the mixture stirred for 15 min at 0 °C and 1 h at rt. The reaction was quenched with sat. aq. $NaHCO_3$ solution, extracted with DCM, dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (EA) afforded the title compound as white solids.

Yield: 54% (54 mg, 0.11 mmol, over 2 steps)

Appearance: white solids

TLC: R_f = 0.38 (EA; UV, Hanessian)

HPLC: R_t = 11.45 min (0 – 100% B in 20 min)

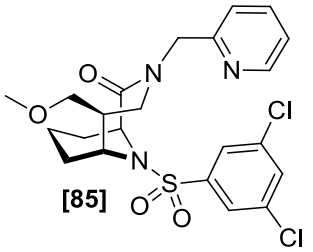
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.18 – 1.26 (m, 2H), 1.33 – 1.45 (m, 1H), 1.45 – 1.58 (m, 6H), 2.12 (m, 1H), 2.29 (m, 1H), 3.10 – 3.21 (m, 2H), 3.44 – 3.57 (m, 2H), 3.89 (m, 1H), 4.70 (dt, *J* = 6.0, 2.0 Hz, 1H), 6.07 (q, *J* = 6.9 Hz, 1H), 7.15 (m, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.47 (t, *J* = 1.8 Hz, 1H), 7.62 (dd, *J* = 7.4, 1.9 Hz, 3H), 8.49 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.1, 15.6, 28.2, 28.3, 43.5, 47.7, 52.5, 55.1, 57.2, 63.6, 122.5, 123.0, 124.9, 132.7, 136.3, 137.1, 144.0, 148.6, 158.9, 169.9.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{26}Cl_2N_3O_4S$ 498.1016; Found 498.1016

Lab book number(s): JK236

5.2.75. Compound [85]: (1*S*,5*S*,6*R*))-10-((3,5-dichlorophenyl)sulfonyl)-5-(methoxymethyl)-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



[85]

Compound **[83]** (85 mg, 0.18 mmol, 1 eq.) was dissolved in DMF (8 ml) and cooled to 0 °C. NaH (21 mg, 0.53 mmol, 3 eq.) and MeI (44 µL, 0.70 mmol, 4 eq.) were added successively. After 90 min the reaction was quenched with sat. aq. NH_4Cl solution, extracted with EA and dried over $MgSO_4$. Removal of solvents followed by column chromatography (EA) afforded the title compound as colorless oil.

Yield: 89% (77 mg, 0.16 mmol)

Appearance: colorless oil

TLC: R_f = 0.32 (EA; UV)

HPLC: R_t = 14.88 min (0 – 100% B in 20 min)

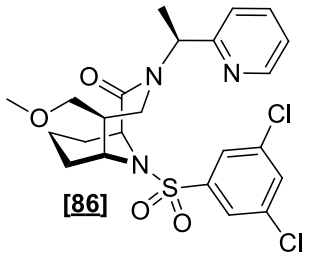
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.19 – 1.38 (m, 1H), 1.45 (m, 1H), 1.50 – 1.73 (m, 3H), 2.25 – 2.41 (m, 2H), 3.14 – 3.30 (m, 6H), 3.73 (dd, *J* = 14.3, 10.7 Hz, 1H), 3.97 (dd, *J* = 6.8, 4.8 Hz, 1H), 4.68 – 4.81 (m, 2H), 4.87 (d, *J* = 15.3 Hz, 1H), 7.18 – 7.25 (m, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.55 (t, *J* = 1.9 Hz, 1H), 7.71 (t, *J* = 2.3 Hz, 3H), 8.54 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.6, 28.1, 28.1, 44.5, 49.6, 52.7, 56.1, 57.0, 59.0, 73.3, 122.0, 122.5, 125.0, 132.6, 136.3, 137.2, 144.0, 149.0, 156.8, 170.4.

Mass (ESI): $[M + H]^+$ = 498.28

Lab book number(s): JK096

5.2.76. Compound [86]: (((1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-5-(methoxymethyl)-3-((*S*)-1-(pyridin-2-yl)ethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



[86]

Compound **[84]** (50 mg, 0.10 mmol, 1 eq.) was dissolved in DMF (5 ml). NaH (12 mg, 0.30 mg, 3 eq.) and MeI (25 µL, 0.40 mmol, 4 eq.) were added successively and the mixture was stirred for 4 h at rt. The reaction was quenched with sat. aq. NH_4Cl solution (20 ml), extracted with EA (80 ml) and dried over $MgSO_4$. Solvents were removed under reduced pressure and the crude was purified by column chromatography (10 g SiO_2, cycH/EA = 1:1)

Yield: 92% (47 mg, 0.09 mmol)

Appearance: white solids

TLC: R_f = 0.23 (cycH/EA = 1:1; UV, Hanessian)

HPLC: R_t = 13.31 min (0 – 100% B in 20 min)

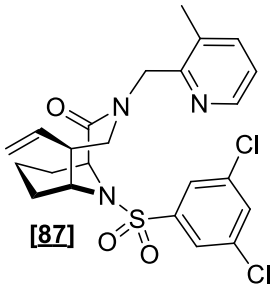
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.25 (m, 1H), 1.37 – 1.46 (m, 1H), 1.46 – 1.58 (m, 6H), 2.09 – 2.20 (m, 1H), 2.29 (m, 1H), 2.99 (dd, *J* = 14.7, 2.1 Hz, 1H), 3.08 (dd, *J* = 14.7, 10.3 Hz, 1H), 3.15 – 3.22 (m, 2H), 3.24 (s, 3H), 3.88 (td, *J* = 5.8, 4.9, 2.0 Hz, 1H), 4.72 (dt, *J* = 6.0, 2.0 Hz, 1H), 6.07 (q, *J* = 6.9 Hz, 1H), 7.14 (dd, *J* = 7.5, 5.0 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 1.8 Hz, 1H), 7.58 – 7.65 (m, 3H), 8.50 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.1, 15.6, 28.2, 28.4, 43.6, 45.6, 52.9, 55.0, 57.2, 59.1, 73.4, 122.4, 122.8, 125.0 (2C), 132.6, 136.2 (2C), 137.0, 144.0, 148.6, 159.0, 170.0.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{27}Cl_2N_3O_4S$ 512.1172; Found 512.1173

Lab book number(s): JK237

5.2.77. Compound [87]: (1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-3-((3-methylpyridin-2-yl) methyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[87]

Compound **[30]** (20 mg, 0.05 mmol, 1 eq.) and 2-(chloromethyl)-3-methylpyridine (29 mg, 0.21 mmol, 4 eq.) were dissolved in dry DMF (2 ml) and NaH (10 mg, 0.26 mmol, 5 eq.) was added. The mixture was stirred for 1 h at 80 °C. Brine (10 ml) was added and the mixture was extracted with Et_2O (4 x 30 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (20 g SiO_2, cycH/EA = 1:1) afforded the title compound as colorless resin.

Yield: 48% (12 mg, 0.024 mmol)

Appearance: colorless resin

TLC: R_f = 0.41 (cycH/EA = 1:1; UV)

HPLC: R_t = 13.43 min (0 – 100% B in 20 min)

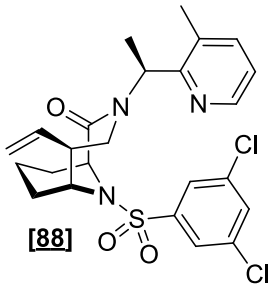
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.19 – 1.38 (m, 2H), 1.52 – 1.61 (m, 2H), 1.81 (m, 1H), 2.33 (s, 4H), 3.06 – 3.21 (m, 2H), 3.93 (dd, *J* = 14.0, 10.4 Hz, 1H), 4.02 (m, 1H), 4.68 (d, *J* = 15.4 Hz, 1H), 4.77 (dt, *J* = 6.2, 2.0 Hz, 1H), 4.99 (d, *J* = 15.3 Hz, 1H), 5.03 – 5.11 (m, 2H), 5.62 – 5.83 (m, 1H), 7.13 (dd, *J* = 7.6, 4.7 Hz, 1H), 7.46 (m, 1H), 7.58 (t, *J* = 1.9 Hz, 1H), 7.73 (d, *J* = 1.8 Hz, 2H), 8.32 – 8.46 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.6, 18.0, 26.4, 27.5, 48.5, 51.8, 53.9, 55.0, 56.9, 116.7, 122.5, 124.9, 131.7, 132.6, 136.3, 137.6, 138.0, 144.2, 146.4, 154.3, 170.1.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{25}Cl_2N_3O_3S$ 494.1066; Found 494.1067

Lab book number(s): JK385

5.2.78. Compound [88]: (1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-3-((*S*)-1-(3-methylpyridin-2-yl)ethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[88]

Compound **[30]** (32 mg, 0.08 mmol, 1 eq.) and **[13]** (38 mg, 0.25 mmol, 3 eq.) were dissolved in dry MeCN (10 ml) and NaH (10 mg, 0.25 mmol, 3 eq.) was added. The mixture was stirred for 4 h at 40 °C. Brine (10 ml) was added and the mixture was extracted with EA (2 x 50 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (30 g SiO_2, cycH/EA = 9:1 → 5:1) afforded the title compound as white solids.

Yield: 19% (8 mg, 0.015 mmol)

Appearance: white solids

TLC: R_f = 0.27 (cycH/EA = 3:1; UV)

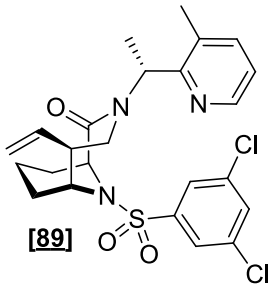
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.05 – 1.62 (m, 8H), 2.19 (s, 3H), 2.30 (m, 1H), 2.46 (q, *J* = 8.9 Hz, 1H), 2.88 (dd, *J* = 14.6, 1.8 Hz, 1H), 3.05 (dd, *J* = 14.7, 10.6 Hz, 1H), 3.77 – 3.93 (m, 1H), 4.66 (dt, *J* = 6.1, 1.9 Hz, 1H), 4.97 – 5.06 (m, 2H), 5.59 (m, 1H), 6.05 (q, *J* = 6.7 Hz, 1H), 7.09 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.41 (m, 1H), 7.44 – 7.53 (m, 1H), 7.53 – 7.69 (m, 2H), 8.35 (dd, *J* = 4.9, 1.7 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.4, 15.6, 17.8, 25.9, 27.4, 45.4, 49.9, 53.1, 55.1, 56.8, 116.9, 122.8, 124.8, 132.6, 133.4, 136.4, 136.9, 138.4, 144.1, 146.2, 156.2, 169.4.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{28}Cl_2N_3O_3S$ 508.1223; Found 508.1224

Lab book number(s): JK414

5.2.79. Compound [89]: (1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-3-((*R*)-1-(3-methylpyridin-2-yl)ethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[89]

This compound was isolated from the previous reaction.

Yield: 35% (15 mg, 0.03 mmol)

Appearance: white solids

TLC: R_f = 0.42 (cycH/EA = 3:1; UV)

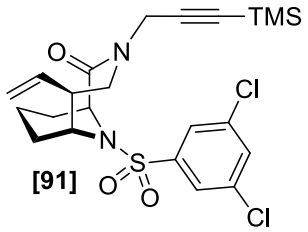
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.12 – 1.41 (m, 5H), 1.43 (d, *J* = 7.0 Hz, 3H), 1.93 – 2.04 (m, 1H), 2.19 (m, 1H), 2.32 (s, 3H), 3.40 (dd, *J* = 14.3, 1.9 Hz, 1H), 3.53 (dd, *J* = 14.3, 10.3 Hz, 1H), 3.78 – 3.93 (m, 1H), 4.60 (dt, *J* = 17.0, 1.2 Hz, 1H), 4.69 (dt, *J* = 6.0, 1.9 Hz, 1H), 4.85 (dd, *J* = 10.0, 1.4 Hz, 1H), 5.42 – 5.63 (m, 1H), 6.10 (q, *J* = 7.0 Hz, 1H), 7.04 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.39 (m, 1H), 7.48 (t, *J* = 1.9 Hz, 1H), 7.62 (d, *J* = 1.9 Hz, 2H), 8.31 (dd, *J* = 4.8, 1.7 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.6, 16.5, 18.4, 26.4, 28.0, 44.8, 49.4, 51.7, 55.0, 57.1, 116.2, 122.5, 124.9, 131.8, 132.6, 136.3, 137.5, 138.2, 144.2, 146.3, 157.5, 169.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{28}Cl_2N_3O_3S$ 508.1223; Found 508.1224

Lab book number(s): JK414

5.2.80. Compound [91]: (1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-3-(3-(trimethylsilyl) prop-2-yn-1-yl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[91]

Compound **[90]** (440 mg, 1.51 mmol, 1 eq.) was dissolved in MeCN (100 ml). DIPEA (900 μl, 5.13 mmol, 3.40 eq.) and 3,5-dichlorobenzenesulfonyl chloride (558 mg, 2.27 mmol, 1.5 eq.) were added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with EA (150 ml) and washed with brine (2 x 50 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (100 g SiO_2, cycH/EA = 1:1) afforded the title compound as colorless resin.

Yield: 53% (400 mg, 0.80 mmol)

Appearance: colorless resin

TLC: R_f = 0.27 (cycH/EA = 9:1; UV, PMA)

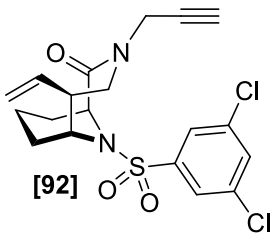
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.00 (d, J = 0.9 Hz, 9H), 0.99 – 1.08 (m, 1H), 1.10 – 1.23 (m, 2H), 1.20 – 1.38 (m, 2H), 2.04 – 2.24 (m, 1H), 2.42 – 2.66 (m, 1H), 3.12 (dd, J = 14.2, 1.9 Hz, 1H), 3.64 (d, J = 17.4 Hz, 1H), 3.73 – 3.91 (m, 2H), 4.55 (d, J = 5.8 Hz, 1H), 4.66 (d, J = 17.5 Hz, 1H), 4.88 – 5.11 (m, 2H), 5.51 – 5.80 (m, 1H), 7.32 – 7.44 (m, 1H), 7.53 (dd, J = 1.9, 0.9 Hz, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = -0.0, 15.5, 26.4, 27.8, 40.2, 49.8, 50.5, 55.1, 57.1, 89.0, 100.4, 117.1, 125.1, 132.9, 136.5, 137.3, 144.2, 169.8.

Mass (ESI): $[M + H]^+$ = 499.64

Lab book number(s): JK308

5.2.81. Compound [92]: (1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-3-(prop-2-yn-1-yl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[92]

Compound **[91]** (390 mg, 0.78 mmol, 1 eq.) was dissolved in THF (50 ml). 1 M NaOH (30 ml) was added and the mixture was stirred at 80 °C for 16 h. The mixture was diluted with EA (150 ml) and washed with brine (50 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (50 g silica; cycH/EA = 6:1 → 3:1) afforded the title compound as white solids.

Yield: 80% (267 mg, 0.62 mmol)

Appearance: white solids

TLC: R_f = 0.35 (cycH/EA = 3:1; UV, Hanessian)

HPLC: R_t = 16.95 min (0 – 100% B in 20 min)

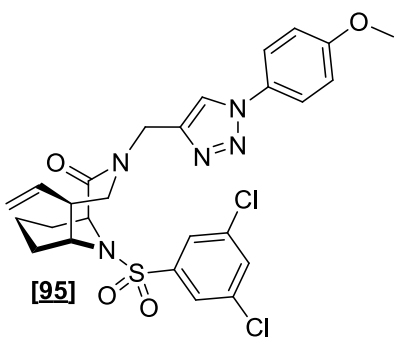
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.16 – 1.37 (m, 2H), 1.47 – 1.64 (m, 3H), 2.22 (t, *J* = 2.4 Hz, 1H), 2.28 (m, 1H), 2.71 (m, 1H), 3.20 (dd, *J* = 14.2, 2.0 Hz, 1H), 3.81 – 4.11 (m, 3H), 4.54 – 4.79 (m, 2H), 5.07 – 5.29 (m, 2H), 5.81 (m, 1H), 7.56 (t, *J* = 1.8 Hz, 1H), 7.69 (d, *J* = 1.8 Hz, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.4, 26.3, 27.6, 39.3, 49.3, 50.9, 55.0, 56.9, 71.7, 78.5, 117.1, 124.9, 132.7, 136.4, 137.1, 144.0, 170.0.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{20}Cl_2N_2O_3S$ 427.0644; Found 427.0645

Lab book number(s): JK313

5.2.82. Compound [95]: (1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-3-((1-(4-methoxy phenyl)-1H-1,2,3-triazol-4-yl)methyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[95]

Compound **[92]** (20 mg, 0.05 mmol, 1 eq.) was dissolved in t-BuOH/H_2O (3 ml, 1:1). $CuSO_4$ (12 mg, 0.05 mmol, 1 eq.) and sodium ascorbate (9 mg, 0.05 mmol, 1 eq.) were added and the mixture was stirred for 10 min. 1-azido-4-methoxybenzene (14 mg, 0.09 mmol, 2 eq.) was added and the mixture was stirred for 16 h at 37 °C. The mixture was diluted with DCM (50 ml) and washed with brine (10 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (10 g silica; cycH/EA = 1 :1) afforded the title compound as white solids.

Yield: 85% (23 mg, 0.04 mmol)

Appearance: white solids

TLC: R_f = 0.29 (cycH/EA = 1:1; UV)

HPLC: R_t = 17.70 min (0 – 100% B in 20 min)

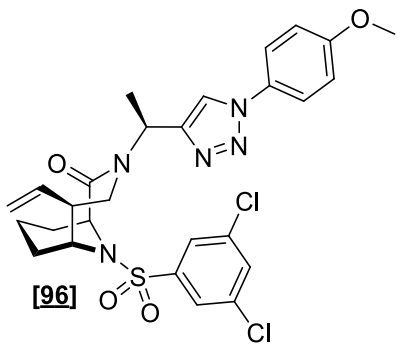
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.17 – 1.49 (m, 5H), 2.14 – 2.25 (m, 1H), 2.60 (m, 1H), 3.22 – 3.37 (m, 1H), 3.79 (s, 3H), 3.90 – 4.04 (m, 2H), 4.63 (dt, *J* = 6.1, 1.9 Hz, 1H), 4.73 (s, 2H), 4.99 – 5.12 (m, 2H), 5.64 – 5.76 (m, 1H), 6.91 – 6.99 (m, 2H), 7.48 (t, *J* = 1.8 Hz, 1H), 7.54 – 7.61 (m, 2H), 7.62 (d, *J* = 1.9 Hz, 2H), 7.89 (s, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.4, 26.4, 27.4, 46.5, 49.0, 52.2, 54.9, 55.6, 56.9, 114.8, 117.2, 120.8, 122.0, 124.9, 130.4, 132.7, 136.4, 136.9, 144.0, 144.4, 159.9, 170.5.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{27}Cl_2N_5O_4S$ 576.1234; Found 576.1243

Lab book number(s): JK350

5.2.83. Compound [96]: (1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-3-((*S*)-1-(1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)ethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[96]

(1*S*,5*S*,6*R*)-3-((*S*)-but-3-yn-2-yl)-10-((3,5-dichlorophenyl)sulfonyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one **[93]** (18 mg, 0.041 mmol, 1 eq.) was dissolved in t-BuOH/H_2O (3 ml, 1:1). $CuSO_4$ (15 mg, 0.061 mmol, 1.5 eq.) and sodium ascorbate (12 mg, 0.061 mmol, 1.5 eq.) were added and the mixture was stirred for 10 min. 1-azido-4-methoxybenzene (12 mg, 0.082 mmol, 2 eq.) was added and the mixture was stirred for 16 h at 37 °C. The mixture was diluted with DCM (50 ml) and washed with brine (10 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (20 g silica; cycH/EA = 2 :1) afforded the title compound as white solids.

Yield: 33% (8 mg, 0.014 mmol)

Appearance: white solids

TLC: R_f = 0.38 (cycH/EA = 1:1; UV)

HPLC: R_t = 18.07 min (0 – 100% B in 20 min)

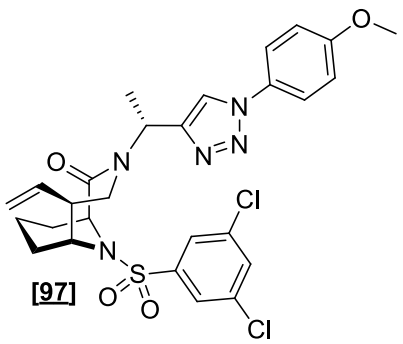
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.15 – 1.24 (m, 1H), 1.26 – 1.37 (m, 1H), 1.51 – 1.57 (m, 3H), 1.63 (d, *J* = 7.0 Hz, 3H), 2.20 – 2.34 (m, 1H), 2.44 – 2.56 (m, 1H), 3.07 (dd, *J* = 14.7, 1.8 Hz, 1H), 3.46 (dd, *J* = 14.8, 10.8 Hz, 1H), 3.80 (s, 3H), 3.89 – 4.02 (m, 1H), 4.62 (dt, *J* = 6.1, 1.9 Hz, 1H), 5.00 – 5.14 (m, 2H), 5.69 (m, 1H), 6.07 – 6.19 (m, 1H), 6.90 – 6.99 (m, 2H), 7.47 (t, *J* = 1.8 Hz, 1H), 7.56 – 7.60 (m, 2H), 7.61 (d, *J* = 1.9 Hz, 2H), 7.77 (d, *J* = 0.7 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.5, 16.0, 26.4, 27.7, 46.0, 47.5, 50.1, 55.2, 55.6, 57.1, 114.8, 117.0, 120.2, 122.1, 124.9, 130.5, 132.7, 136.4, 136.9, 143.9, 147.4, 159.8, 169.9.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{30}Cl_2N_5O_4S$ 590.1390; Found 590.1393

Lab book number(s): JK353

5.2.84. Compound [97]: (1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-3-((R)-1-(1-(4-methoxy phenyl)-1H-1,2,3-triazol-4-yl)ethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[97]

Compound **[94]** (18 mg, 0.041 mmol, 1 eq.) was dissolved in t-BuOH/H_2O (3 ml, 1:1). $CuSO_4$ (15 mg, 0.061 mmol, 1.5 eq.) and sodium ascorbate (12 mg, 0.061 mmol, 1.5 eq.) were added and the mixture was stirred for 10 min. 1-azido-4-methoxybenzene (12 mg, 0.082 mmol, 2 eq.) was added and the mixture was stirred for 16 h at 37 °C. The mixture was diluted with DCM (50 ml) and washed with brine (10 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (20 g silica; cycH/EA = 2 :1) afforded the title compound as white solids.

Yield: 50% (12 mg, 0.020 mmol)

Appearance: white solids

TLC: R_f = 0.38 (cycH/EA = 1:1; UV)

HPLC: R_t = 18.17 min (0 – 100% B in 20 min)

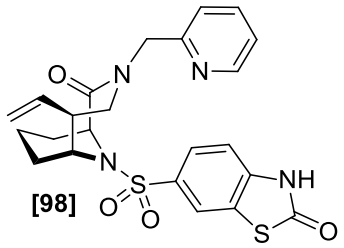
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.14 – 1.47 (m, 3H), 1.49 (s, 2H), 1.53 (d, *J* = 7.1 Hz, 3H), 2.28 (d, *J* = 13.7 Hz, 1H), 2.38 (q, *J* = 8.6 Hz, 1H), 3.06 (dd, *J* = 14.3, 1.9 Hz, 1H), 3.66 (dd, *J* = 14.3, 10.5 Hz, 1H), 3.80 (s, 3H), 3.89 (t, *J* = 6.0 Hz, 1H), 4.71 (dt, *J* = 6.2, 1.9 Hz, 1H), 4.78 (dt, *J* = 16.9, 1.1 Hz, 1H), 4.90 (dd, *J* = 10.1, 1.3 Hz, 1H), 5.59 (m, 1H), 6.02 – 6.26 (m, 1H), 6.92 – 6.98 (m, 2H), 7.49 (t, *J* = 1.9 Hz, 1H), 7.51 – 7.56 (m, 2H), 7.64 (d, *J* = 1.9 Hz, 2H), 7.74 (d, *J* = 0.7 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.1, 159.9, 148.2, 144.2, 137.3, 136.3, 132.6, 130.4, 124.9, 122.1, 120.1, 116.8, 114.8, 57.2, 55.7, 55.0, 48.9, 47.0, 45.7, 27.8, 26.4, 16.9, 15.6.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{30}Cl_2N_5O_4S$ 590.1390; Found 590.1391

Lab book number(s): JK354

5.2.85. Compound [98]: 6-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridine-2-ylmethyl)-5-vinyl-3,10-diazabicyclo [4.3.1]decan-10-yl)sulfonyl)benzo[d]thiazol-2(3H)-one



[98]

Compound **[33]** (40 mg, 0.15 mmol, 1 eq.) was dissolved in DCM (2 ml). DIPEA (38 μl, 0.22 mmol, 1.5 eq.) and 2-oxo-2,3-dihydro-1,3-benzothiazole-6-sulfonyl chloride (73.61 mg, 0.29 mmol, 2 eq.) were added and the mixture was stirred for 18 h at rt. To the reaction mixture was added sat. aq. $NaHCO_3$ (3 ml) and the mixture was extracted with DCM (3 x 20 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Preparative reversed phase HPLC (60 – 80% B in 10 min) afforded the title compound as white solids.

Yield: 5% (4 mg, 0.008 mmol)

Appearance: white solids

TLC: R_f = 0.55 (DCM/MeOH + 3% TEA = 10:1; UV, Hanessian)

HPLC: R_t = 11.42 min (0 – 100% B in 20 min)

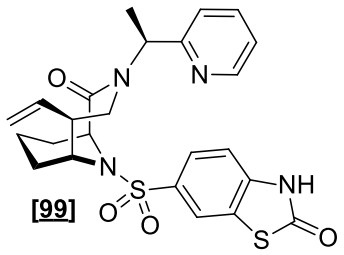
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.17 – 1.39 (m, 2H), 1.45 – 1.54 (m, 2H), 1.60 (m, 1H), 2.25 (d, *J* = 13.5 Hz, 1H), 2.63 – 2.77 (m, 1H), 3.10 (dd, *J* = 14.1, 1.9 Hz, 1H), 4.03 (t, *J* = 6.0 Hz, 1H), 4.09 (dd, *J* = 14.1, 10.7 Hz, 1H), 4.74 – 4.87 (m, 3H), 4.93 – 5.07 (m, 2H), 5.72 (m, 1H), 7.22 (dd, *J* = 8.0, 4.1 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.71 (m, 2H), 7.90 (d, *J* = 1.8 Hz, 1H), 8.46 – 8.61 (m, 1H), 10.40 (s, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.6, 26.3, 27.4, 49.0, 52.4, 54.6, 56.1, 56.8, 111.8, 116.8, 121.3, 122.2, 122.6, 125.2, 125.3, 135.9, 137.3, 137.4, 138.9, 148.8, 156.7, 171.3, 171.3.

Mass (ESI): $[M + H]^+$ = 485.27

Lab book number(s): JK072, JK098, JK186

5.2.86. Compound [99]: 6-(((1*S*,5*S*,6*R*)-2-oxo-3-((*S*)-1-(pyridin-2-yl)ethyl)-5-vinyl-3,10-diaza bicyclo[4.3.1]decan-10-yl)sulfonyl)benzo[d]thiazol-2(3H)-one



[99]

Compound **[37]** (30 mg, 0.11 mmol, 1 eq.), 2-oxo-2,3-dihydro-1,3-benzothiazole-6-sulfonyl chloride (39 mg, 0.16 mmol, 1.5 eq.) and ZnO (17 mg, 0.21 mmol, 2 eq.) were placed in a flask under argon atmosphere. MeCN (10 ml) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with DCM (40 ml) and washed with brine (3 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (20 g SiO_2, cycH/EA = 1:2) afforded the title compound as white solids.

Yield: 60% (33 mg, 0.07 mmol)

Appearance: white solids

TLC: R_f = 0.40 (EA; UV, Hanessian)

HPLC: R_t = 10.41 min (0 – 100% B in 20 min)

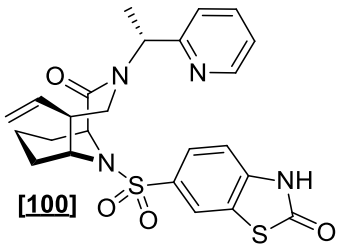
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.13 – 1.29 (m, 3H), 1.45 - 1.54 (m, 5H), 2.14 – 2.32 (m, 1H), 2.39 – 2.58 (m, 1H), 2.82 (dd, *J* = 14.5, 1.7 Hz, 1H), 3.43 (dd, *J* = 14.6, 10.7 Hz, 1H), 3.95 (t, *J* = 5.7 Hz, 1H), 4.75 (dt, *J* = 6.0, 1.9 Hz, 1H), 4.91 – 5.13 (m, 2H), 5.64 (m, 1H), 6.10 (q, *J* = 6.9 Hz, 1H), 7.05 – 7.35 (m, 3H), 7.63 (m, 2H), 7.82 (d, *J* = 1.8 Hz, 1H), 8.50 (m, 1H), 10.67 (s, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 14.2, 15.2, 15.6, 26.3, 27.8, 46.3, 50.1, 54.7, 55.2, 56.9, 111.9, 116.7, 121.3, 122.6, 122.9, 125.2, 125.2, 135.8, 137.2, 139.1, 148.7, 158.8, 170.9, 171.7.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{27}N_4O_4S_2$ 499.1468; Found 499.1471

Lab book number(s): JK086, JK232

5.2.87. Compound [100]: 6-(((1*S*,5*S*,6*R*)-2-oxo-3-((*R*)-1-(pyridin-2-yl)ethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)benzo[d]thiazol-2(3H)-one



[100]

Compound **[38]** (30 mg, 0.11 mmol, 1 eq.), 2-oxo-2,3-dihydro-1,3-benzothiazole-6-sulfonyl chloride (39 mg, 0.16 mmol, 1.5 eq.) and ZnO (17 mg, 0.21 mmol, 2 eq.) were placed in a flask under argon atmosphere. MeCN (10 ml) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with DCM (40 ml) and washed with brine (3 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (20 g SiO_2, cycH/EA = 1:2) afforded the title compound as colorless resin.

Yield: 64% (35 mg, 0.07 mmol)

Appearance: white solids

TLC: R_f = 0.40 (EA; UV, Hanessian)

HPLC: R_t = 10.30 min (0 – 100% B in 20 min)

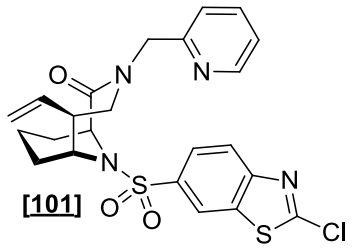
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.11 – 1.44 (m, 5H), 1.50 (d, *J* = 7.1 Hz, 3H), 2.04 – 2.16 (m, 1H), 2.16 – 2.30 (m, 1H), 3.00 (dd, *J* = 14.1, 1.8 Hz, 1H), 3.71 (dd, *J* = 14.2, 10.5 Hz, 1H), 3.81 – 3.95 (m, 1H), 4.58 (dt, *J* = 17.0, 1.0 Hz, 1H), 4.75 (dt, *J* = 6.3, 1.9 Hz, 1H), 4.83 (dd, *J* = 10.1, 1.4 Hz, 1H), 5.53 (m, 1H), 6.06 (q, *J* = 7.0 Hz, 1H), 7.01 – 7.26 (m, 3H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.64 (m, 2H), 7.83 (d, *J* = 1.8 Hz, 1H), 8.51 (dt, *J* = 4.9, 1.5 Hz, 1H), 10.26 (s, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 14.2, 15.7, 15.8, 26.1, 27.7, 46.0, 49.2, 54.5, 55.0, 57.0, 111.9, 116.4, 121.4, 122.6, 122.8, 125.2, 136.0, 137.1, 137.5, 138.8, 148.6, 159.4, 170.7, 171.4.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{27}N_4O_4S_2$ 499.1468; Found 499.1468

Lab book number(s): JK087

5.2.88. Compound [101]: (((1*S*,5*S*,6*R*)-10-((2-chlorobenzo[d]thiazol-6-yl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[101]

Compound **[33]** (156 mg, 0.57 mmol, 1 eq.) was dissolved in MeCN (30 ml). 2-Chloro-1,3-benzothiazole-6-sulfonyl chloride (200 mg, 0.75 mmol, 1.3 eq.) in MeCN (10 ml) and DIPEA (163 µl, 0.96 mmol, 2 eq.) were added successively and the mixture was stirred for 48 h at rt. The mixture was diluted with DCM (50 ml) and washed with brine (2 x 20 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (30 g silica; cycH/EA = 2:3) afforded the title compound as white solids.

Yield: 63% (180 mg, 0.36 mmol)

Appearance: white solids

TLC: R_f = 0.45 (EA; UV, Hanessian)

HPLC: R_t = 11.91 min (0 – 100% B in 20 min)

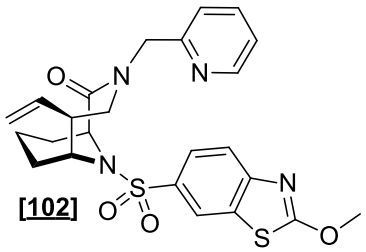
^{1}H-NMR (500 MHz, CD_3OD): δ = 1.10 – 1.36 (m, 3H), 1.39 – 1.53 (m, 2H), 1.53 – 1.67 (m, 1H), 2.17 – 2.34 (m, 1H), 2.63 – 2.76 (m, 1H), 3.12 (dd, *J* = 14.2, 2.0 Hz, 1H), 3.99 – 4.13 (m, 2H), 4.80 (dt, *J* = 6.1, 2.0 Hz, 1H), 4.85 (s, 2H), 4.91 – 5.12 (m, 2H), 5.73 (m, 1H), 7.24 (m, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.72 (t, *J* = 7.4 Hz, 1H), 7.91 (dd, *J* = 8.6, 1.9 Hz, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 8.34 (d, *J* = 1.8 Hz, 1H), 8.53 (m, 1H).

^{13}C-NMR (126 MHz, CD_3OD): δ = 15.5, 26.4, 27.5, 49.1, 52.2, 54.7, 55.9, 56.8, 76.7, 77.0, 77.3, 116.8, 120.6, 122.3, 122.6, 123.8, 124.7, 136.7, 137.3, 137.5, 138.7, 148.5, 153.4, 156.8, 157.5, 170.7.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{23}ClN_4O_3S_2$ 503.0973; Found 503.0975

Lab book number(s): JK167, JK172, JK202, JK329

5.2.89. Compound [102]: (((1*S*,5*S*,6*R*)-10-((2-methoxybenzo[d]thiazol-6-yl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[102]

Compound **[101]** (30 mg, 0.06 mmol, 1 eq.) was dissolved in dry MeOH (10 ml). Sodium methoxide (3.2 mg, 0.06 mmol, 1.0 eq.) was added and the mixture was heated to 80 °C and stirred for 12 h. The mixture was diluted with EA (50 ml) and washed with brine (2 x 20 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (4 g silica; EA) afforded the title compound as white solids.

Yield: 81% (24 mg, 0.05 mmol)

Appearance: white solids

TLC: R_f = 0.53 (EA; UV, Hanessian)

HPLC: R_t = 11.61 min (0 – 100% B in 20 min)

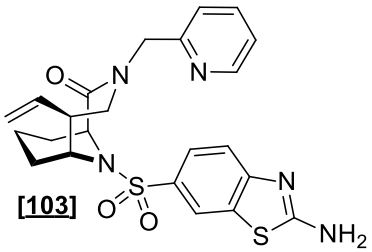
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.15 – 1.36 (m, 2H), 1.39 – 1.50 (m, 2H), 1.57 (dt, *J* = 17.1, 13.5 Hz, 1H), 2.23 (d, *J* = 13.5 Hz, 1H), 2.66 (q, *J* = 8.8 Hz, 1H), 3.07 (dd, *J* = 14.2, 1.9 Hz, 1H), 3.99 – 4.10 (m, 2H), 4.25 (d, *J* = 0.9 Hz, 3H), 4.69 – 4.89 (m, 3H), 4.91 – 5.08 (m, 2H), 5.71 (m, 1H), 7.13 – 7.22 (m, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.66 (td, *J* = 7.7, 1.7 Hz, 1H), 7.71 – 7.84 (m, 2H), 8.11 – 8.22 (m, 1H), 8.51 (d, *J* = 4.8 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.6, 26.2, 27.4, 49.1, 52.1, 54.5, 56.2, 56.8, 59.2, 116.5, 120.6, 121.3, 122.0, 122.4, 124.4, 132.8, 136.1, 136.9, 137.5, 149.1, 152.4, 157.1, 171.0, 176.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{26}N_4O_4S_2$ 499.1468; Found 499.1472

Lab book number(s): JK178

5.2.90. Compound [103]: (((1*S*,5*S*,6*R*)-10-((2-aminobenzo[d]thiazol-6-yl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[103]

Compound **[101]** (19 mg, 0.040 mmol, 1 eq.) was dissolved in dioxane (10 ml). NH_3 (10 ml, 25% in water) was added and the mixture was stirred for 8 h at 80 °C. The mixture was diluted with EA (50 ml) and washed with brine (2 x 20 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (4 g silica; EA + 3% TEA) afforded the title compound as white solids.

Yield: 77% (14 mg, 0.031 mmol)

Appearance: white solids

TLC: R_f = 0.18 (EA + 3% TEA; UV)

HPLC: R_t = 8.75 min (0 – 100% B in 20 min)

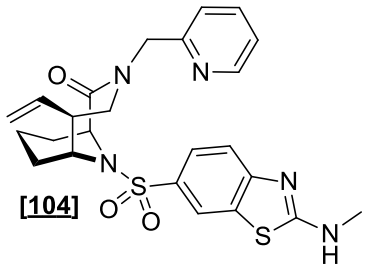
^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.09 – 1.26 (m, 2H), 1.31 – 1.44 (m, 2H), 1.51 (m, 1H), 1.94 – 2.04 (m, 1H), 2.78 (q, *J* = 8.2 Hz, 1H), 3.03 (dd, *J* = 13.9, 1.9 Hz, 1H), 3.28 (s, 1H), 3.81 – 3.97 (m, 2H), 4.57 – 4.70 (m, 2H), 4.78 (d, *J* = 15.5 Hz, 1H), 4.97 – 5.07 (m, 2H), 5.61 – 5.79 (m, 1H), 7.17 – 7.25 (m, 1H), 7.27 (m, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.68 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.76 (td, *J* = 7.7, 1.8 Hz, 1H), 7.95 (s, 1H), 8.29 (t, *J* = 1.4 Hz, 1H), 8.51 (dt, *J* = 4.8, 1.5 Hz, 1H).

^{13}C-NMR (126 MHz, DMSO-d_6): δ = 15.0, 25.7, 26.7, 47.7, 51.6, 53.5, 55.4, 56.1, 116.1, 117.5, 120.3, 121.3, 122.3, 124.2, 131.7, 132.0, 136.8, 137.9, 149.0, 156.3, 157.1, 170.1, 170.1.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{25}N_5O_3S_2$ 484.1472; Found 484.1474

Lab book number(s): JK181

5.2.91. Compound [104]: (((1*S*,5*S*,6*R*)-10-((2-(methylamino)benzo[d]thiazol-6-yl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[104]

Compound **[101]** (30 mg, 0.041 mmol, 1 eq.) was dissolved in dioxane (10 ml). Methylamine hydrochloride (4 mg, 0.06 mmol, 1.5 eq.) and K_2CO_3 (11 mg, 0.08 mmol, 2 eq.) were added successively and the mixture was stirred for 16 h at 80 °C. The mixture was diluted with EA (50 ml) and washed with brine (2 x 20 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (2 g silica; EA + 3% TEA) afforded the title compound as white solids.

Yield: 90% (22 mg, 0.037 mmol)

Appearance: white solids

TLC: R_f = 0.31 (EA + 3% TEA; UV)

HPLC: R_t = 9.47 min (0 – 100% B in 20 min)

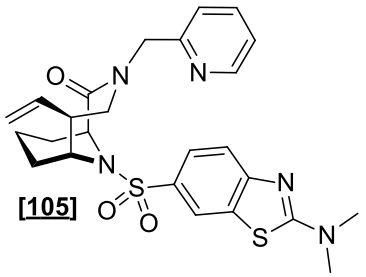
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.16 – 1.37 (m, 2H), 1.45 (dt, *J* = 13.3, 3.4 Hz, 2H), 1.57 (m, 1H), 2.15 – 2.27 (m, 1H), 2.66 (m, 1H), 3.05 (dd, *J* = 14.1, 2.0 Hz, 1H), 3.12 (s, 3H), 4.01 – 4.08 (m, 2H), 4.70 – 4.86 (m, 3H), 4.88 – 5.03 (m, 2H), 5.71 (m, 1H), 6.37 (s, 1H), 7.17 (m, 1H), 7.30 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.65 (td, *J* = 7.7, 1.9 Hz, 1H), 7.70 (dd, *J* = 8.6, 1.9 Hz, 1H), 8.07 (d, *J* = 2.0 Hz, 1H), 8.51 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.7, 26.2, 27.3, 31.7, 49.1, 52.2, 54.4, 56.2, 56.7, 116.4, 118.8, 120.1, 122.0, 122.4, 124.6, 131.1, 133.3, 136.9, 137.6, 149.2, 156.0, 157.1, 171.0, 171.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{27}N_5O_3S_2$ 498.1628; Found 498.1630

Lab book number(s): JK179

5.2.92. Compound [105]: (((1*S*,5*S*,6*R*)-10-((2-(dimethylamino)benzo[d]thiazol-6-yl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[105]

Compound **[101]** (20 mg, 0.041 mmol, 1 eq.) was dissolved in dioxane (10 ml). Dimethylamine hydrochloride (6.5 mg, 0.08 mmol, 2 eq.) and K_2CO_3 (16.5 mg, 0.12 mmol, 3 eq.) were added successively and the mixture was stirred for 16 h at 80 °C. The mixture was diluted with EA (50 ml) and washed with brine (2 x 20 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (4 g silica; EA + 3% TEA) afforded the title compound as white solids.

Yield: 88% (16 mg, 0.036 mmol)

Appearance: white solids

TLC: R_f = 0.17 (EA; UV, Hanessian)

HPLC: R_t = 10.72 min (0 – 100% B in 20 min)

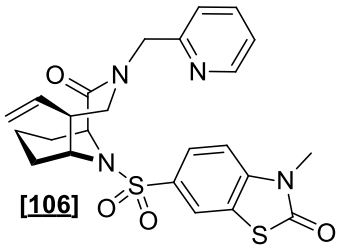
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.18 – 1.37 (m, 3H), 1.37 – 1.50 (m, 2H), 1.56 (m, 1H), 2.21 (dd, *J* = 13.3, 3.1 Hz, 1H), 2.59 – 2.70 (m, 1H), 3.04 (dd, *J* = 14.1, 1.9 Hz, 1H), 3.25 (d, *J* = 0.9 Hz, 6H), 3.95 – 4.09 (m, 2H), 4.70 – 4.87 (m, 3H), 4.90 – 5.05 (m, 2H), 5.71 (m, 1H), 7.17 (m, 1H), 7.31 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.66 (td, *J* = 7.7, 1.8 Hz, 1H), 7.68 – 7.74 (m, 1H), 8.08 (d, *J* = 1.9 Hz, 1H), 8.51 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.7, 26.1, 27.3, 40.3, 49.1, 52.1, 54.3, 56.2, 56.7, 116.4, 118.7, 120.0, 122.0, 122.3, 124.7, 131.7, 132.7, 136.9, 137.7, 149.1, 156.6, 157.2, 171.1, 171.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{29}N_5O_3S_2$ 512.1785; Found 512.1787

Lab book number(s): JK182

5.2.93. Compound [106]: 3-methyl-6-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)benzo[d]thiazol-2(3H)-one



[106]

Compound **[98]** (20 mg, 0.041 mmol, 1 eq.) was dissolved in DMF (2 ml). NaH (5 mg, 0.12 mg, 3 eq.) and MeI (5 µL, 0.08 mmol, 2 eq.) were added successively and the mixture was stirred for 1 h at rt. The reaction was quenched with sat. aq. NH_4Cl solution, extracted with EA and dried over $MgSO_4$. Removal of solvents followed by column chromatography (EA) afforded the title compound as white solids.

Yield: 92% (19 mg, 0.038 mmol)

Appearance: white solids

TLC: R_f = 0.31 (EA; UV)

HPLC: R_t = 13.05 min (0 – 100% B in 20 min)

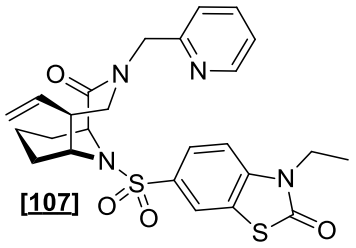
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.06 – 1.32 (m, 2H), 1.37 – 1.46 (m, 2H), 1.46 – 1.61 (m, 1H), 2.18 (dd, *J* = 15.3, 11.9 Hz, 1H), 2.62 (qd, *J* = 8.0, 3.6 Hz, 1H), 3.03 (dd, *J* = 14.2, 2.0 Hz, 1H), 3.44 (s, 3H), 3.89 – 4.07 (m, 2H), 4.63 – 4.82 (m, 3H), 4.86 – 5.01 (m, 2H), 5.65 (m, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 7.14 (m, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.63 (td, *J* = 7.7, 1.8 Hz, 1H), 7.73 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.85 (d, *J* = 1.9 Hz, 1H), 8.46 (dt, *J* = 4.9, 1.4 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.6, 26.3, 27.5, 29.4, 49.1, 52.1, 54.6, 56.1, 56.8, 110.5, 116.7, 121.2, 122.2, 122.5, 123.8, 125.2, 136.1, 137.2, 137.4, 140.9, 148.9, 156.9, 169.5, 170.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{27}N_4O_4S_2$ 499.1468; Found 499.1467

Lab book number(s): JK099

5.2.94. Compound [107]: 3-ethyl-6-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)benzo[d]thiazol-2(3H)-one



[107]

Compound **[98]** (20 mg, 0.041 mmol, 1 eq.) was dissolved in DMF (2 ml). NaH (5 mg, 0.12 mg, 3 eq.) and EtI (16 µL, 0.21 mmol, 5 eq.) were added successively and the mixture was stirred for 1 h at rt. The reaction was quenched with sat. aq. NH_4Cl solution, extracted with EA and dried over $MgSO_4$. Removal of solvents under reduced pressure followed by column chromatography (EA) afforded the title compound as white solids.

Yield: 81% (17 mg, 0.033 mmol)

Appearance: white solids

TLC: R_f = 0.29 (EA; UV)

HPLC: R_t = 11.72 min (0 – 100% B in 20 min)

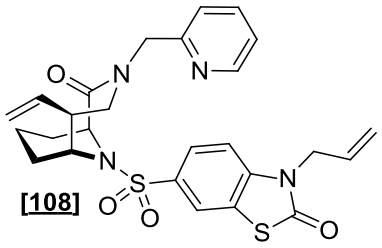
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.13 – 1.42 (m, 6H), 1.44 – 1.54 (m, 2H), 2.20 – 2.34 (m, 1H), 2.69 (m, 1H), 3.10 (dd, *J* = 14.1, 2.0 Hz, 1H), 3.96 – 4.14 (m, 4H), 4.69 – 4.91 (m, 3H), 4.92 – 5.09 (m, 2H), 5.72 (m, 1H), 7.14 (d, *J* = 8.5 Hz, 1H), 7.21 (m, 1H), 7.34 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.69 (td, *J* = 7.7, 1.8 Hz, 1H), 7.79 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.92 (d, *J* = 1.9 Hz, 1H), 8.53 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 12.8, 15.6, 26.4, 27.5, 38.3, 49.1, 52.2, 54.6, 56.1, 56.8, 110.3, 116.6, 121.4, 122.2, 122.5, 124.1, 125.2, 135.9, 137.2, 137.4, 140.1, 148.9, 157.0, 169.1, 170.9.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{29}N_4O_4S_2$ 513.1625; Found 513.1626

Lab book number(s): JK155

5.2.95. Compound [108]: 3-allyl-6-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)benzo[d]thiazol-2(3H)-one



[108]

Compound **[98]** (20 mg, 0.041 mmol, 1 eq.) was dissolved in DMF (2 ml). NaH (5 mg, 0.12 mg, 3 eq.) and allylbromide (15 µL, 0.21 mmol, 5 eq.) were added successively and the mixture was stirred for 2 h at rt. The reaction was quenched with sat. aq. NH_4Cl solution, extracted with EA and dried over $MgSO_4$. Removal of solvents under reduced pressure followed by column chromatography (EA) afforded the title compound as white solids.

Yield: 44% (11 mg, 0.018 mmol)

Appearance: white solids

TLC: R_f = 0.46 (EA; UV)

HPLC: R_t = 11.98 min (0 – 100% B in 20 min)

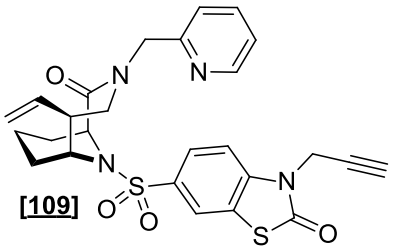
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.15 – 1.38 (m, 2H), 1.44 – 1.54 (m, 2H), 1.60 (dt, *J* = 14.9, 4.2 Hz, 1H), 2.23 – 2.33 (m, 1H), 2.69 (m, 1H), 3.10 (dd, *J* = 14.1, 2.0 Hz, 1H), 3.93 – 4.14 (m, 2H), 4.62 (dt, *J* = 5.4, 1.7 Hz, 2H), 4.71 – 4.81 (m, 2H), 4.85 (d, *J* = 15.1 Hz, 1H), 4.90 – 5.07 (m, 2H), 5.24 (dt, *J* = 16.8, 1.8 Hz, 1H), 5.28 – 5.38 (m, 1H), 5.72 (m, 1H), 5.88 (m, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 7.19 (m, 1H), 7.32 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.67 (td, *J* = 7.7, 1.8 Hz, 1H), 7.76 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.92 (d, *J* = 1.9 Hz, 1H), 8.52 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.6, 26.4, 27.5, 45.3, 49.1, 52.1, 54.6, 56.2, 56.8, 111.1, 116.6, 118.9, 121.3, 122.0, 122.4, 123.8, 125.2, 130.0, 136.1, 136.9, 137.5, 140.1, 149.2, 157.1, 169.2, 170.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{28}N_4O_4S_2$ 525.1625; Found 525.1622

Lab book number(s): JK187

5.2.96. Compound [109]: 6-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo [4.3.1]decan-10-yl)sulfonyl)-3-(prop-2-yn-1-yl)benzo[d]thiazol-2(3H)-one



[109]

Compound **[98]** (20 mg, 0.041 mmol, 1 eq.) was dissolved in DMF (2 ml). NaH (2 mg, 0.05 mg, 1.2 eq.) and propargylbromide (15 µL, 0.21 mmol, 5 eq.) were added successively and the mixture was stirred for 2 h at rt. The reaction was quenched with sat. aq. NH_4Cl solution, extracted with EA and dried over $MgSO_4$. Removal of solvents under reduced pressure followed by column chromatography (EA) afforded the title compound as white solids.

Yield: 57% (14 mg, 0.023 mmol)

Appearance: white solids

TLC: R_f = 0.50 (EA; UV)

HPLC: R_t = 11.67 min (0 – 100% B in 20 min)

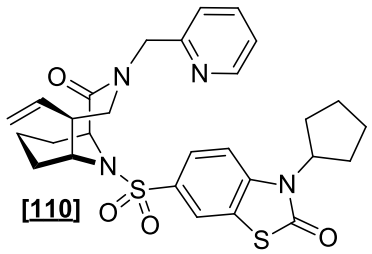
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.19 – 1.36 (m, 2H), 1.43 – 1.54 (m, 2H), 1.60 (m, 1H), 2.27 (d, *J* = 13.6 Hz, 1H), 2.36 (t, *J* = 2.6 Hz, 1H), 2.62 – 2.76 (m, 1H), 3.10 (dd, *J* = 14.2, 1.9 Hz, 1H), 3.94 – 4.14 (m, 2H), 4.68 – 4.89 (m, 5H), 4.92 – 5.09 (m, 2H), 5.72 (dt, *J* = 16.9, 9.4 Hz, 1H), 7.19 (dd, *J* = 7.5, 4.9 Hz, 1H), 7.34 (dd, *J* = 14.1, 8.2 Hz, 2H), 7.67 (td, *J* = 7.7, 1.8 Hz, 1H), 7.82 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.93 (d, *J* = 1.8 Hz, 1H), 8.52 (dd, *J* = 4.9, 1.6 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.6, 26.4, 27.5, 32.2, 49.1, 52.1, 54.6, 56.2, 56.8, 74.1, 75.4, 111.4, 116.6, 121.3, 122.0, 122.4, 123.7, 125.3, 136.6, 136.9, 137.4, 139.2, 149.2, 157.0, 168.7, 170.7.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{26}N_4O_4S_2$ 523.1468; Found 523.1470

Lab book number(s): JK188

5.2.97. Compound [110]: 3-cyclopentyl-6-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)benzo[d]thiazol-2(3H)-one



[110]

Compound **[98]** (26 mg, 0.054 mmol, 1 eq.) was dissolved in DMF (2 ml). NaH (5 mg, 0.13 mg, 3 eq.) and cyclopentyliodide (30 µL, 0.27 mmol, 5 eq.) were added successively and the mixture was stirred for 16 h at rt. The reaction was quenched with sat. aq. NH_4Cl solution, extracted with EA and dried over $MgSO_4$. Solvents were removed under reduced pressure and the compound was purified preparative HPLC (60 – 80% B in 10 min).

Yield: 40% (12 mg, 0.022 mmol)

Appearance: white solids

TLC: R_f = 0.52 (EA; UV)

HPLC: R_t = 13.32 min (0 – 100% B in 20 min)

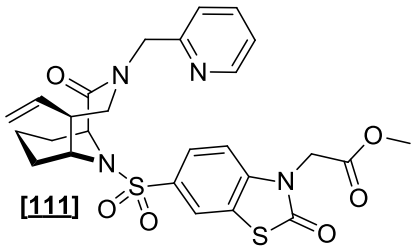
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.26 (m, 1H), 1.35 (m, 1H), 1.47 – 1.65 (m, 3H), 1.69 – 1.84 (m, 2H), 1.95 – 2.10 (m, 4H), 2.10 – 2.30 (m, 3H), 2.73 (m, 1H), 3.11 (dd, *J* = 14.2, 2.0 Hz, 1H), 4.00 – 4.17 (m, 2H), 4.71 – 4.81 (m, 2H), 4.96 (quint., *J* = 8.8 Hz, 1H), 5.00 – 5.10 (m, 2H), 5.15 (d, *J* = 15.8 Hz, 1H), 5.74 (m, 1H), 7.22 (d, *J* = 8.7 Hz, 1H), 7.39 (dd, *J* = 7.3, 5.5 Hz, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.74 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.90 (m, 2H), 8.65 (d, *J* = 5.1 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.6, 25.3, 26.4, 27.4, 28.1, 49.1, 52.5, 54.6, 54.9, 56.1, 56.7, 111.4, 117.0, 121.3, 123.1, 123.3, 124.2, 124.7, 135.2, 137.1, 139.7, 140.1, 146.7, 155.9, 169.2, 171.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{32}N_4O_4S_2$ 553.1938; Found 553.1940

Lab book number(s): JK157, JK174

5.2.98. Compound [111]: Methyl 2-(2-oxo-6-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)benzo[d]thiazol-3(2H)-yl)acetate



[111]

Compound **[98]** (55 mg, 0.11 mmol, 1 eq.) was dissolved in DMF (5 ml). NaH (6 mg, 0.15 mg, 1.3 eq.) and methyl bromoacetate (33 µL, 0.34 mmol, 3 eq.) were added successively and the mixture was stirred for 2 h at rt. The reaction was quenched with sat. aq. NH_4Cl solution, extracted with EA and dried over $MgSO_4$. Removal of solvents under reduced pressure followed by column chromatography (EA) afforded the title compound as white solids.

Yield: 86% (45 mg, 0.095 mmol)

Appearance: white solids

TLC: R_f = 0.44 (EA; UV)

HPLC: R_t = 11.17 min (0 – 100% B in 20 min)

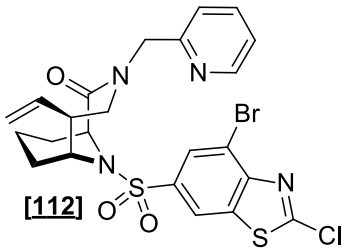
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.15 – 1.38 (m, 2H), 1.49 (dt, *J* = 12.9, 3.4 Hz, 2H), 1.59 (m, 1H), 2.22 – 2.31 (m, 1H), 2.69 (m, 1H), 3.10 (dd, *J* = 14.2, 2.0 Hz, 1H), 3.81 (s, 3H), 3.97 – 4.15 (m, 2H), 4.75 (d, *J* = 20.9 Hz, 4H), 4.85 (d, *J* = 15.2 Hz, 1H), 4.92 – 5.09 (m, 2H), 5.72 (m, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 7.19 (m, 1H), 7.32 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.68 (td, *J* = 7.7, 1.8 Hz, 1H), 7.77 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.94 (d, *J* = 1.8 Hz, 1H), 8.52 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.6, 26.4, 27.5, 43.6, 49.1, 52.1, 53.0, 54.6, 56.2, 56.8, 110.4, 116.6, 121.5, 122.1, 122.4, 123.7, 125.4, 136.7, 136.9, 137.4, 139.7, 149.2, 157.0, 166.7, 169.5, 170.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{28}N_4O_6S_2$ 557.1523; Found 557.1523

Lab book number(s): JK189

5.2.99. Compound [112]: (1*S*,5*S*,6*R*)-10-((4-bromo-2-chlorobenzo[d]thiazol-6-yl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[112]

Compound **[33]** (130 mg, 0.48 mmol, 1 eq.) was dissolved in MeCN (10 ml). 4-Bromo-2-Chloro-1,3-benzothiazole-6-sulfonyl chloride (250 mg, 0.72 mmol, 1.5 eq.) in MeCN (10 ml) and DIPEA (163 µl, 0.96 mmol, 2 eq.) were added successively and the mixture was stirred for 60 h at rt. The mixture was diluted with DCM (30 ml) and washed with brine (2 x 20 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (30 g silica; cycH/EA = 1:1) afforded the title compound as white solids.

Yield: 75% (210 mg, 0.36 mmol)

Appearance: white solids

TLC: R_f = 0.35 (EA; UV)

HPLC: R_t = 13.52 min (0 – 100% B in 20 min)

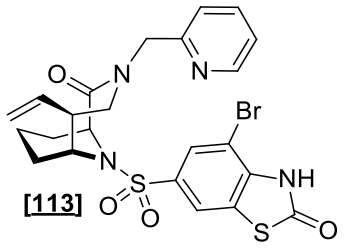
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.13 – 1.36 (m, 2H), 1.43 – 1.66 (m, 3H), 2.23 – 2.33 (m, 1H), 2.65 – 2.78 (m, 1H), 3.13 (dd, *J* = 14.2, 2.0 Hz, 1H), 3.99 – 4.09 (m, 2H), 4.74 – 4.80 (m, 2H), 4.87 (d, *J* = 15.3 Hz, 1H), 5.00 (dt, *J* = 17.0, 1.1 Hz, 1H), 5.05 (dd, *J* = 10.1, 1.4 Hz, 1H), 5.72 (m, 1H), 7.20 (m, 1H), 7.33 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.69 (td, *J* = 7.6, 1.8 Hz, 1H), 8.09 (d, *J* = 1.7 Hz, 1H), 8.25 (d, *J* = 1.7 Hz, 1H), 8.52 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.5, 26.5, 27.6, 49.1, 52.1, 54.9, 56.1, 56.9, 116.8, 117.4, 119.3, 122.1, 122.5, 127.8, 137.0, 137.1, 137.2, 139.7, 149.0, 151.8, 156.8, 158.1, 170.4.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{22}BrClN_4O_3S_2$ 581.0078; Found 581.0080

Lab book number(s): JK150, JK152

5.2.100. Compound [113]: 4-bromo-6-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1] decan-10-yl)sulfonyl)benzo[d]thiazol-2(3H)-one



[113]

Compound **[112]** (50 mg, 0.086 mmol, 1 eq.) was dissolved in THF (10 ml). 1 M NaOH (10 ml) were added and the mixture was stirred at 80 °C for 4 h. The mixture was diluted with DCM (30 ml) and washed with brine (2 x 20 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (6 g silica; EA) afforded the title compound as colorless resin.

Yield: 99% (48 mg, 0.085 mmol)

Appearance: colorless resin

TLC: R_f = 0.33 (EA; UV)

HPLC: R_t = 10.77 min (0 – 100% B in 20 min)

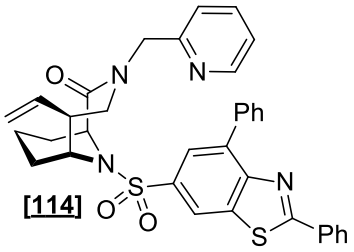
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.13 – 1.40 (m, 2H), 1.46 – 1.72 (m, 3H), 2.30 (d, *J* = 13.5 Hz, 1H), 2.72 (m, 1H), 3.12 (dd, *J* = 14.2, 2.0 Hz, 1H), 3.95 – 4.14 (m, 2H), 4.69 – 4.93 (m, 3H), 4.93 – 5.09 (m, 2H), 5.71 (m, 1H), 7.18 – 7.25 (m, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.71 (td, *J* = 7.7, 1.7 Hz, 1H), 7.83 (d, *J* = 1.6 Hz, 1H), 7.88 (d, *J* = 1.6 Hz, 1H), 8.41 – 8.66 (m, 1H), 9.53 (s, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.6, 26.5, 27.6, 49.0, 52.2, 54.8, 56.1, 56.8, 104.4, 116.8, 120.0, 122.2, 122.6, 125.6, 127.7, 137.2, 137.3, 137.4, 137.7, 148.8, 156.8, 169.1, 170.7.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{24}BrN_4O_4S_2$ 563.0417; Found 563.0415

Lab book number(s): JK153

5.2.101. Compound [114]: (1*S*,5*S*,6*R*)-10-((2,4-diphenylbenzo[d]thiazol-6-yl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[114]

Compound **[112]** (20 mg, 0.034 mmol, 1 eq.), phenylboronic acid (8.4 mg, 0.069 mmol, 2 eq.) and $Pd(PPH_3)_4$ (2.0 mg, 0.0017 mmol, 0.05 eq.) were placed in a flask under argon and dissolved in toluene (5 ml) and ethanol (2 ml). K_2CO_3 (7.1 mg, 0.051 mmol, 1.5 eq., in 400 µl H_2O) was added and the mixture was stirred at 90 °C for 14 h. The mixture was diluted with DCM (20 ml), washed with brine (20 ml), dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (6 g silica; cycH/EA = 1:1) afforded the title compound as colorless crystals.

Yield: 94% (20 mg, 0.032 mmol)

Appearance: colorless crystals

TLC: R_f = 0.21 (cycH/EA = 1:1; UV)

HPLC: R_t = 17.40 min (0 – 100% B in 20 min)

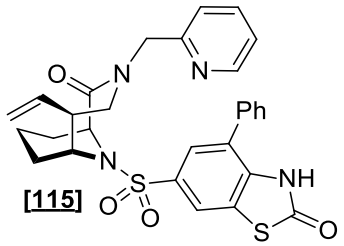
^{1}H-NMR (500 MHz, $CDCl_3$): 1.28 – 1.70 (m, 5H), 2.28 (d, *J* = 13.5 Hz, 1H), 2.54 – 2.84 (m, 1H), 3.12 (dd, *J* = 14.1, 1.9 Hz, 1H), 3.99 – 4.25 (m, 3H), 4.72 – 5.13 (m, 5H), 5.76 (m, 1H), 7.19 (m, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.41 – 7.61 (m, 7H), 7.68 (td, *J* = 7.7, 1.8 Hz, 1H), 7.89 – 8.04 (m, 3H), 8.04 – 8.19 (m, 2H), 8.40 (d, *J* = 1.9 Hz, 1H), 8.47 – 8.59 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.6, 26.4, 27.5, 49.2, 52.2, 54.7, 56.1, 56.9, 116.7, 119.6, 122.1, 122.5, 123.9, 127.9, 128.5, 128.5, 129.1, 129.8, 131.8, 133.0, 136.8, 137.1, 137.3, 137.5, 137.9, 148.9, 154.0, 157.0, 170.9, 171.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{35}H_{33}N_4O_3S_2$ 621.1989; Found 621.1990

Lab book number(s): JK154

5.2.102. Compound [115]: 6-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)-4-phenylbenzo[d]thiazol-2(3H)-one



[115]

Compound **[113]** (25 mg, 0.043 mmol, 1 eq.), phenylboronic acid (10.4 mg, 0.086 mg, 2 eq.) and $Pd(PPH_3)_4$ (2.5 mg, 0.0022 mmol, 0.05 eq) were placed in a flask under argon and dissolved in toluene (5 ml) and ethanol (2 ml). K_2CO_3 (8.9 mg, 0.064 mmol, 1.5 eq., in 400 µl H_2O) was added and the mixture was stirred at 100 °C for 16 h. The mixture was diluted with DCM (20 ml), washed with brine (20 ml), dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (6 g silica; cycH/EA = 1:1) followed by preparative HPLC (50 – 80% B in 10 min) afforded the title compound as colorless solids.

Yield: 42% (10 mg, 0.018 mmol)

Appearance: colorless solids

TLC: R_f = 0.62 (EA; UV)

HPLC: R_t = 11.50 min (0 – 100% B in 20 min)

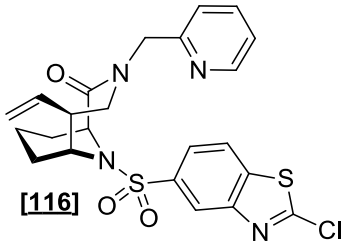
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.16 – 1.71 (m, 4H), 2.00 (d, *J* = 0.9 Hz, 1H), 2.27 (d, *J* = 13.4 Hz, 1H), 2.72 (q, *J* = 8.6 Hz, 1H), 3.12 (dd, *J* = 14.2, 2.0 Hz, 1H), 3.93 – 4.20 (m, 2H), 4.65 – 4.89 (m, 2H), 4.93 – 5.19 (m, 3H), 5.73 (m, 1H), 7.26 – 7.37 (m, 1H), 7.39 – 7.62 (m, 6H), 7.70 (d, *J* = 1.9 Hz, 1H), 7.76 – 7.90 (m, 2H), 8.48 (s, 1H), 8.54 – 8.65 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.6, 26.5, 27.5, 49.1, 52.4, 54.6, 55.3, 56.8, 116.9, 120.1, 122.8, 123.0, 125.3, 125.5, 126.5, 128.1, 129.4, 129.9, 135.5, 136.4, 137.1, 138.9, 147.4, 156.2, 169.6, 171.1.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{29}N_4O_4S_2$ 561.1625; Found 561.1627

Lab book number(s): JK158

5.2.103. Compound [116]: (1*S*,5*S*,6*R*)-10-((2-chlorobenzo[d]thiazol-5-yl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[116]

Compound **[33]** (77 mg, 0.29 mmol, 1 eq.) was dissolved in MeCN (10 ml). 2-Chloro-1,3-benzothiazole-5-sulfonyl chloride (100 mg, 0.37 mmol, 1.3 eq.) in MeCN (10 ml) and DIPEA (150 µl, 0.86 mmol, 3 eq.) were added successively and the mixture was stirred for 20 h at rt. The mixture was diluted with DCM (30 ml) and washed with brine (2 x 20 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (25 g silica; cycH/EA = 2:3) afforded the title compound as white solids.

Yield: 48% (69 mg, 0.14 mmol)

Appearance: colorless solids

TLC: R_f = 0.43 (EA; UV)

HPLC: R_t = 11.86 min (0 – 100% B in 20 min)

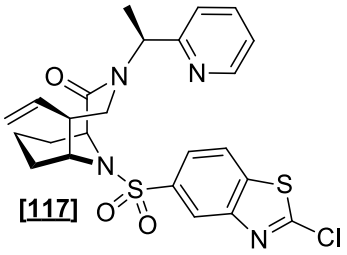
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.14 – 1.34 (m, 2H), 1.39 – 1.52 (m, 2H), 1.58 (m, 1H), 2.19 – 2.30 (m, 1H), 2.70 (m, 1H), 3.11 (dd, *J* = 14.1, 2.0 Hz, 1H), 4.01 – 4.13 (m, 2H), 4.73 – 4.93 (m, 3H), 4.93 – 5.08 (m, 2H), 5.73 (m, 1H), 7.23 (m, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.73 (td, *J* = 7.7, 1.8 Hz, 1H), 7.87 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 8.42 (d, *J* = 1.7 Hz, 1H), 8.53 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.6, 26.3, 27.4, 49.1, 52.2, 54.7, 55.9, 56.9, 116.7, 121.4, 122.2, 122.3, 122.6, 123.2, 137.3, 137.6, 140.4, 140.5, 148.5, 150.9, 156.2, 156.8, 170.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{23}ClN_4O_3S_2$ 503.0973; Found 503.0975

Lab book number(s): JK176

5.2.104. Compound [117]: (1*S*,5*S*,6*R*)-10-((2-chlorobenzo[d]thiazol-5-yl)sulfonyl)-3-((*S*)-1-(pyridin-2-yl)ethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[117]

Compound **[37]** (27 mg, 0.095 mmol, 1 eq.) was dissolved in MeCN (25 ml). 2-Chlorobenzo[d]thiazole-5-sulfonyl chloride (63 mg, 0.24 mmol, 2.5 eq.) and DIPEA (48 μl, 0.24 mmol, 2.5 eq.) were added successively and the mixture was for 16 h at rt. The reaction mixture was diluted with EA (40 ml) and washed with brine (10 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (10 g SiO_2, cycH/EA = 1:1) afforded the title compound as colorless resin.

Yield: 80% (39 mg, 0.076 mmol)

Appearance: white solids

TLC: R_f = 0.19 (cycH/EA = 1:1; UV, Hanessian)

HPLC: R_t = 13.29 min (0 – 100% B in 20 min)

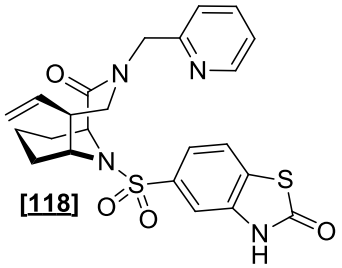
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.16 – 1.38 (m, 2H), 1.46 – 1.67 (m, 6H), 2.30 (dt, *J* = 16.4, 3.0 Hz, 1H), 2.47 – 2.60 (m, 1H), 2.87 (dd, *J* = 14.7, 1.8 Hz, 1H), 3.46 (dd, *J* = 14.7, 10.7 Hz, 1H), 4.05 (m, 1H), 4.84 (dt, *J* = 6.0, 1.9 Hz, 1H), 5.02 – 5.16 (m, 2H), 5.72 (m, 1H), 6.16 (q, *J* = 6.9 Hz, 1H), 7.13 – 7.22 (m, 1H), 7.30 (m, 1H), 7.66 (td, *J* = 7.7, 1.8 Hz, 1H), 7.86 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 8.40 (d, *J* = 1.6 Hz, 1H), 8.54 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.0, 15.6, 26.3, 27.8, 46.1, 50.2, 54.9, 54.9, 57.0, 116.6, 121.3, 122.1, 122.3, 122.9, 123.2, 136.7, 137.3, 140.4 (2C), 148.8, 150.9, 156.1, 159.1, 170.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{25}ClN_4O_3S_2$ 517.1129; Found 517.1131

Lab book number(s): JK193

5.2.105. Compound [118]: 5-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)benzo[d]thiazol-2(3H)-one



[118]

Compound **[116]** (20 mg, 0.040 mmol, 1 eq.) was dissolved in THF (10 ml). 1 M NaOH (10 ml) were added and the mixture was stirred at 80 °C for 16 h. The mixture was diluted with DCM (50 ml) and washed with brine (2 x 20 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (5 g silica; EA) afforded the title compound as colorless resin.

Yield: 68% (13 mg, 0.027 mmol)

Appearance: colorless resin

TLC: R_f = 0.43 (EA; UV)

HPLC: R_t = 10.50 min (0 – 100% B in 20 min)

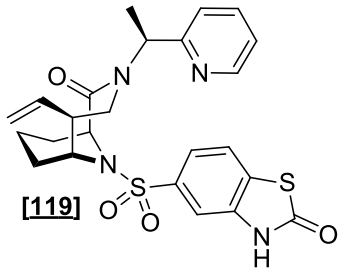
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.23 – 1.69 (m, 5H), 2.18 – 2.29 (m, 1H), 2.66 – 2.78 (m, 1H), 3.13 (dd, *J* = 14.1, 2.0 Hz, 1H), 3.96 – 4.13 (m, 2H), 4.72 – 4.94 (m, 3H), 4.94 – 5.08 (m, 2H), 5.71 (m, 1H), 7.22 (m, 1H), 7.37 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.58 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.65 (d, *J* = 1.7 Hz, 1H), 7.71 (td, *J* = 7.7, 1.8 Hz, 1H), 8.53 (m, 1H), 10.33 (s, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.6, 26.2, 27.4, 49.0, 52.5, 54.6, 56.2, 56.9, 109.6, 116.8, 120.7, 122.4, 122.7, 123.1, 129.7, 136.2, 137.3, 137.6, 139.4, 148.7, 156.4, 170.5, 171.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{24}N_4O_4S_2$ 485.1312; Found 485.1316

Lab book number(s): JK177

5.2.106. Compound [119]: 5-(((1*S*,5*S*,6*R*)-2-oxo-3-((*S*)-1-(pyridin-2-yl)ethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)benzo[d]thiazol-2(3H)-one



[119]

Compound **[117]** (26 mg, 0.050 mmol, 1 eq.) was dissolved in THF (10 ml). 1 M NaOH (10 ml) were added and the mixture was stirred at 80 °C for 16 h. The mixture was diluted with EA (50 ml) and washed with brine (20 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (5 g silica; cycH/EA = 1 :1) afforded the title compound as white solids.

Yield: 60% (15 mg, 0.030 mmol)

Appearance: white solids

TLC: R_f = 0.52 (EA; UV, Hanessian)

HPLC: R_t = 11.30 min (0 – 100% B in 20 min)

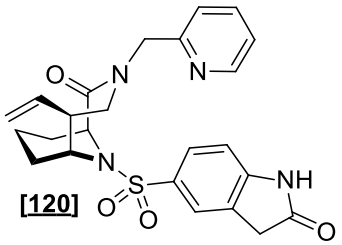
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.37 (m, 2H), 1.45 – 1.64 (m, 6H), 2.22 – 2.35 (m, 1H), 2.54 (m, 1H), 2.91 (dd, *J* = 14.6, 1.8 Hz, 1H), 3.37 (dd, *J* = 14.7, 10.7 Hz, 1H), 4.02 (m, 1H), 4.86 (dt, *J* = 6.2, 1.9 Hz, 1H), 4.98 – 5.16 (m, 2H), 5.69 (m, 1H), 6.15 (q, *J* = 6.9 Hz, 1H), 7.19 (m, 1H), 7.26 – 7.32 (m, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.56 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.60 – 7.73 (m, 2H), 8.54 (m, 1H), 10.17 (s, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.2, 15.6, 26.3, 27.8, 46.1, 50.1, 54.7, 55.3, 57.1, 109.4, 116.7, 120.7, 122.5, 122.8, 123.2, 129.6, 136.2, 136.9, 137.2, 139.5, 149.0, 158.7, 170.4, 170.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{26}N_4O_4S_2$ 499.1468; Found 499.1468

Lab book number(s): JK194

5.2.107. Compound [120]: (1*S*,5*S*,6*R*)-10-((2-oxoindolin-5-yl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[120]

Compound **[33]** (25 mg, 0.092 mmol, 1 eq.), 2-oxoindoline-5-sulfonyl chloride (28 mg, 0.12 mmol, 1.3 eq.) and ZnO (15 mg, 0.18 mmol, 2 eq.) were placed in a flask under argon atmosphere. MeCN (10 ml) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with EA (40 ml) and filtered over cotton. The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (5 g SiO_2, EA) afforded the title compound as white solids.

Yield: 51% (22 mg, 0.047 mmol)

Appearance: white solids

TLC: R_f = 0.15 (EA; UV, Hanessian)

HPLC: R_t = 8.56 min (0 – 100% B in 20 min)

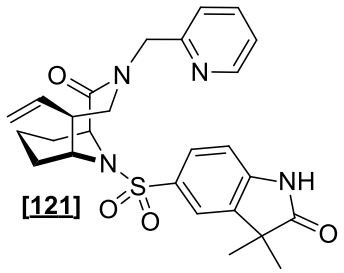
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.13 – 1.31 (m, 2H), 1.38 – 1.60 (m, 3H), 2.13 – 2.22 (m, 1H), 2.63 (m, 1H), 3.03 (dd, *J* = 14.1, 2.0 Hz, 1H), 3.53 (s, 2H), 3.95 (t, *J* = 5.9 Hz, 1H), 4.02 (dd, *J* = 14.1, 10.7 Hz, 1H), 4.68 (dt, *J* = 6.4, 1.9 Hz, 1H), 4.80 (q, *J* = 15.5 Hz, 2H), 4.88 – 5.03 (m, 2H), 5.65 (m, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 7.16 – 7.20 (m, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 1.7 Hz, 1H), 7.67 (m, 2H), 8.48 (m, 1H), 9.00 (s, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.6, 26.3, 27.4, 35.9, 49.1, 52.3, 54.4, 55.8, 56.7, 109.8, 116.6, 122.4, 122.7, 123.2, 126.2, 127.7, 134.9, 137.4, 137.9, 146.7, 148.3, 156.7, 171.2, 176.7.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{26}N_4O_4S$ 467.1748; Found 467.1757

Lab book number(s): JK213

5.2.108. Compound [121]: (1*S*,5*S*,6*R*)-10-((3,3-dimethyl-2-oxoindolin-5-yl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[121]

Compound **[33]** (25 mg, 0.092 mmol, 1 eq.), 3,3-dimethyl-2-oxoindoline-5-sulfonyl chloride (31 mg, 0.12 mmol, 1.3 eq.) and ZnO (15 mg, 0.18 mmol, 2 eq.) were placed in a flask under argon atmosphere. MeCN (10 ml) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with EA (40 ml) and filtered over cotton. The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (5 g SiO_2, EA) afforded the title compound as white solids.

Yield: 44% (20 mg, 0.040 mmol)

Appearance: white solids

TLC: R_f = 0.30 (EA; UV, Hanessian)

HPLC: R_t = 9.97 min (0 – 100% B in 20 min)

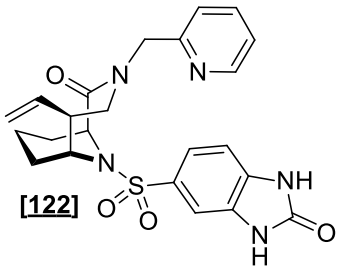
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.09 – 1.30 (m, 2H), 1.36 (d, *J* = 2.4 Hz, 6H), 1.38 – 1.47 (m, 2H), 1.53 (m, 1H), 2.12 – 2.22 (m, 1H), 2.59 – 2.67 (m, 1H), 3.02 (dd, *J* = 14.0, 2.0 Hz, 1H), 3.91 – 4.09 (m, 2H), 4.66 – 4.84 (m, 3H), 4.85 – 5.03 (m, 2H), 5.64 (m, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 7.13 – 7.19 (m, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 1.8 Hz, 1H), 7.60 – 7.72 (m, 2H), 8.47 (dd, *J* = 4.4, 1.4 Hz, 1H), 9.19 (s, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.7, 24.1, 26.2, 27.3, 44.7, 49.1, 52.2, 54.4, 56.0, 56.7, 110.0, 116.6, 121.3, 122.2, 122.6, 127.4, 135.0, 137.4, 137.5, 144.2, 148.6, 156.8, 171.2, 183.4.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{31}N_4O_4S$ 495.2061; Found 495.2071

Lab book number(s): JK214

5.2.109. Compound [122]: (1*S*,5*S*,6*R*)-10-((2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl) sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[122]

Compound **[33]** (25 mg, 0.092 mmol, 1 eq.), 2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-sulfonyl chloride (28 mg, 0.12 mmol, 1.3 eq.) and ZnO (16 mg, 0.19 mmol, 2 eq.) were placed in a flask under argon atmosphere. MeCN (10 ml) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with EA (40 ml) and filtered over cotton. The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (4 g SiO_2, EA) afforded the title compound as colorless resin.

Yield: 21% (9 mg, 0.019 mmol)

Appearance: colorless resin

TLC: R_f = 0.21 (EA + 5% MeOH; UV, Hanessian)

HPLC: R_t = 8.66 min (0 – 100% B in 20 min)

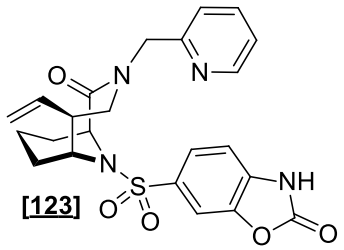
^{1}H NMR (500 MHz, DMSO-d_6) δ 1.13 – 1.30 (m, 2H), 1.32 – 1.47 (m, 2H), 1.47 – 1.62 (m, 1H), 2.02 (d, J = 13.3 Hz, 1H), 2.80 (q, J = 8.6 Hz, 1H), 3.05 (dd, J = 13.9, 1.9 Hz, 1H), 3.77 – 3.99 (m, 2H), 4.54 – 4.70 (m, 2H), 4.80 (d, J = 15.5 Hz, 1H), 4.99 – 5.06 (m, 2H), 5.71 (m, 1H), 7.12 (dd, J = 8.2, 1.1 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.25 – 7.33 (m, 1H), 7.35 (d, J = 1.7 Hz, 1H), 7.51 (dt, J = 8.2, 1.5 Hz, 1H), 7.78 (tt, J = 7.6, 1.4 Hz, 1H), 8.52 (dd, J = 5.1, 1.6 Hz, 1H), 10.96 (s, 1H), 11.17 (s, 1H).

^{13}C-NMR (126 MHz, DMSO-d_6): δ = 15.0, 25.7, 26.8, 47.7, 51.6, 53.6, 55.4, 56.1, 106.3, 108.7, 116.1, 119.9, 121.3, 122.3, 129.9, 132.3, 133.4, 136.8, 137.9, 149.0, 155.2, 157.1, 170.0.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{26}N_5O_4S$ 468.1700; Found 468.1706

Lab book number(s): JK215

5.2.110. Compound [123]: 6-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)benzo[d]oxazol-2(3H)-one



[123]

Compound **[33]** (25 mg, 0.092 mmol, 1 eq.), 2-oxo-2,3-dihydrobenzo[d]oxazole-6-sulfonyl chloride (28 mg, 0.12 mmol, 1.3 eq.) and ZnO (15 mg, 0.18 mmol, 2 eq.) were placed in a flask under argon atmosphere. MeCN (10 ml) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with EA (40 ml) and filtered over cotton. The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (4 g SiO_2, EA) afforded the title compound as white solids.

Yield: 25% (11 mg, 0.023 mmol)

Appearance: white solids

TLC: R_f = 0.24 (EA; UV, Hanessian)

HPLC: R_t = 9.41 min (0 – 100% B in 20 min)

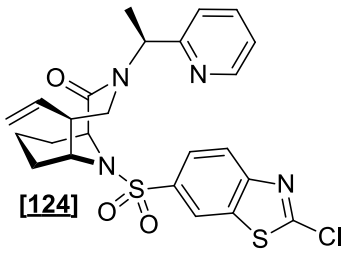
^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.12 – 1.24 (m, 2H), 1.31 – 1.44 (m, 2H), 1.50 (m, 1H), 1.99 (d, *J* = 13.4 Hz, 1H), 2.78 (q, *J* = 8.6 Hz, 1H), 3.04 (dd, *J* = 14.0, 1.9 Hz, 1H), 3.85 (dd, *J* = 14.0, 10.6 Hz, 1H), 3.92 (t, *J* = 5.8 Hz, 1H), 4.63 (d, *J* = 15.5 Hz, 2H), 4.78 (d, *J* = 15.4 Hz, 1H), 4.94 – 5.09 (m, 2H), 5.68 (m, 1H), 7.19 – 7.35 (m, 3H), 7.70 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.76 (td, *J* = 7.6, 1.7 Hz, 1H), 7.86 (d, *J* = 1.6 Hz, 1H), 8.44 – 8.57 (m, 1H), 12.17 (s, 1H).

^{13}C-NMR (126 MHz, DMSO-d_6): δ = 13.9, 24.6, 25.7, 46.6, 50.5, 52.5, 54.2, 55.0, 106.8, 108.9, 115.0, 120.3, 121.2, 122.1, 132.9, 133.4, 135.7, 136.7, 142.2, 147.9, 153.0, 156.0, 168.9.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{24}N_4O_5S$ 469.1540; Found 469.1549

Lab book number(s): JK216

5.2.111. Compound [124]: (((1*S*,5*S*,6*R*)-10-((2-chlorobenzo[d]thiazol-6-yl)sulfonyl)-3-((*S*)-1-(pyridin-2-yl)ethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[124]

Compound **[37]** (200 mg, 0.70 mmol, 1 eq.), 2-chlorobenzo[d]thiazole-6-sulfonyl chloride (300 mg, 1.12 mmol, 1.6 eq.) and DIPEA (357 μl mg, 0.2.10 mmol, 3 eq.) were placed in a flask under argon atmosphere. MeCN (50 ml) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with EA (150 ml) and washed with brine (50 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (50 g SiO_2, cycH/EA = 1:1) afforded the title compound as colorless solids.

Yield: 47% (170 mg, 0.33 mmol)

Appearance: colorless solids

TLC: R_f = 0.35 (EA; UV, Hanessian)

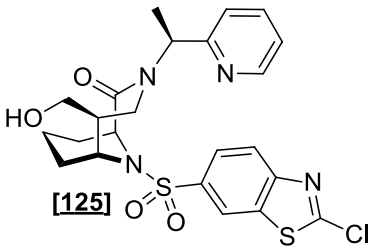
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.11 – 1.31 (m, 3H), 1.41 – 1.48 (m, 2H), 1.51 (d, *J* = 6.9 Hz, 4H), 2.23 (m, 1H), 2.45 – 2.56 (m, 1H), 2.81 (dd, *J* = 14.7, 1.8 Hz, 1H), 3.36 (dd, *J* = 14.7, 10.7 Hz, 1H), 3.99 (tt, *J* = 6.8, 3.4 Hz, 1H), 4.74 (dt, *J* = 6.2, 2.0 Hz, 1H), 4.94 – 5.07 (m, 2H), 5.64 (m, 1H), 6.07 (q, *J* = 6.9 Hz, 1H), 7.11 (m, 1H), 7.16 – 7.23 (m, 1H), 7.58 (td, *J* = 7.7, 1.8 Hz, 1H), 7.81 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 8.25 (d, *J* = 1.8 Hz, 1H), 8.47 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.1, 15.6, 26.4, 27.8, 46.1, 50.2, 54.9, 54.9, 57.0, 116.7, 120.6, 122.4, 122.9, 123.8, 124.6, 136.6, 136.7, 137.3, 138.7, 148.8, 153.3, 157.4, 159.0, 170.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{25}ClN_4O_3S_2$ 517.1129; Found 517.1130

Lab book number(s): JK230, JK242

5.2.112. Compound [125]: (((1*S*,5*S*,6*R*)-10-((2-chlorobenzo[d]thiazol-6-yl)sulfonyl)-5-(hydroxymethyl)-3-((*S*)-1-(pyridin-2-yl)ethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



[125]

Compound **[124]** (120 mg, 0.23 mmol, 1 eq.) was dissolved in Aceton (9 ml) and water (1 ml), 2,6-lutidine (54 μl, 0.46 mmol, 2 eq.), NMO (54 mg, 0.46 mmol, 2 eq.) and OsO_4 (60 µL, 0.0046 mmol, 0.02 eq., 2.5% in t-BuOH) were added successively. After full conversion (2 h, monitored by TLC) $PhI(OAc)_2$ (150 mg, 0.46 mmol, 2 eq.) was added and the mixture stirred for 3 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ solution, extracted with EA, washed with sat. aq. $CuSO_4$ solution, dried over $MgSO_4$ and filtered over silica. Solvents were removed under reduced pressure and the residue was dissolved in EtOH (15 ml). After cooling to 0 °C $NaBH_4$ (9 mg, 0.23 mmol, 1.0 eq.) was added, the mixture stirred for 15 min at 0 °C and 1 h at rt. The reaction was quenched with sat. aq. $NaHCO_3$ solution, extracted with DCM, dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (50 g silica; EA) afforded the title compound as white solids.

Yield: 43% (51 mg, 0.10 mmol, over 2 steps)

Appearance: white solids

TLC: R_f = 0.19 (EA; UV)

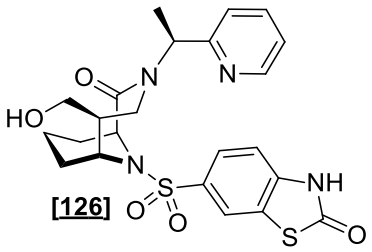
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.11 – 1.26 (m, 2H), 1.30 – 1.41 (m, 1H), 1.40 – 1.50 (m, 2H), 1.53 (d, *J* = 6.9 Hz, 3H), 2.05 – 2.16 (m, 1H), 2.23 (dd, *J* = 13.2, 3.0 Hz, 1H), 3.12 (dd, *J* = 14.7, 2.1 Hz, 1H), 3.20 (dd, *J* = 14.7, 10.3 Hz, 1H), 3.41 – 3.57 (m, 2H), 3.88 – 3.99 (m, 1H), 4.76 (dt, *J* = 6.2, 2.0 Hz, 1H), 6.06 (q, *J* = 6.9 Hz, 1H), 7.13 (m, 1H), 7.16 – 7.22 (m, 1H), 7.58 (td, *J* = 7.7, 1.8 Hz, 1H), 7.81 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.97 (d, *J* = 8.6 Hz, 1H), 8.25 (d, *J* = 1.8 Hz, 1H), 8.40 – 8.52 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.1, 15.6, 28.1, 28.2, 43.5, 47.7, 52.3, 55.1, 57.1, 63.6, 120.6, 122.5, 123.0, 123.8, 124.6, 136.6, 137.0, 138.6, 148.6, 153.3, 157.4, 159.0, 170.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{25}ClN_4O_4S_2$ 521.1079; Found 521.1080

Lab book number(s): JK238, JK244

5.2.113. Compound [126]: 6-(((1*S*,5*S*,6*R*)-5-(hydroxymethyl)-2-oxo-3-((*S*)-1-(pyridin-2-yl) ethyl)-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)benzo[d]thiazol-2(3H)-one



[126]

Compound **[125]** (15 mg, 0.029 mmol, 1 eq.) was dissolved in dioxane (10 ml). 1 M NaOH (10 ml) were added and the mixture was stirred at 100 °C for 4 h. The mixture was diluted with EA (80 ml) and washed with brine (2 x 20 ml). The organic phase was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (6 g silica; EA) afforded the title compound as colorless solids.

Yield: 76% (11 mg, 0.022 mmol)

Appearance: white solids

TLC: R_f = 0.13 (EA; UV)

HPLC: R_t = 7.53 min (0 – 100% B in 20 min)

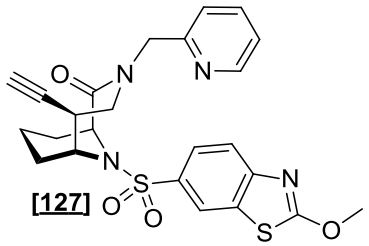
^{1}H-NMR (500 MHz, CD_3OD): δ = 1.36 – 1.57 (m, 3H), 1.58 – 1.72 (m, 6H), 2.20 (m, 1H), 2.25 – 2.32 (m, 1H), 3.09 – 3.26 (m, 2H), 3.39 – 3.44 (m, 1H), 3.52 (dd, *J* = 11.2, 5.1 Hz, 1H), 3.94 (dt, *J* = 5.2, 3.2 Hz, 1H), 4.90 (dt, *J* = 6.0, 1.9 Hz, 1H), 6.12 (q, *J* = 7.0 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 7.35 – 7.47 (m, 2H), 7.83 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.89 (td, *J* = 7.8, 1.8 Hz, 1H), 8.11 (d, *J* = 1.9 Hz, 1H), 8.60 (m, 1H).

^{13}C-NMR (126 MHz, CD_3OD): δ = 15.5, 16.7, 28.7, 29.3, 45.0, 49.2, 53.3, 56.7, 58.4, 63.6, 112.8, 122.8, 123.9, 124.0, 126.5, 126.6, 136.8, 139.0, 141.3, 149.6, 160.2, 172.8, 173.0.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{26}N_4O_5S_2$ 503.1417; Found 503.1418

Lab book number(s): JK240

5.2.114. Compound [127]: (((1*S*,5*S*,6*R*)-5-ethynyl-10-((2-methoxybenzo[d]thiazol-6-yl)sulfonyl)-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



[127]

Compound **[101]** (60 mg, 0.12 mmol, 1 eq.) was dissolved in aceton (9 ml) and water (1 ml), 2,6-lutidine (28 μl, 0.24 mmol, 2 eq.), NMO (28 mg, 0.24 mmol, 2 eq.) and OsO_4 (30 µL, 0.0024 mmol, 0.02 eq., 2.5% in t-BuOH) were added successively. After full conversion (2 h, monitored by TLC) $PhI(OAc)_2$ (77 mg, 0.24 mmol, 2 eq.) was added and the mixture stirred for 3 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ solution, extracted with EA, washed with sat. aq. $CuSO_4$ solution, dried over $MgSO_4$ and filtered over silica. Solvents were removed under reduced pressure and the residue was dissolved in MeOH (5 ml). After cooling to 0 °C, K_2CO_3 (32 mg, 0.24 mmol, 2 eq.) and Bestmann-Ohira reagent (586 μl, 0.24 mmol, 2 eq., 10% in MeCN) were added and the mixture was stirred for 1 h at 0 °C and afterwards 15 h at rt. The reaction was quenched with dest. water (10 ml) and extracted with DCM (5 x 15 ml), dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (10 g silica, cycH/EA = 1 :1) afforded the title compound as white solids.

Yield: 37% (22 mg, 0.044 mmol, over 2 steps)

Appearance: white solids

TLC: R_f = 0.58 (EA; UV)

HPLC: R_t = 11.33 min (0 – 100% B in 20 min)

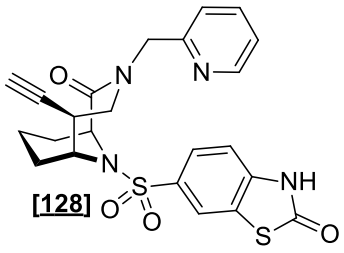
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.20 (m, 2H), 1.36 – 1.52 (m, 2H), 1.63 (d, *J* = 13.6 Hz, 1H), 2.18 (d, *J* = 13.7 Hz, 1H), 2.22 (d, *J* = 2.5 Hz, 1H), 3.14 (m, 1H), 3.34 (dd, *J* = 14.3, 1.9 Hz, 1H), 3.72 – 3.81 (m, 1H), 4.12 (dd, *J* = 14.2, 10.4 Hz, 1H), 4.24 (s, 4H), 4.42 (m, 1H), 4.77 (dt, *J* = 6.4, 1.9 Hz, 1H), 4.85 (d, *J* = 5.3 Hz, 2H), 7.26 (dd, *J* = 6.4, 3.3 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.66 – 7.85 (m, 3H), 8.17 (d, *J* = 1.7 Hz, 1H), 8.43 – 8.60 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.3, 27.0, 27.2, 36.2, 51.9, 55.6, 55.7, 56.5, 59.3, 71.9, 82.6, 120.7, 121.4, 122.4, 122.8, 124.4, 132.8, 135.7, 138.1, 148.1, 152.6, 156.2, 170.8, 176.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{25}N_4O_4S_2$ 497.1312; Found 497.1311

Lab book number(s): JK336

5.2.115. Compound [128]: 6-(((1*S*,5*S*,6*R*)-5-ethynyl-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)benzo[d]thiazol-2(3H)-one



[128]

Compound **[127]** (10 mg, 0.020 mmol, 1 eq.) was dissolved in dioxane (8 ml). Conc. HCl (4 drops) was added and the reaction mixture was stirred for 3 h. The mixture was quenched with sat. aq. $NaHCO_3$ (10 ml), extracted with DCM (5 x 20 ml), dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (5 g silica, EA) afforded the title compound as white solids.

Yield: 82% (8 mg, 0.016 mmol)

Appearance: white solids

TLC: R_f = 0.42 (EA; UV)

HPLC: R_t = 8.99 min (0 – 100% B in 20 min)

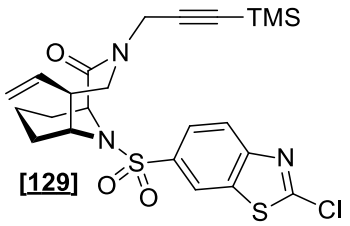
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.08 – 1.21 (m, 1H), 1.27 (tt, *J* = 13.1, 4.8 Hz, 1H), 1.35 – 1.49 (m, 2H), 1.53 (d, *J* = 13.5 Hz, 1H), 1.99 – 2.15 (m, 2H), 3.03 (m, 1H), 3.19 – 3.31 (m, 1H), 4.00 (dd, *J* = 14.3, 10.4 Hz, 1H), 4.26 (t, *J* = 6.0 Hz, 1H), 4.61 (d, *J* = 6.1 Hz, 1H), 4.69 – 4.89 (m, 2H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.15 – 7.23 (m, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.58 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.68 (t, *J* = 7.7 Hz, 1H), 7.76 (d, *J* = 1.8 Hz, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 10.12 (s, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.3, 27.1, 27.3, 36.2, 52.2, 55.4, 55.6, 56.5, 72.1, 82.4, 112.0, 121.4, 122.8, 123.2, 125.2, 125.3, 135.5, 139.0, 139.4, 147.2, 155.7, 171.0, 171.1.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{23}N_4O_4S_2$ 483.1155; Found 483.1160

Lab book number(s): JK344

5.2.116. Compound [129]: (1*S*,5*S*,6*R*)-10-((2-chlorobenzo[d]thiazol-6-yl)sulfonyl)-3-(3-(trimethylsilyl)prop-2-yn-1-yl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[129]

Compound **[90]** (100 mg, 0.41 mmol, 1 eq.) was dissolved in MeCN (25 ml). 2-Chlorobenzo[d]thiazole-6-sulfonyl chloride (120 mg, 0.70 mmol, 1.7 eq.) and DIPEA (140 μl, 0.83 mmol, 2.0 eq.) were added successively and the mixture was for 16 h at rt. The reaction mixture was diluted with EA (60 ml) and washed with brine (10 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (20 g SiO_2, cycH/EA = 4:1) afforded the title compound as colorless resin.

Yield: 77% (138 mg, 0.32 mmol)

Appearance: colorless resin

TLC: R_f = 0.48 (cycH/EA = 3:1; UV, Hanessian)

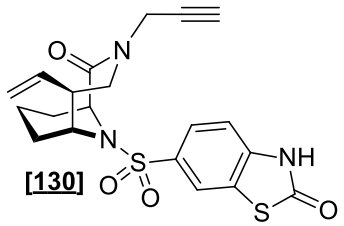
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.00 (d, *J* = 0.7 Hz, 9H), 0.94 – 1.04 (m, 1H), 1.05 – 1.16 (m, 2H), 1.25 – 1.36 (m, 2H), 2.08 (d, *J* = 14.1 Hz, 1H), 2.53 (td, *J* = 9.4, 7.2 Hz, 1H), 3.11 (dd, *J* = 14.2, 2.0 Hz, 1H), 3.64 (dd, *J* = 17.4, 0.7 Hz, 1H), 3.80 – 3.96 (m, 2H), 4.60 (dd, *J* = 5.0, 2.8 Hz, 1H), 4.66 (d, *J* = 17.4 Hz, 1H), 4.91 – 5.01 (m, 2H), 5.62 – 5.76 (m, 1H), 7.74 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.92 (dd, *J* = 8.6, 0.6 Hz, 1H), 8.17 (dd, *J* = 1.9, 0.5 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 0.0, 15.6, 26.4, 27.8, 40.1, 49.8, 50.6, 55.0, 57.0, 88.9, 100.6, 116.9, 120.7, 124.0, 124.8, 136.8, 137.5, 138.9, 153.6, 157.6, 170.1.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{29}ClN_3O_3S_2Si$ 522.1103; Found 522.1101

Lab book number(s): JK203

5.2.117. Compound [130]: 6-((((1*S*,5*S*,6*R*))-2-oxo-3-(prop-2-yn-1-yl)-5-vinyl-3,10-diazabicyclo [4.3.1]decan-10-yl)sulfonyl)benzo[d]thiazol-2(3H)-one



[130]

Compound **[129]** (18 mg, 0.034 mmol, 1 eq.) was dissolved in THF (8 ml). 1 M NaOH (8 ml) were added and the mixture was stirred at 80 °C for 10 h. The mixture was diluted with EA (50 ml) and washed with brine (20 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (5 g silica; cycH/EA = 1 :1) afforded the title compound as white solids.

Yield: 84% (12 mg, 0.029 mmol)

Appearance: white solids

TLC: R_f = 0.22 (cycH/EA = 1:1; UV, Hanessian)

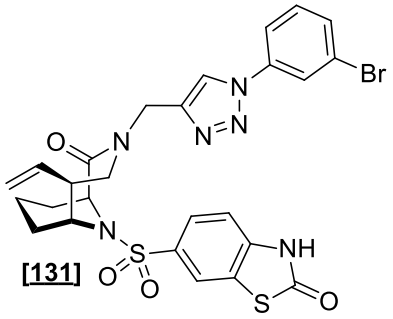
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.15 (m, 1H), 1.20 – 1.25 (m, 1H), 1.39 – 1.53 (m, 3H), 1.98 (s, 1H), 2.15 (q, *J* = 3.0, 2.4 Hz, 1H), 2.64 (m, 1H), 3.13 (dd, *J* = 14.1, 2.1 Hz, 1H), 3.87 (dd, *J* = 17.2, 2.5 Hz, 1H), 3.94 – 4.02 (m, 2H), 4.58 (dd, *J* = 17.2, 2.5 Hz, 1H), 4.69 (dt, *J* = 6.2, 1.9 Hz, 1H), 4.97 – 5.15 (m, 2H), 5.75 (m, 1H), 7.19 (s, 1H), 7.67 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.83 (d, *J* = 1.9 Hz, 1H), 9.68 (s, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.5, 26.2, 27.5, 39.4, 49.3, 51.0, 54.6, 56.8, 71.7, 78.6, 111.7, 117.0, 121.4, 125.3, 136.1, 137.3, 138.6, 170.6, 171.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{21}N_3O_4S_2$ 432.1046; Found 432.1045

Lab book number(s): JK205, JK208, JK373

5.2.118. Compound [131]: 6-(((1*S*,5*S*,6*R*)-3-((1-(3-bromophenyl)-1H-1,2,3-triazol-4-yl)methyl)-2-oxo-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)benzo[d]thiazol-2(3H)-one



[131]

Compound **[130]** (10 mg, 0.023 mmol, 1 eq.) was dissolved in t-BuOH/H_2O (2 ml, 1:1). $CuSO_4$ (8 mg, 0.03 mmol, 1.5 eq.) and sodium ascorbate (5 mg, 0.03 mmol, 1.5 eq.) were added and the mixture was stirred for 10 min. 1-azido-3-bromobenzene (9 mg, 0.05 mmol, 2 eq.) was added and the mixture was stirred for 4 h. The mixture was diluted with DCM (50 ml) and washed with brine (10 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (4 g silica; cycH/EA = 1 :1) afforded the title compound as white solids.

Yield: 62% (9 mg, 0.014 mmol)

Appearance: white solids

TLC: R_f = 0.39 (cycH/EA = 1:5; UV)

HPLC: R_t = 15.40 min (0 – 100% B in 20 min)

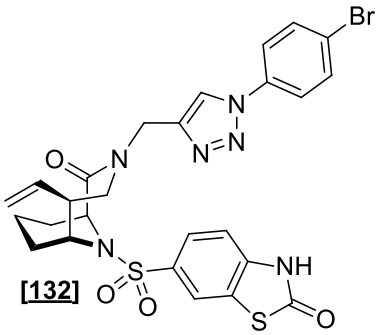
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.02– 1.45 (m, 5H), 2.10 – 2.21 (m, 1H), 2.60 (q, *J* = 8.7 Hz, 1H), 3.26 (dd, *J* = 14.0, 2.0 Hz, 1H), 3.92 – 4.00 (m, 1H), 4.04 (dd, *J* = 14.1, 10.9 Hz, 1H), 4.60 – 4.81 (m, 3H), 4.92 – 5.10 (m, 2H), 5.71 (m, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.33 (t, *J* = 8.1 Hz, 1H), 7.50 (m, 1H), 7.58 – 7.68 (m, 2H), 7.82 (d, *J* = 1.8 Hz, 1H), 7.91 (t, *J* = 2.0 Hz, 1H), 8.00 (s, 1H), 9.24 (s, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.5, 26.3, 27.3, 46.7, 49.0, 52.5, 54.6, 56.7, 111.5, 117.1, 118.8, 120.7, 121.5, 123.4, 123.6, 125.2, 125.2, 131.1, 131.8, 136.1, 137.1, 137.9, 138.4, 145.1, 170.6, 171.1.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{25}BrN_6O_4S_2$ 629.0635; Found 629.0638

Lab book number(s): JK221

5.2.119. Compound [132]: 6-(((1*S*,5*S*,6*R*)-3-((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methyl)-2-oxo-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)benzo[d]thiazol-2(3H)-one



[132]

Compound **[130]** (10 mg, 0.023 mmol, 1 eq.) was dissolved in t-BuOH/H_2O (2 ml, 1:1). $CuSO_4$ (8 mg, 0.03 mmol, 1.5 eq.) and sodium ascorbate (5 mg, 0.03 mmol, 1.5 eq.) were added and the mixture was stirred for 10 min. 1-azido-4-bromobenzene (9 mg, 0.05 mmol, 2 eq.) was added and the mixture was stirred for 4 h. The mixture was diluted with DCM (50 ml) and washed with brine (10 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (4 g silica; cycH/EA = 1 :1) afforded the title compound as white solids.

Yield: 48% (7 mg, 0.011 mmol)

Appearance: white solids

TLC: R_f = 0.29 (cycH/EA = 1:2; UV)

HPLC: R_t = 15.39 min (0 – 100% B in 20 min)

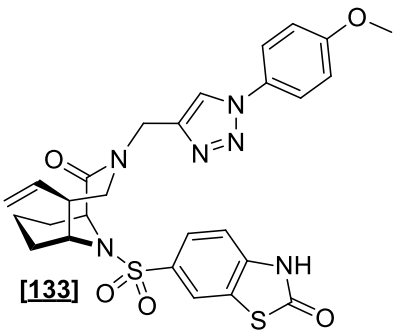
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.72 – 1.50 (m, 5H), 2.08 – 2.20 (m, 1H), 2.61 (q, *J* = 8.8 Hz, 1H), 3.25 (dd, *J* = 14.2, 2.0 Hz, 1H), 3.92 – 4.00 (m, 1H), 4.04 (dd, *J* = 14.2, 10.8 Hz, 1H), 4.61 – 4.70 (m, 2H), 4.81 (d, *J* = 15.0 Hz, 1H), 4.97 – 5.12 (m, 2H), 5.71 (m, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.58 (s, 4H), 7.65 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.82 (d, *J* = 1.9 Hz, 1H), 7.99 (s, 1H), 9.16 (d, *J* = 13.9 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 14.5, 25.3, 26.3, 45.7, 48.0, 51.5, 53.6, 55.7, 110.5, 116.0, 119.6, 120.4, 120.8 (2C), 121.4, 124.2, 124.2, 131.9 (2C), 135.0, 135.1, 136.1, 137.4, 144.1, 169.5, 170.1.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{25}BrN_6O_4S_2$ 629.0635; Found 629.0640

Lab book number(s): JK222

5.2.120. Compound [133]: 6-(((1*S*,5*S*,6*R*)-3-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-2-oxo-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl) sulfonyl)benzo[d]thiazol-2(3H)-one



[133]

Compound **[130]** (10 mg, 0.023 mmol, 1 eq.) was dissolved in t-BuOH/H_2O (2 ml, 1:1). $CuSO_4$ (6 mg, 0.02 mmol, 1 eq.) and sodium ascorbate (5 mg, 0.02 mmol, 1 eq.) were added and the mixture was stirred for 10 min. 1-azido-4-methoxybenzene (5 mg, 0.03 mmol, 1.5 eq.) was added and the mixture was stirred for 4 h. The mixture was diluted with DCM (50 ml) and washed with brine (10 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (5 g silica; cycH/EA = 1 :1) afforded the title compound as white solids.

Yield: 38% (5 mg, 0.0087 mmol)

Appearance: white solids

TLC: R_f = 0.62 (EA; UV, Hanessian)

HPLC: R_t = 13.46 min (0 – 100% B in 20 min)

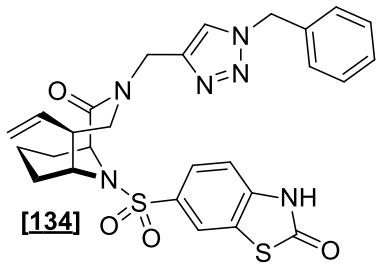
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.19 – 1.25 (m, 1H), 1.27 – 1.35 (m, 1H), 1.44 – 1.53 (m, 3H), 2.17 – 2.27 (m, 1H), 2.66 (q, *J* = 8.9 Hz, 1H), 3.33 (dd, *J* = 14.1, 2.0 Hz, 1H), 3.87 (s, 3H), 3.96 – 4.13 (m, 2H), 4.67 – 4.89 (m, 3H), 5.03 – 5.14 (m, 2H), 5.67 – 5.86 (m, 1H), 6.99 – 7.06 (m, 2H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.59 – 7.68 (m, 2H), 7.71 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.89 (d, *J* = 1.8 Hz, 1H), 7.97 (s, 1H), 9.39 (s, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.5, 26.3, 27.4, 46.6, 49.0, 52.4, 54.6, 55.6, 56.7, 111.6, 114.8, 117.0, 120.8, 121.4, 122.0, 125.2, 125.2, 130.5, 136.1, 137.1, 138.4, 144.5, 159.9, 170.6, 171.0.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{29}N_6O_5S_2$ 581.1635; Found 581.1637

Lab book number(s): JK207

5.2.121. Compound [134]: 6-(((1*S*,5*S*,6*R*)-3-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-2-oxo-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)benzo[d]thiazol-2(3H)-one



[134]

Compound **[130]** (22 mg, 0.051 mmol, 1 eq.) was dissolved in t-BuOH/H_2O (2 ml, 9:1). $CuSO_4$ (19 mg, 0.08 mmol, 1.5 eq.) and sodium ascorbate (15 mg, 0.08 mmol, 1.5 eq.) were added and the mixture was stirred for 10 min. Benzyl azide (10 mg, 0.08 mmol, 1.5 eq.) was added and the mixture was stirred for 4 h. The mixture was diluted with EA (50 ml) and washed with brine (10 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (10 g silica; cycH/EA = 1:3) afforded the title compound as white solids.

Yield: 69% (20 mg, 0.035 mmol)

Appearance: white solids

TLC: R_f = 0.27 (cycH/EA = 1:3; UV)

HPLC: R_t = 13.36 min (0 – 100% B in 20 min)

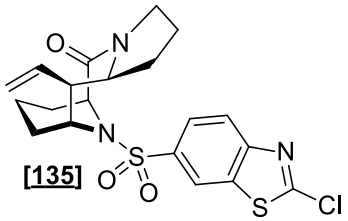
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.07 – 1.33 (m, 5H), 2.04 – 2.12 (m, 1H), 2.34 – 2.51 (m, 1H), 3.18 (dd, *J* = 14.2, 2.0 Hz, 1H), 3.85 – 4.02 (m, 2H), 4.48 – 4.67 (m, 2H), 4.73 (d, *J* = 14.9 Hz, 1H), 4.87 – 5.02 (m, 2H), 5.37 – 5.56 (m, 2H), 5.64 (m, 1H), 7.17 – 7.21 (m, 3H), 7.23 – 7.30 (m, 3H), 7.51 (s, 1H), 7.60 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.79 (d, *J* = 1.8 Hz, 1H), 10.31 (s, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.5, 26.2, 27.4, 46.3, 49.1, 52.1, 54.4, 54.5, 56.7, 111.9, 116.9, 121.3, 122.8, 125.1, 125.2, 128.0, 128.8, 129.1, 134.5, 135.8, 137.1, 138.9, 144.3, 171.0, 171.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{28}N_6O_4S_2$ 565.1686; Found 565.1690

Lab book number(s): JK302

5.2.122. Compound [135]: (6*S*,10*R*,11*R*,11a*S*)-12-((2-chlorobenzo[d]thiazol-6-yl)sulfonyl)-11-vinyloctahydro-1H-6,10-epiminopyrrolo[1,2-a]azonin-5(6H)-one



[135]

Compound **[75]** (70 mg, 0.32 mmol, 1 eq.) was dissolved in MeCN (30 ml). 2-Chloro-1,3-benzothiazole-6-sulfonyl chloride (102 mg, 0.38 mmol, 1.2 eq.) in MeCN (10 ml) and DIPEA (137 µl, 0.64 mmol, 2 eq.) were added successively and the mixture was stirred for 48 h at rt. The mixture was diluted with EA (50 ml) and washed with brine (2 x 20 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (25 g silica; cycH/EA = 2:1) afforded the title compound as white solids.

Yield: 31% (45 mg, 0.10 mmol)

Appearance: white solids

TLC: R_f = 0.24 (cycH/EA = 1:1)

HPLC: R_t = 15.67 min (0 – 100% B in 20 min)

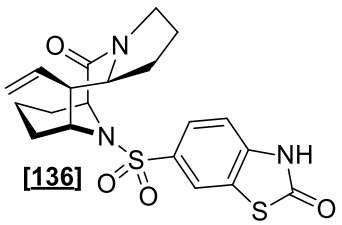
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.02 – 1.12 (m, 2H), 1.33 – 1.42 (m, 2H), 1.43 – 1.54 (m, 2H), 1.59 – 1.69 (m, 1H), 1.79 (dt, *J* = 12.3, 6.3 Hz, 1H), 1.96 (dt, *J* = 11.2, 5.3 Hz, 1H), 2.14 (d, *J* = 13.6 Hz, 1H), 2.22 (td, *J* = 9.7, 6.8 Hz, 1H), 3.38 (td, *J* = 11.5, 6.3 Hz, 1H), 3.72 (dd, *J* = 12.1, 7.7 Hz, 1H), 3.95 (t, *J* = 6.0 Hz, 1H), 4.08 (td, *J* = 9.8, 6.1 Hz, 1H), 4.65 (d, *J* = 6.0 Hz, 1H), 4.90 – 5.11 (m, 2H), 5.70 (dt, *J* = 16.8, 9.9 Hz, 1H), 7.84 (dt, *J* = 8.6, 1.4 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 8.17 – 8.36 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 15.4, 22.3, 25.4, 26.6, 33.5, 49.4, 54.5, 55.3, 56.3, 58.5, 117.2, 120.5, 123.8, 124.7, 136.6, 137.1, 138.8, 153.4, 157.4, 169.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{22}N_3O_3S_2$ 452.0864; Found 452.0866

Lab book number(s): JK356

5.2.123. Compound [136]: 6-(((6*S*,10*R*,11*S*,11a*S*)-5-oxo-11-vinyldecahydro-1H-6,10-epiminopyrrolo[1,2-a]azonin-12-yl)sulfonyl)benzo[d]thiazol-2(3H)-one



[136]

Compound **[135]** (30 mg, 0.066 mmol, 1 eq.) was dissolved in THF (30 ml). 1 M NaOH (10 ml) were added and the mixture was stirred at 80 °C for 16 h. The mixture was diluted with EA (50 ml) and washed with brine (2 x 20 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (20 g silica; cycH/EA = 1:1) afforded the title compound as colorless resin.

Yield: 91% (26 mg, 0.060 mmol)

Appearance: colorless resin

TLC: R_f = 0.29 (EA)

HPLC: R_t = 12.28 min (0 – 100% B in 20 min)

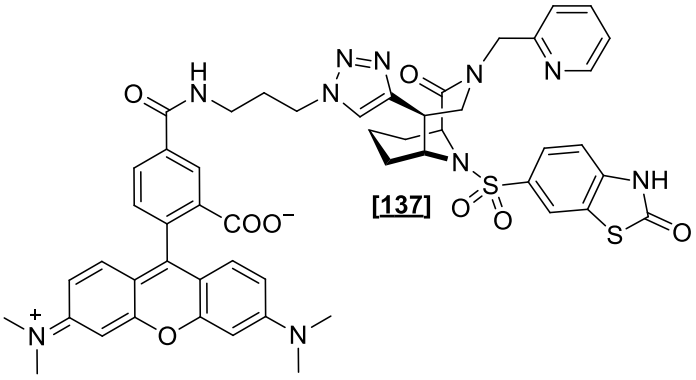
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.07 – 1.21 (m, 2H), 1.39 – 1.50 (m, 2H), 1.57 (m, 1H), 1.63 – 1.76 (m, 1H), 1.79 – 1.85 (m, 1H), 1.99 (m, 1H), 2.10 – 2.21 (m, 2H), 2.26 (td, *J* = 9.7, 6.9 Hz, 1H), 3.44 (td, *J* = 11.5, 6.3 Hz, 1H), 3.77 (dd, *J* = 12.1, 7.6 Hz, 1H), 3.89 – 4.00 (m, 1H), 4.14 (td, *J* = 9.9, 6.0 Hz, 1H), 4.70 (d, *J* = 6.0 Hz, 1H), 4.95 – 5.11 (m, 2H), 5.72 (dt, *J* = 16.9, 9.8 Hz, 1H), 7.22 (d, *J* = 2.5 Hz, 1H), 7.69 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.85 (d, *J* = 1.8 Hz, 1H), 10.42 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 15.5, 22.3, 25.3, 26.6, 33.4, 49.7, 54.3, 55.2, 56.2, 58.8, 111.9, 117.3, 121.3, 125.2, 125.3, 135.9, 137.0, 139.1, 169.9, 171.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{23}N_3O_4S_2$ 434.1203; Found 434.1206

Lab book number(s): JK357

5.2.124. Compound [137]: 2-(6-(dimethylamino)-3-(dimethyliminio)-3H-xanthen-9-yl)-5-((3-(4-((1*S*,5*S*,6*R*)-2-oxo-10-((2-oxo-2,3-dihydrobenzo[d]thiazol-6-yl)sulfonyl)-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)-1H-1,2,3-triazol-1-yl)propyl) carbamoyl)benzoate



Compound [128] (6 mg, 0.012 mmol, 1 eq.) was dissolved in t-BuOH/H_2O (1 ml, 9:1). $CuSO_4$ (4.0 mg, 0.016 mmol, 1 eq.) and sodium ascorbate (3.2 mg, 0.016 mmol, 1 eq.) were added and the mixture was stirred for 10 min. TAMRA-N_3 (5.1 mg, 0.010 mmol, 1 eq.) was added and the mixture was stirred for 4 h. The mixture was diluted with EA (50 ml) and washed with brine (10 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (8 g silica; DCM/MeOH = 9:1) afforded the title compound as purple solids.

Yield: 28% (3.3 mg, 0.033 mmol)

Appearance: purple solids

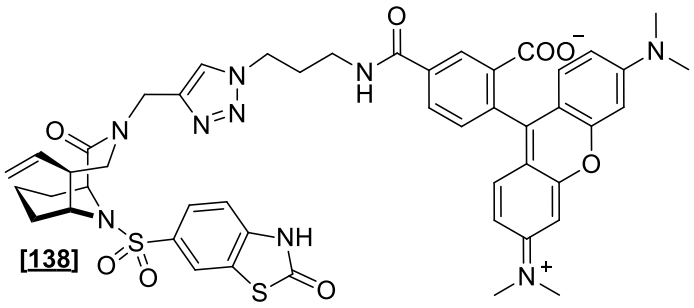
TLC: R_f = 0.46 (DCM/MeOH = 7:1; UV)

HPLC: R_t = 10.43 min (0 – 100% B in 20 min)

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{51}H_{52}N_{10}O_8S_2$ 995.3327; Found 995.3322

Lab book number(s): JK351

5.2.125. Compound [138]: 2-(6-(dimethylamino)-3-(dimethyliminio)-3H-xanthen-9-yl)-5-((3-(4-(((1*S*,5*S*,6*R*)-2-oxo-10-((2-oxo-2,3-dihydrobenzo[d]thiazol-6-yl)sulfonyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-3-yl)methyl)-1H-1,2,3-triazol-1-yl)propyl) carbamoyl)benzoate



[138]

Compound **[130]** (4 mg, 0.093 mmol, 1 eq.) was dissolved in t-BuOH/H_2O (1 ml, 9:1). $CuSO_4$ (2.3 mg, 0.092 mmol, 1 eq.) and sodium ascorbate (1.8 mg, 0.01 mmol, 1 eq.) were added and the mixture was stirred for 10 min. TAMRA-N_3 (4.7 mg, 0.092 mmol, 1 eq.) was added and the mixture was stirred for 4 h. The mixture was diluted with EA (50 ml) and washed with brine (10 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (8 g silica; DCM/MeOH = 9:1) afforded the title compound as purple solids.

Yield: 15% (1.42 mg, 0.015 mmol)

Appearance: purple solids

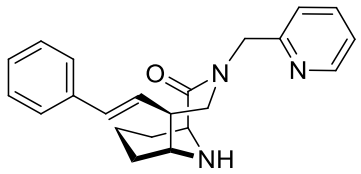
TLC: R_f = 0.27 (cycH/EA = 1:3; UV)

HPLC: R_t = 12.32 min (0 – 100% B in 20 min)

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{48}H_{49}N_9O_8S_2$ 944.3218; Found 944.3228

Lab book number(s): JK301

5.2.126. Compound [139]: (1*S*,5*S*,6*R*)-3-(pyridin-2-ylmethyl)-5-((*E*)-styryl)-3,10-diazabicyclo [4.3.1]decan-2-one



[139]

Compound **[33]** (76 mg, 0.27 mmol, 1 eq.), K_2CO_3 (74 mg, 1.33 mmol, 2.0 eq.) and $Pd(PPh_3)_4$ (62 mg, 0.05 mmol, 0.2 eq.) were placed in a 25 ml flask under argon. 1,4-Dioxane (10 ml) and phenyl bromide (140 μl, 1.33 mmol, 5 eq.) were added and the mixture was heated to 100 °C and stirred for 16 h. The mixture was filtered over celite with EA, solvents were removed under reduced pressure and the crude was purified by column chromatography (10 g SiO_2, EA + 3% TEA + 5% MeOH).

Yield: 94% (88 mg, 0.25 mmol)

Appearance: orange resin

TLC: R_f = 0.11 (EA + 3% TEA + 5% MeOH; UV, ninhydrin)

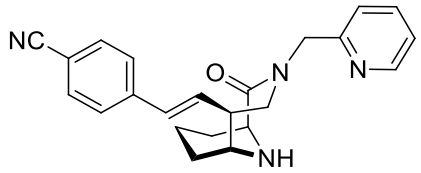
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.45 – 1.67 (m, 5H), 1.82 (d, *J* = 16.8 Hz, 2H), 2.28 (d, *J* = 13.7 Hz, 1H), 2.82 (q, *J* = 9.2 Hz, 1H), 3.08 – 3.22 (m, 1H), 3.94 (d, *J* = 5.5 Hz, 1H), 4.26 (dd, *J* = 13.8, 10.6 Hz, 1H), 4.56 (dd, *J* = 14.8, 6.9 Hz, 1H), 4.77 – 4.90 (m, 1H), 5.75 – 5.99 (m, 1H), 6.16 (dd, *J* = 15.7, 11.1 Hz, 1H), 7.06 – 7.21 (m, 7H), 7.56 (m, 1H), 8.42 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 16.2, 27.1, 28.3, 47.8, 51.3, 53.3, 56.0, 56.8, 122.4, 126.2, 126.3, 127.7, 128.6, 129.3, 131.6, 134.5, 136.4, 136.8, 149.2, 157.2, 172.1.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{26}N_3O$ 348.2070; Found 348.2069

Lab book number(s): JK326

5.2.127. Compound [140]: 4-((*E*)-2-((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)vinyl)benzonitrile



[140]

Compound **[33]** (140 mg, 0.52 mmol, 1 eq.), K_2CO_3 (214 mg, 1.55 mmol, 2.0 eq.) and $Pd(PPh_3)_4$ (119 mg, 0.10 mmol, 0.2 eq.) were placed in a 25 ml flask under argon. DMF (15 ml) and 4-Bromobenzonitrile (187 mg, 1.03 mmol, 3 eq.) were added and the mixture was heated to 120 °C and stirred for 16 h. The mixture was diluted with Et_2O (200 ml) and washed with brine. The aqueous phase was re-extracted with Et_2O (4 x 50 ml) and the organic phases were combined. Solvents were removed under reduced pressure and the crude was purified by column chromatography (30 g SiO_2, EA + 3% TEA + 5% MeOH).

Yield: 40% (80 mg, 0.21 mmol)

Appearance: orange resin

TLC: R_f = 0.10 (EA + 3% TEA + 5% MeOH; UV, ninhydrin)

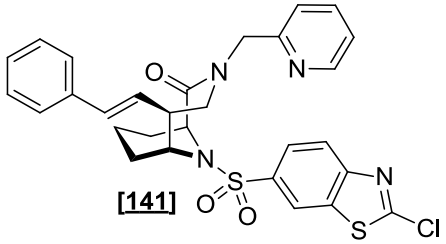
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.07 - 1.98 (m, 7H), 2.33 (d, *J* = 13.7 Hz, 1H), 2.96 (quint., *J* = 8.9, 8.5 Hz, 1H), 3.20 – 3.22 (m, 1H), 4.02 (d, *J* = 5.6 Hz, 1H), 4.38 (dd, *J* = 14.5, 10.8 Hz, 1H), 4.62 (d, *J* = 15.1 Hz, 1H), 4.88 (d, *J* = 15.1 Hz, 1H), 6.11 (dd, *J* = 15.8, 8.8 Hz, 1H), 6.25 (d, *J* = 15.7 Hz, 1H), 7.15 (dd, *J* = 7.6, 4.9 Hz, 1H), 7.30 (dd, *J* = 8.3, 2.4 Hz, 3H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.62 (td, *J* = 7.7, 1.9 Hz, 1H), 8.47 (d, *J* = 1.7 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 16.0, 27.1, 28.3, 47.8, 51.0, 53.1, 56.0, 56.7, 111.1, 118.8, 122.6, 126.8, 130.1, 132.4, 133.3, 136.9, 140.9, 149.1, 157.0, 171.9.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{24}N_4O$ 373.2023; Found 373.2025

Lab book number(s): JK361, JK369

5.2.128. Compound [141]: (((1*S*,5*S*,6*R*)-10-((2-chlorobenzo[d]thiazol-6-yl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-((*E*)-styryl)-3,10-diazabicyclo[4.3.1]decan-2-one



[141]

Compound **[139]** (80 mg, 0.23 mmol, 1 eq.) was dissolved in MeCN (30 ml). 2-Chloro-1,3-benzothiazole-6-sulfonyl chloride (100 mg, 0.35 mmol, 1.5 eq.) in MeCN (10 ml) and DIPEA (120 µl, 0.70 mmol, 3 eq.) were added successively and the mixture was stirred for 48 h at rt. The mixture was diluted with EA (50 ml) and washed with brine (2 x 20 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (25 g silica; cycH/EA = 1:1) afforded the title compound as white solids.

Yield: 38% (50 mg, 0.087 mmol)

Appearance: white solids

TLC: R_f = 0.23 (cycH/EA = 1:1; UV)

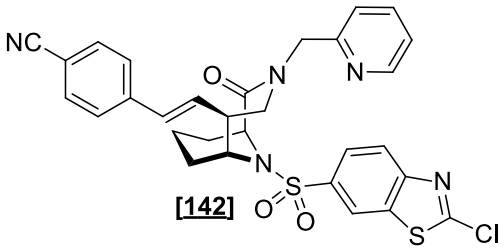
^{1}H-NMR (500 MHz, CD_3OD): δ = 1.21 – 1.31 (m, 3H), 1.48 – 1.59 (m, 2H), 1.66 (m, 1H), 2.24 – 2.36 (m, 1H), 2.83 – 3.00 (m, 1H), 3.21 (dd, *J* = 14.2, 1.9 Hz, 1H), 4.12 – 4.20 (m, 1H), 4.78 – 4.93 (m, 3H), 6.12 (m, 1H), 6.33 (d, *J* = 15.7 Hz, 1H), 7.25 (m, 2H), 7.32 – 7.36 (m, 4H), 7.37 – 7.41 (m, 1H), 7.73 (m, 1H), 7.94 (dt, *J* = 8.6, 1.6 Hz, 1H), 8.09 (dd, *J* = 8.6, 1.2 Hz, 1H), 8.38 (d, *J* = 1.6 Hz, 1H), 8.47 – 8.65 (m, 1H).

^{13}C-NMR (126 MHz, CD_3OD): δ = 15.6, 26.4, 27.5, 48.7, 52.5, 55.1, 56.0, 56.9, 120.6, 122.3, 122.6, 123.8, 124.6, 126.3, 127.9, 128.5, 128.6, 132.0, 136.3, 136.7, 137.4, 138.7, 148.8, 153.4, 156.8, 157.5, 170.7.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{27}ClN_4O_3S_2$ 579.1286; Found 579.1289

Lab book number(s): JK330

5.2.129. Compound [142]: 4-((*E*)-2-((1*S*,5*S*,6*R*)-10-((2-chlorobenzo[d]thiazol-6-yl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)vinyl)benzonitrile



[142]

Compound **[140]** (60 mg, 0.16 mmol, 1 eq.) was dissolved in MeCN (20 ml). 2-Chloro-1,3-benzothiazole-6-sulfonyl chloride (86 mg, 0.32 mmol, 2.0 eq.) in MeCN (10 ml) and DIPEA (120 µl, 0.70 mmol, 3 eq.) were added successively and the mixture was stirred for 48 h at rt. The mixture was diluted with EA (50 ml) and washed with brine (2 x 20 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (20 g silica; cycH/EA = 3:1 → EA) afforded the title compound as colorless resin.

Yield: 12% (12 mg, 0.02 mmol)

Appearance: colorless resin

TLC: R_f = 0.46 (EA, UV)

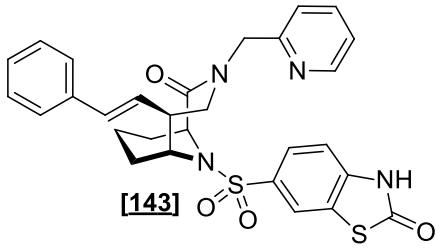
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.09 – 1.62 (m, 5H), 2.19 (d, *J* = 13.7 Hz, 1H), 2.81 – 2.97 (m, 1H), 3.21 (dd, *J* = 14.2, 2.1 Hz, 1H), 4.09 – 4.22 (m, 2H), 4.73 (dt, *J* = 6.2, 1.9 Hz, 1H), 4.84 (d, *J* = 15.5 Hz, 1H), 4.96 (d, *J* = 15.5 Hz, 1H), 6.19 (dd, *J* = 15.8, 9.1 Hz, 1H), 6.34 (d, *J* = 15.8 Hz, 1H), 7.24 – 7.31 (m, 1H), 7.31 – 7.39 (m, 2H), 7.39 – 7.48 (m, 1H), 7.49 – 7.59 (m, 2H), 7.74 – 7.88 (m, 2H), 8.01 (d, *J* = 8.6 Hz, 1H), 8.29 (d, *J* = 1.9 Hz, 1H), 8.45 – 8.59 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.5, 26.7, 27.5, 48.7, 52.4, 54.9, 55.3, 56.8, 111.2, 118.7, 120.6, 123.2, 123.9, 124.5, 126.9, 130.7, 132.3, 132.5, 132.8, 136.7, 138.4, 139.0, 140.7, 153.5, 156.1, 157.6, 170.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{26}ClN_5O_3S_2$ 604.1238; Found 604.1237

Lab book number(s): JK363

5.2.130. Compound [143]: 6-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-((*E*)-styryl)-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)benzo[d]thiazol-2(3H)-one



[143]

Compound **[141]** (50 mg, 0.086 mmol, 1 eq.) was dissolved in THF (10 ml). 2 M NaOH (10 ml) were added and the mixture was stirred at 80 °C for 16 h. The mixture was diluted with EA (50 ml) and washed with brine (2 x 20 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (10 g silica; EA) afforded the title compound as white solids.

Yield: 67% (32 mg, 0.058 mmol)

Appearance: white solids

TLC: R_f = 0.29 (EA; UV)

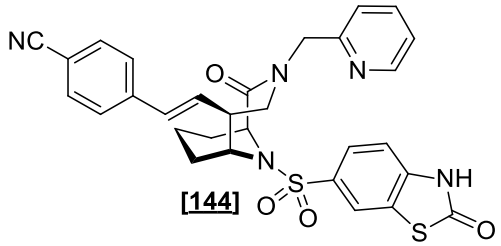
^{1}H-NMR (500 MHz, CD_3OD): δ = 1.22 – 1.28 (m, 2H), 1.44 – 1.57 (m, 2H), 1.64 (m, 1H), 2.21 – 2.31 (m, 1H), 2.89 (td, *J* = 10.3, 5.1 Hz, 1H), 3.18 (dd, *J* = 14.1, 1.9 Hz, 1H), 4.02 – 4.14 (m, 1H), 4.22 (dd, *J* = 14.1, 10.7 Hz, 1H), 4.78 – 4.85 (m, 1H), 4.89 (s, 2H), 6.08 (dd, *J* = 15.7, 9.1 Hz, 1H), 6.31 (d, *J* = 15.7 Hz, 1H), 7.21 – 7.30 (m, 7H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.60 – 7.79 (m, 2H), 7.89 (d, *J* = 1.8 Hz, 1H), 8.55 (dd, *J* = 5.1, 1.6 Hz, 1H), 10.74 (s, 1H).

^{13}C-NMR (126 MHz, CD_3OD): δ = 15.6, 26.3, 27.4, 48.6, 52.8, 55.0, 56.0, 56.8, 112.0, 121.3, 122.3, 122.8, 125.1, 125.3, 126.3, 127.9, 128.4, 128.6, 132.1, 135.8, 136.2, 137.8, 139.2, 148.5, 156.5, 171.4.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{28}N_4O_4S_2$ 561.1625; Found 561.1627

Lab book number(s): JK332

5.2.131. Compound [144]: 4-((*E*)-2-((1*S*,5*S*,6*R*)-2-oxo-10-((2-oxo-2,3-dihydrobenzo[d]thiazol-6-yl)sulfonyl)-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)vinyl) benzonitrile



[144]

Compound **[142]** (12 mg, 0.020 mmol, 1 eq.) was dissolved in THF (10 ml). 2 M NaOH (10 ml) were added and the mixture was stirred at 80 °C for 16 h. The mixture was diluted with EA (50 ml) and washed with brine (2 x 20 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (10 g silica; EA) afforded the title compound as colorless resin.

Yield: 52% (6 mg, 0.010 mmol)

Appearance: colorless resin

TLC: R_f = 0.28 (EA, UV)

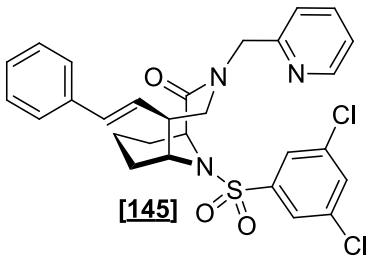
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.04 – 1.31 (m, 2H), 1.36 – 1.63 (m, 3H), 2.21 (d, *J* = 13.5 Hz, 1H), 2.81 – 2.95 (m, 1H), 3.15 (dd, *J* = 14.1, 2.0 Hz, 1H), 4.06 (t, *J* = 5.8 Hz, 1H), 4.17 (dd, *J* = 14.2, 10.7 Hz, 1H), 4.65 – 4.76 (m, 2H), 4.83 (d, *J* = 15.3 Hz, 1H), 6.18 (dd, *J* = 15.8, 9.0 Hz, 1H), 6.28 (d, *J* = 15.8 Hz, 1H), 7.10 – 7.18 (m, 2H), 7.23 – 7.38 (m, 3H), 7.45 – 7.56 (m, 2H), 7.59 – 7.75 (m, 2H), 7.84 (d, *J* = 1.9 Hz, 1H), 8.47 (m, 1H), 9.43 (s, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.6, 26.7, 27.6, 48.7, 52.3, 54.7, 56.3, 56.8, 111.2, 111.6, 118.7, 121.4, 122.3, 122.6, 125.2, 125.3, 126.8, 130.4, 132.5, 132.6, 136.1, 137.2, 138.5, 140.7, 149.0, 156.8, 170.6, 170.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{27}N_5O_4S_2$ 586.1577; Found 586.1580

Lab book number(s): JK365

5.2.132. Compound [145]: (1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-3-(pyridin-2-ylmethyl) -5-((*E*)-styryl)-3,10-diazabicyclo[4.3.1]decan-2-one



[145]

Compound **[34]** (20.9 mg, 0.044 mmol, 1 eq.), bromobenzene (6.9 ml, 0.066 mmol, 1.5 eq.), K_2CO_3 (13.2 mg, 0.096 mmol, 2.2 eq.) and $Pd(PPh_3)_4$ (6.5 mg, 0.0056 mmol, 0.13 eq.) were solved in dry dioxane (8 ml) under argon atmosphere. The reaction mixture was heated to 90 °C and stirred for 18 h. After addition of brine (20 ml), the mixture was extracted with EA (2 x 50 ml), dried over $MgSO_4$ and solvents were removed under reduced pressure. The crude product was purified via preparative HPLC (45 – 70% B in 10 min) yielding a colorless solid.

Yield: 15% (3.5 mg, 0.0066 mmol)

Appearance: colorless solid

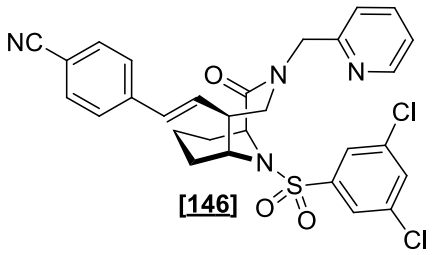
TLC: R_f = 0.26 (cycH/EA = 1:1; UV)

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.19 – 1.40 (m, 2H), 1.49 – 1.73 (m, 3H), 2.28 – 2.38 (m, 1H), 2.90 (m, 1H), 3.20 (dd, *J* = 14.3, 2.0 Hz, 1H), 4.06 – 4.11 (m, 1H), 4.15 (dd, *J* = 14.2, 10.7 Hz, 1H), 4.78 (dt, *J* = 6.4, 1.9 Hz, 1H), 4.81 – 4.95 (m, 2H), 6.08 (dd, *J* = 15.7, 9.2 Hz, 1H), 6.33 (d, *J* = 15.7 Hz, 1H), 7.21 – 7.27 (m, 3H), 7.28 – 7.35 (m, 4H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 1.8 Hz, 1H), 7.69 – 7.78 (m, 3H), 8.55 – 8.60 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.7, 26.7, 27.7, 48.8, 52.7, 55.5, 56.1, 57.1, 122.5, 122.8, 125.1, 126.5, 128.1, 128.4, 128.8, 132.4, 132.9, 136.3, 136.6, 137.7, 144.3, 148.9, 156.8, 170.7.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{28}Cl_2N_3O_3S$ 556.1223; Found 556.1224

5.2.133. Compound [146]: 4-((*E*)-2-((1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)vinyl)benzonitrile



[146]

Compound **[34]** (20.9 mg, 0.044 mmol, 1 eq.), 4-bromobenzonitrile (11.4 mg, 0.06 mmol, 1.5 eq.), K_2CO_3 (13.2 mg, 0.08 mmol, 2 eq.) and $Pd(PPh_3)_4$ (6.5 mg, 0.0056 mmol, 0.13 eq.) were solved in dry dioxane (8 ml) under argon atmosphere. The reaction mixture was heated to 90 °C and stirred for 18 h. After addition of brine (20 ml), the mixture was extracted with EA (2 x 50 ml), dried over $MgSO_4$ and solvents were removed under reduced pressure. The crude product was purified via preparative HPLC (45 – 70% B in 10 min) yielding a colorless solid.

Yield: 29% (7 mg, 0.013 mmol)

Appearance: colorless solid

TLC: R_f = 0.13 (cycH/EA = 1:1; UV)

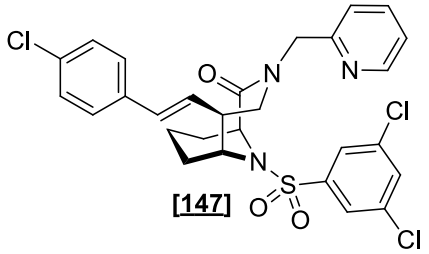
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.20 – 1.33 (m, 1H), 1.35 – 1.48 (m, 1H), 1.55 – 1.71 (m, 3H), 2.31 (d, *J* = 13.7 Hz, 1H), 3.00 (q, *J* = 8.8 Hz, 1H), 3.22 – 3.32 (m, 1H), 4.16 (dt, *J* = 11.4, 8.3 Hz, 2H), 4.74 (dt, *J* = 6.3, 1.8 Hz, 1H), 4.79 (d, *J* = 15.8 Hz, 1H), 5.26 (s, 1H), 6.24 (dd, *J* = 15.8, 9.0 Hz, 1H), 6.47 (d, *J* = 15.8 Hz, 1H), 7.40 – 7.45 (m, 2H), 7.48 (t, *J* = 6.3 Hz, 1H), 7.57 – 7.64 (m, 4H), 7.71 (d, *J* = 1.7 Hz, 2H), 8.01 (t, *J* = 7.8 Hz, 1H), 8.63 – 8.72 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.6, 27.0, 27.7, 48.8, 52.7, 54.5, 55.2, 57.0, 111.5, 118.9, 124.0, 125.0, 127.1, 131.2, 131.9, 132.6, 133.1, 136.7, 140.7, 141.0, 143.9, 146.0, 155.4, 171.1.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{27}Cl_2N_4O_3S$ 581.1175; Found 581.1178

Lab book number(s): JK370

5.2.134. Compound [147]: (1*S*,5*S*,6*R*)-5-((*E*)-4-chlorostyryl)-10-((3,5-dichlorophenyl)sulfonyl)-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



[147]

Compound **[34]** (19.5 mg, 0.041 mmol, 1 eq.), 1-bromo-4-chlorobenzene (13.9 mg, 0.06 mmol, 1.5 eq.), K_2CO_3 (12.4 mg, 0.08 mmol, 2 eq.) and $Pd(PPh_3)_4$ (5.1 mg, 0.0044 mmol, 0.1 eq.) were solved in dry dioxane (8 ml) under argon atmosphere. The reaction mixture was heated to 90 °C and stirred for 18 h. After addition of brine (20 ml), the mixture was extracted with EA (2 x 50 ml), dried over $MgSO_4$ and solvents were removed under reduced pressure. The crude product was purified via preparative HPLC (60 – 80% B in 10 min) yielding a colorless solid.

Yield: 20% (5 mg, 0.0082 mmol)

Appearance: colorless solid

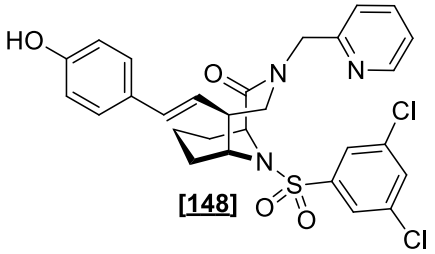
TLC: R_f = 0.26 (cycH/EA = 1:1; UV)

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.28 (m, 1H), 1.36 (m, 1H), 1.49 – 1.77 (m, 3H), 2.33 (dd, *J* = 13.4, 5.3 Hz, 1H), 2.91 (q, *J* = 8.8 Hz, 1H), 3.21 (dd, *J* = 14.2, 2.0 Hz, 1H), 3.66 (dd, *J* = 6.6, 2.9 Hz, 2H), 4.09 (q, *J* = 6.0, 4.2 Hz, 1H), 4.13 – 4.18 (m, 1H), 4.76 (dd, *J* = 4.9, 2.9 Hz, 1H), 4.89 (s, 2H), 6.06 (dd, *J* = 15.7, 9.2 Hz, 1H), 6.30 (d, *J* = 15.8 Hz, 1H), 7.21 – 7.32 (m, 5H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.57 (t, *J* = 1.8 Hz, 1H), 7.72 (d, *J* = 1.9 Hz, 3H), 8.50 – 8.61 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.7, 26.8, 27.8, 48.8, 52.6, 55.4, 57.1, 60.5, 122.7, 122.9, 125.0, 127.7, 129.0, 129.1, 131.2, 132.9, 133.8, 134.9, 136.6, 140.5, 144.2, 148.5, 152.6, 170.6.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{27}Cl_3N_3O_3S$ 590.0833; Found 590.0836

5.2.135. Compound [148]: (1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-5-((*E*)-4-hydroxystyryl)-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



[148]

Compound **[34]** (22.5 mg, 0.047 mmol, 1 eq.), 4-Bromophenol (29.0 mg, 0.06 mmol, 4 eq.), K_2CO_3 (23.2 mg, 0.08 mmol, 2 eq.) and $Pd(PPh_3)_4$ (5.4 mg, 0.0046 mmol, 0.1 eq.) were solved in dry dioxane (8 ml) under argon atmosphere. The reaction mixture was heated to 90 °C and stirred for 18 h. After addition of brine (20 ml), the mixture was extracted with EA (2 x 50 ml), dried over $MgSO_4$ and solvents were removed under reduced pressure. The crude product was purified via preparative HPLC (60 – 80% B in 10 min) yielding a colorless solid.

Yield: 14% (3.4 mg, 0.0066 mmol)

Appearance: colorless solid

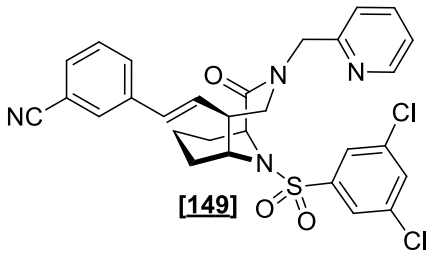
TLC: R_f = 0.19 (cycH/EA = 1:1; UV)

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.19 – 1.37 (m, 2H), 1.50 – 1.69 (m, 3H), 2.33 (d, *J* = 13.7 Hz, 1H), 2.81 (q, *J* = 9.0 Hz, 1H), 3.20 (dd, *J* = 14.3, 2.0 Hz, 1H), 4.03 – 4.18 (m, 2H), 4.77 (dd, *J* = 5.0, 3.0 Hz, 1H), 4.84 (d, *J* = 15.2 Hz, 1H), 4.93 (d, *J* = 15.2 Hz, 1H), 5.87 (dd, *J* = 15.7, 9.1 Hz, 1H), 6.22 (d, *J* = 15.7 Hz, 1H), 6.73 – 6.82 (m, 2H), 7.11 – 7.19 (m, 2H), 7.29 (d, *J* = 5.8 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.57 (td, *J* = 1.8, 0.7 Hz, 1H), 7.71 (dd, *J* = 1.9, 0.7 Hz, 2H), 7.74 – 7.80 (m, 1H), 8.51 – 8.61 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.7, 26.6, 27.7, 48.8, 52.8, 55.7, 55.9, 57.1, 115.7, 122.9, 123.0, 125.0, 126.0, 127.9, 129.0, 131.9, 132.9, 136.6, 144.2, 156.1, 156.9, 170.7.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{28}Cl_2N_3O_4S$ 572.1172; Found 572.1174

5.2.136. Compound [149]: 3-((*E*)-2-((1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)vinyl)benzonitrile



[149]

Compound **[34]** (20.6 mg, 0.043 mmol, 1 eq.), 3-bromobenzonitrile (38.4 ml, 0.21 mmol, 5 eq.), K_2CO_3 (12.5 mg, 0.090 mmol, 2 eq.) and $Pd(PPh_3)_4$ (14.7 mg, 0.0013 mmol, 0.3 eq.) were solved in dry dioxane (8 ml) under argon atmosphere. The reaction mixture was heated to 90 °C and stirred for 18 h. After addition of brine (20 ml), the mixture was extracted with EA (2 x 50 ml), dried over $MgSO_4$ and solvents were removed under reduced pressure. The crude product was purified by column chromatography (8 g SiO_2, cycH/EA = 1:1).

Yield: 65% (16 mg, 0.028 mmol)

Appearance: **c**olorless solid

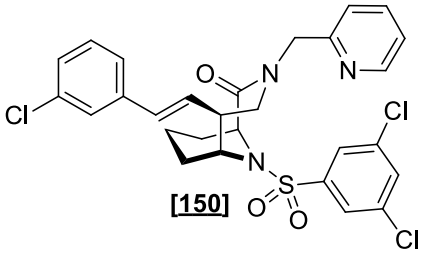
TLC: R_f = 0.12 (cycH/EA = 1:1; UV)

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.20 – 1.32 (m, 2H), 1.42 (d, *J* = 5.6 Hz, 1H), 1.52 – 1.70 (m, 3H), 2.30 – 2.37 (m, 1H), 2.89 – 2.99 (m, 1H), 3.24 (dd, *J* = 14.3, 2.0 Hz, 1H), 4.07 – 4.12 (m, 1H), 4.16 (dd, *J* = 14.3, 10.7 Hz, 1H), 4.77 (dt, *J* = 6.2, 1.9 Hz, 1H), 4.92 (d, *J* = 15.2 Hz, 1H), 6.17 (dd, *J* = 15.8, 9.1 Hz, 1H), 6.33 (d, *J* = 15.7 Hz, 1H), 7.22 – 7.29 (m, 2H), 7.36 – 7.41 (m, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.52 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.54 – 7.60 (m, 3H), 7.69 – 7.77 (m, 3H), 8.55 (dt, *J* = 4.8, 1.3 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.7, 26.9, 27.8, 48.7, 52.4, 55.3, 56.2, 57.1, 113.1, 118.7, 122.6, 122.9, 125.0 (2C), 129.6, 130.2, 130.2, 130.4, 131.3, 131.4, 133.0, 136.6, 137.7, 144.2, 148.9, 156.8, 170.5.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{27}Cl_2N_4O_3S$ 581.1175; Found 581.1180

5.2.137. Compound [150]: (1*S*,5*S*,6*R*)-5-((*E*)-3-chlorostyryl)-10-((3,5-dichlorophenyl)sulfonyl)-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



[150]

Compound **[34]** (20.1 mg, 0.042 mmol, 1 eq.), 1-bromo-3-chlorobenzene (31.9 mg, 0.17 mmol, 4 eq.), K_2CO_3 (23.5 mg, 0.17 mmol, 4 eq.) and $Pd(PPh_3)_4$ (14.9 mg, 0.0013 mmol, 0.3 eq.) were solved in dry dioxane (8 ml) under argon atmosphere. The reaction mixture was heated to 90 °C and stirred for 18 h. After addition of brine (20 ml), the mixture was extracted with EA (2 x 50 ml), dried over $MgSO_4$ and solvents were removed under reduced pressure. The crude product was purified via preparative HPLC (60 – 100% B in 10 min) yielding a colorless solid.

Yield: 24% (6 mg, 0.010 mmol)

Appearance: colorless solid

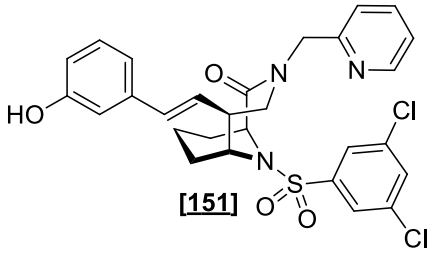
TLC: R_f = 0.19 (cycH/EA = 1:1; UV)

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.26 (m, 1H), 1.35 (m, 1H), 1.53 – 1.71 (m, 3H), 2.28 – 2.37 (m, 1H), 2.91 (m, 1H), 3.21 (dd, *J* = 14.3, 2.0 Hz, 1H), 4.09 (dt, *J* = 6.7, 3.3 Hz, 1H), 4.15 (dd, *J* = 14.2, 10.7 Hz, 1H), 4.78 (dt, *J* = 6.1, 1.9 Hz, 1H), 4.80 – 4.93 (m, 2H), 6.10 (dd, *J* = 15.7, 9.2 Hz, 1H), 6.28 (d, *J* = 15.7 Hz, 1H), 7.17 – 7.21 (m, 1H), 7.21 – 7.23 (m, 1H), 7.26 (s, 2H), 7.31 (d, *J* = 2.0 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 1.8 Hz, 1H), 7.71 – 7.77 (m, 3H), 8.56 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.7, 26.8, 27.8, 48.8, 52.5, 55.4, 56.1, 57.1, 122.6, 122.9, 124.7, 125.0, 126.5, 128.0, 130.0, 130.0, 131.1, 132.9, 134.8, 136.6, 137.7, 138.2, 144.2, 148.8, 156.8, 170.6.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{27}Cl_3N_3O_3S$ 590.0833; Found 590.0836

5.2.138. Compound [151]: (1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-5-((*E*)-3-hydroxystyryl)-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



[151]

Compound **[34]** (32.0 mg, 0.067 mmol, 1 eq.), 3-bromophenol (14.1 mg, 0.13 mmol, 2 eq.), K_3PO_4 (28.6 mg, 0.13 mmol, 2 eq.) and $Pd(OAc)_2$ (1.6 mg, 0.071 mmol, 0.1 eq.) were solved in dry DMF (8 ml) under argon atmosphere. The reaction mixture was heated to 100 °C and stirred for 18 h. After addition of brine (20 ml), the mixture was extracted with EA (2 x 50 ml), dried over $MgSO_4$ and solvents were removed under reduced pressure. The crude product was purified via preparative HPLC (60 – 80% B in 10 min) yielding a colorless solid.

Yield: 21% (8 mg, 0.014 mmol)

Appearance: colorless solid

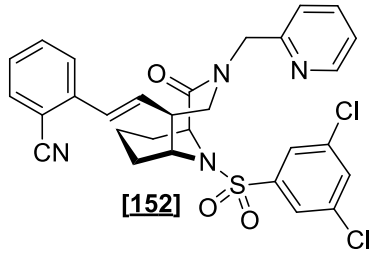
TLC: R_f = 0.19 (cycH/EA = 1:1; UV)

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.20 – 1.37 (m, 1H), 1.50 – 1.68 (m, 3H), 2.33 (d, *J* = 13.7 Hz, 1H), 2.86 (q, *J* = 9.9 Hz, 1H), 3.19 (dd, *J* = 14.3, 2.0 Hz, 1H), 4.06 (t, *J* = 5.7 Hz, 2H), 4.11 (dd, *J* = 14.3, 10.7 Hz, 1H), 4.78 (dt, *J* = 6.3, 1.9 Hz, 1H), 4.85 (q, *J* = 15.2 Hz, 2H), 6.02 (dd, *J* = 15.7, 9.1 Hz, 1H), 6.24 (d, *J* = 15.7 Hz, 1H), 6.68 – 6.73 (m, 1H), 6.78 (t, *J* = 2.1 Hz, 1H), 6.82 – 6.88 (m, 1H), 7.14 (t, *J* = 7.8 Hz, 1H), 7.22 – 7.25 (m, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 1.9 Hz, 1H), 7.72 (dd, *J* = 7.9, 1.9 Hz, 3H), 8.53 – 8.57 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.7, 26.7, 27.8, 48.8, 52.6, 55.5, 56.2, 57.1, 113.3, 115.2, 119.0, 122.6, 122.9, 125.0 (2C), 128.7, 129.9, 132.1, 132.9, 136.6, 137.6, 138.1, 144.2, 149.0, 156.3, 157.0, 170.7.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{28}Cl_2N_3O_4S$ 572.1172; Found 572.1166

5.2.139. Compound [152]: 2-((*E*)-2-((1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)vinyl)benzonitrile



[152]

Compound **[34]** (30.3 mg, 0.063 mmol, 1 eq.), 2-bromobenzonitrile (23.2 mg, 0.12 mmol, 2 eq.), K_3PO_4 (26.5 mg, 0.12 mmol, 2 eq.) and $Pd(OAc)_2$ (3.0 mg, 0.013 mmol, 0.2 eq.) were solved in dry DMF (8 ml) under argon atmosphere. The reaction mixture was heated to 100 °C and stirred for 18 h. After addition of brine (20 ml), the mixture was extracted with EA (2 x 50 ml), dried over $MgSO_4$ and solvents were removed under reduced pressure. The crude product was purified via preparative HPLC (60 – 80% B in 10 min) yielding a colorless solid.

Yield: 44% (16 mg, 0.03 mmol)

Appearance: colorless solid

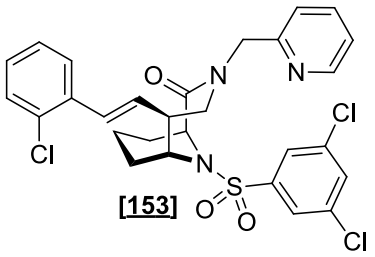
TLC: R_f = 0.25 (cycH/EA = 1:1; UV)

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.17 – 1.28 (m, 1H), 1.34 (m, 1H), 1.58 (m, 3H), 2.29 – 2.41 (m, 1H), 2.89 – 3.01 (m, 1H), 3.29 (dd, *J* = 14.2, 2.0 Hz, 1H), 4.04 – 4.13 (m, 1H), 4.20 (dd, *J* = 14.2, 10.7 Hz, 1H), 4.60 (d, *J* = 15.0 Hz, 1H), 4.78 (dt, *J* = 6.2, 1.9 Hz, 1H), 5.07 (d, *J* = 15.1 Hz, 1H), 6.27 (dd, *J* = 15.6, 9.6 Hz, 1H), 6.67 (d, *J* = 15.6 Hz, 1H), 7.22 – 7.28 (m, 1H), 7.31 – 7.40 (m, 2H), 7.51 – 7.56 (m, 1H), 7.57 (t, *J* = 1.9 Hz, 1H), 7.62 (td, *J* = 8.1, 1.2 Hz, 2H), 7.68 – 7.75 (m, 3H), 8.56 – 8.64 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.7, 26.7, 27.9, 49.2, 52.1, 55.2, 56.2, 57.2, 111.4, 117.8, 122.6, 123.0, 125.0, 125.7, 128.1, 128.2, 132.9, 133.1, 133.7, 136.6, 137.3, 139.6, 144.2, 149.4, 156.9, 170.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{27}Cl_2N_4O_3S$ 581.1175; Found 581.1176

5.2.140. Compound [153]: (1*S*,5*S*,6*R*)-5-((*E*)-2-chlorostyryl)-10-((3,5-dichlorophenyl)sulfonyl)-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



[153]

Compound **[34]** (30.2 mg, 0.063 mmol, 1 eq.), 1-bromo-2-chlorobenzene (14.6 µl, 0.12 mmol, 2 eq.), K_3PO_4 (27.5 mg, 0.12 mmol, 2 eq.) and $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 0.2 eq.) were solved in dry DMF (8 ml) under argon atmosphere. The reaction mixture was heated to 100 °C and stirred for 18 h. After addition of brine (20 ml), the mixture was extracted with EA (2 x 50 ml), dried over $MgSO_4$ and solvents were removed under reduced pressure. The crude product was purified via preparative HPLC (60 – 80% B in 10 min) yielding a colorless solid.

Yield: 10% (3.6 mg, 0.01 mmol)

Appearance: colorless solid

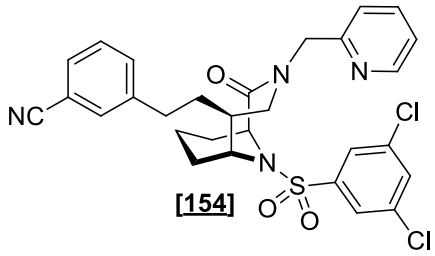
TLC: R_f = 0.40 (cycH/EA = 1:1; UV)

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.22 – 1.31 (m, 1H), 1.31 – 1.39 (m, 1H), 1.53 – 1.71 (m, 3H), 2.34 (d, *J* = 13.7 Hz, 1H), 2.94 (q, *J* = 9.2 Hz, 1H), 3.25 (dd, *J* = 14.0, 1.9 Hz, 1H), 4.09 (t, *J* = 6.0 Hz, 1H), 4.17 (dd, *J* = 14.2, 10.7 Hz, 1H), 4.74 – 4.84 (m, 2H), 4.97 (d, *J* = 15.3 Hz, 1H), 6.06 (dd, *J* = 15.6, 9.3 Hz, 1H), 6.72 (d, *J* = 15.7 Hz, 1H), 7.20 (m, 2H), 7.26 (s, 2H), 7.34 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.49 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.57 (t, *J* = 1.9 Hz, 1H), 7.72 (s, 1H), 7.76 (t, *J* = 7.9 Hz, 1H), 8.55 – 8.60 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.7, 26.6, 27.8, 49.1, 52.5, 55.4, 56.0, 57.1, 77.4, 122.7, 122.9, 125.1, 127.0, 127.1, 128.7, 129.1, 129.9, 131.2, 132.9, 133.2, 134.4, 136.6, 137.8, 137.9, 144.2, 147.5, 156.7, 170.6.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{27}Cl_3N_3O_3S$ 590.0833; Found 590.0833

5.2.141. Compound [154]: 3-(2-((1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)ethyl)benzonitrile



[154]

Compound **[149]** (13 mg, 0.022 mmol, 1 eq.) was dissolved in MeOH (10 ml) and Pt/C (1 mg, 0.0051 mmol, 0.2 eq., 10% loading) was added. H_2 was bubbled through for 2 min and the reaction mixture was stirred for 19 h under hydrogen atmosphere. The solution was filtered through a layer of silica and purified by preparative HPLC (60 – 80% B in 10 min) yielding a colorless solid.

Yield: 30% (3 mg, 0.0066 mmol)

Appearance: colorless solid

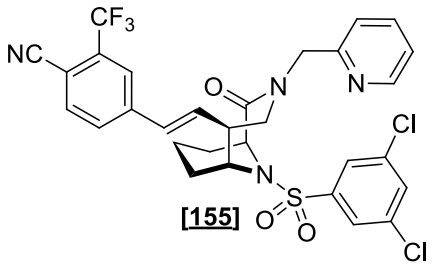
TLC: R_f = 0.07 (cycH/EA = 1:1; UV)

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.16 – 1.28 (m, 1H), 1.31 – 1.44 (m, 1H), 1.49 (m, 2H), 1.53 – 1.74 (m, 2H), 2.25 – 2.33 (m, 1H), 2.43 (m, 1H), 2.69 (m, 1H), 3.30 (dd, *J* = 14.3, 1.8 Hz, 1H), 3.86 (m, 1H), 3.93 (dd, *J* = 14.3, 10.6 Hz, 1H), 4.70 (d, *J* = 15.0 Hz, 1H), 4.74 (dt, *J* = 6.0, 1.9 Hz, 1H), 5.03 (d, *J* = 15.0 Hz, 1H), 7.28 – 7.33 (m, 1H), 7.33 – 7.36 (m, 2H), 7.36 – 7.40 (m, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.49 (dt, *J* = 7.5, 1.6 Hz, 1H), 7.57 (t, *J* = 1.8 Hz, 1H), 7.69 (d, *J* = 1.9 Hz, 2H), 7.79 (td, *J* = 7.7, 1.7 Hz, 1H), 8.57 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.7, 27.4, 27.7, 32.9, 34.8, 43.9, 51.2, 55.7, 55.8, 57.0, 112.8, 118.9, 123.2, 125.1, 129.5, 130.2, 131.8, 132.9, 132.9, 136.6, 138.2, 142.7, 144.2, 148.4, 156.9, 170.6.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{29}Cl_2N_4O_3S$ 583.1332; Found 583.1332

5.2.142. Compound [155]: 4-((*E*)-2-((1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)vinyl)-2-(trifluoromethyl) benzonitrile



[155]

Compound **[34]** (50 mg, 0.10 mmol, 1 eq.), K_3PO_4 (44 mg, 0.21 mmol, 2.0 eq.), $Pd(PPh_3)_4$ (36 mg, 0.03 mmol, 0.3 eq.), $Pd(OAc)_2$ (5 mg, 0.02 mmol, 0.2 eq.) and 4-bromo-2-(trifluoromethyl)benzonitrile (39 mg, 0.16 mmol, 1.5 eq.) were placed in a 25 ml flask under argon. 1,4-Dioxane (10 ml) was added and the mixture was heated to 80 °C and stirred for 16 h. The mixture was filtered over diatomaceous earth with EA, solvents were removed under reduced pressure and the crude was purified by column chromatography (10 g SiO_2, DCM/MeOH = 50:1).

Yield: 40% (27 mg, 0.040 mmol)

Appearance: colorless solids

TLC: R_f = 0.18 (DCM/MeOH = 50:1)

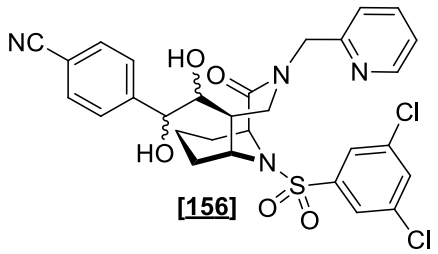
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.18 (m, 1H), 1.25 – 1.38 (m, 1H), 1.44 – 1.64 (m, 3H), 2.20 – 2.34 (m, 1H), 2.96 (m, 1H), 3.20 (dd, *J* = 14.2, 1.9 Hz, 1H), 4.05 (t, *J* = 5.5 Hz, 1H), 4.13 (dd, *J* = 14.2, 10.7 Hz, 1H), 4.70 (dd, *J* = 10.6, 4.6 Hz, 2H), 4.87 (d, *J* = 15.2 Hz, 1H), 6.27 (dd, *J* = 15.8, 8.8 Hz, 1H), 6.36 (d, *J* = 15.9 Hz, 1H), 7.15 – 7.22 (m, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.48 – 7.57 (m, 2H), 7.60 – 7.76 (m, 5H), 8.47 (dt, *J* = 4.9, 1.3 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.5, 26.9, 27.7, 48.6, 52.0, 54.9, 56.1, 57.0, 108.6, 115.4, 121.2, 122.6, 122.8, 123.3, 124.4, 124.4, 124.8, 129.4, 132.9, 133.2, 133.4, 134.5, 135.0, 136.5, 137.5, 141.2, 143.9, 148.7, 156.6, 170.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{25}Cl_2F_3N_4O_3S$ 649.1049; Found 649.1050

Lab book number(s): JK389

5.2.143. Compound [156]: 4-(2-((1*S*,5*S*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-2-oxo-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-5-yl)-1,2-dihydroxyethyl)benzonitrile



[156]

Compound **[146]** (22 mg, 0.038 mmol, 1 eq.) was dissolved in aceton (9 ml) and water (1 ml), 2,6-lutidine (8 μl, 0.08 mmol, 2 eq.), NMO (9 mg, 0.08 mmol, 2 eq.) and OsO_4 (10 µL, 0.0008 mmol, 0.02 eq., 2.5% in t-BuOH) were added successively. After 16 h the reaction was quenched with sat. aq. $Na_2S_2O_3$ solution, extracted with EA, washed with sat. aq. $CuSO_4$ solution, dried over $MgSO_4$ and filtered over silica. Solvents were removed under reduced pressure and column chromatography (30 g SiO_2, EA + 1% MeOH) afforded the title compound as colorless resin.

Yield: 65% (15 mg, 0.024 mmol)

Appearance: colorless resin

TLC: R_f = 0.32 (EA + 1% MeOH; UV)

HPLC: R_t = 12.24 & 12.43 min (0 – 100% B in 20 min)

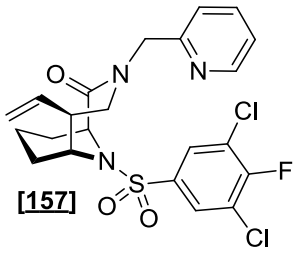
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.02 – 1.53 (m, 3H), 1.68 (d, *J* = 13.5 Hz, 2H), 2.02 (d, *J* = 8.5 Hz, 0.5H), 2.22 (dd, *J* = 8.0, 5.3 Hz, 2H), 2.63 (td, *J* = 9.5, 6.5 Hz, 0.5H), 3.62 (t, *J* = 3.2 Hz, 0.5H), 3.70 – 3.86 (m, 1H), 3.92 – 4.12 (m, 1H), 4.23 (d, *J* = 14.6 Hz, 1H), 4.29 – 4.50 (m, 1.5H), 4.69 – 4.89 (m, 2H), 5.00 (d, *J* = 14.5 Hz, 0.5H), 5.08 – 5.19 (m, 0.5H), 5.26 (d, *J* = 14.6 Hz, 0.5H), 5.45 (s, 0.5H), 7.29 – 7.34 (m, 1H), 7.47 (t, *J* = 8.3 Hz, 2H), 7.56 – 7.68 (m, 3H), 7.69 – 7.83 (m, 4H), 8.33 – 8.64 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.2, 15.4, 27.0, 27.6, 28.3, 29.3, 46.9, 47.2, 48.7, 50.4, 53.6, 53.9, 56.5, 56.7, 57.2, 72.3, 74.8, 111.5, 111.7, 118.6, 118.7, 123.1, 123.2, 124.2, 124.3, 124.9, 125.0, 127.0, 127.1, 132.3, 132.3, 132.8, 132.8, 136.4, 137.8, 137.8, 143.7, 144.0, 146.0, 146.5, 148.7, 149.1, 156.8, 157.0, 169.8, 170.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{28}Cl_2N_4O_5S$ 615.1230; Found 615.1230

Lab book number(s): JK375

5.2.144. Compound [157]: (1*S*,5*S*,6*R*)-10-[(3,5-dichloro-4-fluorophenyl)sulfonyl]3-(pyridine-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[157]

Compound **[33]** (20 mg, 0.074 mmol, 1 eq.) was dissolved in DCM (2 ml). DIPEA (32 yl, 0.11 mmol, 1.5 eq.) and 3,5-dichloro-4-fluorobenzenesulfonyl chloride (30 mg, 0.11 mmol, 1.5 eq.) were added and the mixture was stirred for 36 h at rt. The reaction mixture was washed with sat. aq. $NaHCO_3$ (3 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (4 g SiO_2, cycH/EA = 1:1) afforded the title compound as colorless resin.

Yield: 47% (17 mg, 0.035 mmol)

Appearance: colorless resin

TLC: R_f = 0.19 (cycH/EA = 1:1; UV, PMA)

HPLC: R_t = 13.53 min (0 – 100% B in 20 min)

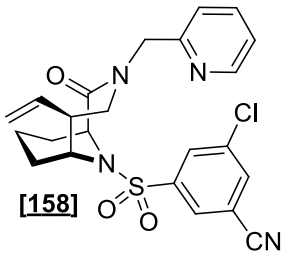
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.80 – 0.90 (m, 2H), 1.20 – 1.30 (m, 4H), 1.50 – 1.62 (m, 3H), 2.25 - 2.37 (m, 1H), 2.71 (q, *J* = 7.4 Hz, 1H), 3.14 (d, *J* = 13.4 Hz, 1H), 3.95 – 4.06 (m, 2H), 4.70 – 5.09 (m, 4H), 5.63 – 5.78 (m, 1H), 7.16 – 7.23 (m, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.63 – 7.72 (dt, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 5.9 Hz, 2H), 8.53 (d, *J* = 5.5 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.5, 26.5, 27.6, 49.0, 52.0, 55.0, 56.2, 56.9, 116.9, 122.3 (d, *J* = 31.9 Hz, 2C), 123.8 (d, *J* = 18.7 Hz, 1C), 127.4, 137.0, 137.1, 138.4, 149.1, 156.6 (d, *J* = 258.2 Hz, 1C), 156.8, 170.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{22}Cl_2FN_3O_3S$ 498.0816; Found 498.0818

Lab book number(s): JK056

5.2.145. Compound [158]: 3-chloro-5-((((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)benzonitrile



[158]

Compound **[33]** (20 mg, 0.074 mmol, 1 eq.), 3-chloro-5-cyanobenzene-1-sulfonyl chloride (23 mg, 0.11 mmol, 1.5 eq.) and ZnO (12 mg, 0.15 mmol, 2 eq.) were placed in a flask under argon atmosphere. MeCN (5 ml) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with DCM (20 ml) and washed with brine (3 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (5 g SiO_2, cycH/EA = 1:1) afforded the title compound as colorless resin.

Yield: 49% (17 mg, 0.036 mmol)

Appearance: colorless resin

TLC: R_f = 0.21 (cycH/EA = 1:1; UV, PMA)

HPLC: R_t = 11.84 min (0 – 100% B in 20 min)

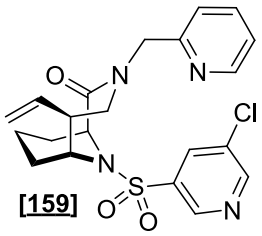
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.19 – 1.31 (m, 3H), 1.50 – 1.64 (m, 2H), 2.26 – 2.42 (m, 1H), 2.74 (m, 1H), 3.15 (dd, *J* = 14.3, 2.0 Hz, 1H), 4.00 (dd, *J* = 9.4, 4.9 Hz, 2H), 4.68 – 5.14 (m, 5H), 5.71 (m, 1H), 7.22 (m, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.71 (td, *J* = 7.7, 1.8 Hz, 1H), 7.83 (t, *J* = 1.7 Hz, 1H), 8.00 (dt, *J* = 11.9, 1.7 Hz, 2H), 8.53 (dt, *J* = 5.1, 1.2 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.4, 26.6, 27.7, 49.0, 52.1, 55.1, 56.1, 57.0, 115.4, 115.8, 117.1, 122.2, 122.6, 128.0, 130.7, 135.5, 136.9, 136.9, 137.3, 144.5, 148.8, 156.7, 170.1.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{24}ClN_4O_3S$ 471.1252; Found 471.1252

Lab book number(s): JK082

5.2.146. Compound [159]: (1*S*,5*S*,6*R*)-10-((5-chloropyridin-3-yl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[159]

Compound **[33]** (30 mg, 0.11 mmol, 1 eq.), **[10]** (35 mg, 0.17 mmol, 1.5 eq.) and DIPEA (39 μl mg, 0.22 mmol, 2 eq.) were placed in a flask under argon atmosphere. MeCN (5 ml) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with EA (20 ml) and washed with brine (10 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (5 g SiO_2, cycH/EA = 1:1) afforded the title compound as colorless resin.

Yield: 14% (7 mg, 0.016 mmol)

Appearance: colorless resin

TLC: R_f = 0.33 (EA; UV)

HPLC: R_t = 10.76 min (0 – 100% B in 20 min)

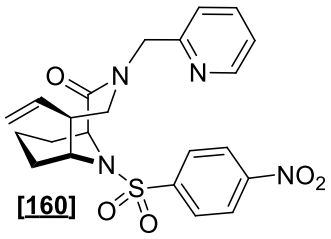
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.02 – 1.30 (m, 2H), 1.40 – 1.64 (m, 3H), 2.17 – 2.33 (m, 1H), 2.67 (m, 1H), 3.08 (dd, *J* = 14.3, 2.0 Hz, 1H), 3.84 – 4.04 (m, 2H), 4.63 – 4.84 (m, 3H), 4.84 – 5.07 (m, 2H), 5.65 (m, 1H), 7.11 – 7.17 (m, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.65 (td, *J* = 7.6, 1.8 Hz, 1H), 8.03 (t, *J* = 2.1 Hz, 1H), 8.47 (dt, *J* = 4.9, 1.4 Hz, 1H), 8.70 (d, *J* = 2.3 Hz, 1H), 8.84 (d, *J* = 2.0 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.5, 26.6, 27.7, 49.0, 52.2, 55.0, 56.1, 56.9, 117.0, 122.3, 122.6, 132.7, 133.7, 137.0, 137.3, 138.7, 145.0, 148.8, 152.3, 156.7, 170.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{24}ClN_4O_3S$; Found

Lab book number(s): JK255

5.2.147. Compound [160]: (1*S*,5*S*,6*R*)-10-((4-nitrophenyl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[160]

Compound **[33]** (60 mg, 0.21 mmol, 1 eq.) was dissolved in MeCN (10 ml). 4-Nitrobenzene sulfonyl chloride (70 mg, 0.32 mmol, 1.5 eq.) in MeCN (10 ml) and DIPEA (107 µl, 0.063 mmol, 3 eq.) were added successively and the mixture was stirred for 24 h at rt. The mixture was diluted with DCM (50 ml) and washed with brine (2 x 20 ml). The organic phase was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Column chromatography (10 g silica; cycH/EA = 2:3) afforded the title compound as white solids.

Yield: 49% (47 mg, 0.10 mmol)

Appearance: colorless resin

TLC: R_f = 0.24 (cycH/EA = 2:3; UV)

HPLC: R_t = 11.59 min (0 – 100% B in 20 min)

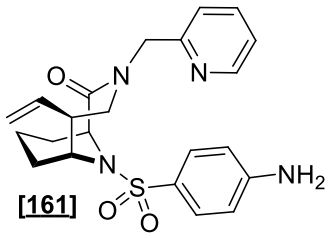
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.12 – 1.31 (m, 2H), 1.51 (m, 1H), 1.55 – 1.76 (m, 2H), 2.25 – 2.34 (m, 1H), 2.73 (m, 1H), 3.13 (dd, *J* = 14.3, 2.0 Hz, 1H), 4.02 (dt, *J* = 14.2, 8.2 Hz, 2H), 4.69 – 4.91 (m, 4H), 4.92 – 5.09 (m, 2H), 5.72 (m, 1H), 7.20 (m, 1H), 7.32 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.68 (td, *J* = 7.6, 1.8 Hz, 1H), 7.97 – 8.06 (m, 2H), 8.32 – 8.40 (m, 2H), 8.52 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.5, 26.4, 27.6, 49.0, 52.1, 55.0, 56.2, 57.0, 116.9, 122.1, 122.5, 124.7, 127.8, 136.9, 137.1, 147.0, 149.2, 150.1, 156.9, 170.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{24}N_4O_5S$ 457.1540; Found 457.1541

Lab book number(s): JK195

5.2.148. Compound [161]: (1*S*,5*S*,6*R*)-10-((4-aminophenyl)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[161]

Compound **[160]** (32 mg, 0.070 mmol, 1 eq.) was dissolved in EtOH (50 ml). Sat. aq. NH_4Cl (100 μl, 0.70 mmol, 10 eq.) and Zn (46 mg, 0.70 mmol, 10 eq.) were added and the mixture was stirred at rt for 4 h. The mixture was filtered over silica and solvents were removed. The residue was dissolved in EA (100 ml) and washed with brine (50 ml). Solvents were removed under reduced pressure and the crude product was purified by column chromatography (3 g silica; EA).

Yield: 98% (29 mg, 0.069)

Appearance: colorless resin

TLC: R_f = 0.39 (EA; UV)

HPLC: R_t = 8.54 min (0 – 100% B in 20 min)

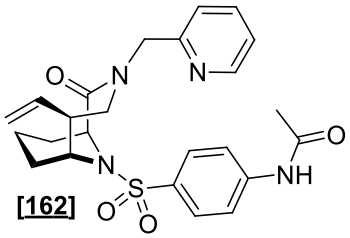
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.23 – 1.39 (m, 2H), 1.39 – 1.51 (m, 2H), 1.51 – 1.66 (m, 1H), 2.16 – 2.27 (m, 1H), 2.63 (m, 1H), 3.02 (dd, *J* = 14.0, 1.9 Hz, 1H), 3.97 (m, 1H), 4.06 (dd, *J* = 14.0, 10.7 Hz, 1H), 4.16 (d, *J* = 23.0 Hz, 2H), 4.75 (dt, *J* = 6.1, 1.8 Hz, 1H), 4.79 (s, 2H), 4.87 – 5.03 (m, 2H), 5.69 (m, 1H), 6.61 – 6.70 (m, 2H), 7.17 (m, 1H), 7.31 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.51 – 7.61 (m, 2H), 7.66 (td, *J* = 7.7, 1.8 Hz, 1H), 8.51 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.8, 26.1, 27.2, 49.1, 52.1, 54.1, 56.2, 56.6, 114.2, 116.3, 122.0, 122.3, 128.7, 129.5, 136.9, 137.8, 149.1, 150.5, 157.2, 171.4.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{26}N_4O_3S$ 427.1798; Found 427.1798

Lab book number(s): JK199

5.2.149. Compound [162]: *N*-(4-(((1*S*,5*S*,6*R*)-2-oxo-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-10-yl)sulfonyl)phenyl)acetamide



[162]

Compound **[161]** (16 mg, 0.038 mmol, 1 eq.) was dissolved in DCM (4 ml). The mixture was cooled to 0 °C with an ice bath and Ac_2O (200 μl, 2 mmol, 50 eq.) was added. The reaction was quenched with water after 4 h and the mixture was extracted with DCM (2 x 50 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (5 g SiO_2, EA) afforded the title compound as colorless resin.

Yield: 98% (17 mg, 0.037 mmol)

Appearance: colorless resin

TLC: R_f = 0.13 (EA; UV)

HPLC: R_t = 9.49 min (0 – 100% B in 20 min)

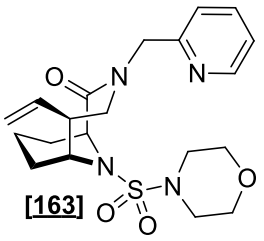
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.10 – 1.39 (m, 2H), 1.47 (dt, *J* = 15.8, 3.8 Hz, 2H), 1.59 (m, 1H), 2.17 (s, 4H), 2.69 (m, 1H), 3.07 (dd, *J* = 14.1, 1.9 Hz, 1H), 3.96 – 4.04 (m, 1H), 4.09 (dd, *J* = 14.1, 10.7 Hz, 1H), 4.66 – 4.76 (m, 1H), 4.76 – 4.89 (m, 2H), 4.92 – 5.07 (m, 2H), 5.71 (m, 1H), 7.18 (m, 1H), 7.30 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.62 – 7.71 (m, 3H), 7.71 – 7.78 (m, 2H), 8.11 (s, 1H), 8.51 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 15.6, 24.6, 26.1, 27.3, 49.1, 52.3, 54.4, 56.3, 56.7, 116.6, 119.4, 121.9, 122.5, 127.8, 135.6, 136.9, 137.4, 142.3, 149.2, 156.9, 168.9, 171.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{29}N_4O_4S$ 469.1904; Found 469.1905

Lab book number(s): JK201

5.2.150. Compound [163]: (1*S*,5*S*,6*R*)-10-(morpholinosulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[163]

Compound **[33]** (30 mg, 0.11 mmol, 1 eq.), morpholine-4-sulfonyl chloride (24.6 mg, 0.13 mmol, 1.2 eq.) and ZnO (22 mg, 0.17 mmol, 1.5 eq.) were placed in a flask under argon atmosphere. MeCN (5 ml) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with DCM (20 ml) and washed with brine (5 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (5 g SiO_2, EA) afforded the title compound as colorless resin.

Yield: 14% (7 mg, 0.015)

Appearance: colorless resin

TLC: R_f = 0.18 (EA; UV)

HPLC: R_t = 7.50 min (0 – 100% B in 20 min)

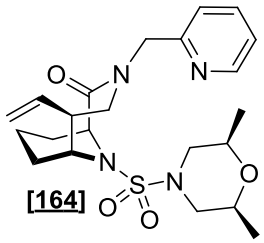
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.68 (d, *J* = 7.2 Hz, 5H), 2.45 (m, 1H), 2.71 (m, 1H), 3.07 (dd, *J* = 14.4, 2.1 Hz, 1H), 3.18 (td, *J* = 4.3, 2.6 Hz, 4H), 3.74 (td, *J* = 4.5, 1.3 Hz, 4H), 3.85 (m, 1H), 4.05 – 4.15 (m, 1H), 4.59 (dt, *J* = 3.8, 2.0 Hz, 1H), 4.75 (d, *J* = 15.4 Hz, 1H), 4.88 – 5.04 (m, 3H), 5.69 (m, 1H), 7.20 (dd, *J* = 7.4, 4.9 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.70 (td, *J* = 7.7, 1.8 Hz, 1H), 8.52 (dd, *J* = 5.1, 1.7 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 15.7, 27.4, 28.6, 46.4, 49.4, 51.9, 55.6, 56.1, 57.6, 66.2, 116.5, 122.1, 122.5, 137.3, 137.7, 148.8, 156.9, 171.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{29}N_4O_4S$ 421.1904; Found 421.1904

Lab book number(s): JK115

5.2.151. Compound [164]: (1*S*,5*S*,6*R*)-10-(((2*S*,6*R*)-2,6-dimethylmorpholino)sulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[164]

Compound **[33]** (30 mg, 0.11 mmol, 1 eq.), (2*R*, 6*S*)-2,6-dimethylmorpholine-4-sulfonyl chloride (28.3 mg, 0.13 mmol, 1.2 eq.) and ZnO (22 mg, 0.17 mmol, 1.5 eq.) were placed in a flask under argon atmosphere. MeCN (5 ml) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with DCM (20 ml) and washed with brine (3 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (5 g SiO_2, EA) afforded the title compound as colorless resin.

Yield: 17% (8 mg, 0.019 mmol)

Appearance: colorless resin

TLC: R_f = 0.30 (EA; UV)

HPLC: R_t = 9.08 min (0 – 100% B in 20 min)

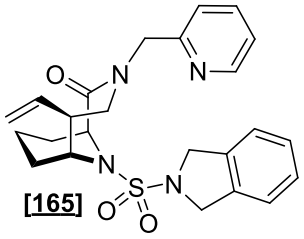
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 6.3 Hz, 6H), 1.58 – 1.81 (m, 5H), 2.44 (m, 3H), 2.62 – 2.78 (m, 1H), 3.07 (dd, *J* = 14.4, 2.1 Hz, 1H), 3.42 (m, 2H), 3.57 – 3.74 (m, 1H), 3.85 (m, 1H), 4.00 – 4.18 (m, 2H), 4.57 (dd, *J* = 3.7, 2.0 Hz, 1H), 4.75 (d, *J* = 15.4 Hz, 1H), 4.86 – 5.09 (m, 3H), 5.70 (m, 1H), 7.20 (m, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.70 (td, *J* = 7.7, 1.8 Hz, 1H), 8.53 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 15.7, 18.7, 27.5, 28.6, 49.4, 51.2, 51.4, 51.8, 55.6, 56.1, 57.6, 116.5, 122.1, 122.5, 137.3, 137.7, 148.7, 156.9, 171.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{33}N_4O_4S$ 449.2217; Found 449.2220

Lab book number(s): JK116

5.2.152. Compound [165]: (1*S*,5*S*,6*R*)-10-(isoindolin-2-ylsulfonyl)-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[165]

Compound **[33]** (30 mg, 0.11 mmol, 1 eq.), 2,3-dihydro-1H-isoindole-2-sulfonyl chloride (28.9 mg, 0.13 mmol, 1.2 eq.) and ZnO (22 mg, 0.17 mmol, 1.5 eq.) were placed in a flask under argon atmosphere. MeCN (5 ml) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with DCM (20 ml) and washed with brine (3 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (5 g SiO_2, cycH/EA = 1:1) afforded the title compound as colorless resin.

Yield: 24% (12 mg, 0.026 mmol)

Appearance: colorless resin

TLC: R_f = 0.30 (EA; UV)

HPLC: R_t = 14.08 min (0 – 100% B in 20 min)

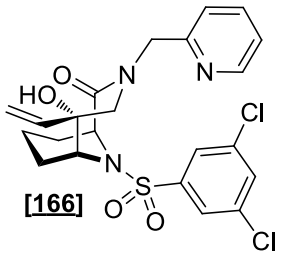
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.56 – 1.76 (m, 5H), 2.40 (dt, *J* = 9.7, 2.5 Hz, 1H), 2.64 – 2.77 (m, 1H), 3.09 (dd, *J* = 14.3, 2.0 Hz, 1H), 3.99 (m, 1H), 4.07 – 4.18 (m, 1H), 4.67 (s, 4H), 4.70 (quint., *J* = 1.9 Hz, 1H), 4.75 (d, *J* = 15.3 Hz, 1H), 4.88 – 5.06 (m, 3H), 5.71 (m, 1H), 7.20 (m, 1H), 7.23 (dd, *J* = 5.5, 3.3 Hz, 2H), 7.30 (dd, *J* = 5.7, 3.2 Hz, 2H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.69 (td, *J* = 7.7, 1.8 Hz, 1H), 8.52 (dt, *J* = 5.0, 1.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 15.8, 27.3, 28.4, 49.2, 51.9, 54.3, 55.3, 56.1, 57.4, 116.4, 122.1, 122.4, 122.6, 127.8, 136.2, 137.2, 137.8, 148.8, 157.0, 171.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{29}N_4O_3S$ 453.1955; Found 453.1958

Lab book number(s): JK114

5.2.153. Compound [166]: (1*S*,5*R*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-5-hydroxy-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[166]

Compound **[34]** (130 mg, 0.27 mmol, 1 eq.) was dissolved in dioxane (5 ml). SeO_2 (60 mg, 0.54 mmol, 2.0 eq.) was added and the mixture was stirred for 16 h at 100 °C. The reaction mixture was diluted with EA and washed with sat. aq. $NaHCO_3$ (50 ml). The organic phase was filtered over Celite and solvents were removed in vacuo. Column chromatography (10 g SiO_2, cycH/EA = 1:1) afforded the title compound as colorless resin.

Yield: 60% (80 mg, 0.16 mmol)

Appearance: colorless resin

TLC: R_f = 0.19 (cycH/EA = 1:1; UV, PMA)

HPLC: R_t = 11.76 min (0 – 100% B in 20 min)

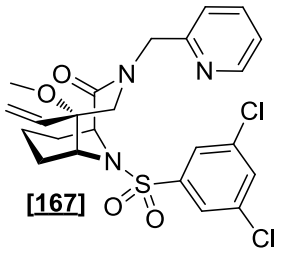
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.51 – 1.61 (m, 1H), 1.69 (m, 2H), 1.88 (m, 2H), 2.00 (m, 1H), 3.30 (dd, *J* = 15.4, 1.3 Hz, 1H), 3.84 (d, *J* = 16.5 Hz, 1H), 4.06 (d, *J* = 15.4 Hz, 1H), 4.20 (m, 1H), 4.96 (m, 1H), 5.18 (dd, *J* = 10.8, 1.4 Hz, 1H), 5.36 (d, *J* = 16.5 Hz, 1H), 5.48 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.84 (dd, *J* = 17.1, 10.8 Hz, 1H), 7.08 – 7.14 (m, 3H), 7.60 (td, *J* = 7.7, 1.8 Hz, 1H), 7.64 (d, *J* = 1.9 Hz, 2H), 8.15 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 17.6, 24.4, 25.2, 53.2, 55.9, 57.5, 58.2, 74.6, 116.2, 122.3, 122.4, 126.1, 131.8, 134.8, 137.4, 139.6, 143.9, 148.2, 156.1, 173.6.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{24}Cl_2N_3O_4S$ 496.0859; Found 496.0870

Lab book number(s): JK210, JK223

5.2.154. Compound [167]: (1*S*,5*R*,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-5-methoxy-3-(pyridin-2-ylmethyl)-5-vinyl-3,10-diazabicyclo[4.3.1]decan-2-one



[167]

Compound **[166]** (12 mg, 0.025 mmol, 1 eq.) was dissolved in DMF (2 ml) and cooled to 0 °C with an ice bath. NaH (2 mg, 0.050 mmol, 2 eq.) was wadded and the mixture stirred for 5 min. MeI (6 μl, 0.100 mmol, 4 eq.) was added and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with EA (80 ml) and washed with brine (20 ml). The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Column chromatography (10 g SiO_2, cycH/EA = 1:1) afforded the title compound as colorless solids.

Yield: 73% (9 mg, 0.018 mmol)

Appearance: colorless solids

TLC: R_f = 0.41 (EA = 1:1; UV, PMA)

HPLC: R_t = 12.87 min (0 – 100% B in 20 min)

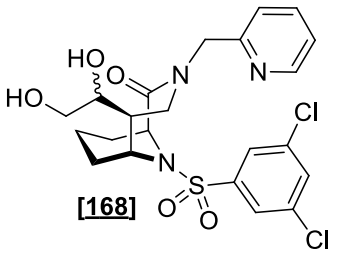
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.47 – 1.66 (m, 3H), 1.73 – 1.85 (m, 1H), 1.92 (m, 2H), 2.69 (s, 3H), 3.58 (d, *J* = 15.8 Hz, 1H), 3.75 (d, *J* = 15.9 Hz, 1H), 4.28 (m, 1H), 4.56 (d, *J* = 15.0 Hz, 1H), 4.69 (d, *J* = 15.0 Hz, 1H), 4.83 – 4.93 (m, 1H), 5.25 (d, *J* = 17.7 Hz, 1H), 5.38 (d, *J* = 11.1 Hz, 1H), 5.50 (dd, *J* = 17.7, 11.2 Hz, 1H), 7.20 – 7.30 (m, 2H), 7.44 (t, *J* = 1.9 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 1.9 Hz, 2H), 8.38 – 8.46 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 17.5, 24.4, 26.2, 49.8, 50.1, 55.3, 57.1, 57.3, 79.7, 119.7, 123.1, 123.8, 126.2, 131.9, 135.2, 136.0, 138.5, 144.0, 147.4, 156.2, 173.6.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{26}Cl_2N_3O_4S$ 510.1016; Found 510.1015

Lab book number(s): JK227

5.2.155. Compound [168]: (1S,5S,6*R*)-10-((3,5-dichlorophenyl)sulfonyl)-5-(1,2-dihydroxyethyl)-3-(pyridin-2-ylmethyl)-3,10-diazabicyclo[4.3.1]decan-2-one



[168]

Compound **[34]** (24 mg, 0.05 mmol, 1 eq.) was dissolved in aceton (9 ml) and water (1 ml), 2,6-lutidine (12 μl, 0.10 mmol, 2 eq.), NMO (12 mg, 0.10 mmol, 2 eq.) and OsO_4 (13 µL, 0.001 mmol, 0.02 eq., 2.5% in t-BuOH) were added successively. After 16 h the reaction was quenched with sat. aq. $Na_2S_2O_3$ solution, extracted with EA, washed with sat. aq. $CuSO_4$ solution, dried over $MgSO_4$ and filtered over silica. Solvents were removed under reduced pressure and column chromatography (15 g SiO_2, cycH/EA → EA + 10% MeOH) afforded the title compound as colorless resin.

Yield: 54% (14 mg, 0.027 mmol)

Appearance: colorless resin

TLC: R_f = 0.23 (EA + 10% MeOH; UV)

HPLC: R_t = 9.93 & 10.09 min (0 – 100% B in 20 min)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.03 – 1.62 (m, 5H), 2.10 – 2.20 (m, 1H), 2.28 (dt, *J* = 27.8, 8.8 Hz, 1H), 3.45 – 3.72 (m, 6H), 3.82 – 3.96 (m, 1H), 4.09 – 4.30 (m, 1H), 4.51 – 4.76 (m, 2H), 4.97 (t, *J* = 15.4 Hz, 1H), 7.24 – 7.40 (m, 1H), 7.40 – 7.57 (m, 2H), 7.65 (t, *J* = 2.3 Hz, 2H), 7.72 – 7.88 (m, 1H), 8.39 – 8.57 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.3, 27.4, 27.9, 28.1, 28.8, 46.5, 47.1, 48.9, 49.5, 52.5, 52.7, 55.1, 55.2, 56.9, 57.1, 64.0, 64.2, 72.4, 73.1, 123.5, 123.7, 124.3, 124.5, 124.9, 125.0, 132.8, 136.4, 139.4, 139.6, 143.9, 143.9, 146.9, 147.1, 155.9, 156.1, 170.4, 170.5.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{26}Cl_2N_3O_5S$ 514.0965; Found 514.0966

Lab book number(s): JK374

5.3. Abbreviations

Aq.	aquoeous
Boc_2O	di-tert-butyldicarbonat
CAN	ceric ammonium nitrate
cycH	cyclohexane
DCM	dichloromethane
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess–Martin periodinane
EA	ethyl acetate
EDC-HCl	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
HDPE	high density polyethylene
HF	hydrofluoric acid
HOBt	hydroxybenzotriazole
NMR	nuclear magnetic resonance
$P(Cy)_3$	tricyclohexylphosphine
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
R_f	retention factor
Rt	room temperature
Sat.	saturated
TEA	triethyl amine
TLC	thin layer chromatography

6. Appendix

6.1. List of Figures

6.2. List of Schemes

6.3. List of Tables

7. References

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