MAX PLANCK INSTITUTE
OF MOLECULAR PHYSIOLOGY

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Macro-Pyrroquidines

Design, Synthesis and Biological Characterization

Dissertation

Zur Erlangung des akademischen Grades eines

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Results of this thesis contributed to the following Publications

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Results of this thesis may also be found in the following bachelor- and master theses

P. Bodenbinder, “Synthesis and Late-Stage Modification of a Cinchona Alkaloid-Based Compound Library of 20-membered Macrocycles via 1,3-Dipolar Cycloaddition”, master thesis 2021

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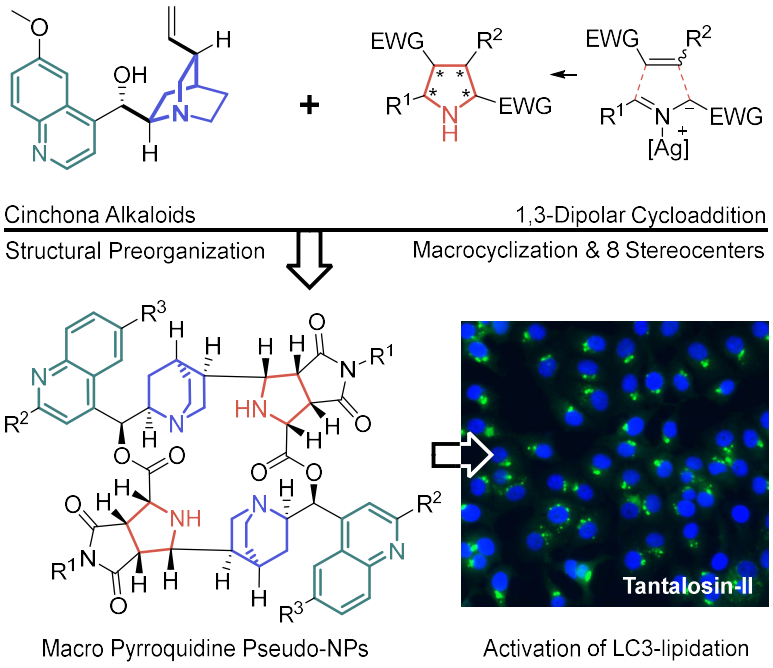
Abstract

The conscious generation of biologically relevant chemical matter is at the heart of medicinal chemistry. Here, natural products (NPs) represent an important source of chemical feedstock and intellectual inspiration. Computational analyses of NP-databanks have shown that core motives are repeated across molecules with distinct bioactivity. The recombination of these privileged fragments in novel three dimensional arrangements, is thought to expand the chemical space in an area already prevalidated by evolutionary processes and constitutes the design principle of pseudo-NPs.

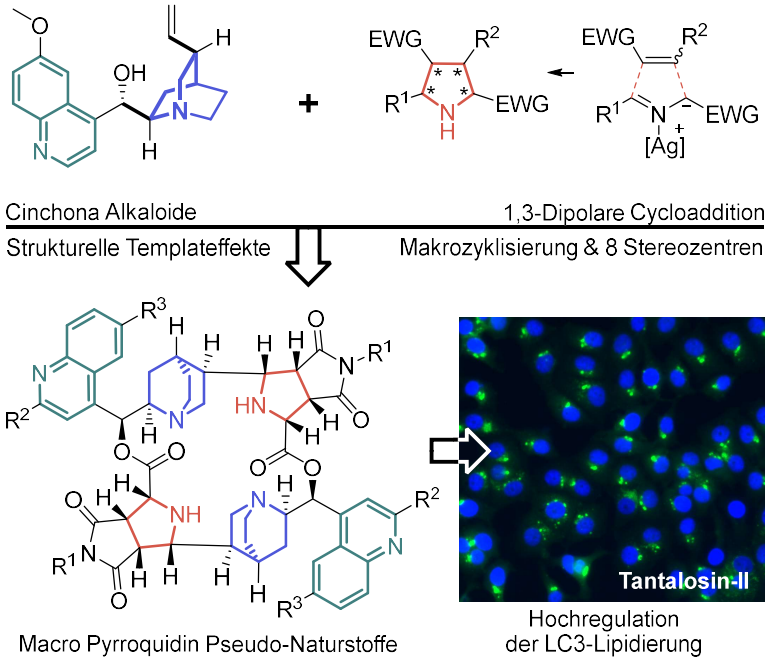


Herein, the design and synthesis of pseudo-natural “Macro Pyrroquidines” via imine-based macrocyclization of chinchona alkaloids and subsequent dual 1,3-dipolar cycloaddition is described. The developed three-step one-pot reaction sequence allowed the deliberate introduction of spacially distal substituents and a rapid generation of a compound library. The absolute configuration of the 20-membered cinchona macrocycles bearing 18 stereocenters could be determined via a combination of X-ray crystallography and NMR-experiments. Thorough biological characterization revealed a potent induction of an unprecedented LC3-lipidation phenotype and could be further refined via an SAR-campaign. Lastly, the introduction of reactive handles to the macrocycles, enabled their use as synthetic platforms for further derivatization and the generation of chemical probes.

Kurzzusammenfassung

Die gezielte Generierung von biologisch relevanten Molekülen gehört zu den Kernzielen der Medizinalchemie. Hierbei dienen besonders Naturstoffe als Quelle der Inspiration, aber auch als Quelle komplexer Ausgangsstoffe.

Durch computergestützte Analysen von Naturstoffdatenbanken konnten wiederkehrende chemische Strukturmotive in Molekülen mit unterschiedlicher Bioaktivität identifiziert werden. Einer Rekombination dieser universellen Fragmente in neuartiger Konnektivität könnte Moleküle erzeugen, die den chemischen Strukturraum um einen evolutionär prä-validierten Bereich erweitern. Auf diese Weise konzipierte Strukturen wären Pseudo-Naturstoffe.



Im Folgenden wird das Design und die Synthese einer neuen Klasse von Pseudo-Naturstoffen namens *Macro Pyrroquidine* beschrieben. Diese konnten über die iminbasierte Makrozyklisierung von Cinchona-Alkaloiden und eine darauf folgende doppelte 1,3-dipolare Cycloaddition generiert werden. Die entwickelte dreistufige Eintopfreaktion erlaubte nicht nur eine effiziente Synthese einer Substanzbibliothek, sondern auch die Installation von Substituenten in distalen Hemisphären des Ringsystems.

Die absolute Konfiguration der 18 Stereozentren der 20-meren Chinchona Makrozyklen konnte durch eine Kombination aus Röntgenkristallographie, NMR-Studien und Monte Carlo Simulationen aufgeklärt werden.

Durch eine breit angelegte biologische Charakterisierung der Substanzbibliothek, konnte ein durch einige Moleküle hervorgerufener Phänotyp beschrieben werden, der durch die verstärkte Lipidierung des in viele verschiedene autophagieassoziierte Prozesse involvierte LC3-Proteins gekennzeichnet ist. In Studien zur Struktur-Aktivitätsbeziehung der Macro Pyrroquidine konnten Substanzen mit verbesserter Bioaktivität identifiziert werden.

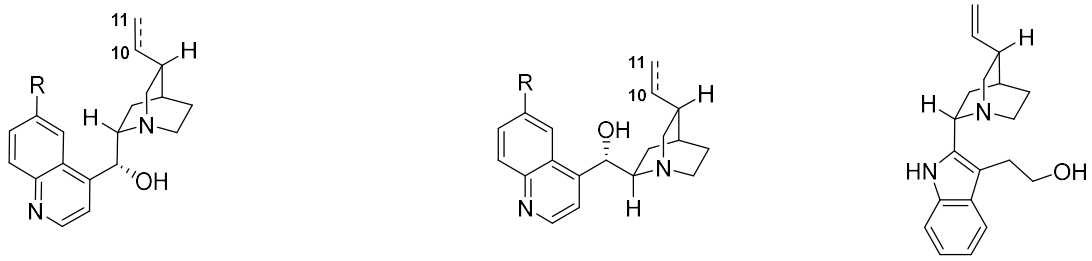
Durch das Einfügen reaktiver Gruppen konnten auch die Makrozyklen selbst für chemische Transformationen nutzbar gemacht werden. Hierdurch konnten weitere Derivate, aber auch *Pulldown Probes* erzeugt werden.

1 Introduction

1.1 Cinchona Alkaloids

1.1.1 Biosynthesis and Relevant Chemistry

Cinchona alkaloids are a class of naturally occurring alkaloids which are, to this day, extracted from the bark of trees of the genus *cinchona*. A well-established extraction process ensures an annual production of between 500 – 700 t. This makes them highly affordable and allows a wide range of uses such as in medicine, food industry or chemical industry and research.[1,2]



Quinine, **1**, R = OMe, C10/11 = alkene
Dihydroquinine, **5**, R = OMe, C10/11 = alkane
Cinchonidine, **3**, R = H, C10/11 = alkene
Dihydrocinchonidine, **7**, R = H, C10/11 = alkane

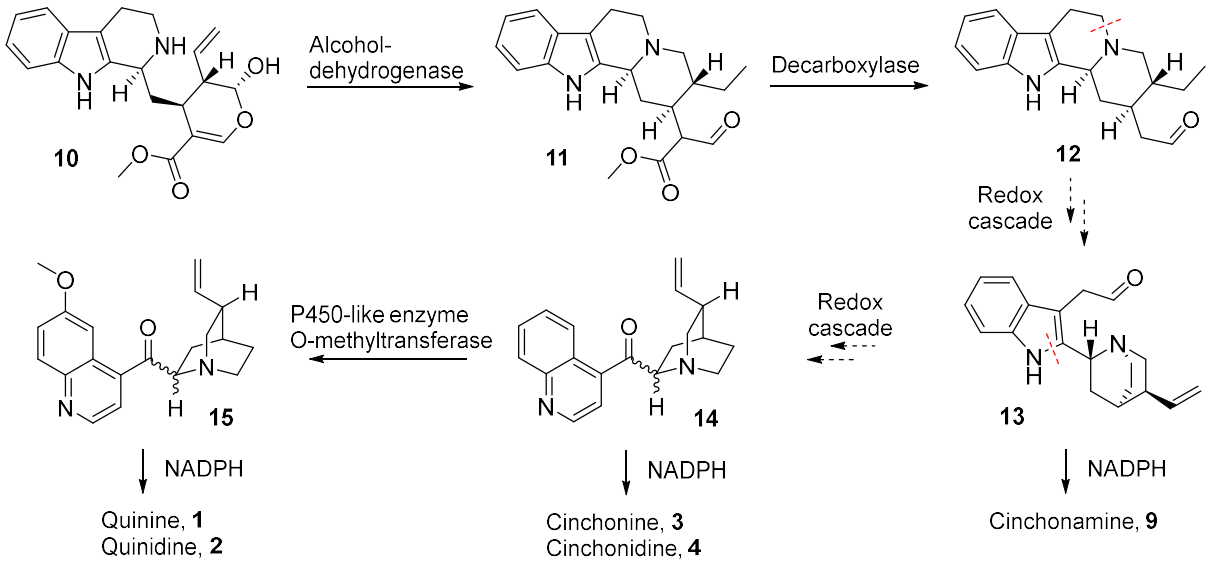
Quinidine, **2**, R = OMe, C10/11 = alkene
Dihydroquinidine, **6**, R = OMe, C10/11 = alkane
Cinchonine, **4**, R = H, C10/11 = alkene
Dihydrocinchonine, **8**, R = H, C10/11 = alkane

Cinchonamine, **9**

Figure 1: Naturally occurring cinchona alkaloids.

While quinine **1** is the most prominent member of this compound class, extracts of the plant also contain close derivatives of it, such as its diastereomer quinidine (**2**) and their respective demethoxy counterparts cinchonidine (**3**) and cinchonine (**4**). All four molecules also exist as their di-hydro derivatives **5**, **6**, **7** and **8** (Figure 1). Cinchonamine **9** can be found in smaller amounts and its indole moiety structurally hints at the biosynthetic pathway in which cinchona alkaloids are produced. Starting from geraniol and tryptophan, this pathway shares important intermediates with the biosynthesis of monoterpene indole alkaloids such as strictosidine aglycone **10** (Scheme 1). Transesterification after oxidation of the hemi-acetal and subsequent decarboxylation results in corynantheal **12**. A set of redox reactions then leads to C/N-cleavage and imine-based quinuclidine formation (cinchonaminal **13**). The oxidative cleavage of the indole C/N-bond and subsequent imine-based quinoline formation leads to cinchoninone **14** epimers. The exact mechanisms and enzymes involved in the last two transformations are yet to be elucidated. Cytochrome P450-like aryl oxidation and SAM-dependent methylation leads to the epimeric 6'-methoxycinchoninone **15**. Reduction of the

respective carbonyl groups then produces the naturally occurring mixture of cinchona alkaloids.[2,3]



Scheme 1: Selected intermediates of the biosynthetic pathway of cinchona alkaloids.[3]

Besides their medicinal use, landmarks in cinchona alkaloid-history were their structure elucidation by Rabe in 1908, the first enantioselective total synthesis by Woodward and Doering in 1944, their use as organo-catalysts by Wynberg in the late 1970s and finally the Nobel prize in 2001 for Sharpless and his use of cinchona alkaloids as chiral ligands for transition metals in the enantioselective dihydroxylation of alkenes.[4]

Their structure comprises of a quinoline and a constant quinuclidine moiety with a C3-(R) olefin substituent. The addition of another substituent to the otherwise symmetrical quinuclidine cage turn its N1- and C4-atoms into stereocenters. Thus, the naturally occurring cinchona alkaloid diastereomers (e.g. **1** and **2**) can be considered pseudo-enantiomers (Figure 2B). Disregarding the C3-stereocenter, quinine and quinidine could be considered enantiomers of each other in regard to their C8- and C9-stereocenters. This has tremendous implications for their use as chiral catalysts, as different enantiomers can be accessed by the mere switch between the two molecules.[5] Another reason for the use of cinchona alkaloids as chiral ligands for transition metals, is the basic nitrogen of the quinuclidine with its favorable cone angle and its 1,4-distance to the adjacent hydroxyl group. This allows both, 5-membered complexes with both atoms chelating a transition metal or organocatalytic 6-membred transition states, with the hydroxyl group as a hydrogen bond donor.

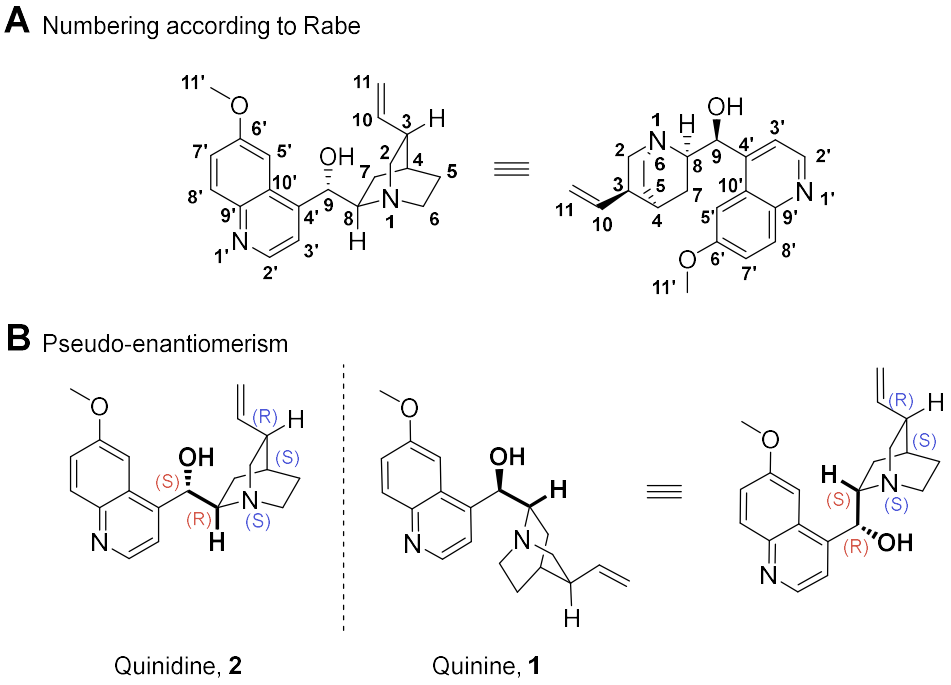
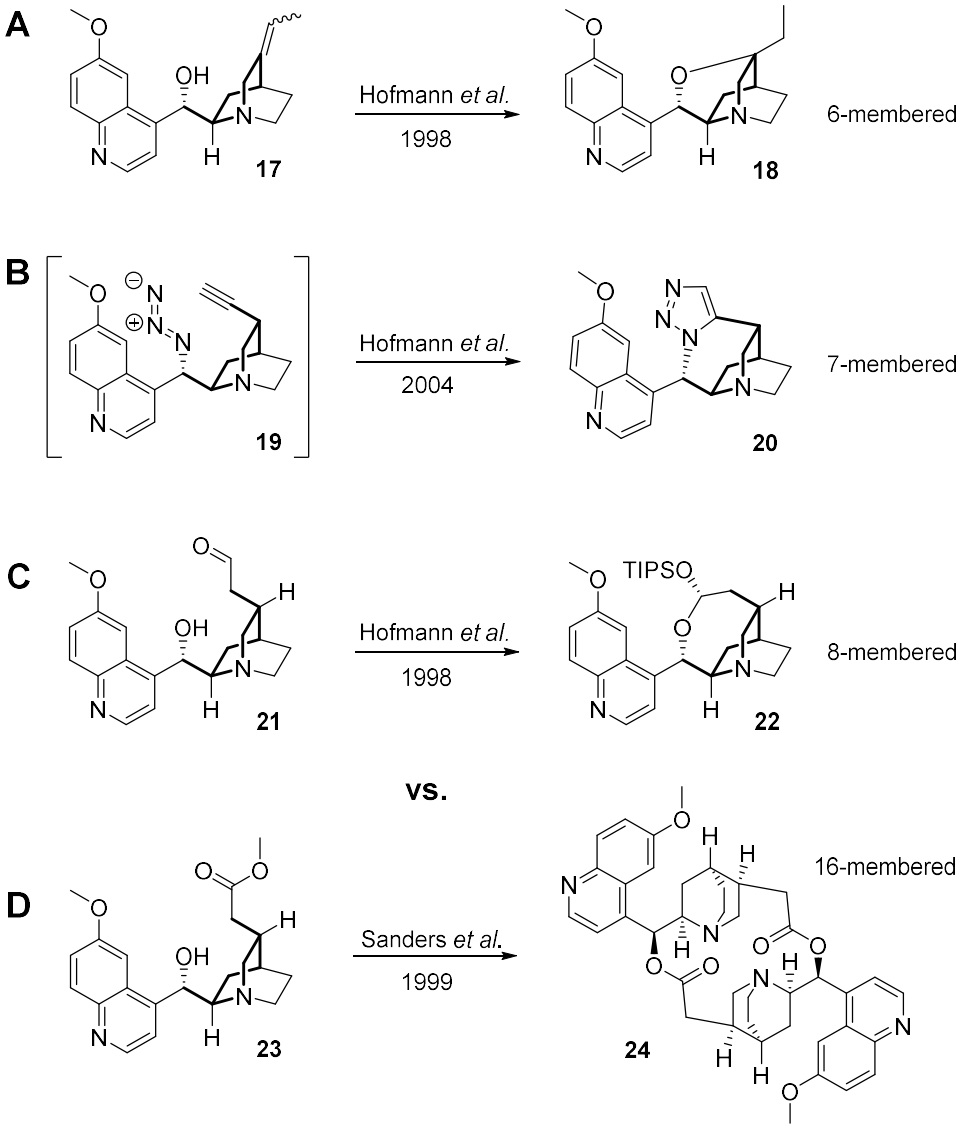


Figure 2: A) general numbering of cinchona alkaloids introduced by Rabe; B) Graphic representation of the pseudo-enantiomerism of quinine and quinidine. Blue stereocenters are not considered in this analysis.

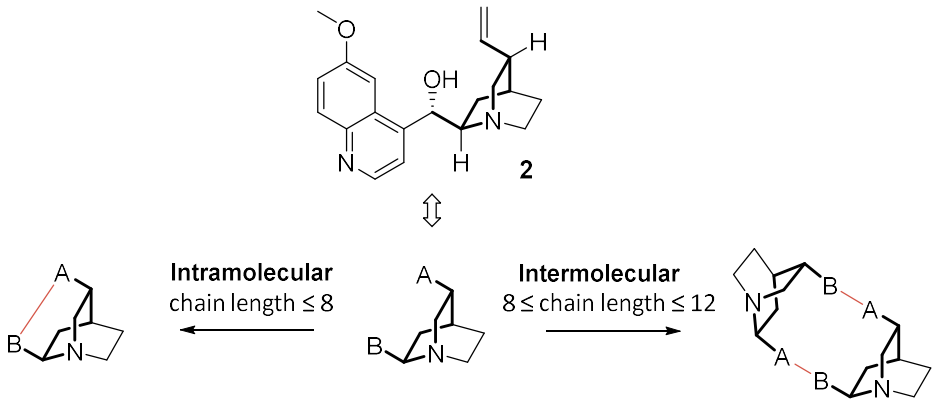
Cinchona alkaloids can be subject to rearrangement and fragmentation reactions, many of which have been identified by Hoffmann *et al*. in the late 1990s. Apart from these transformations, he was also able to exploit the proximity of the C9-hydroxyl group and the C3-ethylene moiety in a study of intramolecular cyclizations (Scheme 2).[5] The following selected examples show some possible cyclization reactions and their capacity to form cage systems of different size.



Scheme 2: Types of cyclizations exploiting the configuration of quinuclidine substituents in quinidine used by Hoffmann and Sanders.[5,6]

A hydroxyl-C3-cyclization towards the oxazatwistane cage could be achieved from **17** through treatment with hydrobromic acid.[7] A cascade reaction from the C3-mesyloxy analogue of intermediate **19** with sodium azide could produce cyclic system **20** via an intramolecular 1,3-dipolar cycloaddition.[8] Treatment of aldehyde **21** with TIPSOTf and a base afforded the 8-membered cycle **22**.[7] A study by Sanders *et al.*, however, found contradictory behavior of a starting material possessing the same number of carbon atoms, the same degree of flexibility and the same configuration. In their hands, methyl ester **23** would form 16-membered dimer **24**, rather than react intramolecularly. This effect will be discussed later in the context of macrocyclization reactions.

Thus, the two effects on cyclization reactions mediated by the orientation of the quinuclidine substituents in quinidine can be schematically summarized as is Scheme 3.



Scheme 3: Schematic modes of cyclization resultant from the spacial proximity of reactive groups A and B, induced by the quinuclidine configuration found in e.g. quinidine.

1.1.2 Bioactivity

The use of cinchona alkaloids by the south American native population predates their introduction to Europe in ca. 1640 and was largely due to their anti-malarial properties. Here, quinine likely disrupts the metabolism of the endogenous parasite *Plasmodium falciparum* responsible for malaria via complexation of heme-bound iron(III).[9,10] The exact mechanism, however, is still elusive.[2] Malaria is responsible for about 400000 annual deaths worldwide (2019). Despite severe cardiovascular side effects and a multitude of synthetic alternatives, quinine remains to play an important role in their prevention.[1,11]

Deviating from the original indication of cinchona alkaloids in the treatment of malaria, countless medicinal chemical campaigns have successfully utilized them as lead structures. A few examples from this century-long endeavor are given Figure 3. The structures showcase, that subtle chemical changes can alter the bioactivity profile of cinchona alkaloids significantly.

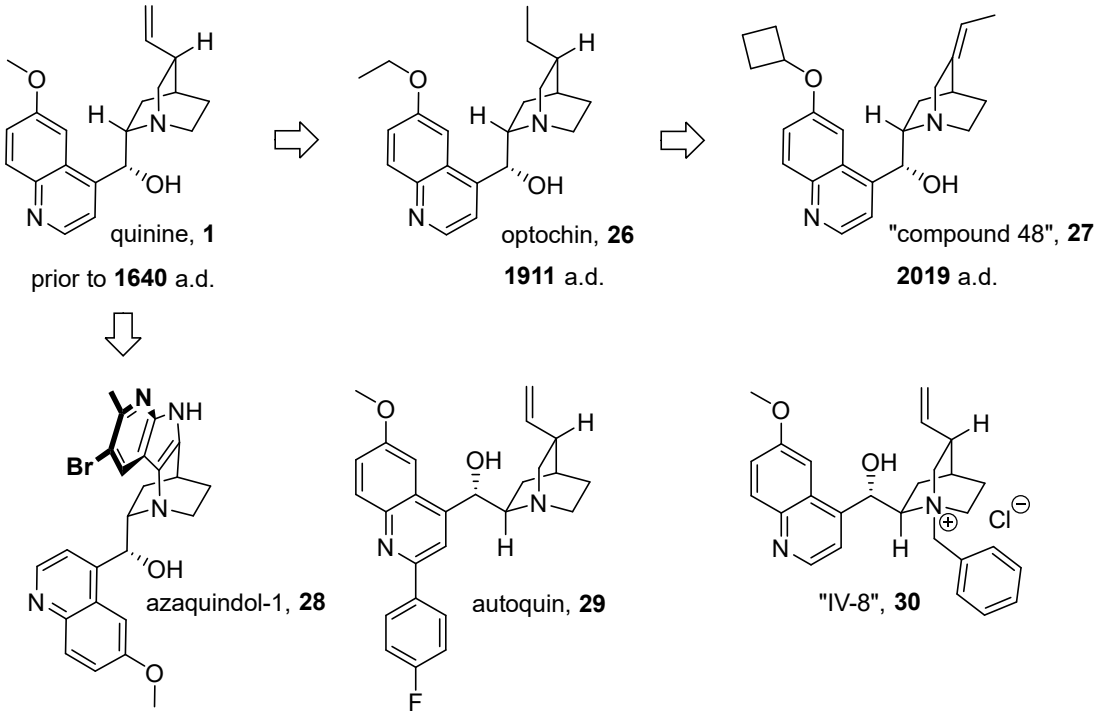


Figure 3: Bioactive derivatives of quinine with no perturbations of the core scaffold.

Optochin was synthesized from dihydroquinine in 1911 by Morgenroth and Levy substituting the natural C6'-methoxy group with an ethoxy substituent. This gave the compound a remarkable bacteriostatic and bactericidal activity against different strains of *pneumococci*.[12] A study by Aldrich *et al*. 100 years later further refined this bioactivity by shifting the vinyl double bond of quinine into exocyclic (C3/C10) position and replacing the C6'-ethyl ether substituent by a cyclobutyl ether (**27**). Furthermore, they were able to show, that this compound appears to target the ATP-synthase of *Streptococcus pneumoniae*.[13] With the annulation of indole scaffolds to the quinuclidine cage, and thus reducing the basicity of the central tertiary amine, Waldmann and coworkers could transform quinine into a VSP34-kinase inhibitor which could efficiently impair autophagy (azaquindol-1, **28**).[14] In 2020 Waldmann *et al*. could also show that the addition of a 4-fluorophenyl group in C2'-position of quinidine produced a potent late-stage inhibitor of autophagy with an entirely different mode of action than **28**. Autoquin (**29**) sequesters Fe^{2+} in lysosomes and ultimately leads to cell death through the production of reactive oxygen species.[15] Lastly, the *N*-benzyl substituted quinuclidine ammonium ion **30** could be shown to induce cardiomyogenesis in murine embryonic stem cells by Sachinidis *et al*.[16]

Collectively, these examples show, that even minor alterations of an otherwise constant cinchona alkaloid core scaffold can tap into various biological processes, rendering them "privileged scaffolds".[17]

1.2 Macrocycles

Macrocycles (Figure 4) are a common class of molecules and represent approximately 20 % of all natural products.[18] They can also be found in all major biosynthetically distinct classes of natural products (e.g. terpenoids, polyketides, peptides…). For example, the C_2-symmetrical marine polyketide Swinholide A acts as a potent actin binder;[19] the almost completely saturated carbocycle Civetone **32** serves as a pheromone;[20] the non-ribosomal peptide Argyrin A **33** inhibits the proteasome (Figure 4).[21] The parallel evolution of macrocylces hints to the advantages cyclic structures have over their putative linear analogues in biological settings.

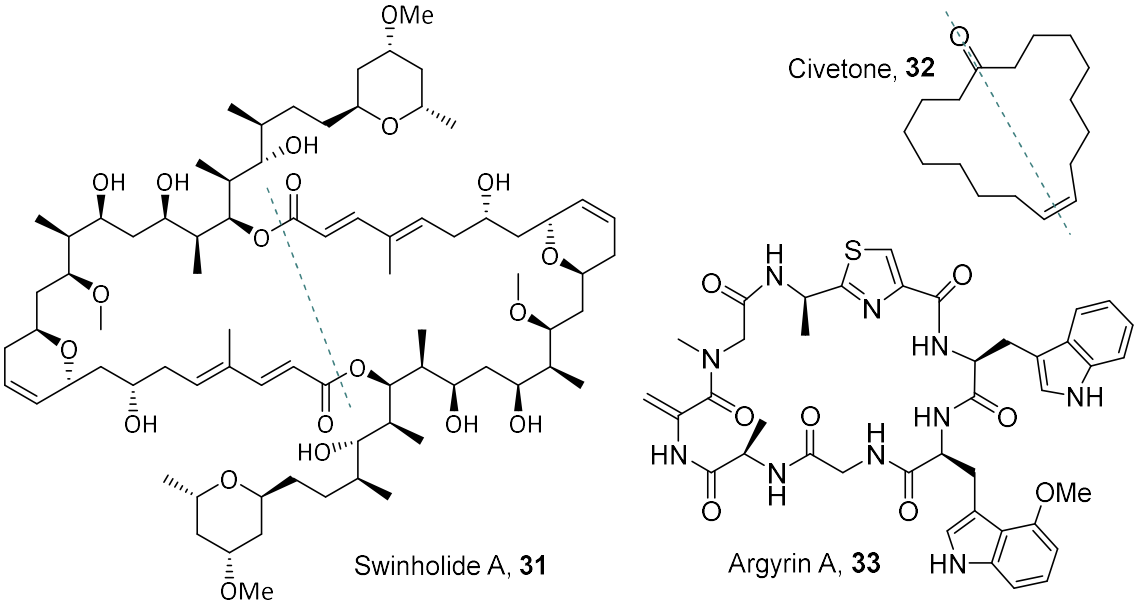


Figure 4: **Selected structures of different types of macrocyclic natural products**. The green dotted line indicates C_2-symmetry.

A cyclized molecule has less degrees of freedom than its linear analogue and can thus adopt significantly fewer conformations. This preorganization can be understood as locking the molecule into a specific bioactive conformation. This minimizes promiscuity but also improves binding affinity, as the energy, that a linear analogue would need to transition through its non-active arrangements into the required shape, is omitted. Macrocycles generally also have less surface area, which increases their cell permeability. It has also been shown, that cyclic peptides are significantly less susceptible to hydrolases.[22] Collectively, these factors allow macrocycles to be potent drug molecules despite their high molecular weight. Moreover, the described prearrangement combined with the large size of macrocycles, grants them the

ability to effectively bind to flat surface areas of proteins, often addressing multiple binding sites simultaneously. This makes them perfect candidates to modulate protein-protein-interactions (PPIs) and thus bearing the potential to help expanding the knowledge about biological mechanisms as well as drugging processes previously deemed “undruggable”.[23–30]

The effect macrocyclization can have on the efficacy of a drug molecule is showcased in development process of Mercks’ farnesyltransferase inhibitor **35** (Figure 5). Due to the observation of NOE signals between protons at the termini of **34** in a protein-bound state, macrocycles **35** and **36** were synthesized via S_NAr. Cyclic derivative **35** showed a 50000-fold decrease in IC_{50}. Cyclization locked the naphthalene/oxopiperazine-portion of the molecule into a conformation so rigidly defined, that these two moieties exhibited a previously not observed atropisomerism (Figure 5). This unusually distinct second “conformer” did not show any bioactivity under assay conditions.[31]

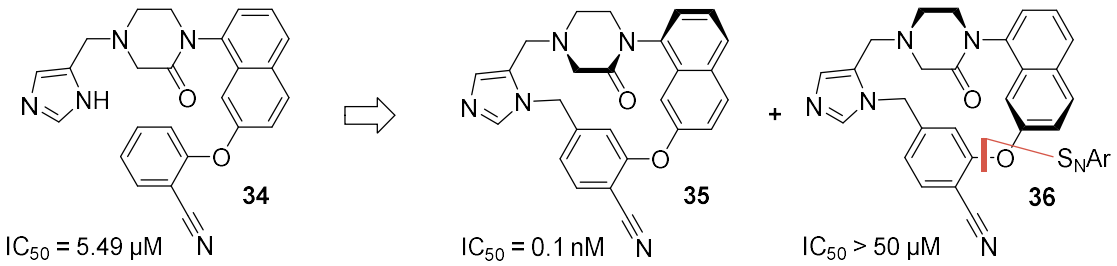


Figure 5: Successful implementation of a macrocyclization strategy in the discovery of the farnesyltransferase inhibitor **35**.

1.2.1 Methodology

A variety of chemical transformations has been used to achieve macrocyclization.[32] Therefore, the following analysis restricts itself to the general challenges intrinsic to intramolecular cyclizations and only covers examples that are highly relevant to the reaction investigated in this work.

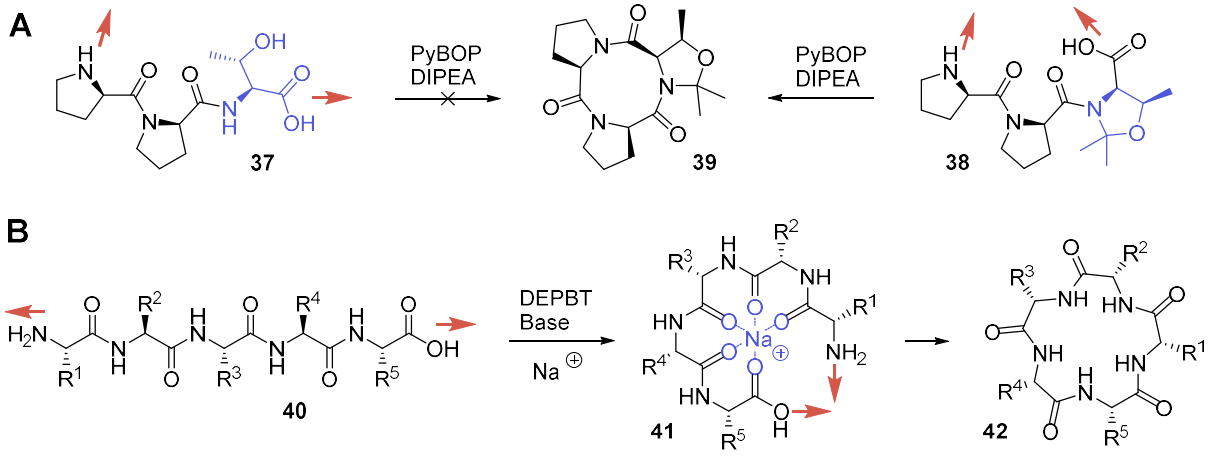
Cyclizations are an interplay between the entropic and enthalpic cost of the reaction. Entropic loss eludes to the difficulty of getting the two reactive sites within the molecule into proximity of each other, and to the fact, that most conformations allowed for the linear precursor are forbidden in the cyclic product. For larger cycles (>11), this is the main contribution to undesired side reactions like dimerization. Enthalpic loss elutes to the ring strain of the resultant cycle. This is the main reason for the difficulty of cyclize small rings (<5). Cycles of

intermediate size (7 – 11) might combine a high number of possible conformations with a non-neglectable ring strain and therefore represent challenging synthetic targets.

The most common solution to effectively suppress intermolecular reactions is to lower the reaction concentration. This way, the frequency of the approach of an extra-molecular reactive group is lowered, while the intra-molecular reactive groups stay at a constant distance. Pseudo-dilution can be achieved when the linear precursor is anchored to a solid support. If the coupling sites are far enough apart, the immobilized molecule will never come into the proximity of an extra-molecular reactive group.[33] Many methodologies combine the cleavage of the molecules from the stationary phase with cyclization.

Regardless in which of the two systems the synthesis is performed, the two intra-molecular reactive groups should be able to effectively come into proximity of each other. Hence, the effects of conformation and configuration of the linear molecule are pivotal. This can be observed indirectly, in the studies of Schmidt and Langner, who tried the same lactamization reaction on all possible connections of the pentapeptide Phe/Leu/Pro/Ala/Ala. They found that only one of the peptide bonds was amenable for intramolecular cyclization, albeit in only 21% yield. All other sequences of the same peptide were not productive or resulted in dimer formation.[34]

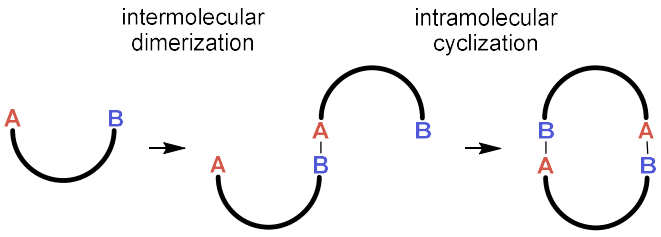
In substrate induced cyclization approaches, bends are introduced into the structure of the molecule in order to bring the two desired reaction partners into proximity of each other. In peptide sequences, this can be the addition of extra proline amino acids or the use of pseudo-proline, derived from serine (Scheme 4A). Another methodology is to add metal ions or hydrogen bond donors/acceptors to the reaction mixture. The complexation of several key groups in the molecule creates a cyclic conformational template, that aids the desired macrocyclization process (Scheme 4B).[32,33]



Scheme 4: Exemplary intramolecular cyclization approaches based on configuration induced conformation (A) or templating induced conformation (B). Red arrows highlight the general orientation of the reactive groups before and after implementation of the respective approach.

Dimerization is a frequently occurring, often undesired, side reaction in cyclization processes. But it can also serve as a tool to quickly build up complexity and is estimated to be found in the biosynthesis of 15 – 20% of all NPs.[35] The tendency of nature to utilize dimerization does not end at the level of small molecules. A vast fraction of proteins form oligomers and of these, approximately half form homodimers.[36] Conversely, homodimeric molecules are strong candidates for inducing functional or inhibitory dimerization of proteins, especially if they are symmetrical. The marine natural product Swinholide A (**31**) is an example of such a naturally occurring C_2-symmetrical homodimer that interferes with actin polymerization via artificial dimerization of G-actin (Figure 4).[37–39]

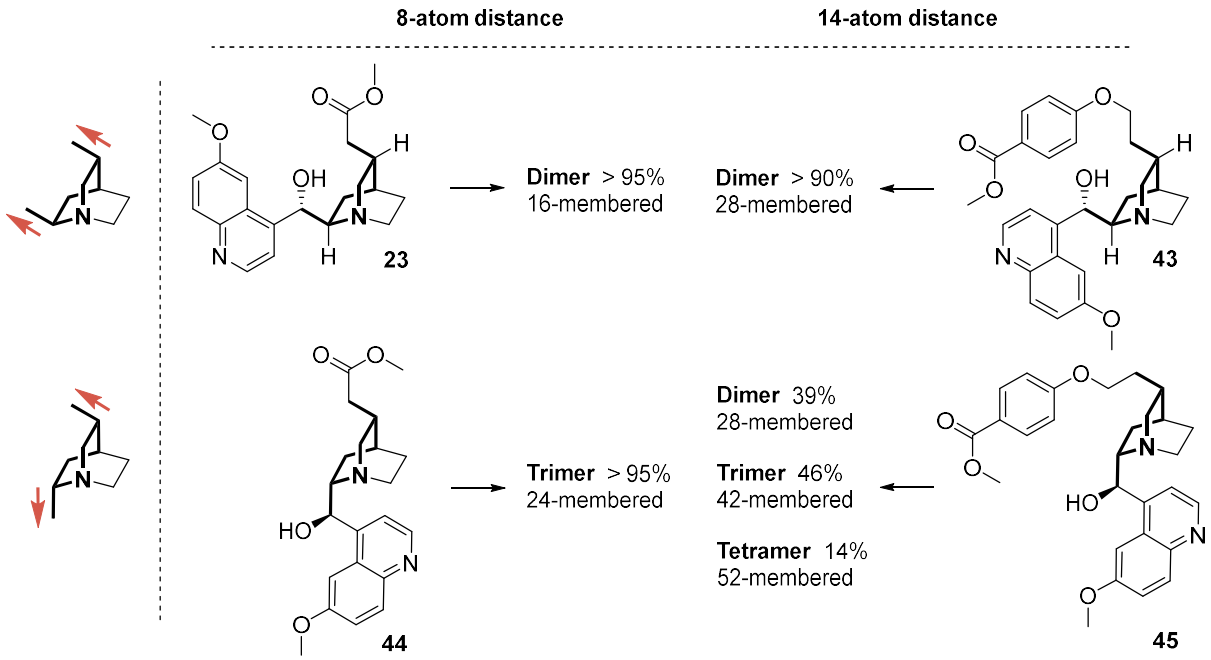
Dimerization-processes, that involve cyclization, are often stepwise processes where initially two of the four involved reactive groups react in an intermolecular dimerization which is then followed by an intramolecular cyclization via the two remaining groups (Scheme 5).



Scheme 5: Schematic homodimerization process involved in macrocycle formation. A and B are the two reactive groups involved in the bond formation reaction.

Analogously to the examples in Scheme 4, productive conformations can be forced via substrate- or template induction in these dimerization/macrocyclization processes as well.[40]

In the late 1990s Rowan and Sanders performed a study on the configurational induction effect of the quinuclidine core scaffold of cinchona alkaloids on macrocyclization.[6] Like proline, the rigid quinuclidine cage is able to bring its two substituents into proximity to one another (discussed for quinidine **2** in the context of intramolecular cyclization in Section 1.1.1). Sanders *et al*. investigated derivatives of the two pseudo enantiomers quinine **1** and quinine **2** with different atom chain distances of the terminal reactive groups (Scheme 6). Compared to quinidine, the quinuclidine substituents of quinine show a more open configuration (Scheme 6). Under thermodynamic equilibration via reversible transesterification conditions, quinidine derivatives **23** and **43** formed predominantly dimers, while **43** (longer chain) was slightly less effective. **23**s' diastereomeric derivative **44** (from quinine) produced predominantly trimers. **45** combines the open configuration of quinine and the long carbon chain linkage of **43**. This starting material produces a mixture of dimeric, trimeric and tetrameric products and seems to represent a limit to the quinuclidine configuration-mediated selection for dimers/trimers over higher oligomers or polymers. Rowan and Sanders termed the observed behavior a “structural temptation effect”.[6,41–43] The data also shows that the induced selectivity gets weaker with growing distance of the reactive handles to the quinuclidine core (**23** versus **43** and **44** versus **45**).



Scheme 6: Effect of configuration induced macrocyclization behavior of cinchona alkaloids observed by Rowan and Sanders under reversible transesterification conditions and thermodynamic equilibration.[43] Highlighted bonds and red arrows visualize the structural templating effect.

In 2017, Spring *et al*. reported the intramolecular macrocyclization of even more flexible quinine derivatives than **45**.[44] Despite low yields, variously functionalized monomers could reportedly be synthesized via ring-closing-metathesis (**46**) and copper mediated alkyne-azide cycloaddition (**47**, Figure 6).

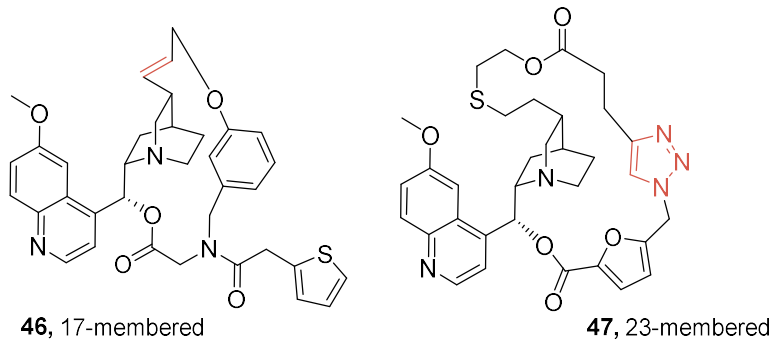


Figure 6: Exemplary quinine derived macrocycles reported by Spring *et al*.[44]

Imine formation is a common reaction type for macrocyclizations. It is especially beneficial in supramolecular assembly as its reversibility enables self-sorting systems.[45] To obtain hydrolytically stable products, the imine bond can be reduced via e.g. reductive amination. Imines are, however, versatile reactive groups and can utilized for many other reactions. Baran (2017) and Waldmann (2020) showed this in their two-step approaches of generating

functionalized peptide macrocycles.[46,47] In Barans' approach, the peptides were cyclized in-solution via the formation of a Schiff base which was successively trapped via an intramolecular nucleophile (Figure 7.A and B). The resultant saturated cyclic systems could then be oxidized to increase stability.[47] Waldmann *et al*. utilized an on-resin approach, where the imine-cyclized peptide was trapped via a 1,3-dipolar cycloaddition and later cleaved from its solid support (Figure 7.B and C). The resultant pyrrolidine did not only serve as a biologically relevant motive, but also fulfed the described structural role of proline in the "hot-loop" peptides used for their studies.[46] This approach was coined by Waldmann *et al*. as PepNats, referring to the fusion of a drug-like motive with a peptide macrocycle.

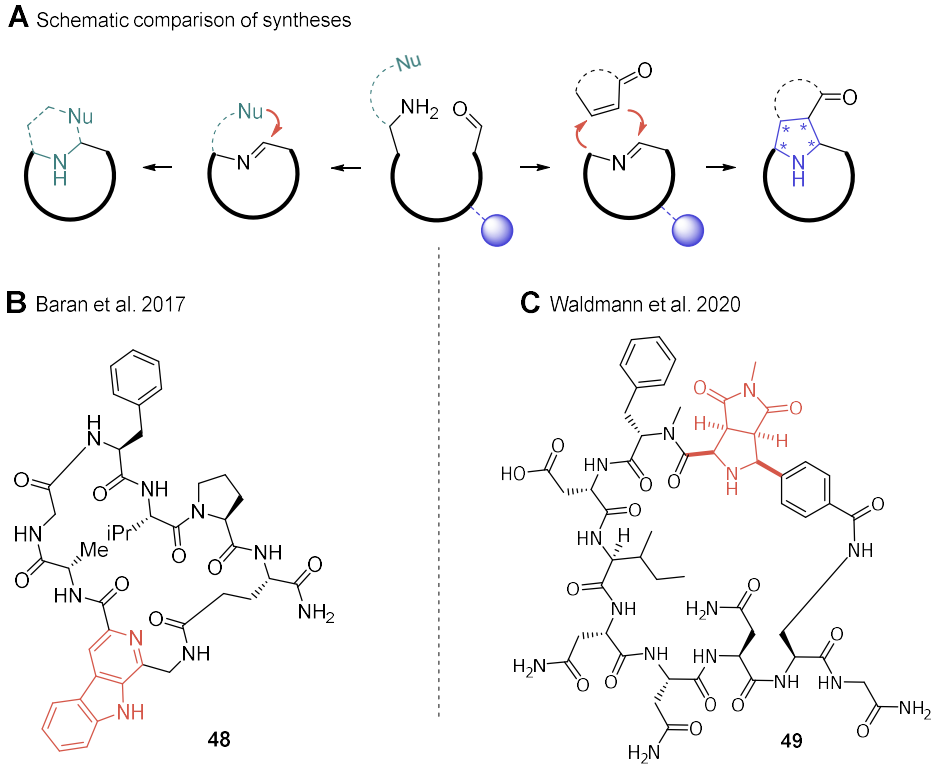
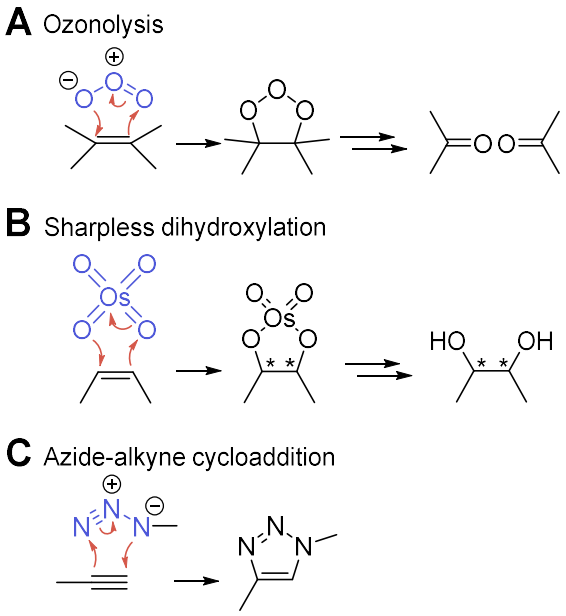


Figure 7: Selected imine-mediated cyclization of peptides and the successive incorporation of structurally and biologically relevant scaffolds (red) into the sequence. A) Schematic representation of the in-solution/intramolecular trapping approach by Baran (left) and the on-resin intermolecular trapping approach by Waldmann (right); B) Exemplary macrocycle by Baran *et al*.;[47] C) Exemplary macrocycle by Waldmann *et al*.[46]

1.3 1,3-dipolar Cycloaddition

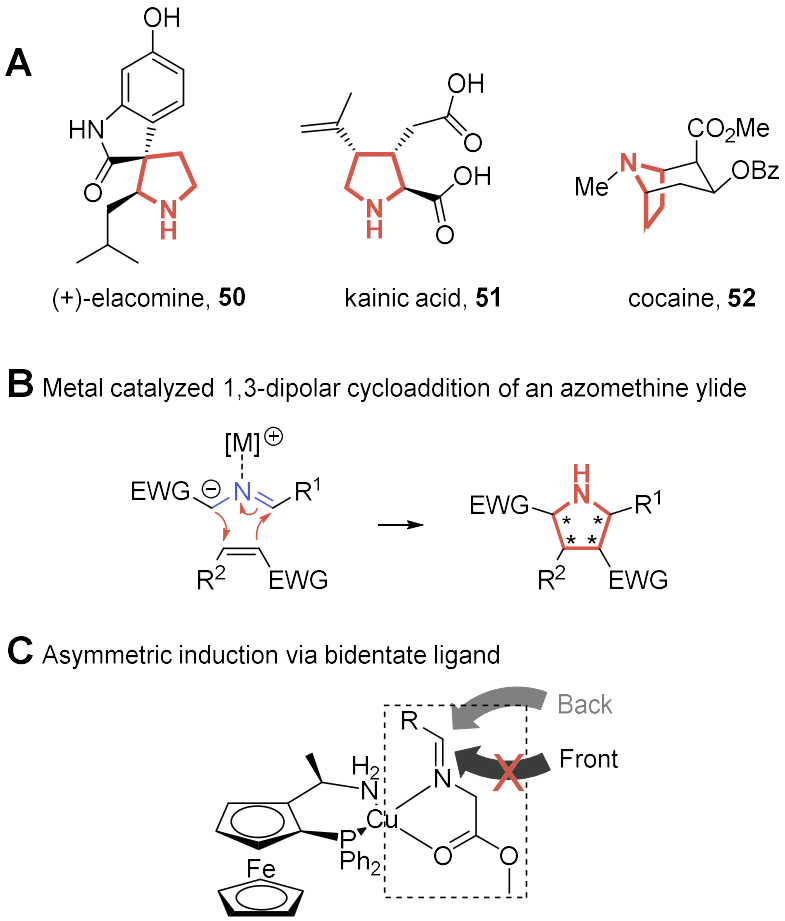
1,3-dipolar cycloaddition reactions are among the most prominent reaction types in organic chemistry. Generally, they involve the formation of a five-membered heterocycle via the [2+3] cycloaddition of a 1,3-dipole to a double or triple bond. Dipoles can be highly reactive gases like ozone (Scheme 7A), transition metal-based like the osmium tetroxide which is the key reactant in the asymmetric dihydroxylation reaction by Sharpless (Scheme 7B) or even be used as bio-orthogonal linking methods inside cells like the reaction of azides and alkynes discovered by Huisgen (Scheme 7C).[48,49]



Scheme 7: Three selected examples for reactions involving [2+3] cycloaddition of different 1,3-dipoles.

Five-membered heterocyclic scaffolds are highly relevant for medicinal chemistry and can accessed conveniently by a plethora of [2+3] cycloadditions. Here, namely the pyrrolidine scaffold with its up to four stereocenters is of great interest, as it is represented in a variety of bioactive NPs and marketed drugs (Scheme 8A). It can be generated by the reaction of azomethine ylides with electron deficient alkenes (Scheme 8B).[50] Enantioselective catalytic versions of this reaction have been developed over the years. Some of the most efficient systems combine silver(I)- or copper(I) catalysts with chiral bidentate ferrocene- or BINOL-type ligands. Here, the metal catalyst chelates the ligand, as well as the imine and the electron withdrawing group of the azomethine ylide, thus shielding one hemisphere of the ylide from dipolarophile approach (Scheme 8C).[50,51] Without chiral induction, the reaction shows a selectivity for *endo* adducts over *exo* aducts.[52]

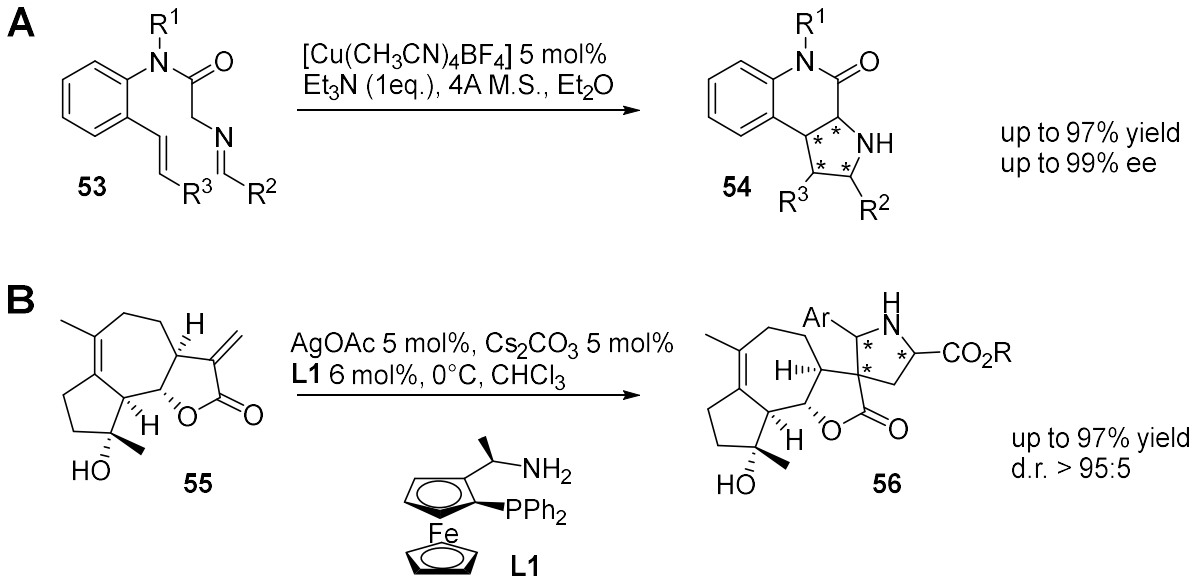
Although this type of 1,3-dipolar cycloaddition could be accomplished under harsh conditions,[53,54] current reaction systems based on transition metal catalysis allow a wide and convenient application of this methodology.



Scheme 8: Core concepts of the 1,3-dipolar cycloaddition of azomethine ylides. A) Bioactive natural products containing the pyrrolidine scaffold;[55–57] B) generalized transition metal catalyzed 1,3-dipolar cycloaddition of an azomethine ylide with an alkene; C) the use of a chiral, bidentate ferrocene ligand confers facial selectivity in a copper catalyzed 1,3-dipolar cycloaddition.[50]

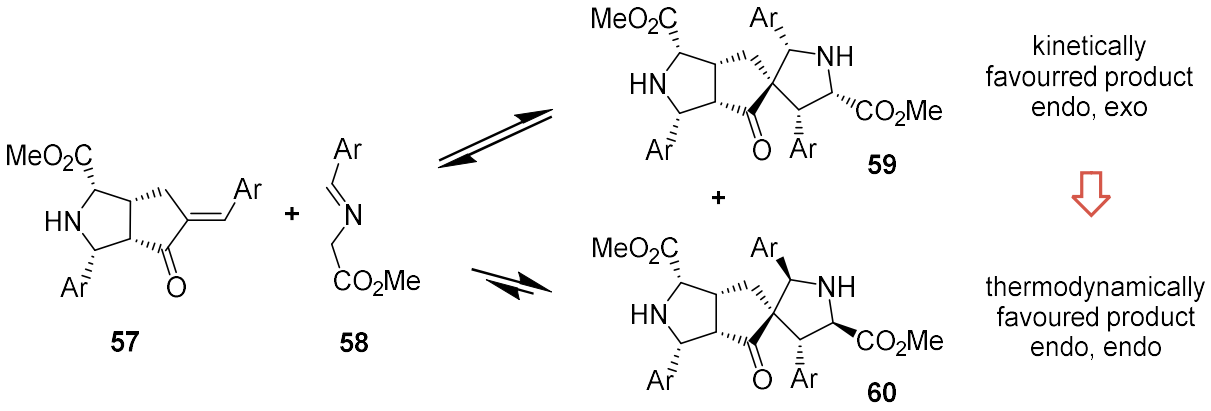
Complimenting the intermolecular reactions discussed so far, intramolecular 1,3-dipolar cycloadditions of e.g. **53** facilitate the generation of piperidino-pyrrolizidines (**54**) featuring fused heterocyclic ring systems with excellent yields and ee-values (Scheme 9A).[50,58] Recently, more complex, terpene-derived NP-dipolarophiles such as **55** could successfully be

utilized to generate spiro connected pyrrolidines (e.g. **56**) in high enantioselectivity (Scheme 9B).[59]



Scheme 9: Enantioselective 1,3-dipolar cycloadditions of azomethine ylides with an intramolecular dipolarophile (A) and complex, natural product derived dipolarophiles generating spiro connected pyrrolidines (B).[58,59]

In the investigation of a dual, consecutive, silver-catalyzed, stereo-divergent 1,3-dipolar cycloaddition, Waldmann *et al*. demonstrated the reversible nature of this reaction. In specific solvent/catalyst systems, the kinetically favored *endo,exo*-adduct **59** was found to transition into the thermodynamically favored *endo,endo*-adduct **60** through its precursors **57** and **58** (Scheme 10).[60]



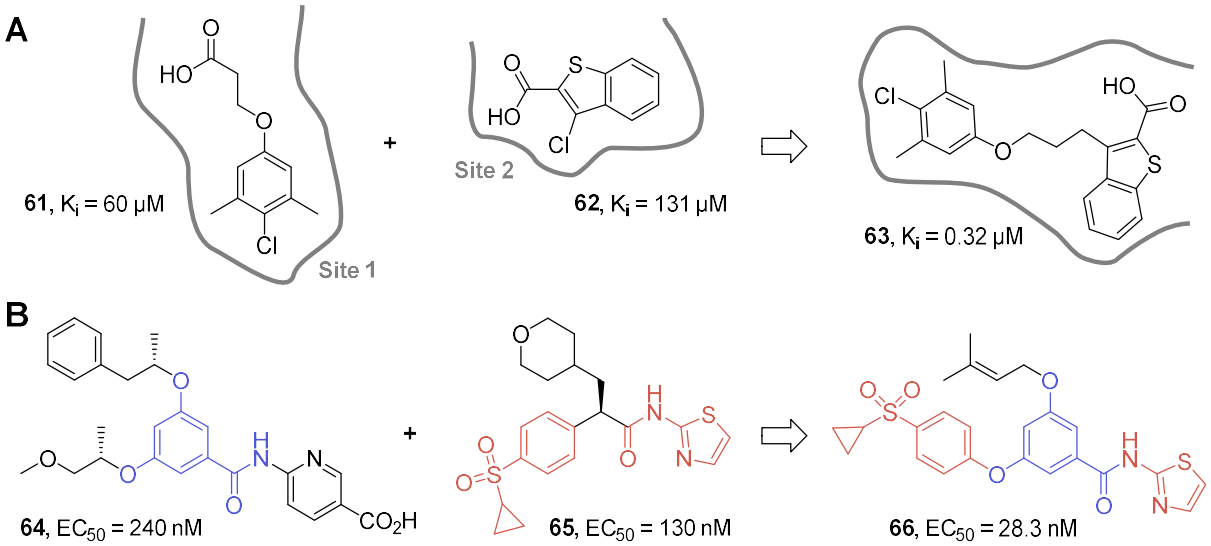
Scheme 10: An equilibrium between pyrrolidine products **59** and **60** with their precursors dipolarophile **57** and azomethine **58** allows interconversion of the kinetic product **59** into the thermodynamically favored product **60**.[60]

1.4 Design Approaches for Bioactive Small Molecules

Small molecules are an excellent tool to modulate biological processes, regardless if in a research- or therapeutical context. Their effect is quick, dose-dependent and reversible. No further *a priori* modifications of the system are needed.[61] The generation and identification of suitable chemical matter has, however, not ceased to be a challenge.[62] On one hand it is difficult to achieve selectivity within a structurally homogenous protein class such as kinases. On the other hand, protein structure can not yet help to guide chemists effectively through the chemical space opened up by e.g. the interactome. Not considering nature as a guide, the chemical space of molecules adhering to Lipinski's "rule of five" contains 10^{60} structures.[63] It is obvious that methods are needed to consciously guide synthetic efforts to identify portions of this space, that are biologically relevant and provide sensible starting points for optimization campaigns.

1.4.1 Fragment-Based Drug Design

Fragment based drug design (FBDD) is one of these methods. Here, the effects of a library of fragment sized molecules are tested in biochemical assays. Although no clear rules exist that define fragment-character, they are generally below a molecular weight of 250 Da and contain less than 25 heavy atoms. Such molecules are, by themselves, promiscuous and low in affinity. If a fragment is identified to modulate the target, usually with an affinity in the low millimolar range, spectroscopic methods like NMR or X-ray crystallography are employed to identify its binding site. Then several strategies can be used to improve the affinity and selectivity of such a hit. The fragment can for example be grown deliberately, by attaching functionality that is thought to interact beneficially with the binding site. If multiple fragments have been identified to bind in distinct proximal sites, they can be connected via a suitable linker. If the sites are extremely close or even overlapping, the molecules can be merged to improve affinity and selectivity (Scheme 11A).[64–66] In case of the Mcl-1-inhibitor **63** merging the two hit fragments **61** and **62** improved protein inhibition by 200-fold.[64] The glucokinase activator **66** by Zang *et al*. (Scheme 11B) was not designed using spectroscopic data. However, it was known that the two activators **64** and **65** bound to the same binding site, so a similar merging strategy could be performed after empirical identification of the privileged fragments responsible for their affinity.[67]

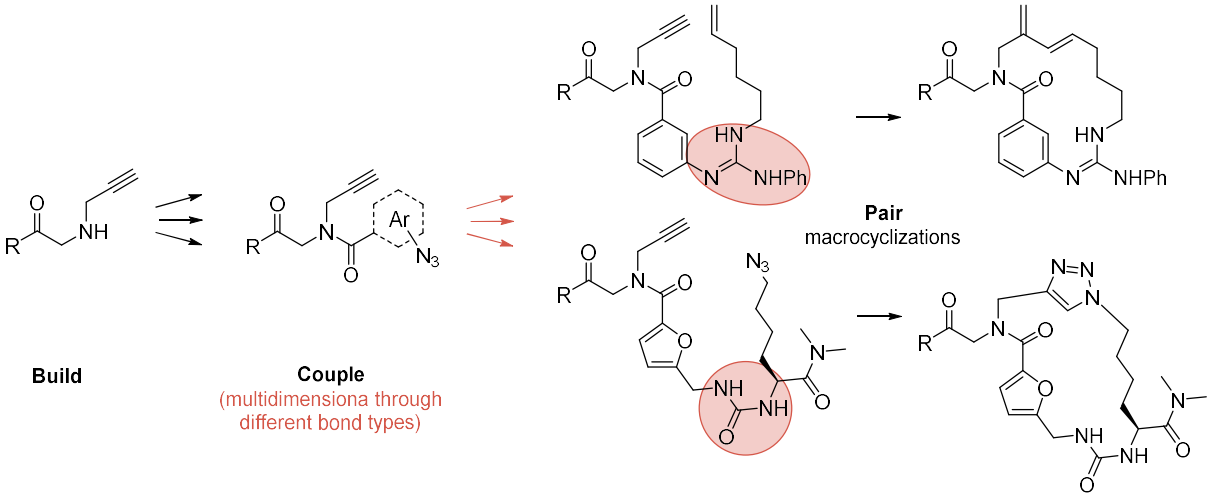


Scheme 11: Merging approaches in fragment-based drug design of the Mcl-1-inhibitor **63** (A)[65] and the experimental design approach for the glucokinase activator **66** (B)[67].

Despite huge leaps in structure elucidation of proteins have been made in the past years,[67] FBDD is relatively high in effort and has no guarantee to succeed in any of its required steps.

1.4.2 Diversity oriented synthesis

A compound collection, that is not geared towards FBDD, should contain a large number of structurally diverse molecules in order to effectively cover chemical space. Diversity oriented synthesis (DOS) is an approach, where simple synthetic building blocks are combined in a small set of reactions that create complexity through varying sequence and connectivity within the resultant molecules. DOS usually incorporate three conceptual steps: “build”, where building blocks are generated to then be connected intermolecularly in the “couple” phase. In the final “pair” phase, different functional groups are then linked intramolecularly via orthogonal chemical transformations. In an approach to generate a library of macrocycles via DOS, Spring *et al*. started with alkyne starting materials and proceeded with two coupling-phase steps (Scheme 12). In the first step, diverse aryl substituents containing a terminal azide, were connected to the starting materials. In the second coupling-step, the diverse reaction profile of the azide was exploited to create different linking groups to the next building block. Head to tail macrocyclization served as the final pairing step and was performed via different reactions – depending on the final building block (Scheme 12).[68–70]



Scheme 12: The build/couple/pair approach of DOS in the synthesis of diverse macrocycles by Spring *et al.*[70]

1.4.3 The Role of Natural Products in Drug discovery

While DOS approaches are very efficient in synthesizing large libraries, the molecules generated often lack biological relevance. Many concepts for the generation of bioactive small molecules therefore lean on natural products for inspiration. An indication for the success of such strategies, is that 32% of all FDA-approved small molecule drugs in the time period from 1981 to 2019 are either natural products, or direct derivatives of such (Figure 8).[62]

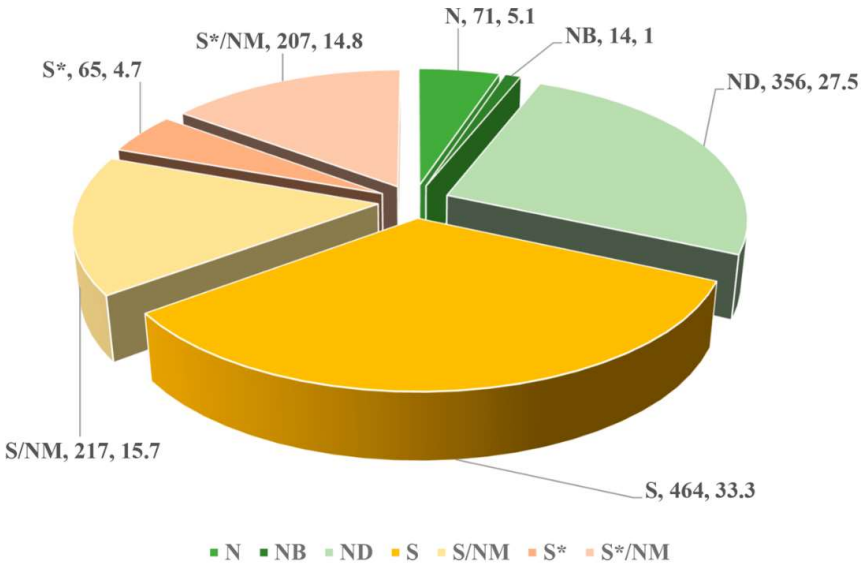
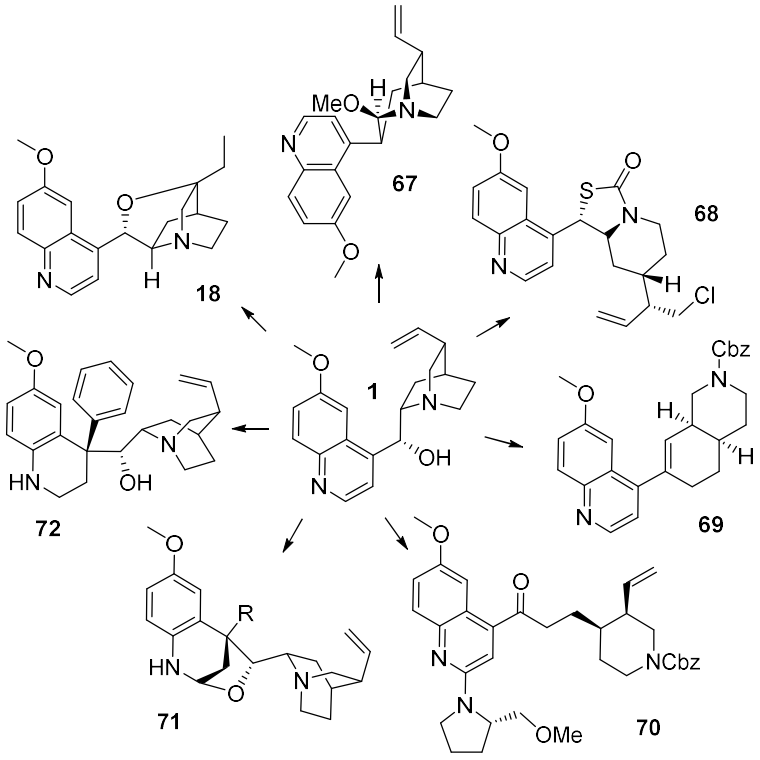


Figure 8: Total number and percentage of all 1394 approved small molecule drugs from 1981 to 2019 sorted by their sources. N: unaltered natural product, NB: botanical drug, ND: natural product derivative, S: synthetic drug, S*/NP synthetic drug from NP pharmacophore, S*/NM: synthetic but mimic of natural product.[62]

The reason for the frequent success of this approach, might be rooted in the coevolution of protein machineries and natural products as modulators of them. Moreover, NPs are created in a cellular context and in order to not perturb the system they are produced in, natural products have to be very selective protein binders in addition to exhibiting high affinity. Most natural products are used for indications that do not involve their natural target. Therefore, it is solely the discussed selectivity and prevalidated protein-binding-potential, that is relevant in the drug discovery context.[71–74]

1.4.4 Complexity to Diversity

The complexity to diversity approach (CTD), described by Hergenrother *et al.*, directly utilizes those complex natural product scaffolds which are readily available through extraction of plant or animal material. These are then subjected to ring distortion reactions to access diverse chemical matter that can be decorated with different functionality in following steps. The paradigm is, that the resultant molecules keep a lot of their natural product character but might hit new targets. Quinine has been in the focus of several CTS-campaigns (Scheme 13, structures **68**, **69**, **70**, **71**, **72**).[75] The rich history of cinchona alkaloids chemistry, however, holds several more examples of ring distortion products, that fit Hergenrother's criteria. Two examples developed by Hoffmann and coworkers are ring-expanded product **67** and cyclized oxazatwistane **18** (Scheme 13).[5]



Scheme 13: Different structures accessed through quinidine 1 in various complexity to diversity campaigns by Hergenrother and Hoffmann *et al*.[5,75]

Although Hergenrother *et al*.'s intriguing structures expand the known chemical space into an area most likely relevant for bioactivity, the chemistry used is complex, narrow and leans heavily on the availability of complex chemical feedstock.

1.4.5 Biology Oriented Synthesis and Pseudo-Natural Products

With BIOS (biology-oriented synthesis) and the pseudo-NP principle, Waldmann *et al*. have developed two main design approaches for novel bioactive molecules. Both concepts take the structures of natural products as an inspiration rather than using them directly as chemical matter.[74,76]

Biology oriented synthesis aims to connect structure analysis of proteins and structure analysis of small molecule protein binders. Protein structure similarity clustering (PSSC) is a methodology that is able to cluster proteins according to their structural similarity of their binding site subfolds. This way, similarity can be identified even if sequence homology is low. The scaffolds of NPs on the other hand, can be correlated via the SCONP (structural classification of natural products) principle.[77] Here, a systematic deconstruction of the ring systems of the Bemis-Murcko scaffolds of NPs is used to identify common substructures

which can be used for their classification in clusters. In pursuit of a synthetically accessible inhibitor of the cortisol producing enzyme 11βHSD1 the biologically unrelated phosphatase Cdc25A was identified as possessing a similar binding site via PSSC. Matching of two known natural product modulators of the two proteins via SCONP (dysidolide **73** and glycyrrhetinic acid **74** respectively), revealed bicyclic 3,4-dehydrodecalin as a common subscaffold. A library of 487 compounds based on this structure yielded, among others, the selective 11βHSD1-inhibitor **75** (Figure 9). Using this approach, relevant substructures of natural products can be identified and used to design radically simplified analogues.[74,78]

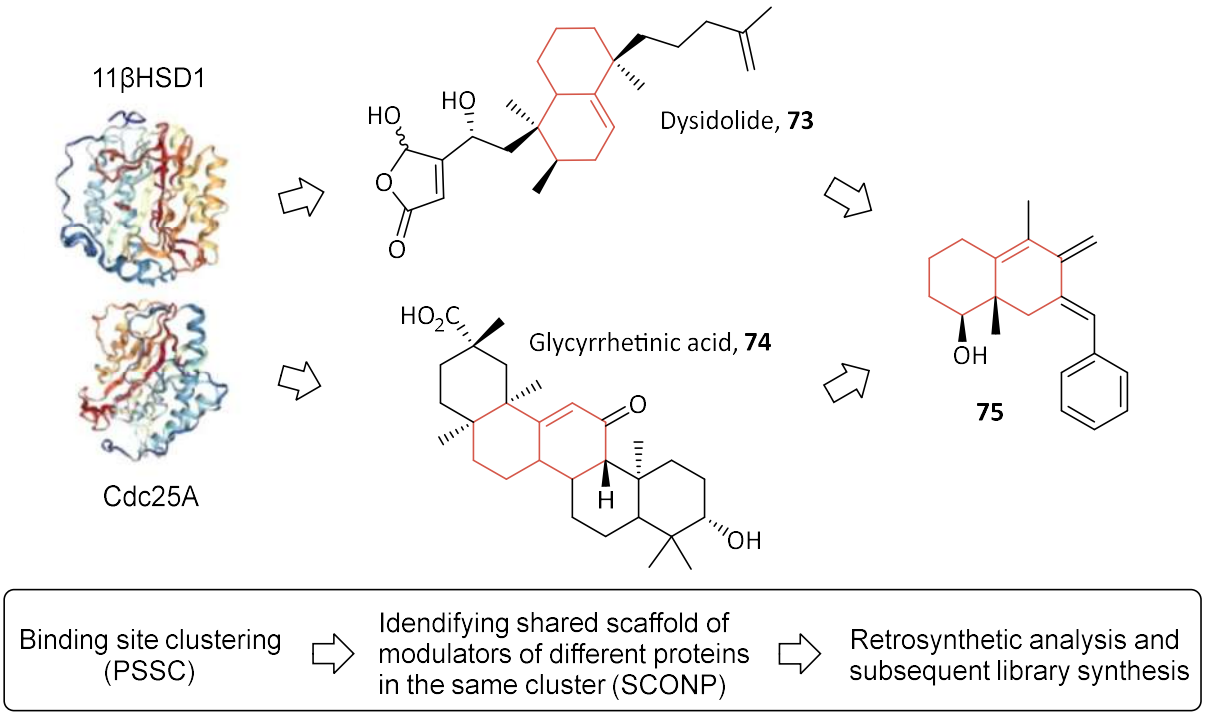


Figure 9: Schematic workflow of a BIOS project exemplified on the 11βHSD1-inhibitor 75.[74]

While this workflow provided an intuitive procedure for the simplification of NPs considered too complex for drug discovery projects, the structures generated exhibited similar biological profiles to their parent molecules. This was considered to be a drawback when it came to creating truly novel chemical matter with biological relevance.

Complimentary to BIOS, while utilizing many of the deductions from nature that led to its creation, the concept of pseudo natural products was recently introduced.[76] Analogous to the limited number of proteinogenic amino acids, nature uses the same core scaffolds again and again in different arrangements to build natural products. The PNP-approach aims at the unprecedented recombination these reoccurring NP-fragments in short complexity

generating reaction sequences. Relevant fragments, were initially identified by exhaustive deconstruction of the scaffolds contained in natural product data banks via an algorithm similar to SCONP and clustering them subsequently.[79] The combination of two such fragments of biosynthetically unrelated clusters constitutes an expansion of natural product chemical space (Figure 10). As NPs do not draw their properties exclusively from their fragments, but their three dimensional and often rigid arrangement, many connection types found in natural products were also used to generate pseudo-NPs.

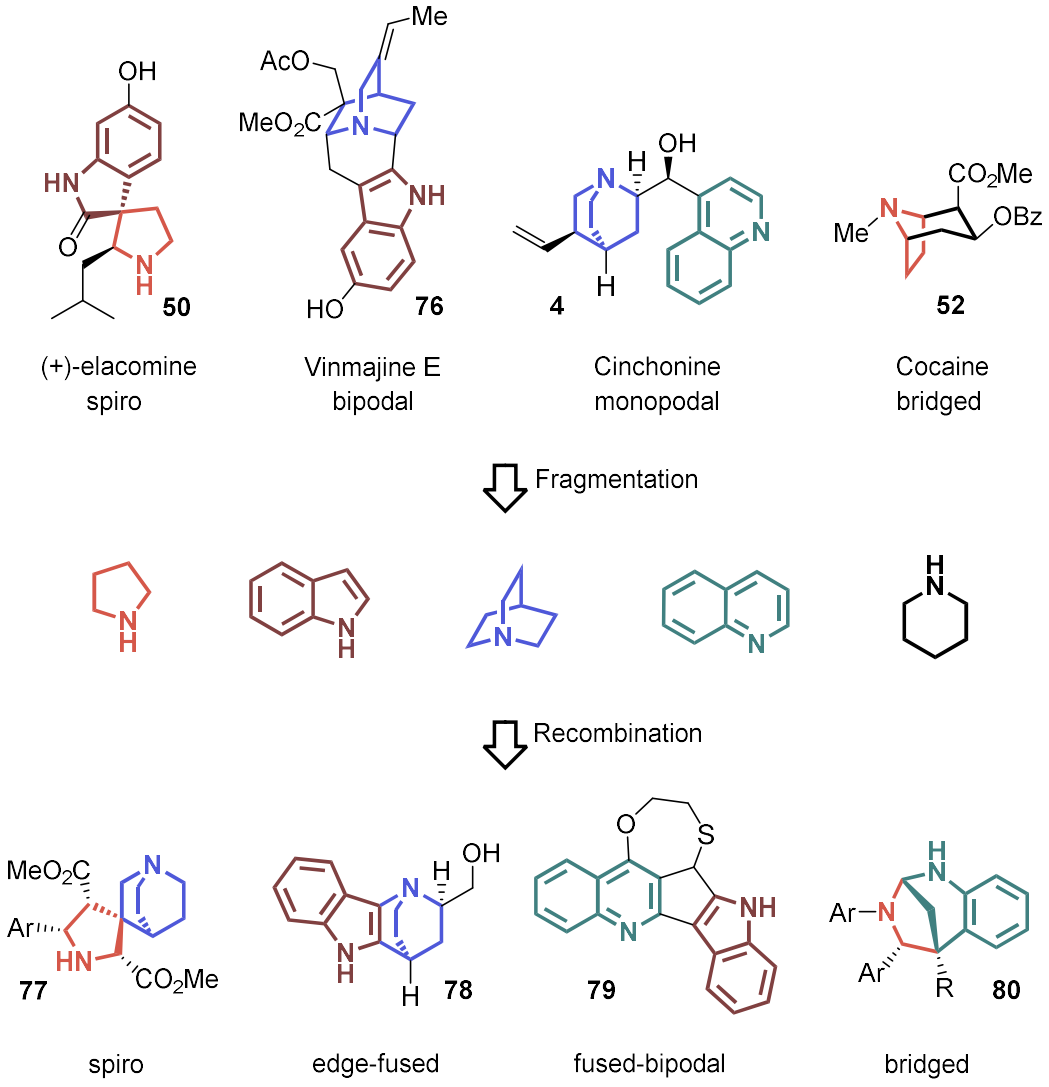


Figure 10: Simplified concept of PNP-design in regard to fragments and connection type. Compound **77** is hypothetical, **78** is from an real PNP-campaign, **79** and **80** are compounds synthesized by other research groups accidentally fitting the concept.[14,80,81]

Elaborate studies were undertaken to investigate the influence of the type of connection of the same fragments[82] or the relative influence of fragments on the overall bioactivity profile.[83] Over the past years, this approach led to the identification of PNPs that inhibit glucose uptake[84], cytokinesis[85], autophagy[14] and others.

1.5 Identification of Bioactivity

Design approaches for molecules like Hergenrother's CTD and Waldmann's pseudo-NPs (Sections 1.4.4 and 1.4.5) claim to produce a higher percentage of bioactive molecules than approaches that do not draw their inspiration or starting materials from nature.[73,75,76] As the produced compounds are designed to be dissimilar to known NPs and to their parent molecules, this is difficult to prove. The plethora of biological targets and processes can not be assessed exhaustively and pseudo-NPs will most likely not hit the same targets as their parent fragments.[76,86]

The first solution to this problem is phenotypic assays. Here the compounds are not screened against individual proteins, but for their ability to modulate a certain phenotype. Such assays can be performed in cells or even more complex systems like organoids. Not only does this approach inherently preselect molecules for their membrane permeability and interaction with metabolic processes of the cell, it can also identify compounds that act up- or downstream of a known target within a biological pathway. Phenotypic assays might even identify compounds that lead to the degradation of a protein in the given pathway without a direct binding event. The exact mode of action of the bioactive molecule identified in a phenotypic assay might be initially unknown, but such assays account for the complexity of a biological system better than biochemical setups.[87,88]

However, the type of readout limits the number of pathways a phenotypic assay can monitor. In order to identify a potential bioactivity of a radically new compound, the ideal assay would show no predisposition towards any kind of target or phenotype. The cell painting assay is such an experiment. This assay monitors the morphological changes in cells via five-channel fluorescent microscopy. Mitochondria, nuclei, nucleoli, golgi, cytoskeleton, cell membrane and the endoplasmic reticulum are stained via six dyes which can be assessed individually via the five different channels of the microscope. Analysis of the morphological changes via an algorithm that translates the relative distances and sizes of the stained structures into a multiparametric fingerprint in the form of a barcode. The barcode of a novel molecule can then be matched with the barcodes of reference compounds. If compound treatment induces morphological changes, this assay can quickly prove a biological effect and provide an initial target hypothesis to guide more detailed investigations.[82–84,87–89]

A combination of diverse phenotypic assays and the cell-painting assay provides a good likelihood of identifying a potential bioactivity of novel molecules. Since the MPG-associated compound management and screening center (COMAS) could provide this service, the foundation for testing the pseudo-NP design principle was given.

The substance class discussed in this work, was tested in diverse assay systems including cell-painting. While cell painting struggles with the identification of bioactivity that does not involve morphological changes, the polar opposite is true as well. Modulation of a cellular process that e.g. remodels vast portions of the cell, leads to morphological changes that are too great for the generation of a fingerprint which would be suitable for a comparison to references. While the identification of the mode of action of such potent inducers of morphological change might be complicated by this, the cell painting assay is ideal for their initial identification. Moreover, processes which are shared physiological responses of to stress, might be dominating the fingerprint, while the exact sources of the stress remain hidden.

1.5.1 Assaying Autophagy

A lot is left to uncover when it comes to the complex cellular mechanisms of autophagy (Greek for self-eating). Since the discovery of the lysosome by de Duve over 60 years ago and the description of the first ATG-proteins (autophagy-related proteins) by Ohsumi in the 1990s, it has become apparent, that autophagy is a vast intertwined network of highly adaptive and selective degradation pathways. The early paradigm of an unselective mechanism which recycles nutrients in times of starvation has shifted. Autophagy is now known to selectively recruit cargo via adapter proteins and facilitate elimination of damaged mitochondria (mitophagy), protein aggregates (aggrephagy) and to even share parts of its machinery with endocytosis and anti-bacterial/anti-viral responses.[90–92] This makes these processes excellent targets for tackling various disease phenotypes including neurodegenerative illnesses based on protein aggregates.

Starvation or growth factor mediated canonical autophagy is regulated by the master switch mTOR (mammalian target of rapamycin). Inhibition or downregulation of this PI3K activates autophagy via the ULK1- and PI3KC3 complex I, which trigger the formation of the phagophore in the cytosol or at the membrane of the rough ER (Figure 11). The phagophore is a double-

membrane structure, that engulfs autophagic cargo during its maturation into an autophagosome. This core autophagic structure is then delivered along microtubules to lysosomes or vacuoles which contain degradative enzymes. Fusion of the two compartments will initiate digestion of the autophagic cargo and thus rid the cell of contaminants while recycling their building blocks.[90]

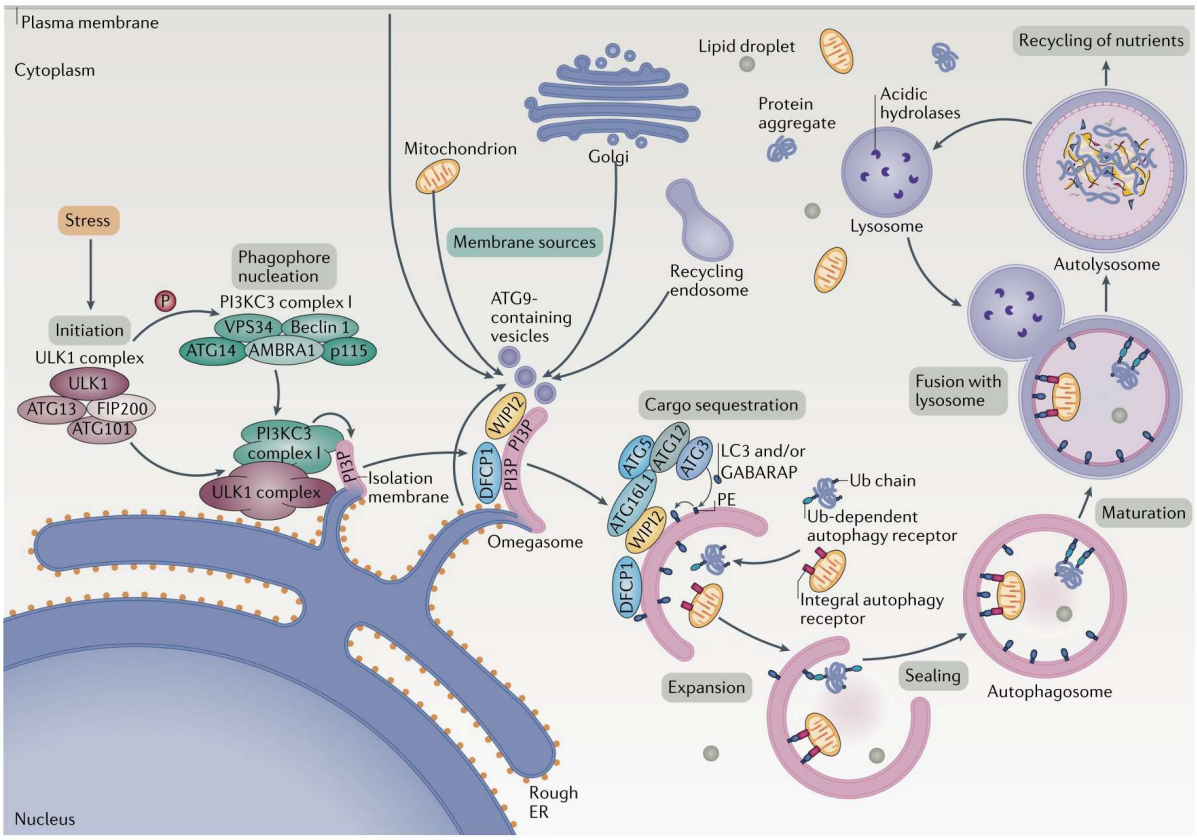


Figure 11: Canonical autophagy pathway; taken from Dikic *et al*.[90]

At the center of autophagic processes is the ATG8 protein family. The human genome contains seven of these ubiquitin-like proteins (LC3A, LC3B, LC3B2, LC3C, GABARAP, GABARAPL1, and GABARAPL2). Unlike ubiquitin, which is attached to lysine sidechains of proteins via their C-terminus, ATG8s are attached to the amino headgroups of membrane lipids of selected cellular compartments. Phosphatidylethanolamine is the predominant lipid anchor, but a linkage to phosphatidylserine has been reported as well.[91,92] In addition to the structural similarities of the ATG8 family to ubiquitin, their conjugation machinery (ATG7, ATG3 and ATG12-ATG5-ATG16L1) works analogously to the E1-E2-E3-complex required for ubiquitinylation. First, a C-terminal glycine residue of ATG8 proteins is exposed via proteolytic cleavage by ATG4. This can happen in the cytosol or by removing already bound ATG8s from

the surface of lipid vesicles, rendering the conjugation-process reversible. The proteins are then transferred to the cysteine residue of the E1-like ATG7 protein, which in turn transfers ATG8s to the E2-like ATG3. The E3-like complex ATG12-ATG5-ATG16L1 then catalyzed the transfer of an ATG8 to a lipid headgroup. Different processes are known to recruit this conjugation machinery and ATG8 decoration is not exclusive to autophagic processes.[91]

The exact roles ATG8 proteins play, are intrinsically not well defined nor are they well understood. Mainly it is believed their accumulation on membranes serves as a binding platform for both autophagy related proteins up- and downstream of ATG8 conjugation, thus creating positive feedback loops. This mode of action is, although not exclusively, mediated by so called LIRs (LC3-interacting-regions) in the recruited proteins. Among the attracted machinery are factors important for membrane remodeling, transport along microtubule and lysosome-fusion. ATG8 proteins were also shown to induce membrane curvature and render the inner autophagosomal membrane a target for lysosomal degradation. They also serve as important binding partners of selective cargo-receptors.

The presence of ATG8s on single membrane structures was described for a process termed LC3-associated phagocytosis (LAP), as well as a stress response to unsaturated fatty acids.[91–94] Both processes are independent of the initiation-complexes required for canonical autophagy which shows the versatility of autophagy related processes and the ATG8-machinery specifically.

The dense conjugation of ATG8 proteins to vesicle structures and the plethora of autophagy related processes they are involved in, make them an ideal marker in an initial phenotypic assay geared towards the identification of tool compounds that modulate the vast network that is autophagy.

2 Aim of the Thesis

With new biological mechanisms being discovered continuously, the identification of selective modulators of these processes holds great promise for the treatment of illnesses. In modern HTS campaigns, millions of potential ligands can be screened against a target or phenotype. Next to the refinement of hit compounds, one of the challenges of medicinal chemists is to improve the biological relevance of the molecules used in the initial screen. The design concept of pseudo-NPs aims to provide a solution to the latter.

Natural products have proven to be a great source of inspiration for drug design, as they are bioactive substances that were preselected by evolutionary processes to be potent and selective protein binders.[62,72] Some structural elements were found to reoccur again and again in different arrangements within NPs with distinct bioactivity.[77,79] In the pseudo-NP concept, these prevalidated NP-fragments are recombined in unprecedented arrangements.[76,82]

With several promising reports already published,[14,59,95–98] the aim of this thesis is to further substantiate the validity of this approach and establish the design principle for the generation of biologically relevant chemical matter. Specifically, it was planned to expand the PNP concept to macrocycles as an unprecedented connection type of NP-fragments.

It was to be investigated, whether the spacial arrangement of key reactive groups within quinidine could be exploited to facilitate controlled macocyclization.[6,7] Macrocyclization was to be achieved via imine formation and subsequent [2+3] cycloaddition. This reaction would not only provide the resultant macrocycle with a proline-like structural element, but enable the unprecedented combination of a pyrrolidine- with a quinuclidine fragment.

The synthetic effort was to be combined with a thorough biological profiling of the novel compound class via the full range of phenotypic and morphological assays of the affiliated Compound Management and Screening Center (COMAS). This initial characterization would then be followed up by in-depth investigation of the mode of action.

3 Results and Discussion

3.1 Reaction Development

Inspired by Sanders *et al.* and Hoffmann *et al.*, a set of reaction conditions was sought, that would transform bifunctional amino-aldehyde derivatives of quinidine into macrocycles. This set of reactions would utilize the 1,3-dipolar cycloaddition of azomethine ylides to combine the cinchona scaffold with the natural product fragment pyrrolidine. The macrocyclization would either be an intramolecular one, as frequently described by Hoffmann, or an intermolecular one as described by Sanders (Figure 12).[6,7]

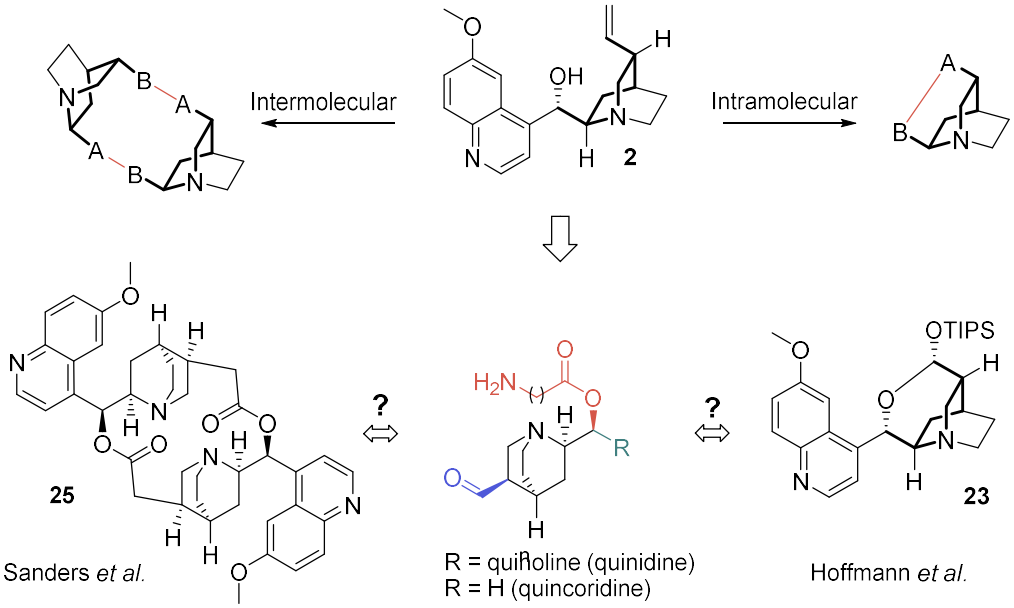
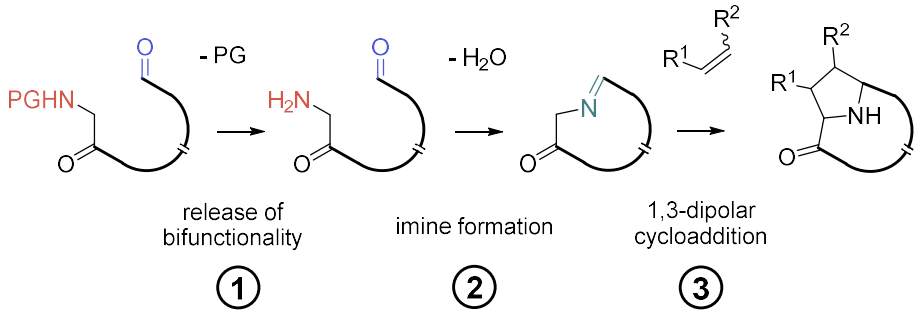


Figure 12: Early considerations in the design of a Cinchona-based starting material capable of 1,3-dipolar cycloaddition-mediated macrocyclization. Beginning with the pre-oriented reactive handles on the quinuclidine core scaffold of quinidine or quincoridine derivatives, two modes of cyclization could occur between bifunctional derivatives.

Regardless of which mode of macrocycle formation was to be achieved ultimately, four goals needed to be met: 1. Design of a bench stable, bifunctional starting material, where one or both reactive handles were protected and could be released under the conditions used for imine formation/cycloaddition or conditions that would prevent premature imine formation (Scheme 14 step 1); 2. Identification of a suitable ring size in combination with reaction conditions, where imine-facilitated macrocyclization would occur and, moreover, be favored over oligomerization (Scheme 14 step 2); 3. Tailoring the 1,3-dipolar cycloaddition to the macrocyclic azomethine starting materials (Scheme 14 step 3).



Scheme 14: Conceptual steps necessary in a macrocyclization based on a 1,3-dipolar azomethine and an external dipolarophile.

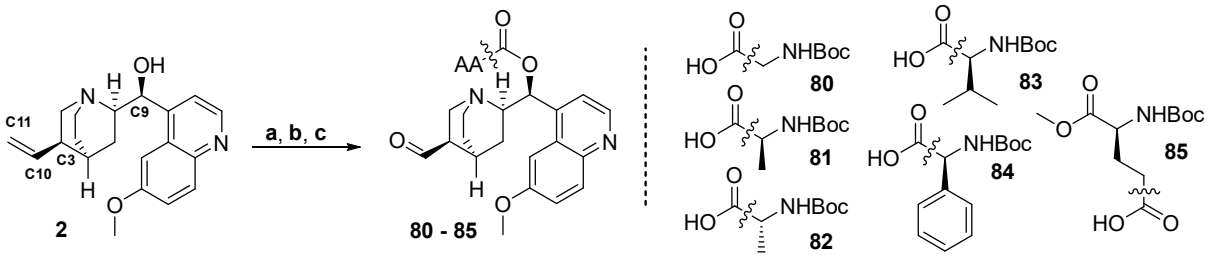
Schiffs' bases are significantly more stable in benzylic position.[99] Therefore, aliphatic imines such as diimine macrocycle **100** would needed to be generated *in situ* and then trapped by 1,3-dipolar cycloaddition (Scheme 17). In order to precisely control the imine-formation, the two reactive handles should be released from a bench-stable starting material at the start of the reaction sequence. Conditions for imine formation should be suitable for trapping via the cycloaddition reaction.

The Boc-protecting group was chosen to mask the amino acid amine, as its removal is traceless and would leave the released primary amine as an ammonium salt.

3.1.1 Finding a suitable starting material

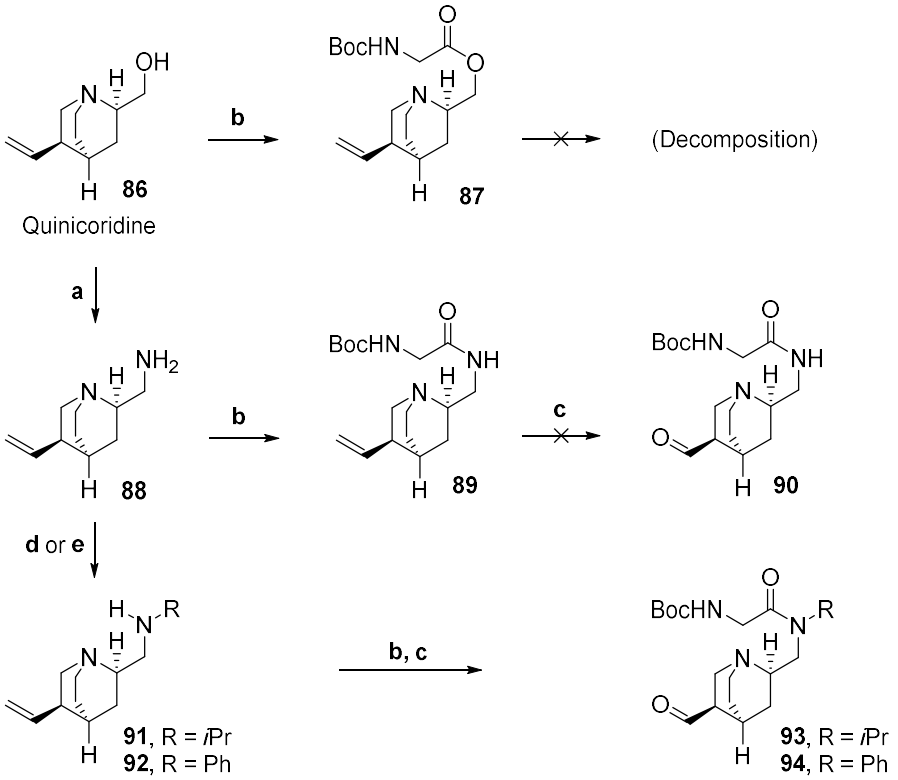
Following a set of reactions published by Braje and Hoffmann, the C10 double bond could be transformed into an aldehyde, while conserving the configuration of the C3 stereocenter.[7] The acetyl protection of the C9-hydroxyl group, required for an efficient process, could be substituted conveniently by an N-protected amino acid ester. This way, a variety of starting materials with varying C9-hydroxyl substituents could be generated under Steglich esterification conditions. Subsequent Sharpless dihydroxylation of the C10/C11 double bond and sodium periodate-mediated diol cleavage produced the desired carbamido aldehydes **80** – **85** in three steps (Table 1, conditions a,b and c).

Table 1: Synthesis of an initial set of carbamido aldehydes **80** – **85** designed to probe tolerated ringsizes and potential α-substitution of the coupled amino acid. a) Boc-Gly-OH, DCC, DMAP (78-96%); b) OsO_4, $K_3[Fe(CN)_6]$, K_2CO_3, H_2O (35-91%); c) $NaIO_4$, SiO_2 (84-93%).



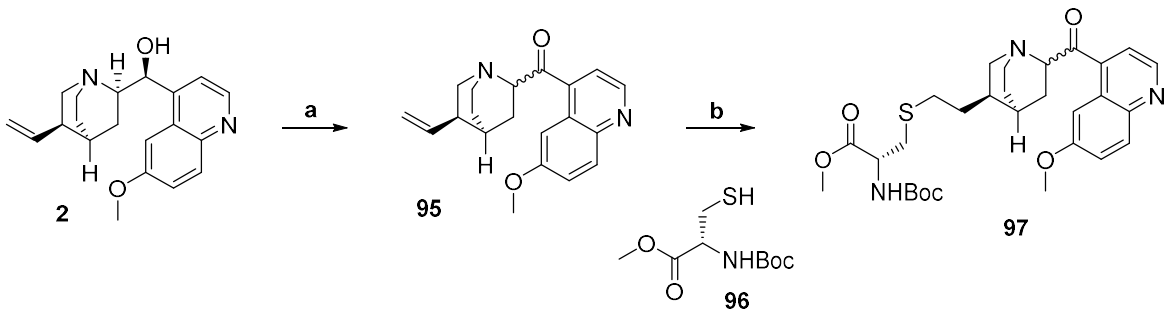
Quinidine			
Entry	**Amino Acid**	**Product**	**Yield o3s [%]**
1	Boc-Gly-OH	**80**	47
2	Boc-L-Ala-OH	**81**	21
3	Boc-D-Ala-OH	**82**	49
4	Boc-Val-OH	**83**	31
5	Boc-Phg-OH	**84**	39
6	Boc-Glu-OMe	**85**	62

Further derivatives could be synthesized from the commercial quinidine-fragment quincoridine **86** (Scheme 15). Unfortunately, the corresponding C9-hydroxyl esters hydrolyzed to a significant extent within days after synthesis. The same observation was made with esters of quinidine, when the C9 stereocenter was inverted (via treatment with tartaric acid after mesylation[100]).



Scheme 15: Synthesis of quincoridine-based carbamido-aldehydes. A) generation of unstable quincoridine esters; B) quincoridine amides did not produce diols under Sharpless dihydroxylation conditions and aldehydes could not be cleanly separated from the shown reaction; C) alkylated amides **91** and **92** yielded the desired aldehyde derivatives **93** and **94**. a) PPh_3, DIAD, DPPA, 0°C to RT, THF, 2h – then PPh_3, 16h – then H_2O, 4h (78% o2s); b) DCC, Boc-Gly-OH, DMAP, CH_2Cl_2, 16h (amide **89** 67%, **91** R=*i*Pr 93%, **92** R=Ph 72%); c) OsO_4, $NaIO_4$, $H_2O/CHCl_3/tBuOH$ (R=*i*Pr 56%, R=Ph 35%) d) Acetone, $NaBH_3CN$, MeOH, 24h (79%); e) Phenyliodite, CuI, K_2CO_3, L-Proline, DMSO, 60°C, 16h (93%);

For quincoridine this was circumvented via substitution of the ester bond by an amide bond. The C9-amine was synthesized by generating the C9-azide via Mitsunobu reaction and subsequent Staudinger reaction (Scheme 15).[101] Amide coupling was performed under the aforementioned Steglich conditions. Dihydroxylation of glycine amide **89**, however, did not proceed smoothly and **90** could not be isolated in sufficient quantity or purity. Hence, primary amine **88** was alkylated prior to coupling to Boc-glycine. This could be achieved by Ullmann amination with iodobenzene and by reductive amination with acetone.[102] Resultant **91** and **92** could be transformed into their corresponding aldehydes **93** and **94** smoothly in a one-step reaction after amide coupling with Boc-glycine.



Scheme 16: Synthesis of inversely oriented carbamido ketone **97** via C9 oxidation and thiol-ene reaction. a) KO*t*Bu, benzophenone, toluene, reflux, 16h (57%); b) Boc-Cys-OMe, DMPA, hv (365 nm), DCM, 30h (45%).

An additional quinidine derivative was synthesized via C9 oxidation and subsequent thiol-ene reaction with cysteine derivative **96**. [103,104] This gave the mixed epimers **97** (Scheme 16).

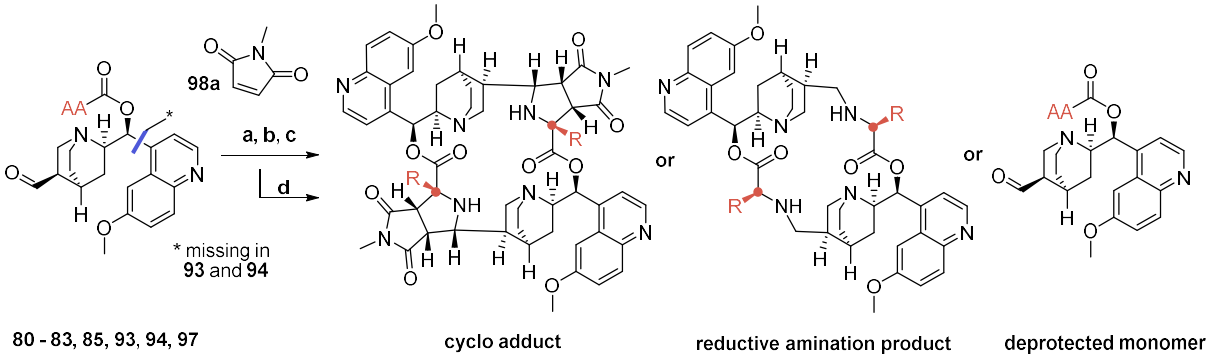
All quinidine derivatives were tested for their capability to react in the desired 1,3-dipolar cycloaddition using methylmaleimide and silver triflate – a test system identified to be one of the most robust among all 1,3-dipolar cycloadditions of azomethines. The use of cyclic and symmetrical maleimide dipolarophiles prevented the formation of regioisomers. If after 16 h no cycloadduct was detected and the starting material was not consumed, a drop of methanol and an excess of sodium cyanoborohydride and were added at 0°C. Using this workflow it could be ascertained whether the given system did form the prerequisite imine intermediate but did then not react further in the desired cycloaddition. The reduction step was necessary, as the labile imine itself could never be detected on HPLC. The results showed:

1. **85, 93, 94** and **97** were not capable of forming any detectable imine- or cycloaddition adducts (Table 2, entries 5 to 7).

2. C-terminally coupled α-substituted amino acids **81 – 85** did form dimeric imine macrocycles, but did not react under 1,3-dipolar cycloaddition conditions (Table 2, entries 2 to 4);

3. **80** could successfully produce **101a** via the dimeric imine **100**.

Table 2: Screening experiments for the identification of suitable macrocyclization conditions via imine-formation and 1,3-dipolar cycloaddition. The data in this table are produced using conditions from the already optimized reaction sequence: a) 10% TFA in DCM, 90 min; b) 3 eq. Et_3N, $MgSO_4$, MeCN (40 µM), 15 min; c) 0.1 eq. AgOTf, 1.5 eq. *N*-methylmaleimide, MeCN (30 µM), 16h; d) addition of 10 eq. $NaCNBH_3$, MeOH, 0 °C. Yields are isolated yields of diastereomeric mixtures.



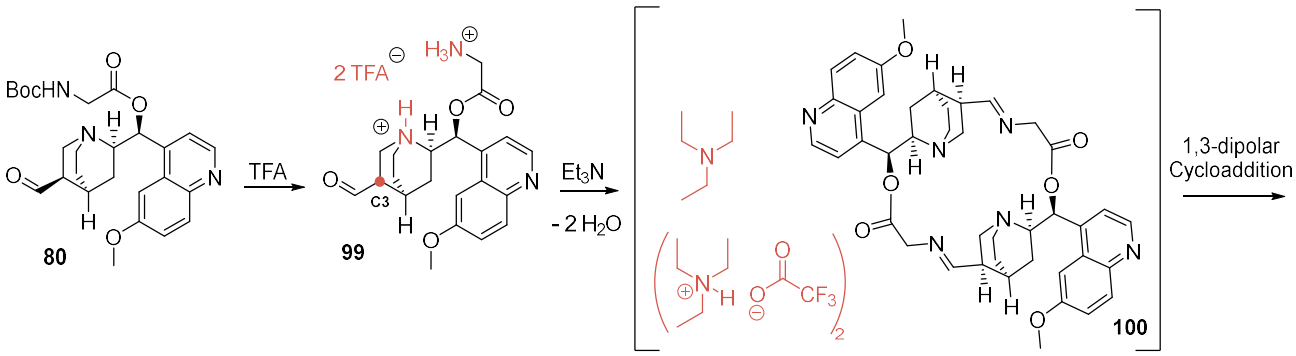
Entry	Amino Acid Ester	Ringsize	Cycloaddition Yield	Red. Amination Yield
1	Boc-Gly, **80**	20	51 %	65 %
2	Boc-L-Ala, **81**	20	-	41 %
3	Boc-D-Ala, **82**	20	-	78 %
4	Boc-Phg, **83**	20	-	67 %
5	Boc-Glu, **85**	24	-	deprot. monomer
6	**93**, **94**	20	-	deprot. monomer
7	**97**	22	-	deprot. monomer

3.1.2 Optimization of reaction conditions

The optimization of the three-step one-pot reaction sequence proved to be a complex endeavor because of the many factors important to the different consecutive reactions involved.

The initial deprotection step proceeded cleanly in a 10% mixture of TFA in dichloromethane within 90 min. Less TFA resulted in significantly longer reaction times, while harsher reaction conditions were avoided to prevent any chance of epimerization. The reaction was performed with low compound concentration, to exclude the possibility of oligomer formation at this stage. Unfortunately, the treatment with TFA epimerized the C3 stereocenter, which is likely the most prominent factor in causing the relatively low yields produced by the reaction sequence. TFA was removed under vacuum and via additional co-evaporation with DCM. The resultant species from this step is likely a di-TFA-salt with residual TFA potentially present in the reaction vessel (Scheme 17).

The following imine formation is a process, that optimally takes place under anhydrous conditions and close to neutral pH under acid or base catalysis.[47,99,105] The addition of an organic base transforms the TFA-salt into the free amine and concomitantly creates buffered conditions (triethylammonium trifluoroacetate, Scheme 17). An excess of base is added, as basic conditions proved to be beneficial and are needed for the subsequent 1,3-dipolar cycloaddition. A minimum of three equivalents of triethylamine were required to produce cycloadduct. Given the likely existence of greater than two equivalents of TFA after the deprotection step, this suggests that the 1,3-dipolar cycloaddition can proceed with sub-stochiometric amounts of base. While this is in agreement with literature[50], greater excess of Et_3N proved to be beneficial (Entries 2 and 7-9, Table 4).

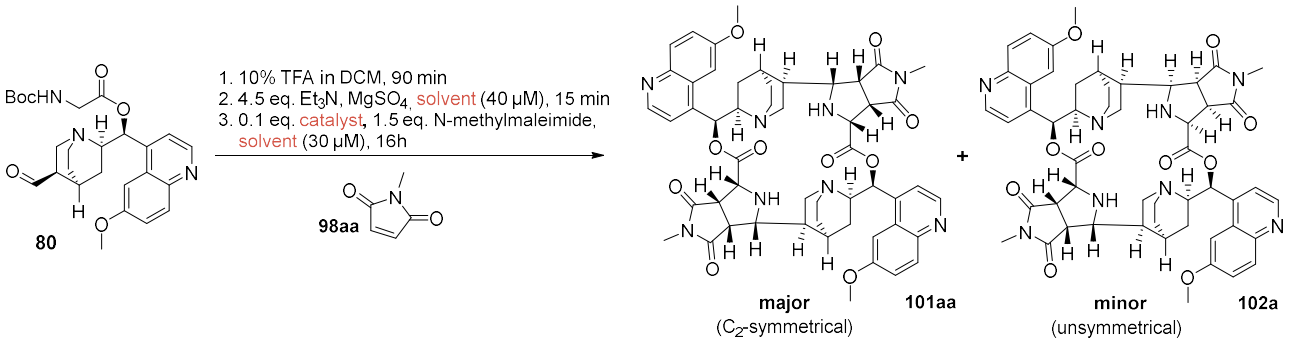


Scheme 17: Intermediates produced in the deprotection and subsequent imine formation step or the reaction sequence.

The exclusion of air and the usage of anhydrous solvents proved the most important for a successful reaction. This is likely due to the unstable nature, or the aliphatic imines involved. Gratifyingly these Schiff bases would form even without the addition of desiccants. However, their addition did affect the overall yield positively (Table 4). Moreover, respective desiccant did influence the selectivity of the 1,3-dipolar cycloaddition. Although slightly detrimental to the selectivity of the cycloaddition, addition of $MgSO_4$ proved to be valuable due to the increased yields (trimethyl orthoformate and molecular sieves did not show the same beneficial balance between yield and selectivity).

Optimization of the subsequent 1,3-dipolar cycloaddition identified dichloromethane as the optimal solvent and silver triflate as the best catalyst to achieve optimal yield and diastereoselectivity. Dichloromethane later proved to be an ineffective solvent for the reaction of quinidine derivatives and N-substituted maleimides other than *N*-methylmaleimide. However, the second-best solvent/catalyst combination, acetonitrile and silver triflate, was broadly applicable and thus the system of choice (compare Entries 1 and 4, Table 3,).

Table 3: Screening for a solvent/catalyst combination for 1,3-dipolar cycloaddition and imine formation.

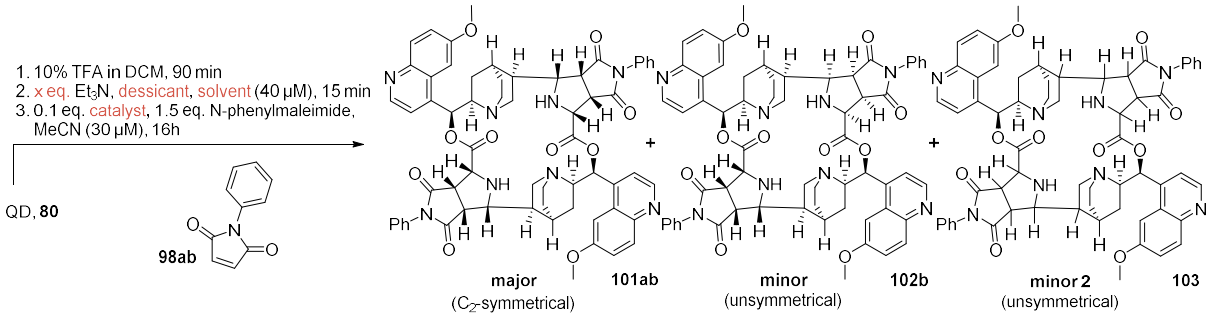


Entry	Catalyst	Solvent	Yield [%]	Isomer Ratio
1	AgOTf	DCM	50	21 : 1
2	AgOTf	DMF	39	13 : 1
3	AgOTf	THF	44	3.5 : 1
4	AgOTf	MeCN	51	19 : 1
8	$AgClO_4$	DCM	47	23 : 1 : 1
9	$AgClO_4$	MeCN	39	13 : 1
10	AgOAc	DCM	32	10.5 : 1 : 1
11	Ag_2O	DCM	37	10.5 : 1 : 0.2
12	$AgNO_3$	DCM	29	10.6 : 1 : 0.4

Dimerization of bifunctional molecules in solution is inherently problematic because oligomerization, polymerization or intramolecular cyclization are frequent side reactions. Intermolecular reactions can be suppressed by lowering the concentration. However, an initial intermolecular reaction is required for dimerizations. Collectively, these factors speak for a concentration window in which dimerization is favored over oligomerization or purely intramolecular cyclization. When intersecting a thermodynamically equilibrated dimerization processes, as described by Sanders et al., with a 1,3-dipolar cycloaddition, mixing rate as well as the rate and sequence of addition of reagents are important factors.

A lot of different approaches were taken over the course of the reaction development, which are not discussed in here. In order to show the trends identified, exemplary conditions were picked and repeated in the reaction of QD (**80**) and *N*-phenyl maleimide. This system was chosen for its high yield and lower selectivity towards the C_2-symmetrical diastereomer (**101ab**). Hence, not only trends in yield could be determined but also trends in selectivity (Table 4).

Table 4: Selected reaction setups and conditions for the reaction of *N*-phenyl maleimide and carbamido aldehyde **80** (QD).



Entry	Starting Materials	Additive	Et_3N	Catalyst	Yield	Isomer Ratio	Conv.	Comment
1	**80, 98ab**	$MgSO_4$	3 eq.	AgOTf	37%	9.6 : 2.6 : 1	-	Desiccant also at deprotection, then filtered before imine formation trimer formation
2	**80, 98ab**	$MgSO_4$	3 eq.	AgOTf	36 %	8 : 2.5 : 1	-	trimer formation
3	**80, 98ab**	$MgSO_4$	3 eq.	AgOTf	37 %	7.2 : 1.6 : 1	+-	AgOTf/maleimide as combined stock solution; trimer formation
4	**80, 98ab**	-	3 eq.	AgOTf	31%	7.5 : 1.9 : 1	-	
5	**80, 98ab**	$MgSO_4$	3 eq.	AgOTf	20 %	10.7 : 3.2 : 1	--	2x dilution trimer formation
6	**80, 98ab**	$MgSO_4$	3 eq.	AgOTf	6 %	n.d.	--	4x dilution
7	**80, 98ab**	$MgSO_4$	4.5 eq.	AgOTf	50 %	7.7 : 1 : 1. 1	++	
8	**80, 98ab**	$MgSO_4$	6 eq.	AgOTf	46 %	8.5 : 1 : 1.4	+	
9	**80, 98ab**	$MgSO_4$	9 eq.	AgOTf	51 %	6.1 : 1 : 1.1	++	
10	**80, 98ab**	MS 4Å powder (p)	3 eq.	AgOTf	37 %	8.8 : 2.8 : 1	-	Open-chain dimer; trimer formation
11	**80, 98ab**	MS 4Å balls (b)	3 eq.	AgOTf	32 %	9.8 : 2.6 : 1	-	Open-chain dimer; trimer formation
12	**80, 98ab**	MS 4Å powder	4.5 eq.	AgOTf	41 %	10.5 : 1 : 1.6	+	
13	**80, 98ab**	MS 4Å (p) , (R)-BINAP	4.5 eq.	AgOTf	< 9%	n.d.	+	
14	**80, 98ab**	MS 4Å (p), (S)-BINAP	4.5 eq.	AgOTf				
15	**80, 98ab**	MS 4Å (p)	4.5 eq.	$Cu(CN)_4OTf$	44 %	26.6 : 1 : 7.7	+	
16	**80, 98ab**	$MgSO_4$	4.5 eq.	$Cu(CN)_4OTf$	39 %	32.9 : 1 : 10.2	+	

Entry one of Table 4 shows the conditions methodology used at early stages of reaction development. Here, the deprotection was performed in a filter syringe and in the presence of $MgSO_4$. After completion, the desiccant could be filtered off via the integrated filter without any contact to ambient air. Entry two shows the corresponding conditions where solid $MgSO_4$ was already filtered off from the TFA solution before addition to the solution of the starting material.

The yields were virtually the same, while condition one seemed to show a slightly better selectivity towards the symmetrical adduct. Entry three probed the sequencing of the addition of maleimide- and catalyst stock solutions. When silver triflate is added after the maleimide, the selectivity dropped slightly and traces of trimer could be detected. In entry 4, no additional $MgSO_4$ was added for the imine formation step. While the yield dropped slightly, the selectivity slightly increased. This trend could be observed for many other quinidine/maleimide combinations as well. Entries 5 and 6 show the negative effect dilution (beyond 30 µM) has on the yield. An increased concentration lead to a drop in yield and more insoluble precipitate. Entries 7 to 9 show the effect of base-equivalents on yield and selectivity. In entries 10 to 12 activated 4 Å molecular sieves were used instead of $MgSO_4$. Here, powdered sieves showed better results than ball shaped ones. Entries 13 and 14 are exemplary for the use of ligands. A list of mono and bidentate as well as aliphatic and aromatic phosphine ligands led to the same, dramatic drop in yields. Even FeSulPhos, a ligand often among the best in any screening for 1,3-dipolar cycloaddition conditions of azomethine ylides, shut down the reaction. The fact, that this transformation did not accept liganded catalysts, might be due to two reasons. Firstly, the starting materials are cinchona alkaloids, which are among the most prominent ligand classes in all of organic chemistry. Together with additional external ligands, the catalytic species might not be able to form. Secondly, the macrocyclic bis-imine system might be sterically congested, so that a liganded silver(I) or copper(I) species can not efficiently coordinate the imines. Arguments in favor of latter hypothesis could be the relatively high stereoselectivities achieved with substrate control alone (compare Table 3). Entries 15 and 16 highlight, that copper(I) catalysts were generally inferior to silver(I) catalysts.

Lastly, dipolarophile classes were explored (Figure 13). The reaction conditions corresponded to Entry 1 in Table 4. Maleimides proved to be optimal, as they produced as little as two diastereomeric products formed, which were easily separable by preparative HPLC. The reaction did, however, proceed with a number of other classic dipolarophiles like cinnamates, nitro styrenes and fumarates. Although nitrostyrenes and fumarate-type reagents could produced relatively high yields, none of them showed a selectivity towards any one specific diastereomeric product, as observed for maleimides. The additional isomers complicated isolation immensely and made reactions with any dipolarophile other than maleimides operationally undesirable.

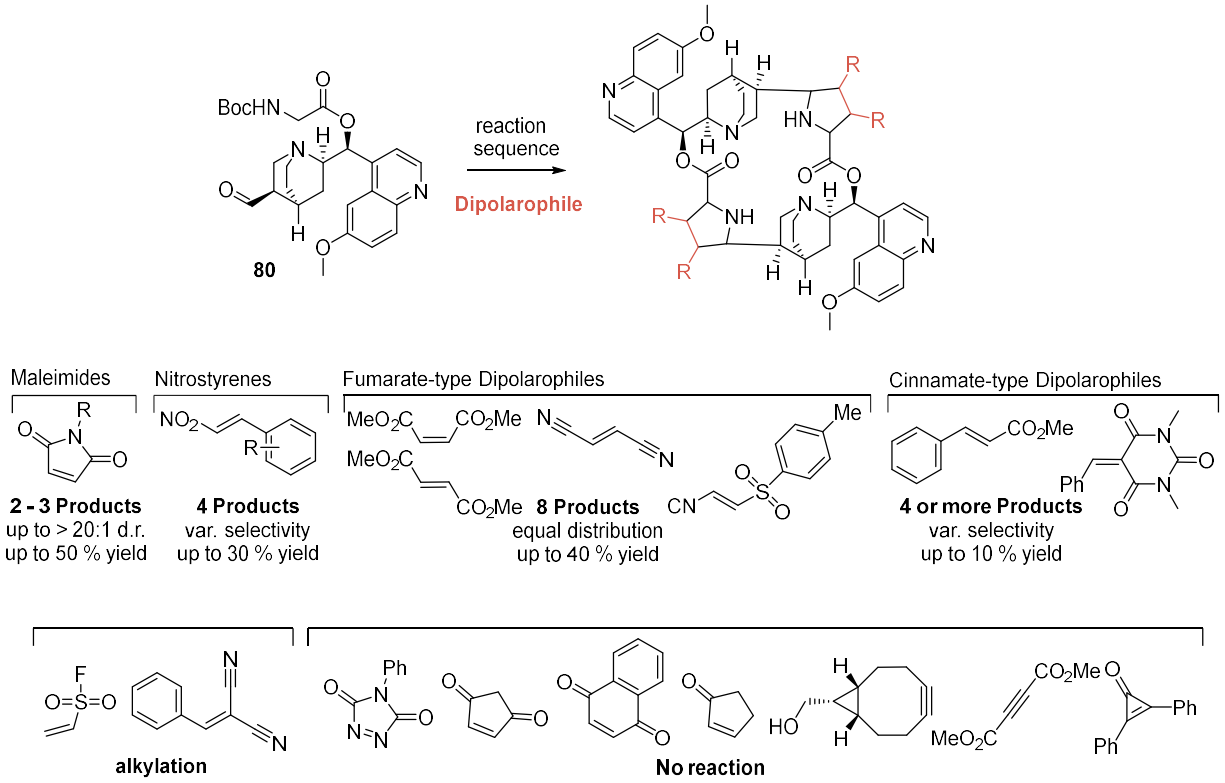


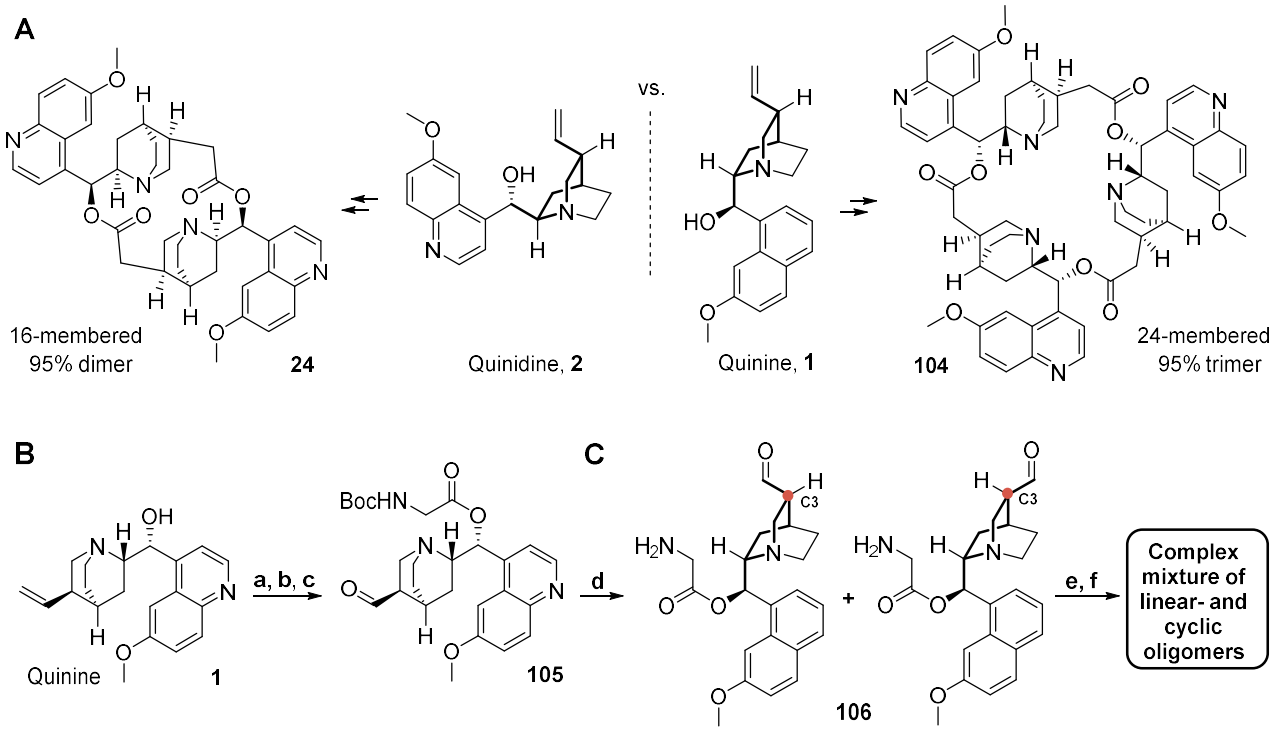
Figure 13: Scope of tolerated dipolarophiles in the reaction with **80**. Reaction conditions correspond to Entry 1 in Table 4.

In summary, the synthesis of a novel class of pseudo-natural, cinchona alkaloid-based, dimeric, 20-membered macrocycles could be developed. Furthermore, the scope was narrowed down to Boc-protected glycine containing quinidine derivatives as starting materials and *N*-alkyl maleimides as reaction partners.

The multitude of interdependent parameters within the developed three-step one-pot reaction sequence lead to the inevitable conclusion that this process could, by no means, be considered fully optimized. The developed methodology did, however, allow a relatively high reaction throughput and thus an efficient library synthesis of a novel class of highly complex pseudo-NPs.

3.1.3 Testing the templating effect hypothesis

The templating effect due to the orientation of functional groups on the quinuclidine core of the natural products quinidine (**2**) and cinchonine (**4**), as outlined in Section 1.1.1 and 1.2.1, was thought to be prerequisite for a successful macrocyclization. In order to put this hypothesis to a test, the developed reaction sequence was applied to **105**. **105** was synthesized from the naturally occurring quinidine diastereomer quinine, following the same tailoring towards the macrocyclization sequence as **80** (Table 1). In the experiments of Rowan and Sanders, quinine derivatives formed predominantly trimers (Scheme 18A).[43] Much like the dimer formation of quinidine derivatives, this observation appeared to be transferable. However, Rowan's and Sander's system differed from the macrocyclization sequence in this work in a crucial point. After Boc-deprotection the C3 stereocenter is epimerized (Scheme 18B). Epi-quinidine derivatives such as **106** likely form polymers or higher oligomers, that were never detected due to the purification sequence used (General Procedures, Supplementary Section). Here, the reaction mixture was filtered through an HPLC-filter, which removed any particle larger than 200 nm. This includes insoluble oligomers and polymers. The natural C3 epimer forms the isolated dimers in the same equilibrium. Quinine derivatives, however, are already prone to from higher oligomers due to the orientation of their quinuclidine substituents (Section 1.2.1). The corresponding C3 epimers, following the deduced logic, are more likely to form linear polymers (Scheme 18). Both species being present in the same reaction, likely leads to even more complex adduct combinations.



Scheme 18: Extension of the developed reaction sequence from quinidine starting materials to quinine starting materials. A) Comparable systems by Sanders *et al*.; B) Synthesis of quinine starting materials; C) Macrocyclization sequence; a) Boc-Gly-OH, DCC, DMAP (*58%*); b) OsO_4, $K_3[Fe(CN)_6]$, K_2CO_3, H_2O (*88%*); c) $NaIO_4$, SiO_2 (*95%*); *d*) 10% TFA in DCM, 90 min; e) 4.5 eq. Et_3N, $MgSO_4$, MeCN (40 µM), 15 min; f) 0.1 eq. AgOTf, 1.5 eq. *N*-methylmaleimide, MeCN (30 µM), 16h.

The reaction was performed with and without the presence of $MgSO_4$, as well as three different base concentrations each. All six reactions showed the same outcome. While quinidine derivative **80** produces a dimeric adduct in a diastereomeric ratio of 19:1, quinine derivatives give a complex mixture of linear and cyclic oligomeric cycloadducts (Supplementary Section). In addition, a white precipitate formed in the reaction vessel which likely corresponded to insoluble polymeric adducts.

This experiment further substantiated the hypothesis of the importance of the templating effect observed by Rowan and Sanders[6] for the newly developed reaction system. It also excludes quinine derivatives from the scope of the described macrocyclization sequence.

3.2 Structure elucidation

3.2.1 Numbering

The numbering of the macrocycle is shown exemplary for **107a** and **108a** (Figure 14A). It is analogous to the numbering for quinidine first introduced by Rabe et al. (Figure 1A), where the quinoline portion of the molecule has a separate numbering pattern.[8] The macrocyclic core and all heterocycles directly annulated to it, are numbered consecutively in a clockwise fashion and according to IUPAC rules (Figure 14A and B). Quinoline rings and succinimide substituents are numbered separately in a clockwise fashion starting with the quinoline nitrogen. The hemispheres are separated by the ester bonds. The numbering of substituents of the macrocyclic core (quinoline and succinimide substituent) restarts for the second hemisphere and identifies them by an added apostrophe. Protons on prochiral methylene groups on the quinuclidine could usually be differentiated and are given the labels a or b (Figure 14C).

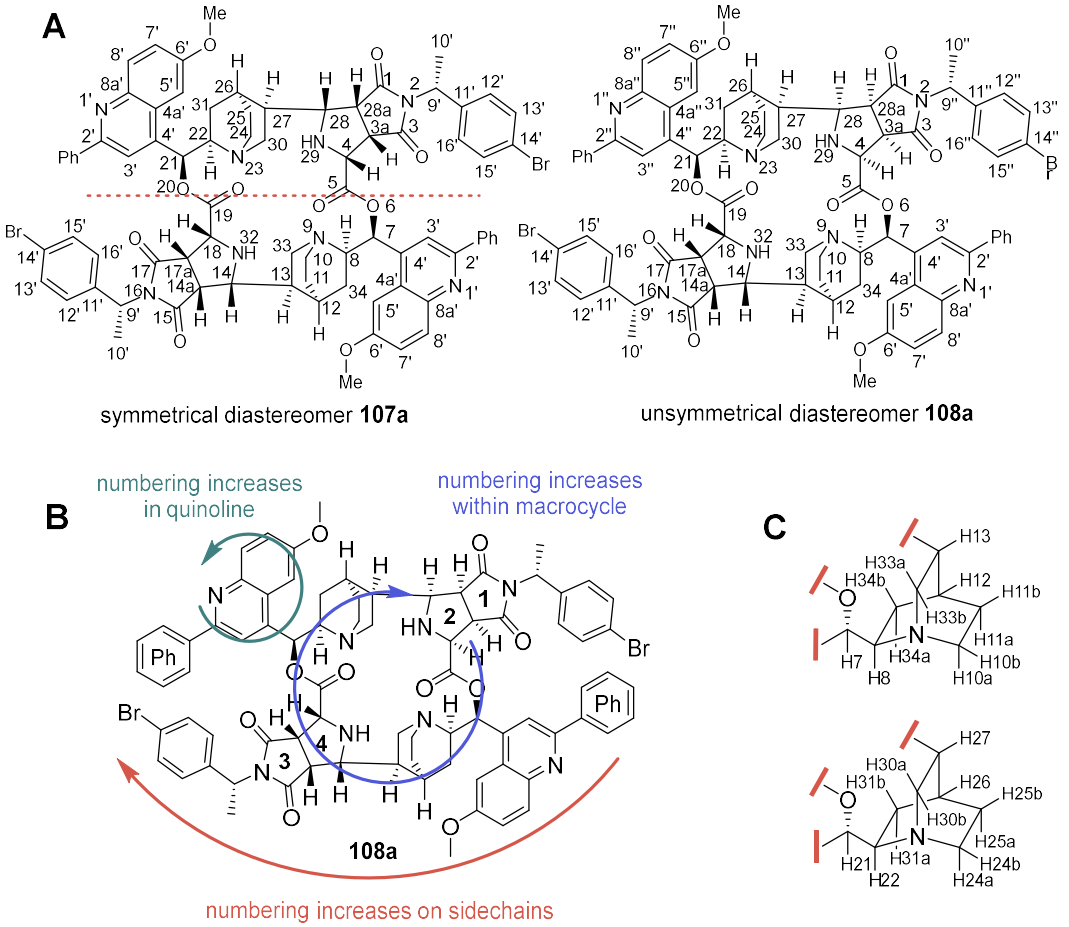


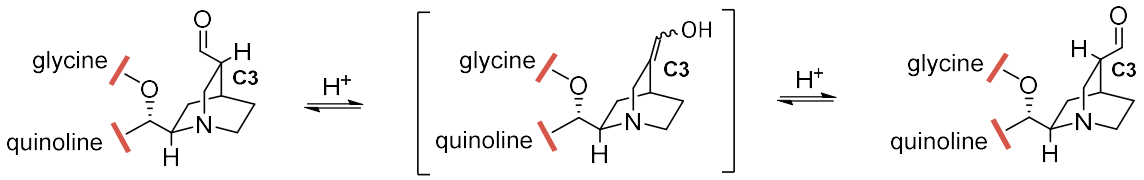
Figure 14: Numbering scheme of Cinchona Macrocycles. A) Numbering pattern of quinidine; B) Schematic numbering pattern; C) Numbering scheme of symmetrical **107a** and unsymmetrical **108a**; D) Numbering of prochiral quinuclidine protons.

3.2.2 Possible Configurational Outcomes of the Developed Reaction Sequence

The optimized reaction sequence yielded mainly only two diastereomeric products. These compounds were clearly distinguishable by their NMR spectra. In the major product, the NMR-signals of the protons of both hemispheres of the macrocycle eclipsed each other perfectly, which was a clear indication, that these molecules were of C_2-symmetrical nature. The minor diastereomer showed a clear splitting of these signals on almost every proton, which indicated that these molecules were unsymmetrical dimers.

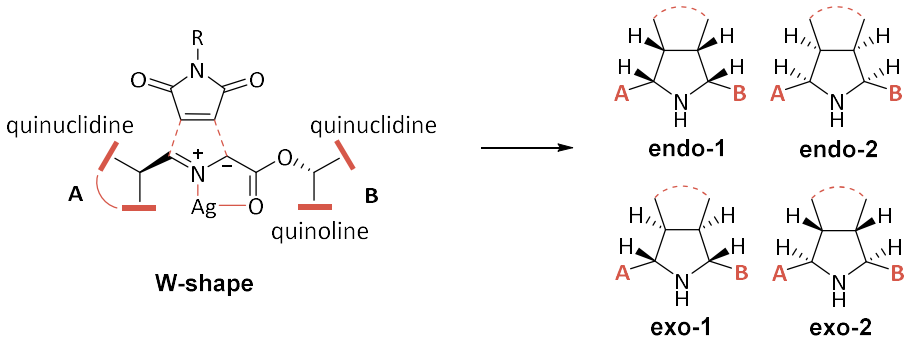
To ascertain the configuration of the produced dimers, all possible configurational outcomes of the reaction sequence need to be considered:

1. The stereocenter in alpha position to the aldehyde (C3) of the quinidine derived starting materials (compare Scheme 18) can epimerize. This could be observed under diol-cleavage-conditions and has been reported before.[7] Keto-enol tautomerism is accelerated under acidic conditions and should lead to complete epimerization under Boc-deprotection conditions, which constitute the first step of the reaction sequence (Scheme 19). Imine-enamine tautomerism during the second step of the reaction sequence is also a viable pathway for the epimerization of one or both C3-stereocenters. Epimerized monomers should favour the formation of linear oligomers over dimers, but the formation of any combination of C13 and/or C27 diastereomeric dimers is conceivable.



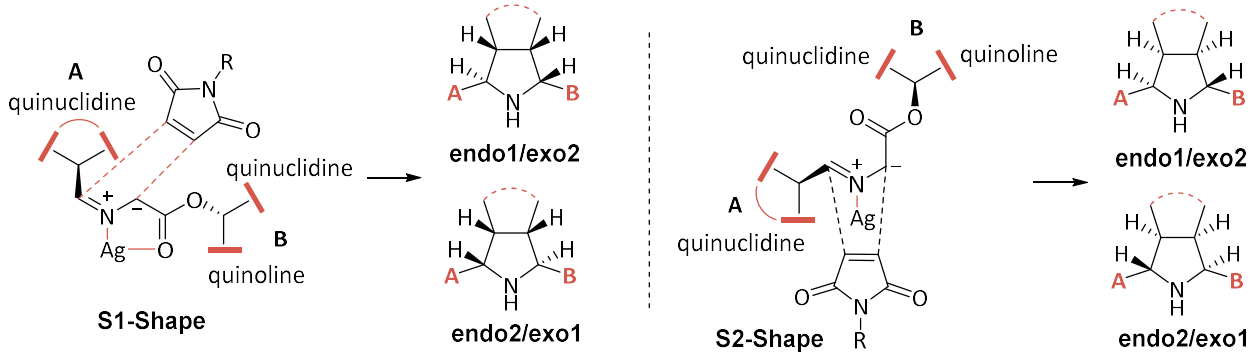
Scheme 19: Keto-enol tautomerism during treatment with TFA under Boc-deprotection conditions leads to epimerization of the C3-stereocenter.

2. 1,3-dipolar cycloadditions of azomethine ylides are known to produce four main products (*endo*1/*endo*2 and *exo*1/*exo*2; Scheme 20).[50,51,60,106]



Scheme 20: Possible 1,3-dipolar cycloaddition adducts from a W-shaped ylide.

3. While azomethine ylides usually adopt a W-shape in 1,3-dipolar cycloadditions, under certain conditions they were shown to react in their S- or U-shape.[50,107] The ring strain of a macrocyclic intermediate could force the ylides involved in product formation into such a conformation/configuration. These ylides can themselves react in *endo*- or *exo* fashion (Scheme 21). Products from ylides in their U-shape are not distinct from products that were formed from ylides in their W-shape and are thus not considered.



Scheme 21: Distinct 1,3-dipolar cycloaddition adducts from a S-shaped ylide.

4. The formation of dimeric Cinchona Macrocycles requires two consecutive and therefore distinct 1,3-dipolar cycloadditions.

5. Cinchona macrocycles are homodimers. Rotation around an axis perpendicular to the plane of the macrocycles exchanges the two hemispheres. Therefore, it is irrelevant which of the two hemispheres produces a certain reaction outcome (A-B = B-A, A-C = C-A, …). The same outcome for both hemispheres (e.g. A-A) produces C_2-symmetrical macrocycles.

First, focusing on one hemisphere, 16 different diastereomers can be produced through epimerization of C3 and the 8 different cycloaddition adducts. Two of these adducts constitute the two hemispheres of the macrocyclic products. Combinational calculations, that take the

interchangeability of the hemispheres of homodimers into account, predict 136 distinct diastereomeric products can be obtained by the developed reaction sequence (Formula 1). Astonishingly, mainly only two are produced.

Formula 1: Combinatorial calculation utilized to predict the number of possible dimeric diastereomers that could be produced by the employed reaction sequence. n = possible diastereomers (16), m = hemispheres (2).

$$\frac{(\mathbf{n}+\mathbf{m}-\mathbf{1})!}{\mathbf{m}!\,(\mathbf{n}-\mathbf{1})!} = \frac{(\mathbf{16}+\mathbf{2}-\mathbf{1})!}{\mathbf{2}!\,(\mathbf{16}-\mathbf{1})!} = \mathbf{136}$$

The following sections describes the investigation of the nature of these two diastereomers.

3.2.3 Crystallization

Given this multitude of possibilities, unambiguous determination of the configuration of the stereoisomers was attempted by means of crystal structure analysis. After established crystallization procedures for small molecules had failed, methodology typically employed in protein crystallization was applied.

As Cinchona Macrocycles are rich in basic amines, they form di-TFA-salts after purification via RP-HPLC (determined via titration against dilute HCl, Supplementary Section). These salts are well soluble in water and therefore compatible with the aqueous screening solutions used for protein crystallography. Moreover, 5-20% of organic solvent could be added to the compound solution. This enabled not only the use of high millimolar concentrations, but created two additional modes of crystallization.

Typically, a solution of analyte (protein) in water is mixed with the screening solution (1:1). The resulting solution is less concentrated in salt than the screening solution itself, so the concentrations equilibrate over time via slow evaporation of water into the screening solution. If a volatile organic solvent is added to the small molecule solution, the same process happens to the organic solvent which is also not present in the screening solution. In this work, acetonitrile was chosen as the volatile additive. The other mode is utilizing a non-volatile solvent. In this work, DMSO was chosen. Here only water evaporates, leading to a higher salt concentration, but also to a higher percentage of DMSO over time. Both modes are distinct and were successfully applied to grow crystals. In contrast to manual crystallization attempts, 288 conditions could be screened on one commercial

screening plate. Pipetting and imaging were also automated. This way over twenty thousand conditions were screened.

Most drug molecules bear at least one amine that could be converted into TFA-salt concomitantly with HPLC purification. The operational ease and the use of existing infrastructure make it possible to screen thousands of conditions in a short time. The outlined concept of how to efficiently repurpose high-throughput protein crystallography setups for the crystallization of small molecules, might be an interesting addition to the traditional toolbox of organic chemists facing challenging crystallizations. However, in contrast to typical small molecule crystals, computational structure solution needed further adjustment to account for the multitude of different additives such as salts. These caused the solvent model of the crystal structures to be substantially more complex. Modern methods, such as calculating the solvent contribution as generally disordered instead of the traditional atomistic solvent disorder model, could smoothly produce the shown solutions (SQUEEZE method)[108]

By means of this methodology two structures of symmetrical bis-cycloadducts could be determined. Namely, the macrocycles **101aa** and **101ab** obtained from quinidine and *N*-methylmaleimide or quinidine and *N*-phenyl maleimide respectively (Figure 15 and Figure 22 respectively). The configuration of both symmetrical adducts was identical. This is of particular importance, as the reaction with *N*-phenyl maleimide is significantly less selective and produces additional diastereomeic products. The conformation of both molecules were virtually identical.

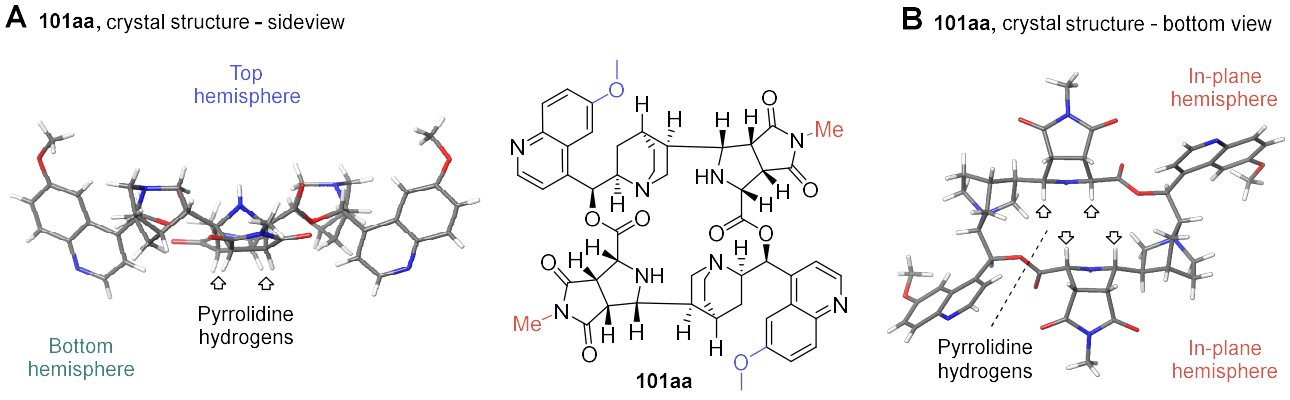


Figure 15: Determination of the absolute configuration of symmetrical **101aa** via crystal structure and positioning of substituents relative to the plane of the macrocycle (middle). A) Sideview of **101aa**; B) Bottom view of **101aa**.

The crystal structures revealed, that the symmetrical diastereomer was formed via a dual *endo*-1 (i.e. *si-re-si-re*) approach of the dipolarophile to a W-shaped ylide, resulting in the all-cis

configuration of the annulated pyrrolidine-hydrogens, that all point down towards the bottom hemisphere of the macrocycle (Figure 15).

Another interesting property of Macro-Pyrroquidines could be observed at the crystal contact interface of **101aa**. Here, bromide is complexed by the top hemispheres of two macrocycles (Figure 16). This interaction seems to be the tetrakis complexation of this central atom by four pyrrolidine nitrogens. While dimeric and even macrocyclic dimeric cinchona alkaloid ligands exist, their ligand properties are traditionally dominated by their quinuclidine substructure.[109] Combining the plethora of stereocenters and conformational preorganization observed for Macro-pyrroquidines with the observed mode of chelation, might make them an interesting class of ligands.[40,109]

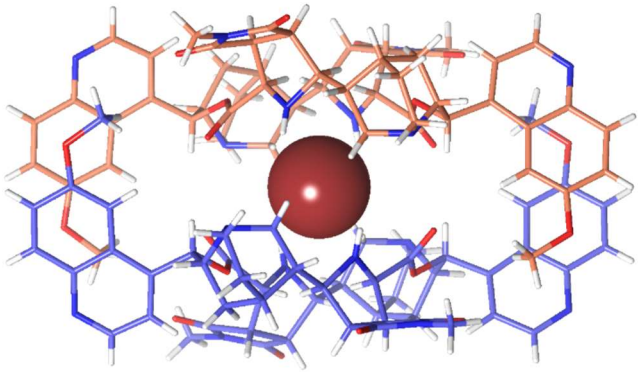


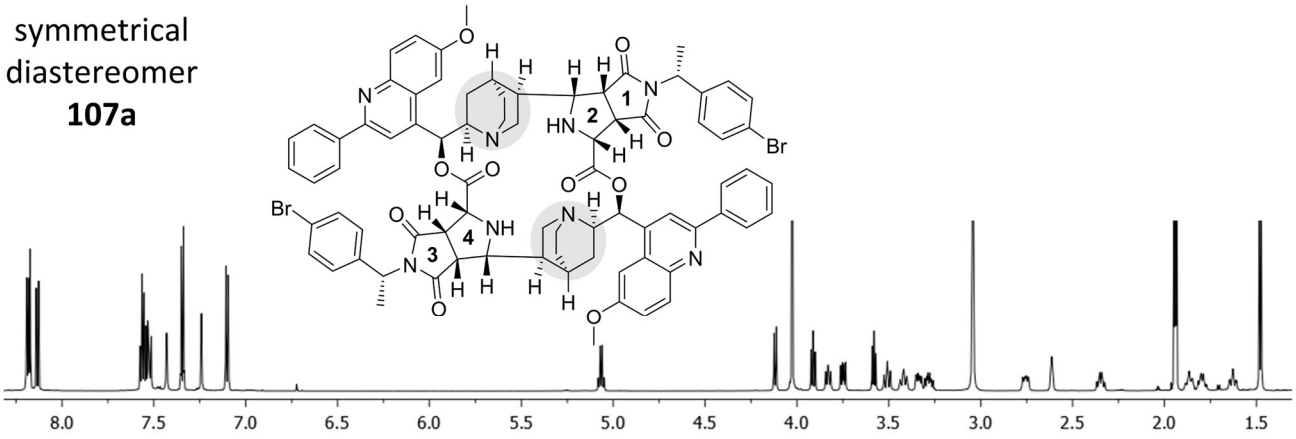
Figure 16: Sandwich structure around a coordinated central bromine atom formed by **101aa** at the crystal contact interface

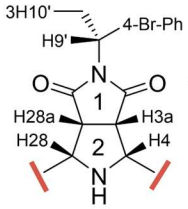
Although substantial efforts were undertaken to crystallize the second minor diastereomer, no crystals sufficient for X-ray analysis could be obtained in the timeframe of this work.

3.2.4 NMR Analysis

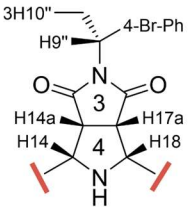
In order to gain insight into the structure of the unsymmetrical diastereomer, which could not be crystallized, the diastereomeric compounds **107a** and **108a,** obtained from the reaction sequence including QD2'Ph (**113d**) and *N*-(R)-1-(4-bromphenyl)ethyl maleimide (**98ac**) were subjected to extensive analysis by means of different NMR-spectroscopic methods.

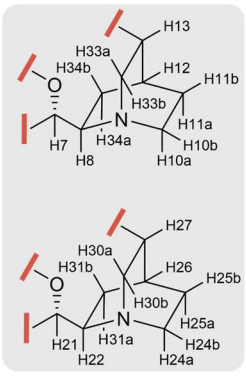
First, symmetrical **107a** was assigned fully and found to be the same diastereomer as the crystallized symmetrical products (Figure 17; full NMR assignments of **107a** and **108a** can be found in Supplementary Section)





entry	Shift [ppm]
3H10'	1.48
H9'	5.07
H4, H18	4.12
H3a, H17a	3.91
H28a, H14a	3.58
H28, H14	3.75
H12', H16'	7.10
H13', H15'	7.34





entry	Shift [ppm]	entry	Shift [ppm]
H7, H21	7.24	H33b, H30b	3.51
H8, H22	3.83	H34a, H34a	1.62
H10a, H25a	3.28	H34b, H34b	2.76
H10b, H25b	3.42	H3'	8.18
H11a, H24a	1.86	H5'	7.43
H11b, H24b	1.79	H7'	7.54
H12, H26	2.62	H8'	8.13
H13, H27	2.34	$4HPh_{m,p}$	7.54
H33a, H30a	3.34	$2HPh_{o}$	8.18

Figure 17: Proton shifts and assignment peaks of the symmetrical diastereomer **101ac.**

The unsymmetrical diastereomer **108a** showed the typical splitting of peaks. Assignment of these peaks to a distinct hemisphere proved to be possible because the atoms responsible for singled out and split signals were positioned in the molecule in a way, that allowed them to be connected via HMBC technique (Figure 18).

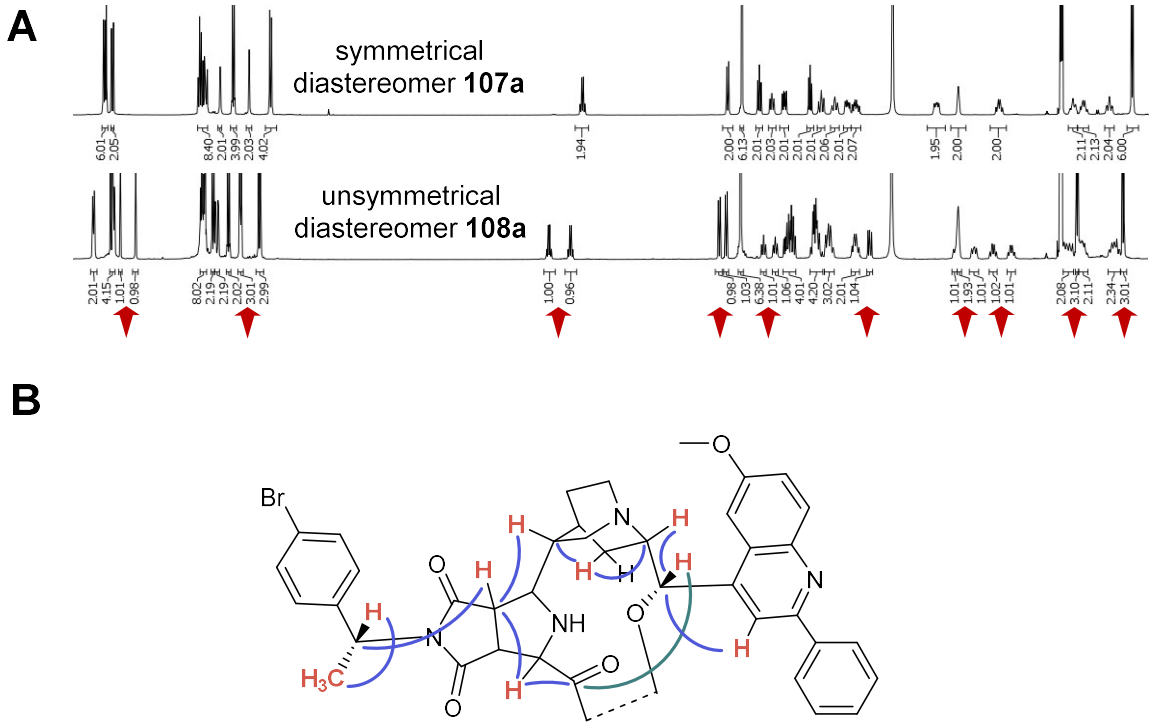
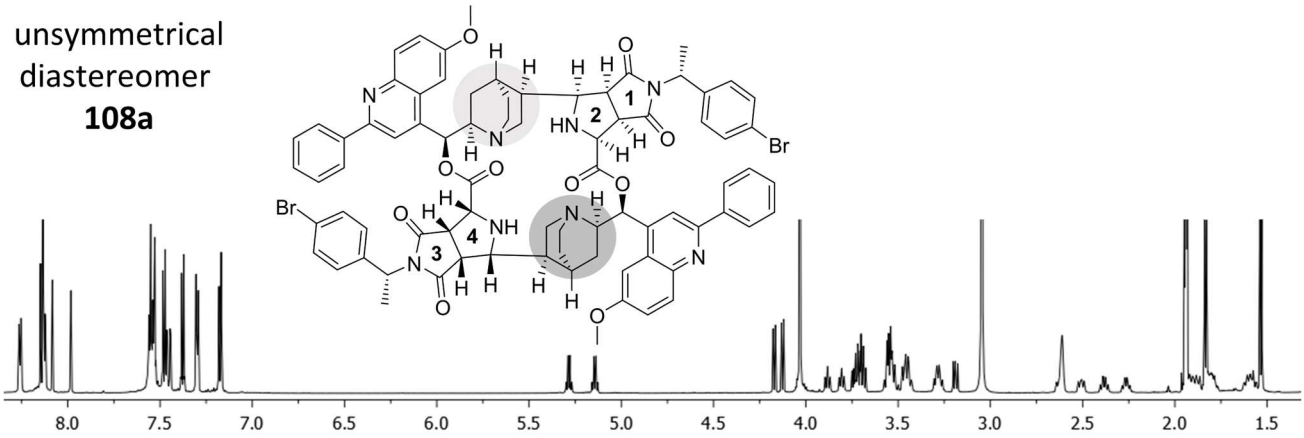
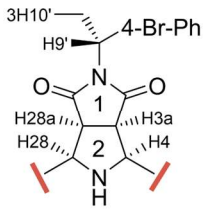


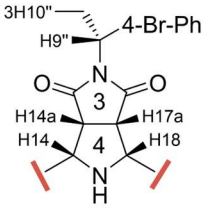
Figure 18: First steps towards configurational analysis of the minor unsymmetrical diastereomer. A) ^{1}H spectra of the symmetrical and asymmetrical diastereomer **107a** and **108a**; red arrows indicate the positions of selected split peaks; B) Red: Sufficiently split proton signals, Blue: exemplary set of HMBC couplings used to match the split signals, Green: HMBC connection across the ester bond and matching the hemispheres.

First, all peaks were assigned by COSY. Then, protons were matched to the respective carbons via HSQC. Sufficiently split protons and carbons (highlighted in Figure 18A) were identified and connected via HMBC (Figure 18B). This gave indicative signals for the two different hemispheres. These results were in agreement with NOE and ROE signals, that were used to validate the postulated positions in their respective hemispheres and relative orientations. The NOE-spectra could also be used to assign protons to either one hemisphere, that only show a sufficient split in proton NMR but not in carbon NMR (Figure 19). Some signals could not be assigned to a specific hemisphere.

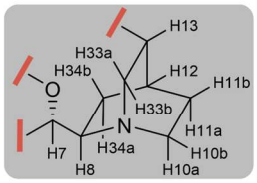


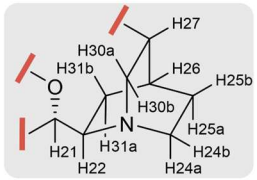


entry	Shift [ppm]
3H10'	1.83
H9'	5.28
H4	4.13
H3a	3.71
H28a	3.19
H28	3.71



entry	Shift [ppm]
3H10''	1.53
H9''	5.14
H18	4.17
H17a	3.71
H14a	3.55
H14	3.71





entry	Shift [ppm]
H7	7.30
H8	3.88
H10a	3.46
H10b	3.28
H11a	1.81
H11b	1.90
H12	2.61
H13	2.27
H33a	3.55
H33b	3.55
H34a	2.51
H34b	1.59

entry	Shift [ppm]
H21	7.17
H22	3.81
H25a	3.46
H25b	3.28
H24a	1.81
H24b	1.90
H26	2.61
H27	2.38
H30a	3.55
H30b	3.46
H34a	2.62
H34b	1.59

Figure 19: Table of assigned peaks in unsymmetrical **108a**. Black protons are clearly assigned to a hemisphere, grey protons could not be assigned to a distinct hemisphere with absolute certainty, protons which are not shown, could not be assigned to a distinct hemisphere.

Vicinal coupling in COSY, NOESY and tROESY spectra were then used to assign the configurational arrangement on prochiral methylene groups. tROESY was used, as the molecule in question is in a mass range (1000 – 2000 Da) that gives minimal NOE signals.[110]

With most proton signals assigned to their exact position and hemisphere, NOESY and tROESY spectra were employed in drawing deductions towards the configuration of the newly formed stereocenters.

All possible configurational scenarios that would produce unsymmetrical molecules were considered and carefully assessed. Asymmetry arises when the two hemispheres do not show the

exact same configuration and could be produced by many singular mechanisms or any combination of these mechanisms. Ab initio, there was no indication whether the asymmetry arised from a singular or a combinational cause (compare Section 2.2.2).

In a first step, it could be excluded, that C3-epimeric starting materials were responsible for the asymmetry in **108a**. NOESY and tROESY couplings clearly suggest a natural R-configuration at both quinuclidine stereocenters in question (C13 and C27) for the asymmetrical diastereomer (Figure 20).

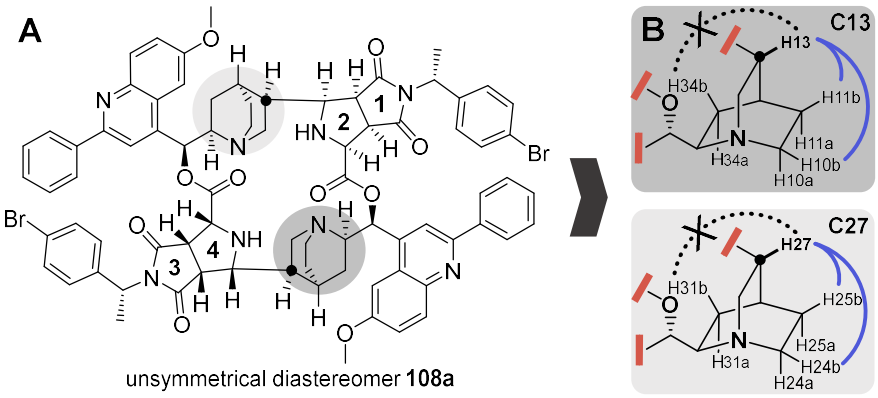


Figure 20: Protons at quinuclidine stereocenters C13 and C27 show coupling (blue arch) in both NOESY and tROESY to the protons at C10b and C11b (C13H), C24b and 25b (C27H). No coupling can be observed with the respective protons on C31 and C34 (grey, dashed arch).

The root of the asymmetry in the minor diastereomer, therefore needed to be caused by differing 1,3-dipolar cycloaddition adducts in the two hemispheres. As outlined in section 2.2.2, special attention needed to be dedicated to differentiating between cycloadducts from W- or S-shaped ylides.

The coupling constants of the pyrrolidine protons H4 and H18 of 8.5 and 8.8 Hz match the symmetrical diastereomer (8.4 Hz). Furthermore, coupling constants in the range of 7-9 Hz are typical for *endo*-adducts of 1,3-dipolar cycloadditions of azomethine ylides with maleimides.[51] Thus, these protons should be in cis-arrangement to neighbouring H3a/H28a and 17a/H14a (Figure 21).

The observed strong NOE- and ROE-interactions of H14 to H34b and H28 to H31b should exclude an adducts from S-shaped ylides, that would leave H14 or H28 *trans* to the rest of the pyrrolidine hydrogens. These interactions, too, are found in the spectra of the symmetrical diastereomer (Figure 21).

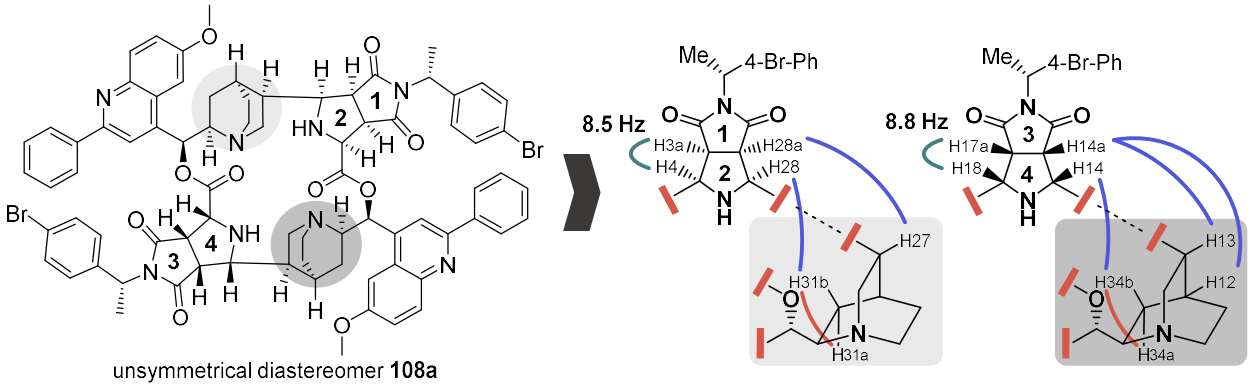


Figure 21: Determining interactions within the pyrrolidine hydrogens and between pyrrolidine and quinuclidine hydrogens. Blue line = NOE/ROE interaction; red line = passed-through tROESY interaction with negative sign; green = indicative coupling constant.

Collectively, these findings suggest that in the unsymmetrical diastereomer all protons within the different pyrrolidine rings are in *cis*-arrangement and that, hence, this product can be described as an *endo*-1/*endo*-2 adduct (endo-1 corresponds to a *si-re-si-re* attack, *endo*-2 corresponds to a *re-si-re-si attack*).

3.2.5 Modeling

To test the plausibility of the proposed configuration and gain further insight into the preferred conformations adopted by the unsymmetrical diastereomers in solution, the conformational space of minor isomer **102b** was sampled using the conformational sampling algorithm in Maestro MacroModel (OPLS3e force field, H_2O; version 12.8, Schrodinger). A minimal number of key constraints was set, to assure that the conformational exploration would yield structures in agreement with the NOE data and yet guarantee sufficient rotational freedom (Figure 22A). Upper limits of 2.5 Å for the strong interactions (H14 to H34b and H28 to H31b, H5’ to H7 and H5’’ to H21) and 5.5 Å for weaker NOE/ROE signals (H3’ to H34b and H3’’ to H31b) were set. Each of the calculated conformers was subsequently subjected to an energy minimization with the same forcefield. The resulting conformers were clustered via RMSD on all atoms (Figure 22B). A representative of the most populated cluster was selected and regarded as the conformation the molecule adopts in solution most of the time (Figure 22C).[51] For comparison, the same calculations were carried out for the symmetrical diastereomer **101ab** (Figure 22D), using the same distance restraints. Superimposition of the calculated conformer of **101ab** with its corresponding crystal structure (Figure 5F) shows, that the chosen *in silico* workflow could accurately predicted the experimentally observed conformation (Figure 5D).

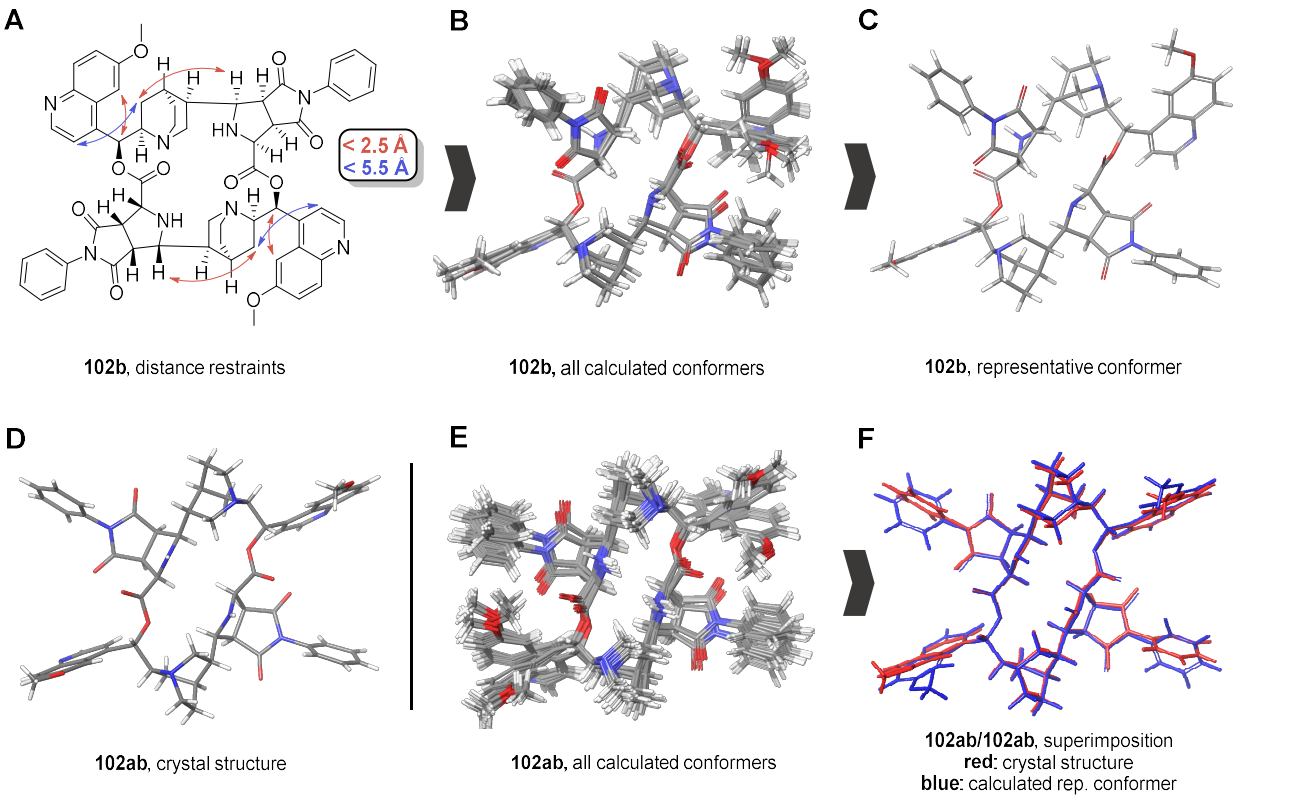


Figure 22: **Schematic workflow for the calculation of a representative conformer of unsymmetrical cycloadduct 7a**. **A)** Distance restraints for **102b** derived from NOE-data, red arrows represent a distance constraint of 2±0.5 Å, blue arrows represent a distance constraint of 3.5±2.0 Å; **B)** Superimposition of all energy-optimized conformers of **102b**; **C)** Selected representative structure of the largest conformer cluster of **102b**; **D)** Crystal structure of symmetrical **101ab**; **E)** Analogously produced conformers for **101ab**; **F)** Superimposition of a representative conformer of the largest conformer cluster of **101ab** with the corresponding crystal structure shows the feasibility of the chosen modelling approach for these macrocycles.

The calculated conformation for the unsymmetrical diastereomer **102b** underlines the plausibility of the NMR-derived configuration, that was used as an input and furthermore created distances within the molecule, that fit the observed NOE/ROE data well. It revealed an opposite spacial orientation of key functional groups, such as the secondary amine of the pyrrolidines, compared to the symmetrical macrocycle (compare Figure 22C and Figure 22D or Figure 27and Figure 28; further details can be found in the Supporting Information).

3.2.6 Mechanistical Deductions from Structural Information and Selectivities

The lack of an additional symmetrical *endo*-2/*endo*-2 adduct suggests, that the first 1,3-dipolar cycloaddition might proceed with a high *endo*-1-selectivity and that only then, depending on the size of the introduced succinimide substituent, the second cycloaddition proceeds via either, an *endo*-1 (bottom approach) or an *endo*-2 (top approach) transition state (Figure 23). A strong

preference for *endo*-adducts in general, has been reported for the 1,3-dipolar cycloaddition of azomethine ylides before.[50,52]

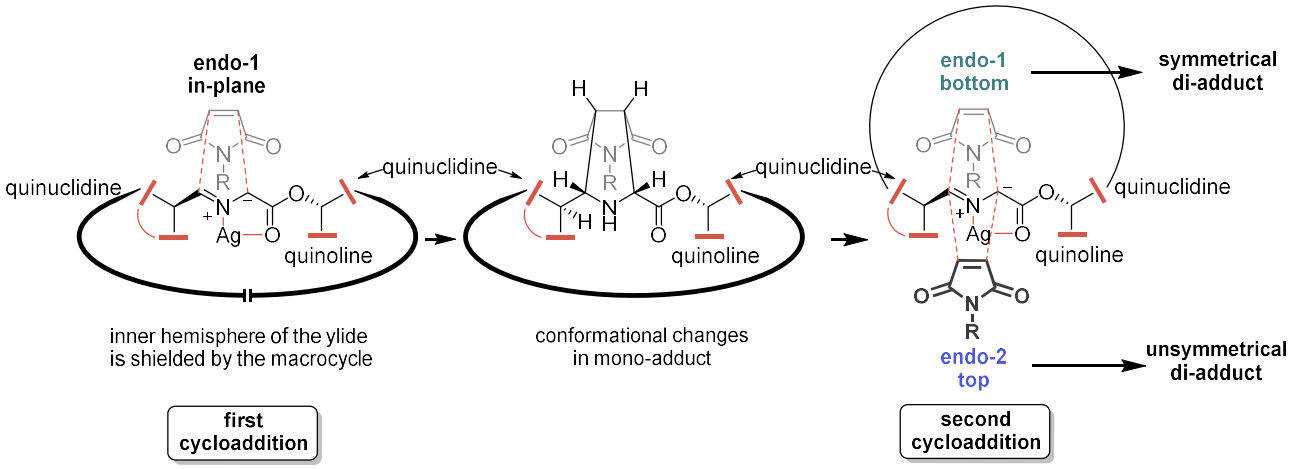


Figure 23: Possible transition states involved in the formation of the dual cycloadducts.

This observed selective formation of *endo*-1/*endo*-1 and *endo*-1/*endo*-2 products can be explained by the macrocyclic nature of the two distinct ylide species involved in the dual cycloaddition, i.e. bis-imine **100** and the mono-cycloaddition-adduct (Figure 23). In bis-imine macrocycle **100**, one face of the ylide might be facing the macrocycle, which would shield this face from approach of the first maleimide. Such a conformation has also been suggested for the related di-adducts synthesized by Rowan and Sanders (see above).[6] The macrocycle formed in the first cycloaddition might adopt a different conformation and thus enable the approach of the dipolarophile from both opposing faces of the remaining ylide (Figure 23). Large maleimide substituents may lead to a more pronounced conformational change, causing the selectivity of the second cycloaddition to approach a product ratio of 1:1. Such a distribution was observed for reactions employing maleimides with bulky substituents such as *tert*-butyl (compare Figure 23 and Figure 29).

3.2.7 Further Isolated Species

The selectivity of developed macrocyclization sequence is almost exclusively dependent on the maleimide (as will be discussed in Section 3.3). Especially for *N*-phenyl maleimides this extends to the formation of additional diastereomers. The combined minor diastereomers of several reactions of **80** with *N*-phenyl maleimide and 2,4,6-trichlorophenylmaleimide amounted to enough analyte to characterize these additional products. It should be noted, that the formation of additional diastereomers is not exclusive for *N*-phenyl maleimides, but could be observed for other bulky phenyl-containing maleimides.

In the reaction employing N-phenyl maleimide, the symmetrical adduct that is the focus of this work was obtained in excess over two unsymmetrical products (Figure 24; compare Table 4). All compounds show clearly distinguishable NMR-spectra and retention times on HPLC. Minor product 2 (**102b**) appears to be the unsymmetrical adduct that is isolated in all the other reactions.

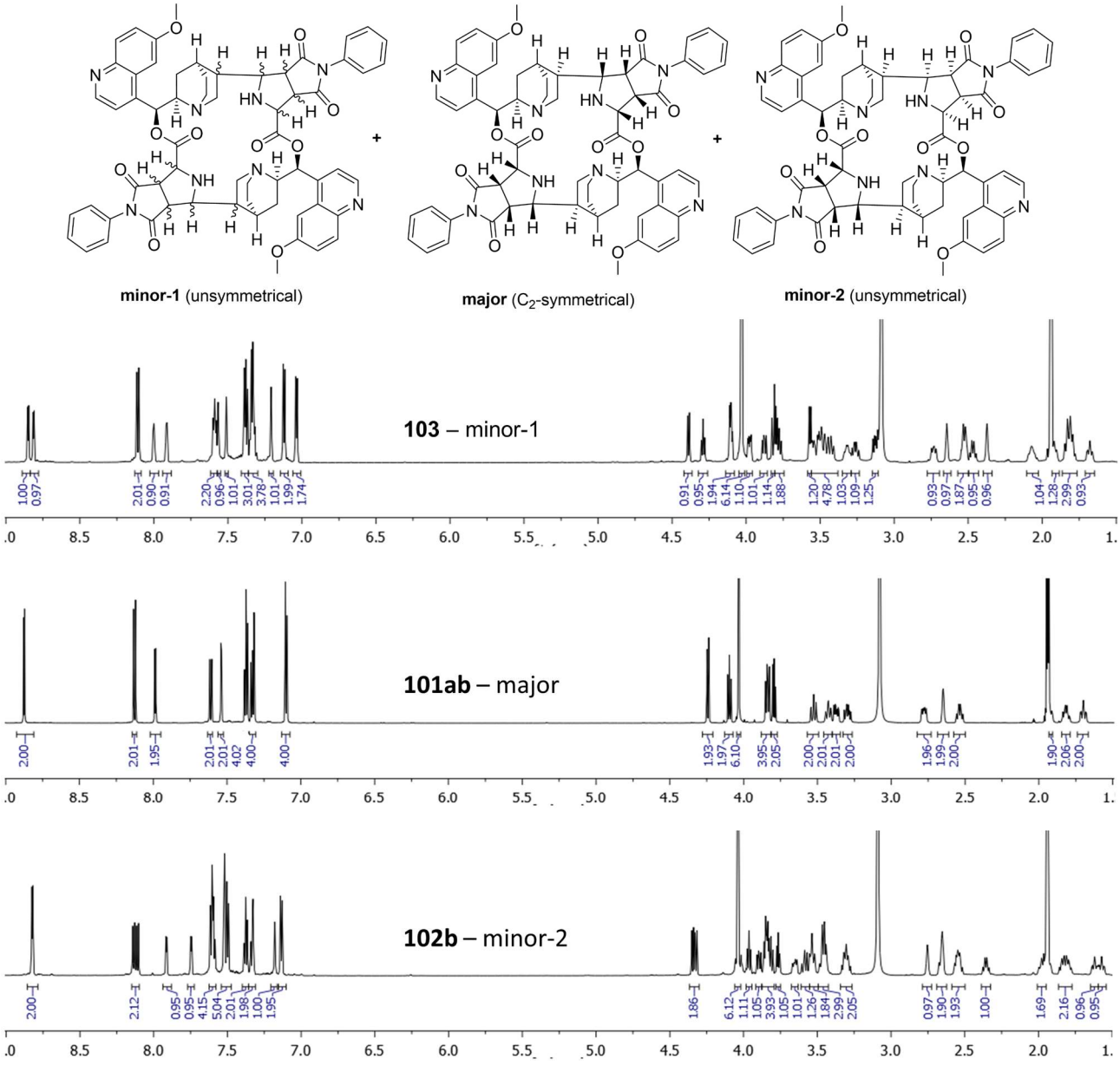


Figure 24: ^{1}H -NMR-spectra of the three diastereomeric dimers produced in the reaction of **80** and *N*-phenyl maleimide. The order of compounds corresponds to their elution times on HPLC.

Moreover, traces of trimer (**109**) could be isolated from the same reaction. This species elutes significantly later on HPLC and is clearly identifiable as a trimer by the isotope patterns of the detected ions via HRMS. The NMR spectra suggest a C_3-symmetric diastereomer. This 30-membered macrocycle could only be observed in trace amounts in low-selectivity screening conditions. Thus,

further analysis was not sought. In ^{1}H-NMR spectroscopy symmetrical di- and tri-adduct show distinct shifts and coupling constants (Figure 25).

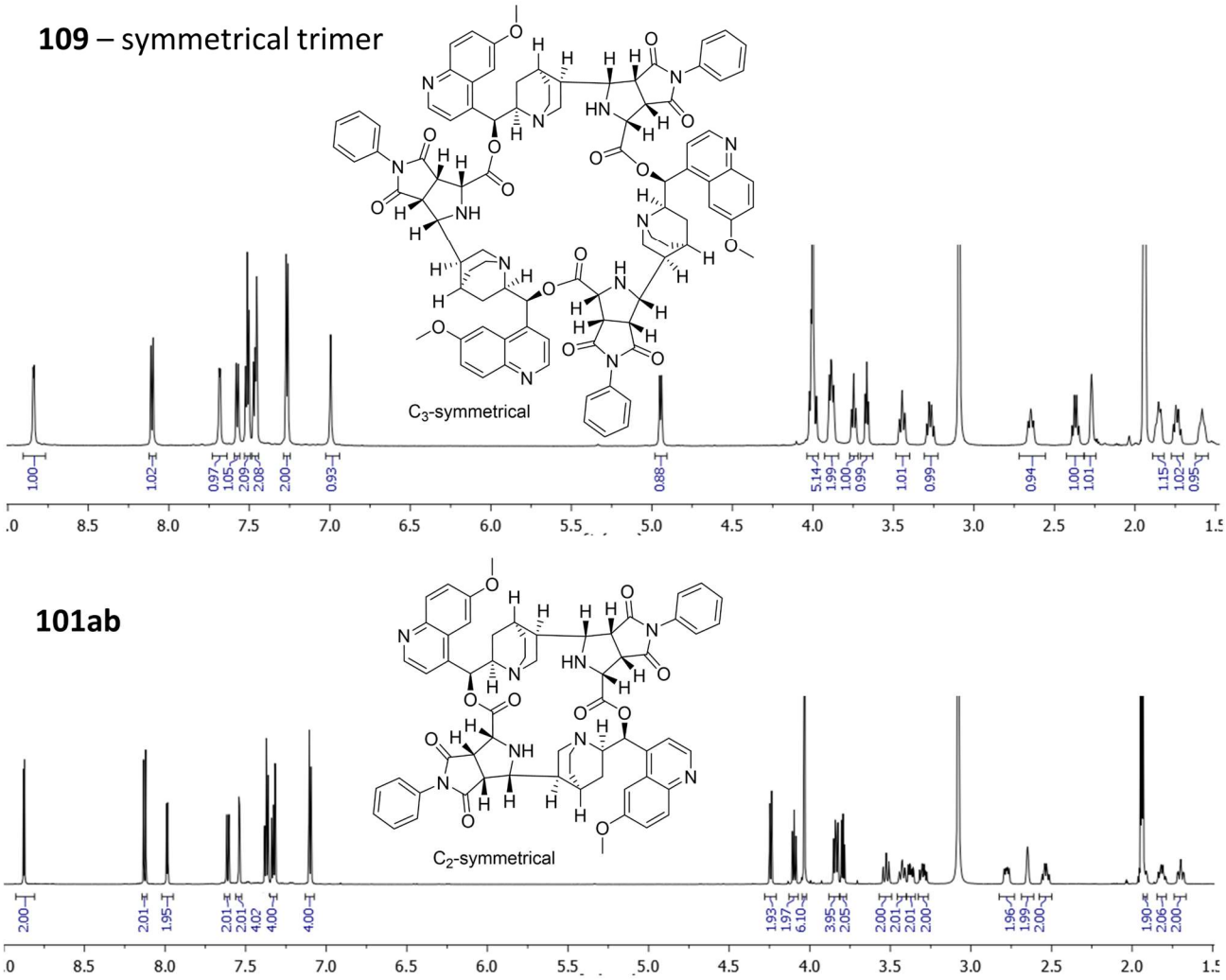


Figure 25: ^{1}H-NMR-spectra of C_3-symmetrical trimer **109** and symmetrical dimer **101ab**. The shown configuration for **109** is hypothetical.

In the reaction employing 2,4,6-trichlorophenylmaleimide, two symmetrical products and one unsymmetrical product could be detected in a ratio of 1 : 3.8 : 2.4 (symmetrical-1 : unsymmetrical : symmetrical 2). Minor product 1 (**101ac**) appears to be the same diastereomer as the symmetrical products isolated from all the other reactions (Figure 26).

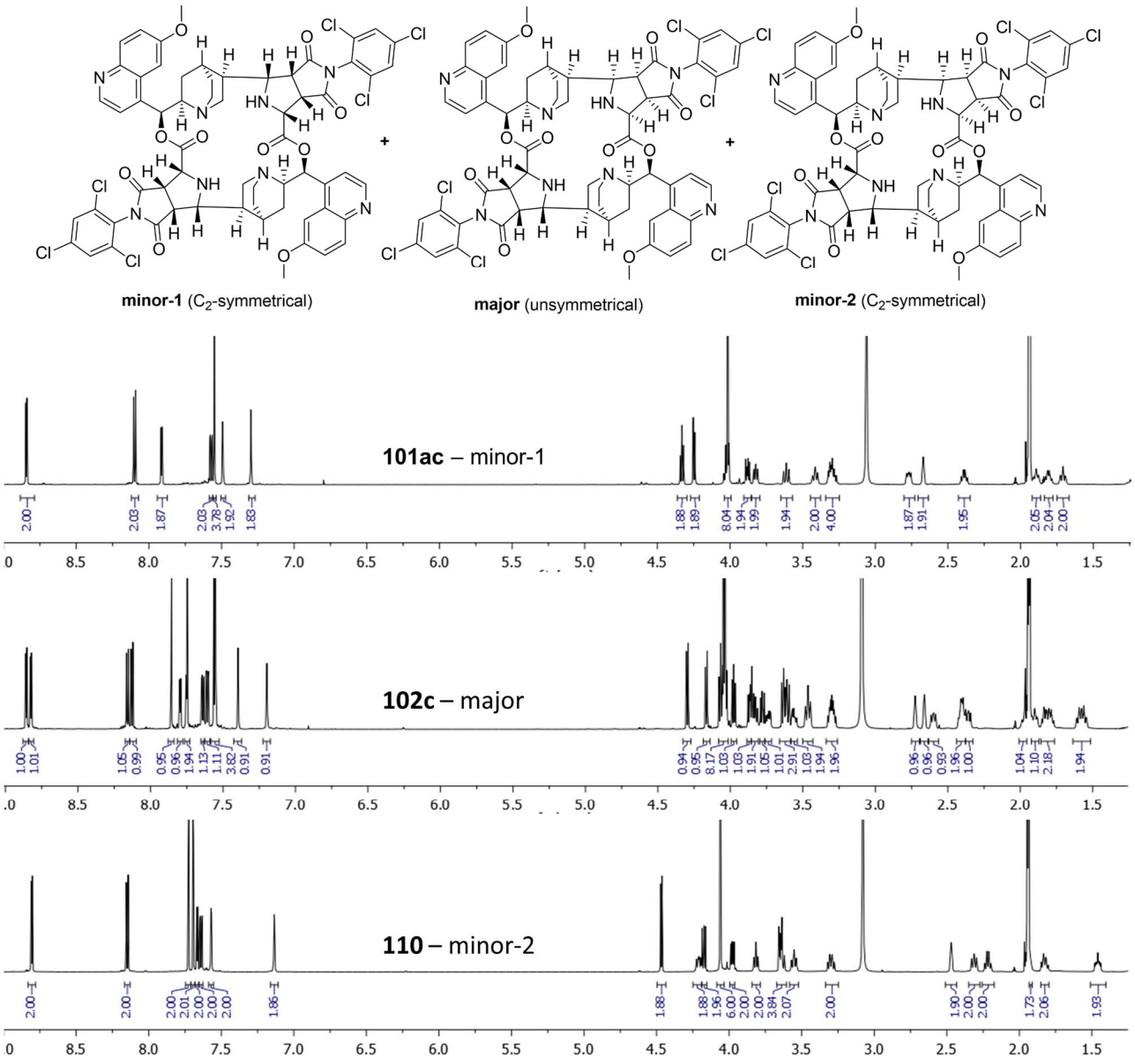


Figure 26: ^{1}H -NMR spectra of the three diastereomeric dimers produced in the reaction of **80** and *N*-2,4,6-trichlorophenyl-maleimide. The order of compounds corresponds to their elution times on HPLC.

Collectively, this data shows, that the reaction sequence is well capable of producing diastereomers apart from the two usually observed. Careful attention needs to be given to which species are actually produced. It also proves, that Macro Pyrroquidines of differing configuration are easily distinguishable by NMR and exhibit distinct retention times on HPLC. Higher oligomers, such as trimer **109** seem to act accordingly.

3.3 Library Synthesis

3.3.1 Design

With a viable synthetic route in hand, a compound collection could be generated. Positions in the macrocycle were identified, that would allow the introduction of substituents in quasi-orthogonal hemispheres of the macrocycle. Therefore, the chances to modify a relevant portion of the inherent pharmacophore could be maximized while minimizing synthetic effort.

The crystal structure of symmetrical **101aa** revealed that the quinoline groups of the molecule are perpendicular to that plane of the macrocycle. C2' and C6'-substituents would therefore point towards opposite faces of the plane of the macrocycle. These positions could thus serve as such orthogonal attachment points (Figure 27).

The third site of derivatization, the succinimide *N*-substituent, could not be chosen freely, as its position is a direct result of the 1,3-dipolar cycloaddition with maleimides. Gratifyingly, these substituents populate the hemisphere in-plane of the macrocycle – again orthogonal to the two sites described above (Figure 27B)

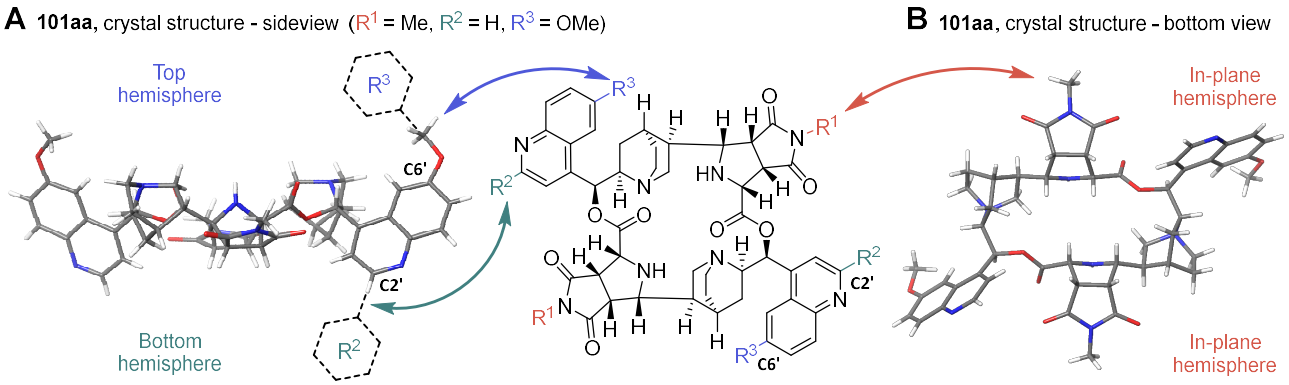


Figure 27: **Identification of optimal positioning of substituents (R^1, R^2, R^3)** relative to the plane of the macrocycle in the symmetrical diastereomer utilizing the crystal structure of **101aa**. A) Sideview of **101aa**; B) Bottom view of **101aa**.

To a lesser extent, this analysis seems to hold true for the respective unsymmetrical diastereomers. This can be observed in the calculated conformer of **102aa** (compare Figure 28 and Figure 27).

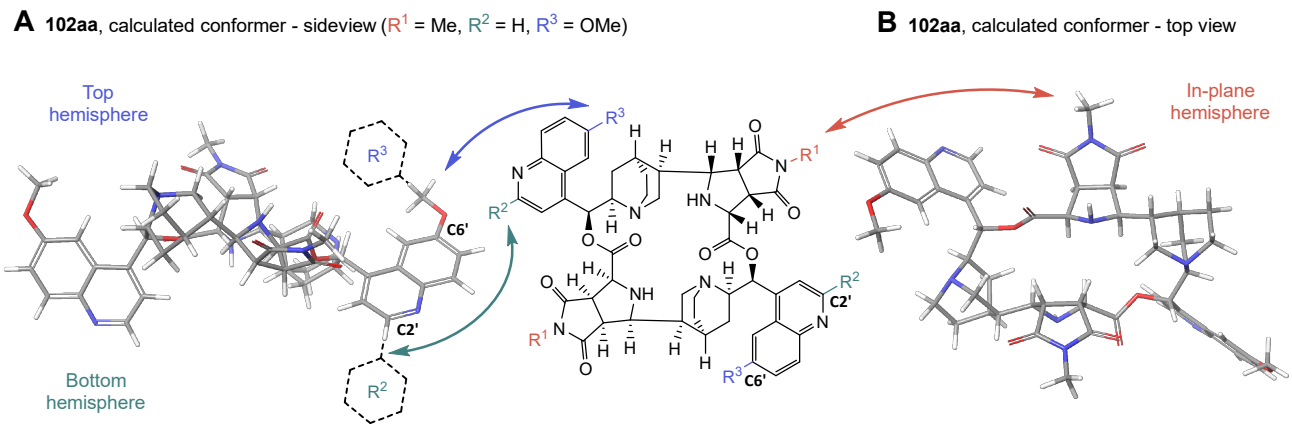


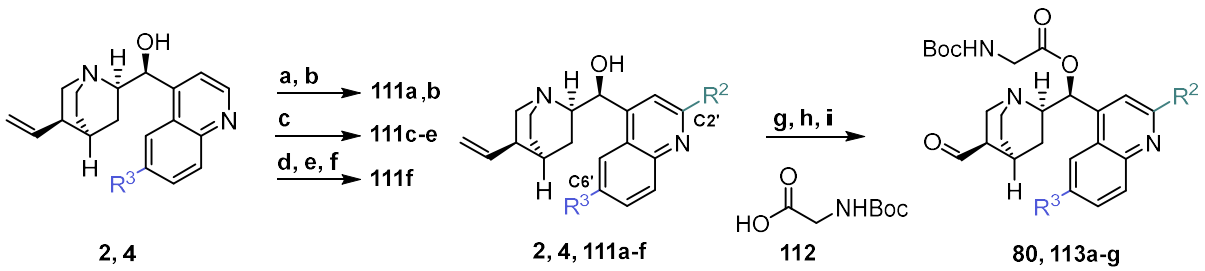
Figure 28: Visualization of the positions of substituents (R^1, R^2, R^3) relative to the plane of the macrocycle in the unsymmetrical diastereomer **102aa** utilizing the calculated conformer of **102aa**. A) Sideview of **102aa**; B) Bottom view of **102aa**.

3.3.2 Synthesis

Quinidine analogs **111a-f** carrying different substituents in the C2' and C6' position of the quinoline ring were synthesized as described by Hintermann *et al.*[111], Shiomi *et al.*[112] and Wang *et al.*[13] All substituents introduced at the three positions, were either meant to be carried through to the synthesis of the final macrocycles for library enlargement, or they served to enable further chemical derivatization of the macrocycles (Scheme 22).

The C2'-position of quinidine and cinchonine were directly alkylated via the nucleophilic addition of alkyllithium reagents. The resulting dihydroquinolines were then re-oxidized using manganese dioxide (Scheme 22, **111c-e**).[111] Chlorination in this position was achieved by first generating the quinoline *N*-oxide by treatment with *m*CPBA, followed by selective reduction of the parallelly formed quinuclidine *N*-oxide using H_2SO_3. Subsequent treatment with $POCl_3$ gave the desired ortho-chloride (Scheme 22, **111f**).[112] C6' ether derivatives were generated from quinidine via boron tribromide mediated demethylation followed by an alkylation with alkyl halides (Scheme 22, **111a** and **111b**).[13]

Tailoring towards the macrocyclization sequence was performed via three consecutive reactions of coupling the C9 hydroxyl group to a Boc-protected glycine and transforming the C10/C11 double bond into an aldehyde. The precursors to carbamido aldehydes **80** and **113a** were the unaltered cinchona alkaloids quinidine and cinchonine (Scheme 22).



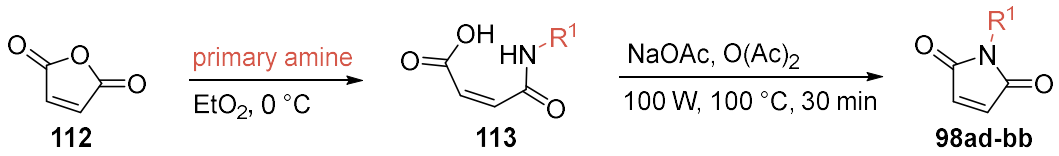
Quinidine, **2**, (R^3 = OMe)
Cinchonine, **4**, (R^3 = H)

111a, R^2 = H, R^3 = OiPr, 60%
111b, R^2 = H, R^3 = OcBu, 45%
111c, R^2 = Ph, R^3 = OMe, 34%
111d, R^2 = C_4H_3S, R^3 = H, 63%
111e, R^2 = nBu, R^3 = H, 71%
111f, R^2 = Cl, R^3 = OMe, 43%

QD, **80**, R^2 = H, R^3 = OMe, 47%
CN, **113a**, R^2 = H, R^3 = H, 48%
QD6'iPr, **113b**, R^2 = H, R^3 = OiPr, 75%
QD6'cBu, **113c**, R^2 = H, R^3 = OcBu, 26%
QD2'Ph, **113d**, R^2 = Ph, R^3 = OMe, 64%
CN2'Thiop, **113e**, R^2 = C_4H_3S, R^3 = H, 39%
CN2'nBu, **113f**, R^2 = nBu, R^3 = H, 75%
QD2'Cl, **113g**, R^2 = Cl, R^3 = OMe, 62%

Scheme 22: Synthesis of cinchona alkaloid-derived aldehydes 80 and 113a-g. a) BBr_4 then NH_3 aq. (78%); b) alkyl halide, Cs_2CO_3 (57-77%); c) organolithium then MnO_2 (34-71%); d) *m*CPBA then e) H_2SO_3 aq. (97% over two steps); f) $POCl_3$ then NH_3 aq. (44%); g) Boc-Gly-OH, DCC, DMAP (78-96%);h) OsO_4, $K_3[Fe(CN)_6]$, K_2CO_3, H_2O (35-91%); i) $NaIO_4$, SiO_2 (84-93%).

Maleimides **98ad-bb** were synthesized from maleic anhydride and the respective enantiopure primary amines (Scheme 23).[113]



98ac R^1 = (R)-1-(4-bromophenyl)ethyl (56%)
98ad R^1 = 4-methylbenzyl (36%)
98ae R^1 = 4-chloro-3-(trifluoromethoxy)-benzyl (36%)
98af R^1 = (R)-2-phenylpropyl (50%)
98ag R^1 = (R)-1-cycohexylethyl (65%)
98ah R^1 = neopentyl (39%)
98ai R^1 = 2-(5-fluoro-1H-indole-3-yl)ethyl (16%)
98aj R^1 = (S)-2-phenylpropyl (52%)
98ak R^1 = 1,1-(diacetoxymethyl)-2-acetoxyethyl (30%)
98al R^1 = cyclohexylmethyl (40%)
98am R^1 = 4-fluorobenzyl (45%)
98an R^1 = homopiperonyl (20%)
98ao R^1 = 4-(4-fluorophenyl)benzyl (67%)

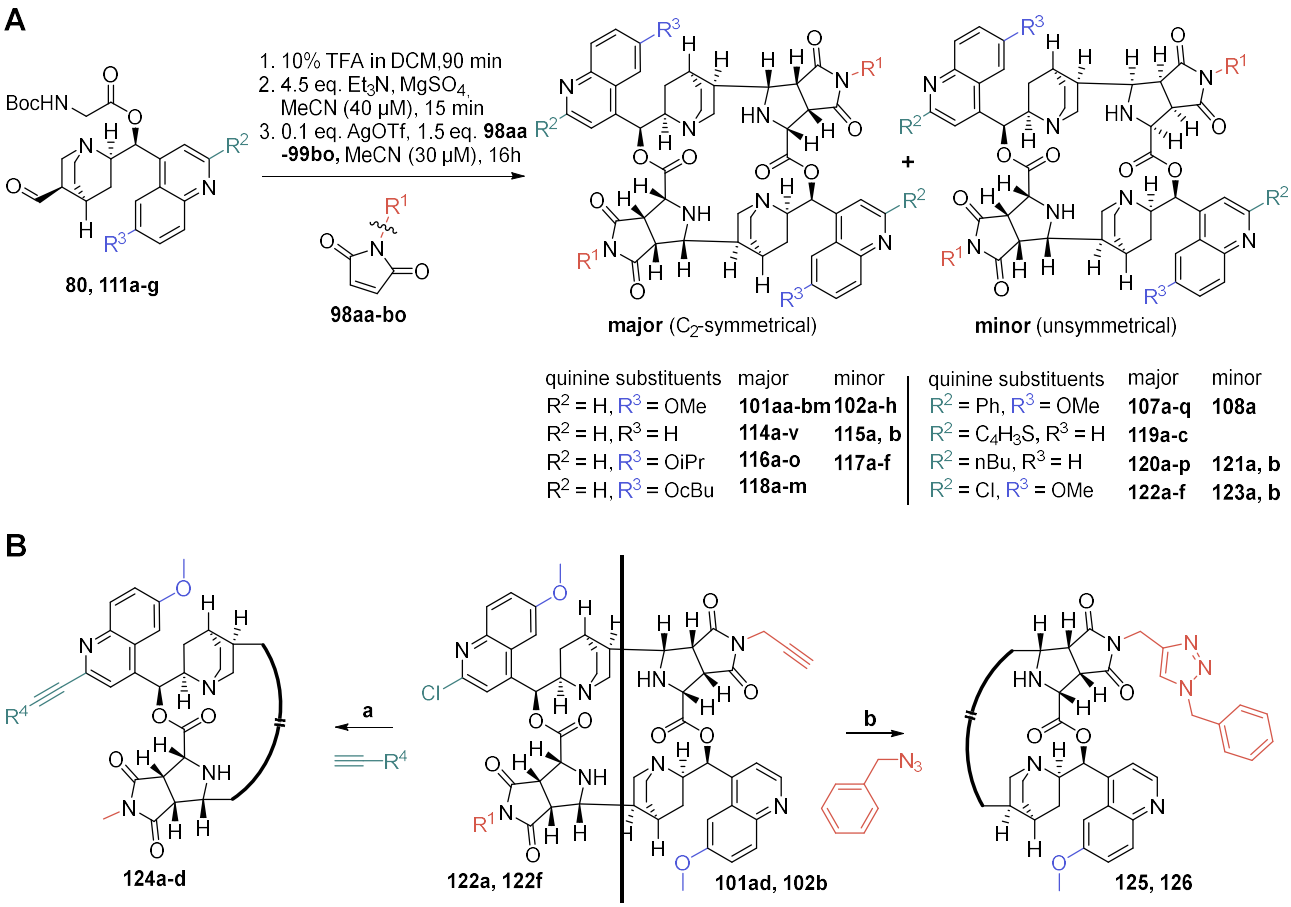
98ap R^1 = (-)-cis-myrthanyl (59%)
98aq R^1 = 3-acetoxybenzyl (42%)
98ar R^1 = piperonyl (42%)
98as R^1 = phenethyl (60%)
98at R^1 = 2-chlorobenzyl (21%)
98au R^1 = 1-phenylcyclopropanyl(74%)
98av R^1 = 1-methyl-1-(2-fluorophenyl)propyl (58%)
98aw R^1 = 1-(2-chorophenyl)cyclopropyl (42%)
98ax R^1 = (R)-3-methylbutan-2-yl (28%)
98ay R^1 = *iso*-propyl (43%)
98az R^1 = (R)-1-cyclopropylethan-1-yl (44%)
98ba R^1 = 1-methyl-1-phenylethyl (25%)
98bb R^1 = propargyl (40%)[a)]

Scheme 23: Synthesis of maleimides **6ac-bb**. [a)] second step performed thermally at 80°C.

The chlorine substituent in the C2'-position of the quinidine enabled functionalization of the macrocycles by means of Sonogashira couplings (detailed in Section 2.5). If one equivalent of alkyne was employed, this reaction could be used to desymmetrize formerly symmetrical starting material (e.g. **122a**), which added significantly more complexity and might completely alter the binding mode to a putative target (Scheme 24B).

In addition, a propargyl group was introduced through the maleimide, employing slightly modified reaction conditions (e.g. **101ad**). The terminal alkyne then enabled further modification via Cu(I)-mediated dipolar cycloadditions with benzylazide of symmetrical and unsymmetrical macrocyclic starting materials (Scheme 24.B; further detailed in Section 2.5).

In total, a collection of 167 macrocyclic PNPs was synthesized by means of the short reaction sequences described above (Scheme 24). The deliberate choices made in the process of the generation of this compound library, are detailed in the SAR study (Section 2.4.1).



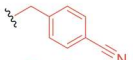
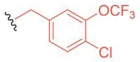
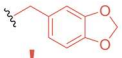
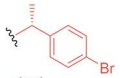
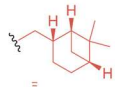
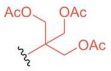
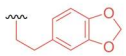
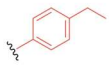
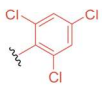
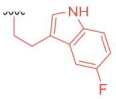
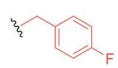
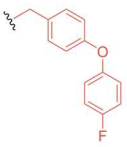
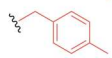
Scheme 24: **Overview of the syntheses involved in the generation of the compound library. A)** The eight classes of macrocycles derived directly from modified cinchona alkaloid starting materials (Scheme 22) and maleimides (e.g. Scheme 23); **B)** Sonogashira reaction and CuAAC could be used to derivatize macrocyclic starting materials; a) $Pd[3,5\text{-}(CF_3)_2C_6H_3]_3$, terminal alkyne, K_2CO_3, Et_3N, DMF/DMSO, 90°C (20-56%); b) Benzylazide, CuI, K_2CO_3, *t*BuOH/H_2O (23-40%)

All ten compound classes shown in Scheme 24A represent a group of compounds sharing the quinoline substitution pattern (R^2 and R^3) but differ in their succinimide substitution (R^1) and their configuration. All yields and diastereomeric ratios for their respective syntheses are listed below (Table 5).

Compounds **101aa-bm** and **102a-h** were synthesized from **80** (QD) which shares its configuration and quinoline substitution pattern with the parent NP quinidine (Table 5).

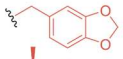
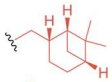
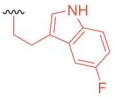
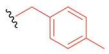
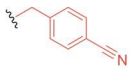
Table 5: Compounds **101aa-bm** and **102a-h** derived from **80**.

QD (R^2 = H, R^3 = OMe)

Entry	Number	R^1	Maleimide	Yield	Isomer Ratio	Entry	Number	R^1	Maleimide	Yield	Isomer Ratio
1	**101aa**		5aa	51	19 : 1	22	**101au**		5bk	32	3.5 : 1
2	**101ac**		5bc	36	12.8 : 1	23	**101av**		5at	27	4.8 : 1
3	**101ad 102b**		5bb	35	4.6 : 1	24	**101aw**		5ae	27	2 : 1
4	**101ae**		5ay	49	3.7 : 1	25	**101ax**		5aq	36	4.2 : 1
5	**101af**		5bd	20	1 : 1	26	**101ay**		5ar	25	3 : 1
6	**101ag**		5ah	39	2.4 : 1	27	**101az**		5bl	40	2.3 : 1
7	**101ah**		5ax	41	2 : 1	28	**101ba 102e**		5bm	34	2 : 1
8	**101ai**		5be	40	7.3 : 1	29	**101bb**		5ac	23	3 : 1
9	**101aj**		5az	32	2.8 : 1	30	**101bc**		5ba	30	2.4 : 1
10	**101ak**		5bf	33	8.7 : 1	31	**101bd 102f**		5au	32	2.2 : 1
11	**101al**		5al	19	4.64 : 1	32	**101be 102g**		5av	33	1 : 1
12	**101am**		5ap	29	1.6 : 1	33	**101bf 102h**		5aw	38	1 : 2.1
13	**101an**		5ag	35	2.1 : 1	34	**101bg**		5as	28	10.3 : 1
14	**102c**		5ak	27	2.2 : 1	35	**101bh**		5an	31	6.7 : 1
15	**101ab 102a 103**		5ab	50	7.7 :1 : 1.1	36	**101bi**		5aj	22	8 : 1
16	**101ao**		5bg	40	6.8 : 1	37	**101bj**		5af	37	6 : 1
17	**101ap 102d 109**		5bh	40	1 : 3.8 : 2.4	38	**101bk**		5ai	30	3.9 : 1
18	**101aq**		5bi	43	4 : 1						
19	**101ar**		5am	27	2.8 : 1	38	**101bl**		5ao	30	2 : 1
20	**101as**		5ad	39	2.3 : 1						
21	**101at**		5bj	23	3 : 1	39	**101bm**		5bn	26	6 : 1

Compounds **114a-w** and **115a-d** were synthesized from **113a** (CN) which shares its configuration and quinoline substitution pattern with the parent NP cinchonine (**4**). The quinoline substitution pattern does not bear any C2' or C6' functionalities (Table 6).

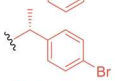
Table 6: Compounds **114a-w** and **115a-b** derived from **113a**.

						CN (R^2 = H, R^3 = H)					
Entry	Number	R^1	Maleimide	Yield	Isomer Ratio	Entry	Number	R^1	Maleimide	Yield	Isomer Ratio
1	**114a**		5aa	42	16.7 : 1	13	**114m**		5aq	33	1.8 : 1 : 2.4
2	**114b**		5bn	15	3 : 1	14	**114n**		5ar	38	3.7 : 1
3	**114c**		5ay	20	4.5 : 1	15	**114o**		5bl	32	3.1:1
4	**114d**		5bd	38	3.8 : 1	16	**114p**		5bm	40	2.4:1
5	**114e**		5ah	20	9.3 : 1	17	**114q** **115a**		5au	20	1.6 : 3.8 : 1
6	**114f**		5bf	15	3.6 : 1	18	**114r**		5av	30	1.6 : 1
7	**114g**		5bp	34	3.8 : 1	19	**114s** **115b**		5aw	15	1 : 1.3
8	**114h**		5ag	29	2.5 : 1	20	**114t**		5aj	22	4.8 : 1 : 1.1
9	**114i**		5ab	46	6 : 1 : 1.1 : 1.2	21	**114u**		5af	37	8 : 1 : 1.3
10	**114j**		5bi	40	4.6 : 1	22	**114v**		5ai	40	3 : 1
11	**114k**		5ad	34	4.5 : 1						
12	**114l**		5bk	13	n.d.						

Compounds **116a-o** and **117a-f** were synthesized from **113b** (QD6'*i*Pr). The quinoline substitution pattern differs from the NP quinidine only in the C6'-hydroxyl substituent consisting of an isopropyl group instead of the natural methyl group (Table 7).

Table 7: Compounds **116a-o** and **117a-f** derived from **113b**.

QD6'iPr (R^2 = H, R^3 = O*i*Pr)

Entry	Number	R^1	Maleimide	Yield	Isomer Ratio	Entry	Number	R^1	Maleimide	Yield	Isomer Ratio
1	**116a**		5aa	43	17.3 : 1	9	**116i** **117c**		5bl	26	1.1 : 5.8 : 1
2	**116b**		5ay	8	5.5 : 1	10	**116j** **117d**		5bm	31	1.7 : 1
3	**116c**		5bd	29	3.8 : 1	11	**116k**		5ac	21	1 : 1.8 : 2.9
4	**116d** **117a**		5ah	50	1.5 : 1	12	**116l**		5ba	24	4.5 : 1
5	**116e**		5az	22	3 : 1	13	**116m**		5au	24	4.6 : 1
6	**116f** **117b**		5ag	34	1.5 : 1	14	**116n** **117e**		5av	25	1.5 : 1
7	**116g**		5ab	25	9.1 : 1	15	**116o** **117f**		5aw	29	1 : 1.6
8	**116h**		5ai	35	4.2 : 1						

Compounds **118a-n** were synthesized by Pia Jasmin Bodenbinder from **113c** (QD6'cPr). The quinoline substitution pattern differs from the NP quinidine only in the C6'-hydroxyl substituent consisting of a cyclobutyl group instead of the natural methyl group (Table 8).

Table 8: Compounds **118a-n** derived from **113c**. All compounds listed in this table were synthesized and characterized by Pia Jasmin Bodenbinder.

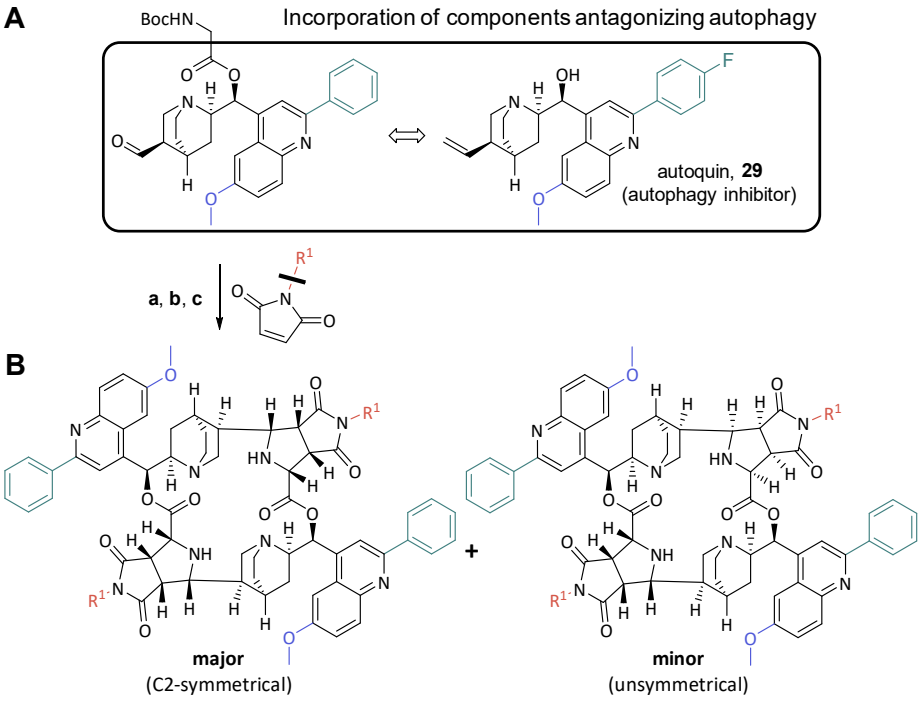
QD6'cBu (R^2 = H, R^3 = OcBu)

Entry	Number	R^1	Maleimide	Yield	Isomer Ratio	Entry	Number	R^1	Maleimide	Yield	Isomer Ratio
1	**118a**		5bj	15	3.3 : 1	8	**118h**		5ag	15	2.5 : 1
2	**118b**		5aa	25	12 : 1	9	**118i**		5ab	27	6 : 1
3	**118c**		5bc	25	5 : 1	10	**118j**		5bp	31	5.5 : 1
4	**118d**		5be	20	5.6 : 1	11	**118k**		5bl	13	2.5 : 1
5	**118e**		5ay	21	4 : 1	12	**118l**		5bm	24	5 : 1
6	**118f**		5bd	20	3.6 : 1	13	**118m**		5av	10	2 : 1
7	**118g**		5bf	10	7.5 : 1						

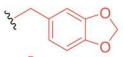
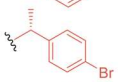
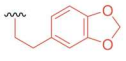
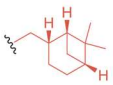
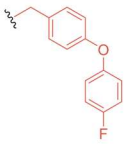
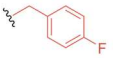
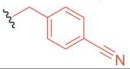
Compounds **107a-p** and **108a** were synthesized from **113d** (QD2'Ph). The quinoline substitution pattern consists of a C2' phenyl- and a C6' methoxy group (Table 9). Both substituents, as well as the configuration of this class of compounds corresponds to a less active derivative of the autophagy inhibitor autoquin (Table 9).[15] The incorporation of structural elements wich, on their own, were

shown to adverse effects, was considered of interest. Especially, because a putative hydrolysis of the macrocyclic esters would render the synthesized compounds prodrugs. Unfortunately, the poor solubility of this compound class overshadowed any putative drop in activity mediated by the phenyl group.

Table 9: A) Design principle of incorporating fragments with nominally antagonistic biological activity. B) Compounds **107a-p** and **108a** derived from **113d**.

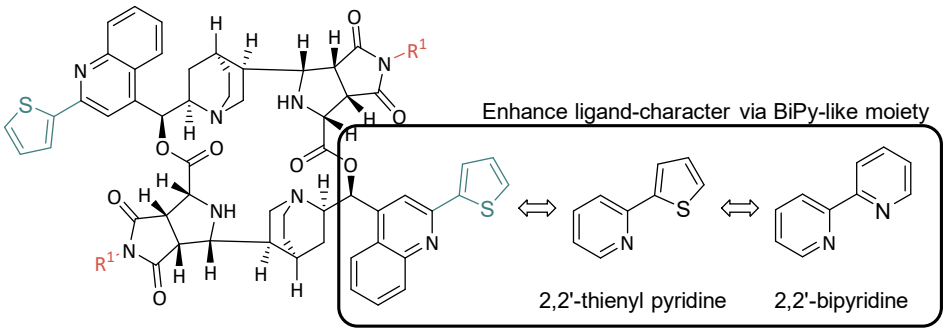


QD2'Ph (R^2 = Ph, R^3 = OMe)

Entry	Number	R^1	Maleimide	Yield	Isomer Ratio	Entry	Number	R^1	Maleimide	Yield	Isomer Ratio
1	**107b**		5aa	45	11 : 1	11	**107l**		5ar	42	2.1 : 1
2	**107c**		5ay	26	2.1 : 1	12	**107m**		5bl	43	1.2 : 1
3	**107d**		5bd	46	1.6 : 1	13	**107n**		5lm	41	1 : 1.1
4	**107e**		5ah	43	1 : 1.5	14	**107a** **108a**		5ac	40	1 : 1.2
5	**107f**		5bf	51	2 : 1	15	**107o**		5as	35	3.5 : 1
6	**107g**		5al	47	2.9 : 1	16	**107p**		5an	41	4.2 : 1
7	**107h**		5ap	38	1.3 : 1	17	**107q**		5ao	56	2.4 : 1
8	**107i**		5bi	45	1.8 : 1						
9	**107j**		5am	40	2 : 1						
10	**107k**		5bk	43	2.2 : 1						

Compounds **116a-c** were synthesized from **113e** (CN2'Th). The quinoline substitution pattern consists of a C2' 2-thienyl group and no C6' substituent (Table 10). This reaction could not be performed under usual conditions and demanded higher catalyst loading and a solvent mixture of DMF and acetonitrile. The reason for this, especially in contrast to the C2'-phenyl derivative **113d**, might originate from its similarity to 2, 2'-bipyridine (or 2,2'-thienyl pyridine). The bioactivity of quinine and quinidine against malaria is attributed to their capability to chelate iron(III).[9,10] Creating a compounds, that possess two additional motives capable of coordinating ions (pseudo-bipyridine-motives), was hoped to create a novel phenotype in comparison to the rest of the library members.

Table 10: Design concept based on the insertion of potentially chelating motives in compounds **116a-c** derived from **113e**.



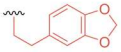
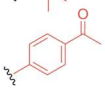
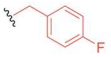
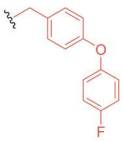
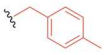
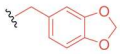
CN2'Th (R^2 = C_4H_3S, R^3 = H)

Number	R^1	Maleimide	Yield	Isomer Ratio
119a		5aa	28	4.5 : 1
119b		5ah	47	4 : 9.9 : 1
119c		5bi	25	11.9 :8.6 : 1.5 : 1

Compounds **120a-p** and **121a-b** were synthesized from **113f** (CN2'*n*Bu). The quinoline substitution pattern consists of a C2' *n*Butyl group and no C6' substituent (Table 11).

Table 11: Compounds **120a-p** and **121a-b** derived from **113f**.

CN2'nBu (R^2 = *n*Bu, R^3 = H)

Entry	Number	R^1	Maleimide	Yield	Isomer Ratio	Entry	Number	R^1	Maleimide	Yield	Isomer Ratio
1	**120a**		5aa	50	8.4 : 1	11	**121a**		5av	28	1 : 2.4
2	**120b**		5ay	40	2.2 : 1	12	**120k 121b**		5aw	28	1 : 3.1
3	**120c**		5ad	47	1.2 : 1	13	**120l**		5as	45	3.1 : 1
4	**120d**		5ah	43	1 : 1.9	14	**120m**		5an	46	3.2 : 1
5	**120e**		5bo	58	3.3 : 1 : 1.5	15	**120n**		5aj	47	1 : 1.4
6	**120f**		5ai	36	1.8 : 1	16	**120o**		5af	35	3.7 : 1 : 1 : 1.2
7	**120g**		5am	28	2.1 : 1	17	**120p**		5ao	52	2.4 : 1
8	**120h**		5ad	42	3.4 : 1						
9	**120i**		5ar	40	3.3 : 1						
10	**120j**		5bm	47	1 : 1.1						

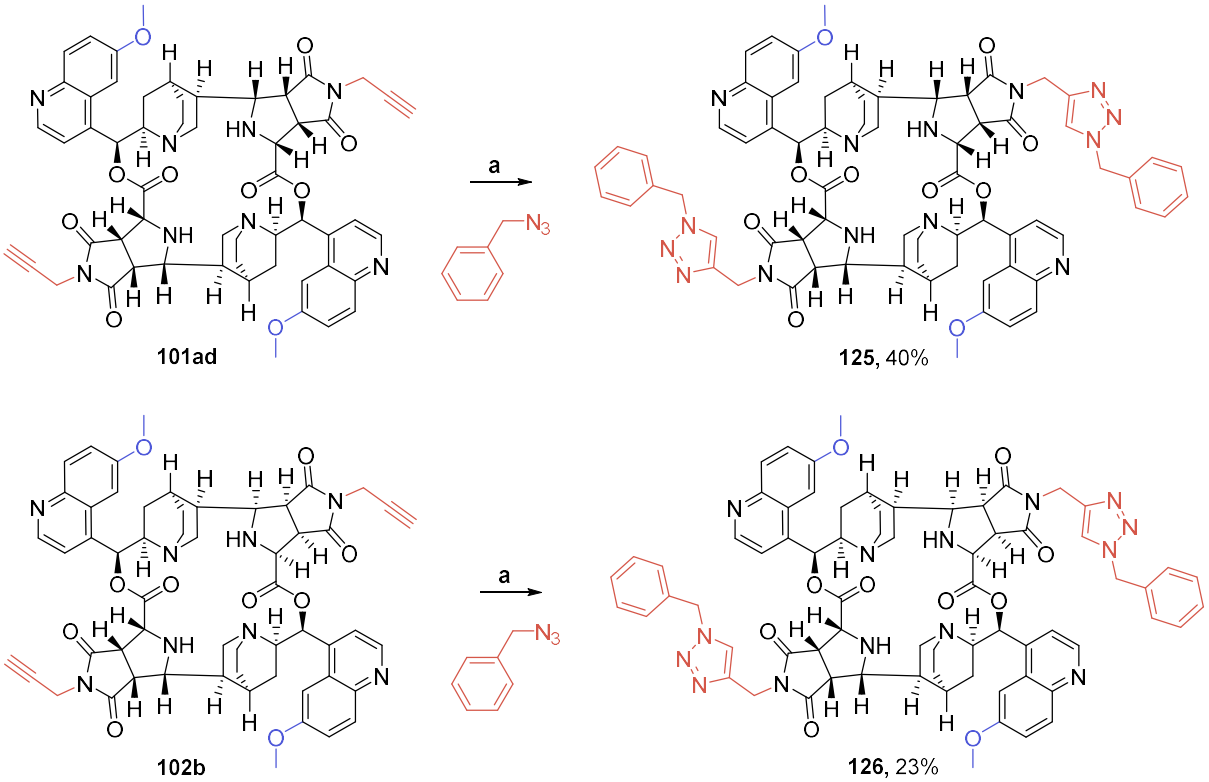
Compounds **122a-f** and **123a-b** were synthesized from **113g** (QD2'Cl). The quinoline substitution pattern consists of a C2' chlorine and a C6' methoxy group (Table 12).

Table 12: Compounds **122a-f** and **123a-b** derived from **113g**.

QD2'Cl (R^2 = Cl, R^3 = OMe)

Entry	Number	R^1	Maleimide	Yield	Isomer Ratio	Entry	Number	R^1	Maleimide	Yield	Isomer Ratio
1	**122a**		5aa	38	16.2 : 1	4	**122d**		5ab	50	4.8 : 1
2	**122b**		5bc	37	3.8 : 1	5	**122e 123a**		5bl	41	2.6 : 1
3	**122c**		5ay	50	3.6 : 1	6	**122f 123b**		5bm	49	2.3 : 1

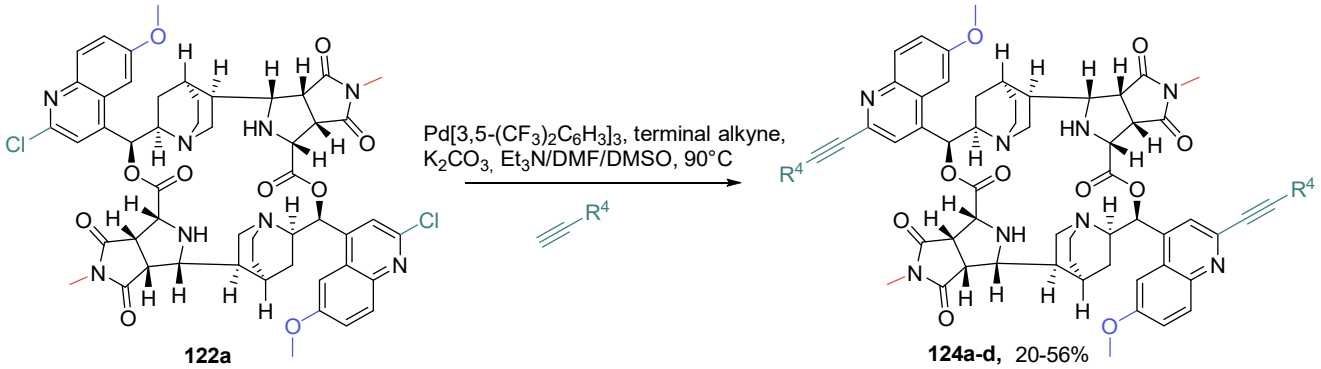
Two more library members, containing a benzyl tetrazole as a succinimide substituent, could be synthesized from the symmetrical- and unsymmetrical diastereomers **101d** and **102b** via CuAAC. The synthesis was performed by Pia Bodenbinder and is detailed in Section 2.5.2.



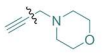
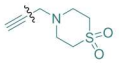
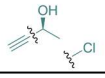
Scheme 25: Functionalization of propargyl containing macrocycles **101d** and **102d** via CuAAC with benzal azide. a) Benzylazide, CuI, K_2CO_3, H_2O/*t*BuOH.

Lastly, the chlorinated C2' positions of symmetrical macrocycle **122a** could be modified via Sonogashira coupling to yield compounds **124a-d** (Table 13**,** the synthesis is detailed in section 2.5.2). For the synthesis of symmetrical macrocycles **124a-c**, an excess of alkyne reagent was used. In case of **124d**, only one equivalent of terminal alkyne was used, resulting in desymmetrization.

Table 13: Symmetrical and desymmetrizing functionalization of macrocycles with C2'clorination (**122a**) via Sonogashira reaction with terminal alkynes.

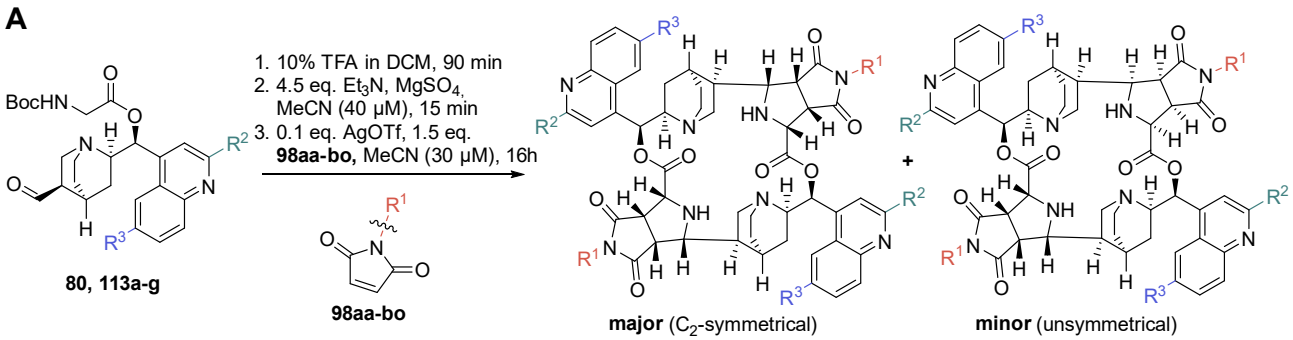


122a (R^1 = Me, R^2 = Cl, R^3 = OMe)

Entry	Entry	R^4	Yield
1	**124a**		48%
2	**124b**		56%
3	**124c**		41%
4	**124d**		20%

3.3.3 Selectivity and Scope of the reaction sequence

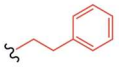
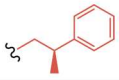
The 1,3-dipolar cycloaddition tolerated a wide range of maleimides as dipolarophiles. The nature of the *N*-substituent largely determined the stereoselectivity and the yield of the reaction (compare Figure 29B and C). For small substituents like methyl groups diastereomeric ratios were high. Introduction of larger substituents, with steric bulk in direct proximity to the maleimide nitrogen, lead to lower diastereoselctivity (Figure 29C, compare entries 1 to 5 and 6 to 10). For some *N*-phenyl maleimides, formation of additional diastereomers was observed. If the phenyl ring was in benzylic or homobenzylic position, selectivity is higher and no additional diastereomers were detected (Figure 29.C, entries 6 and 7). In depth investigation of these additional diastereomers was not pursued and except for two instances (**103** and **110**) they were neither isolated nor submitted for biological testing.



B N-methylmaleimide **5aa**

Entry	Derivative	Yield [%]	Isomer ratio
1	QD, **80**	51[a]	19 : 1
2	QD6'O*i*Pr, **113b**	43	17.4 : 1
3	QD6'OcBu, **113c**	24	12 : 1
4	QD2'Ph, **113d**	45[a]	11 : 1
5	QD2'Cl, **113g**	38	16.2 : 1
6	CN, **113a**	41[a]	16.7 : 1
7	CN2'nBu, **113f**	46[a]	8.4 : 1
8	CN2'Th, **113e**	29[b]	4.5 : 1

C QD **3** (R^2 = H, R^3 = OMe)

Entry	R^1	Yield [%]	Isomer ratio	Entry	R^1	Yield [%]	Isomer ratio
1		51[a]	19 : 1	6		50	7.7 : 1 : 1.1
2		36	12.8 : 1	7		43	4 : 1
3		49	3.7 : 1	8		28	10.3 : 1
4		20	1 : 1	9		40	2.3 : 1
5		39	2.4 : 1	10		37	6 : 1

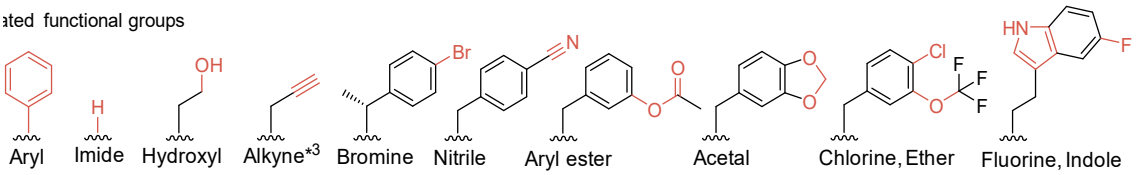


Figure 29: Stereoselective synthesis of homodimeric macrocyclic pseudo-NPs by 1,3-dipolar cycloaddition. A) One-pot three-step reaction sequence for macrocycle generation; B) Diastereomeric ratios observed for *N*-methylmaleimide different starting materials; C) Diastereomeric ratios observed for starting material 3 with differently *N*-substituted maleimides; D) Functional groups tolerated as maleimide *N*-substituent. [a] 3 eq. Et_3N; [b] 1:1 in MeCN:DMF; [c] $Cu(CH_3CN)_4OTf$ instead of AgOTf.

The restrictions on the scope of the developed reaction sequence regarding dipolarophiles, ring size and α-substituted amino acids has been discussed in Section 2.1.

Various quinoline substitution patterns were accepted (Figure 29B). No restrictions appear to apply to the nature of the *N*-substituent of the maleimide reagent (Figure 29.D).

The only quinoline or maleimide substituents (R^1/R^2/R^3) that were detrimental to the reaction outcome were groups intrinsically capable of interacting with the metal catalyst. The incorporation of C2'-thiophene starting material or *N*-propargyl maleimide needed modified conditions. C6'-propargylated starting materials did not react under any reaction condition, regardless of catalyst or solvent.

3.4 Identification and Refinement of a novel LC3-lipidation Phenotype

Biological experiments in this section were performed by Dr. Sonja Sievers

Monitoring ATG8 proteins in phenotypic assays can be an excellent way to identify compounds, that modulate the vast network of autophagic processes. To this end, MCF7 cells stably expressing EGFP-conjugated LC3B were used. If autophagy is induced, cytosolic LC3B-I is attached to membrane lipids of nascent autophagic structures (LC3B-II, Figure 30 and Section 1.5.1). Through this mechanism, the diffuse fluorescence of cytosolic LC3B-I-EGFP will concentrate in so called “puncta” corresponding to e.g. autophagosomes (Figure 30). This type of assay was first introduced by Balgi *et al*.[114] In order to identify compounds that modulate LC3-dependent processes and to preselect for more potent substances, two types of assays were performed in this cell line.

In the first of the two, mTOR-dependent autophagy was induced before compound treatment either by starvation, utilizing Earle's balanced salt solution (EBSS), or via treatment with rapamycin (Rapa). Chloroquine (**127**), which inhibits autophagosome–lysosome fusion (Figure 30),[115] was used to stop autophagosome turnover and thus increase the accumulation of eGFP-LC3-positive vesicles. If a compound negatively affected the total area of LC3-puncta per cell, an autophagy inhibition was assumed. If the compound increased the puncta, a coactivation-mechanism was assumed. If the level of coactivation was above 150% for both assays, the compound was deemed sufficiently potent to be pursued further.

In the second stage, no artificial induction of autophagy was conducted before treatment with the compounds. Again, to increase the readout, CQ was added. If the compound would upregulate LC3-dependent pathways, puncta would accumulate. In a control assay, no CQ was added. Here, no strong accumulation of autophagosomes was expected for activators of canonical autophagy, because of the natural turnover through uninhibited autophagosome-lysosome fusion and subsequent degradation.

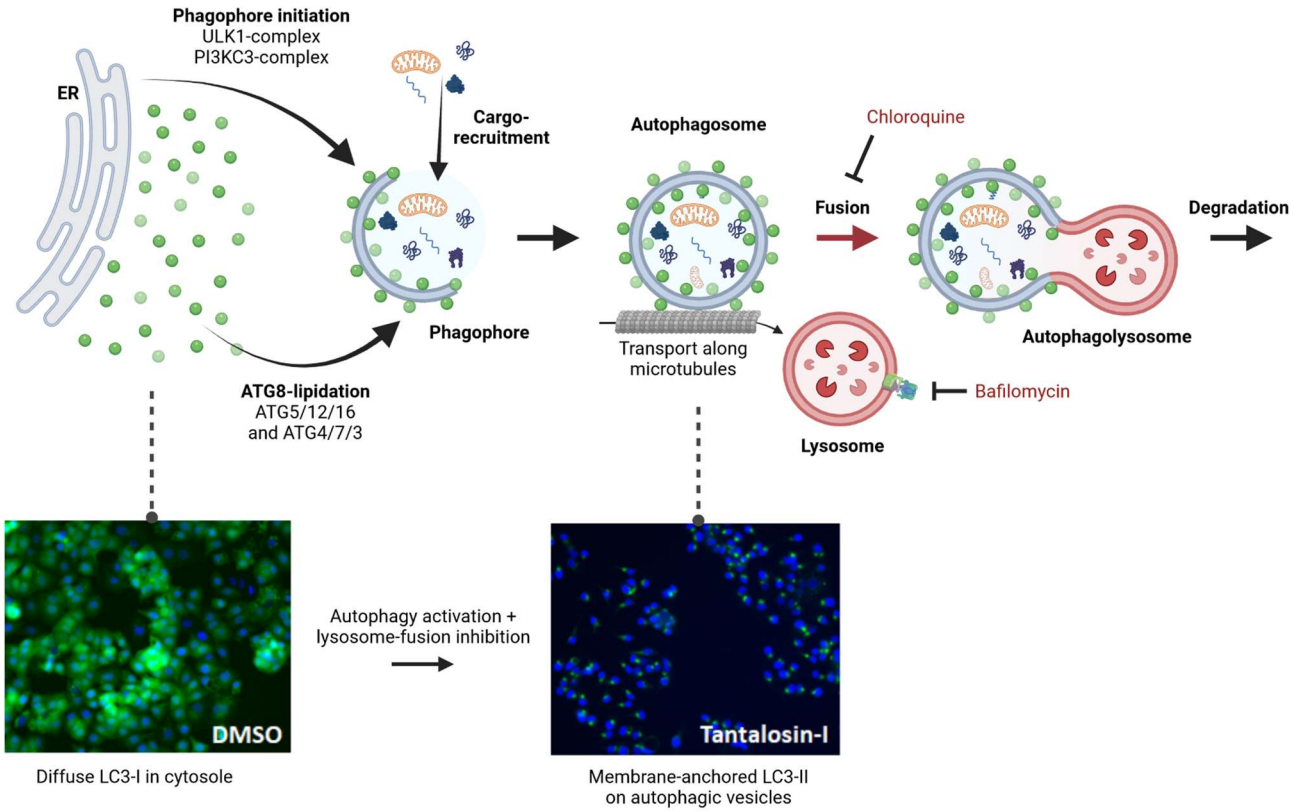


Figure 30: GFP-labeled LC3B-I (green dots) gets recruited to autophagic structures such as the phagophore. LC3B-II-GFP thus concentrates and forms "puncta". An inhibition of autophagic flux through chloroquine or bafilomycin enhance the signal by ultimately inhibiting degradation of autophagosomes. Nuclei are stained blue. (Graphic made with Biorender[116]

To quantify the induction of autophagy mediated by the respective compound, 3 µM Obatoclax (**128**, Figure 31) was used as a reference. Obatoclax triggers apoptosis in several cell lines but is known to increase LC3-positive structures as well.[117,118] Obatoclax is a prodigiosin derivative and might therefore act via the extracellular signal-regulated (ERK) signaling pathway.[119] All cited studies showed, that prodigiosines such as Obatoclax also inhibit the autophagic flux. Together with its capability to induce autophagy, this leads to a pronounced phenotype in the described assay even without addition of chloroquine. This way, meaningful EC_{50}-values could be generated for compounds that do not act as activators of canonical autophagy pathways, but lead to LC3-lipidation-phenotypes via other mechanisms. The EC_{50} of a substance is thus the concentration at which it reaches 50% of the LC3-lipidation induced by Obatoclax in the respective assay (±CQ). The EC_{50} is complimented by the "%activity"-value, which compares the maximum amount of puncta caused by compound treatment with value observed under treatment with 3 µM Obatoclax.

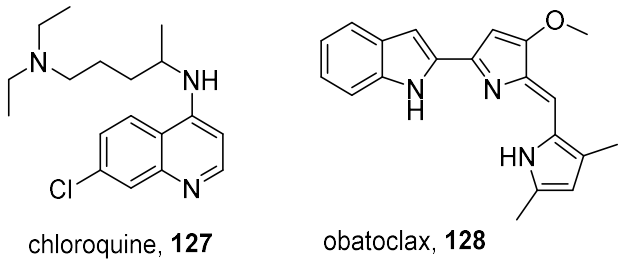


Figure 31: Structures of the two autophagy inhibitors chloroquine and Obatoclax

The most active initial hit (**101ba**) was named Tantalosin-I after the ever-hungry Tantalus of Greek mythology, as treatment with this compound appeared to put the cells into a state resembling the punishment of this mythological figure.

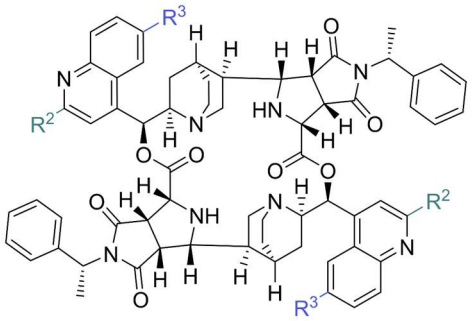
3.4.1 Structure-Activity-Relationship

Using the workflow described above, a number of compounds could be identified, that produced the autophagy activation phenotype. Based on the two first hits Tantalosin-I (**101ba**) and **101af** an SAR study was conducted. The metric used to judge new substances was mainly their EC_{50}-values, but also their capacity to produce a pronounced phenotype. The latter is encoded in their relative "activity" in comparison to the reference (3 µM Obatoclax) and to a lesser extend in the relative activity in the coactivation assays utilizing amino acid starvation or rapamycin cotreatment. Several deductions could be made.

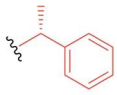
Firstly, the influence on activity of the quinoline substitution pattern was not as pronounced as the effect of the R^1-substituent. If R^1 was either (R)-1-phenylethyl or *tert*-butyl, almost all R^2/R^3 combinations were accepted in the sense, that the compound would either have an EC_{50} below 10 µM or showed at least a slight coactivation (Table 14A and B). Seemingly, C2'-phenyl, C2'-cloro and C6'-OcBu were not tolerated well (Table 14, **107n**, **122f**, **118l**). An SAR encodes all properties of the compounds that are not measured separately. Hence, it could also be hypothesized, that the solubility of these compounds was too low to reach meaningful cellular concentrations, rather than their capability to bind a putative target (solubility is discussed in the Supplementary Section).

Table 14: **Effect of the quinoline substitution pattern (R^2/R^3) on autophagy activation**. A) R^1 = (R)-1-phenylethyl; B) R^1 = *tert*butyl.

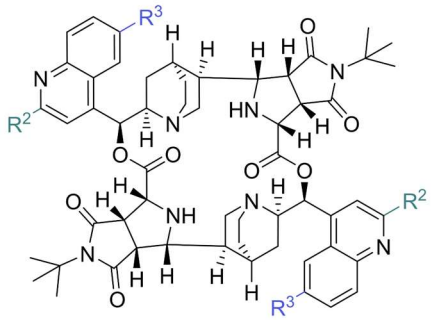
A



C_2-symmetrical

Number	R^1	R^2	R^3	$EC_{50,-CQ}$ [µM]	$Activity_{-CQ}$ [%]	$EC_{50,+CQ}$ [µM]	$Activity_{+CQ}$ [%]	Starv. [%]	Rapa. [%]
Tantalosin-I 101ba		H	OMe	0.80 ± 0.7	119 ± 13	0.97 ± 0.7	118 ± 21	366	1284
114p	"	H	H	1.84 ± 0.1	123 ± 14	3.13 ± 0.6	84 ± 5	237	308
116j	"	H	O*i*Pr	4.71 ± 1.2	95 ± 12	inactive	23 ± 3	170	267
118l	"	H	OcBu	inactive	8 ± 5	inactive	15 ± 1	118	172
107n	"	Ph	OMe	inactive	n.d.	inactive	n.d.	140	152
120j	"	*n*Bu	H	4.47 ± 0.38	58 ± 4	1.60 ± 0.15	73 ± 22	245	311
122f	"	Cl	OMe	Inactive	26 ± 6	inactive	20 ± 14	99	157

B



C_2-symmetrical

Number	R^1	R^2	R^3	$EC_{50,-CQ}$ [µM]	$Activity_{-CQ}$ [%]	$EC_{50,+CQ}$ [µM]	$Activity_{+CQ}$ [%]	Starv. [%]	Rapa. [%]
101af		H	OMe	3.04 ± 0.2	87 ± 2	4.45 ± 0.9	60 ± 7	259	365
114d	"	H	H	inactive	1 ± 0.2	inactive	8 ± 6	104	105
116c	"	H	O*i*Pr	3.45 ± 0.34	150 ± 9	4.30 ± 0.05	96 ± 53	293	288
118f	"	H	OcBu	2.85 ± 0.45	129 ± 13	3.77 ± 0.33	160 ± 5	345	340
107d	"	Ph	OMe	25.2 ± 4	62 ± 8	12.2 ± 2	108 ± 11	292	568
120c	"	*n*Bu	H	>10	35 ± 9	4.64 ± 2.5	76 ± 16	172	279

The effect of the R^1-substituent was probed by keeping the quinoline substitution pattern of Tantalosin-I (R^2=H/R^3=OMe) but varying the R^1-substituent. Here, the capacity of the resultant compound to produce the LC3-lipidation phenotype changed more drastically (Figure 32).

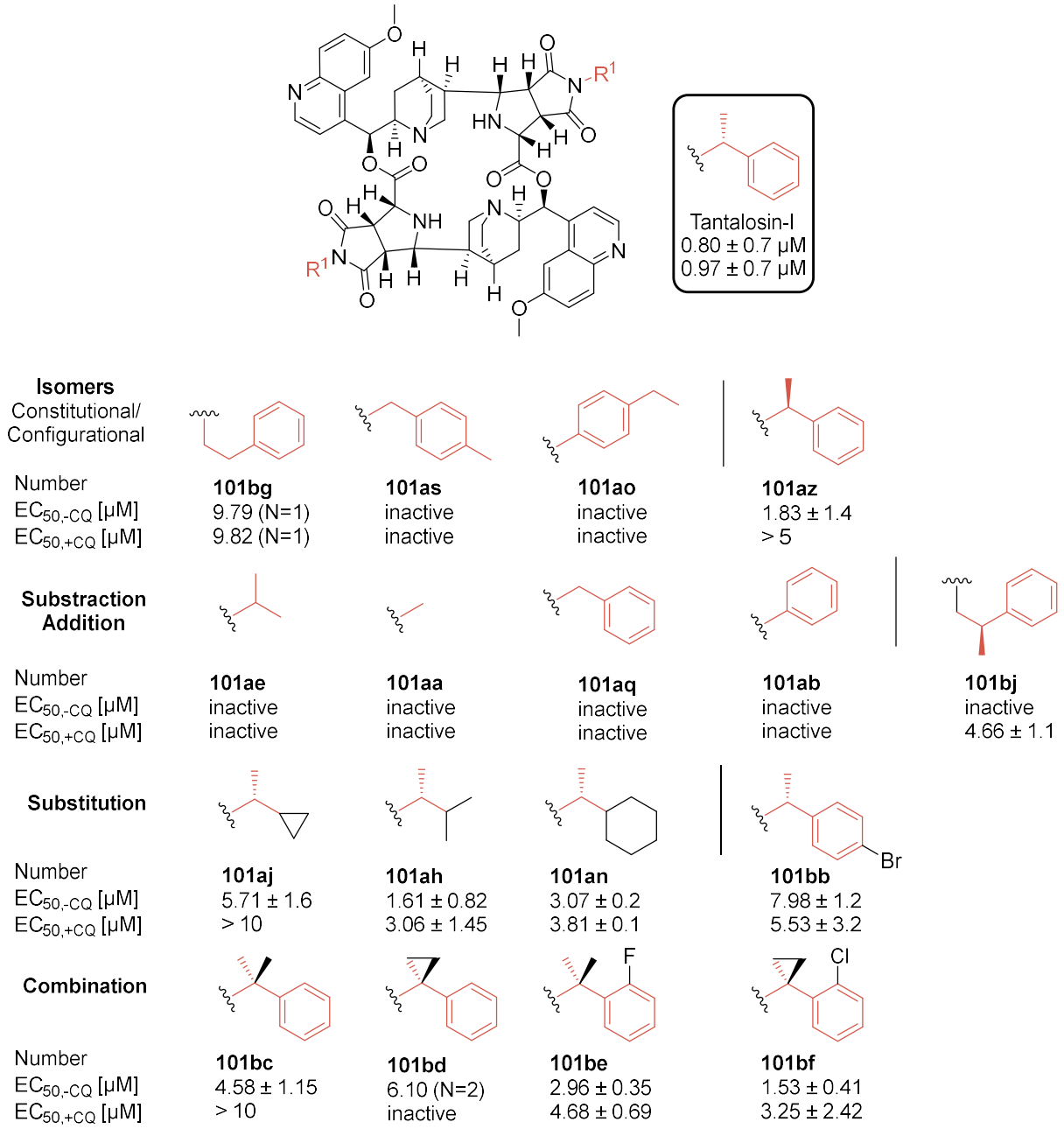


Figure 32: Effect of the succinimide substituents (R^1) on autophagy activation.

Row one contains constitutional isomers of the most active R^1-substituent (R)-1-phenylethyl. It is evident, that these changes were enough to reduce the activity by at least 10-fold (**101bg**) or shut it down entirely (**101as** and **101ao**). Even a configurational change from (R)-1-phenylethyl to (S)-1-phenylethyl reduced the activity by 2-fold (**101az**). Latter corresponds to a change of two of the 20 stereocenters of the molecule. Moreover, the stereocenters in question possess the most rotational freedom as they are located away from the macrocycle itself.

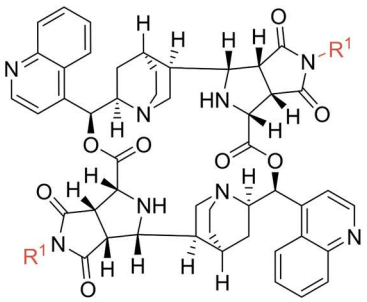
Row two shows the effects on activity, when any part of the α-phenylethyl substituents was omitted. Any deletion of functionality lead to inactivity. This could also be observed monitoring the phenotypic change cells undergo after compound treatment. The cell-painting assay, which analyzes morphological changes on multiple levels, revealed a correlation between the autophagy activation phenotype and an over-induction phenotype in cell-painting. This is likely due to a process along the lines of autophagy-dependent cell death, where cells use the autophagy machinery to engulf vast portions of themselves in vacuoles and ultimately die.[120] This type of process, combined with the resultant decline in the number of cells, lead to phenotypic changes too great for a sensible cell-painting readout (i.e. "over-induction"). Compounds, like **101aa**, that do not show the activation phenotype, often do not show a pronounced induction or toxicity in cell-paining either. In compound **101bj** the α-phenylethyl group was relayed on an additional methylene group. Similar to **101bg**, this did not abolish the activity entirely.

Row three contains compounds, where the phenyl groups of the Tantalosin-I are exchanged for alkyl groups of different size. The loss of aromaticity (i.e. **101an**) never abolished the activity, but lead to compounds with lessened activity.

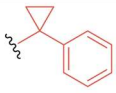
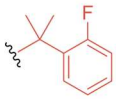
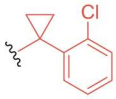
While the α-methyl group has been identified as important for activity (Tantalosin-I vs. **101aq**), the configuration of its corresponding stereocenter seemed exchangeable (Tantalosin-I vs. **101az**). Row four shows compounds were the α-stereocenter is exchanged for symmetrical groups reminiscent of a *tert*-butyl group which, itself, often produced bioactive molecules (Table 14B). **101be** and **101bf** further introduce an ortho halogen substituent to the phenyl group. This was done to twist the phenyl group along its sigma bond due to 1,5-repulson of the α-substituents and the halogen atom. It was hypothesized that this might mimic the conformation the phenyl ring adopts in presence of an α-methyl stereocenter. Compounds of these classes were less active, while the two ortho-halogenated versions were in fact more active than their equivalents without additional halogen atoms (compare **101be** and **101bc** with **101bf** and **101bd**).

In order not to over-fit newly generated derivatives to Tantalosin-I, many compounds outside the deduced logic were synthesized as well. Moreover, in order to identify the local minimum in the SAR-landscape, quinoline derivatives of the most potent succinimide substituents were also synthesized (e.g. Table 7).

Table 15: Close R^1-derivatives of the most active compound Tantalosin-II.



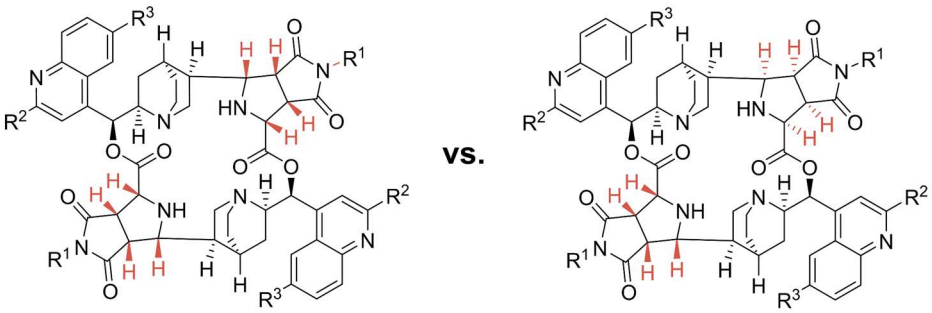
C_2-symmetrical

Number	R^1	R^2	R^3	$EC_{50,-CQ}$ [µM]	$Activity_{-CQ}$ [%]	$EC_{50,+CQ}$ [µM]	$Activity_{+CQ}$ [%]	Starv. [%]	Rapa. [%]
114q		H	H	6.99 (N=2)	48 ± 6	>10	31 ± 7	237	327
114r		H	H	2.56 ± 0.51	142 ± 9	3.63 ± 0.53	220 ± 17	183	756
Tantalosin-II 114s		H	H	0.40 ± 0.01	132 ± 8	0.42 ± 0.05	150 ± 10	288	1023

One of these compounds (Tantalosin-II, **114s**), synthesized from cichonine (**4**) and 1-(2-chlorophenyl)cyclopropyl maleimide (**98aw**), surpassed the EC_{50} of Tantalosin-I. With an EC_{50} of 0.4 µM for the CQ-indipendent phenotype, Tantalosin-II constitutes the most active compound identified in this study.

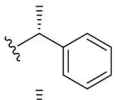
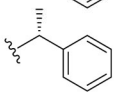
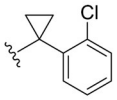
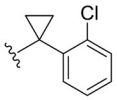
None of the 21 unsymmetrical diastereomers tested, showed any induction of the autophagy activation phenotype. The comparison of the two most active substances (Tantalosin-I and -II) with their respective diastereomers (**102e** and **115b**) highlights this strikingly (Table 16). This comes as no surprise as the three-dimensional shape and orientation of functional groups in these macrocycles greatly differs from the symmetrical diastereomers, as discussed in Section 2.2.5.

Table 16: Comparison of the two most active compounds Tantalosin-I and -II with their respective unsymmetrical diastereomers **102e** and **115b**.



C_2-symmetrical **101ba**, **114s**

unsymmetrical **102e**, **115b**

Number	R^1	R^2	R^3	$EC_{50,-CQ}$ [µM]	$Activity_{-CQ}$ [%]	$EC_{50,+CQ}$ [µM]	$Activity_{+CQ}$ [%]	Starv. [%]	Rapa. [%]
Tantalosin-I **101ba**		H	OMe	0.80 ± 0.7	119 ± 13	0.97 ± 0.7	118 ± 21	366	1284
102e		H	OMe	inactive	3	inactive	4	175	142
Tantalosin-II **114s**		H	H	0.40 ± 0.01	132 ± 8	0.42 ± 0.05	150 ± 10	288	1023
115b		H	H	inactive	4	inactive	7	145	167

As the EC_{50} of these compounds is well below the detection cutoff of 10 µM, this harsh drop in activity can also provide a hint at the biologically active species. It could be questioned, whether the macrocycles themselves constitute the biologically relevant species, as the hydrolysis of one or both ester bonds of these macrolactones would produce new chemical entities. While this data does not exclude that a non-cyclic dimeric molecule is the active species, it should exclude, that a monomer produced by dual ester hydrolysis, is. In this case, a symmetrical macrocycle would produce two equivalents of hydrolysis-product and an unsymmetrical version would produce one equivalent. If dual hydrolysis was prerequisite for a bioactivity, then the EC_{50} of the unsymmetrical diastereomer of e.g. Tantalosin-II should be in the range factor two higher. The observed inactivity might therefore constitute an argument in favor of the macrocycles themselves being the biologically active species.

Collectively this data suggests:

1. Quinoline substituents have a complex but net-negative effect on bioactivity. No substituent in R^2-position could improve the sought bioactivity over the natural unsubstituted derivatives. The same was true for R^3 where the most active compounds were bore a natural methoxy group or no

substituent. While a C6' methoxy group produced a greater number of active compounds, the most active substance (Tantalosin-II) does not bear a C6' substituent.

2. The succinimide substituent is the most sensitive position for variations. Even small changes can lead to complete inactivity. *Tert*butyl- and (R)-1-phenyletyl substituents could be identified as a lead structures, which ultimately lead to the design of the most active compound Tantalosin-II.

3. Unsymmetrical diastereomers of even the most active compounds, never produced the LC3-lipidation phenotype.

3.4.2 Unusual Aspects of the Identified Phenotype

Biological experiments in this section were performed by Anastasia Knyazeva and Dr. Sonja Sievers

The accumulation of EGFP-LC3B positive structures upon compound treatment in absence of chloroquine appears puzzling in the context of classical macroautophagy. A possible explanation for this behavior would be, that Tantalosin and has a dual mode of action. It would activate autophagy and would also be able to inhibit the degradation of the newly generated LC3-positive structures analogously to the proposed mode of action of Obatoclax. A second explanation would be, that a process outside the pathway of canonical macroautophagy is modulated, which also involves LC3-lipidation. The parallels of the phenotypes produced by Obatoclax and Tantalosin-II in the two assay systems, are easily identifiable by the human eye (Figure 33). The same is true for the inactivity of the Tantalosin-II diastereomer **115b**.

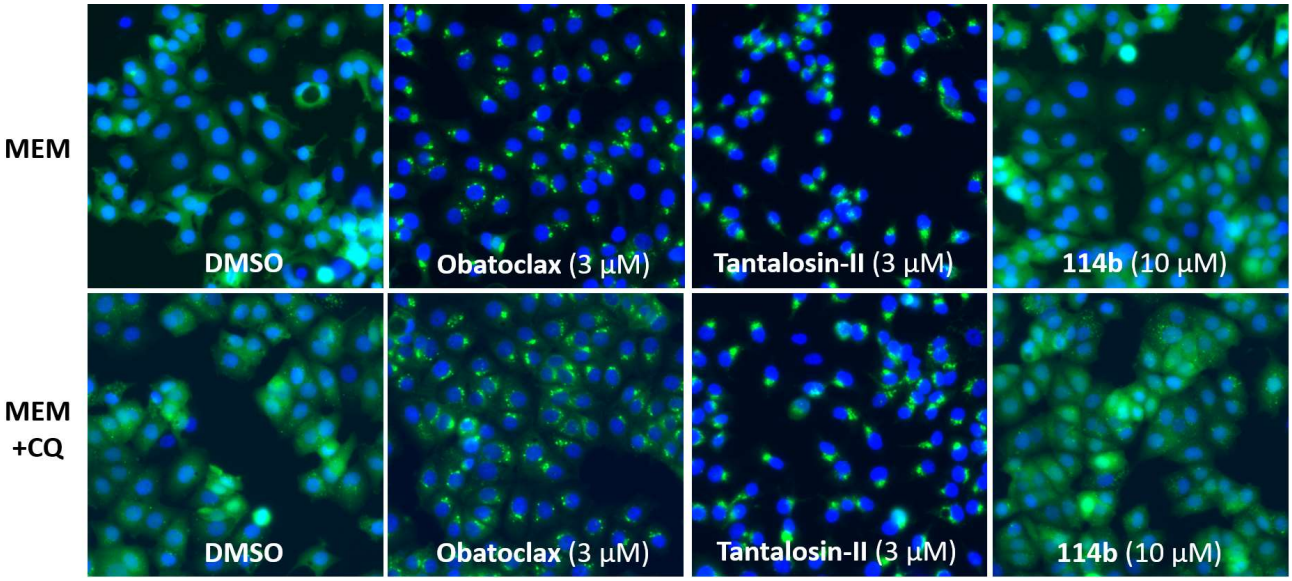


Figure 33: Effect of Tantalosin-II in the two LC3-lipidation assay setups (+/- CQ) in comparison to DMSO, Obatoclax and its unsymmetrical diastereomer **115c**. Nuclei were stained blue with Hoechst dye, LC3B-GFP appears in green.

Chloroquine seemed to have a slightly negative effect on the accumulation of LC3-puncta for Obatoclax as well as for bioactive Macro Pyrroquidines. This unusual impairing character of CQ on the phenotype could be confirmed in prof. Wu's lab on a protein level (Figure 34A) and via fluorescence microscopy (Figure 34B). While cotreatment with CQ enhanced the number if LC3-puncta and the levels of LC3-II protein for the mTOR-dependent autophagy activator Torin-1 (TOR), it slightly decreased both for Tantalosin-I (Figure 34A and B). The effect of Bafilomycin A (BAF) on the phenotype was even more unusual. Bafilomycin is a V-ATPase inhibitor and thus impairs autophagosome/lysosome-fusion via a mode of action distinct to CQ.[115] Analogously to CQ, it enhances the accumulation of autophagosomes in a cotreatment with Torin-1 (Figure 34A, B, C). A cotreatment with Tantalosin-I, however, led to a complete rescue from the activation phenotype mediated by Tantalosin-I alone (Figure 34A, B, C).

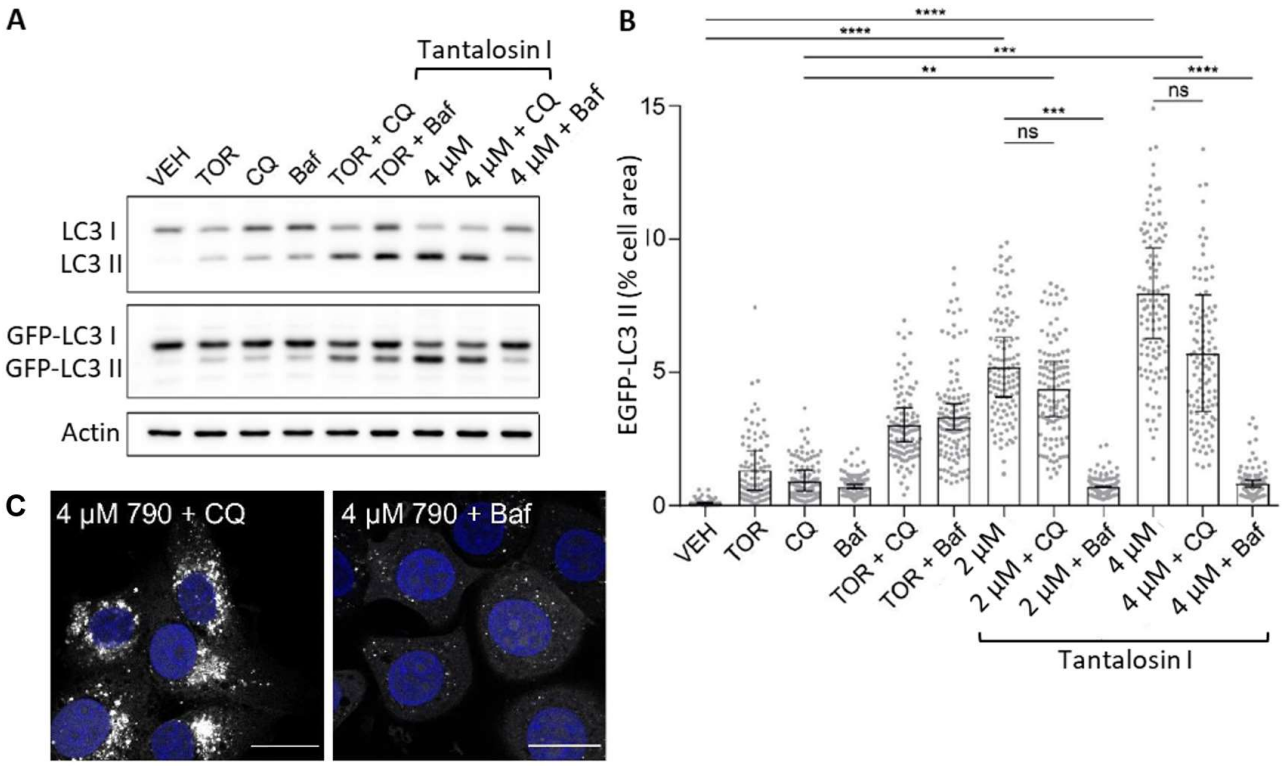


Figure 34: The effect of chloroquine- and bafilomycin A cotreatment with Torin-1 and Tantalosin-I on a protein level (A) and on the accumulation of LC3-puncta (B and C). Nuclei were stained blue with Hoechst dye, LC3B-GFP appears in white.

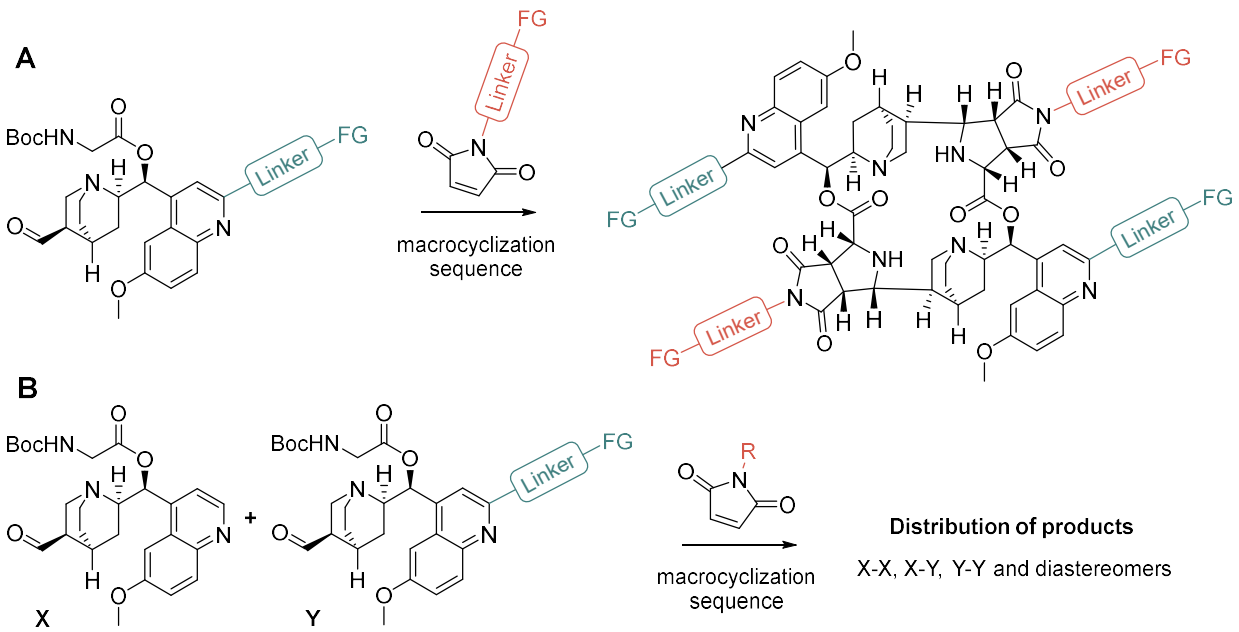
This behavior hints at a mode of action distinct to mTOR-dependent macroautophagy. Tantalosin-I could therefore act as a tool compound to investigate unknown mechanisms of the autophagic machinery. Hence, additional studies on the unique phenotype of Tantalosin-I have been undertaken but will be a part of future publications.

3.5 Design and Synthesis of Pulldown-Probes

3.5.1 Design Aspects in Probe-Generation from Homodimeric Macrocycles

Mono-functionalization a great challenge inherent to C_2-symmetrical homodimeric molecules when it comes to the attachment of a linker motive. Such a transformation simultaneously constitutes a desymmetrization.

If the monomeric starting materials would contain the linker motive, the resultant macrocycles are necessarily biofunctionalized (Scheme 26A). Such molecules are not only twice as dissimilar to the active parent molecule compared to the mono-functionalized analogues, but could also lead to crosslinking of two functional groups on the activated beads or even crosslink two beads. Monofunctionalization could theoretically also be achieved by reacting two different monomeric starting materials, where one would contain the linker motive and one would not. Experiments by Sanders *et al.* show that show that such a reaction results in a product distribution of the respective homodimers and the desired heterodimer.[43] The diastereomers of each of those species produced by the 1,3-dipolar cycloaddition would result in a complex mixture of adducts which would not only diminish the putative yield but would be challenging to purify (Scheme 26B).



Scheme 26: Dimerization during the macrocyclization sequence necessarily produces products containing two linker motives.

Therefore, the attachment of the linker needed to be performed on the macrocycles themselves. The SAR-study indicated R^2 and R^3 as suitable attachment sites, as *n*Butyl groups on C2' and different

alkyl substituents on the C6' hydroxyl group were tolerated with only a slight drop in activity (Table 14A, **120j** and **120c**). Although not likely to be successful, the succinimide substituent was not preemptively excluded as a potential attachment point for a linker. Analogously to the design principle of the compound library, linker motives could be installed in almost all hemispheres of the macrocycles, maximizing the possibility to find a molecule that is able to bind the target (Figure 35A).

In order to facilitate linker installment, functional groups needed to be introduced into the starting materials and carried through the macrocyclization sequence. These functional groups needed to be orthogonal to the macrocyclization conditions. CuAAC (copper(I)-catalyzed azide-alkyne cycloaddition) and Sonogashira coupling were selected as robust transformations which would tolerate the amine-rich macrolactones.

A terminal alkyne, for later CuAAC with an azide-functionalized linker, was introduced via *N*-propargyl maleimide and slightly modified 1,3-dipolar cycloaddition conditions (Figure 35A). The same linker attachment strategy was chosen for C6'-derivatives (Figure 35C). Here, a propargyl group was introduced by alkylation of cupreidine with propargylbromide (analogously to **111a**). C2'-clorination (Scheme 22) enabled the attachment of alkyne functionalized linkers in this position via Sonogashira coupling (Figure 35.B). The synthesis of the quinidine-derived starting materials is detailed in section 2.3.2.

Macrocycle **101ad** could be synthesized via a slightly modified protocol utilizing Cu(I) instead of Ag(I). Macrocycle **122f** was afforded through the conventional reaction sequence. However, terminal alkyne derivative **129** did not form the desired macrocyclic products **130** despite considerable efforts. Here, only deprotected monomer was observed.

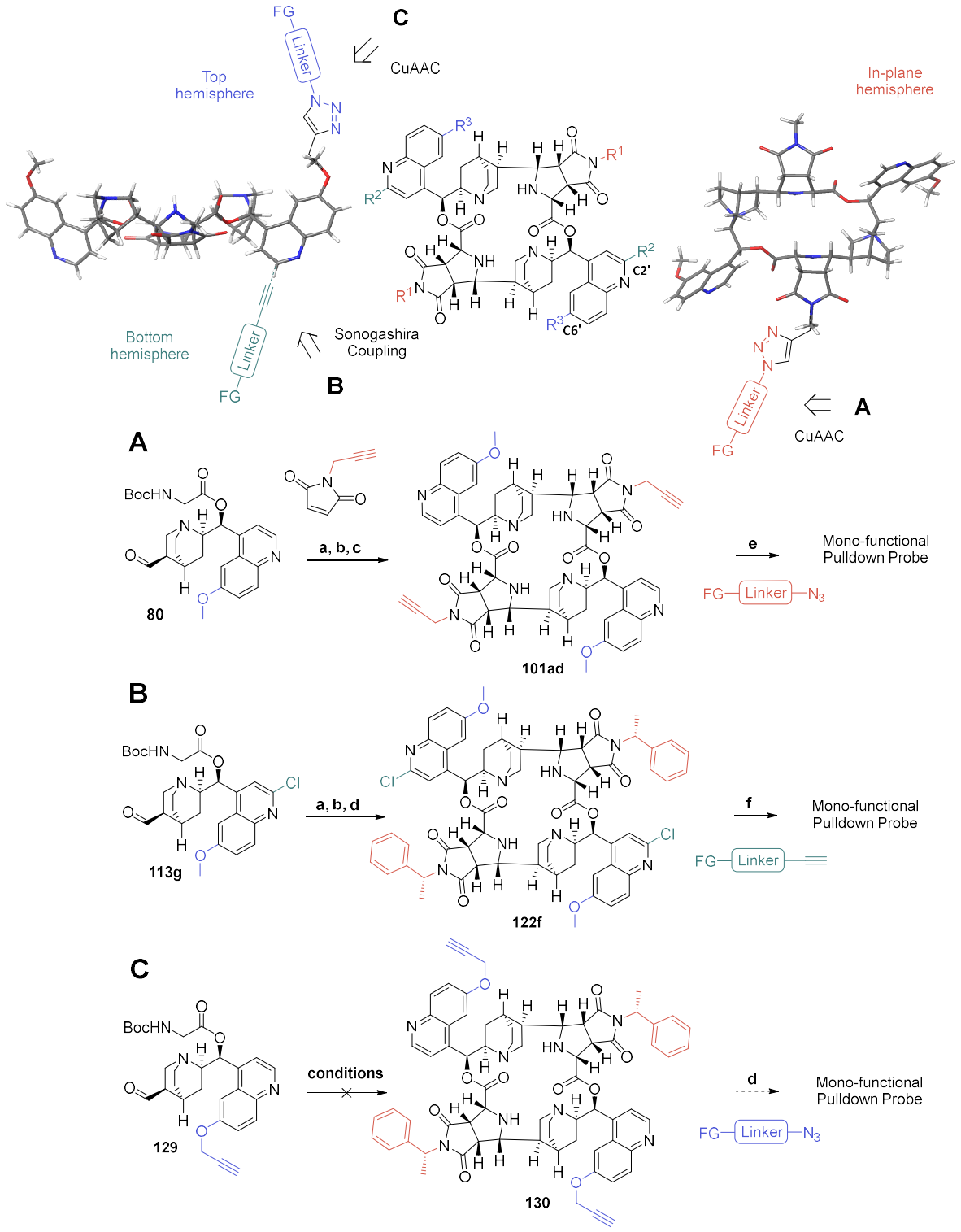
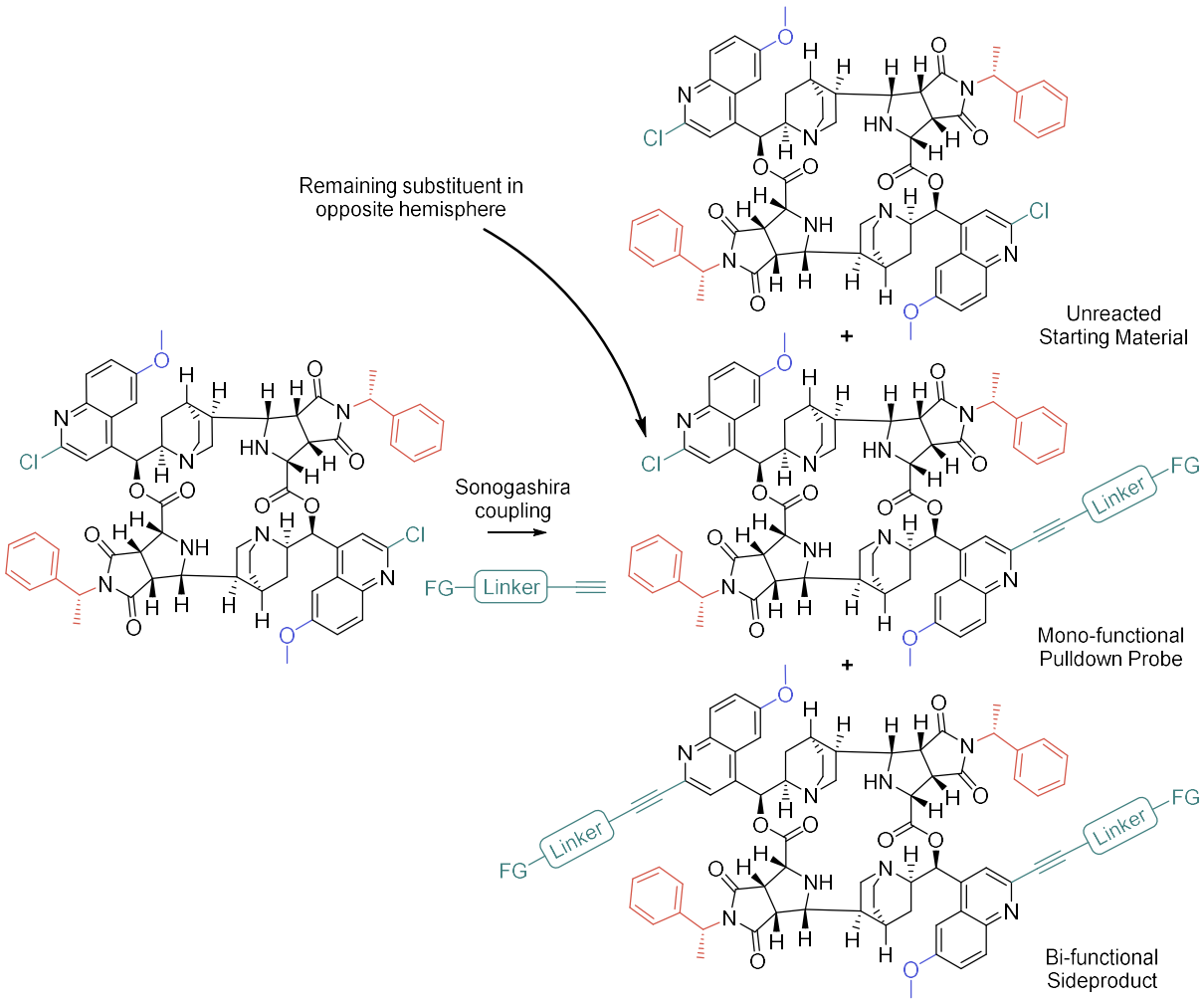


Figure 35: The three functionalization sites (succinimide substituent, C2', C6') allow installment of linker motives in all hemispheres of the macrocycles. A) Introduction a propargyl substituents on the succinimide nitrogens allows CuAAC with azide functionalized linkers; B) C2' chlorinated macrocycles allow Sonogashira coupling with linker molecules containing a terminal alkyne; C) Elusive C6' propargyl ether macrocycles were supposed prime CuAAC with azide functionalized linkers.

Desymmetrization of the functionalized macrocycles, i.e. the introduction of only one linker moiety, was achieved by the use of only one equivalent of functionalized linker. Unfortunately, this

inevitably implied the formation of bi-functionalized products. The linker molecules consumed in their formation were then no longer available for the remaining starting material, which constituted the third species left after completion of the reaction (illustrated for the Sonogashira coupling in Scheme 27).



Scheme 27: Desymmetrization of reactive hit-analogs using one equivalent of linker produces a product distribution of symmetrical bi-functionalized product, unsymmetrical monofunctionalized product and unreacted starting material.

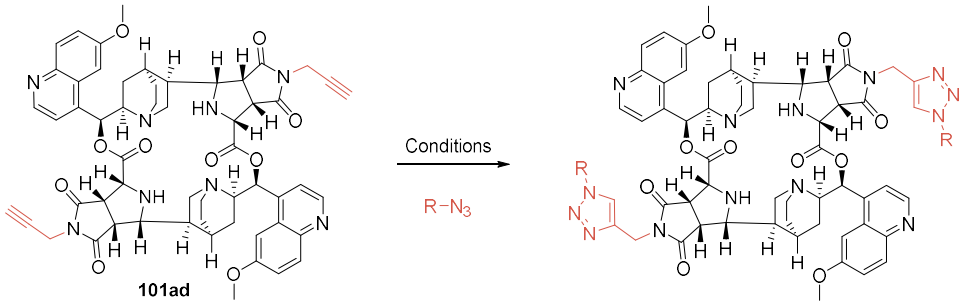
The detailed strategy combines lengthy syntheses with an inherently low-yielding desymmetrization step in the end. Furthermore, one of the functional groups needed to install the linker, will remain in the final molecule as a further deviation from the parent bioactive molecule. However, no other strategy appeared plausible.

3.5.2 Identification of Sonogashira and CuAAC Reaction Conditions for Cinchona Macrocycle Functionalization

Experiments towards CuAAC-mediated linker attachment were performed by Pia Bodenbinder

To identify conditions that would facilitate CuAAC of azide functionalized linkers with *N*-propargyl macrocycle **101ad**, a symmetrical test system with excess of either TMS- or benzyl azide was used (Table 17). This transformation also showed to be applicable the unsymmetrical diastereomer **102d** (entry 6 and 10 Table 17). These findings were not followed up with the attachment of a linker, as promising molecules obtained from the Sonogashira coupling approach had been identified already.

Table 17: **Screening for conditions facilitating CuAAC on macrocycle 101ad and its unsymmetrical diastereomer 102d**. A symmetrical transformation with excess of azide-reagent was chosen.



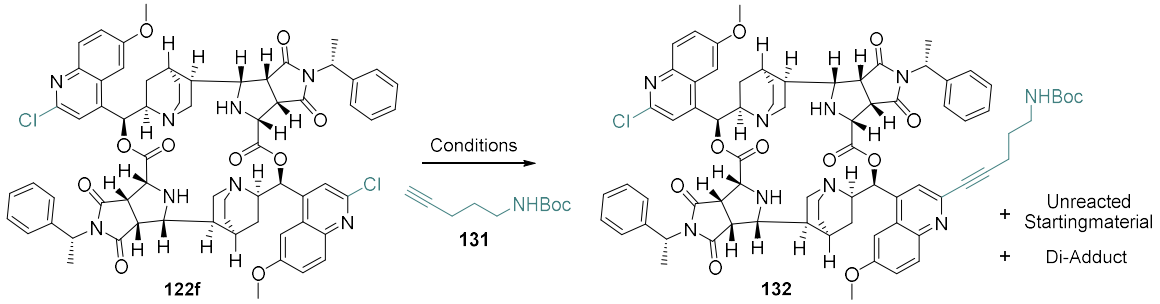
Entry	Solvent	Catalyst	Base	Azide	Yield
1	*t*BuOH/H_2O (1:1, 0.5 M)	CuI (0.2-0.4 eq.)	DIPEA (2-5 eq.)	Bn-azide (4-8 eq.)	-
2	"	CuI (1 eq.)	DIPEA (3 eq.)	TMS-azide (4 eq.)	-
3	"	CuI (1-1.5 eq.)	DIPEA (3-5 eq.)	Bn-azide (4-6 eq.)	-
4	"	CuI (1-1.5 eq.)	DIPEA (4 eq.)	Bn-azide (6 eq.)	-
5	"	CuI (1.5 eq.)	"	TMS-azide (6 eq.)	-
6[a)]	"	CuI (1.5 eq.)	"	Bn-azide (6 eq.)	40 %
7	DMF (0.5 M)	CuI (0.2-0.4 eq.)	DIPEA (2 eq.)	Bn-azide (4-8 eq.)	-
8	"	CuI (0.2-0.4 eq.)	DIPEA (5 eq.)	Bn-azide (4-8 eq.)	-
9	"	$CuSO_4$ (0.2 eq.) NaAsc (0.4 eq.)	-	Bn-azide (4-8 eq.)	-
10[b)]	*t*BuOH/H_2O (1:1, 0.5 M)	CuI (1.5 eq.)	"	Bn-azide (6 eq.)	22 %

[a)] Starting material: **101ad**; [b)] Starting material: **102b**

C2-chlorinated quinolines have been shown to be sufficiently activated for Sonogashira coupling before.[121] Conditions for the reaction of Macro Pyrroquidines with a linker containing a terminal alkyne were screened using *tert*butyl-pent-4-yn-1-ylcarbamate (**131**, Table 18). Boc-protection was

used to prevent undesired *N*-linkage via Ullmann-type amination or an intramolecular cyclization of the linker via an activated terminal alkyne species. Once deprotected, the terminal amine enabled immobilization to NHS-resin.

Table 18: **Screening for Sonogashira coupling conditions capable of facilitating linker attachment at C2' of 122f**. 1.05 eq. of terminal alkyne and 0.1 eq. catalyst were used. The reaction was performed with anhydrous, degassed solvents under argon.



Entry	Pd	Ligand	Cu	Base	Solvent	T [°C]	C [M]	Yield [%]
1	$(PPh_3)_2Cl_2Pd(II)$	-	CuI	Et_3N	THF/Et_3N	rt - 70	0.033	No conv.
2	"	-	CuI	Et_3N	DMF/Et_3N	rt - 70	0.033	No conv.
3	$Na_2Cl_4Pd(II)$	PCy_2tBu	CuI	Et_3N	iPr_2NH	80	0.033	No conv.
4	"	PCy_3	CuI	Et_3N	iPr_2NH	80	0.033	No conv.
5	"	PPh_2Cy	CuI	Et_3N	iPr_2NH	80	0.033	No conv.
6	"	PBn_3	CuI	Et_3N	iPr_2NH	80	0.033	No conv.
7	$(P(tBu)_3)_3$ Pd (0)	-	CuI	Et_3N	DMF/Et_3N	80	0.1	No conv.
8	Superstable Pd(0)	-	-	K_2CO_3	$DMSO/DMF/Et_3N$	90	0.1	28
9	Superstable Pd(0)	-	-	K_2CO_3	DMF/Et_3N	90	0.1	25

Sonogashira coupling could be performed under copper-free conditions utilizing Superstable Pd(0)® (see entry 8 and 9 Table 18). The same conditions could also be used for the attachment of various other terminal alkynes in symmetrical transformations and desymmetrizations (compare Table 13, Section 2.3.2). Following this protocol, four pulldown probes could be synthesized (Figure 36).

3.5.3 Pulldown Probes

Biological experiments shown in this section were performed by Dr. David Grill

To maximize the chance of finding a functional set of molecules, two linker lengths of different polarity were incorporated (Figure 36B). The combination of these with different NHS-resins, endowed themselves with spacers of different length between resin and crosslinking sites, should enable the identification of a suitable distance between resin surface, small molecule and protein of interest (Figure 36). Moreover, the same linkers were attached to biologically inactive molecule **122a** (derived from **101aa**). The comparison of pull-down experiments using active and inactive probes can be used to exclude unspecifically bound proteins and generate more robust leads.

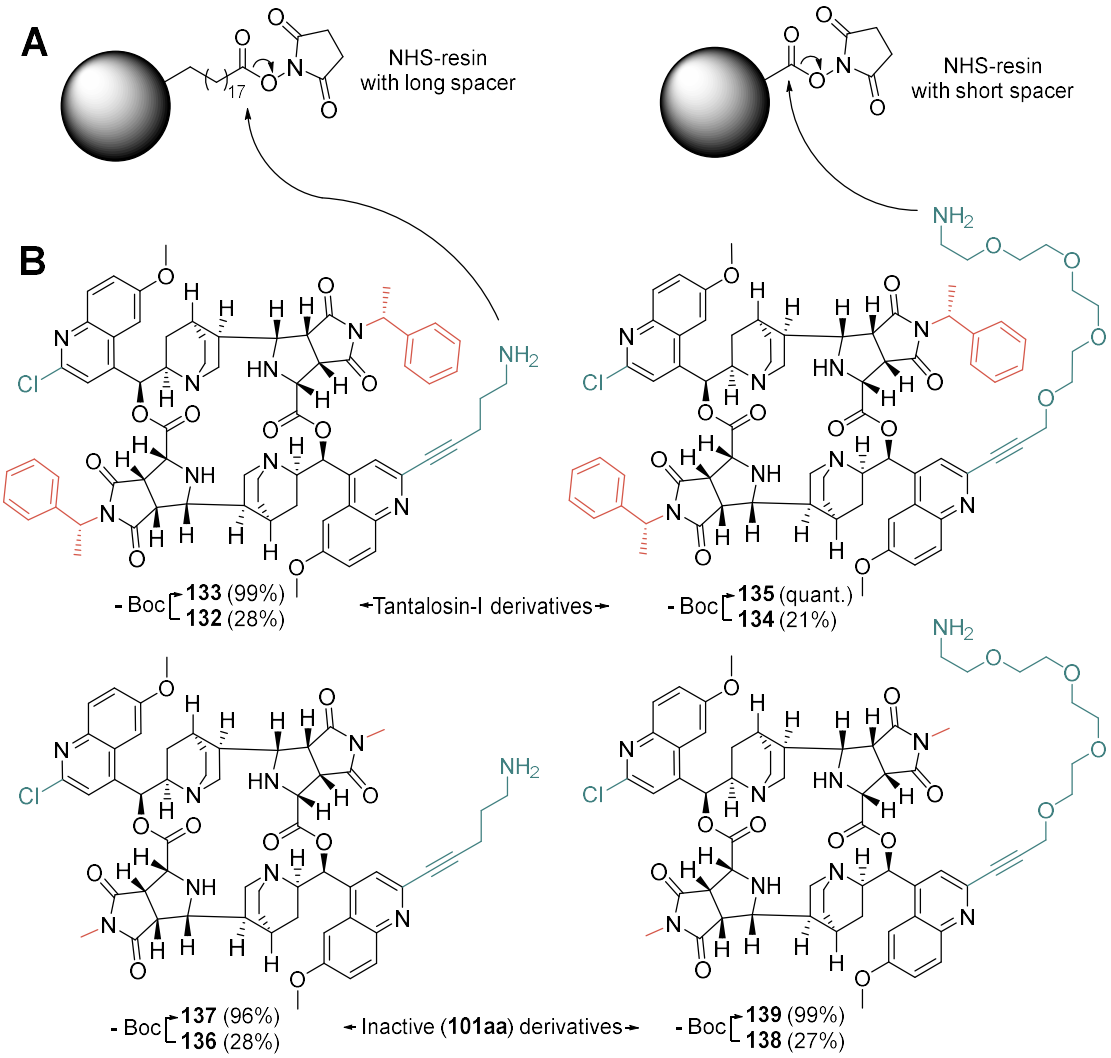


Figure 36: Overview over Sonogashira derived pulldown probes **133 – 139** and their conceptual match with NHS-resins containing spacers of different length. A) NHS-resins and their crosslinking mechanism with primary amines; B) Mono-functional pulldown probes **133 – 139**.

Long PEG_4-linker **140** was synthesized from commercial primary amine precursor via treatment with Boc-anhydride.

Boc-deprotection of the monofunctionalized macrocycles in proceed in quantitative yields. A tri-TFA salt was assumed, as the treatment with TFA left the primary amine of the respective linker protonated. The pulldown probes were not further purified, as the NMR-spectra were clean and purification via preparative HPLC appeared to lead to an unknown process that seemed to produce epimers or rotamers.

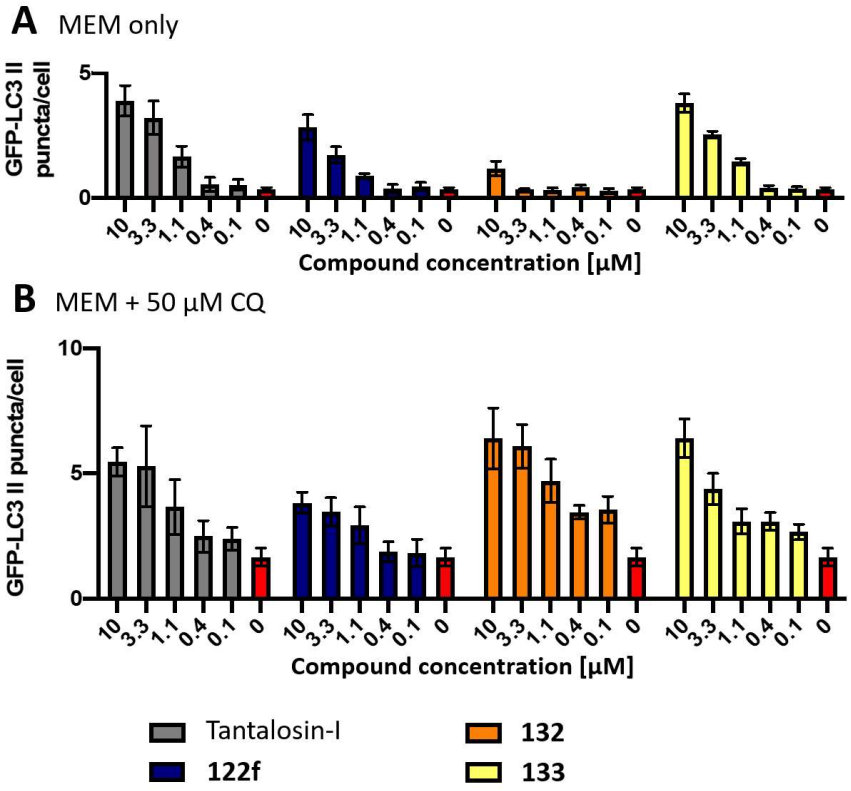


Figure 37: Autophagy activation of Tantalosin-I and its derivatives used in generation of the active C_5-linker-pulldownprobe **133** (**122f** and **132**) via autophagosome accumulation (LC3B-GFP granule count). MCF7-LC3, mean values n = 3 , 3 h treatment. A) Fed medium only, no chloroquine; B) Fed medium containing 50 µM chloroquine.

All precursors of the Tantalosin-I C_5-pulldown probe **133** were tested in the LC3-lipidation assay (Figure 37). Relative to the hit compound (grey), its chlorinated analogue (blue) showed lower induction of autophagy in both assays, a property also reflected in the SAR data (Section 2.4.1). Gratifyingly, deprotected pulldown probe **133** (yellow) triggered dose dependent accumulation of LC3-II coated vesicles in both assays similar to Tantalosin-I. For unknown reasons, its Boc-protected analogue **132** (orange) only induced autophagosome formation in presence of chloroquine (Figure 37). **135**, containing the PEG_4-linker, did not show any activity in cell-based assays. As the longer

linker is attached at the same site, this loss in activity might be attributed to reduced membrane-permeability. Pulldown experiments with pre-immobilized small molecules are performed with cell lysates, where membrane permeability is not needed. Therefore, this probe was not excluded from further experiments. Pulldown probes derived from the inactive molecule (**137** and **139**) did not show any biological effect. With this Data in hand, pulldown experiments could be pursued.

4 Summary

The development of a three-step one-pot reaction sequence combining the 1,3-dipolar cycloaddition of different dipolarophiles with azomethine ylides formed *in situ* from dimeric cinchona-alkaloid-derived bis-Schiff bases, allowed the synthesis of 20-membered macrocycles containing 18 stereocenters. These novel molecules could be characterized utilizing a combination of NMR-analysis, computational modelling and X-ray crystallography. Latter constituted, to our knowledge, the first instance of repurposing of an automated protein crystallography setup for the generation of small molecule crystals. The structural insights allowed conscious design of a compound collection where substituents could be installed in distinct spacial hemispheres. Functional groups, carried through the synthesis of the macrocycles, allowed their use as synthetic platforms for the generation of monofunctionalized pulldown probes or bifunctionalized derivatives.

Thorough characterization of the synthesized collection of 167 compounds in multiple phenotypic assays, revealed potent upregulators of LC3-lipidation, which is the hallmark protein of most autophagic processes. This upregulation was insensitive to the addition of Chloroquine, which sets it apart from mTOR-inhibitors like Torin-1. Most interestingly, co-treatment with Bafilomycin lead to a complete rescue from the observed phenotype. EC_{50} values for this phenotype could be generated using Obatoclax as a reference and were used as the metric for an SAR study. Tantalosin-II could be identified the most potent compound with an EC_{50} of 0.40 ± 0.01 µM and an increase of 32 ± 8% in LC3-accumuation over the reference. Further biological investigations of this unique phenotype are currently undertaken.

Macro Pyrroquidines were designed as pseudo-natural products, combining fragment-sized cinchona alkaloids with the pyrrolidine motive in a rigid macrocyclic system. The biological results detailed, could further substantiate the pseudo-NP concept as *de novo* design principle for the generation of biologically relevant chemical matter.

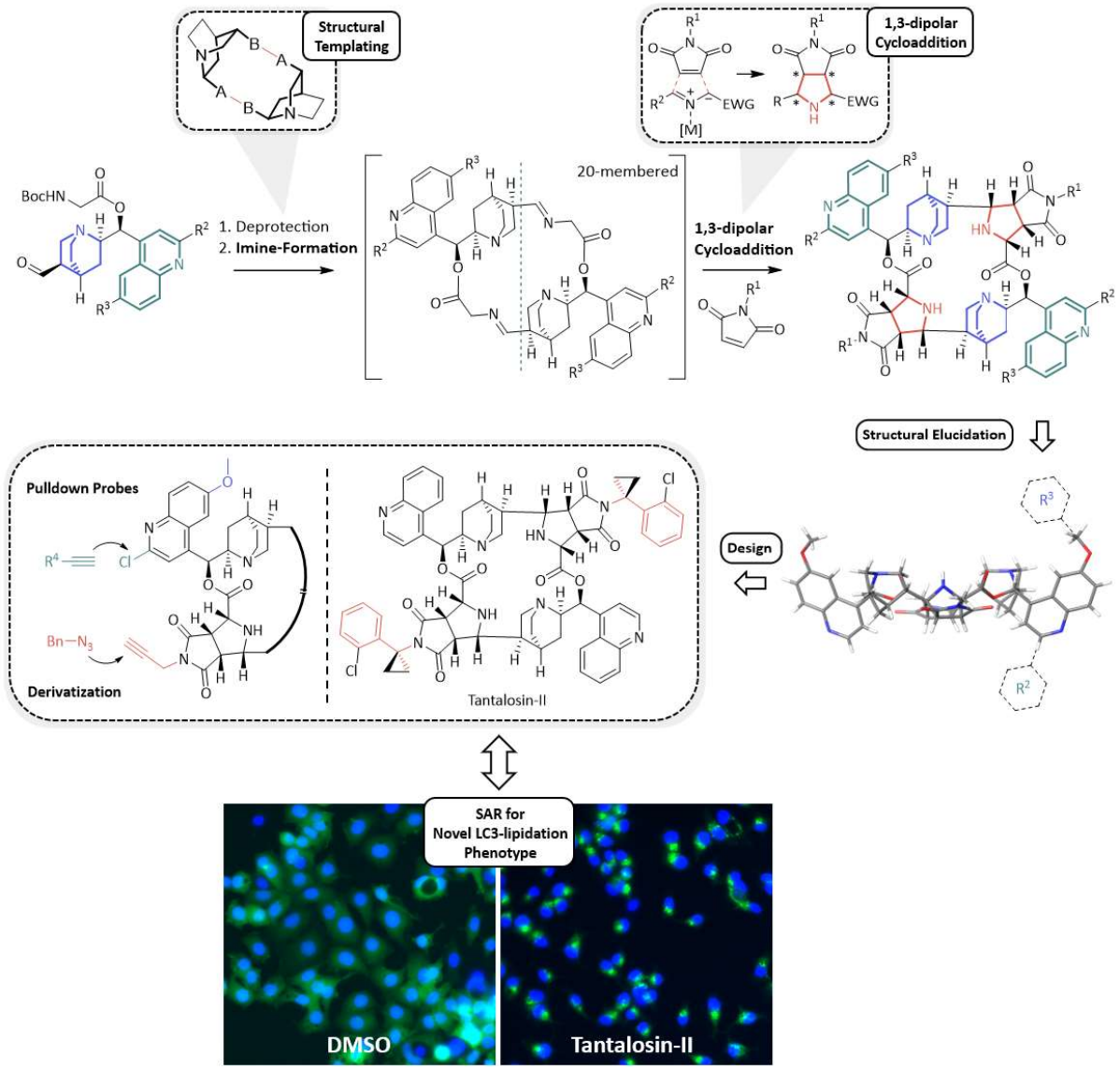


Figure 38: Summary of the thesis.

5 Supplementary Information

5.1 Quinidine- versus quinine-based starting materials

To test the hypothesis of a structural templating mediated by the quinuclidine configuration, diastereomeric quinine (QN) starting material **106** was synthesized and employed in the developed reaction sequence. Six conditions were tested, varying base equivalents and desiccant. N-methylmaleimide was used as it led to high selectivity in reactions with quinidine starting material. All reaction conditions resulted in complex mixtures cyclic or open chain oligomeric adducts (Suppl. Figure 39). The formation of polymers or insoluble higher oligomers could be observed as thick white precipitate in the reaction mixture.

The reaction of the diastereomer used for library synthesis (**80**, QD) is given as a reference in Figure 40.

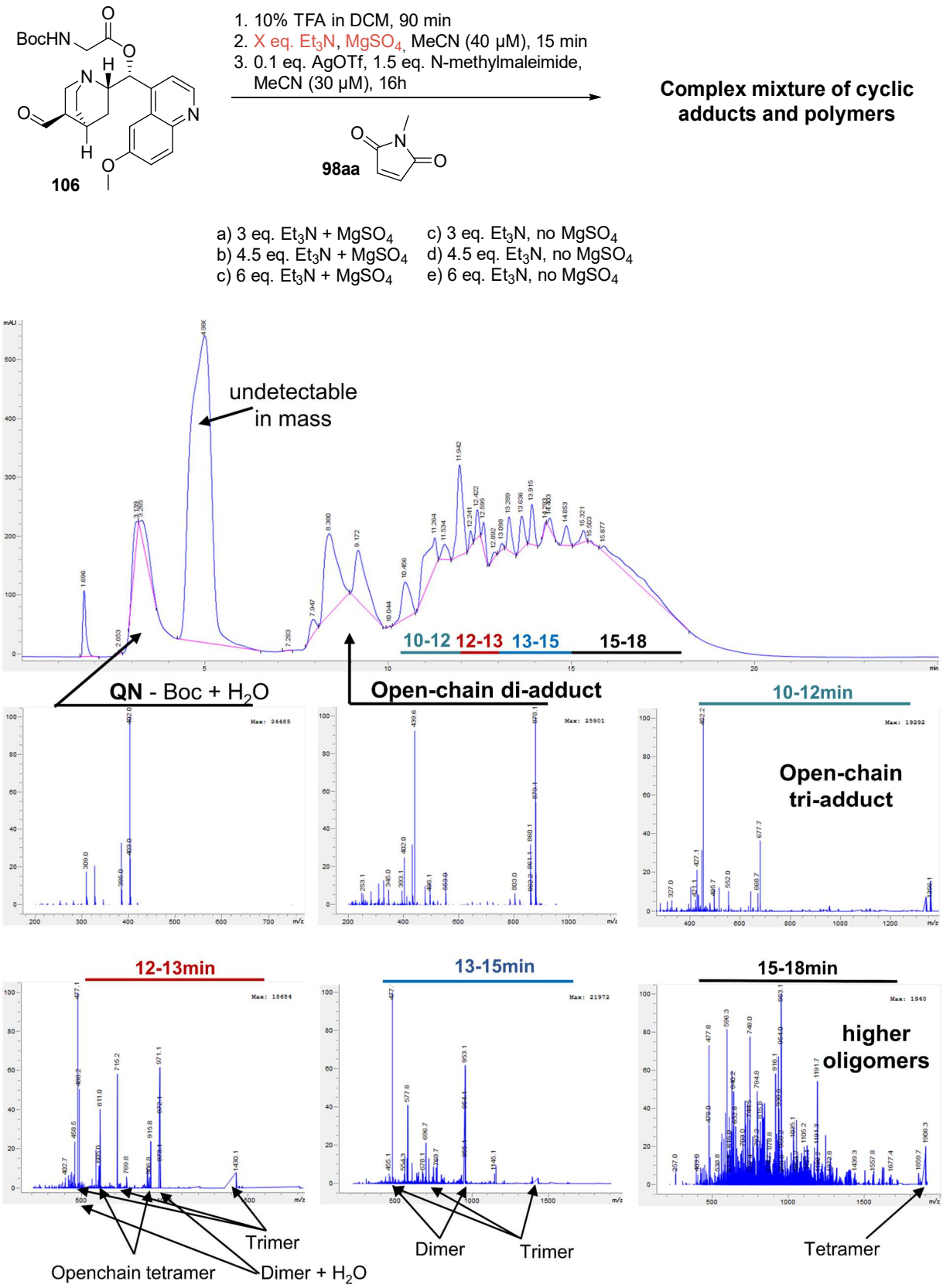


Figure 39: Reaction of quinine (QN, **106**) starting material 12h with N-methylmaleimide results in complex mixtures of products. The top trace shows the UV-trace at 310 nm. The six spectra below show the mass spectra in the indicated ranges.

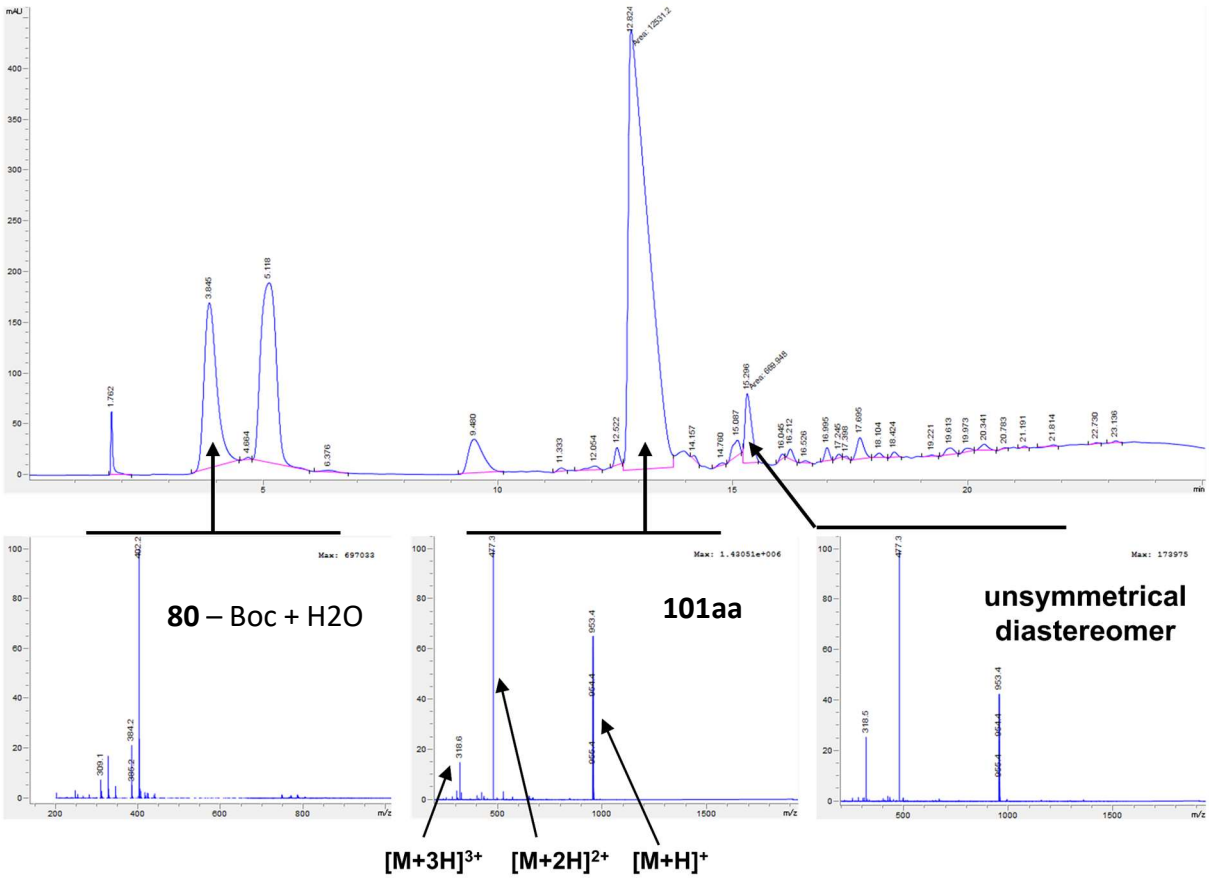
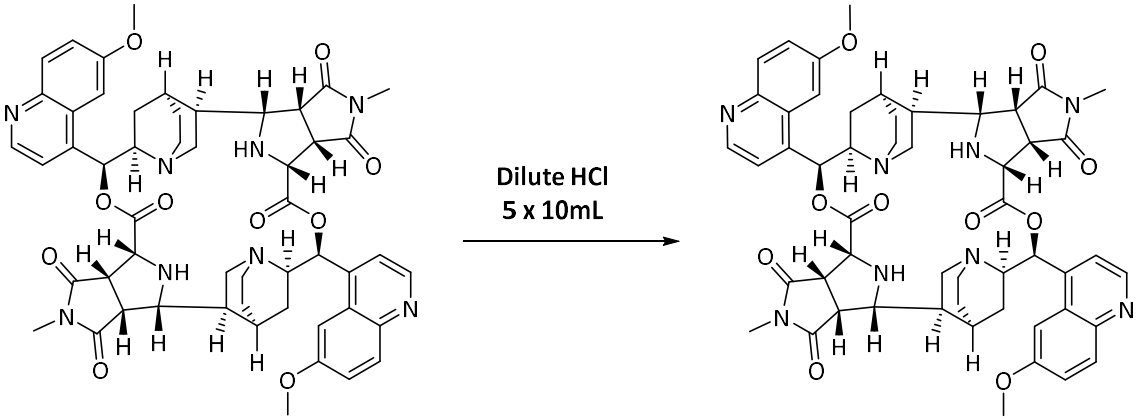


Figure 40: Reaction of the regular quinidine starting material **80** (QD) with N-methylmaleimide produces symmetrical dimer **98aa** in high selectivity. The top trace shows the UV-trace at 310 nm. The three spectra below show the mass spectra over the entirety of the indicated peaks.

5.2 Determination of macrocycle/TFA stoichiometry

To determine the stoichiometry of macrocycle to TFA after HPLC-purification, 10 mg of **6aa** were redissolved in dilute HCl, frozen and freeze dried. This was repeated five times. The significantly lower pKa of HCl leads to a total exchange of the TFA counterion and the subsequent removal of protonated TFA under reduced pressure. The resultant powder was weighed and compared to the values expected for the exchange of different numbers of TFA counterions (Suppl. Table 19).

Table 19: Determination of TFA/macrocycle stoichiometry.



Number of exchanged ions	Hypothetical mass [mg]	Found mass [mg]
0	10	
1	9.27	
2	8.68	8.52
3	8.18	
4	7.78	

5.3 Naming Scheme

To avoid lengthy, automatically generated chemical names for the generated macrocycles, a naming scheme was devised (Figure 41). The molecular identifier consists out of three parts that are separated by hyphens. The first section references to the respective monomeric cinchona alkaloid precursor as it determines the quinoline substitution pattern (R^2/R^3). The second section references to the respective maleimide used, as it determines the succinimide substituents (R^1). The last section refers to the configuration of the macrocycle and which is either symmetrical "S" or unsymmetrical "A". This is shown exemplary for compound **108a**.

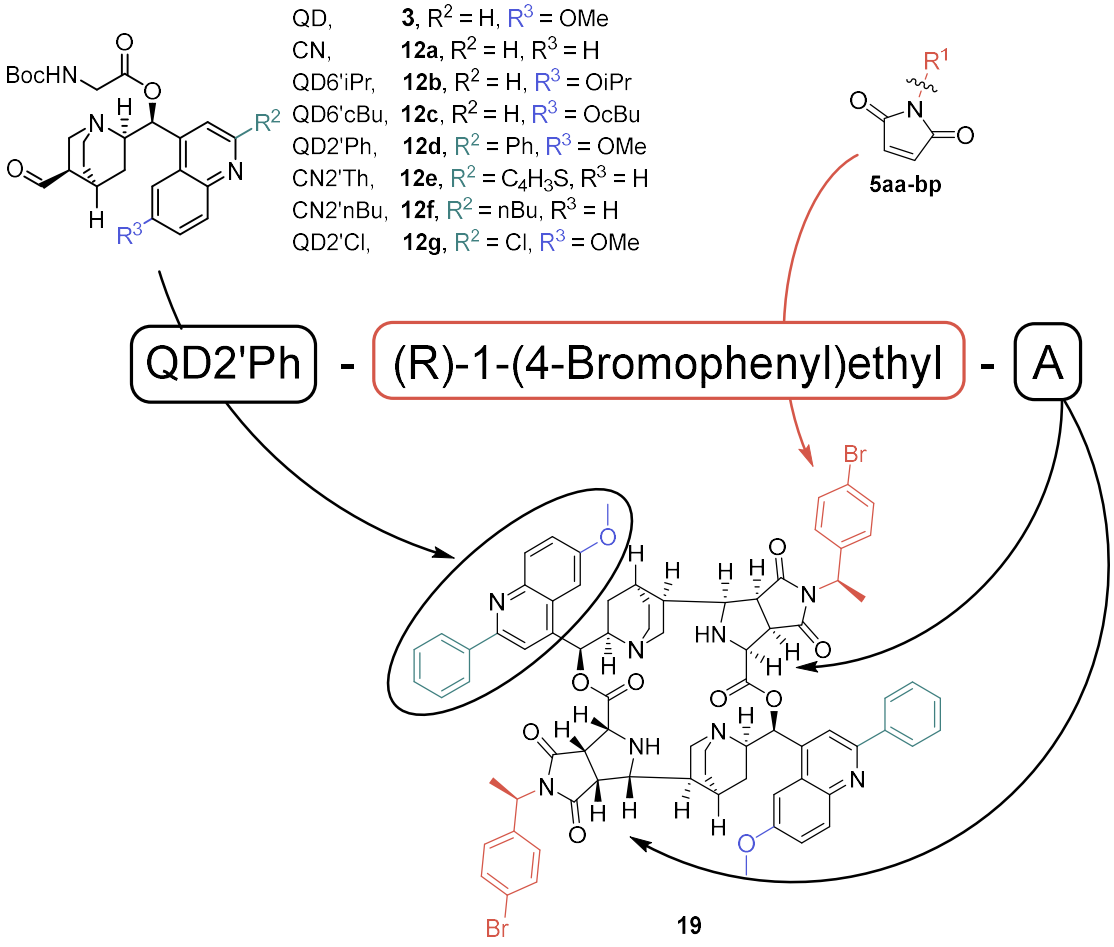
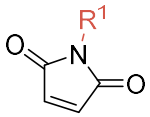


Figure 41: Naming Scheme of Cinchona Macrocycles exemplified for compound **108** (QD2'Ph-(R)-1-(4-Bromophenyl)ethyl-A).

5.3.1 Maleimides



Newly Synthesized Maleimides

98ac R^1 = (R)-1-(4-bromophenyl)ethyl (56%)
98ad R^1 = 4-methylbenzyl (36%)
98ae R^1 = 4-chloro-3-(trifluoromethoxy)-benzyl (36%)
98af R^1 = (R)-2-phenylpropyl (50%)
98ag R^1 = (R)-1-cycohexylethyl (65%)
98ah R^1 = neopentyl (39%)
98ai R^1 = 2-(5-fluoro-1H-indole-3-yl)ethyl (16%)
98aj R^1 = (S)-2-phenylpropyl (52%)
98ak R^1 = 1,1-(diacetoxymethyl)-2-acetoxyethyl (30%)
98al R^1 = cyclohexylmethyl (40%)
98am R^1 = 4-fluorobenzyl (45%)
98an R^1 = homopiperonyl (20%)
98ao R^1 = 4-(4-fluorophenyl)benzyl (67%)
98ap R^1 = (-)-cis-myrthanyl (59%)
98aq R^1 = 3-acetoxybenzyl (42%)
98ar R^1 = piperonyl (42%)
98as R^1 = phenethyl (60%)
98at R^1 = 2-chlorobenzyl (21%)
98au R^1 = 1-phenylcyclopropan-1-yl (74%)
98av R^1 = 2-(2-fluorophenyl)propan-2-yl (58%)
98aw R^1 = 1-(2-chorophenyl)cyclopropan-1-yl (42%)
98ax R^1 = (R)-3-methylbutan-2-yl (28%)
98ay R^1 = *iso*-propyl (43%)
98az R^1 = (R)-1-cyclopropylethan-1-yl (44%)
98ba R^1 = 1-methyl-1-phenylethyl (25%)
98bb R^1 = propargyl (40%)*[1]

Commercial Maleimides

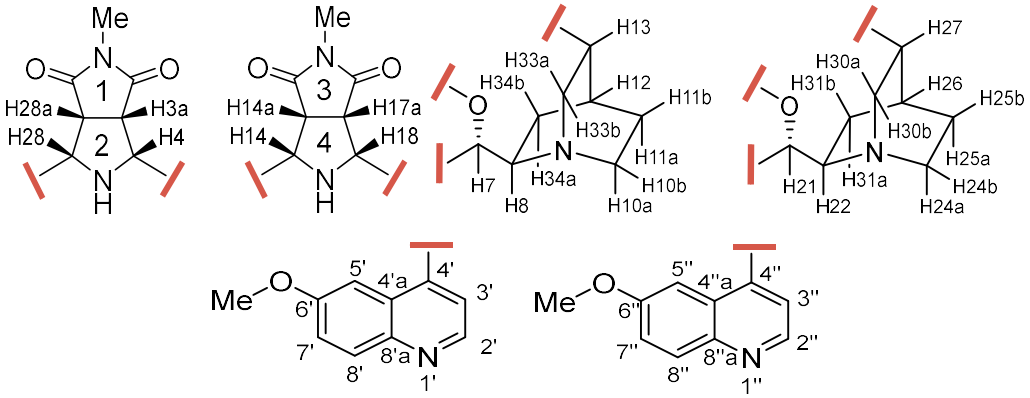
98aa R^1 = methyl
98ab R^1 = phenyl
98bc R^1 = ethyl
98bd R^1 = *tert*-butyl
98be R^1 = n-propyl
98bf R^1 = cyclohexyl
98bg R^1 = 4-ethylpheynl
98bh R^1 = 2,4,6-trichlorophenyl
98bi R^1 = benzyl
98bj R^1 = H
98bk R^1 = 4-cyanobenzyl
98bl R^1 = (S)-1-phenylethyl
98bm R^1 = (R)-1-phenylethyl
98bi R^1 = 2-hydroxyethyl
98bj R^1 = 4-acetophenyl

Figure 42: List of commercial- and synthesized maleimides used in macrocyclization sequences.

5.4 NMR Analyses

Please consult the numbering scheme in 3.2.1

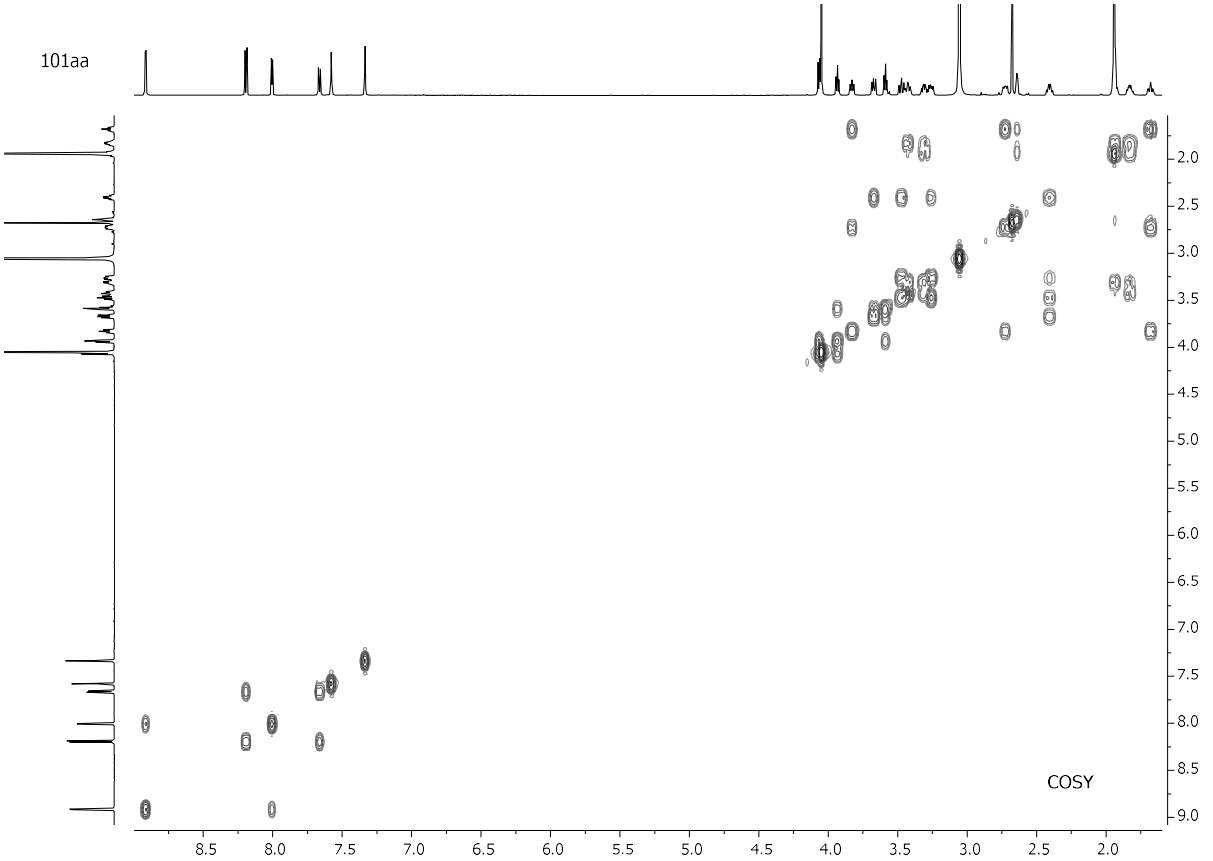
5.4.1 NMR Analysis of 101aa

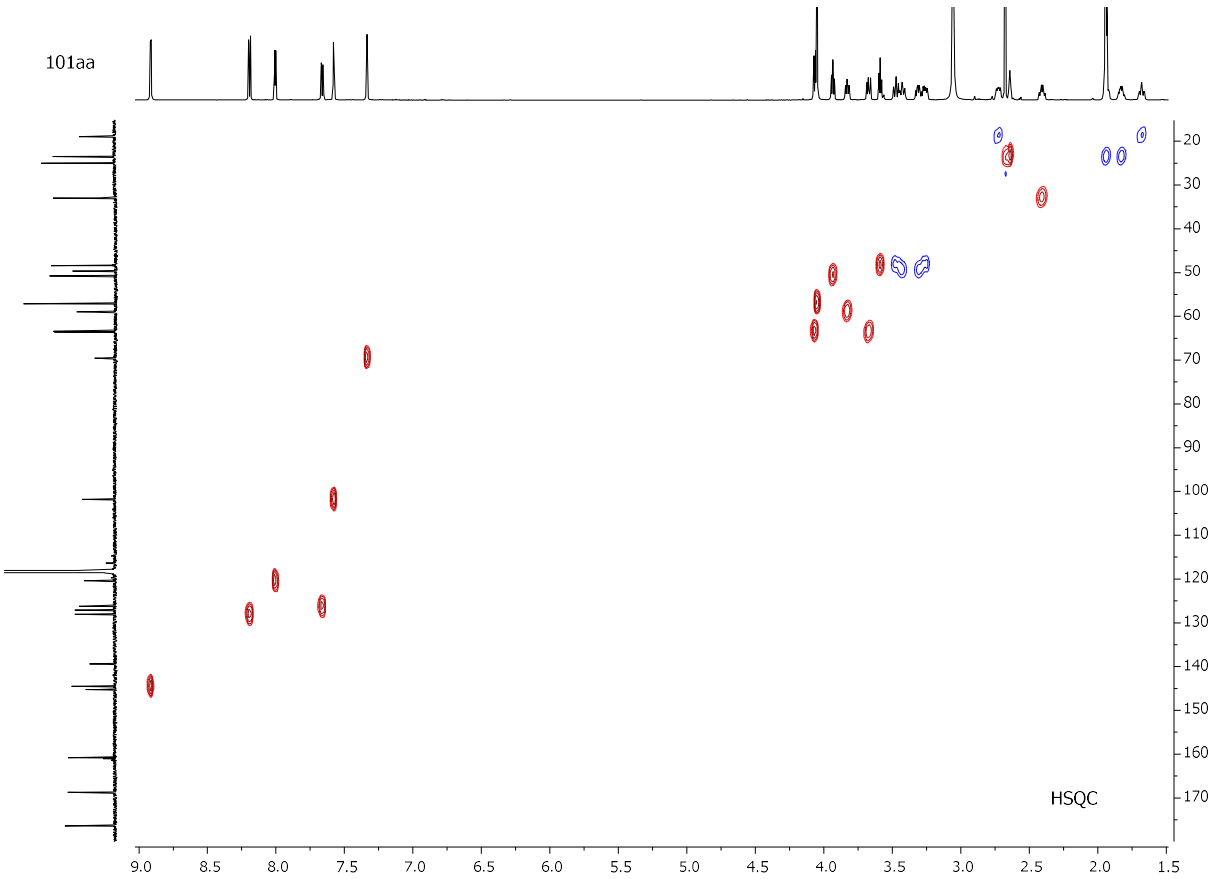


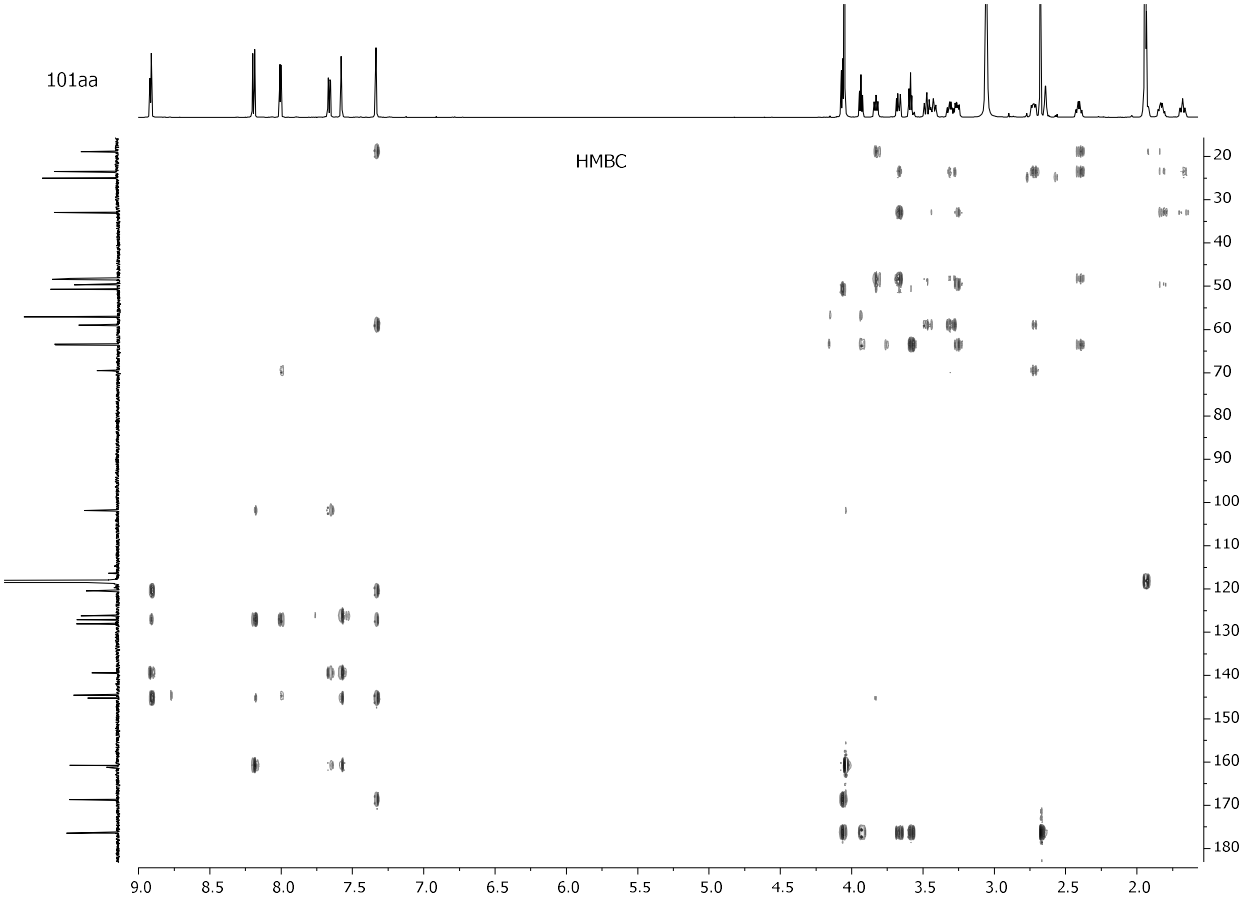
^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.91 (d, J = 5.1 Hz, 2H, C2'H), 8.19 (d, J = 9.3 Hz, 2H, C8'H), 8.01 (d, J = 5.1 Hz, 2H, C3'H), 7.66 (dd, J = 9.3, 2.5 Hz, 2H, C7'), 7.58 (d, J = 2.6 Hz, 2H, C5'), 7.34 (s, 2H, C7H and C21H), 4.07 (d, J = 8.0 Hz, 2H, C4H and C18H), 4.05 (s, 6H, $C9'H_3$), 3.93 (t, J = 7.7 Hz, 2H, C3aH and C17aH), 3.83 (dd, J = 10.8, 7.6 Hz, 2H, C8H and C22H), 3.67 (dd, J = 11.7, 7.0 Hz, 2H, C14H and C28H), 3.59 (t, J = 7.3 Hz, 2H, C14aH and C28aH), 3.47 (ddd, J = 13.0, 11.0, 1.8 Hz, 2H, $C30H_b$ and $C33H_b$), 3.43 (ddt, J = 14.1, 11.3, 4.2 Hz, 2H, $C10H_a$ and $C25H_a$), 3.31 (ddd, J = 13.1, 11.0, 7.3 Hz, 2H, $C10H_b$ and $C24H_b$), 3.26 (ddd, J = 13.7, 7.1, 2.8 Hz, 2H, $C30H_a$ and $C33H_a$), 2.73 (ddd, J = 14.1, 7.5, 2.2 Hz, 2H, $C31H_b$ and $C34H_b$), 2.68 (s, 6H, NMe), 2.64 (s, 2H, C12H and C26H), 2.41 (td, J = 11.2, 7.2 Hz, 2H, C13H and C27H), 1.97 – 1.90 (m, 2H, $C11H_b$ and $C25H_b$), 1.86 – 1.79 (m, 2H, $C11H_a$ and $C24H_a$), 1.68 (ddd, J = 14.2, 10.7, 3.9 Hz, 2H, $C31H_a$ and $C34H_a$).

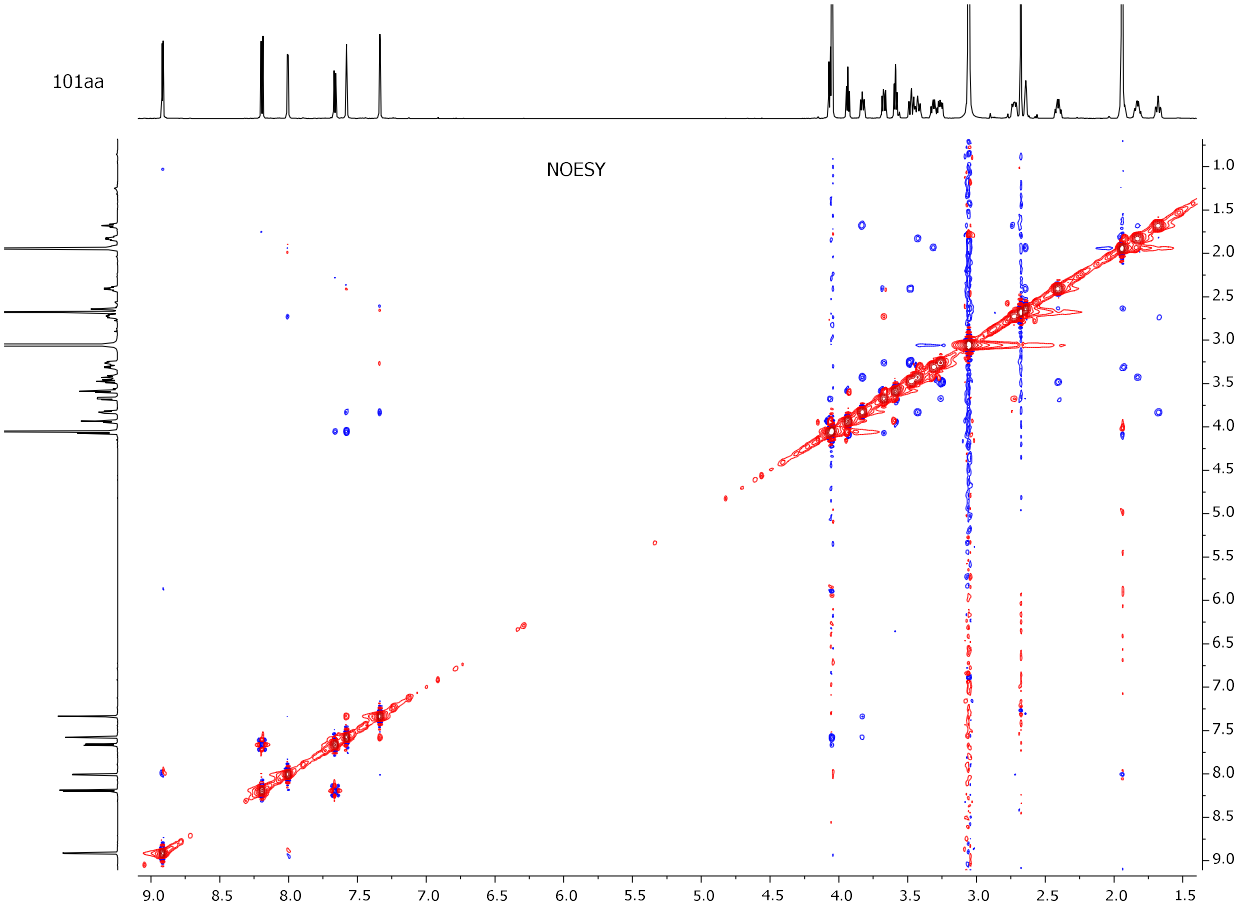
^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.42 (C1 or C3 or C15 or C17), 176.32 (C1 or C3 or C15 or C17), 168.70 (C5 and C19), 160.79, 145.24, 144.54 (C2'), 139.39, 128.03 (C8'), 127.11, 126.20 (C7'), 120.42 (C3'), 101.83 (C5'), 69.54 (C7 and C21), 63.58 (C4 and C18 or C14 and C28), 63.40 (C4 and C18 or C14 and C28), 58.97 (C8 and C22), 57.09 (OMe), 50.73 (C3a and C17a), 49.64 (C10 and C24), 48.43 (C14a and C28a or C30 and C33), 48.22 (C14a and C28a or C30 and C33), 32.97 (C13 and C27), 25.02 (C9'), 23.66 (C11 and C25 or C12 and C26), 23.51 (C11 and C25 or C12 and C26), 18.92 (C31 and C34).

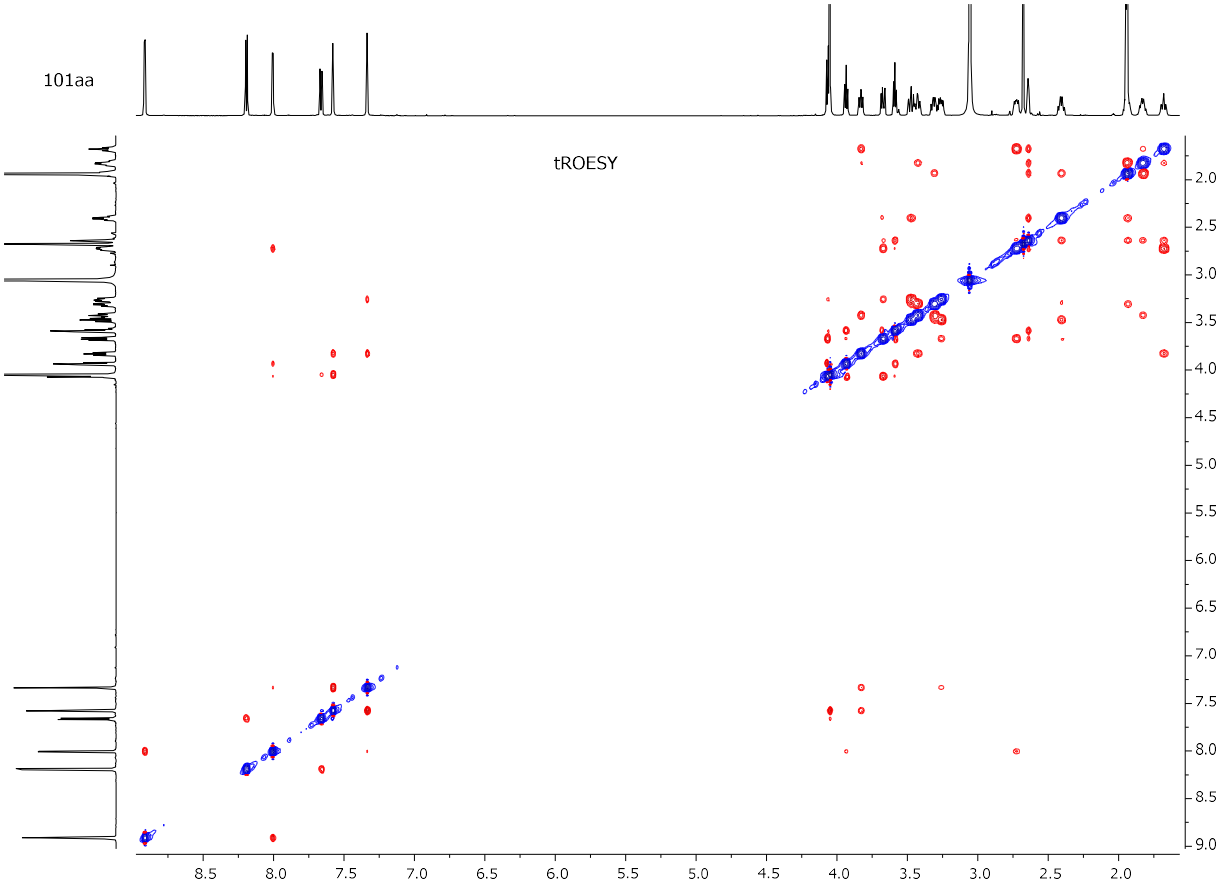
$^{1}H^{15}N$ HMBC (71 MHz, $CD_3CN:D_2O$ [10:1]) δ 249.79 (quinoline, N1'), 177.51 (succinimide, N2 und N16), 53.60 (pyrrolidine, N29 and N32), 41.69 (quinuclidine N8H+).

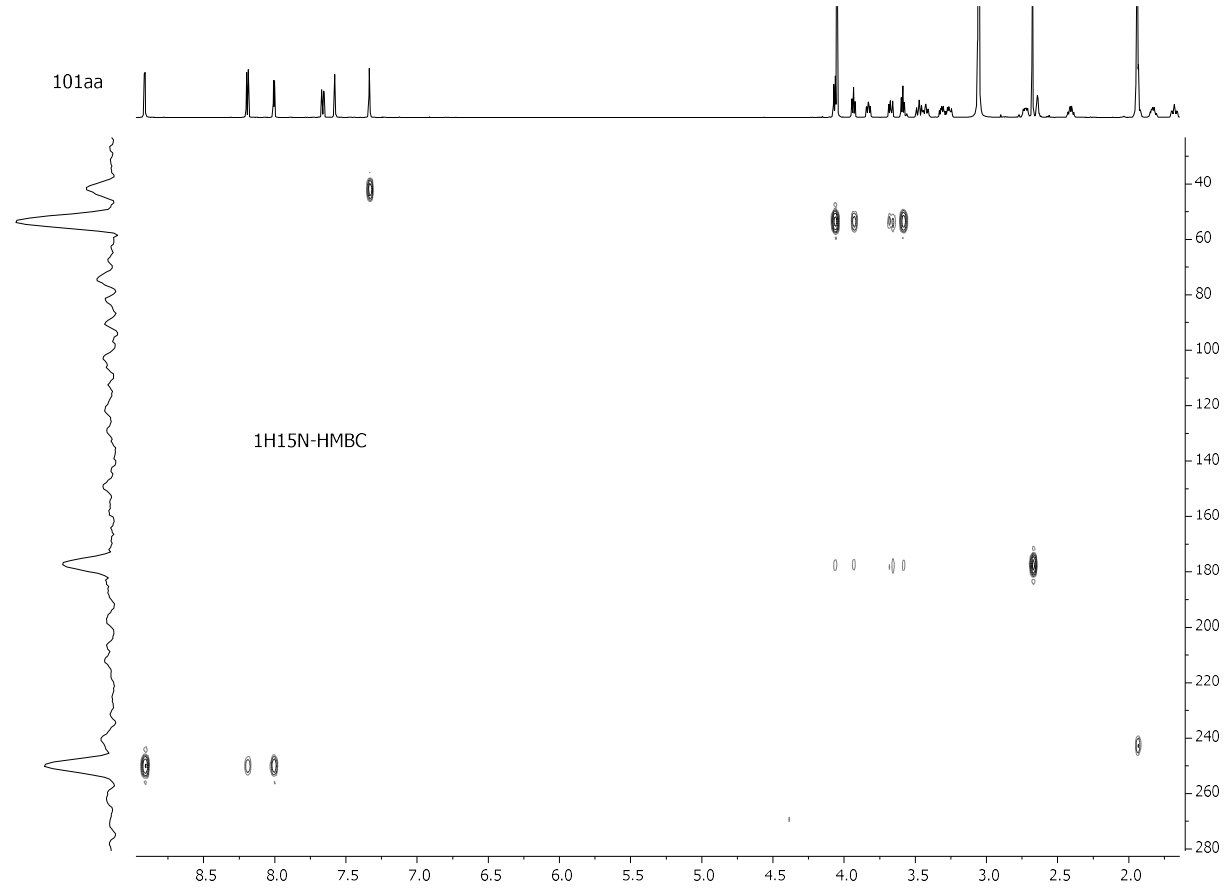




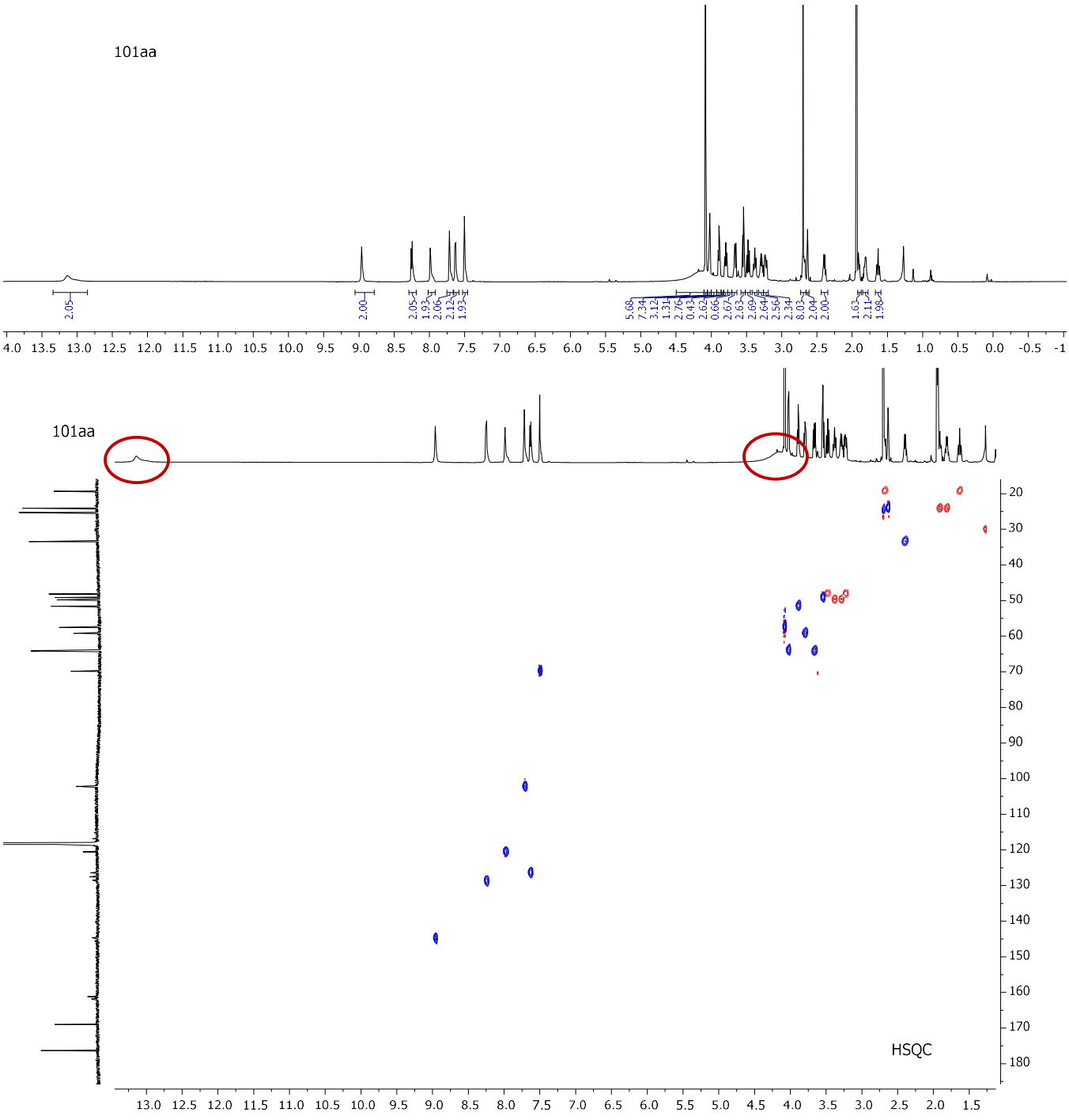

101aa
HMBC
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0
20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180


101aa
NOESY
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0


101aa
tROESY
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
9.0


101aa
1H15N-HMBC
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
280

In spectra without exchangeable deuterium (CD_3CN shown below), protonation of nitrogen atoms can be observed. The ammonium ion of quinuclidine has a relatively sharp peak shape and a chemical shift of 13.14 ppm. The ammonium ion of pyrrolidine has a broadened peak around 4.15 ppm. Position of these signals corresponds to literature precedent for TFA salts of secondary and tertiary amines.[122]

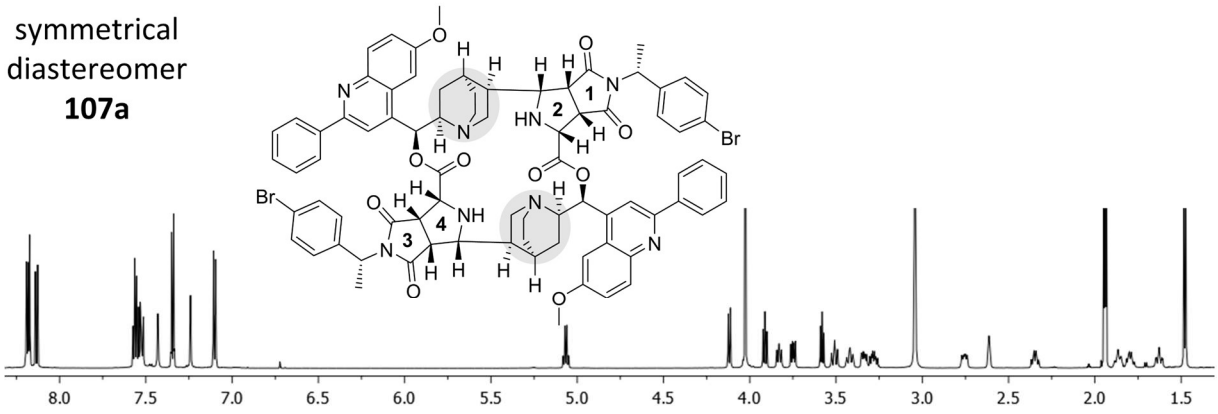


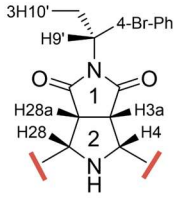
5.4.2 Comparative configurational NMR analysis of 107a and 108a

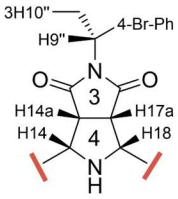
^{1}H, COSY, ^{13}C and $^{1}H^{13}C$-HSQC could be used to determine the position of every proton and carbon on the symmetrical macrocycle. All signals of this C_2-symmetrical molecule eclipse each other completely. The absolute orientation of prochiral methylene groups could further be confirmed via NOESY and tROESY. For easier navigation through the data for the reader, the most indicative proton shifts are given in table format (Suppl. Table 20).

Table 20: Proton shifts and assignment peaks of the symmetrical diastereomer **101ac**

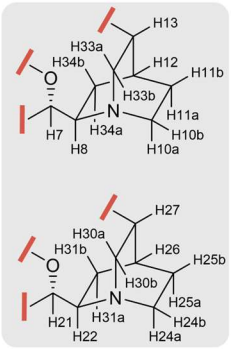
symmetrical diastereomer **107a**







entry	Shift [ppm]
3H10'	1.48
H9'	5.07
H4, H18	4.12
H3a, H17a	3.91
H28a, H14a	3.58
H28, H14	3.75
H12', H16'	7.10
H13', H15'	7.34



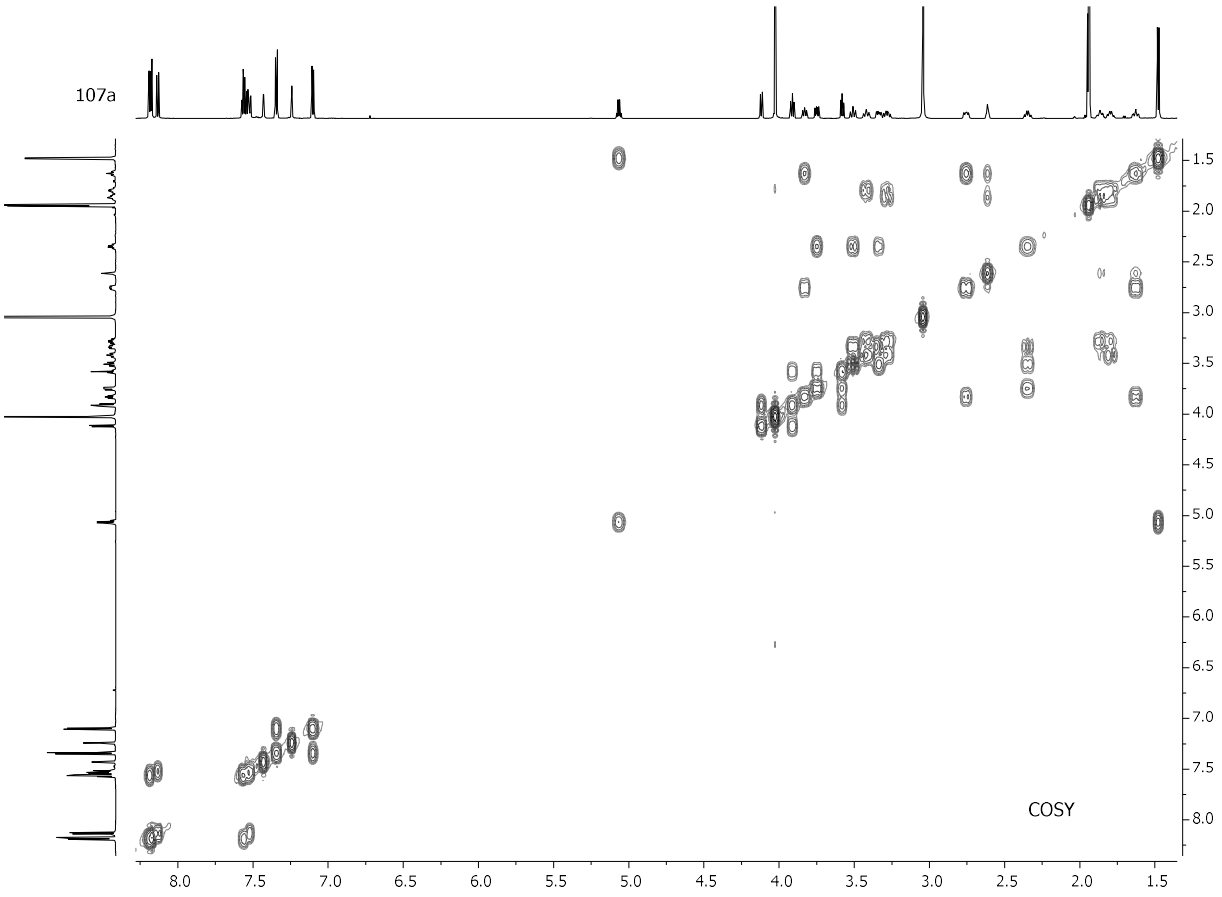
entry	Shift [ppm]
H7, H21	7.24
H8, H22	3.83
H10a, H25a	3.28
H10b, H25b	3.42
H11a, H24a	1.86
H11b, H24b	1.79
H12, H26	2.62
H13, H27	2.34
H33a, H30a	3.34

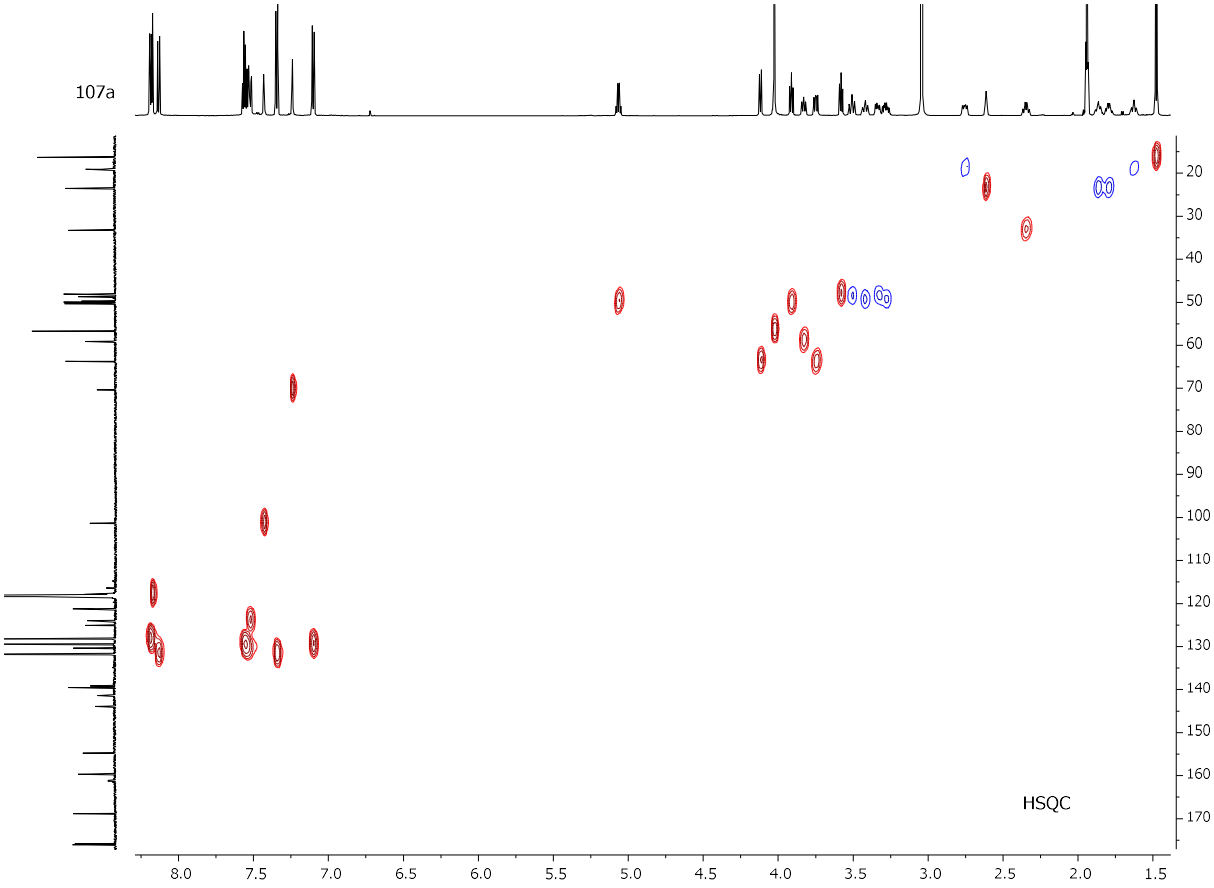
entry	Shift [ppm]
H33b, H30b	3.51
H34a, H34a	1.62
H34b, H34b	2.76
H3'	8.18
H5'	7.43
H7'	7.54
H8'	8.13
$4HPh_{m,p}$	7.54
$2HPh_{o}$	8.18

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.21 – 8.16 (m, 6H, C3'H and Ph_{ortho}), 8.13 (d, J = 9.1 Hz, 2H, C8'H), 7.59 – 7.50 (m, 8H, C7'H and $Ph_{metha/para}$), 7.45 – 7.42 (m, 2H, C5'H), 7.37 – 7.32 (m, 4H, C13'H and C15'H), 7.24 (s, 2H, C7H and C21H), 7.12 – 7.08 (m, 4H, C12'H and C16'H), 5.07 (q, J = 7.2 Hz, 2H, C9'H), 4.12 (d, J = 8.4 Hz, 2H, C4H and C18H), 4.03 (s, 6H, OMe), 3.91 (dd, J = 8.4, 7.7 Hz, 2H, C3aH and C17aH), 3.86 – 3.80 (m, 2H, C8H and C22H), 3.75 (dd, J = 11.6, 7.0 Hz, 2H, C14H and C28H), 3.58 (dd, J = 7.7, 7.0 Hz, 2H, C14aH and C28aH), 3.51 (ddd, J = 12.7, 10.8, 1.8 Hz, 2H, $C30H_a$ and $C34H_a$), 3.42 (ddt, J = 13.9, 11.1, 3.2 Hz, 2H, $C10H_a$ and $C24H_a$), 3.34 (ddd, J = 13.6, 7.1, 2.8 Hz, 2H, $C30H_b$ and $C34H_b$), 3.28 (ddd, J

= 13.1, 10.9, 7.2 Hz, 2H, C10H_b and C24H_b), 2.76 (ddt, J = 12.9, 7.5, 2.2 Hz, 2H, C31H_a and C34H_a), 2.61 (br. s, 2H, C12H and C26H), 2.35 (td, J = 11.1, 7.0 Hz, 2H, C13H and C27H), 1.90 – 1.83 (m, 2H, C11H_a and C25H_a), 1.83 – 1.76 (m, 2H, C11H_b and C25H_b), 1.63 (ddd, J = 14.0, 10.4, 3.8 Hz, 2H, C31H_b and C34H_b), 1.48 (d, J = 7.2 Hz, 6H, C10'H_3).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.08 (C1 or C15 and C3 or C17), 175.86 (C1 or C15 and C3 or C17), 168.82 (C5 and C19), 159.69, 154.77, 143.89, 141.42, 139.51, 139.15, 131.80 (C13' and C15'), 131.73 (C8'), 130.35, 129.55, 129.46 (C12' and C16'), 128.25, 125.08, 124.01, 121.26, 117.85 (C3'), 101.37 (C5'), 70.32 (C7 and C21), 63.93 (C14 and C28), 63.73 (C4 and C18), 59.09 (C8 and C22), 56.74 (OMe), 50.30 (C3a and C17a), 49.98 (C9'), 49.72 (C10 and C24), 48.68 (C30 and C34), 48.10 (C14a and C28a), 33.27 (C13 and C27), 23.63 (C12 and C26 or C11 and C25), 23.58 (C12 and C26 or C11 and C25), 19.10 (C31 and C34), 16.30 (C10').





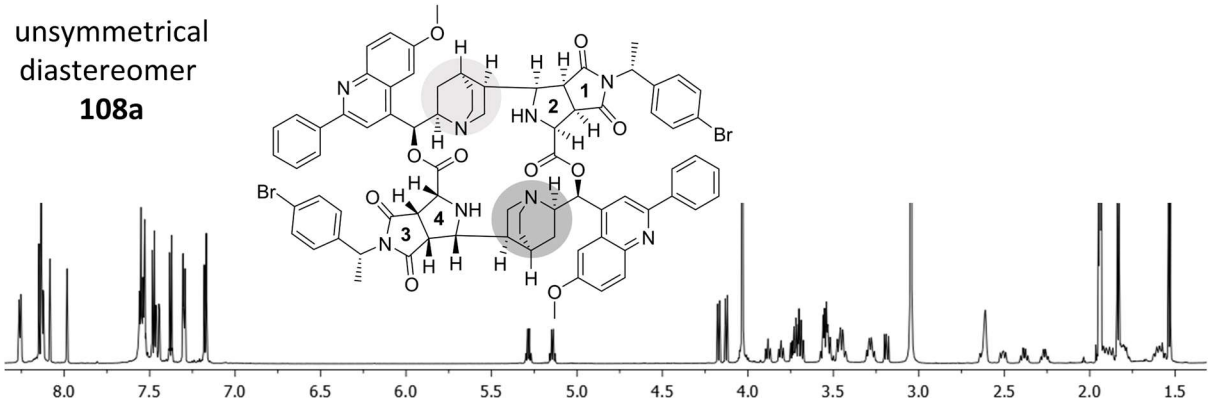
For easier navigation through the data, the most indicative proton shifts are given in table format (Suppl. Table 21). We note, that not all proton signals could be linked to a specific hemisphere, either because of insufficient splitting or eclipse of the signal through other protons (grayed out in Suppl. Table 21).

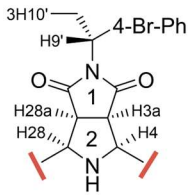
The absolute orientation of prochiral methylene groups could be confirmed via NOESY and tROESY. Although giving similar results, tROESY was prioritized over NOESY because the molecular weight of the compound (1668 Da as the di-TFA salt and 1440 Da as the free amine) falls into a range where NOE signals are minimal.

The configurational analysis is detailed in the main text.

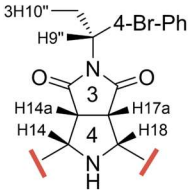
Table 21: Table of assigned peaks in unsymmetrical **108a**. Black protons are clearly assigned to a hemisphere, grey protons could not be assigned to a distinct hemisphere with absolute certainty, protons which are not shown, could not be assigned to a distinct hemisphere.

unsymmetrical diastereomer **108a**

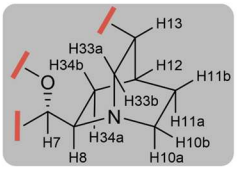


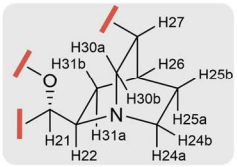


entry	Shift [ppm]
3H10'	1.83
H9'	5.28
H4	4.13
H3a	3.71
H28a	3.19
H28	3.71



entry	Shift [ppm]
3H10''	1.53
H9''	5.14
H18	4.17
H17a	3.71
H14a	3.55
H14	3.71





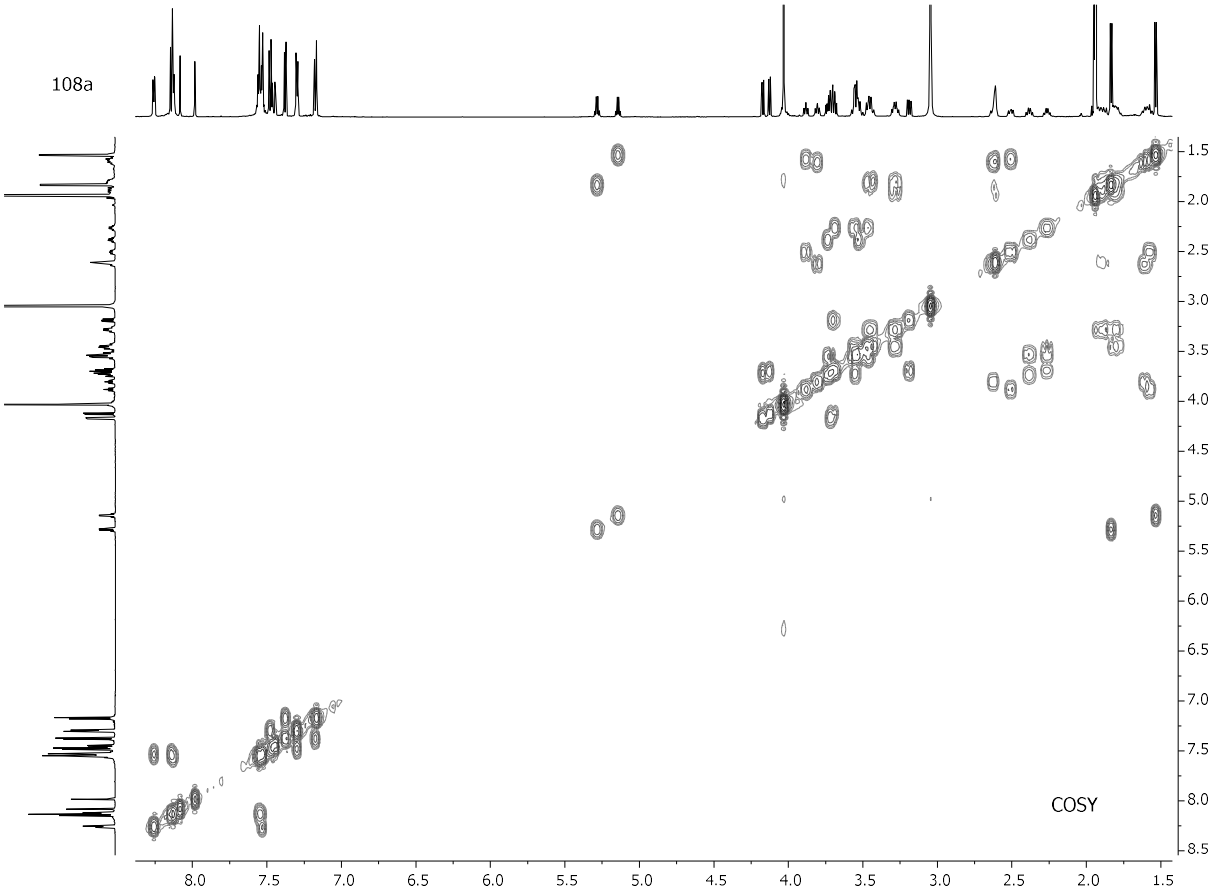
entry	Shift [ppm]
H7	7.30
H8	3.88
H10a	3.46
H10b	3.28
H11a	1.81
H11b	1.90
H12	2.61
H13	2.27
H33a	3.55
H33b	3.55
H34a	2.51
H34b	1.59

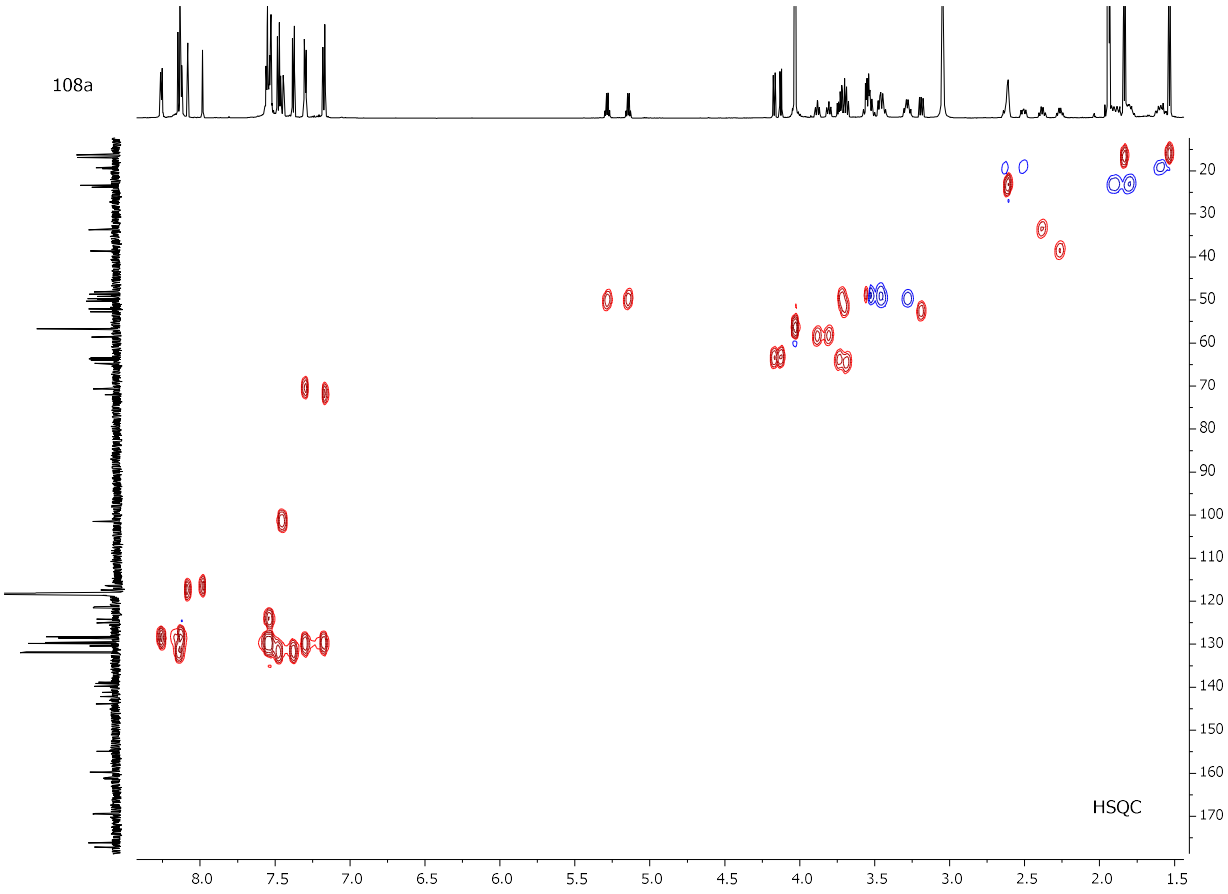
entry	Shift [ppm]
H21	7.17
H22	3.81
H25a	3.46
H25b	3.28
H24a	1.81
H24b	1.90
H26	2.61
H27	2.38
H30a	3.55
H30b	3.46
H34a	2.62
H34b	1.59

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.28 – 8.24 (m, 2H, Ph-ortho), 8.15 (s, 1H, C8'/C8''-H), 8.13 (s, 1H, C8'/C8''-H), 8.13 – 8.12 (m, 2H, Ph-ortho), 8.08 (s, 1H, C3'H), 7.98 (s, 1H, C3''H), 7.59 – 7.51 (m, 8H, Ph-metha/para, C7'H, C7''H), 7.50 – 7.46 (m, 2H, C13'H, C15'H), 7.45 (dd, J = 12.5, 2.7 Hz, 2H, C5'H C5''H), 7.40 – 7.35 (m, 2H, C13''H and C15''H), 7.32 – 7.27 (m, 3H, C12'H, C16'H, C21H), 7.17 (m, 3H, C12''H, C16''H and C7H), 5.28 (q, J = 7.2 Hz, 1H, C9'H), 5.14 (q, J = 7.2 Hz, 1H, C9''H), 4.17 (d, J = 8.8 Hz, 1H, C18H), 4.13 (d, J = 8.5 Hz, 1H, C4H), 4.03 (d, J = 1.3 Hz, 6H, OMe), 3.91 – 3.86 (m, 1H, C8H), 3.83 – 3.78 (m, 1H, C22H), 3.76 – 3.66 (m, 4H, C14H, C17aH, C28H, C3aH), 3.59 – 3.49 (m, 4H, C14aH, $C30H_{a\&b}$, $C33H_b$), 3.49 – 3.41 (m, 3H, $C10H_a$, $C24H_a$, $C33H_a$), 3.28 (dddd, J = 13.1, 10.6, 7.5, 2.0 Hz, 2H, $C10H_b$, $C24H_b$), 3.19 (dd, J = 10.0, 7.2 Hz, 1H, C28aH), 2.64 (m, 1H, $C34H_b$), 2.61 (s, 2H, C12H, C26H), 2.54 – 2.48 (m, 1H, $C31H_b$), 2.38 (q, J = 10.0 Hz, 1H, C13H), 2.26 (q, J = 10.5, 10.0 Hz,

1H, C27H), 1.94 – 1.85 (m, 2H, C11H_b, C25H_b), 1.83 (d, J = 7.2 Hz, 3H, C10'H), 1.83 – 1.75 (m, 2H, C11H_a, C25H_a), 1.64 – 1.54 (m, 2H, C31H_a, C34H_a), 1.53 (d, J = 7.3 Hz, 3H, C10''H_3).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 177.13 (C1), 176.15 (C3 or C15 or C17), 176.13 (C3 or C15 or C17), 176.08 (C3 or C15 or C17), 169.47 (C19), 169.32 (C5), 159.71, 154.96, 154.90, 143.89, 142.15, 141.18, 139.76 (C11'), 139.60 (C11''), 139.08, 138.81, 131.98, 131.79, 131.61, 130.42, 129.84, 129.66, 129.62, 129.44, 128.54, 128.29, 125.12, 125.02, 124.22, 124.18, 121.55, 121.29, 117.42 (C3''), 116.37 (C3'), 101.49 (C5' or C5''), 101.42 (C5' or C5''), 72.03 (C7), 70.66 (C21), 64.75, 63.94, 63.68 (C18), 63.45 (C4), 58.64 (C22), 58.50 (C8), 56.71 (OMe), 52.75, 52.09, 50.26, 50.22, 50.04 (C9'), 49.83 (C9''), 49.68, 49.18, 48.61, 48.09, 38.61 (C27), 33.66 (C13), 23.79 (C12 or C26), 23.37(C12 or C26 and C11 or C25), 23.34 (C11 or C25), 19.48 (C34), 19.23 (C31), 16.89 (C10'), 16.25 (C10'').




108a
HSQC
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
20
30
40
50
60
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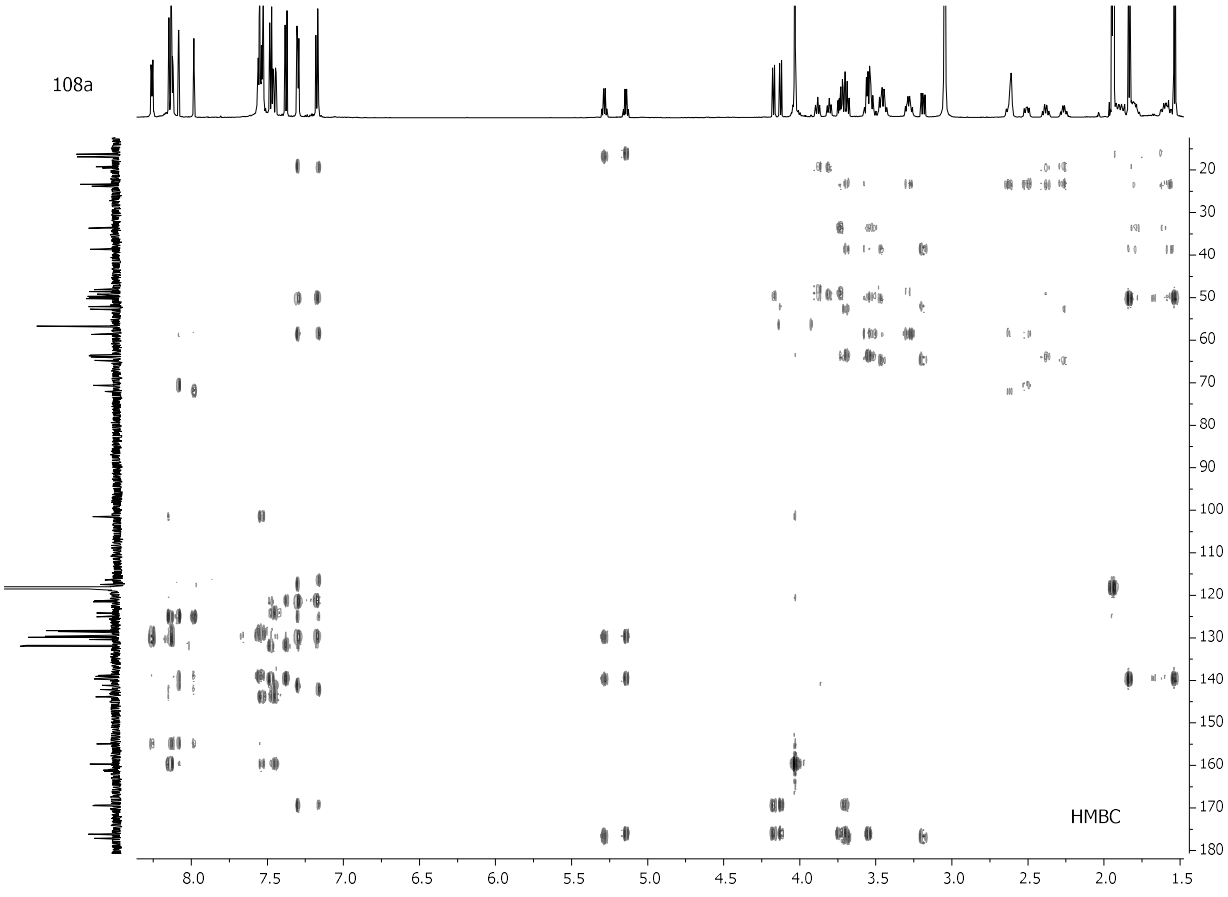
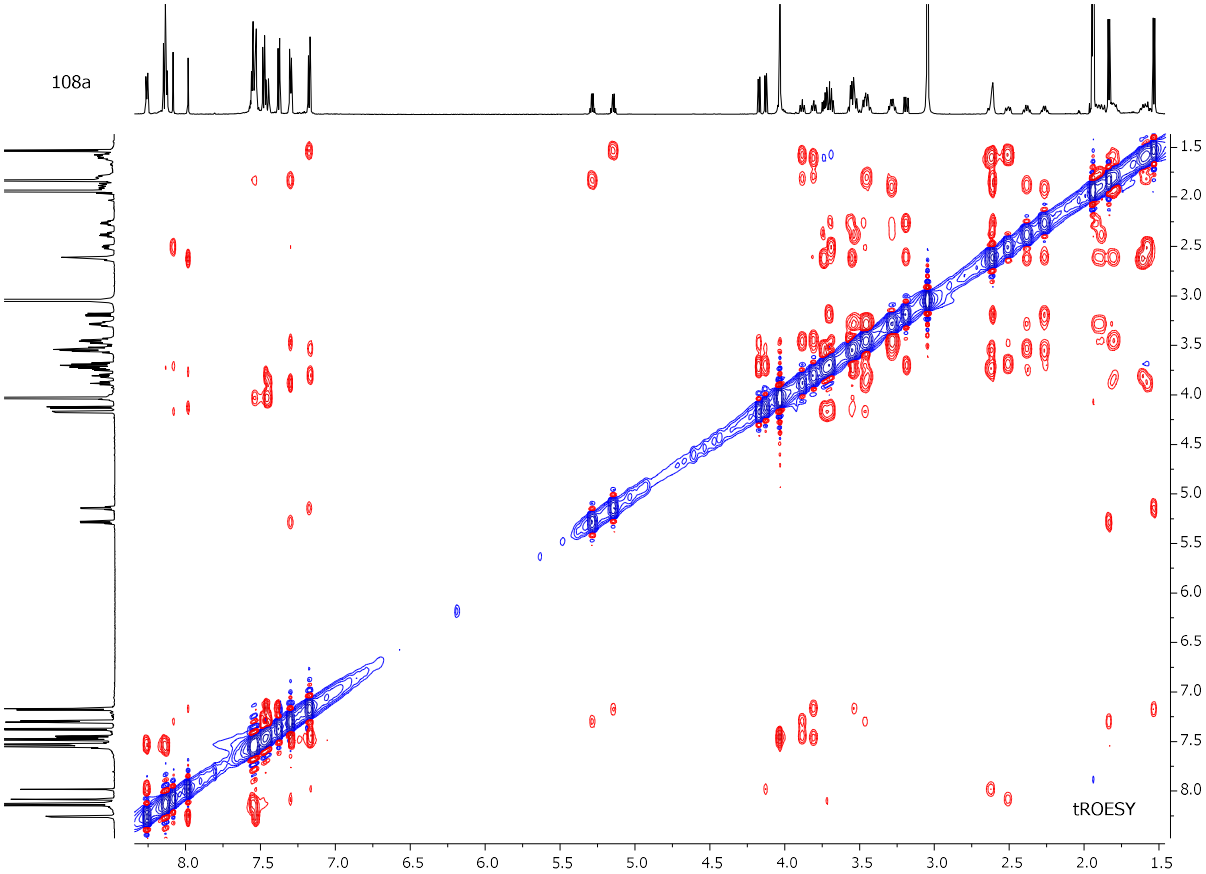
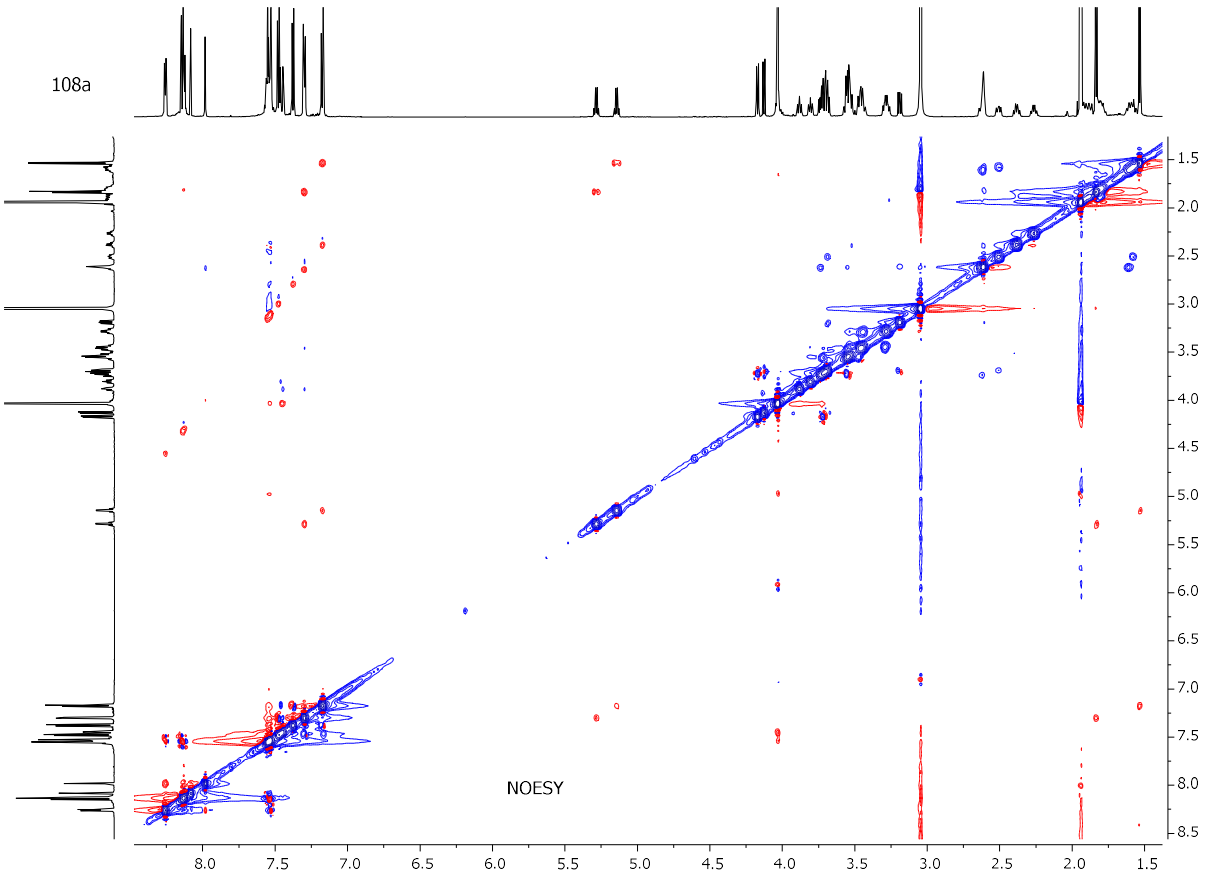
90
100
110
120
130
140
150
160
170


108a
HMBC
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180


108a
tROESY
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5


108a
NOESY
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
8.5

5.5 Modeling

Modeling was performed as indicated in the main text.

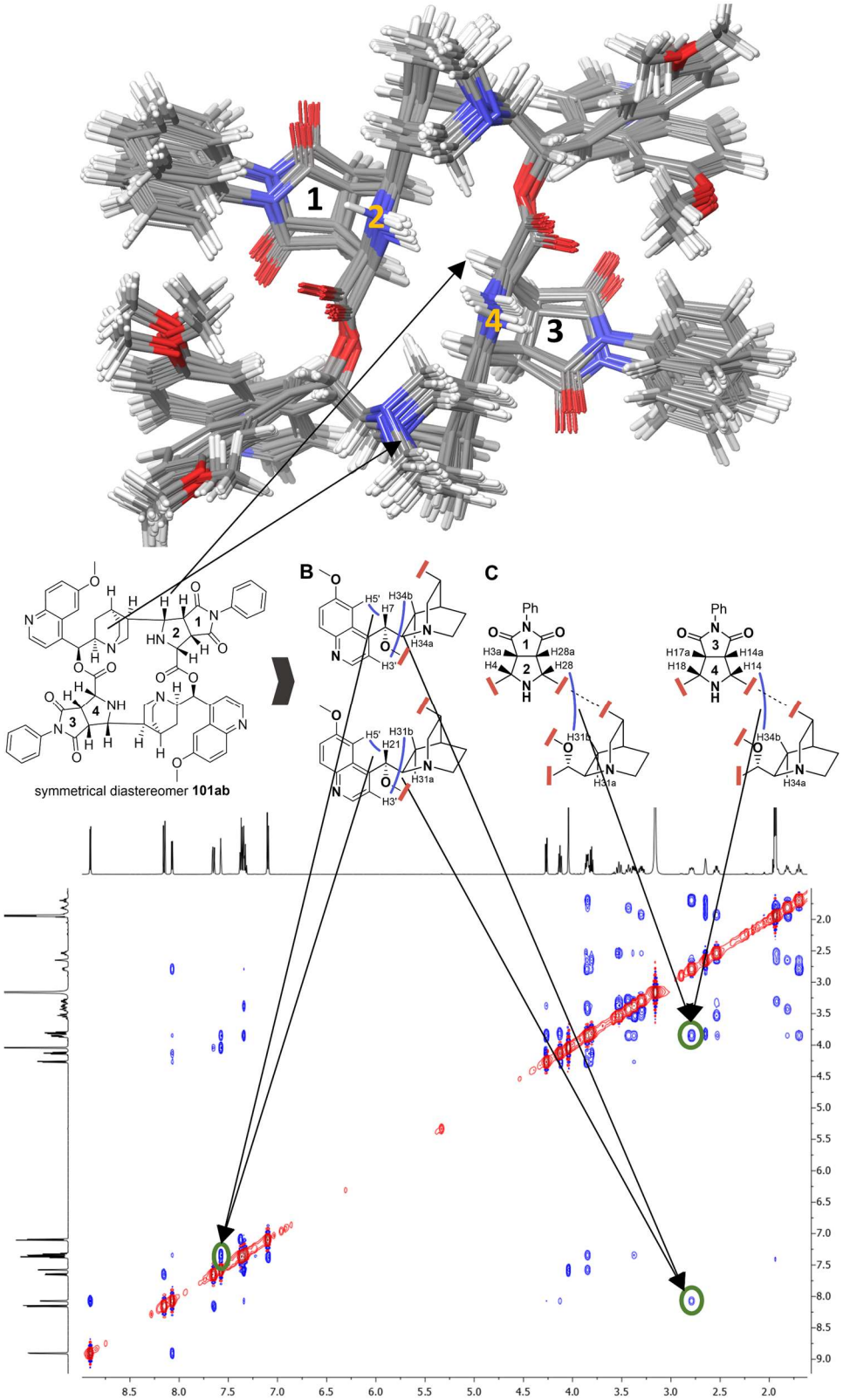
Although many distance restraints could be derived from the 2D-NMR analyses, only a minimal set of indicative correlations were picked for modelling. This was done, to give the molecule maximum degrees of freedom during the calculations. All distance restrictions could be observed in both hemispheres of the unsymmetrical diastereomers **102a** and **108a** and the symmetrical diastereomer **101ab**. Employment of such universal distance restraints was done to enable the calculation of distances that could be checked against the unique coupling signals of the diastereomers.

Restrictions:

1. H5’/H5’’ to H7/H21 and
2. H3’/H3’’ to H34b/H31b are due to the perpendicularity of the quinoline to the respective hemisphere.
3. H14/H28 to H34b/H31b is very indicative for the conformation and is the most determining distance restriction for the calculation of the conformation of the core macrocycle.

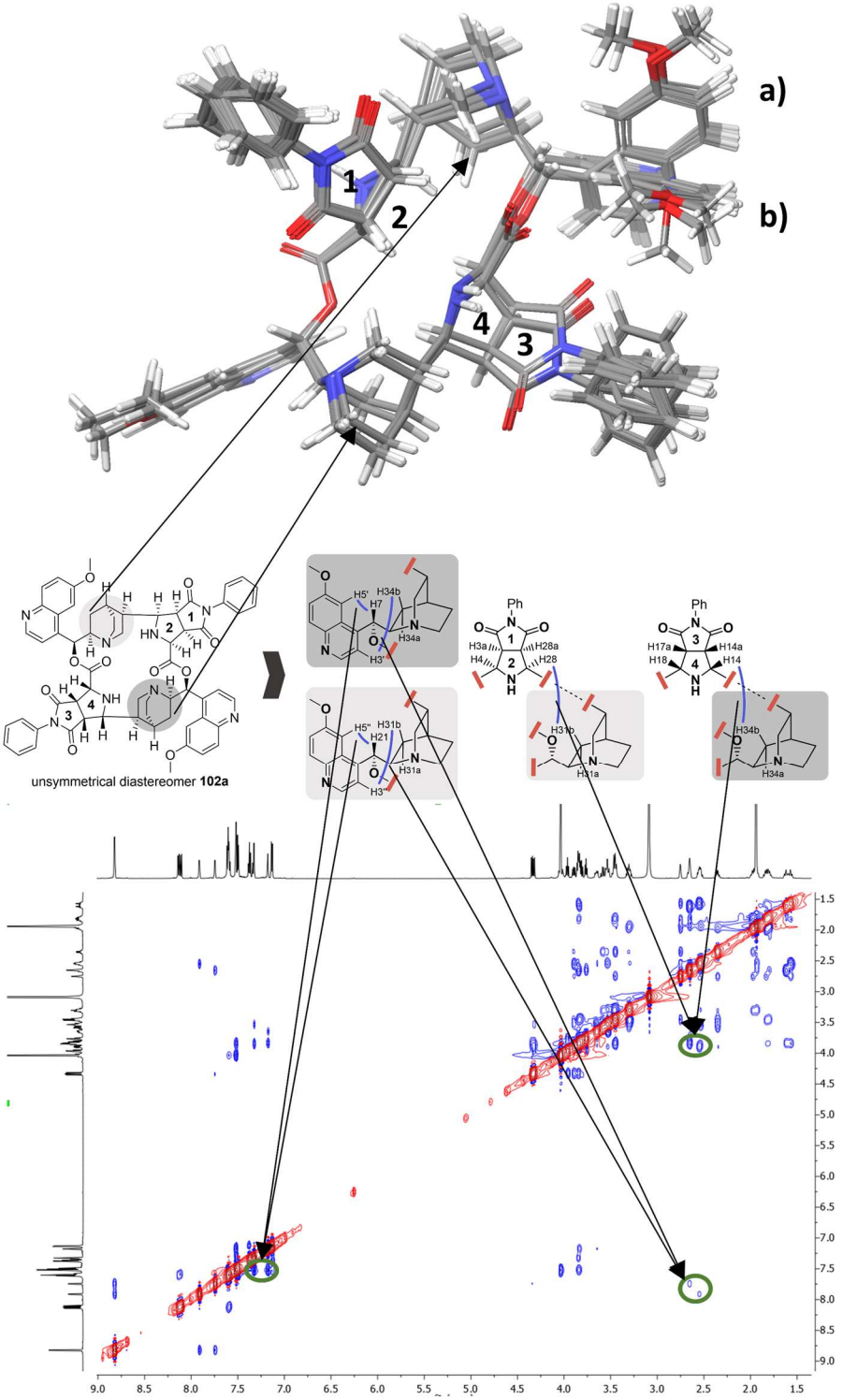
5.5.1 Modeling of 101ab

60/66 calculated conformers with potential energies of 372-390 kj*mol^{-1} are shown as a combined picture.



5.5.2 Modeling 102a

All 83 calculated conformers are shown in superposition. Potential energies lay in the range of 400-421 kj*mol^{-1}. The structure used for Figure 5C was randomly selected from cluster a.

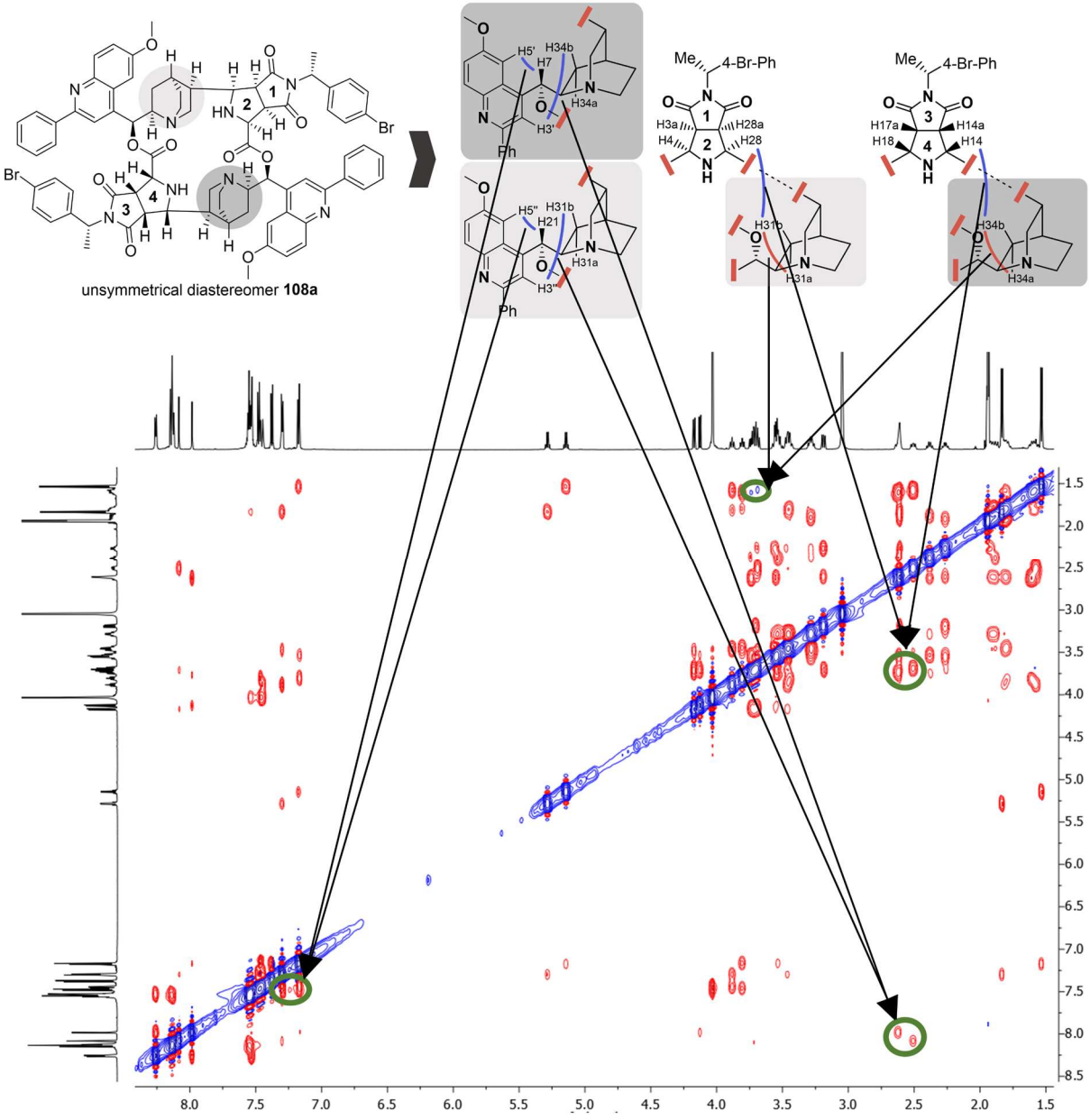


a) 48/83 conformations with 402-421 kj/mol

b) 35/83 conformations with 400-420 kj/mol

5.5.3 Compound 108a as a Structural Reference for Constraints

Compound 108a was used for the determination of the absolute configuration of unsymmetrical diastereomers. Hence, restraints were selected that were also present in this molecule.



5.6 Crystallization methodology and crystallography data

5.6.1 101aa (QD-Me-S)

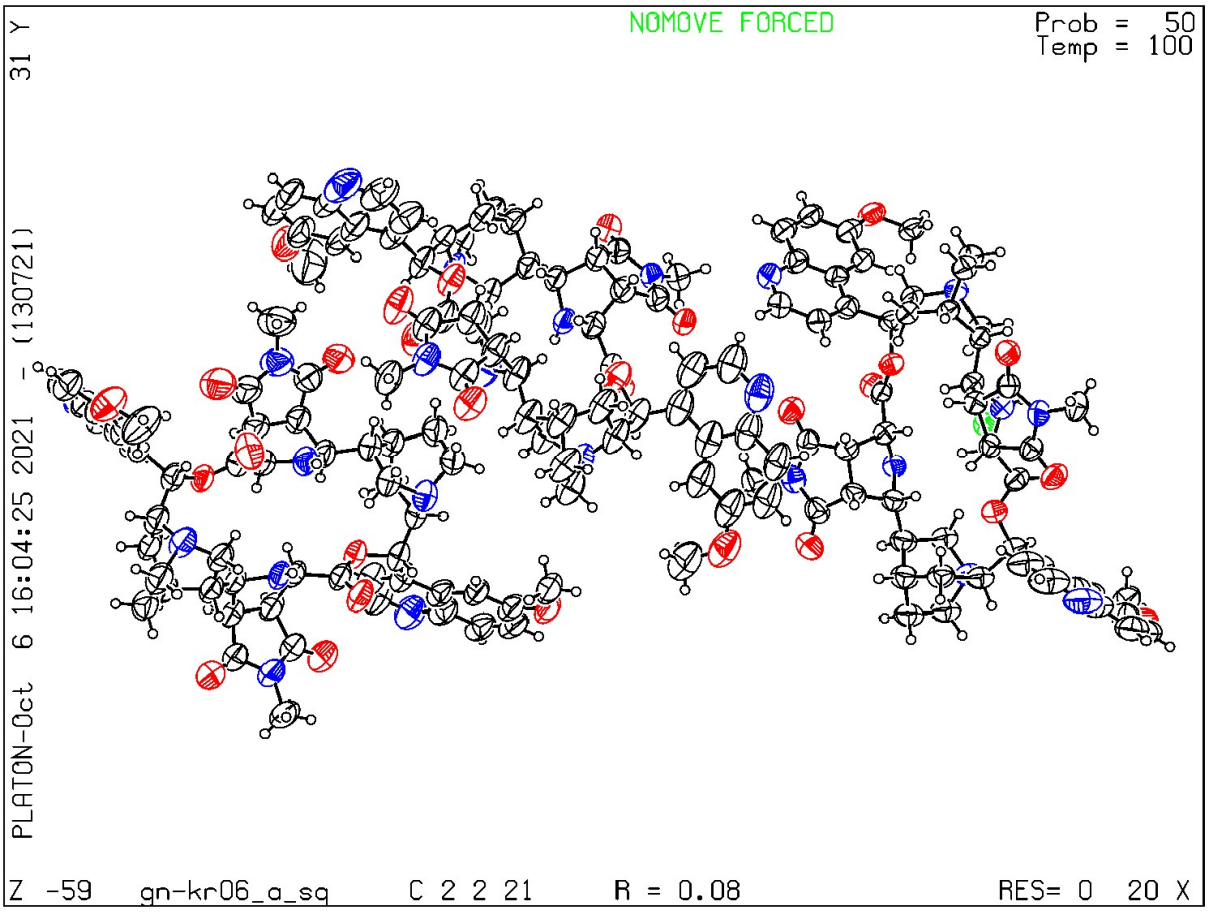


Figure 43: Asymmetric unit of 101aa containing three macrocycles and one bromide (green). Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre and copies can be obtained on request and free of charge, by quoting the publication citation and the deposition number CCDC number 2114032.

Compound **101aa** was crystallized in a hanging drop vapor diffusion setup using 100 nL of compound solution (10 mM in H_2O) mixed with 100 nL of reservoir solution (0.2 M KBr, 0.2 M potassium thiocyanate, 0.1 M NaOAc pH 5, 5 % (w/v) PEG8000, 3 % (w/v) PGA-LM). The crystal started forming after several hours and was harvested after 8 days and flash frozen in liquid nitrogen. A dataset was collected at 100K at the Suisse Light Source beamline X10SA. Data integration and reduction were undertaken using XDS.[123] The structure was solved by intrinsic phasing/direct methods using SHELXT[124] and refined with SHELXL using 22 cpu cores for full-matrix least-squares routines on F^2 and ShelXle[125] as a graphical user interface and the DSR program plugin was employed for modeling.[126] Despite

reaching 0.78 Å resolution, disorder required stereochemical restraints to be employed. Data beyond 0.84 Å I/sig(I) and R_{int} was considered sub-optimal. Hence, only data until 0.84 Å was employed in the structure refinement.

The asymmetric unit contains three molecules of compound **101aa**, one bromide ion and 33% of co-crystallized solvent. Stereochemical restraints for the molecules (residue class GN1) were generated by the GRADE program using the GRADE Web Server (http://grade.globalphasing.org) and applied in the refinement. A GRADE dictionary for SHELXL contains target values and standard deviations for 1,2-distances (DFIX) and 1,3-distances (DANG), as well as restraints for planar groups (FLAT). All displacements for non-hydrogen atoms were refined anisotropically. The refinement of ADP's for carbon, nitrogen and oxygen atoms was enabled by a combination of similarity restraints (SIMU) and rigid bond restraints (RIGU).[127] The contribution of the electron density from disordered counterions and solvent molecules, which could not be modeled with discrete atomic positions were handled using the SQUEEZE[108] routine in PLATON[128]. The solvent mask file (.fab) computed by PLATON were included in the SHELXL refinement via the ABIN instruction leaving the measured intensities untouched.[126]

5.6.2 101ab (QD-Ph-S)

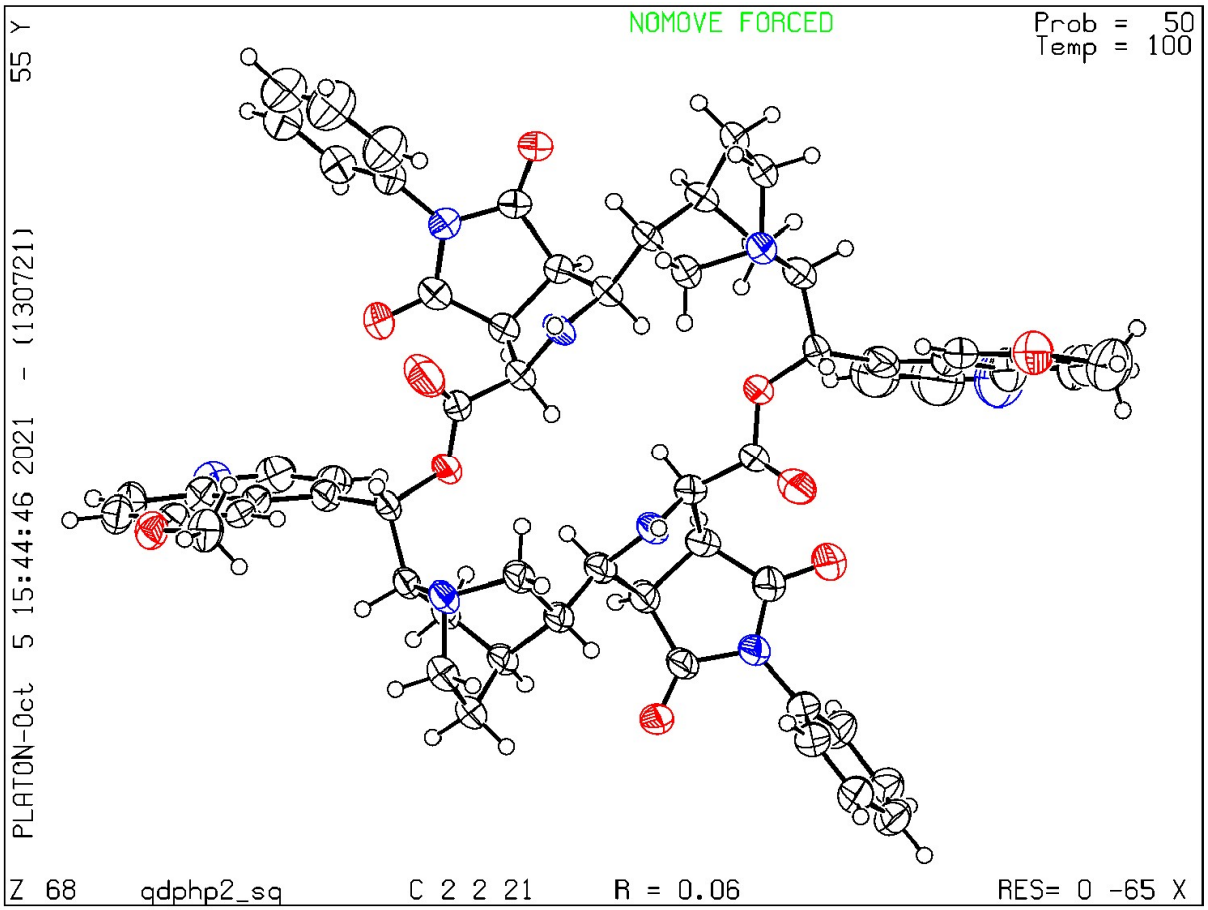
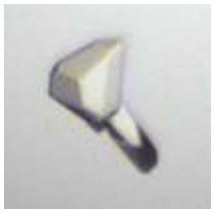


Figure 44: Asymmetric unit of 101ab containing one macrocycle. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre and copies can be obtained on request and free of charge, by quoting the publication citation and the deposition number CCDC number 2114033.



Compound **101ab** was crystallized in a hanging drop vapor diffusion setup using 100 nL of compound solution (5 mM in 20% DMSO in H_2O) mixed with 100 nL of reservoir solution (0.2 M $Ca(OAc)_2$, 0.1 M HEPES pH 7.5, 40% (w/v) PEG400). The crystal started forming after several hours and was harvested after 8 days and flash frozen in liquid nitrogen. A dataset was collected at 100K on a Bruker D8 Discover diffractometer with Photon III detector. The dataset was processed and solved using the Bruker Diffrac Suite.

The asymmetric unit contains one molecule of compound **101ab** and 41% of co-crystallized solvent. Despite reaching 0.9 Å resolution, disorder required stereochemical restraints to be employed. Different regions in molecules show varying atomic displacement factors (ADPs). While these values are small for the atoms in the core macrocycle, which corresponds to a

well defined position, they are lower for the quinoline „side-chains“. Given their rotational freedom, this comes as no surprise and can be observed in the conformational calculations as well (compare Figure 22). Disorder of one of the quinoline groups was treated by employing similarity restraints (SAME) in between both quinoline groups (residue CHI).

All displacements for non-hydrogen atoms were refined anisotropically. The refinement of ADP's for carbon, nitrogen and oxygen atoms was enabled by a combination of similarity restraints (SIMU) and rigid bond restraints (RIGU).[127] The contribution of the electron density from disordered counterions and solvent molecules, which could not be modeled with discrete atomic positions were handled using the SQUEEZE[108] routine in PLATON[128]. The solvent mask file (.fab) computed by PLATON were included in the SHELXL refinement via the ABIN instruction leaving the measured intensities untouched.

In contrast to typical small molecule crystals high disordered solvent content and limited scattering power of crystals complicated the analysis, only allowing for (sub-) atomic resolution for **102ab**. Gaining detailed structural insight required cryogenic crystal handling and highly brilliant synchrotron radiation for **101aa** and carefully adapted macromolecular refinement protocols employing geometrical restraint dictionaries, similarity restraints and restraints for anisotropic displacement parameters (ADPs).

Table 22: Crystal data and structure refinement for **6aa** and **6ab**

Compound	**101aa**	**101ab**
CIF ID	**gn-kr06**	**qdphp2**
CCDC number	**2114032**	**2114033**
Empirical formula	$C_{312}H_{336}BrN_{48}O_{60}$	$C_{62}H_{60}N_8O_{10}$
Formula weight	5798.18	1077.18
Temperature [K]	100(2)	100(2)
Crystal system	orthorhombic	orthorhombic
Space group (number)	$C222_1$ (20)	$C222_1$ (20)
a [Å]	20.370(4)	19.439(3)
b [Å]	25.320(5)	26.725(3)
c [Å]	72.610(15)	30.858(3)
α [Å]	90	90
β [Å]	90	90
γ [Å]	90	90
Volume [Å^3]	37450(13)	16031(3)
Z	4	8
ρ_{calc} [g/cm^3]	1.028	0.893
μ [mm^{-1}]	0.172	0.501
F(000)	12236	4544
Crystal size [mm^3]	0.175×0.065×0.015	0.050×0.050×0.050
Crystal colour	colourless	colourless
Crystal shape	plate	block
Radiation	synchrotron (λ=0.70042 Å)	CuK_α (λ=1.54184 Å)
2Θ range [°]	3.02 to 49.28 (0.84 Å)	5.62 to 117.94 (0.90 Å)
Index ranges	-24 ≤ h ≤ 24	-21 ≤ h ≤ 21
	-30 ≤ k ≤ 30	-29 ≤ k ≤ 29
	-86 ≤ l ≤ 86	-34 ≤ l ≤ 33
Reflections collected	213882	82203
Independent reflections	33050	11484
	R_{int} = 0.2555	R_{int} = 0.0859
	R_{sigma} = 0.1063	R_{sigma} = 0.0569
Completeness to θ = 24.640°	99.8 %	99.8 %
Data / Restraints / Parameters	33050/4146/1896	11484/1308/721
Goodness-of-fit on F^2	1.093	0.803
Final *R* indexes	R_1 = 0.0844	R_1 = 0.0553
[I≥2σ(I)]	wR_2 = 0.2560	wR_2 = 0.1754
Final *R* indexes	R_1 = 0.1004	R_1 = 0.0728
[all data]	wR_2 = 0.2913	wR_2 = 0.1976
Largest peak/hole [eÅ^3]	1.01/-0.60	0.20/-0.19
Flack X parameter using Parsons quotients	0.019(5)	0.28(7)
Flack X parameter using Parsons quotients, before squeeze routine	0.059(7)	0.21(7)

5.7 Biological data

5.7.1 Comparative autophagy induction assay in MEM or MEM+chloroquine, respectively:

Stable EGFP-LC3-MCF7 cells were kindly obtained from Georgios Konstantinidis. Cells were cultured in MEM containing 10% fetal bovine serum, 1% L-glutamine, 1% sodium pyruvate, 1% non-essential amino acids, 0.01 mg/ml human insulin and 200 µg/ml G418. EGFP-LC3-MCF7 (4000 cells/ well) cells were seeded in 384 well plates (Greiner).

The next day, plates were washed three times with PBS using a Biotek plate washer Elx405. After that, compounds were added using Echo dispenser (Labcyte) and full medium or full medium containing 50 µM Chloroquine, respectively, were added using Multidrop Combi dispenser (ThermoFisherScientific). As positive control, full medium or full medium containing 50 µM Chloroquine, respectively, containing 3 µM Obatoclax were added in the control column. Three hours after incubation at 37°C, cells were fixed by addition of 25 µl formaldehyde in 1 x PBS (4% final concentration) for 20 min; while nuclei were simultaneously stained with Hoechst (final 1 µg/ml). Fixed cells were washed three times with 1x PBS using plate washer ELX405 (Biotek). For visualization 4 pictures/well were acquired using ImageXpress Micro XL (Molecular Devices) at 20x and analysed with the granularity algorithm of MetaXpress Software (Molecular Devices). Data was normalized to DMSO treated cells. Dose-response analysis was carried out starting from 10 µM using a three-fold dilution curve over eight steps. The parameter “granule count” was used in EC50 calculations which were done using Quattro Workflow software (Quattro Research GmbH).

5.7.2 List of Inducers of LC3-lipidation with EC_{50} ≤ 7 µM

Table 23: List of active macrocycles in the LC3-lipidation assay with an EC50 ≤ 7 µM

Entry	Name	R^1	R^2	R^3	EC_{50} [µM]	Activity [%]	EC_{50+CQ} [µM]	$Activity_{+CQ}$ [%]
1	**114q**	1-Phenylcyclopropyl	H	H	7.00 ± 1.1	48 ± 5	> 10	31 ± 6
2	**118e**	*iso*-Propyl	H	OcBu	6.43 ± 1.53	79 ± 13	6.21 ± 1.89	69 ± 10
3	**116m**	(R)-1-Cyclopropylethyl	H	O*i*Pr	6.41 ± 2.1	89 ± 18	> 10	42 ± 8
4	**101bd**	1-Phenylcyclopropyl	H	OMe	6.10 ± 4.6	60 ± 19	> 10	3 ± 3
5	**101af**[a)]	*tert*-Butyl	H	OMe	3.04 ± 0.2	87 ± 2	4.50 ± 0.9	60 ± 7
6	**101aj**	(R)-1-Cyclopropylethyl	H	OMe	5.71 ± 1.6	96 ± 15	> 10	21 ± 22
7	**116k**	(R)-1-Phenylethyl	H	O*i*Pr	4.71 ± 1.2	95 ± 12	> 10	23 ± 3
8	**101bc**	1-Methyl-1-phenylethyl	H	OMe	4.58 ± 1.2	114 ± 30	>10	22 ± 13
9	**114p**[a)]	(R)-1-Phenylethyl	H	H	1.84 ± 0.1	123 ± 14	3.13 ± 0.6	84 ± 5
10	**101az**[a)]	(S)-1-Phenylethyl	H	OMe	1.83 ± 1.4	98 ± 25	> 5	n.d.
11	**116d**	*tert*-Butyl	H	O*i*Pr	3.45 ± 0.3	150 ± 8	4.29 ± 0.01	126 ± 4
12	**101an**	(R)-1-Cyclohexylethyl	H	OMe	3.07 ± 0.20	142 ± 12	3.81 ± 0.10	126 ± 19
13	**118f**	*tert*-Butyl	H	OcBu	2.85 ± 0.45	129 ± 13	3.77 ± 0.33	160 ± 5
14	**101be**	1-Methyl-(2-fluorophenyl)ethyl	H	OMe	2.97 ± 0.3	132 ± 27	4.68 ± 0.7	128 ± 10
15	**101bf**	1-(2-Chlorophenyl)cyclopropyl	H	OMe	2.86 ± 1.1	109 ± 10	5.44 ± 1.7	89 ± 17
16	**114r**	1-Methyl-(2-fluorophenyl)ethyl	H	H	2.57 ± 0.50	142 ± 8	3.63 ± 0.50	220 ± 14
17	**114p**	(R)-1-Phenylethyl	H	H	1.84 ± 0.10	123 ± 14	3.13 ± 0.60	84 ± 5
18	**101ah**	(R)-1-Isopropylethyl	H	OMe	1.61 ± 0.82	135 ± 22	3.06 ± 1.45	107 ± 2
19	**101ba**	(R)-1-Phenylethyl	H	OMe	0.80 ± 0.70	119 ± 13	0.97 ± 0.70	118 ± 21
20	**114s**	1-(2-Chlorophenyl)cyclopropyl	H	H	0.40 ± 0.01	132 ± 8	0.42 ± 0.05	150 ± 10

a) tested up to 5 µM from a 5 mM stock solution

5.7.3 Fluorescent imaging

MCF7 cells stably expressing EGFP-LC3B (ref) were seeded in polymer coated chambered coverslips (ibidi, Germany) in 70% confluency. Next day cells were treated with compounds for 4 hours and fixed with 4% methanol-free paraformaldehyde (Sigma-Aldrich, USA) for 10 min. After three washes with Dulbecco Phosphate Buffered Saline (DPBS) supplemented with glycine cells were permeabilized with 0.25% Triton X-100 (Sigma Aldrich, USA) for 5 min. Cells were washed three times with DPBS and stained with 4',6-diamidino-2-phenylindole (DAPI) to visualize nuclei. Fluorescent imaging was performed using Leica SP8 Falcon inverted confocal microscope with build-in 63X oil objective. Images were acquired using LASX software.

5.7.4 EGFP-LC3B puncta quantification analysis

Images were processed using ImageJ software (NIH, USA). Cells were analyzed individually. Cell boundary was marked by freehand selection, and total cell area was quantified. After an automatic threshold was set for the EGFP-LC3B channel, "analyze particles" method was applied to obtain total EFGP-LC3B area. Finally, EFGP-LC3B area was normalized to total cell area.

5.7.5 Western blotting

For Western blotting experiments MCF7 cells stably expressing EGFP-LC3B were seeded to 6-well plates in 80% confluency. Next day cells were treated with compounds for 4 hours, washed from cell culture media and scraped in ice-cold lysis buffer (20 mM Tris-HCl pH 8, 300 mM KCl, 10% glycerol, 0.25% Nonidet P-40, 0.5 mM EDTA, 0.5 mM EGTA) supplemented with 1 mM PMSF and cOmplete™ Protease Inhibitor Cocktail (Sigma Aldrich, USA). Cell lysates were pushed through 22G syringe needle six times and centrifuged at 16000 g at 4 °C for 20 min. Supernatant was mixed with SDS sample buffer with β-mercaptoethanol and boiled at 95 °C for 10 min. Proteins were separated using SDS polyacrylamide gel electrophoresis and transferred to nitrocellulose membrane using Trans-Blot Turbo transfer system (Bio-Rad, USA). After transfer membranes were blocked in 5% Skim Milk (Sigma Aldrich, USA) for 45 min and incubated with anti-LC3B rabbit polyclonal antibodies (#2775, Cell Signaling, USA), anti-GFP rabbit polyclonal antibodies (#A-11122, Thermo Fisher, USA) at 4 °C overnight or anti-beta-actin mouse monoclonal antibodies at 4 °C for 1 hour. Membranes were washed

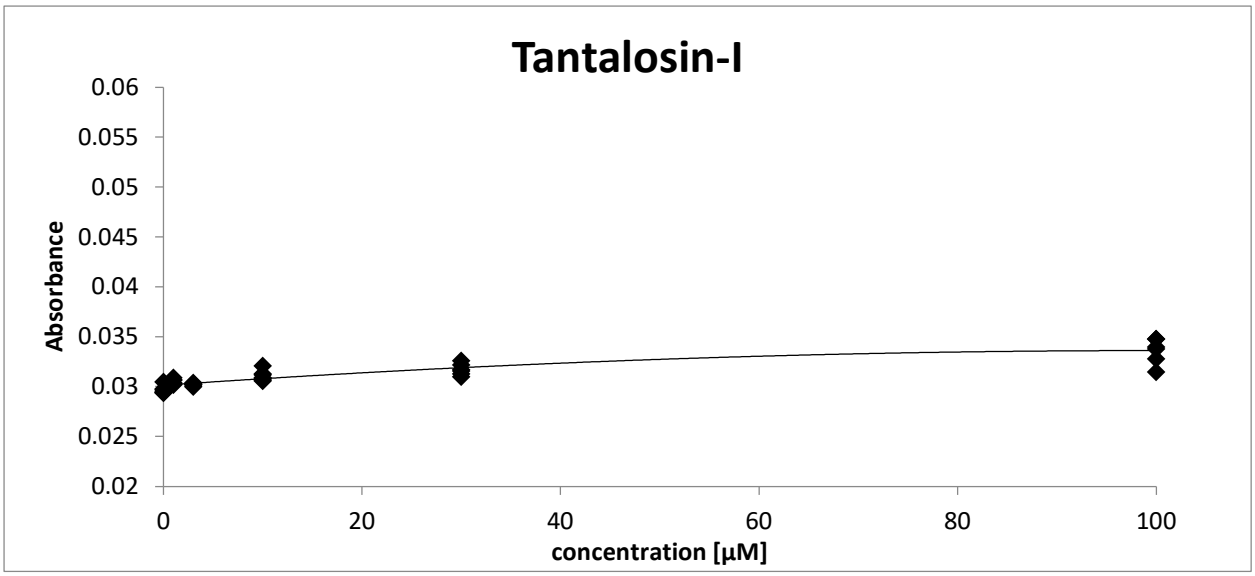
three times with TBS containing 0.1% Tween-20 and incubated with HRP-conjugated secondary antibodies. Chemiluminescent signal was detected using ChemiDoc imaging system (Bio-Rad, USA).

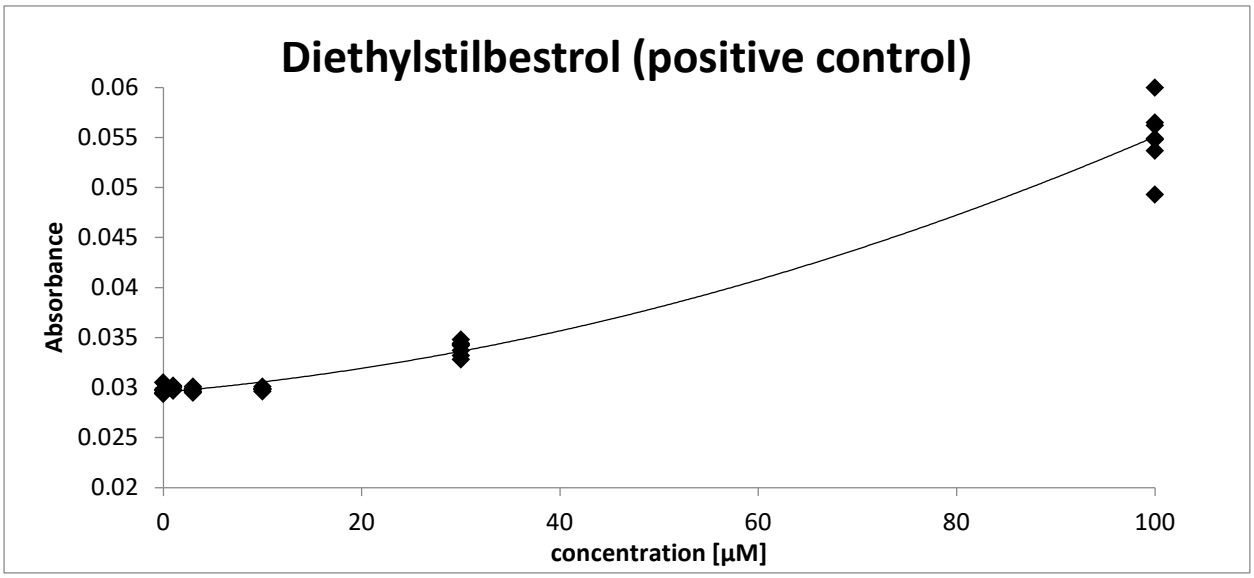
5.7.6 Statistical analysis

For EGFP-LC3B puncta quantification N=3 independent experiments were performed and n > 30 cells per individual experiment were analyzed. Statistical analysis was performed in GraphPad Prism software for N=3 independent experiments using unpaired two-tailed t-test. Statistical significance was determined as: ns – not significant, * $p<0.05$, ** $p<0.001$.

5.8 Solubility

The solubility of Tantalosin-I was determined by the Lead Discovery Certer Dortmund. The thermodynamic solubility in PBS at pH 7.4 (equilibrium) was determined to be 7.38 ± 4.22 µM via LC-MS/MS. The kinetic solubility was determined by the TurbiSol-assay to be in about the same range. However, the absorbance curve appears more flat than of the positive control (diethylstilbestrol) which has a solubility threshold between 10 and 30 µM.





(28.10.2021)

https://www.cyprotex.com/physicochemicalprofiling/physicochemical-properties/turbidimetric-solubility

https://www.cyprotex.com/physicochemicalprofiling/physicochemical-properties/thermodynamic-solubility

5.9 General Procedures

All commercially available compounds were used as provided without further purifications. Anhydrous solvents (CH_2Cl_2, acetonitrile, DMF or THF) were used as commercially available. Solvents for flash column chromatography were technical grade. Solvents for preparative HPLC were HPLC-grade. Chemicals and solvents were purchased from the companies Sigma-Aldrich, Acros Organic, ABCR, TCI and Alfa Aesar.

Analytical thin-layer chromatography (TLC) was performed on Merck silica gel aluminium plates with F-254 indicator. Compounds were visualized by irradiation with UV light or potassium permanganate staining. Column chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm). Solvent mixtures are understood as volume/volume.

HPLC-purification was performed on an Agilent 1260 Infinity II with an Agilent LC MSD and a Macherey-Nagel VP 125/21 Nucleodur C18 Gravity 5µm column.

^{1}H-NMR and ^{13}C-NMR were recorded on a Bruker DRX400 (400 MHz), Bruker DRX500 (500 MHz), INOVA500 (500 MHz), Bruker Avance III HD (600 MHz) and Bruker DRX700 (700 MHz) using $CDCl_3$, CD_3CN, D_2O or indicated mixtures of them. Data are reported in the following order: chemical shift (δ) values are reported in ppm with the solvent resonance as internal standard ($CDCl_3$: δ = 7.26 ppm for ^{1}H, δ = 77.16 ppm for ^{13}C; CD_3CN: δ = 1.94 ppm for ^{1}H, δ = 118.26 ppm for ^{13}C); multiplicities are indicated br s (broadened singlet), s (singlet), d (doublet), t (triplet), q (quartet), p (pentett), hept (heptet), m (multiplet); coupling constants (J) are given in Hertz (Hz). Spectra recorded in mixtures of CD_3CN and D_2O were shimmed and referenced using the acetonitrile solvent peak.

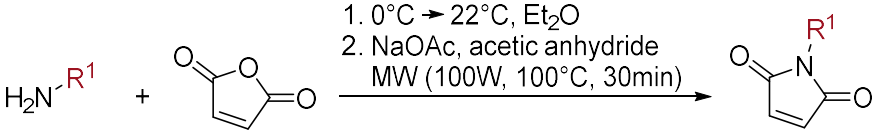
High resolution mass spectra were recorded on a LTQ Orbitrap mass spectrometer coupled to an Acceka HPLC-System (HPLC column: Hypersyl GOLD, 50 mm x 1 mm, particle size 1.9 µm, ionization method: electron spray ionization).

Optical rotations were measured in a Schmidt+Haensch Polartronic HH8 polarimeter.

Yields always refers to isolated substances. The ratio of diastereomers was determined from isolated yields but matches the ratio in HPLC traces of the 254 nm or 310 nm channel well.

MM refers to a solvent mix of 80:20:8 CH_2Cl_2:MeOH:(25% aq. NH_3).

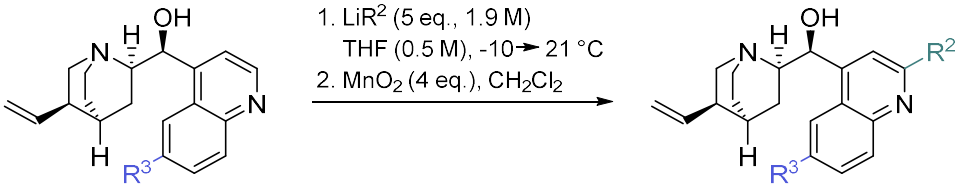
5.9.1 GP1 – N-Alkyl maleimides



To a solution of the respective primary amine (1 eq.) in Et_2O (7 mL) in a 30 mL microwave vial was added maleic anhydride (1.05 eq.) in Et_2O (7 mL) dropwise at 0 °C. The reaction was then stirred at 21 °C for 1 h. The suspension was centrifuged (4000 rpm, 0 °C, 10 min) and the solvent was decanted. The remaining solid was dried under a stream of argon and used for the following step without further purification.

NaOAc (1.3 eq.) and the acetic anhydride (20 eq.) were added to the microwave vial ensuring good stirring. The vial was capped and heated in a microwave reactor (30 min, 100 W irradiation, constant 100 °C). The cooled down solution was diluted with Et_2O and filtered. The solvents were removed under reduced pressure and FCC gave the respective maleimide.

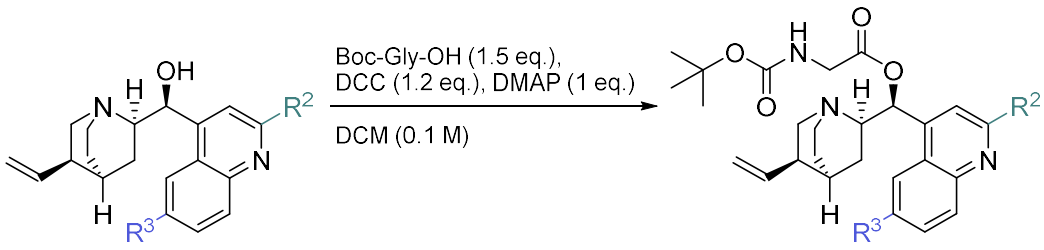
5.9.2 GP2 – C2'-alkylation



The respective cinchona alkaloid (1 eq.) under argon was solved in anhydrous THF (0.5 M). A solution of the respective organo-lithium reagent (5 eq., in hexanes/ether) was added quickly under vigorous stirring at below -10 °C. The reaction was stirred for 30 min and then slowly warmed to 21 °C. After 4 h it was cooled to -10 °C and acetic acid (10 mL) was added dropwise, not exceeding 0 °C. H_2O (60 mL) and EtOAc were added and the solution was brought to pH 8 – 9 by the addition of sat. aq. $NaHCO_3$. The phases were separated, and the watery phase was extracted three times with CH_3Cl/MeOH (50 mL, 5% MeOH). The combined organic phases were washed with brine, dried over Na_2SO_4 and filtered before the solvent was removed under reduced pressure.

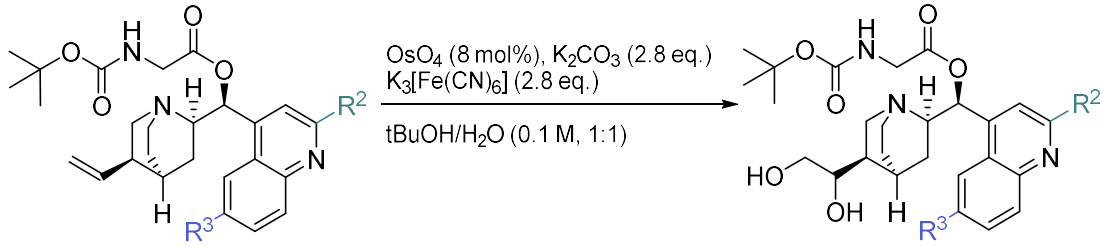
The crude product was then taken up in CH_2Cl_2 (0.1 M) and MnO_2 (4 eq.) was added. The slurry was stirred for 16 h at 21 °C. The solids were removed by filtration and the solvent was removed under reduced pressure. FCC then gave the respective title compound.

5.9.3 GP3 – C9-Hydroxyl esterification



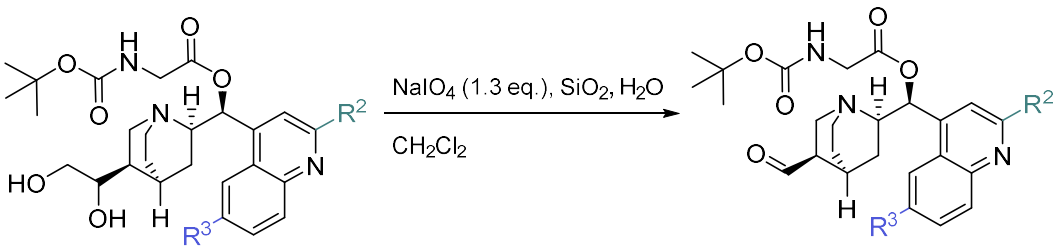
The respective free alcohol (1 eq.), DMAP (1 eq.) and Boc-glycine (1.5 eq.) were solved in CH_2Cl_2 (0.1 M). To this solution under argon was added DCC (1.2 eq.) in CH_2Cl_2 (20 mL) slowly. The reaction was stirred for 16 h. EtOAc was added and CH_2Cl_2 was removed under reduced pressure. The suspension was cooled to 0 °C and filtered. The filter was washed with cold EtOAc several times before the solvent was removed under reduced pressure. FCC gave the respective ester.

5.9.4 GP-4 – C10/C11 dihydroxylation



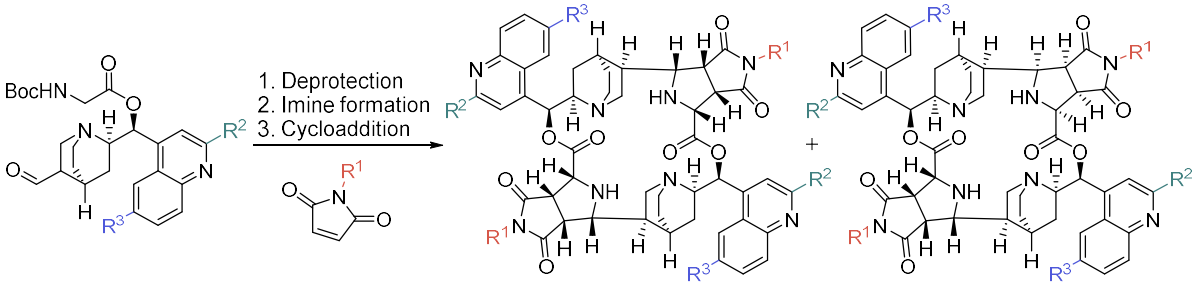
The respective alkene (1 eq.) and $K_3[Fe(CN)_6]$ (2.8 eq.) were solved in *t*BuOH/H_2O (1:1, 0.1 M) before K_2CO_3 (2.8 eq.) was added. A solution of OsO_4 (4 % w/v in H_2O; 0.08 eq.) was added dropwise and the reaction was stirred until disappearance of the starting material (ca. 2 h). $CHCl_3$ and then sat. aq. $NaHSO_3$/brine (1:1) were added. The organic phases were separated and the organic phase was washed with sat. aq. $NaHSO_3$/brine (1:1). The combined watery phases were added $CHCl_3$ and sat. $NaHCO_3$ until pH 9. The phases were separated and the watery phase was extracted with $CHCl_3$/*t*BuOH (5 % *t*BuOH) three times. All organic phases were combined and dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. FCC gave the respective diol.

5.9.5 GP-5 – C10/C11 diol cleavage



To vigorously stirred CH_2Cl_2 (0.025 M) were added silica (2.5 times the value of the mmol of the starting material in gram). $NaIO_4$ (1.3 eq.) was added. Then H_2O was added dropwise is a way, that the resulting suspension stayed homogeneous (two times the value of the mmol of the starting material in mL). To this, the respective diol in CH_2Cl_2 (20 mL) was added quickly. The disappearance of the starting material was monitored via TLC (full completion after 5 to 30 min). Then, the reaction was filtered through a plug of Na_2SO_4. The filter was washed with CH_2Cl_2 several times and the solvent was removed under reduced pressure. FCC gave the respective aldehyde.[7]

5.9.6 GP6 – One-pot macrocyclization sequence



All reactions were performed under argon in oven-dry 10 mL round bottom flasks (220 °C for 24 h) and with anhydrous solvents. The reactions were stirred at 800 rpm with a rod-shaped 3x10 mm Teflon-coated stirring bar. Evaporation of solvents under reduced pressure were done via a Schlenk-technique setups and backfilled with argon. The flasks were sealed with rubber septums with folding clasps. Stock solutions were prepared under argon on the day of the experiment in over dry glassware.

TFA/DCM stock: Oven-dry $MgSO_4$ (400 mg) was added 40 mL CH_2Cl_2 followed by 10 mL TFA. The suspension was swirled several times and was then left standing for 1 h to let the solids settle. Only clear solution close to the surface was taken.

Et_3N stock: 360 µL Et_3N + 4.64 mL anhydrous MeCN

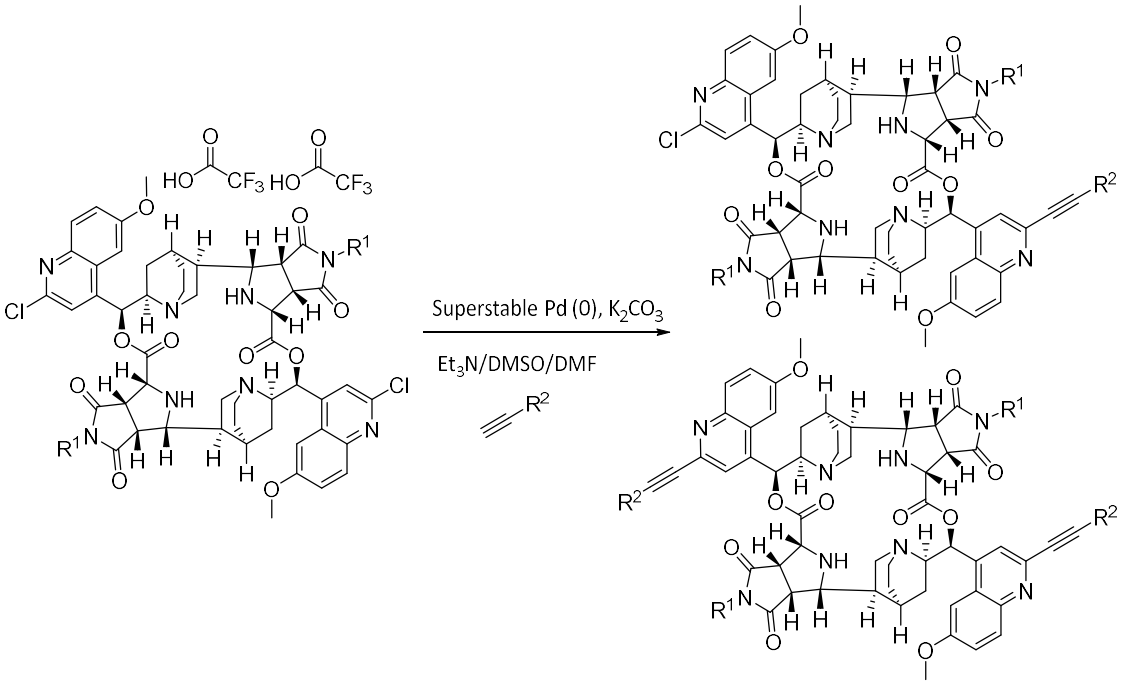
AgOTf-stock-1: 15 mg AgOTf in 2.5 mL anhydrous MeCN

Maleimide stock: 1.5 eq. respective maleimide in 250 µL MeCN

The respective cinchona alkaloid starting material (57.9 µm, 1 eq.) was solved in anhydrous CH_2Cl_2 (2.5 mL) and TFA/DCM stock (2.5 mL) was added. After 90 min the solvents were evaporated at 21 °C under reduced pressure. The residue was taken up in CH_2Cl_2 (1 mL), before the solvent was removed under high vacuum. This was repeated and the residue was dried under high vacuum for 1 h.

The deprotected TFA-salt was solved in 1 mL MeCN and Et_3N stock (500 µL, 4.5 eq.) was added dropwise. Oven-dry coarse $MgSO_4$ (ca. 20 mg) were added quickly after under a positive flow of argon. The reaction was stirred for 10 min before AgOTf-stock and maleimide stock were added subsequently in one go (250 µL each; 0.1 eq. and 1.5 eq. respectively). The gas was exchanged with argon three times and the already sealed vial was further sealed with parafilm. The reaction was then stirred for 16 h before the solvent was removed under reduced pressure and the residue taken up in a total of 1.5 mL methanol/dimethylformamide and filtered through an HPLC-filter (PET, 25 mm, 0.2 µm). Purification was performed via preparative HPLC according to the general purification method below.

5.9.7 GP7 – C2'-Sonogashira coupling



All reactions were performed under argon in oven-dry 5 mL pointy bottom flasks (220 °C for 24 h) and with degassed, anhydrous solvents.

The respective 2',2''-dichloro macrocycle (1 eq.), Superstable Pd(0)® (15 mol%), K_2CO_3 (3 eq. for a desymmetrisizing transformation or 6 eq. for a symmetrical transformation) was added DMSO (50 µL), DMF (100 µL) and Et_3N (100 µL) quickly and under vigorous stirring. The reaction was stirred for 15 min before the respective terminal alkyne was added dropwise as a stock solution in DMSO (in 50 µL DMSO; 1.05 eq. for desymmetrizing transformations, 5 eq. for symmetrical transformations). The reaction was stirred for 15 min before being heated at 90 °C for 16 h. Et_3N was removed under reduced pressure before the residual solution was taken up in MeOH and DMF (2:1) and filtered through an HPLC-filter (PET, 25 mm, 0.2 µm). Purification via preparative HPLC followed according to the general purification method below.

5.9.8 General purification via preparative HPLC

All macrocyclic compounds were purified via preparative HPLC using following method. Percentages “a” and “b” are given for each individual compound.

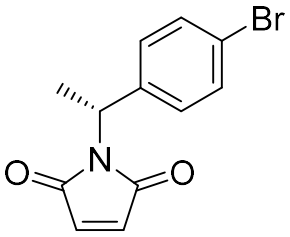
Entry	**Time** [min]	**MeCN** [% in H_2O]
1	0.00 – 02.00	10 %
2	2.00 – 2.10	10 % – a
3	2.10 – 30.0	a – b

5.10 N-substituted maleimides and cinchona alkaloid derivatives

5.10.1 Maleimides

All maleimides were prepared from General Procedure 1.

98ac, N-(R)-1-(4-Bromophenyl)ethyl maleimide



1.50 g (7.50 mmol) 4-methylbenzyl amine afforded **98ac** in 56 % yield (1.18 g, 4.21 mmol), as lightly brown solid after purification via FCC.

Rf (5:1, Hexanes:EtOAc) = 0.36

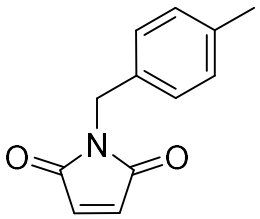
^{1}H NMR (700 MHz, CDl_3) 7.43 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 6.62 (s, 2H), 5.29 (q, J = 7.4 Hz, 1H), 1.79 (dd, J = 7.4, 1.1 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 170.49, 139.29, 134.15, 131.70, 129.15, 121.79, 49.09, 17.60.

HRMS (ESI): $C_{12}H_{11}O_2NBr$ $[M+H]^+$; calculated: 279.99709, found: 279.99677.

$[\alpha]_{20}^{D}$ = + 80 ° (c = 1, $CHCl_3$).

98ad, N-1-(4-methylbenzyl) maleimide



1.25 g (10.32 mmol) 4-methylbenzyl amine afforded **98ad** in 36 % yield (736 mg, 3.66 mmol), as colorless needles after purification via FCC.

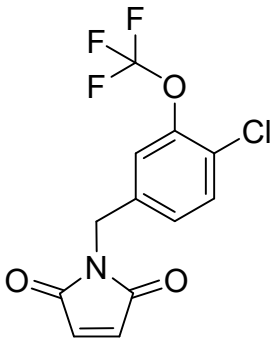
Rf (4:1, Hexanes:EtOAc) = 0.45

^{1}H NMR (700 MHz, CDl_3) δ 7.24 (d, J = 8.1 Hz, 2H), 7.14 – 7.10 (m, 2H), 6.69 (s, 2H), 4.64 (s, 2H), 2.31 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 170.57, 137.75, 134.31, 133.38, 129.47, 128.55, 41.31, 21.24.

HRMS (ESI): $C_{12}H_{12}O_2N$ $[M+H]^+$; calculated: 202.08626, found: 202.08614.

98ae, 1-(4-chloro-3-(trifluoromethoxy)benzyl) maleimide



1g (4.43 mmol) 4-Chloro-3-(trifluoromethoxy)benzyl amine afforded **98ae** in 36 % yield (478 mg, 1.56 mmol), as colorless needles after purification via FCC.

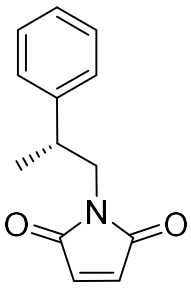
Rf (4:1, Hexanes:EtOAc) = 0.38

^{1}H NMR (700 MHz, CDl_3) δ 7.41 (d, J = 8.3 Hz, 1H), 7.32 (s, 1H), 7.23 (dd, J = 8.3, 2.0 Hz, 1H), 6.74 (s, 2H), 4.65 (s, 2H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 170.19, 145.33, 145.32, 136.65, 134.47, 131.31, 128.07, 127.24, 123.06, 123.06, 122.74, 121.26, 119.79, 118.32, 40.57.

HRMS (ESI): $C_{12}H_8O_3NF_3$ $[M+H]^+$; calculated: 306.01393, found: 306.01416.

98af, (R)-N-2-phenylpropyl maleimide



1.25 g (9.25 mmol) (R)-2-phenylpropylamine afforded **98af** in 50 % yield (941 mg, 4.37 mmol), as colorless needles after purification via FCC.

Rf (7:1, Hexanes:EtOAc) = 0.3

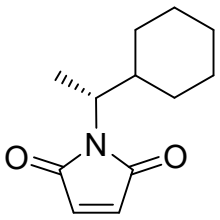
^{1}H NMR (700 MHz, CDl_3) δ 7.38 – 7.32 (m, 2H), 7.30 – 7.26 (m, 3H), 6.66 (s, 2H), 3.76 (dd, J = 13.8, 8.2 Hz, 1H), 3.68 (dd, J = 13.8, 7.9 Hz, 1H), 3.31 (h, J = 7.4 Hz, 1H), 1.33 (d, J = 7.2 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 170.71, 143.14, 133.89, 128.54, 127.32, 126.87, 44.77, 38.48, 18.85.

HRMS (ESI): $C_{13}H_{14}O_2N$ $[M+H]^+$; calculated: 216.10191, found: 216.10193.

$[\alpha]_{20}^{D}$ = + 73 ° (c = 1, $CHCl_3$).

98ag, **N-(R)-1-(1-cyclohexylethyl) maleimide**



1.1 g (8.65 mmol) (R)-cyclohexylethylamine afforded **98ag** in 65 % yield (1.15 g, 5.55 mM), as colorless needles after purification via FCC.

Rf (15:1, Hexanes:EtOAc) = 0.3

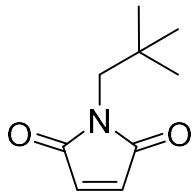
^{1}H NMR (700 MHz, CDl_3) δ 6.62 (s, 2H), 3.81 (dq, J = 10.0, 7.1 Hz, 1H), 1.93 – 1.82 (m, 2H), 1.77 – 1.71 (m, 1H), 1.64 (ddt, J = 19.0, 15.4, 3.5 Hz, 2H), 1.47 – 1.41 (m, 1H), 1.36 (d, J = 7.0 Hz, 3H), 1.23 (tt, J = 12.7, 3.5 Hz, 1H), 1.13 (dddd, J = 37.3, 15.8, 12.7, 9.5 Hz, 2H), 0.90 (qd, J = 12.3, 3.7 Hz, 1H), 0.83 (qd, J = 12.3, 3.6 Hz, 1H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 171.29, 133.87, 52.50, 40.24, 30.61, 30.23, 26.25, 25.93, 25.82, 16.45.

HRMS (ESI): $C_{12}H_{18}O_2N$ $[M+H]^+$; calculated: 208.13321, found: 208.13314.

$[\alpha]_{20}^{D}$ = + 7 ° (c = 1, $CHCl_3$).

98ah, N-neopentyl maleimide



0.85 g (9.75 mmol) neopentyl amine afforded **98ah** in 39 % yield (629 mg, 3.76 mmol), as colorless needles after purification via FCC.

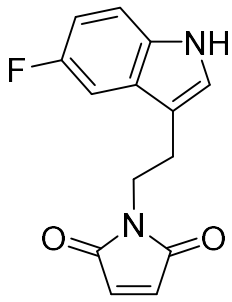
Rf (7:1, Hexanes:EtOAc) = 0.3

^{1}H NMR (700 MHz, CDl_3) δ 6.70 (s, 2H), 3.32 (s, 2H), 0.91 (s, 9H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 171.52, 134.15, 49.27, 33.64, 28.08.

HRMS (ESI): $C_9H_{14}O_2N$ $[M+H]^+$; calculated: 168.10191, found: 168.10166.

98ai, N-2-[5-fluoro-1H-indol-3-yl)ethyl] maleimide



1 g (5.55 mmol) 5-fluorotryptamine afforded **98ai** in 16 % yield (224 mg, 0,86 mmol), as colorless needles after purification via FCC.

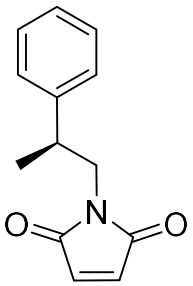
Rf (1% MeOH in MeOH) = 0.71

^{1}H NMR (700 MHz, CDl_3) δ 8.02 (s, 1H), 7.28 (dd, J = 9.5, 2.5 Hz, 1H), 7.25 (dd, J = 8.6, 4.1 Hz, 1H), 7.08 (d, J = 2.4 Hz, 1H), 6.93 (td, J = 9.0, 2.5 Hz, 1H), 6.66 (s, 2H), 3.85 – 3.78 (m, 2H), 3.01 (ddd, J = 8.5, 6.6, 0.9 Hz, 2H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 170.85, 158.65, 157.31, 134.21, 132.79, 127.96, 127.90, 123.93, 112.66, 112.64, 111.94, 111.88, 110.79, 110.64, 103.87, 103.73, 38.41, 24.37.

HRMS (ESI): $C_{14}H_{11}O_2N_2F$ $[M+H]^+$; calculated: 259.08828, found: 259.08776.

98aj, (S)-N-2-phenylpropyl maleimide



1.2 g (8.88 mmol) (S)-2-phenylpropylamine afforded **98aj** in 52 % yield (1.02 g, 4.74 mmol), as colorless needles after purification via FCC.

Rf (7:1, Hexanes:EtOAc) = 0.3

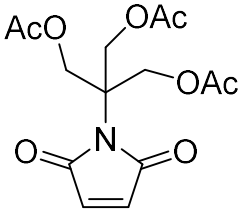
^{1}H NMR (700 MHz, CDl_3) δ 7.25 – 7.17 (m, 2H), 7.17 – 7.08 (m, 3H), 6.53 (s, 2H), 3.62 (dd, J = 13.7, 8.2 Hz, 1H), 3.54 (dd, J = 13.7, 7.8 Hz, 1H), 3.16 (h, J = 7.4 Hz, 1H), 1.19 (d, J = 7.0 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 170.80, 143.21, 133.97, 128.62, 127.41, 126.95, 44.87, 38.56, 18.91.

HRMS (ESI): $C_{13}H_{14}O_2N$ $[M+H]^+$; calculated: 216.10191, found: 216.10192.

$[\alpha]_{20}^{D}$ = - 73 ° (c = 1, $CHCl_3$).

98ak, 2-(acetoxymethyl)-2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propane-1,3-diyl diacetate



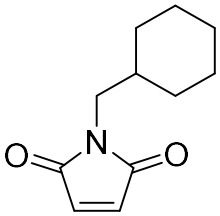
1.297 g (10.71 mmol) 4-methylbenzyl amine afforded **98ak** in 29 % yield (1.03 g, 3.15 mmol), as colorless needles after purification via FCC.

^{1}H NMR (700 MHz, CDl_3) δ 6.63 (d, J = 1.5 Hz, 2H), 4.66 (s, 6H), 2.03 (s, 9H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 171.27, 170.25, 134.38, 63.14, 60.78, 20.79.

HRMS (ESI): $C_{14}H_{18}O_8N$ $[M+H]^+$; calculated: 328.10269, found: 328.10293.

98al, N-(cyclohexylmethyl) maleimide



283 mg (2.5 mmol) cyclohexylmethylamine afforded **98al** in 40 % yield (191 mg, 0.99 mmol), as colorless needles after purification via FCC.

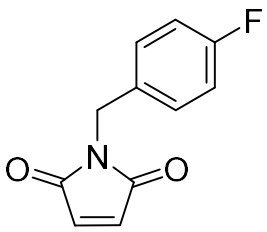
Rf (5:1, Hexanes:EtOAc) = 0.56

^{1}H NMR (700 MHz, CDl_3) δ 6.68 (s, 2H), 3.35 (d, J = 7.4 Hz, 2H), 1.72 – 1.58 (m, 6H), 1.23 – 1.09 (m, 3H), 0.93 (qd, J = 12.0, 3.4 Hz, 2H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 171.26, 134.05, 44.13, 37.03, 30.79, 26.35, 25.74.

HRMS (ESI): $C_{11}H_{16}O_2N$ $[M+H]^+$; calculated: 194.11756, found: 194.11742.

98am, N-1-(4-fluorobenzyl) maleimide



313 mg (2.5 mmol) 4-fluorobenzyl amine afforded **98am** in 45 % yield (228 mg, 1.11 mmol), as colorless needles after purification via FCC.

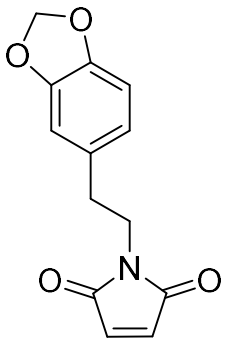
Rf (5:1, Hexanes:EtOAc) = 0.33

^{1}H NMR (500 MHz, CDl_3) δ 7.33 (ddd, J = 8.4, 5.3, 2.5 Hz, 2H), 7.02 – 6.96 (m, 2H), 6.71 (s, 2H), 4.64 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.47, 163.49, 161.53, 134.38, 132.16, 132.13, 130.54, 130.47, 115.80, 115.63, 40.84.

HRMS (ESI): $C_{11}H_9O_2NF$ $[M+H]^+$; calculated: 206.06118, found: 206.06119.

98an, N-1-(Homopiperonyl) maleimide



530 mg (2.63 mmol) homopiperonyl amine hydrochloride was suspended in DCM and sat. $NaHCO_3$ was added dropwise until pH 9. The Phases were separated and the watery phase was extracted two times with 10 ml DCM. The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The free amine was then used without further purification for General Procedure 1. **98an** was isolated in 20 % yield (123 mg, 0.5 mmol), as yellow crystals after purification via FCC.

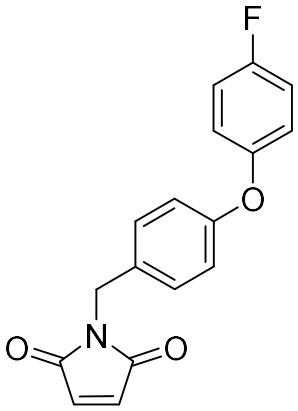
Rf (5:1, Hexanes:EtOAc) = 0.36

^{1}H NMR (500 MHz, CDl_3) δ 6.74 – 6.68 (m, 2H), 6.68 – 6.65 (m, 2H), 6.65 – 6.59 (m, 1H), 5.97 – 5.87 (m, 2H), 3.71 (q, J = 7.4, 6.9 Hz, 2H), 2.81 (q, J = 6.7 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.70, 147.83, 146.41, 134.17, 131.66, 121.90, 109.32, 108.43, 101.03, 39.41, 34.33.

HRMS (ESI): $C_{13}H_{12}O_4N$ $[M+H]^+$; calculated: 246.07608, found: 246.07612.

98ao, N-1-(4-(4-fluorophenoxy)benzyl) maleimide



1 g (3.94 mmol) 4-(4-flourophenoxy)benzyl amine afforded **98ao** in 67% yield (782 mg, 2.63 mmol), as orange needles after purification via FCC.

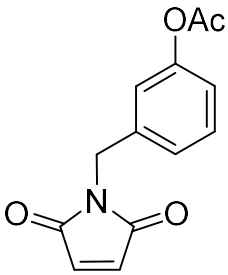
Rf (6:1, Hexanes:EtOAc) = 0.29

^{1}H NMR (500 MHz, CDl_3) δ 7.32 – 7.29 (m, 2H), 7.04 – 6.99 (m, 2H), 6.98 – 6.93 (m, 2H), 6.91 – 6.87 (m, 2H), 6.71 (s, 2H), 4.64 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.55, 160.01, 158.08, 157.56, 152.67, 152.65, 134.36, 131.04, 130.24, 120.87, 120.80, 118.34, 116.57, 116.38, 40.93.

HRMS (ESI): $C_{17}H_{13}O_3NF$ $[M+H]^+$; calculated: 298.08740, found: 298.08758.

98aq, N-1-(3-acetoxybenzyl) maleimide



The first reaction step was performed in DMF. Removal of DMF under reduced pressure at 50 °C afforded intermediary product as a white solid.

849 mg (8.53 mmol) 3-hydroxybenzylamine afforded **98aq** in 42 % yield (827 mg, 3.37 mmol), as orange solid.

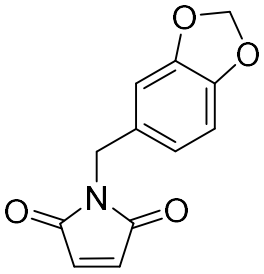
Rf (3:1, Hexanes:EtOAc) = 0.32

^{1}H NMR (700 MHz, CDl_3) δ 7.32 (t, J = 7.9 Hz, 1H), 7.22 (ddd, J = 7.7, 1.7, 1.0 Hz, 1H), 7.08 (t, J = 2.0 Hz, 1H), 7.01 (ddd, J = 8.1, 2.4, 1.0 Hz, 1H), 6.71 (s, 2H), 4.66 (s, 2H), 2.28 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 170.39, 169.46, 150.96, 137.87, 134.38, 129.84, 126.15, 121.88, 121.42, 41.14, 21.24.

HRMS (ESI): $C_{11}H_{12}O_3N$ $[M+H]^+$; calculated: 204.06552, found: 204.06544.

98ar, N-1-piperonyl maleimide



1.5 ml (12.01 mmol) Piperonyl amine afforded **98ar** in 42 % yield (1.16 mg, 4.95 mmol), as colorless needles after purification via FCC.

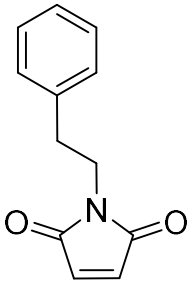
Rf (4:1, Hexanes:EtOAc) = 0.36

^{1}H NMR (500 MHz, CDl_3) δ 6.87 – 6.79 (m, 2H), 6.75 – 6.72 (m, 1H), 6.70 (s, 2H), 5.93 (s, 2H), 4.57 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.53, 147.92, 147.37, 134.33, 130.12, 122.24, 109.20, 108.44, 101.25, 41.36.

HRMS (ESI): $C_{12}H_{10}O_4N$ $[M+H]^+$; calculated: 232.06043, found: 232.06038.

98as, N-Phenethyl maleimide



1.5 ml (11.9 mmol) Phenylethyl amine afforded **98as** in 60 % yield (1.432 mg, 7.12 mmol), as off white needles after purification via FCC.

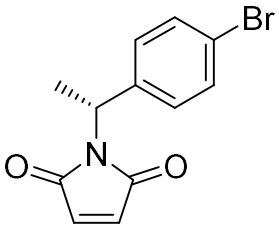
Rf (5:1, Hexanes:EtOAc) = 0.5

^{1}H NMR (500 MHz, CDl_3) δ 7.29 (tt, J = 7.0, 1.0 Hz, 2H), 7.24 – 7.18 (m, 3H), 6.65 (s, 2H), 3.79 – 3.74 (m, 2H), 2.92 – 2.87 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.71, 137.95, 134.17, 128.96, 128.69, 126.82, 39.25, 34.65.

HRMS (ESI): $C_{12}H_{12}O_2N$ $[M+H]^+$; calculated: 202.08626, found: 202.08616.

98at, N-1-((R)-1-(4-bromophenyl)ethyl) maleimide



1.5 g (7.5 mmol) (R)-1-(4-bromophenyl)ethylamine afforded **98at** in 57 % yield (1.18 mg, 4.21 mmol), as colorless needles after purification via FCC.

Rf (7:1, Hexanes:EtOAc) = 0.3

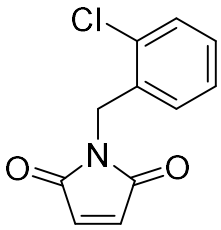
^{1}H NMR (700 MHz, CDl_3) δ 7.43 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 6.62 (s, 2H), 5.29 (q, J = 7.4 Hz, 1H), 1.79 (dd, J = 7.4, 1.1 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 170.49, 139.29, 134.15, 131.70, 129.15, 121.79, 49.09, 17.60.

HRMS (ESI): $C_{12}H_{11}O_2NBr$ $[M+H]^+$; calculated: 279.99677, found: 279.99709.

$[\alpha]_{20}^{D}$ = + 80 ° (c = 1, $CHCl_3$).

98au, N-1-(2-chlorobenzyl) maleimide



1.5 g (10.59 mmol) 2-chlorobenzyl amine afforded **98au** in 21 % yield (483 mg, 2.18 mmol), as colorless needles. after purification via FCC.

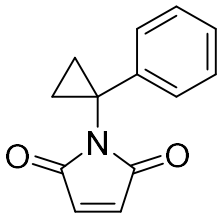
Rf (5:1, Hexanes:EtOAc) = 0.38

^{1}H NMR (700 MHz, CDl_3) δ 7.39 – 7.33 (m, 1H), 7.23 – 7.18 (m, 2H), 7.17 – 7.11 (m, 1H), 6.76 (d, J = 1.0 Hz, 2H), 4.82 (s, 2H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 170.32, 134.41, 133.34, 133.08, 129.80, 129.07, 128.76, 127.02, 39.30.

HRMS (ESI): $C_{11}H_9O_2NCl$ $[M+H]^+$; calculated: 222.03218, found: 222.03163.

98av, N-1-(1-phenylcyclopropyl) maleimide



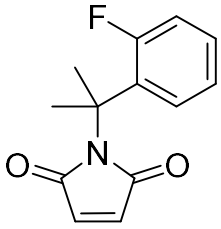
578 mg (5.78 mmol) 1-phenylcyclopropan-1-amine afforded **98av** in 74 % yield (933 mg, 4.38 mmol), as colorless needles after purification via FCC.

Rf (5:1, cHex:EtOAc) = 0.3

^{1}H NMR (700 MHz, CDl_3) δ 7.36 – 7.33 (m, 2H), 7.28 (t, J = 7.7 Hz, 2H), 7.24 – 7.19 (m, 1H), 6.63 (s, 2H), 1.43 – 1.36 (m, 4H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 170.80, 140.52, 133.98, 128.67, 127.54, 127.42, 33.59, 14.44.

98ax, N-1-(1-methyl-1-(2-fluorophenyl)ethyl maleimide



517 mg (5.27 mmol) 2-(2-fluorophenyl)propan-2-amine afforded **98ax** in 58 % yield (706 mg, 3.03 mmol), as colorless needles after purification via FCC.

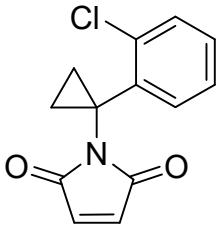
Rf (5:1, cHex:EtOAc) = 0.3

^{1}H NMR (500 MHz, CDl_3) δ 7.36 (td, J = 8.1, 1.7 Hz, 1H), 7.24 (dddd, J = 8.0, 7.3, 5.0, 1.8 Hz, 1H), 7.13 (td, J = 7.6, 1.3 Hz, 1H), 6.97 (ddd, J = 12.4, 8.1, 1.4 Hz, 1H), 6.53 (s, 2H), 1.96 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.35, 161.30, 159.33, 133.95, 132.83, 132.75, 129.01, 128.94, 126.64, 126.61, 124.15, 124.12, 116.50, 116.32, 58.85, 27.78, 27.77.

HRMS (ESI): $C_{13}H_{13}O_2NF$ $[M+H]^+$; calculated: 234.09248, found: 234.09240.

98ay, N-1-(1-(2-chlorophenyl)cyclopropyl) maleimide



480 mg (4.90 mmol) 1-(2-chlorophenyl)cyclopropan-1-amine afforded **98ay** in 42 % yield (510 mg, 2.06 mmol), as colorless needles after purification via FCC.

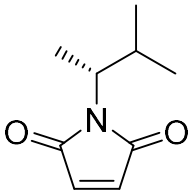
Rf (5:1, cHex:EtOAc) = 0.36

^{1}H NMR (700 MHz, CDl_3) δ 7.93 – 7.78 (m, 1H), 7.31 (dd, J = 7.5, 1.8 Hz, 1H), 7.24 – 7.16 (m, 2H), 6.54 (s, 2H), 1.61 – 1.56 (m, 2H), 1.41 – 1.36 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.48, 136.98, 135.56, 134.28, 133.81, 129.99, 129.54, 126.49, 33.85, 13.79.

HRMS (ESI): $C_{13}H_{11}O_2NCl$ $[M+H]^+$; calculated: 248.04728, found: 248.04724.

98az, N-(R)-1-(3-methylbutan-2-yl) maleimide



1.00 g (11.47 mmol) (R)-(−)-2-Amino-3-methylbutane afforded **98az** in 28 % yield (526 mg, 3.15 mmol), as colorless needles after purification via FCC.

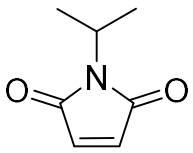
Rf (6:1, cHex:EtOAc) = 0.52

^{1}H NMR (700 MHz, CDl_3) δ 6.63 (s, 2H), 3.75 (dq, J = 10.0, 7.0 Hz, 1H), 2.23 (dp, J = 10.0, 6.7 Hz, 1H), 1.37 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H), 0.77 (d, J = 6.7 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 171.24, 133.89, 53.77, 31.36, 20.27, 20.16, 16.78.

$[\alpha]_{20}^{D}$ = - 4 ° (c = 1, $CHCl_3$).

98ba, N-isopropyl maleimide



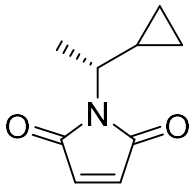
550 mg (9.30 mmol) isopropylamine afforded **98ba** in 43 % yield (559 mg, 4.02 mmol), as lightly orange liquid after purification via FCC.

Rf (5:1, cHex:EtOAc) = 0.43

^{1}H NMR (600 MHz, CDl_3) δ 6.61 (s, 2H), 4.32 (hept, J = 7.0 Hz, 1H), 1.38 (d, J = 7.0 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.98, 134.09, 43.07, 20.26.

98bb, N-(R)-1-(1-cyclopropylethyl) maleimide



553 mg (5.64 mmol) (R)-1-cyclopropylethan-1-amine afforded **98bb** in 44 % yield (340 mg, 2.06 mmol), as colorless solid after purification via FCC.

Rf (3:1, cHex:EtOAc) = 0.7

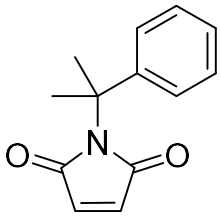
^{1}H NMR (400 MHz, CDl_3) δ 6.64 (d, J = 0.3 Hz, 2H), 3.26 (dq, J = 10.1, 7.0 Hz, 1H), 1.57 – 1.43 (m, 1H), 1.47 (d, J = 7.0 Hz, 3H), 0.60 (dddd, J = 8.7, 8.2, 5.5, 4.3 Hz, 1H), 0.40 (dddd, J = 9.2, 7.9, 5.3, 4.1 Hz, 1H), 0.28 – 0.13 (m, 2H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 171.11, 134.06, 53.12, 18.48, 15.39, 5.05, 3.91.

HRMS (ESI): $C_9H_{12}O_2N$ $[M+H]^+$; calculated: 166.08611, found: 166.08626.

$[\alpha]_{20}^{D}$ = - 35 ° (c = 1, $CHCl_3$).

98bc, N-1-(2-phenylpropan-2-yl) maleimide



1.00 g (7.04 mmol) 4-methylbenzyl amine afforded **98bc** in 25 % yield (392 mg, 1.82 mmol), as colorless needles after purification via FCC.

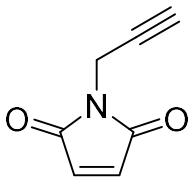
Rf (3:1, Hexanes:EtOAc) = 0.6

^{1}H NMR (700 MHz, CDl_3) δ 7.34 – 7.27 (m, 4H), 7.25 – 7.21 (m, 1H), 6.56 (s, 2H), 1.94 (s, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 171.77, 146.56, 134.14, 128.55, 126.93, 124.52, 61.37, 29.11.

HRMS (ESI): $C_{13}H_{14}O_2N$ $[M+H]^+$; calculated: 216.10191, found: 216.10191.

98bd, N-1-(prop-2-yn-1-yl) maleimide



The first reaction was done as described in general procedure 1

NaOAc (1.2 eq.) was added under argon and the mixture was redissolved in acetic anhydride (20 eq.). The microwave vial was capped and the mixture was heated via hotplate at 65°C over 2 h was then allowed to cool down to 21 °C. The mixture was diluted with Et_2O and poured onto ice. The watery phase was extracted with Et2O three times and dried over $NaSO_4$, filtered through a plug of celite and concentrated under reduced pressure. 550 mg (9.99 mmol) 4 propargyl amine afforded **98bd** in 40 % yield (668 mg, 4.95 mmol), as dark red solid after purification via FCC.

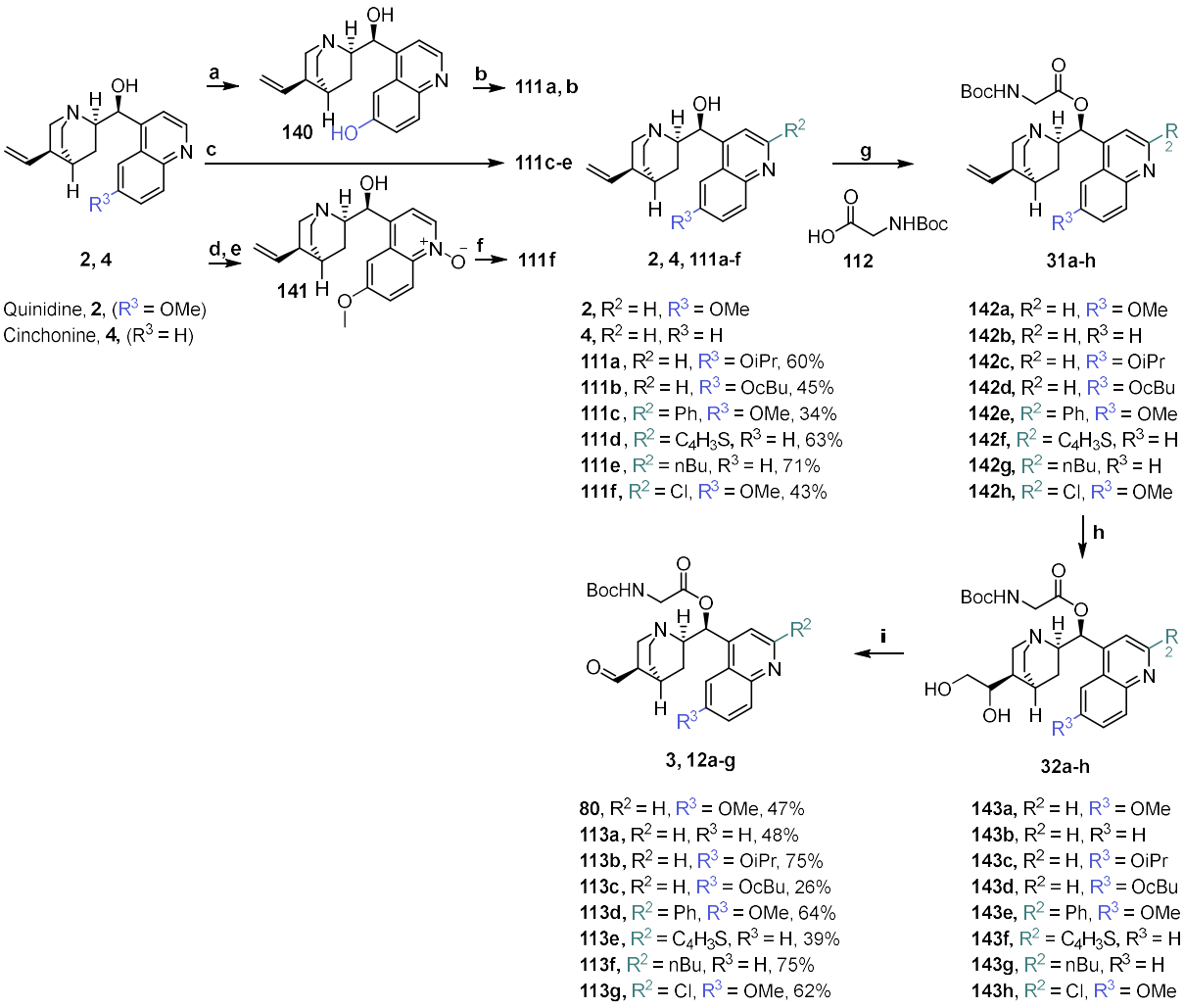
Rf (1:1, Hexanes:EtOAc) = 0.6

^{1}H NMR (400 MHz, CDl_3) δ 6.74 (s, 2H), 4.26 (d, J = 2.6 Hz, 2H), 2.20 (t, J = 2.5 Hz, 1H).

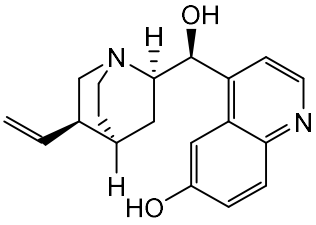
^{13}C NMR (176 MHz, $CDCl_3$) δ 169.38, 134.61, 77.06, 71.67, 26.94.

HRMS (ESI): $C_7H_6O_2N$ $[M+H]^+$; calculated: 136.0390, found: 136.03930.

5.10.2 Cinchona alkaloid starting material



141, Cupreidine



Quinidine (3.25 g, 10.0 mmol) in CH_2Cl_2 at (200 mL) -78 °C was added a solution of BBr_3 (3.85 g, 40.0 mmol in 16 mL CH_2Cl_2) dropwise and was then allowed to slowly warm to room temperature before heating at reflux for 2 h. After cooling to 0 °C, aqueous NH_3 solution (25% v/v, 100 mL) was added slowly. The layers were separated and the watery phase was extracted four times (100 mL, 5% MeOH in CH_2Cl_2). The combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. FCC gave the title compound as a lightly yellow solid in 78 % yield (2.44 g, 7.84 mmol).

R_f = 0.25 (1: 1 DCM:MM)

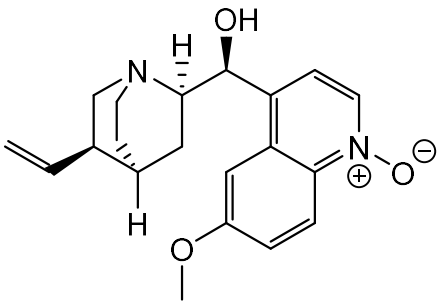
^{1}H NMR (700 MHz, DMSO-d_6) δ 8.60 (d, *J* = 4.4 Hz, 1H), 7.86 (d, *J* = 9.0 Hz, 1H), 7.42 (t, *J* = 3.9 Hz, 2H), 7.28 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.07 (ddd, *J* = 17.5, 10.3, 7.5 Hz, 1H), 5.71 (s, 1H), 5.22 (s, 1H), 5.14 – 5.01 (m, 2H), 3.38 (s, 1H), 3.16 – 3.08 (m, 1H), 3.01 (q, *J* = 8.2 Hz, 1H), 2.77 – 2.69 (m, 1H), 2.68 – 2.63 (m, 0H), 2.60 – 2.53 (m, 1H), 2.20 (q, *J* = 8.5 Hz, 1H), 1.98 – 1.86 (m, 1H), 1.73 – 1.65 (m, 1H), 1.52 – 1.41 (m, 2H), 1.37 – 1.29 (m, 1H).

^{13}C NMR (176 MHz, DMSO-d_6) δ 155.25, 148.10, 146.61, 143.15, 141.04, 131.13, 127.19, 121.20, 118.82, 114.53, 104.87, 70.90, 60.03, 49.17, 48.34, 39.40, 27.72, 26.04, 22.83.

HRMS (ESI): $C_{19}H_{23}O_2N_2$ $[M+H]^+$; calculated: 311.17540, found: 311.17562.

$[\alpha]_{20}^{D}$ = + 27 ° (c = 1, MeCN).

141, 4-((1S)-hydroxy((2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl)-6-methoxyquinoline 1-oxide



Quinidine (2.27 g, 7.00 mmol) in 42 mL $CHCl_3$ at 0 °C was added *m*CPBA (77% w/w, 3.45 g, 15.4 mmol) in portions over 30 min. The solution was stirred for 3 h at 21 °C before aqueous NaOH solution (10% w/v) was added until pH 10 was reached. The layers were separated and the watery phase was extracted tree times (50 mL $CHCl_3$:MeOH, 9:1). The combined organic phases were dried over Na_2SO_4 before the solvent was evaporated under educed pressure. The crude dual N-oxide was used for the following step without further purification.

The resultant yellow solid was solved in 28 mL acetone and cooled to 0 °C. Aqueous H_2SO_3 solution (6% v/v) was added dropwise before the reaction was stirred at 21 °C for 16 h. Then, aqueous NH_3 solution (25% v/v) was added slowly at 0 °C until pH 8. Acetone was removed under educed pressure and the aqueous phase was extracted three times (50 mL $CHCl_3$:MeOH, 9:1). FCC gave the title compound in 97 % yield (2.3 g, 6.76 mmol).

R_f = 0.21 (3: 2 DCM:MM)

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.40 (d, J = 9.5 Hz, 1H), 7.86 (d, J = 6.2 Hz, 1H), 7.16 (d, J = 6.2 Hz, 1H), 7.13 (dd, J = 9.5, 2.5 Hz, 1H), 6.83 (s, 1H), 6.15 – 6.02 (m, 2H), 5.17 (s, 1H), 5.10 – 5.04 (m,

2H), 3.83 (s, 3H), 3.32 – 3.20 (m, 1H), 2.89 – 2.80 (m, 2H), 2.77 (t, J = 11.3 Hz, 1H), 2.71 (dt, J = 13.5, 8.9 Hz, 1H), 2.21 (q, J = 8.5 Hz, 1H), 2.07 – 2.02 (m, 1H), 1.75 (td, J = 4.4, 2.2 Hz, 1H), 1.55 – 1.44 (m, 2H), 1.29 – 1.22 (m, 1H).

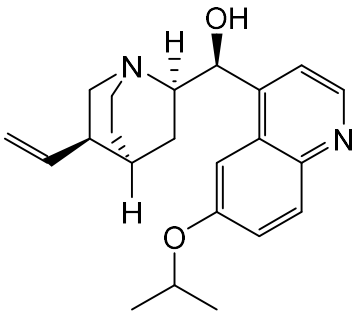
^{13}C NMR (176 MHz, $CDCl_3$) δ 158.90, 142.39, 140.85, 135.37, 133.90, 128.77, 122.71, 121.26, 118.60, 114.67, 101.92, 71.13, 60.35, 55.79, 50.13, 49.60, 40.29, 28.30, 26.63, 22.15.

HRMS (ESI): $C_{20}H_{25}O_3N_2$ $[M+H]^+$; calculated: 341.18597, found: 341.18615.

$[\alpha]_{20}^{D}$ = + 166 ° (c = 1, MeCN).

5.10.3 C6'-ethers 111a and 111b

111a, (1S)-(6-isopropoxyquinolin-4-yl)((2R,4S,5R)-5-vinylquinuclidin-2-yl)methanol



Cupreidine **140** (4.83 g, 15.6 mmol) in anhydrous dimethylformamide (160 mL) was added Cs_2CO_3 (10.2 g, 31.1 mmol) and stirred at 21°C for 30 min. The reaction was cooled to 0 °C and 2-iodopropane (2.91 g, 17.1 mmol) was added dropwise. The reaction was then stirred at 21 °C for 3 h before sat. aq. $NaHCO_3$ (200 ml) was added. The phases were separated and the organic phase was extracted three times (100 mL, 5% MeOH in CH_2Cl_2). The combined organic phases were washed with brine two times (150 ml), dired over Na_2SO_4 and evaporated at reduced pressure. FCC gave title compound **111a** as a white solid in 77 % (4.21 g, 11.9 mmol) yield.

R_f = 0.27 (3:7 MM:DCM)

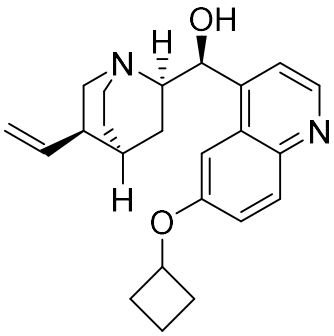
^{1}H NMR (700 MHz, $CDCl_3$) δ 8.65 (d, J = 4.5 Hz, 1H), 7.95 (d, J = 9.1 Hz, 1H), 7.53 (d, J = 4.5 Hz, 1H), 7.27 (dd, J = 9.2, 2.7 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 6.00 (ddd, J = 17.0, 10.6, 7.5 Hz, 1H), 5.69 (s, 1H), 5.09 – 5.00 (m, 2H), 4.63 (hept, J = 6.0 Hz, 1H), 3.96 (s, 1H), 3.40 (t, J = 10.8 Hz, 1H), 3.10 (td, J = 9.3, 4.2 Hz, 1H), 2.97 – 2.89 (m, 2H), 2.83 – 2.76 (m, 1H), 2.25 (q, J = 8.5 Hz, 1H), 2.07 – 2.01 (m, 1H), 1.77 (s, 1H), 1.60 – 1.54 (m, 1H), 1.54 – 1.48 (m, 1H), 1.33 (t, J = 6.3 Hz, 6H), 1.15 (dddd, J = 14.5, 10.7, 4.9, 1.6 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.01, 147.63, 147.05, 144.14, 140.27, 131.81, 126.66, 122.83, 118.58, 114.98, 103.47, 71.73, 70.24, 59.87, 50.32, 49.63, 39.90, 28.28, 26.23, 22.17, 21.74, 21.07.

HRMS (ESI): $C_{22}H_{29}O_2N_2$ $[M+H]^+$; calculated: 353.22235, found: 353.22249.

$[\alpha]_{20}^{D}$ = + 56 ° (c = 1, $CHCl_3$).

111b, (1S)-(6-cyclobutoxyquinolin-4-yl)((2R,4S,5R)-5-vinylquinuclidin-2-yl)methanol



Cupreidine **141** (5.00 g, 16.1 mmol) in anhydrous dimethylformamide (160 mL) was added Cs_2CO_3 (10.5 g, 32.2 mmol) and stirred at 21°C for 30 min. The reaction was cooled to 0 °C and cyclobutylbromide (1.68 mL, 17.7 mmol) was added dropwise. The reaction was then stirred at 21 °C for 30 min and heated at 70 °C for 16 h. Sat. aq. $NaHCO_3$ (200 ml) was added at 21 °C. The phases were separated and the organic phase was extracted three times (100 mL, 5% MeOH in CH_2Cl_2). The combined organic phases were washed with brine two times (150 ml), dired over Na_2SO_4 and evaporated at reduced pressure. FCC gave title compound **111b** as a white solid in 57 % (2.70 g, 7.41 mmol) yield.

R_f = 0.27 (1:1 MM:DCM)

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.70 (d, J = 4.5 Hz, 1H), 7.98 (d, J = 9.1 Hz, 1H), 7.55 (d, J = 4.5 Hz, 1H), 7.27 (dd, J = 9.1, 2.6 Hz, 1H), 7.07 (d, J = 2.7 Hz, 1H), 6.00 (ddd, J = 16.9, 10.5, 7.4 Hz, 1H), 5.70 (s, 1H), 5.10 – 5.00 (m, 2H), 4.67 (p, J = 7.1 Hz, 1H), 3.43 (s, 1H), 3.10 (td, J = 9.2, 4.1 Hz, 1H), 3.00 – 2.91 (m, 2H), 2.82 (dt, J = 13.5, 9.1 Hz, 1H), 2.55 – 2.40 (m, 2H), 2.27 (d, J = 8.7 Hz, 1H), 2.22 – 2.09 (m, 2H), 2.05 – 1.99 (m, 1H), 1.90 – 1.81 (m, 1H), 1.78 (d, J = 2.5 Hz, 1H), 1.68 (dtt, J = 11.3, 10.1, 8.2 Hz, 1H), 1.58 (ddt, J = 10.1, 7.0, 2.9 Hz, 1H), 1.52 (dddd, J = 12.6, 10.0, 7.9, 2.0 Hz, 1H), 1.17 – 1.09 (m, 1H).

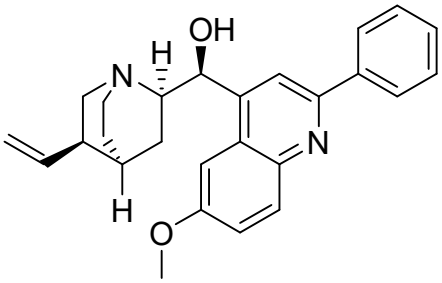
^{13}C NMR (126 MHz, $CDCl_3$) 13C NMR (176 MHz, CDCl3) δ 155.59, 147.55, 146.65, 144.18, 139.97, 131.78, 126.46, 122.03, 118.53, 114.91, 102.52, 71.73, 59.66, 50.17, 49.53, 39.66, 30.59, 30.23, 28.12, 26.00, 20.90, 13.37.

HRMS (ESI): $C_{23}H_{29}O_2N_2$ $[M+H]^+$; calculated: 365.22217, found: 365.22235.

$[\alpha]_{20}^{D}$ = + 32 ° (c = 1, $CHCl_3$).

5.10.4 C2'-alkylated cinchona alkaloids 10c-10e

111c, (1S)-(6-methoxy-2-phenylquinolin-4-yl)((2R,4S,5R)-5-vinylquinuclidin-2-yl)methanol



111c was prepared from quinidine (10.0 g, 30.8 mmol) according to General Procedure 2. FCC gave title compound **111c** as a colorless foam in 34 % (4.20 g, 10.5 mmol) yield.

R_f = 0.25 (1:3 MM:DCM)

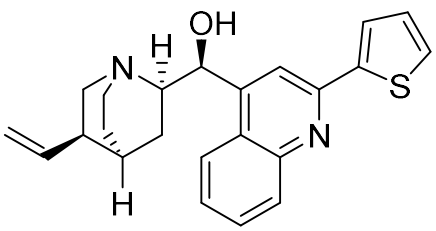
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 9.2 Hz, 1H), 7.95 (dd, J = 7.9, 1.8 Hz, 2H), 7.82 (s, 1H), 7.42 – 7.35 (m, 3H), 7.28 (dd, J = 9.2, 2.7 Hz, 1H), 7.05 (d, J = 2.7 Hz, 1H), 6.10 – 5.98 (m, 1H), 5.49 (d, J = 4.1 Hz, 1H), 5.06 (d, J = 1.1 Hz, 1H), 5.05 – 5.00 (m, 1H), 4.43 (s, 1H), 3.82 (s, 3H), 3.34 (ddd, J = 13.8, 7.8, 2.2 Hz, 1H), 2.98 (td, J = 9.2, 4.0 Hz, 1H), 2.92 – 2.79 (m, 2H), 2.77 – 2.67 (m, 1H), 2.21 (q, J = 8.4 Hz, 1H), 2.05 (ddt, J = 13.1, 9.2, 1.8 Hz, 1H), 1.72 (s, 1H), 1.55 – 1.40 (m, 2H), 1.12 (dddd, J = 14.5, 9.3, 4.9, 1.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.55, 154.57, 148.40, 144.24, 140.71, 139.61, 131.73, 128.99, 128.76, 127.34, 125.59, 121.66, 116.31, 114.68, 101.34, 72.11, 59.90, 55.67, 50.21, 49.67, 40.18, 28.37, 26.44, 21.12.

HRMS (ESI): $C_{26}H_{29}O_2N_2$ $[M+H]^+$; calculated: 401.22235, found: 401.22200.

$[\alpha]_{20}^{D}$ = + 86 ° (c = 1, MeCN).

111d, (1S)-(2-(thiophen-2-yl)quinolin-4-yl)((2R,4S,5R)-5-vinylquinuclidin-2-yl)methanol



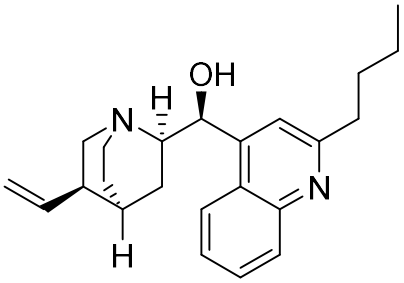
111d was prepared from cinchonine (6.0 g, 20.4 mmol) according to General Procedure 2. FCC gave title compound **111d** as a colorless foam in 63 % (4.82 g, 12.8 mmol) yield.

R_f = 0.16 (3:7 MM:DCM)

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (dd, J = 8.6, 1.2 Hz, 1H), 7.97 (s, 1H), 7.83 (dd, J = 8.5, 1.3 Hz, 1H), 7.75 (dd, J = 3.7, 1.1 Hz, 1H), 7.63 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 7.46 (dd, J = 5.0, 1.1 Hz, 1H), 7.33 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 7.15 (dd, J = 5.0, 3.6 Hz, 1H), 6.03 (ddd, J = 16.6, 10.7, 7.6 Hz, 1H), 5.69 (d, J = 4.3 Hz, 1H), 5.05 (s, 1H), 5.03 (d, J = 8.1 Hz, 1H), 3.48 (s, 1H), 3.32 (dd, J = 12.5, 8.0 Hz, 1H), 3.08 (td, J = 9.3, 4.2 Hz, 1H), 2.95 – 2.87 (m, 2H), 2.82 – 2.73 (m, 1H), 2.23 (q, J = 8.5 Hz, 1H), 2.04 (ddt, J = 13.2, 9.3, 1.9 Hz, 1H), 1.75 (s, 1H), 1.57 – 1.44 (m, 2H), 1.19 (dddd, J = 14.4, 9.4, 4.8, 1.6 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 152.23, 149.54, 148.35, 145.68, 140.73, 130.27, 129.48, 128.70, 128.19, 126.25, 126.18, 124.84, 122.91, 114.80, 114.75, 72.24, 60.20, 50.31, 49.80, 40.21, 28.44, 26.54, 21.17.

111e, (1S)-(2-butylquinolin-4-yl)((2R,4S,5R)-5-vinylquinuclidin-2-yl)methanol



111e was prepared from cinchonine (1.5 g, 5.1 mmol) according to General Procedure 2. FCC gave title compound **111e** as a colorless resin in 71 % (1.27 g, 2.62 mmol) yield.

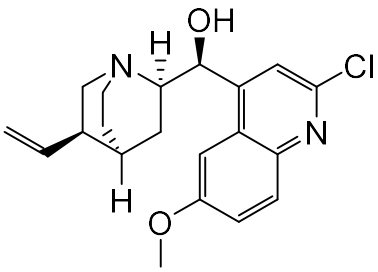
R_f = 0.23 (3:7 MM:DCM)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 8.4 Hz, 1H), 7.83 (t, J = 6.7 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.52 (s, 1H), 7.29 (d, J = 6.8 Hz, 1H), 6.07 – 5.96 (m, 2H), 5.77 (s, 1H), 5.05 (s, 1H), 5.03 (d, J = 4.7 Hz, 1H), 4.05 (s, 1H), 3.40 (dd, J = 12.5, 8.1 Hz, 1H), 3.06 (s, 1H), 2.92 (q, J = 13.7, 10.5 Hz, 4H), 2.82 – 2.71 (m, 1H), 2.24 (q, J = 8.1 Hz, 1H), 2.08 – 1.99 (m, 1H), 1.80 – 1.70 (m, 3H), 1.52 (dt, J = 22.1, 10.7 Hz, 2H), 1.40 (h, J = 8.5, 7.7 Hz, 2H), 1.17 – 1.08 (m, 1H), 0.93 (t, J = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.97, 148.10, 140.47, 129.79, 129.00, 125.84, 124.21, 122.77, 118.55, 114.89, 71.68, 60.12, 50.22, 49.68, 40.06, 39.40, 32.40, 28.40, 26.31, 22.85, 20.85, 14.14.

HRMS (ESI): $C_{23}H_{31}ON_2$ $[M+H]^+$; calculated: 351.24309, found: 351.24313.

5.10.5 111f, (1S)-(2-chloro-6-methoxyquinolin-4-yl)((2R,4S,5R)-5-vinylquinuclidin-2-yl)methanol



141 (9.25 g, 27.2 mmol) in 55 mL $CHCl_3$ at 0 °C was added $POCl_3$ (10.2 mL, 109 mmol) dropwise and stirred for 30 min before heating at reflux for 2 h. After cooling to 21°C, ice (100 g) was added before aqueous NH_3 solution (25% v/v) was added until pH 8. The layers were separated and the watery phase was extracted three times (50 mL, 5% MeOH in $CHCl_3$). The combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. FCC gave the title compound **111f** as a white solid in 44 % yield (4.31 g, 12.0 mmol).

R_f = 0.23 (2:1 DCM:MM)

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.83 (d, J = 9.2 Hz, 1H), 7.54 (s, 1H), 7.29 – 7.25 (m, 1H), 7.08 (d, J = 2.7 Hz, 1H), 6.00 (ddd, J = 17.0, 10.6, 7.4 Hz, 1H), 5.63 (s, 1H), 5.07 (s, 1H), 5.05 (d, J = 9.6 Hz, 1H), 4.26 (s, 1H), 3.80 (s, 3H), 3.39 (s, 1H), 3.03 (td, J = 9.3, 4.1 Hz, 1H), 2.92 (q, J = 12.7 Hz, 2H), 2.77 (dt, J = 13.2, 9.3 Hz, 1H), 2.26 (q, J = 8.6 Hz, 1H), 2.03 (t, J = 11.3 Hz, 1H), 1.79 (s, 1H), 1.60 – 1.54 (m, 1H), 1.51 (q, J = 11.0, 9.8 Hz, 1H), 1.15 (ddd, J = 13.3, 9.5, 4.5 Hz, 1H).

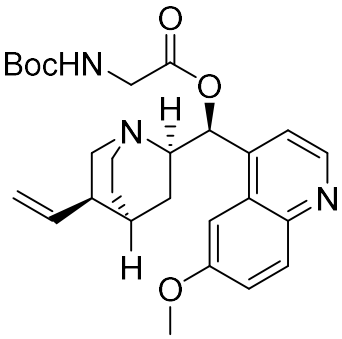
^{13}C NMR (176 MHz, $CDCl_3$) δ 158.07, 150.95, 148.43, 143.90, 140.07, 130.74, 125.36, 122.34, 119.78, 115.17, 101.76, 71.41, 59.90, 55.87, 50.20, 49.60, 39.77, 28.22, 26.13, 20.90.

HRMS (ESI): $C_{20}H_{24}O_2N_2Cl$ $[M+H]^+$; calculated: 359.15208, found: 359.15308.

$[\alpha]_{20}^{D}$ = + 108 ° (c = 1, MeCN).

5.10.6 Boc-glycine esters 142a-h

142a, (1S)-(6-methoxyquinolin-4-yl)((2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl (tert-butoxy-carbonyl)glycinate



142a was prepared from quinidine (10 g, 30.8 mmol) according to General Procedure 3. FCC gave title compound **142a** as a colorless foam in 94 % (13.9 g, 28.8 mmol) yield.

R_f = 0.3 (5:1 MM:DCM)

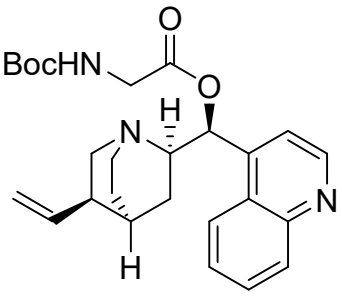
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.72 (d, J = 4.5 Hz, 1H), 8.00 (d, J = 9.5 Hz, 1H), 7.43 – 7.31 (m, 3H), 6.54 (d, J = 7.0 Hz, 1H), 6.01 (ddd, J = 17.4, 10.4, 7.2 Hz, 1H), 5.17 – 5.06 (m, 2H), 5.03 (s, 1H), 4.05 (dd, J = 18.5, 5.9 Hz, 1H), 3.94 (s, 3H), 3.93 – 3.89 (m, 1H), 3.29 (q, J = 8.5 Hz, 1H), 2.95 – 2.84 (m, 2H), 2.83 – 2.76 (m, 1H), 2.71 (dt, J = 13.4, 8.7 Hz, 1H), 2.26 (q, J = 8.4 Hz, 1H), 1.86 – 1.77 (m, 2H), 1.54 (td, J = 14.8, 11.9, 7.8 Hz, 3H), 1.43 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.73, 158.10, 155.71, 147.59, 144.85, 143.25, 140.34, 132.01, 127.00, 121.98, 118.71, 115.12, 101.35, 80.28, 74.88, 59.15, 55.72, 49.95, 49.41, 42.73, 39.79, 28.40, 27.83, 26.45, 23.58.

HRMS (ESI): $C_{27}H_{36}O_5N_3$ $[M+H]^+$; calculated: 482.26495, found: 482.26427.

$[\alpha]_{20}^{D}$ = + 52 ° (c = 1, MeCN).

142b, (1S)-quinolin-4-yl((2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl (tert-butoxycarbonyl)-glycinate



142a was prepared from cinchonine (8.5 g, 28.9 mmol) according to General Procedure 3. FCC gave title compound **142a** as a colorless foam in 88 % (11.5 g, 25.4 mmol) yield.

R_f = 0.31 (1:5 MM:DCM)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (d, J = 4.4 Hz, 1H), 8.18 (d, J = 7.8 Hz, 1H), 8.12 (dd, J = 8.6, 1.3 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.38 (d, J = 4.5 Hz, 1H), 6.62 (s, 1H), 6.01 (ddd, J = 17.4, 10.4, 7.2 Hz, 1H), 5.18 – 5.06 (m, 2H), 5.00 (s, 1H), 4.05 (dd, J = 18.4, 5.8 Hz, 1H), 3.98 – 3.88 (m, 1H), 3.32 (q, J = 8.5 Hz, 1H), 2.97 – 2.85

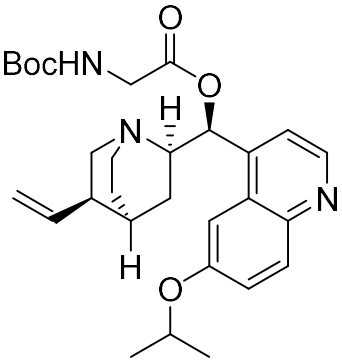
(m, 2H), 2.84 – 2.76 (m, 1H), 2.75 – 2.66 (m, 1H), 2.27 (q, J = 8.7 Hz, 1H), 1.83 (s, 2H), 1.60 – 1.50 (m, 3H), 1.43 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.66, 155.72, 150.12, 148.68, 144.78, 140.13, 130.67, 129.40, 127.13, 125.96, 123.30, 118.66, 115.27, 80.30, 74.94, 59.58, 49.92, 49.29, 42.71, 39.70, 28.41, 27.79, 26.31, 23.68.

HRMS (ESI): $C_{26}H_{34}O_4N_3$ $[M+H]^+$; calculated: 452.25438, found: 452.25395.

$[\alpha]_{20}^{D}$ = + 55 ° (c = 1, MeCN).

142c, (1S)-(6-isopropoxyquinolin-4-yl)((2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl (tert-butoxycarbonyl)glycinate



142c was prepared from **111a** (4.10 g, 11.6 mmol) according to General Procedure 3. FCC gave title compound **31c** as a colorless foam in 87 % (5.12 g, 10.1 mmol) yield.

R_f = 0.48 (1:4 MM:DCM)

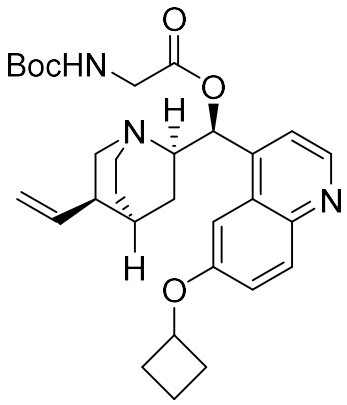
^{1}H NMR (700 MHz, $CDCl_3$) δ 8.70 (d, J = 4.5 Hz, 1H), 7.99 (d, J = 9.1 Hz, 1H), 7.38 (s, 1H), 7.33 (dd, J = 9.2, 2.6 Hz, 1H), 7.31 (d, J = 4.5 Hz, 1H), 6.56 (s, 1H), 6.00 (ddd, J = 17.4, 10.4, 7.2 Hz, 1H), 5.15 – 5.07 (m, 2H), 5.05 (s, 1H), 4.75 (s, 1H), 4.05 (dd, J = 18.4, 5.9 Hz, 1H), 3.93 (dd, J = 18.4, 5.5 Hz, 1H), 3.30 (q, J = 8.4 Hz, 1H), 2.95 – 2.84 (m, 2H), 2.84 – 2.77 (m, 1H), 2.77 – 2.69 (m, 1H), 2.27 (q, J = 8.4 Hz, 1H), 1.90 – 1.78 (m, 2H), 1.60 – 1.53 (m, 2H), 1.53 – 1.47 (m, 1H), 1.47 – 1.28 (m, 15H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 169.63, 156.35, 155.72, 147.45, 144.65, 142.90, 140.19, 132.04, 126.94, 123.17, 118.69, 115.21, 103.52, 80.26, 74.83, 70.35, 59.20, 50.02, 49.37, 42.74, 39.67, 28.41, 27.83, 26.35, 23.43, 22.16, 21.88.

HRMS (ESI): $C_{29}H_{40}O_5N_3$ $[M+H]^+$; calculated: 510.29625, found: 510.29563.

$[\alpha]_{20}^{D}$ = + 46 ° (c = 1, MeCN).

142d, (1S)-(6-cyclobutoxyquinolin-4-yl)((2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl (tert-butoxycarbonyl)glycinate



142d was prepared from **111b** (4.00 g, 11.0 mmol) according to General Procedure 3. FCC gave title compound **142d** as a colorless foam in 87 % (5.12 g, 10.1 mmol) yield.

R_f = 0.5 (5:1 DCM:MM)

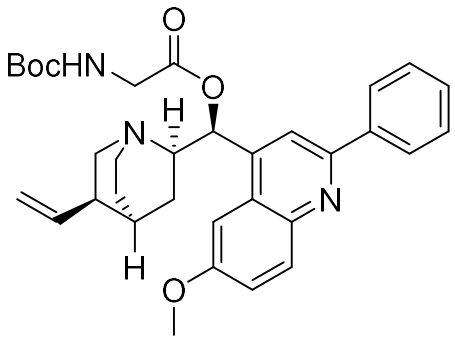
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (d, J = 4.5 Hz, 1H), 8.00 (d, J = 9.2 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.29 – 7.22 (m, 2H), 6.56 (s, 1H), 6.02 (ddd, J = 17.4, 10.4, 7.3 Hz, 1H), 5.18 – 5.07 (m, 2H), 5.03 – 4.94 (m, 1H), 4.86 – 4.79 (m, 1H), 4.07 (dd, J = 18.4, 5.8 Hz, 1H), 3.96 (s, 0H), 3.94 – 3.90 (m, 0H), 3.38 – 3.24 (m, 1H), 3.02 – 2.70 (m, 4H), 2.66 – 2.53 (m, 2H), 2.34 – 2.17 (m, 3H), 1.97 – 1.48 (m, 7H), 1.43 (s, 9H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 169.70, 156.01, 155.72, 147.52, 144.80, 143.01, 140.39, 132.10, 131.90, 126.94, 122.45, 118.73, 115.12, 102.88, 80.31, 72.05, 59.12, 50.09, 49.47, 42.75, 39.80, 30.76, 30.56, 28.43, 27.86, 26.50, 23.60, 13.63.

HRMS (ESI): $C_{30}H_{40}O_5N_3$ $[M+H]^+$; calculated: 522.29568, found: 522.29625.

$[\alpha]_{20}^{D}$ = + 52 ° (c = 1, $CHCl_3$).

142e, (1S)-(6-methoxy-2-phenylquinolin-4-yl)((2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl (tert-butoxycarbonyl)glycinate



142e was prepared from **111c** (4.11 g, 10.3 mmol) according to General Procedure 3. FCC gave title compound **142e** as a colorless foam in 82 % (4.66 g, 8.36 mmol) yield.

R_f = 0.29 (6:1 DCM:MM)

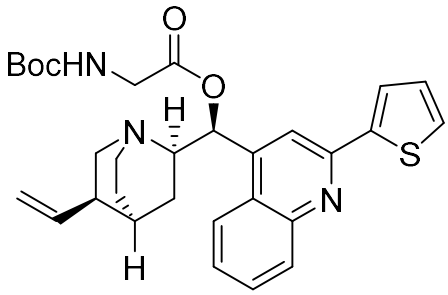
^{1}H NMR (400 MHz, $CDCl_3$) 1H NMR δ 8.18 – 8.11 (m, 2H), 8.09 (d, J = 9.8 Hz, 1H), 7.83 (s, 1H), 7.55 – 7.46 (m, 2H), 7.47 – 7.34 (m, 3H), 6.62 (d, J = 6.6 Hz, 1H), 6.04 (ddd, J = 17.4, 10.4, 7.3 Hz, 1H), 5.19 – 5.05 (m, 3H), 4.07 (dd, J = 18.3, 6.0 Hz, 1H), 3.95 (s, 3H), 3.97 – 3.88 (m, 1H), 3.35 (q, J = 8.5 Hz, 1H), 2.97 – 2.89 (m, 2H), 2.81 (t, J =

6.3 Hz, 1H), 2.73 (dt, J = 13.3, 8.7 Hz, 1H), 2.27 (q, J = 8.6 Hz, 1H), 1.89 (dd, J = 13.4, 9.1 Hz, 1H), 1.82 (s, 1H), 1.60 – 1.49 (m, 3H), 1.42 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.68, 157.99, 155.76, 154.77, 144.90, 143.85, 140.30, 139.85, 132.25, 129.05, 128.84, 127.53, 125.80, 122.02, 116.56, 115.15, 101.33, 80.23, 75.11, 59.20, 55.73, 49.97, 49.45, 42.79, 39.79, 28.36, 27.88, 26.36, 23.34.

HRMS (ESI): $C_{33}H_{40}O_5N_3$ $[M+H]^+$; calculated: 558.29625, found: 558.29608.

142f, (1S)-(2-(thiophen-2-yl)quinolin-4-yl)((2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl (tert-butoxycarbonyl)glycinate



142f was prepared from **111d** (2.9 g, 7.55 mmol) according to General Procedure 3. FCC gave title compound **142f** as a colorless foam in 88 % (3.53 g, 6.61 mmol) yield.

R_f = 0.49 (4:1 DCM:MM)

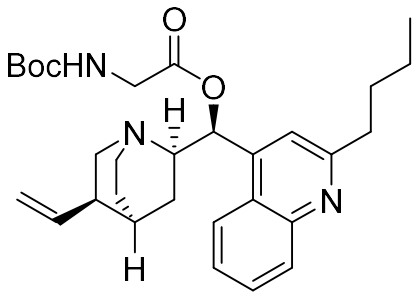
^{1}H NMR (700 MHz, $CDCl_3$) 1H NMR δ 8.10 (dd, J = 8.5, 1.2 Hz, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 3.7 Hz, 1H), 7.79 (s, 1H), 7.68 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 7.52 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 7.46 (dd, J = 5.0, 1.1 Hz, 1H), 7.16 (dd, J = 5.0, 3.7 Hz, 1H), 6.58 (d, J = 6.8 Hz, 1H), 6.06 (ddd, J = 17.4, 10.2, 7.3 Hz, 1H), 5.15 – 5.08 (m, 2H), 4.99 (s, 1H), 4.09 (dd, J = 18.4, 6.1 Hz, 1H), 3.93 (dd, J = 18.5, 5.4 Hz, 1H), 3.33 (q, J = 8.4 Hz, 1H), 2.95 – 2.85 (m, 2H), 2.83 – 2.74 (m, 1H), 2.70 (dt, J = 13.4, 8.7 Hz, 1H), 2.27 (q, J = 8.5 Hz, 1H), 1.86 (dd, J = 13.5, 9.0 Hz, 1H), 1.82 (s, 1H), 1.59 – 1.50 (m, 3H), 1.44 (s, 9H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 169.64, 155.80, 152.18, 148.72, 145.51, 145.41, 140.46, 130.48, 129.65, 128.77, 128.15, 126.50, 126.41, 124.97, 123.16, 115.27, 115.14, 80.35, 75.52, 59.62, 50.02, 49.51, 42.86, 39.99, 28.44, 27.97, 26.52, 23.59.

HRMS (ESI): $C_{30}H_{36}O_4N_3S$ $[M+H]^+$; calculated: 534.24210, found: 534.24175.

$[\alpha]_{20}^{D}$ = + 73 ° (c = 0.1, MeCN).

142g, (1S)-(2-butylquinolin-4-yl)((2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl (tert-butoxy-carbonyl)glycinate



142g was prepared from **111e** (5.01 g, 14.3 mmol) according to General Procedure 3. FCC (1:4 MM:DCM, Rf = 0.4) gave title compound **142g** as a colorless foam in 96 % (6.95 g, 13.78 mmol) yield.

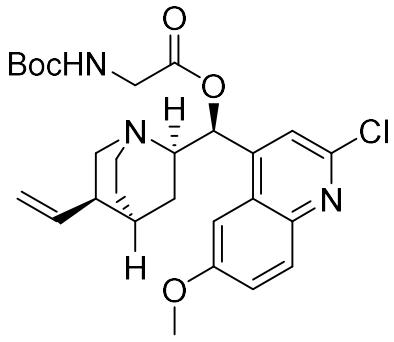
R_f = 0.40 (4:1 DCM:MM)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 8.5 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.67 (dd, J = 8.4, 6.9 Hz, 1H), 7.52 (dd, J = 8.4, 7.0 Hz, 1H), 7.27 (s, 1H), 6.55 (d, J = 6.9 Hz, 1H), 6.02 (ddd, J = 17.4, 10.4, 7.3 Hz, 1H), 5.11 (s, 1H), 5.10 (dd, J = 28.4, 1.5 Hz, 1H), 4.97 (s, 1H), 4.05 (dd, J = 18.4, 5.7 Hz, 1H), 3.92 (dd, J = 18.4, 5.4 Hz, 1H), 3.30 (q, J = 8.4 Hz, 1H), 2.99 – 2.92 (m, 2H), 2.92 – 2.81 (m, 2H), 2.81 – 2.64 (m, 4H), 2.26 (q, J = 8.1 Hz, 2H), 1.86 – 1.80 (m, 2H), 1.80 – 1.74 (m, 2H), 1.54 (t, J = 6.9 Hz, 3H), 1.43 (s, 9H), 1.47 – 1.29 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.67, 162.73, 155.72, 148.50, 144.68, 140.38, 130.02, 129.23, 126.10, 124.45, 123.06, 118.99, 115.13, 80.26, 75.43, 59.51, 50.01, 49.39, 42.75, 39.91, 39.30, 32.28, 28.42, 27.90, 26.47, 23.69, 22.85, 14.14.

HRMS (ESI): $C_{30}H_{42}O_4N_3$ $[M+H]^+$; calculated: 508.31698 found: 508.31650.

142h, (1S)-(2-chloro-6-methoxyquinolin-4-yl)((2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl (tert-butoxycarbonyl)glycinate



142h was prepared from **111f** (4.30 g, 12.0 mmol) according to General Procedure 3. FCC gave title compound **142h** as a colorless foam in 76 % (4.70 g, 9.12 mmol) yield.

R_f = 0.50 (5:1 DCM:MM)

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.92 (d, J = 9.2 Hz, 1H), 7.37 (dd, J = 9.2, 2.6 Hz, 1H), 7.33 (d, J = 8.8 Hz, 2H), 6.47 (d, J = 7.4 Hz, 1H), 5.99 (ddd, J = 17.3, 10.4, 7.1 Hz, 1H), 5.12 (d, J = 10.3 Hz, 1H), 5.09 (d, J = 17.2 Hz, 1H), 5.01 (s, 1H), 4.06 (dd, J = 18.4, 6.1 Hz, 1H), 3.93 (s, 3H), 3.95 – 3.89 (m, 1H), 3.26 (q, J = 8.3 Hz, 1H), 2.91 (dd, J = 13.9, 9.9 Hz, 1H), 2.80 (ddd, J = 25.3, 13.2, 6.8 Hz, 2H), 2.70 (dt, J = 13.5, 8.7

Hz, 1H), 2.26 (q, J = 8.0 Hz, 1H), 1.83 (s, 1H), 1.79 (dd, J = 13.5, 9.2 Hz, 1H), 1.55 (s, 3H), 1.43 (s, 9H).

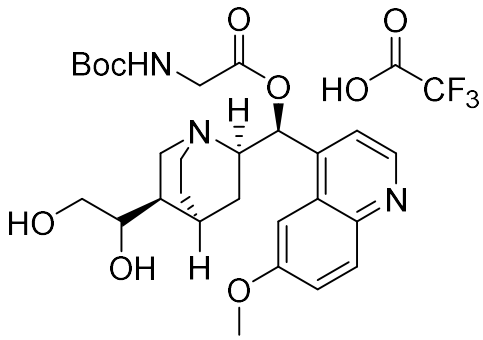
^{13}C NMR (176 MHz, $CDCl_3$) δ 169.75, 158.33, 155.72, 148.01, 146.98, 144.38, 140.20, 131.00, 125.96, 122.81, 119.90, 115.21, 101.91, 80.37, 74.14, 59.44, 55.79, 49.90, 49.39, 42.71, 39.70, 28.40, 27.75, 26.40, 23.77.

HRMS (ESI): $C_{27}H_{35}O_5N_3Cl$ $[M+H]^+$; calculated: 516.22598, found: 516.22545.

$[\alpha]_{20}^{D}$ = + 61 ° (c = 1, MeCN).

5.10.7 Diol carbamates 143a-h

143a, (1S)-((2R,4S,5R)-5-((S)-1,2-dihydroxyethyl)quinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl-(tert-butoxycarbonyl)glycinate -TFA



143a was prepared from **142a** (12.3 g, 25.6 mmol) according to General Procedure 4. FCC gave title compound **143a** as a colorless foam in 56 % (7.4 g, 12.3 mmol) yield and in a diastereomeric ratio of 1:1 (by NMR). Preparative HPLC (5 – 30 % MeCN; RT = 18.7 min) was used for a better peak resolution.

R_f = 0.3 (1:1 MM:DCM)

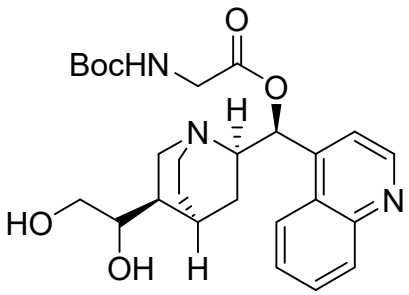
^{1}H NMR (600 MHz, CD_3CN:D_2O [10:1], NH and OH not observed) δ 8.85 (dd, J = 5.5, 2.7 Hz, 2H), 8.19 (dd, J = 9.3, 1.5 Hz, 2H), 7.90 (dd, J = 10.3, 5.5 Hz, 2H), 7.70 (dt, J = 9.3, 2.3 Hz, 2H), 7.62 (t, J = 3.1 Hz, 2H), 7.02 (d, J = 7.6 Hz, 2H), 4.05 (s, 6H), 4.07 – 3.96 (m, 4H), 3.93 (ddd, J = 8.7, 5.2, 3.5 Hz, 1H), 3.82 (dt, J = 9.6, 4.8 Hz, 1H), 3.79 – 3.74 (m, 1H), 3.71 (t, J = 9.3 Hz, 2H), 3.60 (ddd, J = 16.2, 11.7, 3.8 Hz, 2H), 3.54 – 3.40 (m, 7H), 3.23 (ddd, J = 12.8, 10.2, 8.3 Hz, 2H), 2.44 – 2.33 (m, 3H), 2.15 (q, J = 9.2 Hz, 1H), 2.11 (s, 1H), 2.09 – 2.02 (m, 1H), 1.90 – 1.80 (m, 2H), 1.79 – 1.68 (m, 2H), 1.40 (d, J = 8.7 Hz, 20H).

^{13}C NMR (151 MHz, CD_3CN:D_2O [10:1]) δ 161.04, 161.01, 157.37, 148.10, 147.97, 143.14, 143.08, 137.46, 137.31, 127.62, 127.57, 127.20, 127.15, 126.29, 126.19, 119.82, 119.73, 102.21, 102.19, 80.63, 80.58, 72.48, 71.43, 71.31, 70.92, 64.84,

64.64, 58.20, 58.14, 57.07, 50.21, 50.13, 48.30, 47.66, 43.02, 42.93, 36.54, 35.68, 28.12, 28.10, 23.96, 23.38, 23.04, 22.09, 20.33, 19.65.

HRMS (ESI): $C_{27}H_{38}O_7N_3$ $[M+H]^+$; calculated: 561.267043, found: 516.26986.

143b, (1S)-((2R,4S,5R)-5-((S)-1,2-dihydroxyethyl)quinuclidin-2-yl)(quinolin-4-yl)methyl (tert-butoxycarbonyl)glycinate



143b was prepared from **142b** (7.92 g, 17.6 mmol) according to General Procedure 4. FCC (1:2 MM:DCM, Rf = 0.24) gave title compound **143b** as a colorless foam in 61 % (5.14 g, 10.6 mmol) yield and in a diastereomeric ratio of 1:1 (by NMR). Preparative HPLC (10 – 40% MeCN; RT = 9.12 min) was used for a better peak resolution.

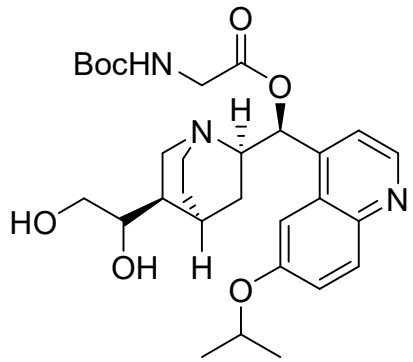
R_f = 0.43 (1:1 MM:DCM)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (dd, J = 22.6, 4.5 Hz, 1H), 8.22 – 8.02 (m, 2H), 7.80 – 7.64 (m, 1H), 7.57 (tdd, J = 7.7, 5.5, 2.8 Hz, 1H), 7.34 (dd, J = 21.6, 4.5 Hz, 1H), 6.72 (dd, J = 75.5, 5.0 Hz, 1H), 5.64 (dt, J = 59.5, 6.0 Hz, 1H), 4.08 (td, J = 17.5, 17.1, 6.5 Hz, 1H), 3.99 (ddd, J = 12.0, 6.7, 3.3 Hz, 1H), 3.83 (dt, J = 17.7, 4.9 Hz, 2H), 3.78 – 3.66 (m, 1H), 3.43 (ddd, J = 39.0, 11.3, 7.3 Hz, 1H), 3.25 – 2.88 (m, 2H), 2.86 – 2.61 (m, 3H), 2.22 (d, J = 5.2 Hz, 0H), 2.03 – 1.88 (m, 1H), 1.72 (d, J = 4.3 Hz, 1H), 1.60 (dq, J = 48.3, 8.6 Hz, 1H), 1.52 – 1.29 (m, 11H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.70, 156.36, 156.22, 149.98, 148.35, 144.95, 144.86, 130.38, 129.56, 129.52, 127.30, 127.23, 125.58, 125.49, 123.21, 123.17, 118.04, 80.61, 80.49, 75.06, 73.46, 72.71, 65.39, 59.37, 59.16, 58.25, 50.16, 47.40, 46.90, 42.94, 42.75, 37.96, 37.84, 28.41, 26.82, 26.37, 24.47, 22.50, 22.25, 18.49.

HRMS (ESI): $C_{26}H_{36}O_6N_3$ $[M+H]^+$; calculated: 486.25986, found: 486.25947.

143c, (1S)-((2R,4S,5R)-5-((S)-1,2-dihydroxyethyl)quinuclidin-2-yl)(6-isopropoxyquinolin-4-yl)methyl (tert-butoxycarbonyl)glycinate



143c was prepared from **142c** (4.85 g, 9.52 mmol) according to General Procedure 4. FCC gave title compound **143c** as a colorless foam in 97 % (5.03 g, 9.25 mmol) yield and in a diastereomeric ratio of 1:1 (by NMR).

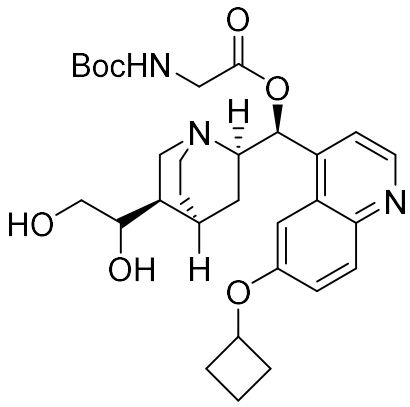
R_f = 0.41 (1:1 MM:DCM)

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.67 (t, J = 4.4 Hz, 1H), 7.95 (dt, J = 9.2, 1.9 Hz, 1H), 7.49 (dd, J = 38.3, 2.7 Hz, 1H), 7.41 (t, J = 3.6 Hz, 1H), 7.33 (ddd, J = 9.2, 4.7, 2.6 Hz, 1H), 6.40 (dd, J = 57.8, 8.4 Hz, 1H), 5.85 – 5.24 (m, 1H), 4.90 – 4.76 (m, J = 6.0 Hz, 1H), 3.87 (ddd, J = 18.0, 6.5, 4.5 Hz, 1H), 3.82 – 3.65 (m, 2H), 3.56 (dt, J = 11.3, 3.6 Hz, 1H), 3.37 – 3.25 (m, 2H), 3.14 (s, 1H), 3.09 – 3.03 (m, 1H), 3.00 (s, 1H), 2.72 – 2.50 (m, 3H), 2.30 – 2.05 (m, 1H), 1.83 – 1.70 (m, 2H), 1.64 – 1.46 (m, 3H), 1.45 – 1.28 (m, 15H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 171.00, 170.96, 157.00, 156.91, 148.44, 145.47, 145.13, 132.55, 128.10, 123.78, 123.72, 119.98, 104.85, 104.78, 80.08, 75.07, 74.27, 72.88, 71.19, 71.14, 65.95, 65.68, 60.63, 50.30, 50.27, 47.66, 47.27, 43.22, 39.21, 38.62, 28.50, 28.19, 27.70, 27.22, 25.54, 24.88, 23.25, 22.25, 22.21, 22.10, 22.03.

HRMS (ESI): $C_{29}H_{42}O_7N_3$ $[M+H]^+$; calculated: 544.30173, found: 544.30173.

143, (1S)-(6-cyclobutoxyquinolin-4-yl)((2R,4S,5R)-5-((S)-1,2-dihydroxyethyl)quinuclidin-2-yl)methyl (tert-butoxycarbonyl)glycinate



143d was prepared from **142d** (4.69g, 8.45 mmol) according to General Procedure 4. FCC gave title compound **143d** as a colorless foam in 35 % (1.72 g, 3.10 mmol) yield and in a diastereomeric ratio of 1:1 (by NMR).

R_f = 0.70 (2:3 MM:DCM)

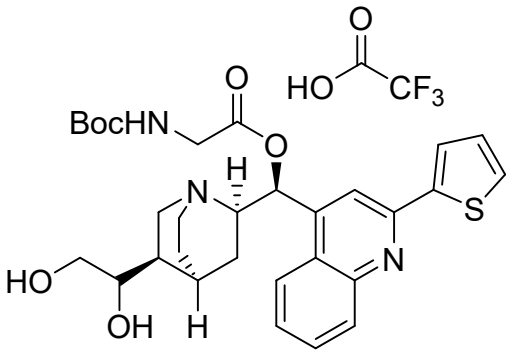
^{1}H NMR (700 MHz, $CDCl_3$) δ 8.69 (t, J = 4.5 Hz, 1H), 8.01 (dd, J = 9.2, 1.0 Hz, 1H), 7.33 (dt, J = 9.2, 2.9 Hz, 1H), 7.30 (dd, J

= 9.0, 4.5 Hz, 1H), 7.23 – 7.15 (m, 1H), 6.70 (d, J = 110.3 Hz, 1H), 5.42 – 5.24 (m, 1H), 4.81 (dt, J = 24.6, 7.1 Hz, 1H), 4.18 (ddd, J = 18.6, 11.9, 7.0 Hz, 1H), 4.06 – 3.99 (m, 1H), 3.88 – 3.69 (m, 3H), 3.48 (s, 2H), 3.48 – 3.35 (m, 0H), 3.23 – 3.14 (m, 2H), 2.99 – 2.70 (m, 3H), 2.63 – 2.53 (m, 2H), 2.30 – 2.24 (m, 1H), 2.23 – 2.15 (m, 1H), 2.06 – 1.97 (m, 1H), 1.95 – 1.87 (m, 1H), 1.83 – 1.72 (m, 2H), 1.69 – 1.53 (m, 1H), 1.53 – 1.46 (m, 2H), 1.45 (s, 9H), 1.41 – 1.26 (m, 0H), 1.24 (t, J = 7.0 Hz, 1H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 169.59, 169.56, 156.25, 156.15, 147.38, 147.24, 144.54, 143.78, 143.21, 143.02, 131.99, 131.76, 126.49, 126.43, 122.69, 122.57, 118.50, 118.01, 102.82, 102.63, 80.91, 80.78, 73.52, 73.13, 72.08, 72.02, 71.48, 71.41, 65.59, 65.54, 65.09, 60.14, 59.12, 58.85, 58.53, 52.37, 50.89, 50.46, 50.32, 48.11, 47.51, 47.01, 43.10, 42.87, 38.00, 30.72, 30.70, 30.61, 30.47, 30.43, 30.08, 28.56, 28.46, 28.45, 26.95, 26.53, 24.60, 22.32, 21.95, 18.56, 13.58, 13.49.

HRMS (ESI): $C_{30}H_{42}O_7N_3$ $[M+H]^+$; calculated: 556.30130, found: 556.30173.

143f, (1S)-((2R,4S,5R)-5-((S)-1,2-dihydroxyethyl)quinuclidin-2-yl)(2-(thiophen-2-yl)quinolin-4-yl)methyl-(tert-butoxycarbonyl)glycinate -TFA



143f was prepared from **142f** (3.20 g, 6.0 mmol) according to General Procedure 4. FCC gave title compound **143f** as a colorless foam in 56 % (1.9 g, 3.35 mmol) yield and in a diastereomeric ratio of 1:1 (by NMR). Preparative HPLC (10 – 60 % MeCN; RT = 19.7 min) was used for a better peak resolution.

R_f = 0.20 (2:3 MM:DCM)

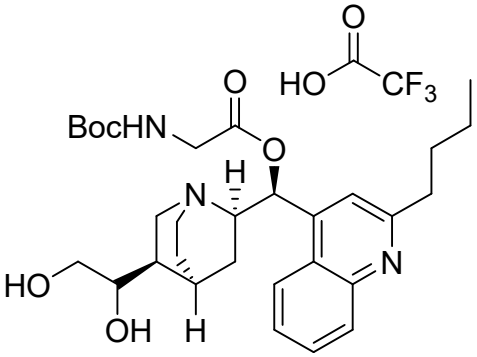
^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH and OH not observed) δ 8.24 – 8.15 (m, 4H), 8.06 – 7.99 (m, 4H), 7.83 – 7.78 (m, 2H), 7.65 (dddd, J = 8.3, 6.9, 2.9, 1.3 Hz, 2H), 7.60 (dt, J = 5.0, 1.2 Hz, 2H), 7.21 (ddd, J = 4.7, 3.7, 0.9 Hz, 2H), 6.96 (d, J = 9.3 Hz, 2H), 4.05 (s, 2H), 4.00 (s, 2H), 3.97 (ddd, J = 8.8, 5.1, 3.4 Hz, 1H), 3.88 (dt, J = 9.5, 4.6 Hz, 1H), 3.80 (ddd, J = 13.5, 8.6, 2.6 Hz, 1H), 3.75 – 3.70 (m, 2H), 3.63 (ddd, J = 18.7, 11.6, 3.7 Hz, 2H), 3.59 – 3.55 (m, 1H), 3.52 (ddd, J = 20.6, 11.6, 5.0 Hz, 2H), 3.48 – 3.40 (m, 4H), 3.22 (ddd, J = 12.8, 10.1, 8.3 Hz, 2H), 2.46 –

2.36 (m, 3H), 2.16 (q, J = 9.4 Hz, 1H), 2.06 (h, J = 9.7, 8.7 Hz, 2H), 1.85 – 1.74 (m, 3H), 1.74 – 1.67 (m, 1H), 1.49 (dt, J = 9.0, 4.8 Hz, 2H), 1.46 (s, 18H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 169.93, 169.85, 157.49, 157.47, 152.86, 152.83, 148.50, 145.10, 145.06, 143.19, 131.36, 130.59, 130.07, 130.04, 129.17, 128.85, 128.80, 128.08, 128.07, 124.12, 124.09, 123.65, 115.34, 115.30, 80.68, 80.58, 72.38, 71.87, 71.72, 70.83, 65.05, 64.69, 59.11, 59.05, 50.32, 50.23, 48.69, 47.82, 43.39, 43.32, 37.05, 35.95, 28.31, 28.28, 23.96, 23.54, 23.23, 22.34, 20.26, 19.67.

HRMS (ESI): $C_{30}H_{38}O_6N_3S$ $[M+H]^+$; calculated: 568.24758, found: 568.24712.

143g, (1S)-(2-butylquinolin-4-yl)((2R,4S,5R)-5-((S)-1,2-dihydroxyethyl)quinuclidin-2-yl)methyl (tert-butoxycarbonyl)glycinate - TFA



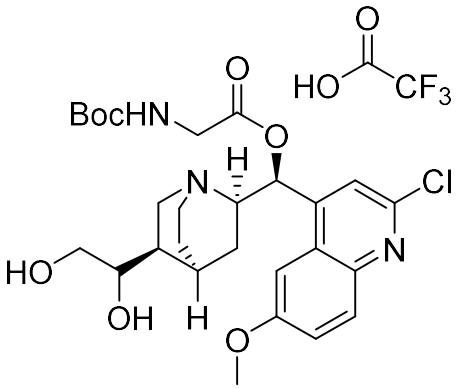
143g was prepared from **142g** (6.90 g, 13.6 mmol) according to General Procedure 4. FCC (1:1 MM:DCM, Rf = 0.52) gave title compound **143g** as a colorless foam in 86 % (6.35 g, 11.7 mmol) yield and in a diastereomeric ratio of 1:1 (by NMR). Preparative HPLC (10 – 60 % MeCN; RT = 12.47 min) was used for a better peak resolution.

^{1}H NMR (600 MHz, CD_3CN, OH and NH^+ not observed) δ 8.62 (dd, J = 8.6, 2.9 Hz, 1H), 8.44 (dt, J = 8.6, 1.4 Hz, 1H), 8.07 (ddt, J = 8.5, 7.0, 1.4 Hz, 1H), 7.97 – 7.86 (m, 2H), 7.16 (s, 1H), 6.16 (s, 1H), 4.11 – 3.84 (m, 3H), 3.80 (ddd, J = 13.6, 8.4, 2.5 Hz, 1H), 3.72 – 3.60 (m, 2H), 3.54 – 3.48 (m, 1H), 3.48 – 3.43 (m, 1H), 3.39 (t, J = 12.0 Hz, 1H), 3.27 – 3.16 (m, 3H), 2.47 – 2.00 (m, 3H), 1.92 – 1.79 (m, 3H), 1.71 (ddddd, J = 32.3, 13.0, 10.4, 8.4, 1.9 Hz, 1H), 1.51 – 1.37 (m, 12H), 0.95 (td, J = 7.4, 1.3 Hz, 3H).

^{13}C NMR (151 MHz, CD_3CN) δ 170.04, 169.97, 162.64, 162.62, 157.49, 157.44, 152.10, 152.04, 140.22, 140.15, 135.04, 135.02, 130.68, 130.66, 125.05, 124.84, 124.81, 123.09, 123.04, 120.88, 120.84, 80.75, 80.63, 72.69, 71.78, 71.60, 71.31, 65.46, 65.17, 58.72, 58.65, 50.44, 50.37, 48.40, 47.73, 43.70, 43.63, 37.23, 36.18, 35.20, 32.34, 32.28, 28.52, 28.49, 24.37, 23.91, 23.53, 23.14, 23.12, 22.59, 20.38, 19.77, 13.85.

HRMS (ESI): $C_{30}H_{44}O_6N_3$ $[M+H]^+$; calculated: 542.32246, found: 542.32183.

143h, (1S)-(2-chloro-6-methoxyquinolin-4-yl)((2R,4S,5R)-5-((S)-1,2-dihydroxyethyl)quinuclidin-2-yl)methyl (tert-butoxycarbonyl)glycinate -TFA



143h was prepared from **142h** (4.50 g, 8.72 mmol) according to General Procedure 4. FCC (2:3 MM:DCM, Rf = 0.5) gave title compound **143h** as a colorless foam in 91 % (4.34 g, 7.89 mmol) yield and in a diastereomeric ratio of 1:1 (by NMR). Preparative HPLC (5 – 35 % MeCN; RT = 27.6 min) was used for a better peak resolution.

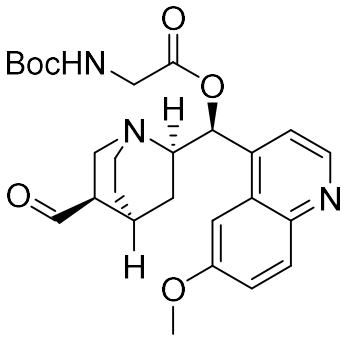
^{1}H NMR (600 MHz, CD_3CN:D_2O [10:1], NH^+ and OH not observed) δ 7.90 (d, J = 9.2 Hz, 2H), 7.55 (d, J = 10.0 Hz, 2H), 7.48 (dd, J = 9.2, 2.6 Hz, 2H), 7.40 (dd, J = 6.2, 2.7 Hz, 2H), 6.93 – 6.82 (m, 2H), 4.04 – 3.96 (m, 10H), 3.94 – 3.90 (m, 1H), 3.83 (dt, J = 9.6, 4.7 Hz, 1H), 3.74 (ddd, J = 13.6, 8.5, 2.7 Hz, 1H), 3.67 (td, J = 8.3, 7.4, 3.4 Hz, 2H), 3.61 (ddd, J = 25.4, 11.7, 3.8 Hz, 2H), 3.50 (dt, J = 11.2, 5.1 Hz, 2H), 3.46 – 3.37 (m, 5H), 3.22 (ddd, J = 12.9, 10.2, 8.2 Hz, 2H), 2.43 – 2.30 (m, 3H), 2.16 (q, J = 9.3 Hz, 1H), 2.11 – 2.08 (m, 1H), 2.07 – 2.00 (m, 1H), 1.88 – 1.68 (m, 4H), 1.50 – 1.44 (m, 2H), 1.42 (s, 18H).

^{13}C NMR (151 MHz, CD_3CN:D_2O [10:1]) δ 169.86, 169.81, 159.64, 157.33, 148.17, 148.14, 144.40, 144.38, 144.03, 131.18, 125.15, 125.11, 124.12, 124.10, 120.01, 101.99, 101.97, 80.56, 80.52, 72.37, 71.25, 71.13, 70.80, 64.90, 64.49, 58.36, 58.32, 56.63, 50.19, 50.10, 48.44, 47.64, 43.12, 43.06, 36.71, 35.62, 28.16, 28.14, 23.82, 23.34, 23.03, 22.14, 20.21, 19.61.

HRMS (ESI): $C_{27}H_{37}O_7N_3Cl$ $[M+H]^+$; calculated: 550.23145, found: 550.23098.

5.10.8 Aldehydes 80 and 113a-g

80, (1S)-((2R,4S,5R)-5-formylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl(tert-butoxycarbonyl)glycinate



80 was prepared from **143a** (7.28 g, 14.1 mmol) according to General Procedure 5. FCC gave title compound **80** as a colorless foam in 87 % (5.96 g, 12.3 mmol) yield.

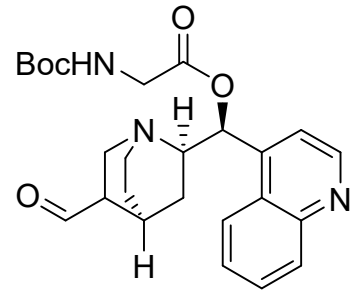
R_f = 0.3 (1:4 MM:DCM)

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.85 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.01 (d, J = 9.2 Hz, 1H), 7.47 (d, J = 2.7 Hz, 1H), 7.37 (dd, J = 9.2, 2.7 Hz, 1H), 7.30 (d, J = 4.5 Hz, 1H), 6.60 (d, J = 6.3 Hz, 1H), 5.16 (t, J = 5.7 Hz, 1H), 4.12 (dd, J = 18.4, 6.3 Hz, 1H), 4.00 (s, 3H), 3.91 (dd, J = 18.3, 5.4 Hz, 1H), 3.61 (ddd, J = 14.4, 6.9, 2.4 Hz, 1H), 3.25 (q, J = 8.1 Hz, 1H), 2.94 – 2.84 (m, 1H), 2.75 (ddd, J = 13.7, 9.9, 7.2 Hz, 1H), 2.68 (dd, J = 14.3, 10.0 Hz, 1H), 2.49 (t, J = 8.6 Hz, 1H), 2.49 – 2.45 (m, 1H), 1.71 – 1.53 (m, 4H), 1.46 – 1.41 (m, 9H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 203.73, 169.64, 158.27, 155.88, 147.59, 144.82, 143.14, 131.98, 126.86, 122.25, 118.32, 101.17, 80.14, 74.68, 58.90, 55.85, 50.51, 49.30, 42.77, 42.34, 28.45, 26.11, 24.65, 23.52.

HRMS (ESI): $C_{26}H_{34}O_6N_3$ $[M+H]^+$; calculated: 484.24421, found: 484.24363.

113a, (1S)-((2R,4S)-5-formylquinuclidin-2-yl)(quinolin-4-yl)methy(tert-butoxycarbonyl)-glycinate



113a was prepared from **143b** (5.14 g, 10.6 mmol) according to General Procedure 5. FCC gave title compound **113a** as a colorless foam in 90 % (4.29 g, 9.46 mmol) yield and in a diastereomeric ratio of 1.5 : 1 (by NMR).

R_f = 0.36 (1:3 MM:DCM)

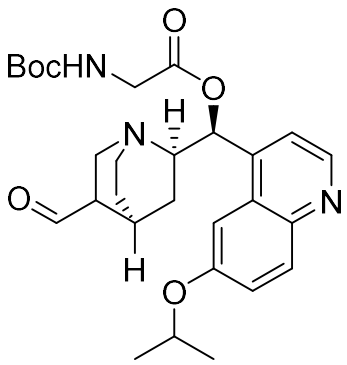
^{1}H NMR (700 MHz, $CDCl_3$) δ 9.82 (d, J = 52.9 Hz, 1H), 8.98 – 8.77 (m, 1H), 8.23 – 8.14 (m, 1H), 8.13 (t, J = 8.4 Hz, 1H), 7.76 – 7.70 (m, 1H), 7.65 – 7.58 (m, 1H), 7.37 (dd, J = 21.5, 4.5 Hz, 1H), 6.62 (d, J = 32.2 Hz, 1H), 5.07 (d, J = 100.8 Hz, 1H), 4.09 (ddd, J = 46.9, 18.0, 5.9 Hz, 1H), 3.97

– 3.87 (m, 1H), 3.68 – 3.39 (m, 1H), 3.25 (q, J = 9.0 Hz, 1H), 3.17 – 2.84 (m, 1H), 2.78 – 2.68 (m, 2H), 2.57 (d, J = 108.9 Hz, 1H), 2.46 (t, J = 3.4 Hz, 1H), 1.88 – 1.76 (m, 1H), 1.70 – 1.58 (m, 2H), 1.58 – 1.45 (m, 1H), 1.45 (s, 9H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 203.61, 169.55, 155.89, 155.80, 150.16, 150.13, 148.76, 148.67, 144.75, 130.79, 130.69, 129.50, 129.43, 127.22, 125.78, 123.23, 123.16, 118.55, 118.24, 80.45, 80.14, 74.89, 59.36, 59.20, 53.56, 50.57, 50.20, 49.49, 49.22, 42.80, 42.45, 42.39, 28.46, 28.44, 26.05, 24.35, 23.61, 23.57, 21.56.

HRMS (ESI): $C_{25}H_{32}O_5N_3$ $[M+H]^+$; calculated: 454.23365, found: 454.23324.

113b, (1S)-((2R,4S)-5-formylquinuclidin-2-yl)(6-isopropoxyquinolin-4-yl)methyl (tert-butoxycarbonyl)glycinate



113b was prepared from **143c** (4.55 g, 8.27 mmol) according to General Procedure 5. FCC gave title compound **113b** as a colorless foam in 89 % (3.81 g, 7.45 mmol) yield and in a diastereomeric ratio of 1.4:1 (by NMR).

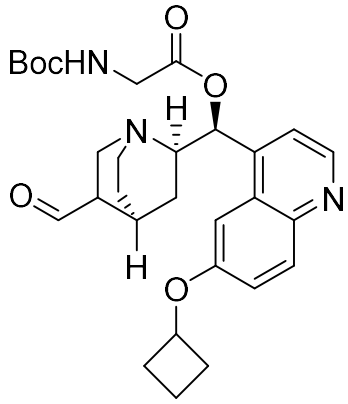
R_f = 0.38 (1:4 MM:DCM)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (d, J = 37.2 Hz, 2H), 8.70 (dd, J = 11.3, 4.6 Hz, 2H), 8.00 (t, J = 9.6 Hz, 2H), 7.53 – 7.27 (m, 6H), 6.54 (dd, J = 30.9, 6.1 Hz, 2H), 5.13 (dt, J = 46.7, 6.0 Hz, 2H), 4.77 (dh, J = 46.4, 6.0 Hz, 2H), 4.09 (ddd, J = 29.0, 18.3, 6.2 Hz, 2H), 3.95 – 3.83 (m, 2H), 3.60 (ddd, J = 14.4, 6.8, 2.4 Hz, 1H), 3.43 – 3.35 (m, 1H), 3.31 – 3.20 (m, 2H), 3.08 (dd, J = 14.4, 10.0 Hz, 1H), 2.94 – 2.58 (m, 6H), 2.53 – 2.41 (m, 3H), 1.86 – 1.74 (m, 2H), 1.69 – 1.59 (m, 2H), 1.59 – 1.51 (m, 2H), 1.47 – 1.33 (m, 32H).

^{13}C NMR (126 MHz, $CDCl_3$) 13C NMR δ 203.75, 169.58, 156.40, 156.35, 155.84, 147.44, 144.59, 144.54, 142.92, 132.10, 131.98, 126.85, 123.28, 122.98, 118.50, 118.29, 103.58, 103.14, 80.39, 80.08, 74.65, 70.34, 70.31, 58.95, 58.84, 50.59, 50.26, 49.52, 49.27, 42.78, 42.72, 42.39, 42.34, 28.42, 26.09, 24.59, 23.60, 23.48, 22.14, 21.89, 21.81, 21.58.

HRMS (ESI): $C_{28}H_{38}O_6N_3$ $[M+H]^+$; calculated: 512.27551, found: 512.27505.

113c, (1S)-(6-cyclobutoxyquinolin-4-yl)((2R,4S)-5-formylquinuclidin-2-yl)methyl (tert-butoxycarbonyl)glycinate



113c was prepared from **143d** (100 mg, 0.18 mmol) according to General Procedure 5. FCC gave title compound **113c** as a colorless foam in 84 % (83.7 mg, 0.15 mmol) yield and in a diastereomeric ratio of 5:3 (by NMR).

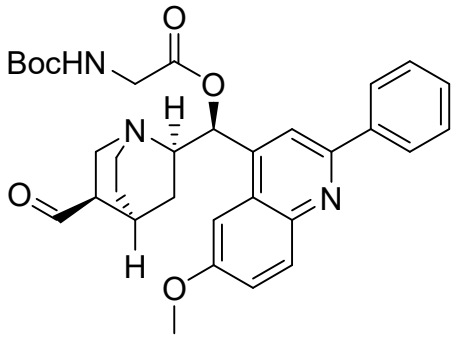
R_f = 0.5 (1:2 MM:DCM)

^{1}H NMR (600 MHz, CD_3CN) δ 9.74 (d, J = 42.7 Hz, 1H), 8.63 (dd, J = 7.2, 4.5 Hz, 1H), 7.95 (dd, J = 9.2, 6.3 Hz, 1H), 7.49 – 7.25 (m, 3H), 6.38 (s, 1H), 4.99 – 4.83 (m, 1H), 3.95 – 3.71 (m, 2H), 3.55 – 3.12 (m, 2H), 3.10 (s, 3H), 2.76 – 2.50 (m, 5H), 2.40 (q, J = 3.2 Hz, 1H), 2.23 – 2.10 (m, 2H), 1.91 – 1.64 (m, 3H), 1.64 – 1.44 (m, 2H), 1.37 (d, J = 15.0 Hz, 9H).

^{13}C NMR (151 MHz, CD_3CN) δ 205.94, 205.88, 170.70, 170.58, 156.95, 156.86, 156.35, 156.32, 147.93, 147.91, 144.63, 144.37, 144.29, 131.77, 131.69, 127.40, 127.05, 123.11, 123.08, 103.45, 80.06, 79.96, 72.44, 72.41, 72.28, 59.12, 59.05, 50.28, 50.26, 49.31, 49.00, 42.81, 42.64, 42.29, 30.72, 30.70, 30.65, 30.48, 28.11, 28.07, 27.71, 25.71, 25.26, 23.82, 23.58, 21.44, 13.51, 13.46.

HRMS (ESI): $C_{29}H_{38}O_6N_3[M+H]^+$; calculated: 524.27501, found: 524.27551.

113d, (1S)-((2R,4S,5R)-5-formylquinuclidin-2-yl)(6-methoxy-2-phenylquinolin-4-yl)methyl (tert-butoxycarbonyl)glycinate



113d was prepared from **143e** (4.00 g, 6.76 mmol) according to General Procedure 5. FCC gave title compound **113d** as a colorless foam in 93 % (3.53 g, 6.31 mmol) yield and in a diastereomeric ratio of 17 : 1 (by NMR).

R_f = 0.28 (1:4 EtOAc:MeCN)

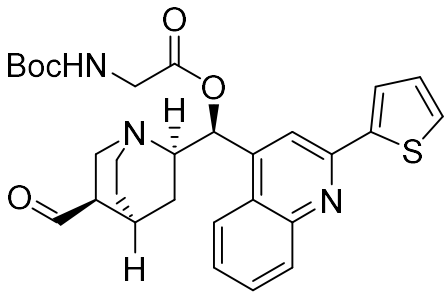
^{1}H NMR (700 MHz, $CDCl_3$) δ 9.84 (s, 1H), 8.15 (d, J = 7.6 Hz, 2H), 8.08 (d, J = 9.1 Hz, 1H), 7.78 (s, 1H), 7.49 (dt, J = 8.6, 7.2 Hz, 3H), 7.45 – 7.39 (m, 1H), 7.38 (dd, J = 9.2, 2.7 Hz, 1H), 6.67 (d,

J = 5.8 Hz, 1H), 5.25 (s, 1H), 4.15 (dd, J = 18.4, 6.4 Hz, 1H), 4.00 (s, 3H), 3.94 (dd, J = 18.4, 5.4 Hz, 1H), 3.73 – 3.63 (m, 1H), 3.31 (q, J = 8.0 Hz, 1H), 2.97 – 2.88 (m, 1H), 2.81 – 2.71 (m, 2H), 2.52 – 2.45 (m, 2H), 1.70 – 1.59 (m, 3H), 1.59 – 1.54 (m, 1H), 1.41 (s, 9H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 202.47, 168.57, 157.18, 154.91, 153.77, 143.86, 142.57, 138.77, 131.23, 128.07, 127.84, 126.56, 124.58, 121.32, 115.07, 100.10, 79.05, 73.69, 57.91, 54.87, 49.42, 48.02, 41.81, 41.37, 27.39, 24.85, 23.24, 22.47.

HRMS (ESI): $C_{32}H_{38}O_6N_3$ $[M+H]^+$; calculated: 560.27551, found: 560.27546.

113e, (1S)-((2R,4S)-5-formylquinuclidin-2-yl)(2-(thiophen-2-yl)quinolin-4-yl)methyl (tert-butoxycarbonyl)glycinate



113e was prepared from **143f** (1.75 g, 3.08 mmol) according to General Procedure 5. FCC (3:7 MM:DCM, Rf = 0.34) gave title compound **113e** as a lightly yellow foam in 78 % (1.28 g, 2.39 mmol) yield and in a diastereomeric ratio of > 20:1 (by NMR).

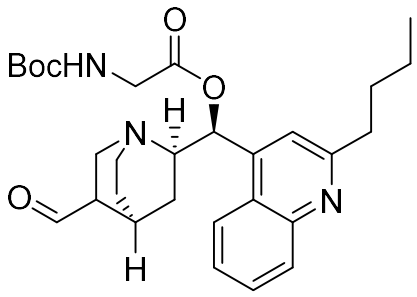
R_f = 0.34 (3:7 MM:DCM)

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.86 (s, 1H), 8.09 (dt, J = 8.4, 2.3 Hz, 2H), 7.91 (d, J = 3.7 Hz, 1H), 7.77 (s, 1H), 7.68 (t, J = 7.7 Hz, 1H), 7.53 (ddd, J = 8.2, 6.7, 1.3 Hz, 1H), 7.44 (dd, J = 5.0, 1.1 Hz, 1H), 7.14 (dd, J = 5.0, 3.7 Hz, 1H), 6.64 (s, 1H), 5.28 (s, 1H), 4.17 (dd, J = 18.4, 6.6 Hz, 1H), 3.93 (dd, J = 18.4, 5.4 Hz, 1H), 3.63 (dd, J = 13.4, 6.2 Hz, 1H), 3.27 (td, J = 8.9, 5.3 Hz, 1H), 2.95 – 2.87 (m, 1H), 2.80 – 2.69 (m, 2H), 2.50 – 2.43 (m, 2H), 1.73 – 1.67 (m, 1H), 1.67 – 1.62 (m, 1H), 1.62 – 1.56 (m, 1H), 1.55 – 1.50 (m, 1H), 1.43 (s, 9H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 203.85, 169.42, 156.02, 152.25, 148.59, 145.41, 145.14, 130.40, 129.67, 128.78, 128.17, 126.72, 126.58, 124.59, 123.06, 114.59, 80.06, 75.22, 59.15, 50.50, 49.12, 42.90, 42.54, 28.44, 26.01, 23.88, 23.62.

HRMS (ESI): $C_{29}H_{34}O_5N_3S$ $[M+H]^+$; calculated: 536.22137, found: 536.22117.

113f, (1S)-(2-butylquinolin-4-yl)((2R,4S)-5-formylquinuclidin-2-yl)methyl(tert-butoxycarbonyl)glycinate



113f was prepared from **143g** (2.59 g, 4.78 mmol) according to General Procedure 5. FCC (2:7 MM:DCM, Rf = 0.5) gave title compound **113f** as a colorless foam in 90 % (2.19 g, 4.30 mmol) yield and in a diastereomeric ratio of 1.6:1 (by NMR).

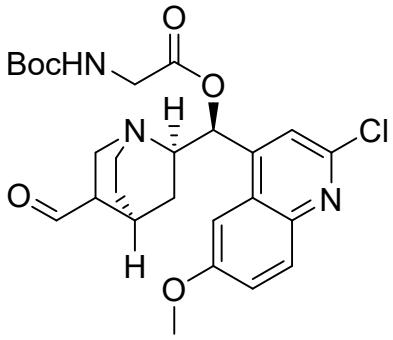
R_f = 0.50 (2:7 MM:DCM)

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.82 (d, J = 55.9 Hz, 1H), 8.10 (dd, J = 15.1, 8.4 Hz, 1H), 8.06 (t, J = 7.6 Hz, 1H), 7.74 – 7.63 (m, 1H), 7.59 – 7.50 (m, 1H), 7.26 (d, J = 23.3 Hz, 1H), 6.67 – 6.53 (m, 1H), 5.21 – 4.94 (m, 1H), 4.09 (ddd, J = 56.0, 18.3, 6.3 Hz, 1H), 3.91 (ddd, J = 18.3, 12.9, 5.5 Hz, 1H), 3.64 – 3.38 (m, 1H), 3.24 (p, J = 8.2, 7.1 Hz, 1H), 3.12 (t, J = 12.3 Hz, 0H), 2.95 (dt, J = 15.8, 7.9 Hz, 2H), 2.91 – 2.85 (m, 1H), 2.77 – 2.68 (m, 2H), 2.66 – 2.42 (m, 2H), 1.83 – 1.73 (m, 3H), 1.69 – 1.62 (m, 1H), 1.62 – 1.50 (m, 1H), 1.44 (d, J = 3.8 Hz, 9H), 1.42 – 1.31 (m, 3H), 0.96 (dt, J = 7.2 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 203.79, 203.58, 169.59, 169.52, 162.83, 162.72, 155.89, 155.79, 148.57, 148.47, 144.54, 144.18, 130.12, 130.03, 129.33, 129.26, 126.22, 126.20, 124.19, 123.00, 122.96, 118.92, 118.53, 80.39, 80.05, 75.58, 75.31, 59.24, 59.08, 50.59, 50.26, 49.55, 49.24, 42.82, 42.51, 42.40, 39.30, 39.25, 32.26, 32.20, 28.46, 28.43, 26.10, 24.18, 23.67, 23.65, 22.84, 22.80, 21.59, 14.13, 14.12.

HRMS (ESI): $C_{29}H_{40}O_5N_3$ $[M+H]^+$; calculated: 510.29625, found: 510.29574.

113g, (1S)-(2-chloro-6-methoxyquinolin-4-yl)((2R,4S)-5-formylquinuclidin-2-yl)methyl (tert-butoxycarbonyl)glycinate



113g was prepared from **143h** (3.95 g, 7.18 mmol) according to General Procedure 5. FCC (1:5 MM:DCM, Rf = 0.24) gave title compound **113g** as a colorless foam in 89 % (3.31 g, 6.39 mmol) yield and in a diastereomeric ratio of 5:1 (by NMR).

R_f = 0.24 (1:5 MM:DCM)

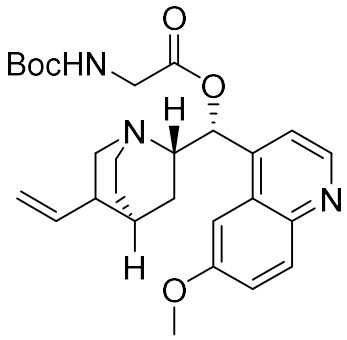
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (d, J = 34.6 Hz, 1H), 7.93 (t, J = 9.3 Hz, 1H), 7.50 (d, J = 2.7 Hz, 1H), 7.39 (ddd, J = 9.2, 6.2, 2.7 Hz, 1H), 7.32 (d, J = 15.8 Hz, 1H), 6.57 (s, 1H), 5.19 – 5.02 (m, 1H), 4.17 – 4.03 (m, 1H), 3.98 (d, J = 25.3 Hz, 3H), 3.91 (dd, J = 18.4, 5.4 Hz, 1H), 3.66 – 3.30 (m, 1H), 3.23 (q, J = 8.1 Hz, 1H), 2.99 – 2.84 (m, 1H), 2.76 (q, J = 11.7, 10.2 Hz, 1H), 2.67 (t, J = 12.3 Hz, 1H), 2.58 – 2.44 (m, 2H), 1.87 – 1.51 (m, 4H), 1.44 (d, J = 4.9 Hz, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.72, 158.64, 155.96, 148.12, 144.46, 131.21, 131.07, 125.87, 123.32, 119.63, 101.71, 80.35, 73.99, 59.16, 56.09, 50.53, 49.27, 42.81, 42.29, 28.54, 26.05, 24.86, 23.45.

HRMS (ESI): $C_{26}H_{33}O_6N_3Cl$ $[M+H]^+$; calculated: 518.20524, found: 518.20479.

5.10.9 Quinine derivatives 105, 144 and 106

105, (1R)-(6-methoxyquinolin-4-yl)((2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl (tert-butoxycarbonyl)glycinate



105 was prepared from quinine hydrochloride dihydrate (6.50 g, 16.4 mmol) according to General Procedure 3 after addition of 1 g 4 Å MS and 1.2 eq. Et_3N before adding the remainder of the reagents. FCC (1:4 MM:DCM, Rf = 0.36) gave title compound **105** as a colorless foam in 45 % (3.55 g, 7.37 mmol) yield.

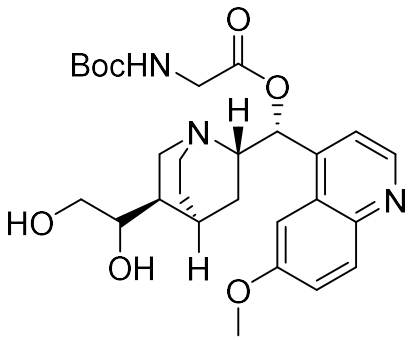
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.69 (d, J = 4.5 Hz, 1H), 7.99 (d, J = 9.2 Hz, 1H), 7.39 (s, 1H), 7.36 – 7.31 (m, 2H), 6.55 (s, 1H), 5.77 (ddd, J = 17.4, 10.4, 7.3 Hz, 1H), 5.31 (s, 1H), 5.02 – 4.95 (m, 2H), 4.02 (dd, J = 18.3, 6.2 Hz, 1H), 3.93 (s, 3H), 3.88 (dd, J = 18.3, 5.5 Hz, 1H), 3.35 (q, J = 8.1 Hz, 1H), 3.13 – 3.00 (m, 2H), 2.67 – 2.58 (m, 2H), 2.27 (s, 1H), 1.87 – 1.80 (m, 2H), 1.75 – 1.67 (m, 1H), 1.57 – 1.48 (m, 2H), 1.41 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.72, 158.15, 155.79, 147.48, 144.78, 142.92, 141.37, 131.89, 126.86, 122.03, 118.84, 114.83, 101.33, 80.14, 74.62, 59.12, 56.50, 55.86, 42.69, 42.60, 39.47, 28.37, 27.47, 23.97.

HRMS (ESI): $C_{27}H_{36}O_5N_3$ $[M+H]^+$; calculated: 482.26495, found: 482.26435.

$[\alpha]_{20}^{D}$ = - 22 ° (c = 1, MeCN).

144, (1R)-((2S,4S,5R)-5-((S)-1,2-dihydroxyethyl)quinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl (tert-butoxycarbonyl)glycinate



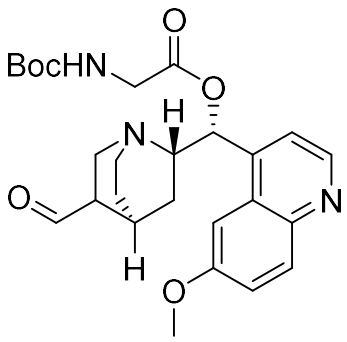
144 was prepared from **105** (4.50 g, 9.34 mmol) according to General Procedure 4. FCC (1:1 MM:DCM, Rf = 0.35) gave title compound **144** as a colorless foam in 89 % (4.23 g, 8.20 mmol) yield and in a diastereomeric ratio of 1:1 (by NMR).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.68 – 8.53 (m, 2H), 7.97 (dd, J = 9.2, 5.2 Hz, 2H), 7.38 (d, J = 9.9 Hz, 2H), 7.36 – 7.31 (m, 2H), 7.28 (d, J = 4.6 Hz, 1H), 7.26 (d, J = 3.4 Hz, 1H), 6.57 (d, J = 19.4 Hz, 2H), 5.43 – 5.18 (m, 2H), 4.00 (dt, J = 18.2, 6.2 Hz, 2H), 3.92 (d, J = 7.5 Hz, 6H), 3.90 – 3.85 (m, 2H), 3.62 – 3.52 (m, 3H), 3.46 – 3.37 (m, 3H), 3.36 – 3.23 (m, 4H), 3.08 (s, 2H), 2.96 – 2.85 (m, 3H), 2.70 – 2.54 (m, 2H), 2.31 (d, J = 14.0 Hz, 1H), 2.21 – 2.14 (m, 1H), 1.83 – 1.76 (m, 2H), 1.76 – 1.62 (m, 3H), 1.61 – 1.45 (m, 4H), 1.41 (s, 18H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.79, 169.72, 158.43, 158.40, 155.97, 147.35, 144.60, 143.23, 131.73, 131.67, 126.93, 126.89, 122.36, 122.23, 118.68, 101.54, 101.50, 80.43, 80.41, 74.91, 74.37, 73.88, 65.59, 64.90, 59.50, 59.09, 56.11, 56.04, 54.50, 54.25, 43.02, 42.81, 38.12, 37.63, 28.49, 24.37, 22.33.

HRMS (ESI): $C_{27}H_{38}O_7N_3$ $[M+H]^+$; calculated: 516.27043, found: 516.27981.

106, (1R)-((2S,4S)-5-formylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl (tert-butoxycarbonyl)glycinate



106 was prepared from **144** (3.50 g, 6.79 mmol) according to General Procedure 5. FCC (1:3 MM:DCM, Rf = 0.27) gave title compound **106** as a colorless foam in 95 % (3.10 g, 6.41 mmol) yield and in a diastereomeric ratio of 1 : 1 (by NMR).

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.74 (s, 2H), 8.72 (dd, J = 7.2, 4.5 Hz, 2H), 8.01 (dd, J = 9.5, 7.6 Hz, 2H), 7.36 (dtt, J = 6.8, 4.2, 2.3 Hz, 4H), 7.32 (dd, J = 7.9, 4.5 Hz, 2H), 6.51 (d, J = 56.9 Hz, 2H), 5.07 (d, J = 21.2 Hz, 2H), 4.03 (ddd, J = 31.5, 18.1, 6.1 Hz, 2H), 3.95 (d, J = 10.6 Hz, 6H), 3.88 (ddd, J = 29.9, 18.4, 5.6 Hz, 2H), 3.40 – 3.32 (m, 3H), 3.23 (dd, J = 13.9, 7.1 Hz, 1H), 3.16 – 3.01 (m, 2H), 2.80 (ddd, J = 49.8, 12.8, 9.3

Hz, 2H), 2.74 – 2.64 (m, 2H), 2.50 (q, J = 9.3, 8.3 Hz, 2H), 2.43 (d, J = 28.5 Hz, 2H), 1.86 – 1.73 (m, 3H), 1.70 – 1.60 (m, 2H), 1.57 – 1.46 (m, 2H), 1.42 (s, 18H), 1.35 – 1.29 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 203.49, 203.25, 169.78, 169.68, 158.21, 158.18, 155.79, 155.76, 147.57, 147.53, 144.90, 144.84, 142.95, 142.70, 132.07, 132.01, 126.99, 126.86, 122.06, 121.98, 119.13, 118.70, 101.36, 80.36, 80.31, 74.66, 59.64, 58.69, 55.82, 55.80, 49.61, 49.37, 48.91, 48.47, 42.91, 42.75, 42.68, 29.07, 28.41, 27.15, 25.51, 23.63, 23.54, 22.58.

HRMS (ESI): $C_{26}H_{34}O_6N_3$ $[M+H]^+$; calculated: 484.24421, found: 484.24377.

5.10.10 Characterization of Cinchona Macrocycles

For the naming- and numbering schemes consult Supplementary Section 2.

The HRMS spectra of all macrocycles also show appropriate signals for $[M+2H]^{2+}$ and $[M+3H]^{3+}$ within the required tolerance and the correct isotope pattern. The $[M+2H]^{2+}$ the by far most dominant species

5.10.11 Macrocycles from aldehyde 80

101aa, QD-Me-S

101aa was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (10 – 30 % MeCN; RT = 12.8 min) gave title compound **101aa** and its diastereomer (RT = 16.3 min) in a ratio of 19:1 and a yield of 50 % (17.2 mg, 14.7 µmol; yield of only title compound).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.91 (d, J = 5.1 Hz, 2H), 8.19 (d, J = 9.3 Hz, 2H), 8.01 (d, J = 5.1 Hz, 2H), 7.66 (dd, J = 9.3, 2.5 Hz, 2H), 7.58 (d, J = 2.6 Hz, 2H), 7.34 (s, 2H), 4.07 (d, J = 8.0 Hz, 2H), 4.05 (s, 6H), 3.93 (t, J = 7.7 Hz, 2H), 3.83 (dd, J = 10.8, 7.6 Hz, 2H), 3.67 (dd, J = 11.7, 7.0 Hz, 2H), 3.59 (t, J = 7.3 Hz, 2H), 3.47 (ddd, J = 13.0, 11.0, 1.8 Hz, 2H), 3.43 (ddt, J = 14.1, 11.3, 4.2 Hz, 2H), 3.31 (ddd, J = 13.1, 11.0, 7.3 Hz, 2H), 3.26 (ddd, J = 13.7, 7.1, 2.8 Hz, 2H), 2.73 (ddd, J = 14.1, 7.5, 2.2 Hz, 2H), 2.68 (s, 6H), 2.64 (s, 2H), 2.41 (td, J = 11.2, 7.2 Hz, 2H), 1.97 – 1.90 (m, 2H), 1.86 – 1.79 (m, 2H), 1.68 (ddd, J = 14.2, 10.7, 3.9 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.42, 176.32, 168.70, 160.79, 145.24, 144.54, 139.39, 128.03, 127.11, 126.20, 120.42, 101.83, 69.54, 63.58, 63.40, 58.97, 57.09, 50.73, 49.64, 48.43, 48.22, 32.97, 25.02, 23.66, 23.51, 18.92.

^{15}N HMBC (71 MHz, CD_3CN:D_2O [10:1]) δ 249.79 (Quinoline N), 177.51 (Succinimid N-Me), 53.60 (Pyrrolidine NH), 41.69 (Quinuclidine NH^+).

HRMS (ESI): $C_{52}H_{57}O_{10}N_8$ $[M+H]^+$; calculated: 953.41976, found: 953.41961.

$[\alpha]_{20}^{D}$ = +62° (c = 1, MeCN).

101ab, QD-Ph-S; 7a, QD-Ph-A; 29, QD-Ph-A2; 30, QD-Ph-S-Trimer

101ab was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (10 – 35 % MeCN, 30 ml/min) gave the 3 diastereomers compound **103** (RT = 19.4 min), **101ab** (RT = 20.0 min) and **102a** (RT = 23.7 min) in a ratio of 1 : 7.7 : 1.1 and a combined yield of 50 % (18.8 mg, 14.4 µmol).

It has to be noted that miniscule amounts of trimer **109** (RT = 28.2 min) was observed under certain conditions during the optimization of this reaction. Trimer **109** was collected from 10 different reactions to give the shown spectrum.

103, QD-Ph-A2

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.85 (d, J = 5.0 Hz, 1H), 8.81 (d, J = 5.1 Hz, 1H), 8.11 (d, J = 9.1 Hz, 2H), 8.03 – 7.98 (m, 1H), 7.94 – 7.89 (m, 1H), 7.59 (ddd, J = 9.0, 4.5, 1.8 Hz, 2H), 7.57 (s, 1H), 7.51 (s, 1H), 7.39 – 7.36 (m, 3H), 7.36 – 7.30 (m, 4H), 7.21 (s, 1H), 7.12 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 7.7 Hz, 2H), 4.39 (d, J = 8.3 Hz, 1H), 4.29 (t, J = 7.9 Hz, 1H), 4.10 (dt, J = 8.0, 4.1 Hz, 2H), 4.03 (d, J = 3.5 Hz, 6H), 3.98 (dd, J = 11.2, 5.1 Hz, 1H), 3.88 (dd, J = 11.7, 6.8 Hz, 1H), 3.82 (d, J = 11.7 Hz, 1H), 3.78 (dd, J = 16.5, 8.2 Hz, 2H), 3.57 (d, J = 8.0 Hz, 1H), 3.56 – 3.39 (m, 5H), 3.35 – 3.29 (m, 1H), 3.26 (td, J = 12.2, 11.7, 7.6 Hz, 1H), 3.13 (dd, J = 14.2, 8.4 Hz, 1H), 2.73 (dd, J = 13.7, 8.5 Hz, 1H), 2.64 (s, 1H), 2.55 – 2.50 (m, 2H), 2.47 (q, J = 10.2 Hz, 1H), 2.37 (s, 1H), 2.11 – 2.02 (m, 1H), 1.93 – 1.89 (m, 1H), 1.86 – 1.77 (m, 3H), 1.68 (ddd, J = 14.1, 10.5, 4.0 Hz, 1H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 177.49, 175.75, 175.70, 175.59, 169.65, 169.31, 160.51, 160.40, 145.35, 144.70, 143.66, 143.05, 140.69, 139.79, 132.59, 132.53, 129.62, 129.43, 129.41, 129.13, 128.44, 127.47, 127.30, 126.95, 126.75, 125.56, 125.29, 121.39, 120.32, 101.73, 101.70, 70.77, 69.84, 64.73, 63.85, 63.80, 62.56, 59.03, 58.39, 56.93, 56.91, 52.09, 51.53, 50.86, 50.82, 49.86, 49.68, 48.90, 48.58, 36.83, 33.02, 24.88, 23.74, 23.65, 23.20, 19.41, 17.83.

HRMS (ESI): $C_{62}H_{61}O_{10}N_8$ $[M+H]^+$; calculated: 1077.45052, found: 1077.45174.

$[\alpha]_{20}^{D}$ = + 51° (c = 0.1, MeCN).

101ab, QD-Ph-S

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.88 (d, J = 5.1 Hz, 2H), 8.13 (d, J = 9.3 Hz, 2H), 7.99 (d, J = 5.1 Hz, 2H), 7.61 (dd, J = 9.3, 2.6 Hz, 2H), 7.54 (d, J = 2.6 Hz, 2H), 7.40 – 7.35 (m, 4H), 7.35 – 7.30 (m, 4H), 7.13 – 7.07 (m, 4H), 4.24 (d, J = 8.3 Hz, 2H), 4.13 – 4.08 (m, 2H), 4.03 (s, 6H), 3.84 (dd, J = 11.3, 7.0 Hz, 4H), 3.81 – 3.77 (m, 2H), 3.53 (ddd, J = 13.7, 10.9, 1.7 Hz, 2H), 3.43 (ddt, J = 13.8, 11.2, 3.1 Hz, 2H), 3.37 (ddd, J = 13.8, 7.1, 2.9 Hz, 2H), 3.30 (ddd, J = 13.1, 11.0, 7.2 Hz, 2H), 2.78 (ddt, J = 13.1, 7.8, 2.4 Hz, 2H), 2.65 (s, 2H), 2.54 (td, J = 10.8, 6.8 Hz, 2H), 1.93 – 1.90 (m, 2H), 1.82 (dddd, J = 18.3, 9.5, 4.9, 1.7 Hz, 2H), 1.70 (ddd, J = 13.9, 10.6, 3.3 Hz, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 175.61, 175.50, 168.96, 160.62, 144.80, 144.59, 139.79, 132.55, 129.61, 129.42, 128.36, 127.44, 126.95, 125.87, 120.29, 101.76, 69.90, 63.97, 63.87, 58.90, 57.01, 50.90, 49.68, 48.83, 48.36, 32.96, 23.62, 23.59, 19.03.

HRMS (ESI): $C_{62}H_{61}O_{10}N_8$ $[M+H]^+$; calculated: 1077.45052, found: 1077.45152.

$[\alpha]_{20}^{D}$ = +45 ° (c = 0.3, MeCN).

102a, QD-Ph-A

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.82 (d, J = 5.0 Hz, 2H), 8.12 (dd, J = 18.3, 9.2 Hz, 2H), 7.91 (d, J = 5.1 Hz, 1H), 7.75 (d, J = 5.0 Hz, 1H), 7.60 (dd, J = 9.2, 5.7 Hz, 4H), 7.51 (dd, J = 15.3, 5.4 Hz, 5H), 7.38 (t, J = 7.9 Hz, 2H), 7.35 – 7.31 (m, 2H), 7.18 (s, 1H), 7.16 – 7.11 (m, 2H), 4.33 (dd, J = 15.7, 8.6 Hz, 2H), 4.04 (d, J = 2.8 Hz, 6H), 3.96 (t, J = 8.1 Hz, 1H), 3.90 (dd, J = 10.9, 7.3 Hz, 1H), 3.83 (ddd, J = 23.7, 10.9, 7.6 Hz, 4H), 3.76 (t, J = 7.1 Hz, 1H), 3.65 (ddd, J = 13.8, 7.4, 2.7 Hz, 1H), 3.62 – 3.54 (m, 1H), 3.53 (t, J = 11.2 Hz, 2H), 3.50 – 3.42 (m, 3H), 3.30 (ddd, J = 20.4, 11.9, 8.2 Hz, 2H), 2.75 (s, 1H), 2.68 – 2.63 (m, 2H), 2.58 – 2.51 (m, 2H), 2.36 (q, J = 10.1 Hz, 1H), 2.01 – 1.95 (m, 2H), 1.82 (ddt, J = 23.3, 12.4, 8.6 Hz, 2H), 1.65 – 1.60 (m, 1H), 1.57 (td, J = 14.2, 12.3, 4.2 Hz, 1H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.41, 175.89, 175.66, 175.63, 169.54, 169.49, 160.44, 160.36, 145.61, 145.16, 143.84, 143.58, 141.14, 140.47, 132.73, 132.68, 129.74, 129.58, 129.45, 129.36, 128.84, 127.67, 127.45, 126.81, 126.76, 125.60, 125.35, 119.78, 118.96, 116.46, 101.70, 72.07, 70.42, 64.73, 64.01, 63.82, 63.33, 58.50, 58.26, 56.91, 56.88,

53.12, 52.81, 50.15, 50.12, 49.77, 49.23, 49.07, 48.10, 38.50, 33.48, 23.81, 23.39, 23.33, 19.40, 19.16.

HRMS (ESI): $C_{62}H_{61}O_{10}N_8$ $[M+H]^+$; calculated: 1077.45052, found:1077.452003.

109, QD-Ph-S-Trimer

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.84 (d, J = 4.7 Hz, 3H), 8.10 (d, J = 9.3 Hz, 3H), 7.68 (d, J = 4.7 Hz, 3H), 7.57 (d, J = 9.4 Hz, 3H), 7.51 (t, J = 7.5 Hz, 6H), 7.49 – 7.44 (m, 6H), 7.27 (d, J = 7.8 Hz, 6H), 7.00 (s, 3H), 4.95 (d, J = 8.4 Hz, 3H), 4.00 (s, 9H), 4.04 – 3.96 (m, 6H), 3.88 (dd, J = 11.9, 7.6 Hz, 6H), 3.75 (t, J = 9.7 Hz, 3H), 3.67 (t, J = 7.4 Hz, 3H), 3.45 (t, J = 11.9 Hz, 3H), 3.27 (q, J = 10.0 Hz, 3H), 2.65 (t, J = 11.9 Hz, 3H), 2.37 (q, J = 9.9 Hz, 3H), 2.27 (s, 3H), 1.89 – 1.82 (m, 3H), 1.74 (q, J = 10.9 Hz, 3H), 1.62 – 1.54 (m, 3H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 177.23, 175.68, 169.83, 159.97, 146.51, 143.28, 142.23, 132.19, 130.19, 129.92, 129.80, 127.43, 126.46, 124.67, 101.52, 71.97, 62.18, 61.51, 58.57, 56.70, 50.32, 49.90, 48.59, 48.25, 34.49, 24.10, 22.73, 18.56.

HRMS (ESI): $C_{93}H_{91}O_{15}N_{12}$ $[M+H]^+$; calculated: 1615.67214, found: 1615.67265.

$C_{93}H_{92}O_{15}N_{12}$ $[M+2H]2^+$; calculated: 808.33990, found: 808.33971.

101ac, QD-Et-S

101ac was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (10 – 35 % MeCN; RT = 12.46 min) gave title compound **101ac** and its diastereomer (RT = 14.15 min) in a ratio of 12.8:1 and a combined yield of 36 % (12.4 mg, 10.3 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.90 (d, J = 4.9 Hz, 2H), 8.20 – 8.13 (m, 2H), 7.89 (dd, J = 4.9, 0.7 Hz, 2H), 7.59 (d, J = 8.0 Hz, 4H), 7.37 (s, 2H), 4.06 (d, J = 8.2 Hz, 2H), 4.05 (s, 6H), 3.87 (t, J = 7.8 Hz, 2H), 3.80 (dd, J = 10.3, 8.2 Hz, 2H), 3.68 (dd, J = 11.6, 6.9 Hz, 2H), 3.54 (t, J = 7.2 Hz, 2H), 3.49 (ddd, J = 13.0, 10.9, 1.7 Hz, 2H), 3.41 (ddt, J = 14.1, 11.5, 3.2 Hz, 2H), 3.27 (pd, J = 7.5, 3.7 Hz, 8H), 2.71 (ddt, J = 13.1, 7.6, 2.4 Hz, 2H), 2.64 (s, 2H), 2.42 (td, J = 11.1, 7.0 Hz, 2H), 1.91 (dt, J = 6.7, 3.7 Hz, 2H), 1.82 (dddt, J = 15.8, 11.0, 7.3, 2.4 Hz, 2H), 1.64 (ddd, J = 14.2, 10.4, 3.8 Hz, 2H), 0.94 (t, J = 7.2 Hz, 6H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.18, 176.05, 168.90, 160.61, 145.83, 143.62, 141.58, 129.77, 126.97, 125.40, 120.20, 101.79, 69.85, 63.85, 63.69, 59.14, 57.17, 50.77, 49.72, 48.57, 48.46, 34.44, 33.36, 23.91, 23.86, 19.21, 13.02.

HRMS (ESI): $C_{54}H_{61}O_{10}N_8$ $[M+H]^+$; calculated: 981.45080, found: 981.45052.

$[\alpha]_{20}^{D}$ = + 69 ° (c = 0.5, MeCN).

101ad, QD-Propargyl-S; 102b, QD-Propargyl-A

101ad was prepared from aldehyde **80** according to General Procedure 6 (replacement of AgOTf with $Cu(NCCH_3)_4OTf$). Preparative HPLC (10 – 30 % MeCN; RT = 18.2 min) gave title compounds **101ad** and its diastereomer **102b** (RT = 21.2 min) in a ratio of 4.6:1 and a combined yield of 35 % (12.3 mg, 10.0 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.89 (d, J = 5.0 Hz, 2H), 8.16 (d, J = 9.9 Hz, 2H), 7.93 (d, J = 5.0 Hz, 2H), 7.62 (dd, J = 9.2, 2.3 Hz, 2H), 7.52 (s, 2H), 7.29 (s, 2H), 4.08 (d, J = 8.1 Hz, 2H), 4.04 (s, 6H), 4.03 – 3.92 (m, 6H), 3.83 (t, J = 9.2 Hz, 2H), 3.69 (dd, J = 11.6, 7.0 Hz, 2H), 3.65 (t, J = 7.2 Hz, 2H), 3.48 (dd, J = 13.5, 11.1 Hz, 2H), 3.43 (t, J = 12.2 Hz, 2H), 3.31 (dd, J = 11.9, 7.5 Hz, 2H), 3.26 (dd, J = 14.3, 7.8 Hz, 2H), 2.72 (dd, J = 14.3, 7.8 Hz, 2H), 2.65 (s, 2H), 2.45 – 2.43 (m, 2H), 2.43 – 2.38 (m, 2H), 1.97 – 1.95 (m, 2H), 1.87 – 1.80 (m, 2H), 1.71 – 1.65 (m, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 175.12, 174.93, 168.50, 160.48, 145.35, 143.88, 140.60, 129.01, 126.80, 125.51, 120.16, 101.62, 77.32, 72.20, 69.70, 63.61, 63.40, 58.95, 56.95, 50.60, 49.63, 48.51, 48.26, 33.01, 28.20, 23.59, 23.48, 18.92.

HRMS (ESI): $C_{56}H_{57}O_{10}N_8$ $[M+H]^+$; calculated: 1001.41922, found: 1001.41987.

$[\alpha]_{20}^{D}$ = + 59 ° (c = 0.5, MeCN).

102b, QD-Propargyl-A

^{1}H NMR (600 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.92 (dd, J = 5.2, 3.0 Hz, 2H), 8.18 (dd, J = 9.3, 3.2 Hz, 2H), 7.94 (d, J = 5.1 Hz, 1H), 7.82 (d, J = 5.1 Hz, 1H), 7.65 (ddd, J = 9.3, 2.6, 1.2 Hz, 2H), 7.55 (dd, J = 11.4, 2.6 Hz, 2H), 7.35 (s, 1H), 7.17 (s, 1H), 4.30 (d, J = 2.5 Hz, 2H), 4.13 (dd, J = 8.5, 4.4 Hz, 2H), 4.04 (d, J = 3.7 Hz, 6H), 4.04 – 3.94 (m, 4H), 3.84 (dt, J = 12.1, 8.7 Hz, 3H), 3.70 (ddd, J = 11.1, 7.2, 4.5 Hz, 1H), 3.66 (dd, J = 10.0, 8.6 Hz, 1H), 3.61 (t, J

= 7.2 Hz, 1H), 3.58 – 3.49 (m, 2H), 3.45 (td, J = 13.7, 3.2 Hz, 2H), 3.40 (ddd, J = 13.9, 7.3, 2.7 Hz, 1H), 3.34 – 3.25 (m, 3H), 2.72 (s, 1H), 2.65 (s, 1H), 2.64 (t, J = 2.5 Hz, 1H), 2.63 – 2.58 (m, 1H), 2.50 – 2.45 (m, 1H), 2.43 (t, J = 2.5 Hz, 1H), 2.42 – 2.38 (m, 1H), 2.28 (ddd, J = 12.7, 9.8, 4.5 Hz, 1H), 1.98 – 1.95 (m, 2H), 1.86 – 1.77 (m, 2H), 1.59 (dddd, J = 18.7, 14.1, 10.3, 4.0 Hz, 2H).

^{13}C NMR (151 MHz, CD_3CN:D_2O [10:1]) δ 175.35, 174.72, 174.71, 174.68, 168.80, 168.47, 160.10, 160.02, 144.41, 144.33, 144.04, 143.96, 139.41, 139.05, 127.84, 127.58, 126.44, 126.40, 125.57, 125.38, 119.30, 118.55, 101.17, 76.95, 76.80, 72.07, 71.58, 71.29, 69.48, 63.76, 63.02, 62.67, 62.30, 57.87, 57.62, 56.40, 56.36, 52.57, 52.50, 49.49, 49.39, 49.09, 48.35, 48.22, 47.43, 37.50, 32.92, 27.85, 27.59, 23.03, 22.87, 22.75, 22.68, 18.70, 18.51.

HRMS (ESI): $C_{56}H_{57}O_{10}N_8$ $[M+H]^+$; calculated: 1001.41922, found: 1001.41950.

$[\alpha]_{20}^{D}$ = + 38 ° (c = 1, MeCN).

101ae QD-iPr-S

101ae was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (10 – 60 % MeCN; RT = 16.9 min) gave title compound **101ae** and its diastereomer (RT = 19.4 min) in a ratio of 3.7:1 and a combined yield of 49 % (17.5 mg, 14.1 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.92 (ddd, J = 5.8, 4.3, 1.7 Hz, 2H), 8.20 (d, J = 9.3 Hz, 2H), 8.01 (td, J = 8.3, 6.7, 3.9 Hz, 2H), 7.66 (d, J = 9.3 Hz, 2H), 7.58 (s, 2H), 7.34 (s, 2H), 4.09 (d, J = 8.1 Hz, 2H), 4.07 – 4.01 (m, 8H), 3.87 – 3.80 (m, 4H), 3.67 (ddd, J = 11.9, 6.9, 2.1 Hz, 2H), 3.54 – 3.47 (m, 4H), 3.43 (ddt, J = 14.0, 11.3, 3.2 Hz, 2H), 3.32 – 3.27 (m, 2H), 3.25 (ddd, J = 13.7, 7.2, 2.8 Hz, 2H), 2.75 – 2.66 (m, 2H), 2.63 (s, 2H), 2.43 (td, J = 11.2, 7.2 Hz, 2H), 1.93 – 1.90 (m, 2H), 1.86 – 1.79 (m, 2H), 1.69 – 1.62 (m, 2H), 1.15 (d, J = 6.9 Hz, 6H), 1.12 (d, J = 6.9 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.29, 168.79, 160.83, 145.51, 144.33, 139.03, 127.74, 127.13, 126.36, 120.34, 101.84, 69.62, 63.70, 63.48, 58.88, 57.08, 50.22, 49.68, 48.40, 47.94, 44.54, 32.99, 23.60, 23.55, 19.07, 18.98, 18.73.

HRMS (ESI): $C_{56}H_{65}O_{10}N_8$ $[M+H]^+$; calculated: 1009.48182, found: 1009.48184.

$[\alpha]_{20}^{D}$ = + 72 ° (c = 1, MeCN).

101af, QD-*t*Bu-S

101af was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 45 % MeCN; RT = 18.1 min) gave title compound **101af** and its diastereomer (RT = 21.1 min) in a ratio of 5:1 and a combined yield of 39 % (12.6 mg, 9.45 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.87 (d, J = 5.0 Hz, 2H), 8.15 (d, J = 9.3 Hz, 2H), 7.92 (d, J = 5.0 Hz, 2H), 7.63 (dd, J = 9.2, 2.6 Hz, 2H), 7.56 (d, J = 2.6 Hz, 2H), 7.35 (s, 2H), 4.07 – 4.03 (m, 8H), 3.82 (t, J = 9.3 Hz, 2H), 3.72 (t, J = 7.8 Hz, 2H), 3.64 (dd, J = 11.7, 6.9 Hz, 2H), 3.47 (t, J = 12.2 Hz, 2H), 3.41 (t, J = 7.3 Hz, 4H), 3.31 – 3.25 (m, 2H), 3.25 – 3.21 (m, 2H), 2.71 – 2.64 (m, 2H), 2.63 (s, 2H), 2.35 (q, J = 10.9, 10.3 Hz, 2H), 1.90 (d, J = 11.6 Hz, 2H), 1.85 – 1.77 (m, 2H), 1.68 – 1.61 (m, 2H), 1.31 (s, 18H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 177.01, 176.94, 168.86, 160.38, 145.26, 143.89, 140.45, 128.84, 126.80, 125.46, 120.15, 101.94, 69.58, 64.13, 63.80, 58.97, 58.90, 57.20, 50.34, 49.67, 48.38, 47.87, 33.14, 27.83, 23.45, 23.32, 18.91.

HRMS (ESI): $C_{58}H_{69}O_{10}N_8$ $[M+H]^+$; calculated: 1037.51312, found: 1037.51410.

$[\alpha]_{20}^{D}$ = + 69 ° (c = 0.25, MeCN).

101ag, QD-Neopentyl-S

101ag was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 50 % MeCN; RT = 16.3 min) gave title compound **101ag** and its diastereomers (RT = 18.6 min) and zz3 (RT = 22.4 min) in a ratio of 4.75:2:1 and a combined yield of 39 % (14.3 mg, 11.1 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.87 (d, J = 5.0 Hz, 2H), 8.15 (d, J = 9.3 Hz, 2H), 7.92 (d, J = 5.0 Hz, 2H), 7.62 (dd, J = 9.3, 2.5 Hz, 2H), 7.51 (d, J = 2.6 Hz, 2H), 7.30 (s, 2H), 4.08 (d, J = 8.0 Hz, 2H), 4.03 (s, 6H), 3.94 (t, J = 7.8 Hz, 2H), 3.82 (dd, J = 10.5, 8.1 Hz, 2H), 3.67 (dd, J = 11.5, 7.1 Hz, 2H), 3.61 (t, J = 7.3 Hz, 2H), 3.52 (ddd, J = 13.7, 10.8, 1.7 Hz, 2H), 3.41 (ddt, J = 14.0, 11.2, 3.2 Hz, 2H), 3.28 (ddd, J = 13.1, 10.9, 7.3 Hz, 2H), 3.21 (ddd, J = 13.7, 7.1, 2.8 Hz, 2H), 3.07 (s, 4H), 2.74 – 2.67 (m, 4H), 2.31 (td, J = 11.1, 7.2 Hz, 2H), 1.89 (ddt, J = 14.3, 6.4, 3.2 Hz, 2H), 1.82 (dddd, J = 13.3, 11.0, 6.4, 2.4 Hz, 2H), 1.66 (td, J = 12.4, 10.6, 3.8 Hz, 2H), 0.74 (s, 18H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.92, 176.58, 168.59, 160.45, 145.37, 143.89, 140.66, 129.04, 126.82, 125.48, 120.14, 101.72, 69.50, 63.66, 63.39, 59.10, 56.95, 50.57, 50.26, 49.65, 48.42, 47.93, 33.51, 33.48, 27.91, 23.59, 23.45, 18.95.

HRMS (ESI): $C_{60}H_{73}O_{10}N_8$ $[M+H]^+$; calculated: 1065.54496, found: 1037.54508.

$[\alpha]_{20}^{D}$ = + 57 ° (c = 0.5, MeCN).

101ah, QD-(R)-3-Methyl-2-butly-S

101ah was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (10 – 55 % MeCN; RT = 18.1 min) gave title compound **101ah** and its diastereomer (RT = 19.0 min) in a ratio of 2:1 and a combined yield of 41 % (15.2 mg, 11.8 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.96 – 8.87 (m, 2H), 8.19 (dd, J = 9.3, 1.3 Hz, 2H), 8.03 – 7.97 (m, 2H), 7.66 (dd, J = 9.3, 2.5 Hz, 2H), 7.57 (s, 2H), 7.33 (s, 2H), 4.10 (d, J = 8.2 Hz, 2H), 4.05 (s, 6H), 3.90 (t, J = 7.8 Hz, 2H), 3.84 – 3.80 (m, 2H), 3.68 (dd, J = 11.6, 6.9 Hz, 2H), 3.57 (t, J = 7.2 Hz, 2H), 3.55 – 3.50 (m, 2H), 3.48 (dt, J = 10.2, 7.0 Hz, 2H), 3.43 (ddt, J = 14.0, 11.3, 3.1 Hz, 2H), 3.29 (ddd, J = 13.2, 11.0, 7.3 Hz, 2H), 3.23 (ddd, J = 13.7, 7.2, 2.8 Hz, 2H), 2.73 – 2.67 (m, 2H), 2.65 (s, 2H), 2.39 (td, J = 11.1, 7.1 Hz, 2H), 2.00 (dp, J = 10.2, 6.7 Hz, 2H), 1.93 – 1.89 (m, 2H), 1.84 – 1.78 (m, 2H), 1.64 (ddd, J = 14.4, 10.7, 4.0 Hz, 2H), 1.12 (d, J = 7.0 Hz, 6H), 0.79 (d, J = 6.7 Hz, 6H), 0.65 (d, J = 6.7 Hz, 6H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.60, 176.43, 168.61, 160.83, 145.41, 144.34, 139.13, 127.81, 127.14, 126.33, 120.31, 101.84, 69.60, 63.76, 63.48, 58.89, 57.07, 55.31, 49.81, 49.65, 48.47, 47.52, 33.23, 30.45, 23.59, 23.57, 20.12, 19.74, 19.01, 15.62.

HRMS (ESI): $C_{60}H_{73}O_{10}N_8$ $[M+H]^+$; calculated: 1065.54442, found: 1065.54484.

$[\alpha]_{20}^{D}$ = + 59 ° (c = 0.5, MeCN).

101ai, QD-*n*Pr-S

101ai was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (10 – 30 % MeCN; RT = 22.15 min) gave title compound **101ai** and its diastereomer (RT = 25.69 min) in a ratio of 7.25:1 and a combined yield of 41 % (14.4 mg, 11.6 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.89 (d, J = 5.0 Hz, 2H), 8.16 (d, J = 9.2 Hz, 2H), 7.94 (d, J = 5.0 Hz, 2H), 7.62 (dd, J = 9.3, 2.6 Hz, 2H), 7.54 (d, J = 2.6 Hz,

2H), 7.31 (s, 2H), 4.08 (d, J = 8.2 Hz, 2H), 4.04 (s, 6H), 3.92 (t, J = 7.8 Hz, 2H), 3.82 (dd, J = 10.5, 8.0 Hz, 2H), 3.68 (dd, J = 11.6, 6.9 Hz, 2H), 3.58 (t, J = 7.2 Hz, 2H), 3.49 (ddd, J = 13.0, 10.9, 1.7 Hz, 2H), 3.42 (ddt, J = 14.0, 11.2, 3.1 Hz, 2H), 3.29 (ddd, J = 13.4, 11.2, 7.5 Hz, 2H), 3.25 (ddd, J = 13.7, 7.3, 2.9 Hz, 2H), 3.17 (t, J = 7.3 Hz, 4H), 2.71 (ddt, J = 13.2, 7.6, 2.4 Hz, 2H), 2.64 (s, 2H), 2.40 (td, J = 11.0, 6.9 Hz, 2H), 1.93 – 1.90 (m, 2H), 1.86 – 1.77 (m, 2H), 1.66 (ddd, J = 14.4, 10.9, 4.2 Hz, 2H), 1.40 – 1.30 (m, 4H), 0.73 (t, J = 7.5 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.40, 176.25, 168.71, 160.53, 145.22, 144.14, 140.42, 128.85, 126.87, 125.63, 120.21, 101.69, 69.63, 63.60, 63.41, 58.97, 56.98, 50.39, 49.65, 48.35, 48.19, 41.02, 33.12, 23.62, 23.55, 21.23, 18.97, 11.15.

HRMS (ESI): $C_{56}H_{65}O_{10}N_8$ $[M+H]^+$; calculated: 1009.48182, found: 1009.48230.

$[\alpha]_{20}^{D}$ = + 69 ° (c = 0.5, MeCN).

101aj, QD-(R)-1-Cyclopropylethyl-S

101aj was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 50 % MeCN; RT = 15.4 min) gave title compound **101aj** and its diastereomer (RT = 17.7 min) in a ratio of 2.84:1 and a combined yield of 32 % (11.8 mg, 9.15 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.86 (d, J = 4.9 Hz, 2H), 8.13 (d, J = 9.3 Hz, 2H), 7.87 (d, J = 4.9 Hz, 2H), 7.58 (dd, J = 9.3, 2.6 Hz, 2H), 7.48 (s, 2H), 7.27 (s, 2H), 4.08 (d, J = 8.2 Hz, 2H), 4.02 (s, 6H), 3.88 (t, J = 7.9 Hz, 2H), 3.83 – 3.78 (m, 2H), 3.68 (dd, J = 11.6, 6.9 Hz, 2H), 3.55 (t, J = 7.2 Hz, 2H), 3.54 – 3.48 (m, 2H), 3.42 (ddt, J = 14.1, 11.4, 3.2 Hz, 2H), 3.32 – 3.26 (m, 2H), 3.24 (ddd, J = 13.7, 7.0, 2.6 Hz, 2H), 3.01 (dq, J = 10.1, 6.9 Hz, 2H), 2.69 (ddt, J = 13.2, 7.6, 2.4 Hz, 2H), 2.64 (s, 2H), 2.41 (td, J = 11.1, 7.0 Hz, 2H), 1.93 – 1.89 (m, 2H), 1.85 – 1.78 (m, 2H), 1.65 (ddd, J = 13.8, 10.2, 3.7 Hz, 2H), 1.29 – 1.24 (m, 2H), 1.24 (d, J = 7.0 Hz, 6H), 0.44 (tdd, J = 8.5, 5.9, 4.3 Hz, 2H), 0.27 (dddd, J = 8.9, 7.9, 5.7, 4.4 Hz, 2H), 0.12 (ddt, J = 9.2, 5.7, 4.5 Hz, 2H), -0.02 (ddt, J = 9.3, 5.8, 4.5 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.38, 176.09, 168.81, 160.25, 146.02, 142.87, 141.61, 129.81, 126.60, 124.97, 120.03, 101.55, 69.71, 63.74, 63.50, 59.02, 56.89, 54.54, 50.24, 49.72, 48.48, 47.95, 33.19, 23.57, 19.02, 17.50, 14.52, 4.82, 3.86.

HRMS (ESI): $C_{60}H_{69}O_{10}N_8$ $[M+H]^+$; calculated: 1061.51312, found: 1061.51408.

$[\alpha]_{20}^{D}$ = + 25 ° (c = 1, MeCN).

101ak, QD-Cyclohexyl-S

101ak was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 45 % MeCN; RT = 20.4 min) gave title compound **101ak** and its diastereomer (RT = 23.5 min) in a ratio of 8.69:1 and a combined yield of 33 % (12.3 mg, 9.34 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) 8.87 (d, J = 4.8 Hz, 2H), 8.14 (d, J = 9.0 Hz, 2H), 7.83 (d, J = 4.8 Hz, 2H), 7.59 – 7.53 (m, 4H), 7.34 (s, 2H), 4.04 (d, J = 8.1 Hz, 2H), 4.04 (s, 6H), 3.82 – 3.77 (m, 4H), 3.69 – 3.63 (m, 4H), 3.52 – 3.46 (m, 4H), 3.40 (ddt, J = 14.1, 11.4, 3.2 Hz, 2H), 3.30 – 3.21 (m, 4H), 2.68 (ddt, J = 13.2, 7.6, 2.5 Hz, 2H), 2.63 (s, 2H), 2.40 (td, J = 11.2, 7.2 Hz, 2H), 1.93 – 1.88 (m, 2H), 1.82 (ddtd, J = 29.3, 21.1, 12.6, 3.6 Hz, 6H), 1.67 (d, J = 13.6 Hz, 4H), 1.62 (ddd, J = 14.4, 10.7, 3.9 Hz, 2H), 1.54 – 1.42 (m, 6H), 1.16 (dddd, J = 16.7, 13.2, 9.7, 3.4 Hz, 4H), 1.00 (qt, J = 13.1, 3.6 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.35, 176.20, 168.95, 160.39, 146.45, 142.64, 142.52, 130.52, 126.79, 124.90, 120.07, 101.71, 69.88, 63.99, 63.80, 59.17, 57.10, 52.62, 50.42, 49.74, 48.52, 48.13, 33.36, 29.45, 29.10, 26.18, 26.17, 25.60, 23.89, 23.86, 19.24.

HRMS (ESI): $C_{62}H_{73}O_{10}N_8$ $[M+H]^+$; calculated: 1089.54442, found: 1089.54482.

$[\alpha]_{20}^{D}$ = + 63 ° (c = 0.5, MeCN).

101al, QD-Cyclohexanemethyl-S

101al was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (20 – 50 % MeCN; RT = 18.1 min) gave title compound **101al** and its diastereomer (RT = 21.1 min) in a ratio of 4.64:1 and a combined yield of 19 % (7.1 mg, 5.28 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not) δ 8.87 (d, J = 5.0 Hz, 2H), 8.15 (d, J = 9.3 Hz, 2H), 7.93 (d, J = 5.0 Hz, 2H), 7.63 (dd, J = 9.3, 2.6 Hz, 2H), 7.57 (d, J = 2.6 Hz, 2H), 7.34 (s, 2H), 4.08 (d, J = 8.1 Hz, 2H), 4.06 (s, 6H), 3.93 (t, J = 7.8 Hz, 2H), 3.81 (dd, J = 10.5, 8.0 Hz, 2H), 3.67 (dd, J = 11.9, 6.7 Hz, 2H), 3.60 (t, J = 7.2 Hz, 2H), 3.47 (ddd, J = 13.0, 10.8, 1.7 Hz, 2H), 3.41 (ddt, J = 13.9, 11.2, 3.1 Hz, 2H), 3.31 – 3.26 (m, 2H), 3.26 – 3.22 (m, 2H), 3.04 (ddd, J = 27.7, 13.5, 7.3 Hz, 4H), 2.76 – 2.68 (m, 2H), 2.66 (s, 2H), 2.37 (q, J = 10.8 Hz, 2H), 1.93 – 1.88

(m, 2H), 1.85 – 1.79 (m, 2H), 1.70 – 1.63 (m, 2H), 1.61 – 1.51 (m, 6H), 1.48 (d, J = 13.0 Hz, 4H), 1.39 (dqd, J = 11.0, 7.4, 3.6 Hz, 2H), 1.11 – 1.02 (m, 6H), 0.80 – 0.69 (m, 4H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.58, 176.33, 168.64, 160.45, 145.41, 143.83, 140.69, 129.06, 126.81, 125.47, 120.22, 101.91, 69.60, 63.62, 63.40, 59.01, 57.24, 50.23, 49.67, 48.41, 48.05, 45.66, 36.43, 33.15, 30.93, 30.84, 26.38, 25.93, 25.88, 23.54, 23.51, 18.98..

HRMS (ESI): $C_{64}H_{77}O_{10}N_8$ $[M+H]^+$; calculated: 1117.57572, found: 1117.57727.

$[\alpha]_{20}^{D}$ = + 64 ° (c = 0.3, MeCN).

101am, QD-cis-Myrtanyl-S

101am was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 60 % MeCN; RT = 21.0 min) gave title compound **101am** and its diastereomer (RT = 23.7 min) in a ratio of 1.59:1 and a combined yield of 29 % (11.8 mg, 8.28 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.88 (d, J = 5.0 Hz, 2H), 8.16 (d, J = 9.3 Hz, 2H), 7.92 (d, J = 4.9 Hz, 2H), 7.63 (dd, J = 9.3, 2.4 Hz, 2H), 7.54 (d, J = 2.5 Hz, 2H), 7.30 (s, 2H), 4.05 (d, J = 10.5 Hz, 8H), 3.91 (t, J = 7.8 Hz, 2H), 3.86 – 3.81 (m, 2H), 3.66 (dd, J = 11.5, 7.1 Hz, 2H), 3.58 (t, J = 7.3 Hz, 2H), 3.52 (t, J = 12.3 Hz, 2H), 3.43 (ddt, J = 14.0, 11.1, 3.2 Hz, 2H), 3.28 (ddd, J = 13.3, 10.9, 7.2 Hz, 2H), 3.26 – 3.20 (m, 6H), 2.74 – 2.68 (m, 2H), 2.67 (s, 2H), 2.33 (td, J = 11.1, 7.3 Hz, 2H), 2.29 – 2.23 (m, 2H), 2.10 (qd, J = 9.5, 4.7 Hz, 2H), 1.92 – 1.87 (m, 2H), 1.87 – 1.77 (m, 6H), 1.77 – 1.64 (m, 8H), 1.35 – 1.27 (m, 2H), 1.07 (s, 6H), 0.91 (s, 6H), 0.74 (d, J = 9.6 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.56, 176.25, 168.59, 160.53, 145.23, 144.13, 140.49, 128.88, 126.92, 125.63, 120.28, 101.79, 69.55, 63.60, 63.35, 59.07, 57.00, 50.35, 49.65, 48.34, 48.06, 44.86, 43.95, 41.57, 39.50, 38.86, 33.43, 33.01, 27.65, 26.09, 23.70, 23.51, 22.74, 19.23, 18.99.

HRMS (ESI): $C_{70}H_{85}O_{10}N_8$ $[M+H]^+$; calculated: 1197.63832, found: 1197.63885.

$[\alpha]_{20}^{D}$ = + 61 ° (c = 0.5, MeCN).

101an, QD-(R)-1-Cyclohexylethyl-S

101an was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 60 % MeCN; RT = 18.9 min) gave title compound **101an** and its diastereomer (RT = 21.6 min) in a ratio of 2.06:1 and a combined yield of 35 % (13.9 mg, 10.1 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.89 (d, J = 5.0 Hz, 2H), 8.17 (d, J = 9.3 Hz, 2H), 7.94 (d, J = 5.1 Hz, 2H), 7.64 (dd, J = 9.3, 2.5 Hz, 2H), 7.52 (d, J = 2.6 Hz, 2H), 7.28 (s, 2H), 4.08 (d, J = 8.2 Hz, 2H), 4.04 (s, 6H), 3.87 (t, J = 7.9 Hz, 2H), 3.82 (dd, J = 10.4, 8.3 Hz, 2H), 3.66 (dd, J = 11.6, 6.8 Hz, 2H), 3.59 – 3.54 (m, 4H), 3.51 (ddd, J = 12.8, 10.8, 1.7 Hz, 2H), 3.42 (ddt, J = 14.0, 11.3, 3.1 Hz, 2H), 3.29 (ddd, J = 13.2, 11.0, 7.3 Hz, 2H), 3.22 (ddd, J = 13.7, 7.2, 2.8 Hz, 2H), 2.69 (ddt, J = 13.2, 7.6, 2.3 Hz, 2H), 2.64 (s, 2H), 2.39 (td, J = 11.2, 7.2 Hz, 2H), 1.93 – 1.88 (m, 2H), 1.85 – 1.78 (m, 2H), 1.69 – 1.50 (m, 12H), 1.45 – 1.38 (m, 2H), 1.15 – 1.09 (m, 2H), 1.09 (d, J = 7.0 Hz, 6H), 1.08 – 0.97 (m, 4H), 0.74 (qd, J = 12.5, 3.1 Hz, 2H), 0.60 (qd, J = 12.3, 3.6 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.41, 176.24, 168.54, 160.43, 144.98, 144.09, 140.10, 128.59, 126.76, 125.60, 120.06, 101.62, 69.52, 63.66, 63.39, 58.85, 56.86, 53.85, 49.74, 49.60, 48.38, 47.53, 39.21, 33.02, 30.29, 30.18, 26.18, 25.88, 23.43, 18.87, 15.17.

HRMS (ESI): $C_{66}H_{81}O_{10}N_8$ $[M+H]^+$; calculated: 1145.60702, found: 1145.60766.

$[\alpha]_{20}^{D}$ = + 55 ° (c = 0.5, MeCN).

102c, QD-Triacetyl-TRIS-A

102c was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (10 – 60 % MeCN 30 mL/min; RT = 15.2 min) gave title compound **102c** and its diastereomer (RT = 14.3 min) in a ratio of 2.2:1 (**7c**:symmetrical diastereomer) and a combined yield of 27 % (12.7 mg, 13.6 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.81 (d, J = 4.8 Hz, 2H), 8.11 (dd, J = 9.2, 6.8 Hz, 2H), 7.68 (dd, J = 4.7, 0.8 Hz, 1H), 7.59 (d, J = 4.8 Hz, 1H), 7.57 (ddd, J = 9.2, 2.6, 1.6 Hz, 2H), 7.47 (dd, J = 4.8, 2.6 Hz, 2H), 7.30 (s, 1H), 7.12 (s, 1H), 4.83 (d, J = 11.8 Hz, 3H), 4.65 (d, J = 11.8 Hz, 3H), 4.49 (d, J = 11.6 Hz, 3H), 4.42 (d, J = 11.6 Hz, 3H), 4.24 (d, J = 8.5 Hz, 1H), 4.05 (d, J = 8.3 Hz, 1H), 4.02 (s, 6H), 3.83 (td, J = 9.3, 6.0 Hz, 2H), 3.72 (dd, J = 10.9, 7.2 Hz, 1H), 3.70 – 3.67 (m, 2H), 3.66 (dd, J = 9.7, 7.4 Hz, 1H), 3.61 (ddd, J = 13.8, 7.5, 2.7 Hz,

1H), 3.56 – 3.51 (m, 3H), 3.49 – 3.41 (m, 3H), 3.32 (ddd, J = 13.2, 10.9, 7.5 Hz, 1H), 3.29 – 3.24 (m, 2H), 2.65 (s, 2H), 2.56 – 2.47 (m, 2H), 2.44 (td, J = 11.1, 7.5 Hz, 1H), 2.26 (td, J = 10.7, 6.9 Hz, 1H), 2.09 (s, 9H), 1.91 (t, J = 5.4 Hz, 2H), 1.90 (s, 9H), 1.86 – 1.79 (m, 2H), 1.63 (ddd, J = 14.2, 10.0, 3.8 Hz, 1H), 1.57 (ddd, J = 14.3, 10.6, 4.1 Hz, 1H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 178.57, 177.69, 177.19, 176.82, 171.77, 171.55, 169.19, 169.14, 160.09, 160.06, 146.49, 146.40, 142.57, 142.39, 142.34, 141.70, 130.48, 130.39, 126.51, 126.41, 124.71, 124.64, 119.36, 118.65, 101.56, 72.02, 70.46, 65.09, 64.88, 64.83, 64.42, 63.92, 63.48, 61.03, 60.53, 58.57, 58.29, 56.82, 56.79, 52.38, 52.27, 50.17, 49.76, 49.01, 48.34, 48.03, 38.34, 33.61, 23.63, 23.42, 23.27, 20.93, 20.51, 19.44, 19.22.

$[\alpha]_{20}^{D}$ = + 24 ° (c = 0.5, MeCN).

101ao, QD-(4-ethyl)phenyl-S

101ao was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 50 % MeCN; RT = 18.2 min) gave title compound **101ao** and its diastereomer (RT = 22.0 min) in a ratio of 6.8:1 and a combined yield of 40 % (15.6 mg, 11.5 µmol).

^{1}H NMR (600 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.89 (d, J = 5.2 Hz, 2H), 8.14 (d, J = 9.3 Hz, 2H), 8.02 (d, J = 5.2 Hz, 2H), 7.62 (dd, J = 9.3, 2.5 Hz, 2H), 7.58 (d, J = 2.6 Hz, 2H), 7.35 (s, 2H), 7.20 (d, J = 8.4 Hz, 4H), 7.02 – 6.96 (m, 4H), 4.25 (d, J = 8.3 Hz, 2H), 4.09 (t, J = 7.9 Hz, 2H), 4.04 (s, 6H), 3.84 (ddd, J = 10.2, 7.0, 3.3 Hz, 4H), 3.80 – 3.76 (m, 2H), 3.52 (t, J = 11.9 Hz, 2H), 3.42 (tt, J = 11.0, 3.1 Hz, 2H), 3.37 (ddd, J = 13.8, 7.1, 2.8 Hz, 2H), 3.29 (ddd, J = 12.9, 10.9, 7.2 Hz, 2H), 2.82 – 2.75 (m, 2H), 2.64 (s, 2H), 2.57 (q, J = 7.6 Hz, 4H), 2.52 (dd, J = 11.3, 7.5 Hz, 2H), 1.93 – 1.89 (m, 2H), 1.84 – 1.78 (m, 2H), 1.69 (ddd, J = 14.2, 10.6, 3.8 Hz, 2H), 1.11 (t, J = 7.6 Hz, 6H).

^{13}C NMR (151 MHz, CD_3CN:D_2O [10:1]) δ 175.74, 175.60, 168.94, 160.74, 146.01, 145.17, 144.42, 139.22, 130.09, 128.97, 127.90, 127.35, 127.07, 126.16, 120.39, 101.83, 69.86, 63.94, 63.85, 58.83, 57.11, 50.85, 49.63, 48.76, 48.33, 32.95, 28.65, 23.62, 23.59, 19.03, 15.52.

HRMS (ESI): $C_{66}H_{81}O_{10}N_8$ $[M+H]^+$; calculated: 1133.51312, found: 1133.51618.

$[\alpha]_{20}^{D}$ = + 46 ° (c = 1.0, MeCN).

101ap, QD-2,4,6-trichlorophenyl-S; 102d, QD-2,4,6-trichlorophenyl-A;

110, QD-2,4,6-trichlorophenyl-S2

101ap was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (10 – 60 % MeCN) gave title compound in three diastereomeric version **101ap** (RT = 20.0 min), **102d** (RT = 21.2 min) and **110** (RT = 22.9 min) in a ratio of 1 : 3.8 : 2.4 and a combined yield of 40 % (17.2 mg, 11.4 µmol).

101ap, QD-2,4,6-trichlorophenyl-S

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.84 (d, J = 4.9 Hz, 2H), 8.10 (d, J = 9.2 Hz, 2H), 7.91 (dd, J = 5.0, 0.7 Hz, 2H), 7.57 (dd, J = 9.2, 2.6 Hz, 2H), 7.55 (s, 4H), 7.49 (d, J = 2.6 Hz, 2H), 7.30 (s, 2H), 4.33 (t, J = 8.0 Hz, 2H), 4.25 (d, J = 8.1 Hz, 2H), 4.04 – 3.99 (m, 8H), 3.88 (dd, J = 11.7, 7.1 Hz, 2H), 3.85 – 3.79 (m, 2H), 3.61 (ddd, J = 13.8, 10.8, 1.7 Hz, 2H), 3.41 (ddt, J = 14.0, 11.3, 3.2 Hz, 2H), 3.34 – 3.25 (m, 4H), 2.77 (ddt, J = 12.9, 7.5, 2.2 Hz, 2H), 2.67 (s, 2H), 2.39 (td, J = 11.0, 6.8 Hz, 2H), 1.89 (td, J = 12.1, 10.5, 6.9 Hz, 1H), 1.84 – 1.77 (m, 2H), 1.71 (ddd, J = 14.4, 10.6, 3.7 Hz, 3H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 173.94, 173.50, 168.24, 160.40, 145.55, 143.39, 140.95, 137.25, 134.93, 134.88, 129.48, 129.41, 129.30, 127.48, 126.67, 125.30, 120.10, 101.55, 69.83, 64.13, 63.85, 58.94, 56.93, 51.31, 49.64, 49.23, 48.22, 33.59, 23.57, 23.52, 18.99.

HRMS (ESI): $C_{62}H_{55}O_{10}N_8Cl_6$ $[M+H]^+$; calculated: 1281.21668, found: 1281.21704.

$[\alpha]_{20}^{D}$ = + 17 ° (c = 0.25, MeCN).

102d, QD-2,4,6-trichlorophenyl-A

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.86 (dd, J = 5.1, 0.7 Hz, 1H), 8.83 (dd, J = 5.1, 0.8 Hz, 1H), 8.16 (d, J = 9.3 Hz, 1H), 8.13 (d, J = 9.3 Hz, 1H), 7.86 (d, J = 2.2 Hz, 1H), 7.80 (d, J = 5.0 Hz, 1H), 7.75 (dd, J = 4.7, 1.8 Hz, 2H), 7.64 (dd, J = 9.3, 2.6 Hz, 1H), 7.61 (dd, J = 9.2, 2.6 Hz, 1H), 7.58 – 7.54 (m, 4H), 7.40 (s, 1H), 7.20 (s, 1H), 4.30 (d, J = 8.2 Hz, 1H), 4.17 (d, J = 8.5 Hz, 1H), 4.07 (dd, J = 8.5, 7.9 Hz, 1H), 4.06 – 4.01 (m, 7H), 3.98 (dd, J = 7.9, 7.0 Hz, 1H), 3.89 – 3.85 (m, 1H), 3.86 – 3.80 (m, 2H), 3.78 (dd, J = 10.8, 7.6 Hz, 1H), 3.74 (ddd, J = 14.0, 7.3, 2.7 Hz, 1H), 3.66 – 3.58 (m, 3H), 3.56 (ddd, J = 14.2, 5.2, 2.3 Hz, 1H), 3.47 (td, J =

12.1, 10.8, 3.0 Hz, 2H), 3.30 (dddd, J = 13.3, 10.8, 7.7, 6.2 Hz, 2H), 2.72 (s, 1H), 2.66 (s, 1H), 2.60 (ddt, J = 13.3, 8.6, 2.3 Hz, 1H), 2.44 – 2.37 (m, 2H), 2.35 (dt, J = 10.8, 2.5 Hz, 1H), 2.00 – 1.95 (m, 1H), 1.92 – 1.87 (m, 1H), 1.86 – 1.76 (m, 2H), 1.58 (dddd, J = 23.2, 13.8, 10.5, 4.1 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 174.45, 174.04, 173.77, 173.35, 168.81, 168.48, 160.66, 160.59, 144.94, 144.69, 144.67, 144.07, 140.34, 139.93, 137.49, 137.15, 135.79, 135.19, 134.99, 134.95, 130.11, 129.69, 129.46, 129.37, 128.65, 128.35, 127.64, 127.29, 127.00, 126.91, 126.04, 125.91, 119.56, 118.81, 101.76, 101.73, 72.28, 70.47, 65.84, 64.23, 64.22, 64.00, 58.39, 58.11, 56.98, 56.93, 53.50, 52.95, 50.55, 50.22, 49.87, 49.80, 49.21, 48.28, 38.05, 34.17, 23.84, 23.34, 23.23, 23.17, 19.53, 19.27.

HRMS (ESI): $C_{62}H_{55}O_{10}N_8Cl_6$ $[M+H]^+$; calculated: 1281.21668, found: 1281.21666.

$[\alpha]_{20}^{D}$ = + 33 ° (c = 0.5, MeCN).

110, QD-2,4,6-trichlorophenyl-S2

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.81 (d, J = 5.0 Hz, 2H), 8.15 (d, J = 9.2 Hz, 2H), 7.73 (d, J = 2.2 Hz, 2H), 7.69 (d, J = 2.2 Hz, 2H), 7.67 (d, J = 5.1 Hz, 2H), 7.64 (dd, J = 9.2, 2.6 Hz, 2H), 7.57 (d, J = 2.6 Hz, 2H), 7.13 (s, 2H), 4.47 (d, J = 6.9 Hz, 2H), 4.21 (ddd, J = 13.8, 8.4, 2.6 Hz, 2H), 4.17 (dd, J = 9.4, 6.9 Hz, 2H), 4.06 (s, 6H), 3.98 (dd, J = 10.6, 5.6 Hz, 2H), 3.82 (t, J = 9.6 Hz, 2H), 3.67 – 3.60 (m, 4H), 3.55 (tt, J = 10.7, 2.5 Hz, 2H), 3.30 (ddd, J = 12.8, 10.2, 8.4 Hz, 2H), 2.47 (s, 2H), 2.31 (ddt, J = 13.6, 9.8, 1.9 Hz, 2H), 2.22 (q, J = 10.0 Hz, 2H), 1.93 – 1.91 (m, 2H), 1.86 – 1.79 (m, 2H), 1.46 (ddd, J = 14.2, 9.6, 5.4 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) 13C NMR δ 175.22, 174.54, 169.20, 160.53, 144.92, 144.45, 140.23, 137.42, 135.56, 135.07, 129.90, 129.56, 128.51, 127.31, 126.92, 125.86, 118.90, 101.90, 72.52, 64.15, 63.32, 57.75, 56.90, 54.14, 50.10, 50.02, 49.00, 39.32, 24.02, 22.83, 19.63.

HRMS (ESI): $C_{62}H_{55}O_{10}N_8Cl_6$ $[M+H]^+$; calculated: 1281.21668, found: 1281.21716.

$[\alpha]_{20}^{D}$ = + 17 ° (c = 0.5, MeCN).

101aq, QD-Bn-S

6aq was prepared from only 20 mg aldehyde **3** according to General Procedure 6. Preparative HPLC (15 – 40 % MeCN; RT = 20.0 min) gave title compound **6aq** and its diastereomer (RT = 24.0 min) in a ratio of 4 : 1 and a combined yield of 43% (12.5 mg, 9.37 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.91 (d, J = 5.0 Hz, 2H), 8.19 (d, J = 9.2 Hz, 2H), 7.91 (d, J = 4.9 Hz, 2H), 7.63 (s, 2H), 7.59 (d, J = 9.3 Hz, 2H), 7.42 (s, 2H), 7.23 (dt, J = 14.7, 7.2 Hz, 6H), 7.15 (d, J = 7.3 Hz, 4H), 4.48 (d, J = 15.1 Hz, 2H), 4.39 (d, J = 15.0 Hz, 2H), 4.10 (d, J = 8.2 Hz, 2H), 4.06 (s, 6H), 3.96 (t, J = 7.8 Hz, 2H), 3.79 (t, J = 9.3 Hz, 2H), 3.71 (dd, J = 11.6, 7.0 Hz, 2H), 3.62 (t, J = 7.3 Hz, 2H), 3.54 (t, J = 12.4 Hz, 2H), 3.39 (t, J = 12.6 Hz, 2H), 3.28 (ddd, J = 21.2, 13.2, 7.6 Hz, 4H), 2.70 (dd, J = 14.2, 8.0 Hz, 2H), 2.66 (s, 2H), 2.39 (q, J = 10.6 Hz, 2H), 1.91 – 1.86 (m, 2H), 1.80 (q, J = 10.9 Hz, 2H), 1.66 – 1.59 (m, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.53, 176.26, 168.97, 161.00, 145.59, 144.39, 141.33, 136.74, 129.57, 129.47, 128.54, 128.52, 127.31, 125.93, 120.34, 102.06, 70.09, 64.17, 63.93, 59.29, 57.45, 50.99, 49.85, 48.81, 48.68, 43.25, 33.78, 24.16, 24.12, 19.46.

HRMS (ESI): $C_{64}H_{65}O_{10}N_8$ $[M+H]^+$; calculated: 1105.48237, found: 1105.48329.

$[\alpha]_{20}^{D}$ = + 56 ° (c = 0.5, MeCN).

101ar, QD-4-Fluorobenzyl-S

101ar was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 50 % MeCN; RT = 18.2 min) gave title compound **101ar** and its diastereomer (RT = 20.2 min) in a ratio of 2.25:1 and a combined yield of 39 % (15.1 mg, 11.0 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.87 (d, J = 4.9 Hz, 2H), 8.15 (d, J = 9.3 Hz, 2H), 7.89 (d, J = 4.7 Hz, 2H), 7.61 (dt, J = 9.3, 2.3 Hz, 2H), 7.51 (d, J = 2.5 Hz, 2H), 7.28 (s, 2H), 7.19 – 7.14 (m, 4H), 6.99 (td, J = 8.9, 2.1 Hz, 4H), 4.44 (d, J = 15.1 Hz, 2H), 4.36 (d, J = 15.0 Hz, 2H), 4.11 (d, J = 8.1 Hz, 2H), 4.05 (s, 6H), 3.97 (dd, J = 8.8, 6.8 Hz, 2H), 3.83 (t, J = 9.3 Hz, 2H), 3.70 (dd, J = 11.5, 7.0 Hz, 2H), 3.65 (t, J = 7.2 Hz, 2H), 3.51 (t, J = 12.2 Hz, 2H), 3.44 (tt, J = 11.3, 3.0 Hz, 2H), 3.34 – 3.24 (m, 4H), 2.77 – 2.69 (m, 2H), 2.66 (s, 2H), 2.40 (td, J = 11.1, 7.3 Hz, 2H), 1.95 – 1.90 (m, 2H), 1.87 – 1.80 (m, 2H), 1.68 (td, J = 12.6, 10.9, 3.8 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.20, 175.93, 168.71, 163.34, 161.95, 160.31, 145.92, 143.04, 141.47, 132.31, 132.29, 130.42, 130.37, 129.71, 126.65, 125.09, 120.04, 115.78, 115.65, 101.60, 69.75, 63.68, 63.47, 59.06, 56.92, 50.49, 49.71, 48.44, 48.37, 42.19, 33.16, 23.59, 23.53, 18.99.

HRMS (ESI): $C_{64}H_{63}O_{10}N_8F_2$ $[M+H]^+$; calculated: 1141.46297, found: 1141.46387.

$[\alpha]_{20}^{D}$ = +48 (c = 0.3, MeCN).

101as, QD-4-Methylbenzyl-S

101as was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 40 % MeCN; RT = 24.7 min) gave title compound **101as** and its diastereomer (RT = 26.8 min) in a ratio of 2.75:1 and a combined yield of 27 % (10.2 mg, 7.49 µmol).

^{1}H NMR (600 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.88 (d, J = 5.2 Hz, 2H), 8.17 (d, J = 9.3 Hz, 2H), 8.02 (d, J = 5.3 Hz, 2H), 7.69 (dd, J = 9.3, 2.5 Hz, 2H), 7.56 (d, J = 2.6 Hz, 2H), 7.29 (s, 2H), 7.06 – 7.00 (m, 4H), 6.98 (d, J = 8.1 Hz, 4H), 4.37 (d, J = 15.0 Hz, 2H), 4.29 (d, J = 15.0 Hz, 2H), 4.10 (d, J = 8.1 Hz, 2H), 4.05 (s, 6H), 4.00 (t, J = 7.6 Hz, 2H), 3.82 (dd, J = 10.7, 7.8 Hz, 2H), 3.72 – 3.63 (m, 4H), 3.47 (t, J = 12.5 Hz, 2H), 3.45 – 3.38 (m, 2H), 3.28 (ddd, J = 13.1, 10.9, 7.4 Hz, 2H), 3.23 (ddd, J = 13.7, 7.2, 2.7 Hz, 2H), 2.76 – 2.68 (m, 2H), 2.64 (s, 2H), 2.38 (q, J = 10.7 Hz, 2H), 2.21 (s, 6H), 1.93 – 1.89 (m, 2H), 1.85 – 1.78 (m, 2H), 1.72 – 1.64 (m, 2H).

^{13}C NMR (151 MHz, CD_3CN:D_2O [10:1]) δ 176.14, 175.95, 168.44, 160.57, 145.30, 143.96, 138.43, 137.84, 132.72, 129.40, 127.94, 127.26, 126.85, 126.25, 120.21, 101.76, 69.35, 63.34, 63.11, 58.64, 57.04, 50.12, 49.51, 48.13, 47.97, 42.44, 32.71, 23.21, 23.15, 20.38, 18.67.

HRMS (ESI): $C_{66}H_{69}O_{10}N_8$ $[M+H]^+$; calculated: 1133.51367, found: 1133.51295.

$[\alpha]_{20}^{D}$ = + 60 ° (c = 0.2, MeCN).

101at, QD-H-S

101at was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (0 – 30 % MeCN; RT = 16.7 min) gave title compound **101at** and its diastereomer (RT = 18.2 min) in a ratio of 3.25 : 1 and a combined yield of 22 % (7.50 mg, 6.52 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.86 (d, J = 5.0 Hz, 2H), 8.14 (d, J = 9.3 Hz, 2H), 7.88 (d, J = 5.0 Hz, 2H), 7.61 (dd, J = 9.3, 2.6 Hz, 2H), 7.52 (d, J = 2.6 Hz, 2H), 7.28 (s, 2H), 4.05 – 4.01 (m, 8H), 3.90 (t, J = 7.8 Hz, 2H), 3.82 (dd, J = 10.3, 8.1 Hz, 2H), 3.65 (dd, J = 11.6, 7.0 Hz, 2H), 3.59 (t, J = 7.3 Hz, 2H), 3.48 (ddd, J = 12.9, 10.9, 1.8 Hz, 2H), 3.41 (ddt, J = 14.1, 11.5, 3.1 Hz, 2H), 3.33 – 3.24 (m, 4H), 2.73 – 2.68 (m, 2H), 2.59 (s, 2H), 2.44 (td, J = 11.2, 7.1 Hz, 2H), 1.93 – 1.89 (m, 2H), 1.84 – 1.77 (m, 2H), 1.70 – 1.64 (m, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 177.37, 176.94, 168.79, 160.42, 145.44, 143.79, 140.73, 129.09, 126.81, 125.39, 120.27, 101.71, 69.63, 63.55, 63.39, 59.05, 56.96, 51.90, 49.66, 49.58, 48.28, 33.01, 23.62, 23.50, 18.95.

HRMS (ESI): $C_{50}H_{53}O_{10}N_8$ $[M+H]^+$; calculated: 925.38792, found: 925.38784.

$[\alpha]_{20}^{D}$ = + 76 ° (c = 0.3, MeCN).

101au, QD-4-Cyonobenzyl-S

101au was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 60 % MeCN; RT = 14.3 min) gave title compound **101au** and its diastereomer (RT = 15.6 min) in a ratio of 3.5:1 and a combined yield of 32 % (12.7 mg, 9.18 μmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.86 (dd, J = 5.0, 1.1 Hz, 2H), 8.12 (d, J = 9.3 Hz, 2H), 7.94 – 7.87 (m, 2H), 7.61 – 7.57 (m, 6H), 7.51 (s, 2H), 7.30 – 7.26 (m, 6H), 4.51 (d, J = 15.7 Hz, 2H), 4.45 (d, J = 15.7 Hz, 2H), 4.14 (d, J = 8.1 Hz, 2H), 4.03 (s, 6H), 4.00 (t, J = 7.8 Hz, 2H), 3.83 – 3.78 (m, 2H), 3.72 (dd, J = 11.5, 6.9 Hz, 2H), 3.67 (t, J = 7.2 Hz, 2H), 3.51 (ddd, J = 13.2, 10.9, 1.7 Hz, 2H), 3.41 (ddt, J = 14.0, 11.4, 3.2 Hz, 2H), 3.32 – 3.25 (m, 4H), 2.71 (ddt, J = 13.1, 7.6, 2.4 Hz, 2H), 2.63 (s, 2H), 2.38 (td, J = 10.8, 6.9 Hz, 2H), 1.89 (tt, J = 10.6, 3.2 Hz, 2H), 1.80 (tdd, J = 13.4, 8.4, 2.3 Hz, 2H), 1.66 (ddd, J = 14.4, 10.4, 3.8 Hz, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.19, 175.95, 168.69, 160.46, 145.42, 143.77, 141.49, 140.71, 133.00, 129.08, 128.84, 126.77, 125.47, 120.07, 119.16, 111.50, 101.63, 69.79, 63.66, 63.45, 58.95, 56.95, 50.39, 49.64, 48.43, 48.36, 42.50, 33.19, 23.58, 23.54, 19.00.

HRMS (ESI): $C_{66}H_{63}O_{10}N_{10}$ $[M+H]^+$; calculated: 1155.47231, found: 1155.47314.

$[\alpha]_{20}^{D}$ = + 45 ° (c = 0.5, MeCN).

101av, QD-2-Chlorobenzyl-S

101av was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 50 % MeCN and 30 ml/min; RT = 17.5 min) gave title compound **101av** and its diastereomer (RT = 19.8 min) in a ratio of 4.78:1 and a combined yield of 28 % (11.0 mg, 7.84 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.85 (d, J = 4.9 Hz, 2H), 8.11 (d, J = 9.2 Hz, 2H), 7.90 (d, J = 4.9 Hz, 2H), 7.57 (dd, J = 9.2, 2.6 Hz, 2H), 7.49 (d, J = 2.6 Hz, 2H), 7.34 – 7.29 (m, 2H), 7.27 (s, 2H), 7.23 – 7.16 (m, 4H), 7.12 – 7.06 (m, 2H), 4.52 (s, 4H), 4.16 (d, J = 8.1 Hz, 2H), 4.06 (dd, J = 8.1, 7.3 Hz, 2H), 4.02 (s, 6H), 3.81 (dd, J = 10.6, 8.0 Hz, 2H), 3.77 – 3.70 (m, 4H), 3.53 (ddd, J = 13.7, 10.8, 1.7 Hz, 2H), 3.41 (ddt, J = 13.9, 11.2, 3.2 Hz, 2H), 3.33 – 3.25 (m, 4H), 2.74 (ddd, J = 13.1, 7.7, 2.5 Hz, 2H), 2.65 (s, 2H), 2.39 (td, J = 10.9, 7.5 Hz, 2H), 1.92 – 1.86 (m, 2H), 1.80 (dddd, J = 13.5, 10.6, 7.2, 2.4 Hz, 2H), 1.67 (ddd, J = 14.3, 10.5, 3.8 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.14, 175.90, 168.66, 160.39, 145.60, 143.48, 140.99, 132.91, 132.73, 129.92, 129.63, 129.32, 128.67, 127.81, 126.71, 125.29, 120.08, 101.59, 69.77, 63.68, 63.47, 59.00, 56.92, 50.28, 49.63, 48.46, 48.25, 40.62, 33.29, 23.59, 23.55, 19.03.

HRMS (ESI): $C_{64}H_{63}O_{10}N_8Cl_2$ $[M+H]^+$; calculated: 1173.40387, found: 1173.40306.

$[\alpha]_{20}^{D}$ = + 54 ° (c = 0.5, MeCN).

101aw, QD-3-Trifluoromethoxy-4-chlorobenzyl-S

101aw was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (20 – 65 % MeCN; RT = 19.1 min) gave title compound **101aw** and its diastereomer (RT = 18.1 min) in a ratio of 2:1 and a combined yield of 27 % (12.3 mg, 7.82 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.83 (d, J = 4.9 Hz, 2H), 8.11 (d, J = 9.2 Hz, 2H), 7.83 (d, J = 4.7 Hz, 2H), 7.57 (dd, J = 9.2, 2.6 Hz, 2H), 7.45 (d, J = 2.6 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 7.24 – 7.21 (m, 4H), 7.12 (dd, J = 8.3, 2.1 Hz, 2H), 4.45 (d, J = 15.3 Hz, 2H), 4.37 (d, J = 15.3 Hz, 2H), 4.09 (d, J = 8.2 Hz, 2H), 4.02 (s, 6H), 3.96 (t, J = 7.8 Hz, 2H), 3.80 (dd, J = 10.7, 7.8 Hz, 2H), 3.69 (dd, J = 11.5, 6.9 Hz, 2H), 3.65 (t, J = 7.2 Hz, 2H), 3.47 (ddd, J = 13.6, 10.8, 1.7 Hz, 2H), 3.41 (ddt, J = 13.9, 11.1, 3.1 Hz, 2H), 3.30 – 3.24 (m, 4H), 2.73 – 2.68

(m, 2H), 2.63 (s, 2H), 2.36 (td, J = 10.9, 7.4 Hz, 2H), 1.92 – 1.87 (m, 2H), 1.84 – 1.78 (m, 2H), 1.66 (ddd, J = 14.4, 11.6, 3.9 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.05, 175.80, 168.62, 160.09, 146.21, 145.01, 144.99, 142.40, 141.90, 137.20, 131.46, 130.03, 128.50, 126.46, 126.44, 124.70, 123.09, 121.59, 120.12, 119.90, 101.44, 69.78, 63.59, 63.40, 58.98, 56.79, 50.34, 49.63, 48.37, 48.33, 41.80, 33.08, 23.52, 23.45, 18.92.

HRMS (ESI): $C_{66}H_{61}O_{12}N_8Cl_2F_6$ $[M+H]^+$; calculated: 1341.36847, found: 1341.36871.

$[\alpha]_{20}^{D}$ = + 44 ° (c = 0.5, MeCN).

101ax, QD-3-Acetoxybenzyl-S

101ax was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (10 – 55 % MeCN; RT = 17.7 min) gave title compound **101ax** and its diastereomer (RT = 19.1 min) in a ratio of 4.23:1 and a combined yield of 36 % (15.1 mg, 10.4 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.87 (dd, J = 5.0, 1.0 Hz, 2H), 8.14 (d, J = 9.3 Hz, 2H), 7.91 (d, J = 4.9 Hz, 2H), 7.60 (dd, J = 9.3, 2.6 Hz, 2H), 7.51 (d, J = 2.4 Hz, 2H), 7.29 (s, 2H), 7.26 (t, J = 7.9 Hz, 2H), 7.03 (d, J = 8.0 Hz, 2H), 6.93 (dd, J = 8.1, 1.7 Hz, 2H), 6.88 (t, J = 2.1 Hz, 2H), 4.47 (d, J = 15.2 Hz, 2H), 4.37 (d, J = 15.2 Hz, 2H), 4.12 (dd, J = 8.1, 1.1 Hz, 2H), 4.03 (s, 6H), 4.00 (t, J = 7.7 Hz, 2H), 3.83 – 3.78 (m, 2H), 3.71 (dd, J = 11.5, 7.0 Hz, 2H), 3.66 (t, J = 7.2 Hz, 2H), 3.50 (ddd, J = 12.9, 10.8, 1.7 Hz, 2H), 3.41 (ddt, J = 14.1, 11.3, 2.9 Hz, 2H), 3.31 – 3.24 (m, 4H), 2.75 – 2.69 (m, 2H), 2.64 (s, 2H), 2.35 (td, J = 11.2, 7.2 Hz, 2H), 2.19 (s, 6H), 1.92 – 1.87 (m, 2H), 1.83 – 1.77 (m, 2H), 1.66 (ddd, J = 14.2, 10.4, 3.9 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.18, 175.93, 170.78, 168.64, 160.44, 151.45, 145.49, 143.71, 140.82, 137.85, 130.21, 129.18, 126.76, 125.66, 125.40, 121.52, 121.44, 120.08, 101.62, 69.72, 63.65, 63.47, 58.99, 56.95, 50.47, 49.62, 48.39, 48.26, 42.37, 33.21, 23.61, 23.51, 20.84, 18.97.

HRMS (ESI): $C_{68}H_{69}O_{14}N_8$ $[M+H]^+$; calculated: 1221.49278, found: 1221.49242.

$[\alpha]_{20}^{D}$ = + 56 ° (c = 0.5, MeCN).

101ay, QD-Piperonyl-S

101ay was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 40 % MeCN; RT = 20.8 min) gave title compound **101ay** and its diastereomer (RT = 23.7 min) in a ratio of 2.96:1 and a combined yield of 25 % (10.2 mg, 7.18 µmol).

^{1}H NMR (600 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.92 (d, J = 5.2 Hz, 2H), 8.19 (d, J = 9.3 Hz, 2H), 8.11 (d, J = 5.3 Hz, 2H), 7.72 (d, J = 9.3 Hz, 2H), 7.65 (s, 2H), 7.38 (s, 2H), 6.70 – 6.65 (m, 2H), 6.62 – 6.57 (m, 4H), 5.86 (s, 4H), 4.33 (d, J = 15.0 Hz, 2H), 4.24 (d, J = 14.9 Hz, 2H), 4.15 (d, J = 8.3 Hz, 2H), 4.07 (s, 6H), 4.03 (t, J = 7.8 Hz, 2H), 3.83 (t, J = 9.4 Hz, 2H), 3.73 (dd, J = 11.4, 7.0 Hz, 2H), 3.69 – 3.64 (m, 2H), 3.50 – 3.45 (m, 2H), 3.43 – 3.38 (m, 2H), 3.27 (dtd, J = 21.7, 10.5, 4.8 Hz, 4H), 2.78 – 2.70 (m, 2H), 2.64 (s, 2H), 2.38 (q, J = 9.9, 9.1 Hz, 2H), 1.92 (s, 2H), 1.86 – 1.76 (m, 2H), 1.71 – 1.63 (m, 2H).

^{13}C NMR (151 MHz, CD_3CN:D_2O [10:1]) δ 176.22, 176.09, 168.48, 160.95, 147.95, 147.34, 146.62, 143.32, 137.42, 129.70, 127.22, 126.96, 126.45, 121.71, 120.48, 108.53, 108.42, 102.08, 101.77, 69.46, 63.45, 63.22, 58.63, 57.38, 50.12, 49.53, 48.25, 48.00, 42.49, 32.85, 23.34, 23.29, 18.82.

HRMS (ESI): $C_{66}H_{65}O_{14}N_8$ $[M+H]^+$; calculated: 1193.46203, found: 1193.46157.

$[\alpha]_{20}^{D}$ = +59° (c = 0.5, MeCN).

101az, QD-(S)-1-Phenethyl-S

101az was prepared from 25 mg aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 60 % MeCN; RT = 18.5 min) gave title compound **101az** and its diastereomer (RT = 21.0 min) in a ratio of 2.25:1 and a combined yield of 41 % (14.2 mg, 10.4 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.90 (d, J = 5.1 Hz, 2H), 8.17 (d, J = 9.3 Hz, 2H), 7.95 (d, J = 5.1 Hz, 2H), 7.63 (dd, J = 9.2, 2.5 Hz, 2H), 7.55 (d, J = 2.6 Hz, 2H), 7.31 (s, 2H), 7.26 – 7.16 (m, 10H), 5.09 (q, J = 7.2 Hz, 2H), 4.11 (d, J = 8.2 Hz, 2H), 4.05 (s, 6H), 3.95 (t, J = 7.9 Hz, 2H), 3.80 (dd, J = 10.4, 8.2 Hz, 2H), 3.70 (dd, J = 11.6, 6.8 Hz, 2H), 3.55 – 3.50 (m, 4H), 3.41 (ddt, J = 14.1, 11.6, 3.2 Hz, 2H), 3.31 – 3.23 (m, 4H), 2.73 – 2.66 (m, 2H), 2.61 (s, 2H), 2.41 (td, J = 11.2, 7.2 Hz, 2H), 1.92 – 1.87 (m, 2H), 1.82 – 1.76 (m, 2H), 1.63 (ddd, J = 14.3, 10.4, 3.9 Hz, 2H), 1.58 (d, J = 7.2 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.20, 176.09, 168.74, 160.70, 144.92, 144.61, 140.02, 140.00, 128.87, 128.53, 127.98, 127.37, 126.98, 125.94, 120.21, 101.77, 69.71, 63.75, 63.51, 58.95, 57.06, 50.81, 50.15, 49.70, 48.52, 47.90, 33.22, 23.62, 23.54, 19.03, 17.00.

HRMS (ESI): $C_{66}H_{69}O_{10}N_8$ $[M+H]^+$; calculated: 1133.51367, found: 1133.51318.

$[\alpha]_{20}^{D}$ = + 39 ° (c = 0.5, MeCN).

101ba, QD-(R)-1-Phenethyl-S, 102e, QD-(R)-1-Phenethyl-A

101ba and **102e** were prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 40 % MeCN; RT = 23.8 min) gave title compound **101ba** and its diastereomer **102e** (RT = 27.2 min) in a ratio of 2.3 : 1 and a combined yield of 34 % (13.1 mg, 9.62 µmol).

101ba, QD-(R)-1-Phenethyl-S

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.87 (d, J = 4.8 Hz, 2H), 8.15 (d, J = 9.2 Hz, 2H), 7.83 (d, J = 4.9 Hz, 2H), 7.59 (d, J = 2.6 Hz, 2H), 7.56 (dd, J = 9.2, 2.6 Hz, 2H), 7.39 (s, 2H), 7.28 – 7.23 (m, 4H), 7.21 (d, J = 7.7 Hz, 6H), 5.17 (q, J = 7.2 Hz, 2H), 4.10 (d, J = 8.3 Hz, 2H), 4.05 (s, 6H), 3.84 (t, J = 7.9 Hz, 2H), 3.81 – 3.76 (m, 2H), 3.69 (dd, J = 11.6, 6.8 Hz, 2H), 3.58 – 3.55 (m, 2H), 3.55 – 3.50 (m, 2H), 3.38 (ddt, J = 14.0, 11.1, 3.2 Hz, 2H), 3.26 (tdd, J = 13.0, 6.5, 3.7 Hz, 4H), 2.67 (ddd, J = 13.4, 6.5, 2.5 Hz, 2H), 2.63 (s, 2H), 2.34 (td, J = 11.2, 7.3 Hz, 2H), 1.85 (dddd, J = 12.5, 10.0, 6.9, 3.5 Hz, 2H), 1.82 – 1.76 (m, 2H), 1.60 (td, J = 14.0, 12.4, 3.9 Hz, 2H), 1.54 (d, J = 7.2 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.44, 176.25, 169.14, 160.75, 146.21, 143.37, 142.27, 140.75, 130.34, 129.30, 128.31, 127.68, 127.12, 125.41, 120.17, 101.97, 70.25, 64.37, 64.13, 59.29, 57.36, 50.87, 50.67, 49.87, 48.76, 48.54, 33.77, 30.92, 24.15, 19.49, 16.91.

HRMS (ESI): $C_{66}H_{69}O_{10}N_8$ $[M+H]^+$; calculated: 1133.51367, found: 1133.51445.

$[\alpha]_{20}^{D}$ = + 83 ° (c = 0.5, MeCN).

102e, QD-(R)-1-Phenethyl-A

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.83 (dd, J = 9.1, 4.8 Hz, 2H), 8.12 (dd, J = 9.2, 1.9 Hz, 2H), 7.77 (d, J = 4.8 Hz, 1H), 7.61 – 7.57 (m, 2H), 7.57 (dd, J = 2.6, 0.9 Hz, 1H), 7.48 (dd, J = 8.3, 2.6 Hz, 2H), 7.46 – 7.43 (m, 2H), 7.41 – 7.38 (m, 2H), 7.33 – 7.30

(m, 2H), 7.27 – 7.23 (m, 4H), 7.21 (ddd, J = 8.5, 5.4, 2.3 Hz, 1H), 7.12 (s, 1H), 5.39 (q, J = 7.2 Hz, 1H), 5.19 (q, J = 7.2 Hz, 1H), 4.12 (d, J = 8.6 Hz, 1H), 4.09 (d, J = 8.4 Hz, 1H), 4.03 (d, J = 3.8 Hz, 6H), 3.81 (q, J = 10.1 Hz, 2H), 3.72 – 3.68 (m, 2H), 3.66 (dd, J = 10.0, 8.4 Hz, 1H), 3.61 (dd, J = 10.8, 7.2 Hz, 1H), 3.58 (dd, J = 7.6, 6.8 Hz, 1H), 3.56 – 3.54 (m, 1H), 3.54 – 3.47 (m, 2H), 3.47 – 3.40 (m, 3H), 3.30 – 3.23 (m, 2H), 3.19 (dd, J = 10.0, 7.2 Hz, 1H), 2.63 (s, 2H), 2.58 – 2.52 (m, 1H), 2.42 (ddt, J = 13.2, 8.4, 2.2 Hz, 1H), 2.37 (td, J = 11.0, 7.6 Hz, 1H), 2.24 (td, J = 10.8, 7.9 Hz, 1H), 1.93 – 1.89 (m, 2H), 1.88 (d, J = 7.2 Hz, 3H), 1.83 – 1.76 (m, 2H), 1.63 – 1.58 (m, 1H), 1.56 (d, J = 7.2 Hz, 3H), 1.53 (td, J = 10.2, 4.7 Hz, 1H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 177.15, 176.31, 176.22, 176.15, 169.30, 169.27, 160.18, 160.12, 146.30, 146.10, 142.75, 142.20, 141.88, 140.44, 140.31, 130.18, 129.97, 129.07, 128.89, 128.31, 127.96, 127.75, 127.41, 126.59, 126.52, 124.94, 124.80, 119.54, 118.77, 101.60, 101.53, 71.96, 70.28, 64.72, 63.72, 63.58, 63.34, 58.55, 58.26, 56.83, 56.81, 52.69, 52.19, 50.75, 50.64, 50.15, 49.74, 49.57, 49.03, 48.56, 48.04, 38.45, 33.63, 23.78, 23.37, 23.28, 19.41, 19.14, 16.75, 16.41.

HRMS (ESI): $C_{66}H_{69}O_{10}N_8$ $[M+H]^+$; calculated: 1133.51312, found: 1133.51449.

$[\alpha]_{20}^{D}$ = + 48 ° (c = 0.5, MeCN).

101bb, QD-(R)-1-(4-Bromophenyl)ethyl-S

101bb was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (20 – 60 % MeCN; RT = 17.0 min) gave title compound **101bb** and its diastereomer (RT = 16.66 min) in a ratio of 3:1 and a combined yield of 23 % (10.1 mg, 6.65 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.84 (d, J = 4.9 Hz, 2H), 8.13 (d, J = 9.4 Hz, 2H), 7.85 (d, J = 4.5 Hz, 2H), 7.59 (dd, J = 9.3, 2.6 Hz, 2H), 7.49 (s, 2H), 7.42 – 7.38 (m, 4H), 7.26 (s, 2H), 7.14 – 7.10 (m, 4H), 5.09 (q, J = 7.2 Hz, 2H), 4.10 (d, J = 8.3 Hz, 2H), 4.03 (s, 6H), 3.85 (t, J = 7.9 Hz, 2H), 3.81 (dd, J = 10.6, 7.9 Hz, 2H), 3.68 (dd, J = 11.6, 6.8 Hz, 2H), 3.59 – 3.56 (m, 2H), 3.49 (ddd, J = 12.7, 10.7, 1.7 Hz, 2H), 3.41 (ddt, J = 14.0, 11.1, 3.2 Hz, 2H), 3.30 – 3.22 (m, 4H), 2.70 – 2.64 (m, 2H), 2.60 (s, 2H), 2.33 (td, J = 11.1, 7.1 Hz, 2H), 1.89 – 1.84 (m, 2H), 1.80 (dddd, J = 13.3, 10.4, 7.4, 2.3 Hz, 2H), 1.63 (ddd, J = 14.3, 10.3, 3.8 Hz, 2H), 1.50 (d, J = 7.2 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.06, 175.92, 168.85, 160.32, 145.74, 143.17, 141.25, 139.48, 131.84, 129.51, 129.48, 126.68, 125.17, 121.31, 119.97, 101.64, 69.89, 63.83, 63.60, 58.97, 56.90, 50.09, 49.97, 49.71, 48.54, 48.03, 33.11, 23.55, 19.04, 16.23.

HRMS (ESI): $C_{66}H_{67}O_{10}N_8Br_2$ $[M+H]^+$; calculated: 1289.33414, found: 1289.33519.

$[\alpha]_{20}^{D}$ = + 75 ° (c = 0.25, MeCN).

101bc, QD-1-Methyl-1-phenylethyl-S

101bc was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 50 % MeCN; RT = 19.3 min) gave title compound **101bc** and its diastereomer (RT = 21.9 min) in a ratio of 2.39:1 and a combined yield of 30 % (11.9 mg, 8.56 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.86 (d, J = 5.1 Hz, 2H), 8.15 (d, J = 9.2 Hz, 2H), 7.94 (dd, J = 5.2, 1.7 Hz, 2H), 7.64 (dd, J = 9.2, 2.6 Hz, 2H), 7.55 (s, 2H), 7.33 (s, 2H), 7.24 – 7.17 (m, 8H), 7.14 – 7.10 (m, 2H), 4.12 (d, J = 8.0 Hz, 2H), 4.04 (s, 6H), 3.82 (t, J = 7.9 Hz, 2H), 3.81 – 3.78 (m, 2H), 3.68 (dd, J = 11.6, 6.9 Hz, 2H), 3.54 (ddd, J = 13.7, 10.8, 1.7 Hz, 2H), 3.47 – 3.44 (m, 2H), 3.42 – 3.36 (m, 2H), 3.25 (ddd, J = 13.8, 6.9, 2.9 Hz, 4H), 2.67 – 2.61 (m, 2H), 2.53 (s, 2H), 2.23 (tt, J = 11.1, 4.3 Hz, 2H), 1.76 – 1.70 (m, 4H), 1.65 (s, 6H), 1.60 (s, 8H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.69, 168.93, 160.68, 146.69, 145.04, 144.51, 139.40, 128.73, 127.99, 127.07, 127.02, 126.11, 125.00, 120.14, 101.84, 69.60, 64.10, 63.77, 63.09, 58.88, 57.01, 50.41, 49.64, 48.38, 47.62, 33.34, 28.87, 27.74, 23.49, 23.30, 18.90.

HRMS (ESI): $C_{68}H_{73}O_{10}N_8$ $[M+H]^+$; calculated: 1161.54442, found: 1161.54619.

$[\alpha]_{20}^{D}$ = + 73 ° (c = 0.5, MeCN).

101bd, QD-1-Phenylcyclopropyl-S; 102f, QD-1-Phenylcyclopropyl-A

101bd was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 50 % MeCN; RT = 18.3 min) gave title compound **101bd** and its diastereomer **102f** (RT = 20.6 min) in a ratio of 2.17:1 and a combined yield of 32 % (12.8 mg, 9.10 µmol).

6bd, QD-1-Phenylcyclopropyl-S

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.90 (dd, J = 5.1, 1.7 Hz, 2H), 8.17 (dd, J = 9.3, 1.0 Hz, 2H), 7.98 – 7.93 (m, 2H), 7.64 (dd, J = 9.3, 2.5 Hz, 2H), 7.55 (s, 2H), 7.31 (s, 2H), 7.26 – 7.20 (m, 4H), 7.20 – 7.15 (m, 2H), 7.09 – 7.05 (m, 4H), 4.17 (d, J = 8.2 Hz, 2H), 4.06 (s, 6H), 3.94 (td, J = 8.0, 1.3 Hz, 2H), 3.87 – 3.82 (m, 2H), 3.76 (dd, J = 11.6, 6.8 Hz, 2H), 3.64 (t, J = 7.2 Hz, 2H), 3.55 (dd, J = 13.4, 11.1 Hz, 2H), 3.45 (ddt, J = 14.0, 11.4, 3.0 Hz, 2H), 3.35 – 3.28 (m, 4H), 2.73 (ddd, J = 13.3, 6.4, 2.5 Hz, 2H), 2.67 (s, 2H), 2.43 (td, J = 11.1, 7.1 Hz, 2H), 1.95 (d, J = 3.2 Hz, 2H), 1.86 – 1.80 (m, 2H), 1.67 (td, J = 12.3, 10.4, 3.9 Hz, 2H), 1.36 – 1.31 (m, 2H), 1.28 – 1.24 (m, 2H), 1.24 – 1.20 (m, 2H), 1.12 – 1.07 (m, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.44, 176.28, 168.81, 160.53, 145.07, 144.17, 140.19, 128.92, 128.69, 127.38, 126.84, 125.89, 125.69, 120.07, 101.68, 69.85, 63.83, 63.59, 58.87, 56.95, 49.79, 49.67, 48.50, 47.84, 34.92, 33.17, 23.54, 23.53, 19.02, 16.70, 16.25.

HRMS (ESI): $C_{68}H_{69}O_{10}N_8$ $[M+H]^+$; calculated: 1157.51312, found: 1157.51446.

$[\alpha]_{20}^{D}$ = + 44 ° (c = 0.5, MeCN).

102f, QD-1-Phenylcyclopropyl-A

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.83 (dd, J = 13.4, 4.8 Hz, 2H), 8.11 (d, J = 9.2 Hz, 2H), 7.73 (d, J = 4.8 Hz, 1H), 7.65 (d, J = 4.8 Hz, 1H), 7.58 (ddd, J = 9.3, 4.1, 2.6 Hz, 2H), 7.47 (dd, J = 4.1, 2.6 Hz, 2H), 7.39 (t, J = 7.8 Hz, 2H), 7.33 – 7.30 (m, 1H), 7.30 – 7.27 (m, 3H), 7.23 – 7.20 (m, 2H), 7.18 – 7.14 (m, 1H), 7.12 – 7.09 (m, 3H), 4.16 (d, J = 8.8 Hz, 1H), 4.14 (d, J = 8.4 Hz, 1H), 4.03 (d, J = 1.4 Hz, 6H), 3.82 (q, J = 8.7 Hz, 2H), 3.75 (dd, J = 11.5, 6.8 Hz, 1H), 3.69 (ddd, J = 10.2, 8.1, 5.3 Hz, 2H), 3.62 (dd, J = 10.8, 7.4 Hz, 1H), 3.60 – 3.56 (m, 2H), 3.56 – 3.48 (m, 2H), 3.45 (ddt, J = 16.7, 9.8, 4.2 Hz, 3H), 3.32 – 3.27 (m, 2H), 3.25 (dd, J = 10.2, 7.4 Hz, 1H), 2.70 (s, 1H), 2.63 (s, 1H), 2.61 – 2.56 (m, 1H), 2.43 (q, J = 10.7 Hz, 1H), 2.40 – 2.35 (m, 1H), 2.27 (q, J = 10.3 Hz, 1H), 1.92 (d, J = 3.3 Hz, 2H), 1.81 (ddt, J = 10.7, 8.3, 2.8 Hz, 2H), 1.61 – 1.56 (m, 1H), 1.56 – 1.51 (m, 2H), 1.51 – 1.45 (m, 3H), 1.35 – 1.24 (m, 4H), 1.22 – 1.15 (m, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 177.33, 176.40, 169.49, 169.34, 160.16, 160.12, 146.30, 146.13, 142.81, 142.18, 142.01, 140.78, 140.37, 130.19, 130.08, 129.24, 128.93, 127.84, 127.46, 126.59, 126.47, 126.25, 124.90, 124.80, 119.45, 118.75, 101.59, 70.38, 64.69,

63.77, 63.62, 63.29, 58.51, 58.25, 56.81, 52.54, 51.79, 50.24, 49.87, 49.38, 49.11, 48.11, 38.60, 35.03, 34.99, 33.66, 23.84, 23.31, 23.24, 19.50, 19.19, 16.54, 16.05, 15.91.

HRMS (ESI): $C_{68}H_{69}O_{10}N_8$ $[M+H]^+$; calculated: 1157.51312, found: 1157.51439.

$[\alpha]_{20}^{D}$ = + 31 ° (c = 0.3, MeCN).

101be, QD-1-Methyl-1-(2-fluorophenyl)ethyl-S;

102g, QD-1-Methyl-1-(2-fluorophenyl)ethyl-A

101be and **102g** was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 50 % MeCN; RT = 18.9 min) gave title compound **101be** and its diastereomer **102g** (RT = 21.2 min) in a ratio of 1:1 and a combined yield of 33 % (13.6 mg, 9.54 µmol).

6be, QD-1-Methyl-1-(2-fluorophenyl)ethyl-S

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.85 (d, J = 5.1 Hz, 2H), 8.15 (d, J = 9.3 Hz, 2H), 7.92 (d, J = 5.1 Hz, 2H), 7.63 (dd, J = 9.3, 2.6 Hz, 2H), 7.53 (d, J = 2.6 Hz, 2H), 7.32 (s, 2H), 7.25 – 7.17 (m, 4H), 7.05 (td, J = 7.6, 1.3 Hz, 2H), 7.01 (ddd, J = 12.8, 8.2, 1.3 Hz, 2H), 4.07 (d, J = 7.9 Hz, 2H), 4.04 (s, 6H), 3.81 (t, J = 7.8 Hz, 2H), 3.81 – 3.77 (m, 2H), 3.64 (dd, J = 11.7, 7.1 Hz, 2H), 3.53 (ddd, J = 13.8, 10.8, 1.7 Hz, 2H), 3.45 (t, J = 7.4 Hz, 2H), 3.38 (ddt, J = 14.0, 11.2, 3.2 Hz, 2H), 3.28 – 3.19 (m, 4H), 2.62 (ddt, J = 13.2, 8.1, 2.5 Hz, 2H), 2.52 (s, 2H), 2.16 (td, J = 11.2, 7.2 Hz, 2H), 1.77 – 1.69 (m, 2H), 1.68 (s, 6H), 1.68 – 1.62 (m, 2H), 1.63 (s, 6H), 1.63 – 1.56 (m, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.13, 176.09, 168.80, 160.85, 160.57, 159.46, 144.80, 144.57, 139.87, 132.99, 132.93, 129.51, 129.45, 128.35, 127.32, 127.30, 126.94, 125.88, 124.82, 124.80, 120.14, 116.38, 116.36, 101.83, 69.43, 64.15, 63.81, 60.59, 58.96, 56.98, 50.72, 49.63, 48.20, 47.71, 33.38, 27.07, 26.54, 23.49, 23.24, 18.81.

HRMS (ESI): $C_{68}H_{71}O_{10}N_8F_2$ $[M+H]^+$; calculated: 1197.52557, found: 1197.52647.

$[\alpha]_{20}^{D}$ = + 70 ° (c = 1, MeCN).

102g, QD-1-Methyl-1-(2-fluorophenyl)ethyl-A

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.84 (d, J = 4.9 Hz, 1H), 8.69 (d, J = 4.9 Hz, 1H), 8.11 (dd, J = 12.4, 9.2 Hz, 2H), 7.68 (d, J = 4.8 Hz, 1H), 7.58 (ddd, J = 9.2, 4.9, 2.6 Hz, 2H), 7.51 (ddd, J = 9.1, 8.0, 1.7 Hz, 1H), 7.49 (d, J = 2.6 Hz, 1H), 7.46 (d, J = 2.6 Hz, 1H), 7.45 (d, J = 4.9 Hz, 1H), 7.45 – 7.40 (m, 1H), 7.33 (s, 1H), 7.30 (td, J = 7.7, 1.2 Hz, 1H), 7.27 (td, J = 8.2, 1.7 Hz, 1H), 7.20 (dddd, J = 15.6, 13.0, 7.6, 1.5 Hz, 2H), 7.09 (s, 1H), 7.07 (td, J = 7.6, 1.3 Hz, 1H), 7.01 (ddd, J = 12.8, 8.2, 1.3 Hz, 1H), 4.13 (d, J = 8.4 Hz, 1H), 4.03 (s, 3H), 4.02 (s, 3H), 4.00 (d, J = 8.2 Hz, 1H), 3.78 (dt, J = 16.3, 8.8 Hz, 3H), 3.73 (dd, J = 11.5, 6.9 Hz, 1H), 3.63 – 3.50 (m, 6H), 3.40 (dddd, J = 21.3, 14.0, 8.8, 2.9 Hz, 3H), 3.26 (ddd, J = 13.1, 10.6, 7.7 Hz, 2H), 3.14 (dd, J = 10.1, 7.2 Hz, 1H), 2.56 (q, J = 4.4, 3.3 Hz, 2H), 2.54 – 2.49 (m, 1H), 2.32 – 2.21 (m, 3H), 1.97 (s, 3H), 1.95 (s, 3H), 1.92 – 1.86 (m, 1H), 1.81 – 1.75 (m, 1H), 1.75 (s, 3H), 1.72 (dt, J = 10.9, 2.6 Hz, 2H), 1.68 (s, 3H), 1.57 – 1.51 (m, 1H), 1.43 (ddd, J = 14.1, 10.9, 3.9 Hz, 1H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 177.25, 176.49, 176.12, 169.27, 169.15, 161.23, 160.95, 160.22, 160.21, 159.85, 159.56, 145.89, 145.86, 143.08, 142.34, 141.79, 141.64, 133.70, 133.64, 133.10, 133.05, 129.86, 129.76, 129.72, 129.50, 129.45, 127.76, 127.40, 126.64, 126.54, 125.42, 125.05, 124.83, 119.36, 118.83, 116.54, 116.50, 116.41, 116.37, 101.67, 101.57, 71.87, 70.24, 65.42, 64.26, 64.00, 63.94, 60.69, 60.44, 58.62, 58.16, 56.85, 56.83, 52.31, 52.18, 50.22, 50.09, 49.78, 48.97, 48.24, 48.17, 38.19, 33.86, 27.15, 27.02, 26.70, 23.50, 23.37, 23.23, 23.16, 19.35, 19.07.

HRMS (ESI): $C_{68}H_{71}O_{10}N_8F_2$ $[M+H]^+$; calculated: 1197.52557, found: 1197.52659.

$[\alpha]_{20}^{D}$ = + 37 ° (c = 0.5, MeCN).

101bf, QD-(2-Chlorophenyl)cyclopropyl-S; 7h, QD-(2-Chlorophenyl)cyclopropyl-A

101bf and **7h** were prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 50 % MeCN; RT = 19.7 min) gave title compound **101bf** and its diastereomer **102h** (RT = 21.9 min) in a ratio of 1:2.1 and a combined yield of 38 % (15.7 mg, 10.8 µmol).

101bf, QD-(2-Chlorophenyl)cyclopropyl-S

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.89 (d, J = 5.2 Hz, 2H), 8.22 (d, J = 9.3 Hz, 2H), 7.96 (d, J = 5.2 Hz, 2H), 7.71 (dd, J = 9.3, 2.5 Hz, 2H), 7.56 (d, J = 2.6 Hz,

2H), 7.52 (dd, J = 7.9, 1.7 Hz, 2H), 7.27 (s, 2H), 7.25 (d, J = 8.0 Hz, 2H), 7.16 (td, J = 7.6, 1.7 Hz, 2H), 7.07 (td, J = 7.7, 1.2 Hz, 2H), 4.06 (s, 6H), 4.00 (d, J = 8.3 Hz, 2H), 3.82 (dd, J = 10.6, 8.0 Hz, 2H), 3.74 (t, J = 7.9 Hz, 2H), 3.59 (dd, J = 11.7, 6.9 Hz, 2H), 3.48 – 3.40 (m, 8H), 3.17 (ddd, J = 13.7, 7.2, 2.9 Hz, 2H), 2.63 (ddd, J = 13.4, 7.7, 2.6 Hz, 2H), 2.59 (s, 2H), 2.37 (td, J = 11.2, 7.2 Hz, 2H), 1.93 (s, 2H), 1.82 (dddd, J = 13.5, 10.4, 7.4, 2.3 Hz, 2H), 1.64 (ddd, J = 14.4, 10.7, 4.0 Hz, 2H), 1.47 – 1.41 (m, 2H), 1.27 – 1.20 (m, 4H), 1.13 – 1.08 (m, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.09, 175.91, 168.86, 160.85, 145.52, 144.33, 139.03, 136.62, 135.35, 134.96, 130.36, 130.27, 127.69, 127.23, 126.96, 126.48, 120.35, 102.06, 69.66, 63.90, 63.57, 58.96, 57.12, 49.88, 49.83, 48.46, 47.81, 35.61, 32.93, 23.56, 23.51, 19.02, 14.24, 14.18.

HRMS (ESI): $C_{68}H_{67}O_{10}N_8Cl_2$ $[M+H]^+$; calculated: 1225.43517, found: 1225.43631.

$[\alpha]_{20}^{D}$ = + 48 ° (c = 0.5, MeCN).

102h, QD-(2-Chlorophenyl)cyclopropyl-A

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.92 (d, J = 4.9 Hz, 1H), 8.88 (d, J = 5.0 Hz, 1H), 8.18 (d, J = 9.2 Hz, 1H), 8.14 (d, J = 9.3 Hz, 1H), 7.85 (dd, J = 7.5, 2.1 Hz, 1H), 7.68 (d, J = 4.9 Hz, 1H), 7.66 – 7.61 (m, 2H), 7.63 – 7.59 (m, 2H), 7.51 (d, J = 2.6 Hz, 1H), 7.49 (d, J = 2.6 Hz, 1H), 7.47 (dd, J = 7.4, 1.8 Hz, 1H), 7.39 – 7.31 (m, 2H), 7.29 (s, 1H), 7.28 (dd, J = 7.9, 1.4 Hz, 1H), 7.18 (td, J = 7.6, 1.7 Hz, 1H), 7.12 (td, J = 7.6, 1.4 Hz, 1H), 7.10 (s, 1H), 4.05 (s, 3H), 4.03 (s, 3H), 3.97 (d, J = 8.6 Hz, 1H), 3.87 (d, J = 8.3 Hz, 1H), 3.80 (q, J = 9.5 Hz, 2H), 3.58 (dd, J = 11.5, 6.7 Hz, 1H), 3.57 – 3.53 (m, 1H), 3.54 – 3.39 (m, 8H), 3.35 – 3.27 (m, 2H), 3.28 – 3.21 (m, 1H), 3.10 (dd, J = 10.0, 7.3 Hz, 1H), 2.64 (s, 1H), 2.60 (s, 1H), 2.49 – 2.40 (m, 2H), 2.32 – 2.25 (m, 1H), 2.22 (td, J = 10.9, 4.6 Hz, 1H), 1.98 – 1.95 (m, 1H), 1.93 – 1.88 (m, 1H), 1.84 – 1.76 (m, 3H), 1.71 (ddd, J = 10.4, 7.4, 5.7 Hz, 1H), 1.57 (ddd, J = 14.3, 10.4, 4.1 Hz, 1H), 1.54 – 1.43 (m, 3H), 1.38 (ddd, J = 10.3, 7.5, 5.7 Hz, 1H), 1.34 – 1.26 (m, 2H), 1.16 (ddd, J = 9.3, 7.6, 5.0 Hz, 1H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.89, 176.20, 175.93, 175.85, 169.18, 169.11, 160.40, 160.36, 145.61, 143.73, 143.01, 141.20, 141.16, 137.28, 136.73, 135.41, 135.40, 135.14, 134.81, 130.49, 130.40, 130.37, 130.24, 129.40, 129.36, 127.36, 126.96, 126.77, 126.71, 125.44, 125.38, 119.44, 118.84, 101.74, 101.63, 71.88, 70.18, 65.03, 63.81, 63.58,

58.56, 58.17, 56.91, 56.88, 52.04, 51.85, 50.17, 49.78, 49.34, 48.90, 48.24, 48.11, 38.22, 36.08, 35.55, 33.40, 23.71, 23.41, 23.25, 23.19, 19.38, 19.13, 14.46, 14.17, 13.40, 13.33.

HRMS (ESI): $C_{68}H_{67}O_{10}N_8Cl_2$ $[M+H]^+$; calculated: 1225.43517, found: 1225.43637.

$[\alpha]_{20}^{D}$ = + 35 ° (c = 0.5, MeCN).

101bg, QD-Phenethyl-S

101bg was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 40 % MeCN; RT = 22.3 min) gave title compound **101bg** and its diastereomer (RT = 25.3 min) in a ratio of 10.3:1 and a combined yield of 28 % (11 mg, 8.08 µmol).

^{1}H NMR (600 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.95 (d, J = 5.4 Hz, 2H), 8.23 (d, J = 9.2 Hz, 2H), 8.20 (d, J = 5.4 Hz, 2H), 7.80 – 7.73 (m, 4H), 7.51 (s, 2H), 7.27 (qd, J = 6.5, 4.6 Hz, 6H), 7.18 – 7.13 (m, 4H), 4.12 (d, J = 4.9 Hz, 2H), 4.11 (s, 6H), 3.99 (t, J = 7.6 Hz, 2H), 3.83 (dd, J = 10.9, 7.6 Hz, 2H), 3.66 (dd, J = 11.7, 7.2 Hz, 2H), 3.63 – 3.58 (m, 2H), 3.56 (t, J = 7.4 Hz, 2H), 3.47 – 3.44 (m, 2H), 3.41 – 3.38 (m, 2H), 3.34 – 3.28 (m, 2H), 3.22 (ddd, J = 12.9, 10.7, 7.5 Hz, 2H), 3.15 (ddd, J = 13.6, 7.0, 2.8 Hz, 2H), 2.77 – 2.66 (m, 4H), 2.54 (dp, J = 16.7, 3.9 Hz, 4H), 1.80 – 1.71 (m, 4H), 1.62 (ddd, J = 14.5, 10.8, 3.9 Hz, 2H), 1.58 – 1.50 (m, 2H).

^{13}C NMR (151 MHz, CD_3CN:D_2O [10:1]) δ 176.22, 175.69, 168.55, 161.17, 147.52, 142.85, 138.60, 136.66, 134.91, 129.79, 128.94, 127.44, 127.02, 125.83, 120.73, 102.34, 69.24, 63.21, 63.17, 58.60, 57.65, 50.60, 49.54, 48.10, 47.94, 40.12, 33.30, 32.92, 23.30, 23.01, 18.69.

HRMS (ESI): $C_{66}H_{69}O_{10}N_8$ $[M+H]^+$; calculated: 1133.51366, found: 1133.51489.

$[\alpha]_{20}^{D}$ = + 112 ° (c = 0.3, MeCN).

101bh, QD-Homopiperonyl-S

101bh was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (20 – 50 % MeCN; RT = 16.0 min) gave title compound **101bh** and its diastereomer (RT = 17.8 min) in a ratio of 6.68:1 and a combined yield of 31 % (12.8 mg, 8.83 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.89 (d, J = 5.1 Hz, 2H), 8.18 (d, J = 9.3 Hz, 2H), 7.96 (dd, J = 5.2, 0.8 Hz, 2H), 7.66 (dd, J = 9.3, 2.5 Hz, 2H), 7.57 (d, J = 2.6 Hz, 2H), 7.35 (s, 2H), 6.75 (d, J = 7.8 Hz, 2H), 6.70 (d, J = 1.7 Hz, 2H), 6.59 (dd, J = 7.9, 1.7

Hz, 2H), 5.90 (dd, J = 15.1, 0.9 Hz, 4H), 4.06 (s, 6H), 4.02 (d, J = 7.9 Hz, 2H), 3.88 (t, J = 7.6 Hz, 2H), 3.83 (dd, J = 10.5, 8.0 Hz, 2H), 3.60 (dd, J = 11.7, 7.3 Hz, 2H), 3.54 (ddd, J = 13.5, 9.0, 6.9 Hz, 2H), 3.50 (t, J = 7.4 Hz, 2H), 3.45 (tt, J = 10.9, 3.3 Hz, 2H), 3.42 – 3.37 (m, 2H), 3.37 – 3.32 (m, 2H), 3.23 (ddd, J = 13.2, 11.0, 7.3 Hz, 2H), 3.18 (ddd, J = 13.9, 7.2, 2.8 Hz, 2H), 2.67 – 2.60 (m, 4H), 2.55 (s, 2H), 2.46 (ddd, J = 13.7, 8.9, 7.2 Hz, 2H), 1.84 – 1.73 (m, 4H), 1.70 (td, J = 11.1, 7.1 Hz, 2H), 1.64 (tt, J = 10.8, 2.3 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 175.97, 175.62, 168.71, 160.66, 148.14, 146.73, 144.78, 144.67, 139.76, 132.71, 128.32, 126.95, 125.98, 122.89, 120.21, 110.20, 108.47, 101.78, 101.70, 69.45, 63.37, 63.27, 58.91, 57.03, 50.71, 49.67, 48.23, 48.15, 40.43, 33.38, 33.19, 23.64, 23.21, 18.72.

HRMS (ESI): $C_{68}H_{69}O_{14}N_8$ $[M+H]^+$; calculated: 1221.49278, found: 1221.49349.

$[\alpha]_{20}^{D}$ = + 113 ° (c = 0.5, MeCN).

101bi, QD-(S)-β-Methylphenethyl-S

101bi was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 50 % MeCN 30 mL/min; RT = 18.1 min) gave title compound **101bi** and its diastereomer (RT = 20.8 min) in a ratio of 8:1 and a combined yield of 22 % (8.8 mg, 6.33 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.87 (d, J = 4.9 Hz, 2H), 8.15 (d, J = 9.3 Hz, 2H), 7.87 (d, J = 4.9 Hz, 2H), 7.61 (dd, J = 9.3, 2.6 Hz, 2H), 7.52 (d, J = 2.7 Hz, 2H), 7.30 (s, 2H), 7.29 – 7.24 (m, 4H), 7.22 – 7.17 (m, 2H), 7.11 – 7.07 (m, 4H), 4.05 (s, 6H), 3.97 (d, J = 7.9 Hz, 2H), 3.87 (t, J = 7.6 Hz, 2H), 3.80 (dd, J = 10.4, 8.1 Hz, 2H), 3.54 (dd, J = 11.7, 7.2 Hz, 2H), 3.45 – 3.33 (m, 10H), 3.27 (ddd, J = 13.3, 11.0, 7.4 Hz, 2H), 3.14 – 3.11 (m, 2H), 3.07 – 3.03 (m, 2H), 2.65 – 2.59 (m, 2H), 2.54 (s, 2H), 1.94 – 1.90 (m, 2H), 1.87 – 1.76 (m, 4H), 1.63 (ddd, J = 14.1, 10.4, 3.5 Hz, 2H), 1.07 (d, J = 7.0 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.11, 175.97, 168.52, 160.33, 145.81, 143.94, 143.28, 141.29, 129.53, 129.15, 127.93, 127.29, 126.69, 125.18, 120.05, 101.65, 69.42, 63.46, 63.31, 59.07, 56.94, 50.61, 49.62, 48.10, 47.99, 45.82, 37.63, 33.17, 23.51, 23.29, 19.22, 18.80.

HRMS (ESI): $C_{68}H_{73}O_{10}N_8$ $[M+H]^+$; calculated: 1161.54442, found: 1161.54500.

$[\alpha]_{20}^{D}$ = + 45 ° (c = 0.5, MeCN).

101bj, QD-(R)-β-Methylphenethyl-S

101bj was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 50 % MeCN; RT = 20.0 min) gave title compound **101bj** and its diastereomers (RT = 19.4 min) and (RT = 21.5 min) in a ratio of 5.94:1.1:1 and a combined yield of 37 % (14.6 mg, 10.5 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.84 (d, J = 5.0 Hz, 2H), 8.16 (d, J = 9.3 Hz, 2H), 7.85 (d, J = 4.7 Hz, 2H), 7.63 (dd, J = 9.3, 2.5 Hz, 2H), 7.56 (d, J = 2.6 Hz, 2H), 7.34 (tt, J = 7.0, 3.6 Hz, 8H), 7.27 – 7.22 (m, 4H), 4.08 (s, 6H), 3.88 (d, J = 7.7 Hz, 2H), 3.78 (q, J = 8.2, 7.4 Hz, 4H), 3.65 (dd, J = 13.5, 11.2 Hz, 2H), 3.45 – 3.41 (m, 4H), 3.38 (t, J = 7.4 Hz, 2H), 3.28 (dd, J = 13.5, 5.3 Hz, 2H), 3.21 – 3.14 (m, 4H), 3.00 (ddd, J = 13.8, 7.1, 2.9 Hz, 2H), 2.79 – 2.71 (m, 2H), 2.57 – 2.49 (m, 2H), 2.44 (s, 2H), 1.77 – 1.70 (m, 2H), 1.63 (td, J = 10.7, 5.4 Hz, 2H), 1.58 (ddd, J = 14.4, 10.6, 3.8 Hz, 2H), 1.11 (d, J = 7.1 Hz, 6H), 0.78 (td, J = 11.2, 7.1 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 175.87, 174.92, 168.69, 160.44, 145.60, 144.11, 143.47, 141.05, 129.36, 129.12, 129.06, 127.45, 126.73, 125.38, 120.03, 101.68, 69.37, 63.33, 63.20, 58.97, 57.02, 51.00, 49.58, 48.33, 47.89, 45.48, 38.87, 33.18, 23.41, 22.94, 19.30, 18.63.

HRMS (ESI): $C_{68}H_{73}O_{10}N_8$ $[M+H]^+$; calculated: 1161.54442, found: 1161.54593.

$[\alpha]_{20}^{D}$ = + 137 ° (c = 0.4, MeCN).

101bk, QD-2-(5-fluoroindol-3-yl)ethyl-S

101bk was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (20 – 65 % MeCN; RT = 14.3min) gave title compound **101bk** and its diastereomer (RT = 15.4 min) in a ratio of 3.87:1 and a combined yield of 30 % (12.5 mg, 8.47 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.83 (d, J = 4.9 Hz, 2H), 8.14 (d, J = 9.3 Hz, 2H), 7.83 (d, J = 4.9 Hz, 2H), 7.61 (dd, J = 9.3, 2.6 Hz, 2H), 7.52 (d, J = 2.7 Hz, 2H), 7.43 (dd, J = 8.9, 4.5 Hz, 2H), 7.32 (s, 2H), 7.25 (dd, J = 10.0, 2.5 Hz, 2H), 7.14 (s, 2H), 6.92 (td, J = 9.2, 2.5 Hz, 2H), 4.07 (s, 6H), 3.90 (d, J = 7.7 Hz, 2H), 3.83 (ddd, J = 13.6, 10.2, 6.2 Hz,

2H), 3.81 (t, J = 7.5 Hz, 2H), 3.77 (dd, J = 10.5, 8.0 Hz, 2H), 3.48 – 3.41 (m, 4H), 3.40 (t, J = 7.3 Hz, 2H), 3.39 – 3.34 (m, 2H), 3.20 – 3.14 (m, 2H), 3.12 (ddd, J = 13.3, 11.2, 7.1 Hz, 2H), 3.06 – 3.02 (m, 2H), 2.86 – 2.80 (m, 2H), 2.70 (ddd, J = 14.5, 10.1, 6.9 Hz, 2H), 2.56 – 2.51 (m, 2H), 2.38 (s, 2H), 1.69 – 1.61 (m, 2H), 1.55 (ddd, J = 14.6, 11.5, 4.0 Hz, 2H), 1.24 (t, J = 13.2 Hz, 4H), 0.88 – 0.81 (m, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 175.73, 175.03, 168.66, 160.31, 158.51, 157.19, 145.89, 143.01, 141.47, 133.64, 129.70, 128.20, 128.14, 126.76, 126.63, 125.11, 120.02, 112.66, 112.60, 111.69, 111.67, 110.42, 110.27, 104.58, 104.45, 101.64, 69.38, 63.27, 63.21, 59.05, 56.97, 50.91, 49.65, 48.28, 47.95, 38.91, 33.32, 23.35, 23.30, 22.85, 18.57.

HRMS (ESI): $C_{70}H_{69}O_{10}N_{10}F_2$ $[M+H]^+$; calculated: 1247.51607, found: 1247.51665.

101bl, QD-4-(4-fluorophenoxy)benzyl-S

101bl was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (15 – 60 % MeCN; RT = 22.5 min) gave title compound **101bl** and its diastereomer (RT = 24.0 min) in a ratio of 1.98:1 and a combined yield of 30 % (13.5 mg, 8.69 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.88 (d, J = 5.0 Hz, 2H), 8.16 (d, J = 9.2 Hz, 2H), 7.94 (d, J = 5.0 Hz, 2H), 7.62 (dd, J = 9.3, 2.6 Hz, 2H), 7.54 (d, J = 2.6 Hz, 2H), 7.31 (s, 2H), 7.12 – 7.07 (m, 8H), 6.98 – 6.94 (m, 4H), 6.82 – 6.79 (m, 4H), 4.42 (d, J = 15.0 Hz, 2H), 4.34 (d, J = 15.0 Hz, 2H), 4.11 (d, J = 8.1 Hz, 2H), 4.04 (s, 6H), 3.97 (t, J = 7.8 Hz, 2H), 3.81 (dd, J = 10.4, 8.1 Hz, 2H), 3.70 (dd, J = 11.5, 6.9 Hz, 2H), 3.63 (t, J = 7.2 Hz, 2H), 3.50 (ddd, J = 12.9, 10.9, 1.7 Hz, 2H), 3.42 (ddt, J = 14.0, 11.3, 3.2 Hz, 2H), 3.32 – 3.23 (m, 4H), 2.71 (ddt, J = 13.4, 7.8, 2.5 Hz, 2H), 2.65 (s, 2H), 2.38 (td, J = 11.2, 7.2 Hz, 2H), 1.93 – 1.87 (m, 2H), 1.84 – 1.78 (m, 2H), 1.66 (ddd, J = 14.4, 10.6, 4.0 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.26, 176.04, 168.69, 160.63, 160.23, 158.87, 157.84, 153.26, 153.25, 145.14, 144.31, 140.34, 131.02, 129.98, 128.79, 126.93, 125.77, 121.59, 121.54, 120.18, 118.42, 117.07, 116.94, 101.75, 69.72, 63.70, 63.47, 59.00, 57.03, 50.47, 49.67, 48.46, 48.34, 42.29, 33.21, 23.65, 23.58, 19.03.

HRMS (ESI): $C_{76}H_{71}O_{12}N_8F_2$ $[M+H]^+$; calculated: 1325.51540, found: 1325.51579.

$[\alpha]_{20}^{D}$ = + 38 ° (c = 0.5, MeCN).

101bm, QD-Hydroxyethyl-S

101bm was prepared from aldehyde **80** according to General Procedure 6. Preparative HPLC (0 – 30 % MeCN; RT = 18.0 min) gave title compound **101bm** and its diastereomer (RT = 20.3 min) in a ratio of 6.7 : 1 and a combined yield of 26 % (9.30 mg, 7.51 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.89 (d, J = 5.1 Hz, 2H), 8.16 (d, J = 9.3 Hz, 2H), 7.98 (d, J = 5.1 Hz, 2H), 7.65 (dd, J = 9.3, 2.6 Hz, 2H), 7.50 (d, J = 2.6 Hz, 2H), 7.27 (s, 2H), 4.10 (d, J = 8.1 Hz, 2H), 4.03 (s, 6H), 3.96 (t, J = 7.8 Hz, 2H), 3.83 (dd, J = 10.4, 8.2 Hz, 2H), 3.69 (dd, J = 11.6, 7.1 Hz, 2H), 3.64 (t, J = 7.2 Hz, 2H), 3.49 (ddd, J = 13.0, 10.9, 1.7 Hz, 2H), 3.46 – 3.40 (m, 4H), 3.39 (dd, J = 6.5, 4.8 Hz, 2H), 3.32 (dddd, J = 16.9, 13.2, 7.0, 4.1 Hz, 6H), 3.25 (ddd, J = 13.7, 7.2, 2.8 Hz, 2H), 2.71 (ddt, J = 13.0, 7.5, 2.3 Hz, 2H), 2.65 (s, 2H), 2.42 (td, J = 11.2, 7.3 Hz, 2H), 1.98 – 1.95 (m, 2H), 1.86 – 1.79 (m, 2H), 1.68 (ddd, J = 14.4, 10.7, 3.9 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.49, 176.39, 168.63, 160.46, 144.80, 144.41, 139.63, 128.23, 126.79, 125.77, 120.18, 101.63, 69.54, 63.46, 63.26, 58.85, 58.27, 56.88, 50.35, 49.62, 48.18, 48.16, 41.83, 32.78, 23.38, 23.29, 18.76.

HRMS (ESI): $C_{54}H_{61}O_{12}N_8$ $[M+H]^+$; calculated: 1013.44035, found: 1013.44054.

$[\alpha]_{20}^{D}$ = + 62 ° (c = 0.5, MeCN).

5.10.12 Macrocycles synthesized from aldehyde 113a

114a, CN-Me-S

114a was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (10 – 40 % MeCN; RT = 8.8 min) gave title compound **114a** and its diastereomer (RT = 11.7 min) in a ratio of 16.7:1 and yield of 41 % (13.4 mg, 11.95 µmol; yield only from title compound).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 9.06 (d, J = 4.9 Hz, 2H), 8.43 (d, J = 8.5 Hz, 2H), 8.25 (d, J = 8.5 Hz, 2H), 7.99 (ddd, J = 8.4, 6.9, 1.2 Hz, 2H), 7.94 (d, J = 4.9 Hz, 2H), 7.86 (ddd, J = 8.3, 6.9, 1.2 Hz, 2H), 7.35 (s, 2H), 4.05 (d, J = 8.0 Hz, 2H), 3.92 (t, J = 7.7 Hz, 2H), 3.83 (dd, J = 10.5, 7.9 Hz, 2H), 3.68 (dd, J = 11.7, 7.0 Hz, 2H), 3.59 (t, J = 7.2 Hz,

2H), 3.46 (ddd, J = 13.1, 10.9, 1.8 Hz, 2H), 3.42 (tt, J = 11.3, 3.3 Hz, 2H), 3.34 – 3.25 (m, 4H), 2.79 – 2.74 (m, 2H), 2.66 (s, 6H), 2.64 (s, 2H), 2.41 (td, J = 11.3, 7.2 Hz, 2H), 1.93 – 1.89 (m, 2H), 1.86 – 1.80 (m, 2H), 1.72 (ddd, J = 14.4, 10.7, 3.8 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.40, 176.19, 168.74, 148.91, 145.28, 145.13, 132.46, 129.75, 127.90, 125.30, 123.91, 120.06, 69.66, 63.54, 63.41, 59.49, 50.72, 49.78, 48.47, 48.18, 33.03, 25.02, 23.70, 23.53, 18.90.

HRMS (ESI): $C_{50}H_{53}O_8N_8$ $[M+H]^+$; calculated: 893.39809, found: 893.39815.

$[\alpha]_{20}^{D}$ = + 103 ° (c = 0.5, MeCN).

114b, CN-EtOH-S

114b was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (0 – 30 % MeCN; RT = 15.3 min) gave title compound **114b** and its diastereomer (RT = 17.5 min) in a ratio of 3 : 1 and a combined yield of 15 % (5.2 mg, 4.41 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 9.02 (d, J = 4.8 Hz, 2H), 8.31 (d, J = 8.4 Hz, 2H), 8.22 (d, J = 8.3 Hz, 2H), 7.97 (ddd, J = 8.3, 6.9, 1.2 Hz, 2H), 7.90 (d, J = 4.8 Hz, 2H), 7.86 (ddd, J = 8.3, 6.9, 1.2 Hz, 2H), 7.29 (s, 2H), 4.08 (d, J = 8.1 Hz, 2H), 3.95 (t, J = 7.8 Hz, 2H), 3.85 – 3.81 (m, 2H), 3.69 (dd, J = 11.7, 7.0 Hz, 2H), 3.64 (t, J = 7.2 Hz, 2H), 3.47 (ddd, J = 13.0, 10.9, 1.7 Hz, 2H), 3.45 – 3.39 (m, 4H), 3.38 – 3.36 (m, 2H), 3.31 (tdd, J = 11.7, 6.3, 1.7 Hz, 6H), 3.26 (ddd, J = 13.7, 7.3, 3.0 Hz, 2H), 2.74 (ddt, J = 13.1, 7.4, 2.3 Hz, 2H), 2.64 (s, 2H), 2.42 (td, J = 11.2, 7.1 Hz, 2H), 1.97 – 1.95 (m, 2H), 1.85 – 1.79 (m, 2H), 1.71 (ddd, J = 14.5, 10.6, 3.7 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.46, 176.24, 168.63, 149.21, 145.56, 144.09, 132.05, 129.49, 128.25, 124.94, 123.46, 119.74, 69.69, 63.43, 63.28, 59.39, 58.27, 50.33, 49.77, 48.22, 48.20, 41.80, 32.81, 23.38, 23.28, 18.71.

HRMS (ESI): $C_{52}H_{57}O_{10}N_8$ $[M+H]^+$; calculated: 953.41922, found: 953.41950.

$[\alpha]_{20}^{D}$ = + 51 ° (c = 0.25, MeCN).

114c, CN-*i*Pr-S

114c was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (10 – 40 % MeCN; RT = 15.6 min) gave title compound **114c** and its diastereomer (RT = 18.9 min) in a ratio of 4.46 : 1 and a combined yield of 20 % (6.8 mg, 5.78 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 9.05 (d, J = 4.9 Hz, 2H), 8.40 (dd, J = 8.6, 1.2 Hz, 2H), 8.25 (dd, J = 8.5, 1.2 Hz, 2H), 7.99 (ddd, J = 8.3, 6.9, 1.2 Hz, 2H), 7.94 (dd, J = 4.9, 0.8 Hz, 2H), 7.87 (ddd, J = 8.3, 6.9, 1.3 Hz, 2H), 7.33 (s, 2H), 4.06 (d, J = 8.2 Hz, 2H), 4.02 (p, J = 6.9 Hz, 2H), 3.83 (q, J = 8.6, 8.2 Hz, 4H), 3.68 (dd, J = 11.7, 6.9 Hz, 2H), 3.52 (t, J = 7.2 Hz, 2H), 3.47 (ddd, J = 13.0, 10.8, 1.8 Hz, 2H), 3.42 (ddt, J = 14.1, 11.3, 3.2 Hz, 2H), 3.32 – 3.23 (m, 4H), 2.74 (ddt, J = 13.1, 7.7, 2.5 Hz, 2H), 2.63 (s, 2H), 2.43 (td, J = 11.3, 7.2 Hz, 2H), 1.94 – 1.89 (m, 2H), 1.82 (dddd, J = 18.4, 9.5, 4.9, 1.8 Hz, 2H), 1.69 (ddd, J = 14.4, 10.5, 3.5 Hz, 2H), 1.13 (d, J = 6.9 Hz, 6H), 1.11 (d, J = 6.9 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.24, 176.11, 168.84, 148.89, 145.09, 145.07, 132.46, 129.76, 127.89, 125.22, 123.83, 119.96, 69.74, 63.66, 63.49, 59.44, 50.24, 49.88, 48.42, 48.02, 44.54, 32.99, 23.59, 23.51, 19.06, 18.92, 18.70.

HRMS (ESI): $C_{50}H_{53}O_8N_8$ $[M+H]^+$; calculated: 893.39833, found: 893.39809.

$[\alpha]_{20}^{D}$ = + 104 ° (c = 0.5, MeCN).

114d, CN-*t*Bu-S

114d was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (15 – 40 % MeCN; RT = 14.8 min) gave title compound **114d** and its diastereomer (RT = 19.4 min) in a ratio of 3.78:1 and a combined yield of 38 % (13.1 mg, 10.9 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 9.03 (d, J = 4.8 Hz, 2H), 8.35 (d, J = 8.5 Hz, 2H), 8.23 (d, J = 8.5 Hz, 2H), 7.97 (dd, J = 8.5, 6.9 Hz, 2H), 7.89 (d, J = 4.9 Hz, 2H), 7.85 (t, J = 7.7 Hz, 2H), 7.32 (s, 2H), 4.03 (d, J = 8.0 Hz, 2H), 3.84 – 3.79 (m, 2H), 3.71 (t, J = 7.8 Hz, 2H), 3.64 (dd, J = 11.7, 6.9 Hz, 2H), 3.48 (ddd, J = 12.9, 10.8, 1.7 Hz, 2H), 3.44 – 3.39 (m, 4H), 3.31 – 3.29 (m, 4H), 2.69 (ddd, J = 13.3, 7.7, 2.7 Hz, 2H), 2.62 (s, 2H), 2.35 (td, J = 11.2, 7.2 Hz, 2H), 1.89 (tt, J = 10.7, 3.3 Hz, 2H), 1.83 – 1.77 (m, 2H), 1.67 (ddd, J = 14.4, 10.8, 3.9 Hz, 2H), 1.29 (s, 18H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.91, 176.89, 168.86, 149.06, 145.39, 144.52, 132.17, 129.55, 128.09, 125.08, 123.67, 119.77, 69.64, 64.08, 63.78, 59.42, 58.84, 50.34, 49.82, 48.35, 47.89, 33.15, 27.79, 23.48, 23.27, 18.79.

HRMS (ESI): $C_{56}H_{65}O_8N_8$ $[M+H]^+$; calculated: 977.49199, found: 977.49291.

$[\alpha]_{20}^{D}$ = + 97 ° (c = 0.5, MeCN).

114e, CN-Neopentyl-S

114e was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (15 – 45 % MeCN; RT = 16.7 min) gave title compound **114e** and its diastereomers (RT = 16.3 min) and (RT = 20.5 min) in a ratio of 9.25:1:2.7 and a combined yield of 20 % (6.9 mg, 5.59 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.99 (d, J = 4.7 Hz, 2H), 8.31 (d, J = 8.3 Hz, 2H), 8.22 – 8.20 (m, 2H), 7.93 (ddd, J = 8.4, 6.9, 1.2 Hz, 2H), 7.84 (d, J = 4.7 Hz, 2H), 7.81 (ddd, J = 8.3, 6.9, 1.3 Hz, 2H), 7.30 (s, 2H), 4.06 (d, J = 8.0 Hz, 2H), 3.93 (t, J = 7.8 Hz, 2H), 3.81 (dd, J = 10.5, 7.6 Hz, 2H), 3.67 (dd, J = 11.6, 7.1 Hz, 2H), 3.61 (t, J = 7.4 Hz, 2H), 3.50 (ddd, J = 13.7, 10.8, 1.7 Hz, 2H), 3.41 (ddt, J = 14.0, 11.2, 3.2 Hz, 2H), 3.28 (ddd, J = 13.2, 10.9, 7.3 Hz, 2H), 3.23 (ddd, J = 13.6, 7.2, 2.8 Hz, 2H), 3.06 (s, 4H), 2.76 – 2.71 (m, 2H), 2.69 (s, 2H), 2.31 (q, J = 10.8 Hz, 2H), 1.88 (ddt, J = 13.1, 9.6, 2.7 Hz, 2H), 1.85 – 1.78 (m, 2H), 1.70 (ddd, J = 14.4, 11.1, 4.0 Hz, 2H), 0.72 (s, 18H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.87, 176.42, 168.62, 149.80, 146.69, 143.30, 131.63, 129.23, 129.17, 125.00, 123.55, 119.72, 69.59, 63.60, 63.39, 59.61, 50.54, 50.27, 49.82, 48.39, 48.01, 33.51, 33.45, 27.87, 23.57, 23.41, 18.87.

HRMS (ESI): $C_{58}H_{69}O_8N_8$ $[M+H]^+$; calculated: 1005.52329, found: 1005.52446.

$[\alpha]_{20}^{D}$ = + 96 ° (c = 0.3, MeCN).

114f, CN-Cyclohexyl-S

114f was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (10 – 40 % MeCN; RT = 23.8 min) gave title compound **114f** and its diastereomer (RT = 27.5 min) in a ratio of 3.6 : 1 and a combined yield of 15 % (5.40 mg, 4.30 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 9.02 (d, J = 4.8 Hz, 2H), 8.31 (d, J = 8.4 Hz, 2H), 8.23 (d, J = 8.4 Hz, 2H), 7.97 (ddd, J = 8.3, 6.8, 1.2 Hz, 2H), 7.88 (d, J = 4.8 Hz, 2H), 7.86 (ddd, J = 8.2, 6.8, 1.2 Hz, 2H), 7.28 (s, 2H), 4.03 (d, J = 8.2 Hz, 2H), 3.82 (dd, J = 9.6, 6.1 Hz, 4H), 3.65 (dd, J = 11.7, 6.9 Hz, 2H), 3.61 (ddt, J = 12.2, 7.5, 3.7 Hz, 2H), 3.52 (t, J = 7.2 Hz, 2H), 3.43 (dddd, J = 25.9, 14.1, 11.1, 2.5 Hz, 4H), 3.28 (ddd, J = 13.3, 11.1, 7.3 Hz, 2H), 3.24 (ddd, J = 13.6, 7.2, 2.8 Hz, 2H), 2.74 – 2.68 (m, 2H), 2.62 (s, 2H), 2.40 (td, J = 11.2, 7.2 Hz, 2H), 1.91 (dt, J = 10.5, 3.1 Hz, 2H), 1.84 – 1.62 (m, 12H), 1.51 – 1.46 (m, 2H), 1.45 – 1.39 (m, 4H), 1.12 (qt, J = 13.4, 3.6 Hz, 4H), 0.96 (qt, J = 13.4, 3.7 Hz, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.17, 175.99, 168.70, 149.22, 145.65, 143.99, 132.03, 129.48, 128.33, 124.94, 123.46, 119.75, 69.62, 63.51, 63.35, 59.37, 52.43, 50.02, 49.80, 48.31, 47.78, 32.79, 29.02, 28.65, 25.79, 25.78, 25.19, 23.40, 23.31, 18.75.

HRMS (ESI): $C_{60}H_{69}O_8N_8$ $[M+H]^+$; calculated: 1029.52330, found: 1029.52329.

$[\alpha]_{20}^{D}$ = + 88 ° (c = 0.3, MeCN).

114g, CN-(cis)-Myrthanyl-S

114g was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (20 – 60 % MeCN; RT = 18.8 min) gave title compound **114g** and its diastereomer (RT =23 min) in a ratio of 3.75:1 and a combined yield of 34 % (13.4 mg, 9.81 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 9.03 (d, J = 4.8 Hz, 2H), 8.40 (d, J = 8.4 Hz, 2H), 8.24 (d, J = 8.4 Hz, 2H), 7.96 (ddd, J = 8.3, 6.8, 1.2 Hz, 2H), 7.89 (d, J = 4.8 Hz, 2H), 7.84 (ddd, J = 8.3, 6.9, 1.2 Hz, 2H), 7.33 (s, 2H), 4.04 (d, J = 8.0 Hz, 2H), 3.90 (t, J = 7.7 Hz, 2H), 3.84 (dd, J = 10.4, 8.1 Hz, 2H), 3.68 (dd, J = 11.6, 7.1 Hz, 2H), 3.58 (t, J = 7.3 Hz, 2H), 3.50 (ddd, J = 13.0, 10.9, 1.7 Hz, 2H), 3.42 (ddt, J = 14.1, 11.2, 3.3 Hz, 2H), 3.32 – 3.24 (m, 4H), 3.23 – 3.19 (m, 4H), 2.75 (ddt, J = 13.0, 7.3, 2.4 Hz, 2H), 2.67 (s, 2H), 2.33 (td, J = 11.1, 7.1 Hz, 2H), 2.28 – 2.24 (m, 2H), 2.12 – 2.06 (m, 2H), 1.90 (tt, J = 10.6, 3.1 Hz, 2H), 1.86 – 1.77 (m, 6H), 1.75 – 1.68 (m, 6H), 1.65 (ddd, J = 6.9, 5.0, 2.1 Hz, 2H), 1.33 – 1.27 (m, 2H), 1.07 (s, 6H), 0.90 (s, 6H), 0.74 (d, J = 9.6 Hz, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.55, 176.16, 168.61, 149.21, 145.72, 144.59, 132.17, 129.56, 128.37, 125.25, 123.87, 119.97, 69.65, 63.55, 63.37, 59.54, 50.35, 49.79,

48.29, 48.12, 44.84, 43.95, 41.59, 39.51, 38.88, 33.48, 33.02, 27.66, 26.10, 23.75, 23.53, 22.73, 19.23, 18.96.

HRMS (ESI): $C_{68}H_{81}O_8N_8$ $[M+H]^+$; calculated: 1137.61719, found: 1137.61726.

$[\alpha]_{20}^{D}$ = + 88 ° (c = 0.5, MeCN).

114h, CN-(R)-1-Cyclohexylethyl -S

114h was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (10 – 60 % MeCN; RT = 20.4 min) gave title compound **114h** and its diastereomer (RT = 23.6 min) in a ratio of 2.48:1 and a combined yield of 29 % (10.9 mg, 8.30 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 9.04 (d, J = 5.0 Hz, 2H), 8.37 (d, J = 8.4 Hz, 2H), 8.24 (d, J = 8.4 Hz, 2H), 7.98 (ddd, J = 8.4, 6.9, 1.4 Hz, 2H), 7.91 (d, J = 4.8 Hz, 2H), 7.86 (ddd, J = 8.3, 6.9, 1.4 Hz, 2H), 7.31 (s, 2H), 4.06 (d, J = 8.3 Hz, 2H), 3.82 (dd, J = 10.7, 7.9 Hz, 2H), 3.87 (t, J = 7.8 Hz, 2H), 3.67 (dd, J = 11.6, 6.9 Hz, 2H), 3.57 (t, J = 6.7 Hz, 2H), 3.56 – 3.53 (m, 2H), 3.52 – 3.47 (m, 2H), 3.42 (tt, J = 11.6, 3.1 Hz, 2H), 3.32 – 3.27 (m, 2H), 3.27 – 3.22 (m, 2H), 2.75 – 2.69 (m, 2H), 2.64 (s, 2H), 2.39 (td, J = 11.2, 7.2 Hz, 2H), 1.91 (dt, J = 10.2, 3.2 Hz, 2H), 1.85 – 1.78 (m, 2H), 1.65 (tdd, J = 27.0, 11.8, 3.4 Hz, 8H), 1.59 – 1.50 (m, 4H), 1.44 – 1.38 (m, 2H), 1.14 – 1.08 (m, 2H), 1.07 (d, J = 7.0 Hz, 6H), 1.06 – 0.98 (m, 4H), 0.79 – 0.70 (m, 2H), 0.59 (qd, J = 12.3, 3.3 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.48, 176.23, 168.66, 149.09, 145.46, 144.56, 132.25, 129.63, 128.19, 125.13, 123.71, 119.83, 69.71, 63.72, 63.49, 59.42, 53.93, 49.86, 49.84, 48.48, 47.68, 39.29, 33.13, 30.37, 30.26, 26.26, 25.97, 23.53, 23.51, 18.90, 15.25.

$[\alpha]_{20}^{D}$ = + 89 ° (c = 0.5, MeCN).

114i, CN-Ph -S

114i was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (10 – 50 % MeCN; RT = 15.4 min) gave title compound **114i** and its 3 diastereomers (RT = 15.0 min, 18.2 min, 20.1 min) in a ratio of 6.03:1:1.12:1.17 and a combined yield of 46 % (16.5 mg, 13.25 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 9.02 (d, J = 4.8 Hz, 2H), 8.39 (d, J = 8.5 Hz, 2H), 8.20 (d, J = 8.5 Hz, 2H), 7.95 (td, J = 7.1, 1.5 Hz, 4H), 7.83 (ddd, J = 8.3,

6.9, 1.2 Hz, 2H), 7.39 – 7.29 (m, 8H), 7.11 – 7.07 (m, 4H), 4.22 (d, J = 8.2 Hz, 2H), 4.09 (t, J = 7.9 Hz, 2H), 3.85 (dd, J = 11.3, 7.0 Hz, 4H), 3.80 (t, J = 7.2 Hz, 2H), 3.51 (t, J = 12.2 Hz, 2H), 3.45 – 3.37 (m, 4H), 3.29 (ddd, J = 13.0, 11.0, 7.2 Hz, 2H), 2.86 – 2.77 (m, 2H), 2.65 (s, 2H), 2.54 (td, J = 11.0, 6.9 Hz, 2H), 1.93 – 1.88 (m, 2H), 1.85 – 1.79 (m, 2H), 1.74 (ddd, J = 14.2, 10.8, 3.7 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 175.51, 175.48, 168.98, 148.97, 145.26, 144.84, 132.57, 132.31, 129.64, 129.61, 129.41, 128.03, 127.45, 125.19, 123.79, 119.95, 70.03, 63.93, 63.89, 59.41, 50.90, 49.84, 48.89, 48.35, 33.01, 23.62, 19.00.

HRMS (ESI): $C_{60}H_{57}O_8N_8$ $[M+H]^+$; calculated: 1017.42939, found: 1017.43001.

$[\alpha]_{20}^{D}$ = + 97 ° (c = 0.5, MeCN).

114j, CN-Bn -S

114j was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (15 – 45 % MeCN; RT = 19.9 min) gave title compound **114j** and its diastereomer (RT = 20.7 min) in a ratio of 4.55:1 and a combined yield of 40 % (14.5 mg, 11.4 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) 1H NMR (700 MHz, Acetonitrile-d3) δ 9.03 (d, J = 4.9 Hz, 2H), 8.40 (d, J = 8.5 Hz, 2H), 8.23 (d, J = 8.4 Hz, 2H), 7.97 (ddd, J = 8.3, 6.8, 1.2 Hz, 2H), 7.91 (d, J = 4.9 Hz, 2H), 7.85 (ddd, J = 8.3, 6.9, 1.3 Hz, 2H), 7.33 (s, 2H), 7.25 – 7.18 (m, 6H), 7.13 – 7.10 (m, 4H), 4.44 (d, J = 15.0 Hz, 2H), 4.35 (d, J = 15.1 Hz, 2H), 4.10 (d, J = 8.1 Hz, 2H), 3.99 (t, J = 7.8 Hz, 2H), 3.82 (dd, J = 10.3, 8.2 Hz, 2H), 3.71 (dd, J = 11.6, 7.0 Hz, 2H), 3.66 (t, J = 7.2 Hz, 2H), 3.49 (ddd, J = 12.9, 10.8, 1.8 Hz, 2H), 3.41 (ddt, J = 14.0, 11.3, 3.1 Hz, 2H), 3.32 – 3.26 (m, 4H), 2.80 – 2.72 (m, 2H), 2.65 (s, 2H), 2.39 (td, J = 11.2, 7.2 Hz, 2H), 1.90 (td, J = 12.4, 10.7, 7.1 Hz, 2H), 1.84 – 1.78 (m, 2H), 1.70 (ddd, J = 14.3, 10.7, 3.9 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.25, 175.94, 168.68, 149.08, 145.44, 144.81, 136.18, 132.31, 129.66, 129.09, 128.18, 128.17, 128.14, 125.20, 123.81, 119.88, 69.78, 63.63, 63.46, 59.46, 50.45, 49.82, 48.38, 48.35, 42.88, 33.20, 23.63, 23.53, 18.94.

HRMS (ESI): $C_{62}H_{61}O_8N_8$ $[M+H]^+$; calculated: 1045.46069, found: 1045.46136.

$[\alpha]_{20}^{D}$ = + 89 ° (c = 0.5, MeCN).

114k, CN-4-Methylbenzyl -S

114k was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (15 – 60 % MeCN; RT = 15.8 min) gave title compound **114k** and its diastereomer (RT = 18.5 min) in a ratio of 4.46:1 and a combined yield of 34 % (12.5 mg, 9.61 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 9.02 (dd, J = 4.8, 1.5 Hz, 2H), 8.38 (d, J = 8.5 Hz, 2H), 8.22 (d, J = 8.5 Hz, 2H), 7.95 (t, J = 7.7 Hz, 2H), 7.90 – 7.87 (m, 2H), 7.83 (t, J = 7.7 Hz, 2H), 7.32 (s, 2H), 7.03 (d, J = 7.8 Hz, 4H), 6.99 (d, J = 8.1 Hz, 4H), 4.39 (d, J = 14.9 Hz, 2H), 4.30 (d, J = 14.9 Hz, 2H), 4.08 (d, J = 8.1 Hz, 2H), 3.96 (t, J = 7.8 Hz, 2H), 3.81 (dd, J = 10.5, 8.0 Hz, 2H), 3.70 (dd, J = 11.6, 6.9 Hz, 2H), 3.64 (t, J = 7.2 Hz, 2H), 3.48 (dd, J = 13.3, 11.2 Hz, 2H), 3.41 (ddt, J = 14.0, 11.3, 3.2 Hz, 2H), 3.32 – 3.25 (m, 4H), 2.78 – 2.71 (m, 2H), 2.65 (s, 2H), 2.39 (td, J = 11.1, 7.3 Hz, 2H), 2.22 (s, 6H), 1.90 (tt, J = 10.7, 3.2 Hz, 2H), 1.81 (dddd, J = 13.5, 11.0, 7.2, 2.4 Hz, 2H), 1.69 (ddd, J = 14.4, 10.6, 3.8 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.24, 175.90, 168.66, 149.29, 145.80, 144.37, 137.98, 133.16, 132.09, 129.62, 129.51, 128.45, 128.18, 125.13, 123.72, 119.82, 69.76, 63.60, 63.43, 59.46, 50.41, 49.79, 48.36, 48.31, 42.64, 33.18, 23.61, 23.51, 20.63, 18.92.

HRMS (ESI): $C_{64}H_{65}O_8N_8$ $[M+H]^+$; calculated: 1073.49199, found: 1073.49253.

$[\alpha]_{20}^{D}$ = + 90 ° (c = 0.5, MeCN).

114l, CN-4-Cyanobenzyl -S

114l was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (15 – 60 % MeCN; RT = 13.5 min) gave title compound **114l** and a diastereomer was not observed – likely due to the low yield of 13 % (5 mg, 3.78 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.99 (d, J = 4.7 Hz, 2H), 8.31 (d, J = 8.4 Hz, 2H), 8.19 (d, J = 8.0 Hz, 2H), 7.92 (ddd, J = 8.3, 6.8, 1.2 Hz, 2H), 7.83 (d, J = 4.9 Hz, 2H), 7.81 (ddd, J = 8.3, 6.9, 1.3 Hz, 2H), 7.61 – 7.57 (m, 4H), 7.28 (s, 4H), 7.26 (s, 2H), 4.50 (d, J = 15.6 Hz, 2H), 4.43 (d, J = 15.6 Hz, 2H), 4.10 (d, J = 8.1 Hz, 2H), 3.99 (t, J = 7.8 Hz, 2H), 3.81 (dd, J = 10.5, 8.1 Hz, 2H), 3.72 (dd, J = 11.5, 6.9 Hz, 2H), 3.67 (t, J = 7.2 Hz, 2H), 3.48 (ddd, J = 12.9, 10.8, 1.7 Hz, 2H), 3.41 (ddt, J = 14.0, 11.3, 3.2 Hz, 2H), 3.32 – 3.24 (m, 4H), 2.74 (ddt, J = 13.0, 7.4, 2.3 Hz, 2H), 2.63 (s, 2H), 2.37 (td, J = 11.0, 7.0 Hz, 2H), 1.88 (ddd, J = 13.9,

10.9, 3.3 Hz, 2H), 1.81 (dddd, J = 13.4, 10.6, 7.2, 2.3 Hz, 2H), 1.70 (ddd, J = 14.4, 10.5, 3.7 Hz, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.14, 175.80, 168.72, 149.82, 146.71, 143.26, 141.49, 133.00, 131.65, 129.24, 129.20, 128.86, 124.98, 123.54, 119.68, 119.16, 111.51, 69.91, 63.61, 63.47, 59.48, 50.44, 49.83, 48.43, 48.42, 42.50, 33.19, 23.58, 23.51, 18.94.

HRMS (ESI): $C_{64}H_{59}O_8N_{10}$ $[M+H]^+$; calculated: 1095.45119, found: 1095.45165.

$[\alpha]_{20}^{D}$ = + 89 ° (c = 0.3, MeCN).

114m, CN-3-Hydroxybenzyl -S

114m was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (10 – 50 % MeCN; RT = 14.8 min) gave title compound **114m** and its two diastereomers (RT = 16.4 min, RT = 16.9 min) in a ratio of 1.8:1:2.42 and a combined yield of **13m** and "distereomer 3" of 33 % (12.5 mg, 9.58 µmol; yield excludes zz2).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.99 (d, J = 4.7 Hz, 2H), 8.30 (d, J = 8.4 Hz, 2H), 8.22 – 8.18 (m, 2H), 7.93 (ddd, J = 8.3, 6.9, 1.2 Hz, 2H), 7.84 (d, J = 4.7 Hz, 2H), 7.82 (ddd, J = 8.3, 6.9, 1.3 Hz, 2H), 7.28 (s, 2H), 7.04 (t, J = 7.8 Hz, 2H), 6.64 (ddd, J = 8.2, 2.5, 0.9 Hz, 2H), 6.58 (ddd, J = 7.6, 1.7, 0.9 Hz, 2H), 6.54 (t, J = 2.1 Hz, 2H), 4.37 (d, J = 15.0 Hz, 2H), 4.27 (d, J = 15.0 Hz, 2H), 4.08 (d, J = 8.1 Hz, 2H), 3.98 (t, J = 7.8 Hz, 2H), 3.85 – 3.79 (m, 2H), 3.70 (dd, J = 11.5, 7.0 Hz, 2H), 3.66 (t, J = 7.2 Hz, 2H), 3.48 (ddd, J = 12.9, 10.8, 1.7 Hz, 2H), 3.41 (ddt, J = 14.0, 11.3, 3.1 Hz, 2H), 3.32 – 3.25 (m, 4H), 2.78 – 2.71 (m, 2H), 2.66 (s, 2H), 2.39 (q, J = 10.9 Hz, 2H), 1.93 – 1.88 (m, 2H), 1.85 – 1.78 (m, 2H), 1.70 (ddd, J = 13.7, 10.1, 3.5 Hz, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.20, 175.81, 168.72, 157.58, 149.83, 146.69, 143.22, 137.66, 131.65, 130.22, 129.27, 129.21, 124.97, 123.50, 119.75, 119.24, 114.98, 114.78, 69.84, 63.61, 63.45, 59.56, 50.49, 49.88, 48.42, 48.36, 42.75, 33.15, 23.57, 23.47, 18.90.

HRMS (ESI): $C_{62}H_{61}O_{10}N_8$ $[M+H]^+$; calculated: 1077.451067, found: 1077.45111.

$[\alpha]_{20}^{D}$ = +83° (c = 0.3, MeCN).

114n, CN-Piperonyl-S

114n was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (10 – 50 % MeCN; RT = 18.3 min) gave title compound **114n** and its diastereomer (RT = 21.0 min) in a ratio of 3.65:1 and a combined yield of 38 % (14.7 mg, 10.8 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 9.04 (d, J = 4.9 Hz, 2H), 8.39 (d, J = 8.5 Hz, 2H), 8.24 (d, J = 8.4 Hz, 2H), 7.98 (t, J = 7.6 Hz, 2H), 7.92 (d, J = 4.8 Hz, 2H), 7.86 (t, J = 7.6 Hz, 2H), 7.32 (s, 2H), 6.67 (d, J = 7.7 Hz, 2H), 6.62 – 6.58 (m, 4H), 5.87 (s, 4H), 4.34 (d, J = 14.9 Hz, 2H), 4.24 (d, J = 14.9 Hz, 2H), 4.08 (d, J = 8.1 Hz, 2H), 3.96 (t, J = 7.8 Hz, 2H), 3.82 (t, J = 9.3 Hz, 2H), 3.69 (dd, J = 11.5, 7.0 Hz, 2H), 3.63 (dd, J = 8.5, 6.0 Hz, 2H), 3.48 (ddd, J = 13.2, 10.8, 1.8 Hz, 2H), 3.42 (ddt, J = 14.0, 11.2, 3.1 Hz, 2H), 3.32 – 3.25 (m, 4H), 2.78 – 2.71 (m, 2H), 2.65 (s, 2H), 2.38 (td, J = 11.1, 7.3 Hz, 2H), 1.92 – 1.87 (m, 2H), 1.84 – 1.78 (m, 2H), 1.70 (td, J = 12.9, 10.8, 4.1 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.18, 175.90, 168.65, 148.96, 148.15, 147.52, 145.21, 144.90, 132.38, 129.95, 129.71, 127.99, 125.17, 123.75, 121.85, 119.87, 108.68, 108.52, 101.93, 69.77, 63.58, 63.40, 59.42, 50.38, 49.81, 48.37, 48.28, 42.62, 33.10, 23.57, 23.47, 18.89.

HRMS (ESI): $C_{64}H_{61}O_{12}N_8$ $[M+H]^+$; calculated: 1133.44035, found: 1133.44076.

$[\alpha]_{20}^{D}$ = + 88 ° (c = 0.5, MeCN).

114o, CN-(S)-1-Phenylethyl-S

114o was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (10 – 60 % MeCN; RT = 17.3 min) gave title compound **114o** and its diastereomer (RT = 19.7 min) in a ratio of 3.37:1 and a combined yield of 28 % (10.3 mg, 7.92 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) 1H NMR (700 MHz,) δ 9.02 (d, J = 4.8 Hz, 2H), 8.36 (d, J = 8.5 Hz, 2H), 8.21 (d, J = 8.4 Hz, 2H), 7.94 (ddd, J = 8.4, 6.9, 1.2 Hz, 2H), 7.88 – 7.84 (m, 2H), 7.82 (ddd, J = 8.3, 6.8, 1.3 Hz, 2H), 7.30 (s, 2H), 7.25 – 7.20 (m, 4H), 7.21 – 7.15 (m, 6H), 5.07 (q, J = 7.2 Hz, 2H), 4.09 (d, J = 8.1 Hz, 2H), 3.93 (t, J = 7.9 Hz, 2H), 3.83 – 3.78 (m, 2H), 3.70 (dd, J = 11.6, 6.9 Hz, 2H), 3.54 (t, J = 7.2 Hz, 2H), 3.50 (ddd, J = 13.0, 10.8, 1.7 Hz, 2H), 3.41 (ddt, J = 14.1, 11.3, 3.2 Hz, 2H), 3.31 – 3.24 (m, 4H), 2.72 (ddt, J = 13.1,

7.6, 2.5 Hz, 2H), 2.60 (s, 2H), 2.41 (td, J = 11.1, 7.1 Hz, 2H), 1.93 – 1.86 (m, 2H), 1.79 (tdd, J = 13.4, 8.4, 2.4 Hz, 2H), 1.67 (ddd, J = 14.3, 10.9, 4.0 Hz, 2H), 1.57 (d, J = 7.3 Hz, 6H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.14, 175.93, 168.77, 149.51, 146.16, 143.92, 139.98, 131.92, 129.42, 128.83, 128.75, 127.96, 127.34, 125.07, 123.65, 119.76, 69.81, 63.67, 63.50, 59.45, 50.79, 50.14, 49.84, 48.46, 47.95, 33.19, 23.57, 23.48, 18.94, 16.97.

HRMS (ESI): $C_{64}H_{65}O_8N_8$ $[M+H]^+$; calculated: 1073.49199, found: 1073.49261.

$[\alpha]_{20}^{D}$ = + 72 ° (c = 0.5, MeCN).

114p, CN-(R)-1-Phenylethyl-S

114p was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (15 – 55 % MeCN; RT = 17.1 min) gave title compound **114p** and its diastereomer (RT = 20.0 min) in a ratio of 2.44:1 and a combined yield of 40 % (15.0 mg, 11.5 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 9.02 (d, J = 4.8 Hz, 2H), 8.40 (d, J = 8.4 Hz, 2H), 8.23 (d, J = 8.4 Hz, 2H), 7.96 (ddd, J = 8.3, 6.8, 1.2 Hz, 2H), 7.88 (d, J = 4.8 Hz, 2H), 7.84 (ddd, J = 8.3, 6.9, 1.2 Hz, 2H), 7.33 (d, J = 3.2 Hz, 2H), 7.26 – 7.22 (m, 4H), 7.22 – 7.14 (m, 6H), 5.13 (q, J = 7.2 Hz, 2H), 4.10 (d, J = 8.2 Hz, 2H), 3.86 (t, J = 7.9 Hz, 2H), 3.83 – 3.79 (m, 2H), 3.70 (dd, J = 11.6, 6.8 Hz, 2H), 3.59 (t, J = 7.2 Hz, 2H), 3.49 (ddd, J = 12.9, 10.9, 1.7 Hz, 2H), 3.41 (tt, J = 11.2, 3.2 Hz, 2H), 3.31 – 3.23 (m, 4H), 2.75 – 2.69 (m, 2H), 2.62 (s, 2H), 2.35 (td, J = 11.1, 7.1 Hz, 2H), 1.88 – 1.83 (m, 2H), 1.82 – 1.77 (m, 2H), 1.67 (tt, J = 11.6, 2.4 Hz, 2H), 1.50 (d, J = 7.2 Hz, 6H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.16, 175.95, 168.87, 149.17, 145.68, 144.57, 140.24, 132.22, 129.60, 128.95, 128.36, 128.00, 127.29, 125.23, 123.86, 119.81, 69.92, 63.85, 63.67, 59.45, 50.59, 50.16, 49.87, 48.52, 48.10, 33.22, 23.64, 23.60, 19.02, 16.44.

HRMS (ESI): $C_{64}H_{65}O_8N_8$ $[M+H]^+$; calculated: 1073.49199, found: 1073.49276.

$[\alpha]_{20}^{D}$ = +105° (c = 0.5, MeCN).

114q, CN-1-Phenylcyclopropyl-S; 115a, CN-1-Phenylcyclopropyl-A

114q was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (10 – 50 % MeCN; RT = 19.6 min) gave title compound **114q** and its diastereomers **115a**

(RT = 20.0 min, RT = 22.9 min) in a ratio of 1.6 : 3.8 : 1 and a combined yield of 20 % (7.7 mg, 5.81 µmol).

114q, CN-1-Phenylcyclopropyl-S

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 9.02 (t, J = 4.9 Hz, 2H), 8.40 (d, J = 8.5 Hz, 1H), 8.35 (d, J = 8.5 Hz, 1H), 8.23 (td, J = 8.8, 1.2 Hz, 2H), 8.01 – 7.95 (m, 3H), 7.89 – 7.85 (m, 2H), 7.84 (ddd, J = 8.3, 6.8, 1.2 Hz, 1H), 7.34 (s, 1H), 7.22 – 7.12 (m, 7H), 7.08 – 7.04 (m, 2H), 6.96 – 6.92 (m, 2H), 4.23 (d, J = 8.2 Hz, 1H), 4.07 (t, J = 7.9 Hz, 1H), 3.99 (d, J = 7.9 Hz, 1H), 3.96 – 3.90 (m, 2H), 3.80 – 3.75 (m, 2H), 3.73 – 3.71 (m, 1H), 3.62 (t, J = 7.3 Hz, 1H), 3.53 – 3.38 (m, 6H), 3.32 – 3.23 (m, 2H), 3.07 (s, 1H), 2.75 – 2.69 (m, 1H), 2.64 (s, 1H), 2.51 – 2.45 (m, 1H), 2.42 – 2.33 (m, 2H), 2.30 (s, 1H), 2.08 – 2.00 (m, 1H), 1.92 (s, 1H), 1.83 – 1.75 (m, 3H), 1.74 – 1.69 (m, 1H), 1.32 (ddd, J = 10.5, 7.4, 5.5 Hz, 1H), 1.25 (ddd, J = 10.1, 7.5, 5.5 Hz, 1H), 1.22 – 1.13 (m, 3H), 1.08 – 1.02 (m, 2H), 0.85 – 0.80 (m, 1H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 178.27, 176.51, 176.38, 176.22, 169.71, 169.23, 149.09, 148.48, 145.52, 144.64, 144.51, 143.90, 140.23, 140.15, 132.51, 132.24, 129.75, 129.61, 128.96, 128.95, 128.30, 127.47, 127.42, 125.89, 125.34, 125.08, 123.84, 123.70, 121.11, 119.92, 70.95, 69.82, 64.54, 63.63, 63.54, 62.27, 59.52, 58.82, 51.18, 51.05, 50.94, 50.01, 49.88, 49.71, 48.73, 47.99, 36.67, 34.97, 34.86, 33.23, 24.69, 23.65, 23.58, 23.22, 19.41, 17.78, 16.31, 15.91.

HRMS (ESI): $C_{66}H_{65}O_8N_8$ $[M+H]^+$; calculated: 1097.49199, found: 1097.490300.

$[\alpha]_{20}^{D}$ = + 51 ° (c = 0.3, MeCN).

115a, CN-1-Phenylcyclopropyl-A

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 9.00 (d, J = 4.7 Hz, 2H), 8.32 (dd, J = 8.6, 1.3 Hz, 2H), 8.20 (dd, J = 8.5, 1.2 Hz, 2H), 7.93 (ddd, J = 8.3, 6.8, 1.2 Hz, 2H), 7.84 – 7.79 (m, 4H), 7.27 (s, 2H), 7.22 – 7.18 (m, 4H), 7.16 – 7.13 (m, 2H), 7.06 – 7.02 (m, 4H), 4.10 (d, J = 8.2 Hz, 2H), 3.90 (t, J = 7.9 Hz, 2H), 3.81 (dd, J = 10.5, 8.0 Hz, 2H), 3.72 (dd, J = 11.6, 6.8 Hz, 2H), 3.61 (t, J = 7.2 Hz, 2H), 3.49 (ddd, J = 13.0, 10.8, 1.8 Hz, 2H), 3.42 (ddt, J = 14.1, 11.4, 3.2 Hz, 2H), 3.33 – 3.25 (m, 4H), 2.73 (ddt, J = 13.1, 7.6, 2.4 Hz, 2H), 2.64 (s, 2H), 2.40 (td, J = 11.1, 7.0 Hz, 2H), 1.93 – 1.89 (m, 2H), 1.81 (dddd, J = 13.6, 10.7, 7.2, 2.3 Hz, 2H), 1.68 (ddd,

J = 14.4, 10.5, 3.9 Hz, 2H), 1.30 (ddd, J = 10.6, 7.5, 5.6 Hz, 2H), 1.25 – 1.20 (m, 2H), 1.19 – 1.15 (m, 2H), 1.05 – 1.00 (m, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.38, 176.10, 168.88, 149.72, 146.57, 143.37, 140.22, 131.72, 129.30, 129.11, 128.94, 127.43, 125.97, 125.01, 123.57, 119.68, 70.01, 63.83, 63.66, 59.46, 49.90, 49.88, 48.55, 47.99, 34.95, 33.21, 23.55, 18.99, 16.67, 16.19.

HRMS (ESI): $C_{66}H_{65}O_8N_8$ $[M+H]^+$; calculated: 1097.49199, found: 1097.490300.

$[\alpha]_{20}^{D}$ = + 81 ° (c = 0.3, MeCN).

114r, CN-1-Methyl-1-(2-Fluorophenyl)ethyl-S

13r was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (10 – 55 % MeCN; RT = 19.2 min) gave title compound **114r** and its diastereomer (RT = 21.8 min) in a ratio of 1.55 : 1 and a combined yield of 30 % (11.7 mg, 8.57 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.96 (d, J = 4.7 Hz, 2H), 8.31 (dd, J = 8.5, 1.2 Hz, 2H), 8.19 (dd, J = 8.5, 1.2 Hz, 2H), 7.93 (ddd, J = 8.2, 6.8, 1.2 Hz, 2H), 7.83 – 7.78 (m, 4H), 7.31 (s, 2H), 7.24 – 7.17 (m, 4H), 7.05 (td, J = 7.6, 1.3 Hz, 2H), 7.01 (ddd, J = 12.8, 8.2, 1.3 Hz, 2H), 4.04 (d, J = 7.8 Hz, 2H), 3.80 (t, J = 7.8 Hz, 2H), 3.78 – 3.76 (m, 2H), 3.64 (dd, J = 11.8, 7.1 Hz, 2H), 3.51 (ddd, J = 13.0, 10.9, 1.7 Hz, 2H), 3.45 (t, J = 7.4 Hz, 2H), 3.38 (ddt, J = 14.0, 11.2, 3.3 Hz, 2H), 3.27 – 3.21 (m, 4H), 2.69 – 2.62 (m, 2H), 2.52 (s, 2H), 2.18 – 2.12 (m, 2H), 1.76 – 1.70 (m, 2H), 1.66 (s, 6H), 1.66 – 1.63 (m, 2H), 1.61 (s, 8H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.08, 175.92, 168.89, 159.48, 149.68, 146.58, 143.41, 133.04, 132.98, 131.72, 129.54, 129.49, 129.28, 129.07, 127.36, 127.34, 125.00, 124.85, 123.63, 119.64, 116.36, 69.59, 64.16, 63.89, 60.58, 59.56, 50.78, 49.84, 48.27, 47.82, 33.48, 27.12, 26.50, 23.53, 23.23, 18.76.

HRMS (ESI): $C_{66}H_{67}O_8N_8F_2$ $[M+H]^+$; calculated: 1137.50444, found: 1137.50607.

$[\alpha]_{20}^{D}$ = + 76 ° (c = 0.3, MeCN).

114s, CN-1-(2-Chlorophenyl)cyclopropyl-S; 115b, CN-1-(2-Chlorophenyl)cyclo-propyl -A

114s was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (10 – 55 % MeCN; RT = 20.0 min) gave title compound **114s** and its diastereomer **115b** (RT = 22.4 min) in a ratio of 1 : 1.3 and a combined yield of 15 % (5.9 mg, 4.23 µmol).

114s, CN-1-(2-Chlorophenyl)cyclopropyl-S

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.99 (d, J = 4.9 Hz, 2H), 8.30 (d, J = 8.3 Hz, 2H), 8.23 (d, J = 8.5 Hz, 2H), 7.96 (ddd, J = 8.4, 6.9, 1.3 Hz, 2H), 7.84 (ddd, J = 8.3, 6.9, 1.3 Hz, 2H), 7.79 (d, J = 4.6 Hz, 2H), 7.53 (dd, J = 7.8, 1.7 Hz, 2H), 7.28 – 7.23 (m, 4H), 7.16 (td, J = 7.6, 1.7 Hz, 2H), 7.07 (td, J = 7.6, 1.3 Hz, 2H), 3.97 (d, J = 8.3 Hz, 2H), 3.80 (dd, J = 10.7, 7.9 Hz, 2H), 3.72 (t, J = 8.0 Hz, 2H), 3.59 (dd, J = 11.7, 6.9 Hz, 2H), 3.46 – 3.42 (m, 2H), 3.40 (d, J = 11.0 Hz, 4H), 3.27 (ddd, J = 13.2, 11.0, 7.2 Hz, 2H), 3.20 (ddd, J = 13.6, 7.2, 2.8 Hz, 2H), 2.68 – 2.63 (m, 2H), 2.60 (s, 2H), 2.37 (q, J = 11.0 Hz, 2H), 1.91 (d, J = 13.4 Hz, 2H), 1.85 – 1.78 (m, 2H), 1.68 – 1.62 (m, 2H), 1.44 (ddd, J = 9.2, 7.7, 5.0 Hz, 2H), 1.26 – 1.19 (m, 4H), 1.10 (ddd, J = 10.0, 7.6, 5.0 Hz, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 175.80, 175.75, 168.85, 149.90, 136.65, 135.32, 134.96, 131.59, 130.33, 130.22, 129.38, 129.20, 126.91, 125.02, 123.61, 119.66, 69.82, 63.85, 63.60, 59.56, 49.95, 49.89, 48.51, 47.88, 35.53, 32.99, 23.54, 23.48, 18.92, 14.25, 14.16.

HRMS (ESI): $C_{66}H_{63}O_8N_8Cl_2$ $[M+H]^+$; calculated: 1165.41404, found: 1165.41553.

$[\alpha]_{20}^{D}$ = + 80 ° (c = 0.2, MeCN).

115b, CN-1-(2-Chlorophenyl)cyclopropyl-A

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 9.05 (d, J = 4.6 Hz, 1H), 9.00 (d, J = 4.7 Hz, 1H), 8.27 (dd, J = 8.4, 3.9 Hz, 2H), 8.24 (dd, J = 8.6, 1.2 Hz, 1H), 8.20 (dd, J = 8.5, 1.2 Hz, 1H), 7.96 (ddd, J = 8.4, 6.8, 1.2 Hz, 1H), 7.92 (ddd, J = 8.3, 6.8, 1.2 Hz, 1H), 7.85 (td, J = 8.1, 1.7 Hz, 3H), 7.63 – 7.60 (m, 2H), 7.55 (d, J = 4.7 Hz, 1H), 7.48 (dd, J = 7.5, 1.7 Hz, 1H), 7.39 – 7.33 (m, 2H), 7.29 – 7.27 (m, 2H), 7.18 (td, J = 7.6, 1.8 Hz, 1H), 7.11 (td, J = 7.6, 1.4 Hz, 1H), 7.08 (s, 1H), 3.94 (d, J = 8.6 Hz, 1H), 3.84 (d, J = 8.4 Hz, 1H), 3.80 (t, J = 9.4 Hz, 2H), 3.57 (dd, J = 11.6, 6.8 Hz, 1H), 3.56 – 3.53 (m, 1H), 3.52 – 3.41 (m, 8H), 3.30 (dddd, J = 12.9, 10.4, 6.4, 3.1 Hz, 2H), 3.26 – 3.21 (m, 1H), 3.10 (dd, J = 10.0, 7.4 Hz, 1H), 2.65 (s, 1H), 2.59 (s, 1H), 2.50 – 2.45 (m, 1H), 2.42 (q, J = 10.4, 10.0 Hz, 1H), 2.33 – 2.28 (m, 1H), 2.24 – 2.19 (m, 1H), 1.92 – 1.87 (m, 1H), 1.83 – 1.76 (m, 3H), 1.72 (ddd, J = 10.4, 7.3, 5.6 Hz, 1H), 1.60 (ddd, J = 14.2, 10.5, 4.1 Hz, 1H), 1.55 (ddd, J = 14.3, 10.3, 4.2 Hz, 1H), 1.49 – 1.43 (m, 2H), 1.39 (ddd, J = 10.2, 7.2, 5.5 Hz, 1H), 1.32 – 1.24 (m, 3H), 1.17 – 1.12 (m, 1H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.81, 176.06, 175.81, 175.77, 169.20, 169.16, 149.96, 147.15, 143.12, 142.38, 137.29, 136.71, 135.40, 135.12, 134.81, 131.60, 130.50, 130.40, 130.36, 130.25, 129.57, 129.50, 129.22, 129.13, 127.37, 126.94, 124.97, 124.91, 123.54, 123.46, 71.91, 70.19, 65.01, 63.78, 63.59, 59.12, 58.71, 52.03, 51.91, 50.39, 50.02, 49.40, 49.00, 48.26, 38.17, 36.10, 35.54, 33.36, 23.65, 23.38, 23.23, 23.10, 19.32, 19.05, 14.41, 14.13, 13.38, 13.31.

HRMS (ESI): $C_{66}H_{63}O_8N_8Cl_2$ $[M+H]^+$; calculated: 1165.41404, found: 1165.41553.

$[\alpha]_{20}^{D}$ = + 54 ° (c = 0.2, MeCN).

114t, CN-(S)-β-Methylphenethyl-S

114t was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (10 – 60 % MeCN; RT = 18.1 min) gave title compound **114t** and its 2 diastereomers (RT = 18.0 min, RT = 22.2 min) in a ratio of 4.8:1.1:1 and a combined yield of 22 % (8.2 mg, 6.17 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) 1H NMR (700 MHz,) δ 9.01 (d, J = 4.7 Hz, 2H), 8.34 (d, J = 8.4 Hz, 2H), 8.25 – 8.19 (m, 2H), 7.94 (ddd, J = 8.4, 6.9, 1.2 Hz, 2H), 7.85 – 7.80 (m, 4H), 7.32 (s, 2H), 7.29 – 7.24 (m, 4H), 7.22 – 7.17 (m, 2H), 7.11 – 7.04 (m, 4H), 3.95 (d, J = 7.9 Hz, 2H), 3.86 (t, J = 7.7 Hz, 2H), 3.80 (dd, J = 10.7, 7.7 Hz, 2H), 3.55 (dd, J = 11.7, 7.3 Hz, 2H), 3.44 (t, J = 7.4 Hz, 2H), 3.43 – 3.38 (m, 4H), 3.38 – 3.31 (m, 4H), 3.26 (ddd, J = 13.3, 10.8, 7.4 Hz, 2H), 3.14 (ddd, J = 13.6, 7.1, 2.8 Hz, 2H), 3.08 – 3.05 (m, 2H), 2.70 – 2.61 (m, 2H), 2.54 (s, 2H), 1.94 – 1.91 (m, 2H), 1.87 – 1.74 (m, 4H), 1.66 (ddd, J = 14.3, 10.7, 3.8 Hz, 2H), 1.05 (d, J = 7.1 Hz, 6H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 175.99, 175.94, 168.55, 149.92, 146.88, 143.96, 143.24, 131.61, 129.31, 129.22, 129.15, 127.94, 127.29, 125.02, 123.61, 119.71, 69.53, 63.44, 63.34, 59.58, 50.60, 49.82, 48.14, 48.04, 45.83, 37.66, 33.21, 23.53, 23.28, 19.20, 18.77.

HRMS (ESI): $C_{66}H_{69}O_8N_8$ $[M+H]^+$; calculated: 1101.52329, found: 1101.52383.

$[\alpha]_{20}^{D}$ = + 86 ° (c = 0.4, MeCN).

114u, CN-(R)-β-Methylphenethyl-S

114u was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (10 – 50 % MeCN; RT = 20.5 min) gave title compound **114u** and its 2 diastereomers (RT = 20.3 min, RT = 23.3 min) in a ratio of 8.01:1:1.32 and a combined yield of 37 % (14.2 mg, 10.7 µmol). **13s** and its asymmetric diastereomer eluting at 20.3min could not be fully separated. The following spectrum shows a 5:1 mix of the two species.

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.97 (d, J = 4.7 Hz, 2H), 8.37 (d, J = 8.3 Hz, 2H), 8.22 (dd, J = 8.6, 1.3 Hz, 2H), 7.95 (ddd, J = 8.4, 6.9, 1.2 Hz, 2H), 7.84 (ddd, J = 8.3, 6.9, 1.3 Hz, 2H), 7.78 (dd, J = 4.7, 0.8 Hz, 2H), 7.36 (s, 2H), 7.35 – 7.29 (m, 6H), 7.27 – 7.20 (m, 4H), 3.87 (d, J = 7.7 Hz, 2H), 3.81 – 3.75 (m, 4H), 3.63 (dd, J = 13.5, 11.2 Hz, 2H), 3.47 – 3.36 (m, 6H), 3.27 (dd, J = 13.4, 5.3 Hz, 2H), 3.20 – 3.12 (m, 4H), 3.05 – 3.01 (m, 2H), 2.78 – 2.69 (m, 2H), 2.57 (tt, J = 10.2, 2.6 Hz, 2H), 2.45 (s, 2H), 1.78 – 1.71 (m, 2H), 1.65 – 1.58 (m, 4H), 1.09 (d, J = 7.1 Hz, 6H), 0.79 (td, J = 11.3, 7.2 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 175.72, 174.89, 168.69, 149.89, 146.88, 144.12, 143.14, 131.63, 129.33, 129.26, 129.10, 129.04, 127.43, 124.98, 123.59, 119.66, 69.52, 63.34, 63.17, 59.48, 50.93, 49.81, 48.31, 47.95, 45.49, 38.84, 33.23, 23.42, 22.90, 19.25, 18.59.

HRMS (ESI): $C_{66}H_{69}O_8N_8$ $[M+H]^+$; calculated: 1101.52329, found: 1101.52377.

13v, CN-2-(5-Fluoro-1H-indole-3-yl)ethyl-S

13v was prepared from aldehyde **113a** according to General Procedure 6. Preparative HPLC (20 – 60 % MeCN; RT = 14.3 min) gave title compound **13v** and its diastereomer (RT = 16.1 min) in a ratio of 2.98:1 and a combined yield of 40 % (16.1 mg, 11.4 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 9.04 (d, J = 5.0 Hz, 2H), 8.48 (d, J = 8.4 Hz, 2H), 8.26 (d, J = 8.3 Hz, 2H), 8.01 (ddd, J = 8.4, 6.9, 1.2 Hz, 2H), 7.92 – 7.87 (m, 4H), 7.43 (dd, J = 8.9, 4.5 Hz, 2H), 7.41 (s, 2H), 7.24 (dd, J = 10.0, 2.5 Hz, 2H), 7.12 (s, 2H), 6.92 (td, J = 9.2, 2.5 Hz, 2H), 3.91 (d, J = 7.7 Hz, 2H), 3.86 – 3.79 (m, 4H), 3.80 – 3.75 (m, 2H), 3.48 (dd, J = 11.8, 7.5 Hz, 2H), 3.44 – 3.38 (m, 4H), 3.36 (tt, J = 11.5, 3.3 Hz, 2H), 3.18 (ddd, J = 13.0, 11.0, 1.7 Hz, 2H), 3.16 – 3.10 (m, 2H), 3.10 – 3.09 (m, 2H), 2.84 – 2.79 (m, 2H), 2.67 (ddd, J = 14.4, 10.3, 6.7 Hz, 2H), 2.58 (ddt, J = 12.8, 7.4, 2.4 Hz, 2H), 2.36 (s, 2H), 1.67 – 1.61 (m, 2H), 1.59 (ddd, J = 14.5, 10.8, 3.7 Hz, 2H), 1.24 – 1.18 (m, 2H), 0.83 (td, J = 11.2, 7.0 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 175.74, 175.02, 168.64, 158.51, 157.19, 148.69, 145.54, 144.81, 133.65, 132.67, 129.89, 128.21, 128.15, 127.64, 126.77, 125.29, 123.97, 119.91, 112.66, 112.60, 111.68, 111.66, 110.42, 110.27, 104.59, 104.46, 69.43, 63.24, 63.14, 59.40, 50.89, 49.75, 48.28, 47.86, 38.88, 33.38, 23.36, 22.87, 18.52.

HRMS (ESI): $C_{68}H_{65}O_8N_{10}F_2$ $[M+H]^+$; calculated: 1187.49494, found: 1187.49510.

$[\alpha]_{20}^{D}$ = + 136 ° (c = 0.5, MeCN).

5.10.13 Macrocycles from aldehyde 113b

116a, QD6*i*Pr-Me-S

116a was prepared from aldehyde **113b** according to General Procedure 6. Preparative HPLC (10 – 50 % MeCN; RT = 14.8 min) gave title compound **116a** and its diastereomer (RT = 16.6 min) in a ratio of 17.3 : 1 and a combined yield of 43 % (15.3 mg, 12.3 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.92 (d, J = 5.3 Hz, 2H), 8.21 (d, J = 9.4 Hz, 2H), 8.05 (d, J = 5.3 Hz, 2H), 7.64 (dd, J = 9.3, 2.5 Hz, 2H), 7.61 (s, 2H), 7.35 (s, 2H), 5.09 (hept, J = 6.3 Hz, 2H), 4.07 (d, J = 8.1 Hz, 2H), 3.94 (t, J = 7.7 Hz, 2H), 3.87 – 3.80 (m, 2H), 3.67 (dd, J = 11.7, 7.1 Hz, 2H), 3.59 (t, J = 7.2 Hz, 2H), 3.48 (ddd, J = 13.1, 10.9, 1.7 Hz, 2H), 3.33 (t, J = 8.3 Hz, 4H), 3.25 (dd, J = 13.8, 7.2 Hz, 2H), 2.75 – 2.69 (m, 2H), 2.68 (s, 6H), 2.64 (s, 2H), 2.40 (td, J = 11.2, 7.2 Hz, 2H), 1.93 (d, J = 10.2 Hz, 2H), 1.87 – 1.80 (m, 2H), 1.67 (ddd, J = 14.4, 10.7, 3.9 Hz, 2H), 1.38 (dd, J = 5.9, 4.2 Hz, 12H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.44, 176.38, 168.64, 159.21, 146.26, 143.56, 137.87, 127.70, 127.41, 127.20, 120.45, 103.56, 71.74, 69.43, 63.55, 63.35, 58.96, 50.69, 49.79, 48.38, 48.17, 32.96, 25.01, 23.65, 23.48, 21.64, 21.17, 18.89.

HRMS (ESI): $C_{56}H_{65}O_{10}N_8$ $[M+H]^+$; calculated: 1009.48182, found: 1009.48284.

$[\alpha]_{20}^{D}$ = + 52 ° (c = 1, MeCN).

116b, QD6*i*Pr-*i*Pr-S

116b was prepared from aldehyde **113b** according to General Procedure 6. Preparative HPLC (10 – 40 % MeCN; RT = 23.6 min) gave title compound **116b** and its diastereomer (RT = 25.4 min) in a ratio of 5.5 : 1 and a combined yield of 16 % (5.9 mg, 4.56 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.83 (d, J = 4.8 Hz, 2H), 8.12 (d, J = 9.2 Hz, 2H), 7.82 (d, J = 4.8 Hz, 2H), 7.53 (dd, J = 9.2, 2.5 Hz, 2H), 7.47 (d, J = 2.6 Hz, 2H), 7.23 (s, 2H), 5.02 (hept, J = 6.1 Hz, 2H), 4.07 – 4.01 (m, 4H), 3.83 – 3.78 (m, 4H), 3.64 (dd, J = 11.6, 6.9 Hz, 2H), 3.50 (t, J = 7.2 Hz, 2H), 3.49 – 3.45 (m, 2H), 3.35 – 3.27 (m, 4H), 3.24 (ddd, J = 13.8, 7.2, 2.5 Hz, 2H), 2.71 – 2.65 (m, 2H), 2.63 (s, 2H), 2.42 (td, J = 11.1, 7.1 Hz, 2H), 1.91 (d, J = 3.3 Hz, 2H), 1.86 – 1.79 (m, 2H), 1.65 (ddd, J = 14.3, 10.7, 4.0 Hz, 2H), 1.38 (d, J = 2.7 Hz, 6H), 1.37 (d, J = 2.7 Hz, 6H), 1.31 – 1.23 (m, 2H), 1.15 (d, J = 6.9 Hz, 6H), 1.12 (d, J = 6.9 Hz, 6H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.24, 176.09, 168.84, 158.26, 146.12, 142.34, 141.69, 130.23, 126.62, 125.65, 119.97, 103.40, 71.35, 69.66, 63.72, 63.53, 59.16, 50.24, 49.89, 48.43, 48.01, 44.54, 33.03, 23.59, 23.53, 21.73, 21.32, 19.09, 18.98, 18.74.

$[\alpha]_{20}^{D}$ = + 45 ° (c = 0.5, MeCN).

116c, QD6*i*Pr-*t*Bu-S

116c was prepared from aldehyde **113b** according to General Procedure 6. Preparative HPLC (15 – 50 % MeCN; RT = 19.6 min) gave title compound **116c** and its diastereomer (RT = 21.5 min) in a ratio of 3.78 : 1 and a combined yield of 29 % (11.0 mg, 8.32 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.84 (d, J = 4.9 Hz, 2H), 8.12 (d, J = 9.2 Hz, 2H), 7.83 (d, J = 4.9 Hz, 2H), 7.53 (dd, J = 9.2, 2.5 Hz, 2H), 7.50 – 7.48 (m, 2H), 7.26 (s, 2H), 5.03 (hept, J = 6.0 Hz, 2H), 4.02 (d, J = 8.0 Hz, 2H), 3.80 (td, J = 8.6, 4.1 Hz, 2H), 3.69 (t, J = 7.8 Hz, 2H), 3.63 (dd, J = 11.7, 6.9 Hz, 2H), 3.50 (ddd, J = 13.7, 10.8, 1.7 Hz, 2H), 3.39 (t, J = 7.3 Hz, 2H), 3.34 – 3.26 (m, 4H), 3.23 (ddd, J = 13.8, 7.2, 2.3 Hz, 2H), 2.69 – 2.64 (m, 2H), 2.63 (s, 2H), 2.34 (td, J = 11.1, 7.0 Hz, 2H), 1.92 – 1.86 (m, 2H), 1.85 – 1.78 (m, 2H), 1.64 (ddd, J = 15.1, 10.7, 4.3 Hz, 2H), 1.37 (t, J = 5.9 Hz, 12H), 1.31 (s, 18H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.97, 176.96, 168.92, 158.32, 145.88, 142.74, 141.38, 129.93, 126.72, 125.81, 119.95, 103.45, 71.35, 69.57, 64.20, 63.89, 59.17, 58.88, 50.48, 49.87, 48.37, 47.99, 33.29, 27.91, 23.58, 23.41, 21.76, 21.27, 18.95.

HRMS (ESI): $C_{62}H_{77}O_{10}N_8$ $[M+H]^+$; calculated: 1093.57572, found: 1093.57703.

$[\alpha]_{20}^{D}$ = + 43 ° (c = 0.5, MeCN).

116d, QD6*i*Pr-Neopentyl-S, 117a, QD6*i*Pr-Neopentyl-A

116d and was prepared from aldehyde **113b** according to General Procedure 6. Preparative HPLC (10 – 50 % MeCN, 30 ml/min; RT = 21.6 min) gave title compound **116d** and its diastereomer **117a** (RT = 22.7 min) in a ratio of 1.45 : 1 and a combined yield of 50 % (19.6 mg, 14.52 µmol).

15d, QD6*i*Pr-Neopentyl-S

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.89 (d, J = 4.7 Hz, 2H), 8.19 (d, J = 9.2 Hz, 2H), 7.99 (t, J = 4.8 Hz, 2H), 7.61 (d, J = 9.3 Hz, 2H), 7.58 (s, 2H), 7.33 (s, 2H), 5.07 (dq, J = 12.5, 6.0 Hz, 2H), 4.09 (d, J = 7.5 Hz, 2H), 3.94 (t, J = 7.8 Hz, 2H), 3.85 – 3.80 (m, 2H), 3.68 (dd, J = 11.6, 7.1 Hz, 2H), 3.60 (t, J = 7.3 Hz, 2H), 3.56 – 3.50 (m, 2H), 3.31 (t, J = 8.2 Hz, 4H), 3.21 (dd, J = 13.8, 7.2 Hz, 2H), 3.06 (s, 4H), 2.74 – 2.69 (m, 2H), 2.69 (s, 2H), 2.31 (td, J = 11.2, 7.3 Hz, 2H), 1.89 (dtp, J = 9.8, 6.0, 3.0 Hz, 2H), 1.86 – 1.80 (m, 2H), 1.67 (ddd, J = 14.5, 11.0, 3.9 Hz, 2H), 1.38 (dd, J = 6.0, 4.7 Hz, 12H), 0.73 (s, 18H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.95, 176.66, 168.51, 159.00, 145.48, 144.08, 138.68, 127.81, 127.26, 120.25, 103.54, 71.64, 69.37, 63.63, 63.34, 59.07, 50.56, 50.19, 49.79, 48.38, 47.88, 33.55, 33.46, 27.90, 23.62, 23.44, 21.68, 21.17, 18.95.

HRMS (ESI): $C_{64}H_{81}O_{10}N_8$ $[M+H]^+$; calculated: 1121.60702, found: 1121.60861.

$[\alpha]_{20}^{D}$ = + 43 ° (c = 0.5, MeCN).

117a, QD6*i*Pr-Neopentyl-A

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.79 (d, J = 4.7 Hz, 2H), 8.07 (dd, J = 9.2, 2.8 Hz, 2H), 7.66 (dd, J = 4.7, 0.8 Hz, 1H), 7.62 (d, J = 4.7 Hz, 1H), 7.48 (ddd, J = 9.2, 2.6, 1.1 Hz, 2H), 7.42 (dd, J = 9.3, 2.6 Hz, 2H), 7.27 (s, 1H), 7.06 (s, 1H), 5.00 (pd, J = 6.0, 4.1 Hz, 2H), 4.08 (d, J = 8.3 Hz, 1H), 4.02 (d, J = 8.5 Hz, 1H), 3.82 – 3.76 (m, 3H), 3.70 (dd, J =

10.1, 8.6 Hz, 1H), 3.67 (dd, J = 11.5, 7.0 Hz, 1H), 3.62 (dd, J = 10.9, 7.5 Hz, 1H), 3.57 (t, J = 7.4 Hz, 1H), 3.55 – 3.47 (m, 3H), 3.38 (s, 2H), 3.36 – 3.25 (m, 6H), 3.12 – 3.07 (m, 2H), 2.72 (s, 1H), 2.69 (s, 1H), 2.62 – 2.57 (m, 1H), 2.47 – 2.41 (m, 1H), 2.33 (q, J = 9.9 Hz, 1H), 2.26 (q, J = 10.7 Hz, 1H), 1.93 – 1.86 (m, 2H), 1.86 – 1.79 (m, 2H), 1.66 – 1.60 (m, 1H), 1.56 (ddd, J = 14.2, 10.6, 4.2 Hz, 1H), 1.39 – 1.36 (m, 12H), 0.94 (s, 9H), 0.76 (s, 9H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 177.87, 177.22, 177.07, 176.68, 169.52, 169.26, 157.90, 157.86, 147.22, 147.10, 143.40, 143.29, 141.08, 140.42, 131.50, 131.45, 126.34, 126.26, 124.92, 124.85, 119.40, 118.72, 103.32, 103.25, 71.85, 71.19, 71.17, 69.75, 64.72, 63.61, 63.33, 63.28, 58.94, 58.58, 52.84, 52.63, 50.58, 50.39, 50.36, 49.88, 49.82, 48.94, 48.19, 48.13, 38.13, 34.00, 33.53, 27.93, 23.53, 23.51, 23.29, 23.27, 21.77, 21.70, 21.39, 19.31, 19.14.

HRMS (ESI): $C_{64}H_{81}O_{10}N_8$ $[M+H]^+$; calculated: 1121.60702, found: 1121.60828.

$[\alpha]_{20}^{D}$ = + 22 ° (c = 0.3, MeCN).

116e, QD6*i*Pr-(R)-1-Cyclopropylethyl-S

116e was prepared from aldehyde **113b** according to General Procedure 6. Preparative HPLC (15 – 50 % MeCN; RT = 20.4 min) gave title compound **116e** and its diastereomer (RT = 22.53 min) in a ratio of ~ 3 : 1 and a combined yield of 22 % (8.6 mg, 6.39 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.83 (d, J = 4.8 Hz, 2H), 8.11 (d, J = 9.2 Hz, 2H), 7.82 (dt, J = 5.1, 1.4 Hz, 2H), 7.52 (dd, J = 9.2, 2.5 Hz, 2H), 7.47 (d, J = 2.5 Hz, 2H), 7.23 (s, 2H), 5.02 (hept, J = 5.9 Hz, 2H), 4.07 (d, J = 8.2 Hz, 2H), 3.87 (t, J = 7.9 Hz, 2H), 3.82 – 3.77 (m, 2H), 3.67 (dd, J = 11.6, 6.9 Hz, 2H), 3.54 (t, J = 7.2 Hz, 2H), 3.51 (ddd, J = 12.9, 10.8, 1.7 Hz, 2H), 3.35 – 3.26 (m, 4H), 3.24 (ddd, J = 13.9, 7.1, 2.4 Hz, 2H), 3.01 (dq, J = 10.1, 7.0 Hz, 2H), 2.69 (ddt, J = 13.2, 7.6, 2.4 Hz, 2H), 2.64 (s, 2H), 2.40 (td, J = 11.2, 7.1 Hz, 2H), 1.93 – 1.88 (m, 2H), 1.86 – 1.79 (m, 2H), 1.65 (ddd, J = 14.3, 10.6, 3.9 Hz, 2H), 1.37 (dd, J = 6.0, 1.3 Hz, 12H), 1.29 – 1.25 (m, 2H), 1.24 (d, J = 7.0 Hz, 6H), 0.44 (tdd, J = 8.5, 5.9, 4.3 Hz, 2H), 0.27 (dddd, J = 8.9, 7.9, 5.7, 4.4 Hz, 2H), 0.12 (dq, J = 9.9, 4.6 Hz, 2H), -0.02 (dq, J = 9.5, 4.7 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.38, 176.06, 168.79, 158.25, 146.17, 142.29, 141.76, 130.27, 126.59, 125.63, 119.92, 103.35, 71.32, 69.67, 63.74, 63.50, 59.14, 54.53, 50.22, 49.88, 48.47, 47.95, 33.21, 23.57, 23.55, 21.73, 21.29, 19.01, 17.50, 14.51, 4.82, 3.86.

HRMS (ESI): $C_{64}H_{77}O_{10}N_8$ $[M+H]^+$; calculated: 1117.57572, found: 1117.57693.

$[\alpha]_{20}^{D}$ = + 49 ° (c = 0.5, MeCN).

116f, QD6*i*Pr-(R)-1- Cyclohexylethyl-S; 117b, QD6*i*Pr-(R)-1-Cyclohexylethyl-A

116f was prepared from aldehyde **113b** according to General Procedure 6. Preparative HPLC (20 – 65 % MeCN; RT = 20.0 min) gave title compound **116f** and its diastereomer **117b** (RT = 21.9 min) in a ratio of 1.46:1 and a combined yield of 34 % (13.7 mg, 9.58 µmol).

116f, QD6*i*Pr-(R)-1- Cyclohexylethyl-S

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.88 (d, J = 5.1 Hz, 2H), 8.18 (d, J = 9.3 Hz, 2H), 7.94 (d, J = 5.1 Hz, 2H), 7.60 (dd, J = 9.3, 2.4 Hz, 2H), 7.54 (d, J = 2.5 Hz, 2H), 7.28 (s, 2H), 5.06 (hept, J = 6.0 Hz, 2H), 4.07 (d, J = 8.2 Hz, 2H), 3.86 (t, J = 7.9 Hz, 2H), 3.81 (dd, J = 10.4, 8.2 Hz, 2H), 3.65 (dd, J = 11.6, 6.8 Hz, 2H), 3.59 – 3.54 (m, 4H), 3.52 (dd, J = 13.7, 11.3 Hz, 2H), 3.34 – 3.28 (m, 4H), 3.22 (dd, J = 13.4, 7.1 Hz, 2H), 2.71 – 2.66 (m, 2H), 2.64 (s, 2H), 2.38 (td, J = 11.1, 7.1 Hz, 2H), 1.93 – 1.88 (m, 2H), 1.86 – 1.80 (m, 2H), 1.70 – 1.59 (m, 8H), 1.59 – 1.50 (m, 4H), 1.42 (d, J = 12.9 Hz, 2H), 1.38 (t, J = 5.5 Hz, 12H), 1.09 (d, J = 6.9 Hz, 6H), 1.16 – 0.98 (m, 6H), 0.74 (qd, J = 12.6, 3.4 Hz, 2H), 0.60 (qd, J = 12.1, 3.5 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.53, 176.37, 168.62, 158.83, 144.59, 139.46, 128.46, 127.08, 126.86, 120.16, 103.50, 71.59, 69.55, 63.78, 63.49, 59.03, 53.96, 49.88, 49.86, 48.49, 47.64, 39.34, 33.17, 30.43, 30.30, 26.31, 26.02, 23.58, 23.56, 21.70, 21.21, 19.00, 15.30.

HRMS (ESI): $C_{70}H_{89}O_{10}N_8$ $[M+H]^+$; calculated: 1201.66962, found: 1201.67058.

$[\alpha]_{20}^{D}$ = + 44 ° (c = 0.5, MeCN).

117b, QD6*i*Pr-(R)-1-Cyclohexylethyl-A

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.77 (dd, J = 13.1, 4.6 Hz, 2H), 8.07 (dd, J = 9.2, 4.2 Hz, 2H), 7.56 (d, J = 4.6 Hz, 2H), 7.47 (ddd, J = 9.3, 2.6, 0.8 Hz, 2H), 7.40 (dd, J = 14.5, 2.6 Hz, 2H), 7.23 (s, 1H), 7.03 (s, 1H), 4.98 (hept, J = 6.3 Hz, 2H), 4.10 (d, J =

8.2 Hz, 1H), 3.99 (d, J = 8.7 Hz, 1H), 3.84 (dq, J = 10.1, 7.0 Hz, 1H), 3.82 – 3.78 (m, 2H), 3.74 (dd, J = 11.6, 6.8 Hz, 1H), 3.66 – 3.62 (m, 2H), 3.62 – 3.58 (m, 1H), 3.57 – 3.46 (m, 5H), 3.39 – 3.25 (m, 5H), 3.21 (dd, J = 10.0, 7.6 Hz, 1H), 2.74 (s, 1H), 2.64 (s, 1H), 2.61 – 2.56 (m, 1H), 2.41 (q, J = 10.2, 9.7 Hz, 1H), 2.37 – 2.32 (m, 1H), 2.27 (q, J = 10.4 Hz, 1H), 1.93 – 1.90 (m, 3H), 1.86 – 1.81 (m, 1H), 1.80 – 1.74 (m, 2H), 1.69 (dd, J = 16.0, 7.6 Hz, 3H), 1.64 – 1.51 (m, 6H), 1.45 (d, J = 7.0 Hz, 4H), 1.38 (ddd, J = 6.3, 4.6, 1.9 Hz, 12H), 1.32 – 1.21 (m, 4H), 1.11 (d, J = 7.0 Hz, 4H), 1.03 (tt, J = 21.3, 10.7 Hz, 3H), 0.97 – 0.90 (m, 1H), 0.81 – 0.72 (m, 1H), 0.69 – 0.60 (m, 1H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 177.34, 176.74, 176.62, 176.30, 169.45, 169.28, 157.78, 157.74, 147.37, 147.25, 143.75, 131.78, 126.24, 126.12, 124.66, 119.16, 103.24, 71.17, 71.15, 70.01, 65.38, 63.67, 63.55, 63.39, 58.77, 58.48, 52.40, 52.19, 50.48, 49.99, 49.49, 49.04, 48.17, 39.86, 39.49, 38.23, 33.57, 30.56, 30.51, 30.43, 30.30, 26.40, 26.36, 26.31, 26.11, 26.02, 23.72, 23.35, 23.19, 23.06, 21.73, 21.67, 21.42, 19.39, 19.18, 15.47, 15.23.

HRMS (ESI): $C_{70}H_{89}O_{10}N_8$ $[M+H]^+$; calculated: 1201.66962, found: 1201.67079.

$[\alpha]_{20}^{D}$ = + 25 ° (c = 0.2, MeCN).

116g, QD6*i*Pr-Ph-S

116g was prepared from aldehyde **113b** according to General Procedure 6. Preparative HPLC (10 – 50 % MeCN; RT = 21.0 min) gave title compound **116g** and its diastereomer (RT = 22.3 min) in a ratio of 9.1 : 1 and a combined yield of 25 % (9.9 mg, 7.27 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.83 (d, J = 4.9 Hz, 2H), 8.09 (d, J = 9.1 Hz, 2H), 7.90 (d, J = 5.0 Hz, 2H), 7.54 – 7.49 (m, 4H), 7.39 – 7.35 (m, 4H), 7.34 – 7.31 (m, 2H), 7.27 (s, 2H), 7.11 – 7.07 (m, 4H), 5.03 (hept, J = 6.0 Hz, 2H), 4.23 (d, J = 8.3 Hz, 2H), 4.08 (t, J = 7.9 Hz, 2H), 3.83 (dd, J = 11.3, 7.0 Hz, 4H), 3.80 – 3.77 (m, 2H), 3.52 (ddd, J = 12.9, 10.9, 1.7 Hz, 2H), 3.37 (ddd, J = 13.6, 7.0, 2.3 Hz, 2H), 3.35 – 3.29 (m, 4H), 2.77 (ddt, J = 13.1, 7.7, 2.3 Hz, 2H), 2.65 (s, 2H), 2.53 (td, J = 11.0, 6.7 Hz, 2H), 1.93 – 1.89 (m, 2H), 1.86 – 1.80 (m, 2H), 1.70 (td, J = 12.3, 10.5, 3.8 Hz, 2H), 1.37 (d, J = 2.7 Hz, 6H), 1.36 (d, J = 2.6 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 175.55, 175.50, 168.95, 158.46, 145.44, 143.26, 140.68, 132.58, 129.60, 129.42, 129.40, 127.44, 126.79, 126.10, 120.07, 103.43, 71.42, 69.91, 63.98, 63.89, 59.05, 50.86, 49.83, 48.84, 48.35, 33.01, 23.62, 23.60, 21.68, 21.28, 19.04.

$[\alpha]_{20}^{D}$ = + 28 ° (c = 0.5, MeCN).

116h, QD6*i*Pr-Bn-S

116h was prepared from aldehyde **113b** according to General Procedure 6. Preparative HPLC (15 – 50 % MeCN; RT = 22.1 min) gave title compound **116h** and its diastereomer (RT = 23.3 min) in a ratio of 4.19 : 1 and a combined yield of 35 % (14.0 mg, 10.1 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.78 (d, J = 4.7 Hz, 2H), 8.07 (d, J = 9.2 Hz, 2H), 7.75 (d, J = 4.7 Hz, 2H), 7.47 (dd, J = 9.2, 2.6 Hz, 2H), 7.43 (d, J = 2.5 Hz, 2H), 7.27 – 7.18 (m, 8H), 7.14 – 7.10 (m, 4H), 5.02 (hept, J = 6.0 Hz, 2H), 4.46 (d, J = 15.1 Hz, 2H), 4.37 (d, J = 15.0 Hz, 2H), 4.08 (d, J = 8.1 Hz, 2H), 3.96 (t, J = 7.8 Hz, 2H), 3.83 – 3.76 (m, 2H), 3.69 (dd, J = 11.5, 7.0 Hz, 2H), 3.64 (t, J = 7.2 Hz, 2H), 3.49 (ddd, J = 13.0, 10.9, 1.7 Hz, 2H), 3.35 – 3.22 (m, 6H), 2.70 (ddt, J = 13.1, 7.6, 2.4 Hz, 2H), 2.65 (s, 2H), 2.38 (td, J = 11.1, 7.1 Hz, 2H), 1.92 – 1.86 (m, 2H), 1.85 – 1.79 (m, 2H), 1.65 (ddd, J = 14.4, 10.5, 3.9 Hz, 2H), 1.37 (d, J = 2.9 Hz, 6H), 1.36 (d, J = 2.8 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.26, 175.86, 168.67, 157.93, 147.06, 143.08, 140.99, 136.21, 131.32, 129.08, 128.15, 126.32, 124.92, 119.77, 103.27, 71.17, 69.74, 63.69, 63.49, 59.23, 50.42, 49.81, 48.43, 48.35, 42.88, 33.23, 23.59, 23.53, 21.76, 21.35, 18.97.

HRMS (ESI): $C_{68}H_{73}O_{10}N_8$ $[M+H]^+$; calculated: 1161.54442, found: 1161.54631.

$[\alpha]_{20}^{D}$ = + 38 ° (c = 0.5, MeCN).

116i, QD6*i*Pr-(S)-1-Phenylethyl-S, **116c, QD6*i*Pr-(S)-1-Phenylethyl-A**

116i was prepared from aldehyde **113b** according to General Procedure 6. Preparative HPLC (15 – 60 % MeCN; RT = 19.9 min) gave title compound **116i** P2S and its diastereomers (RT = 19.3 min, RT = 21.4 min) in a ratio of 1.1 : 5.8 : 1 and a combined yield of 26 % (10.4 mg, 7.34 µmol).

116i, QD6*i*Pr-(S)-1-Phenylethyl-S

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.87 (d, J = 5.1 Hz, 2H), 8.15 (d, J = 9.2 Hz, 2H), 7.93 (dd, J = 5.1, 0.8 Hz, 2H), 7.58 (dd, J = 9.2, 2.5 Hz, 2H), 7.53 (d, J = 2.5 Hz, 2H), 7.27 (s, 2H), 7.25 – 7.14 (m, 10H), 5.11 – 5.06 (m, 2H), 5.08 – 5.02 (m, 2H), 4.10 (d, J = 8.2 Hz, 2H), 3.94 (t, J = 7.9 Hz, 2H), 3.82 – 3.77 (m, 2H), 3.69 (dd, J = 11.6, 6.8 Hz, 2H), 3.56 – 3.49 (m, 4H), 3.35 – 3.26 (m, 4H), 3.24 (ddd, J = 13.9, 7.1, 2.4 Hz, 2H), 2.68 (ddt, J = 13.2, 7.7, 2.4 Hz, 2H), 2.60 (s, 2H), 2.41 (td, J = 11.1, 7.2 Hz, 2H), 1.92 – 1.86 (m, 2H), 1.80 (dddd, J = 13.0, 10.3, 7.9, 2.4 Hz, 2H), 1.63 (ddd, J = 14.1, 10.2, 3.5 Hz, 2H), 1.58 (d, J = 7.2 Hz, 6H), 1.38 (t, J = 5.9 Hz, 12H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.17, 176.05, 168.68, 158.74, 144.79, 144.29, 139.93, 139.70, 128.81, 128.65, 127.93, 127.31, 126.97, 126.71, 120.08, 103.41, 71.54, 69.60, 63.68, 63.44, 58.98, 50.77, 50.07, 49.83, 48.45, 47.85, 33.16, 23.54, 23.46, 21.66, 21.22, 18.95, 16.94.

HRMS (ESI): $C_{70}H_{77}O_{10}N_8$ $[M+H]^+$; calculated: 1189.57572, found: 1189.57662.

$[\alpha]_{20}^{D}$ = + 15 ° (c = 1, MeCN).

117c, QD6*i*Pr-(S)-1-Phenylethyl-A

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.84 (d, J = 4.7 Hz, 1H), 8.81 (d, J = 4.8 Hz, 1H), 8.09 (dd, J = 9.2, 5.5 Hz, 2H), 7.64 (d, J = 4.8 Hz, 1H), 7.59 (d, J = 4.8 Hz, 1H), 7.52 (ddd, J = 9.3, 2.5, 1.8 Hz, 2H), 7.50 – 7.38 (m, 7H), 7.26 – 7.23 (m, 4H), 7.22 (s, 1H), 7.21 – 7.16 (m, 1H), 7.05 (s, 1H), 5.40 (q, J = 7.3 Hz, 1H), 5.14 (q, J = 7.2 Hz, 1H), 5.00 (dp, J = 10.0, 6.0 Hz, 2H), 4.09 (dd, J = 10.4, 8.5 Hz, 2H), 3.82 – 3.73 (m, 4H), 3.63 (dd, J = 10.0, 8.3 Hz, 1H), 3.60 – 3.46 (m, 5H), 3.40 – 3.24 (m, 5H), 3.23 (dd, J = 10.0, 7.5 Hz, 1H), 2.67 (s, 1H), 2.59 (d, J = 15.4 Hz, 2H), 2.48 – 2.42 (m, 1H), 2.32 – 2.21 (m, 2H), 1.90 (d, J = 11.9 Hz, 2H), 1.87 (d, J = 7.3 Hz, 3H), 1.83 – 1.78 (m, 2H), 1.61 (d, J = 7.2 Hz, 3H), 1.59 – 1.55 (m, 1H), 1.49 (ddd, J = 14.4, 11.2, 4.4 Hz, 1H), 1.40 – 1.36 (m, 12H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) 13C NMR (176 MHz, ACN_D2O) δ 176.83, 176.26, 169.41, 169.38, 158.18, 158.13, 146.38, 140.02, 130.75, 130.63, 129.11, 128.82, 128.29, 127.96, 127.60, 127.45, 126.56, 126.40, 125.47, 119.23, 103.40, 103.26, 72.07, 71.34, 70.16, 64.87, 63.62, 63.49, 58.67, 58.39, 52.57, 52.33, 50.75, 50.66, 50.42, 50.05, 49.73, 49.07,

48.47, 48.12, 38.33, 33.58, 23.70, 23.35, 23.25, 23.16, 21.73, 21.66, 21.40, 19.42, 19.08, 16.81, 16.68.

HRMS (ESI): $C_{70}H_{77}O_{10}N_8$ $[M+H]^+$; calculated: 1189.57572, found: 1189.57664.

$[\alpha]_{20}^{D}$ = + 7 ° (c = 0.2, MeCN).

116j, QD6*i*Pr-(R)-1-Phenylethyl-S, **117d, QD6*i*Pr-(R)-1-Phenylethyl-A**

116j and **117d** were prepared from aldehyde **113b** according to General Procedure 6. Preparative HPLC (15 – 50 % MeCN 30 mL/min; RT = 21.3 min) gave title compound **116j** and its diastereomer **117d** (RT = 22.7 min) in a ratio of 1.65 : 1 and a combined yield of 31 % (12.6 mg, 8.89 µmol).

116j, QD6*i*Pr-(R)-1-Phenylethyl-S

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.81 (d, J = 4.9 Hz, 2H), 8.11 (d, J = 9.2 Hz, 2H), 7.84 (d, J = 4.9 Hz, 2H), 7.54 (dd, J = 9.2, 2.4 Hz, 2H), 7.49 (d, J = 2.6 Hz, 2H), 7.26 – 7.16 (m, 12H), 5.14 (q, J = 7.2 Hz, 2H), 5.03 (hept, J = 6.1 Hz, 2H), 4.09 (d, J = 8.3 Hz, 2H), 3.85 (t, J = 7.9 Hz, 2H), 3.82 – 3.77 (m, 2H), 3.68 (dd, J = 11.6, 6.8 Hz, 2H), 3.59 (t, J = 7.1 Hz, 2H), 3.49 (t, J = 12.1 Hz, 2H), 3.35 – 3.21 (m, 6H), 2.67 (dd, J = 13.8, 8.0 Hz, 2H), 2.61 (s, 2H), 2.34 (td, J = 11.1, 7.1 Hz, 2H), 1.89 – 1.84 (m, 2H), 1.84 – 1.78 (m, 2H), 1.64 (ddd, J = 14.3, 10.6, 4.0 Hz, 2H), 1.51 (d, J = 7.2 Hz, 6H), 1.37 (t, J = 5.3 Hz, 12H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.14, 175.95, 168.80, 158.38, 145.66, 142.89, 141.07, 140.15, 129.70, 128.89, 127.95, 127.23, 126.72, 125.94, 119.91, 103.41, 71.39, 69.73, 63.81, 63.58, 59.07, 50.54, 50.07, 49.85, 48.47, 48.00, 33.12, 23.54, 23.52, 21.71, 21.26, 19.00, 16.38.

HRMS (ESI): $C_{70}H_{77}O_{10}N_8$ $[M+H]^+$; calculated: 1189.57572, found: 1189.57636.

$[\alpha]_{20}^{D}$ = + 58 ° (c = 0.5, MeCN).

117d, QD6*i*Pr-(R)-1-Phenylethyl-A

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.80 (dd, J = 8.8, 4.8 Hz, 2H), 8.10 (dd, J = 9.2, 4.0 Hz, 2H), 7.74 (d, J = 4.8 Hz, 1H), 7.55 (d, J = 4.8 Hz, 1H), 7.52 (ddd, J = 9.2, 2.6, 1.2 Hz, 2H), 7.47 – 7.42 (m, 4H), 7.39 (dd, J = 8.6, 7.0 Hz, 2H), 7.34 – 7.29 (m, 1H), 7.28 – 7.22 (m, 5H), 7.21 (td, J = 6.3, 2.6 Hz, 1H), 7.06 (s, 1H), 5.39 (q, J = 7.2 Hz, 1H), 5.19 (q,

J = 7.2 Hz, 1H), 5.00 (dp, J = 8.0, 5.9 Hz, 2H), 4.10 (d, J = 8.6 Hz, 1H), 4.06 (d, J = 8.4 Hz, 1H), 3.79 (q, J = 8.3 Hz, 2H), 3.73 – 3.66 (m, 2H), 3.65 (dd, J = 10.0, 8.5 Hz, 1H), 3.60 (dd, J = 10.9, 7.2 Hz, 1H), 3.60 – 3.55 (m, 1H), 3.56 – 3.45 (m, 3H), 3.39 (ddd, J = 13.9, 7.3, 2.5 Hz, 1H), 3.36 – 3.31 (m, 2H), 3.32 – 3.24 (m, 2H), 3.18 (dd, J = 10.0, 7.2 Hz, 1H), 2.63 (s, 2H), 2.57 – 2.51 (m, 1H), 2.44 – 2.39 (m, 1H), 2.36 (q, J = 10.4 Hz, 1H), 2.24 (q, J = 10.0 Hz, 1H), 1.92 – 1.89 (m, 2H), 1.88 (d, J = 7.2 Hz, 3H), 1.84 – 1.78 (m, 2H), 1.61 (q, J = 9.6, 9.0 Hz, 2H), 1.56 (d, J = 7.2 Hz, 3H), 1.38 (dd, J = 6.0, 2.2 Hz, 12H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 177.10, 176.24, 176.19, 176.10, 169.36, 169.31, 158.14, 146.44, 146.21, 142.27, 141.62, 140.43, 140.29, 130.40, 129.07, 128.90, 128.33, 127.99, 127.75, 127.42, 126.56, 125.60, 125.46, 119.50, 118.72, 103.38, 71.38, 71.33, 70.15, 64.71, 63.70, 63.58, 63.31, 58.74, 58.42, 52.69, 52.26, 50.76, 50.64, 50.40, 49.63, 49.02, 48.55, 48.05, 38.40, 33.58, 23.73, 23.36, 23.26, 23.23, 21.74, 21.65, 21.41, 21.38, 19.37, 19.09, 16.76, 16.40.

HRMS (ESI): $C_{70}H_{77}O_{10}N_8$ $[M+H]^+$; calculated: 1189.57572, found: 1189.57653.

$[\alpha]_{20}^{D}$ = + 31 ° (c = 0.5, MeCN).

116k, QD6*i*Pr-(R)-1-(4-Bromophenyl)ethyl-S

116k was prepared from aldehyde **113b** according to General Procedure 6. Preparative HPLC (20 – 65 % MeCN; RT = 20.6 min) gave title compound **116k** and its diastereomers (RT = 19.8 min, RT = 21.7 min) in a ratio of 1 : 1.8 : 2.9 and a combined yield of 21 % (9.50 mg, 6.03 µmol)

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.79 (d, J = 4.8 Hz, 2H), 8.09 (d, J = 9.2 Hz, 2H), 7.75 (d, J = 4.8 Hz, 2H), 7.51 (dd, J = 9.2, 2.5 Hz, 2H), 7.42 (d, J = 2.6 Hz, 2H), 7.42 – 7.38 (m, 4H), 7.18 (s, 2H), 7.14 – 7.09 (m, 4H), 5.09 (q, J = 7.2 Hz, 2H), 4.99 (hept, J = 6.1 Hz, 2H), 4.07 (d, J = 8.3 Hz, 2H), 3.82 (t, J = 7.9 Hz, 2H), 3.80 – 3.76 (m, 2H), 3.66 (dd, J = 11.6, 6.8 Hz, 2H), 3.57 (t, J = 7.2 Hz, 2H), 3.50 – 3.44 (m, 2H), 3.35 – 3.26 (m, 4H), 3.24 (ddd, J = 13.7, 7.2, 2.7 Hz, 2H), 2.69 – 2.64 (m, 2H), 2.60 (s, 2H), 2.33 (q, J = 10.8 Hz, 2H), 1.89 – 1.78 (m, 4H), 1.68 – 1.61 (m, 2H), 1.49 (d, J = 7.2 Hz, 6H), 1.38 (dd, J = 6.1, 2.1 Hz, 12H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.01, 175.81, 168.91, 158.06, 146.64, 142.48, 139.48, 131.85, 130.86, 129.50, 126.44, 125.18, 121.32, 119.79, 103.46, 71.32, 69.86, 63.82, 63.62, 59.20, 50.15, 49.97, 48.55, 48.12, 33.10, 23.52, 21.75, 21.40, 19.04, 16.21.

HRMS (ESI): $C_{70}H_{75}O_{10}N_8Br^{81}Br$ $[M+H]^+$; calculated: 1347.39470, found: 1347.39687.

$[\alpha]_{20}^{D}$ = + 49 ° (c = 0.1, MeCN).

116l, QD6*i*Pr-1-Methyl-1-Phenylethyl-S

116l was prepared from aldehyde **113b** according to General Procedure 6. Preparative HPLC (15 – 55 % MeCN; RT = 22.2 min) gave title compound **116l** and its diastereomer (RT = 21.8 min) in a ratio of 4.5 : 1 and a combined yield of 24 % (10.0 mg, 6.92 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.82 (d, J = 5.1 Hz, 2H), 8.12 (d, J = 9.2 Hz, 2H), 7.87 (dd, J = 5.1, 0.7 Hz, 2H), 7.56 (dd, J = 9.2, 2.5 Hz, 2H), 7.53 (d, J = 2.5 Hz, 2H), 7.29 (s, 2H), 7.25 – 7.21 (m, 4H), 7.20 – 7.18 (m, 4H), 7.14 – 7.10 (m, 2H), 5.05 (hept, J = 6.0 Hz, 2H), 4.10 (d, J = 8.0 Hz, 2H), 3.83 – 3.76 (m, 4H), 3.67 (dd, J = 11.6, 6.9 Hz, 2H), 3.53 (ddd, J = 13.7, 10.8, 1.7 Hz, 2H), 3.45 (dd, J = 7.7, 6.9 Hz, 2H), 3.33 – 3.21 (m, 6H), 2.64 (ddt, J = 13.1, 7.8, 2.4 Hz, 2H), 2.52 (s, 2H), 2.22 (td, J = 10.9, 6.9 Hz, 2H), 1.77 – 1.68 (m, 4H), 1.65 (s, 6H), 1.63 – 1.60 (m, 2H), 1.59 (s, 6H), 1.38 (dd, J = 9.2, 6.0 Hz, 12H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.68, 176.63, 168.92, 158.63, 146.70, 144.86, 144.09, 139.90, 128.75, 128.73, 127.06, 126.95, 126.55, 125.00, 119.99, 103.48, 71.50, 69.54, 64.10, 63.77, 63.08, 59.01, 50.40, 49.81, 48.35, 47.64, 33.36, 28.88, 27.73, 23.49, 23.29, 21.69, 21.21, 18.90.

HRMS (ESI): $C_{72}H_{81}O_{10}N_8$ $[M+H]^+$; calculated: 1217.60702, found: 1217.60795.

$[\alpha]_{20}^{D}$ = + 53 ° (c = 1, MeCN).

116m, QD6*i*Pr-1-Phenylcyclopropyl-S

116m was prepared from aldehyde **113b** according to General Procedure 6. Preparative HPLC (15 – 55 % MeCN; RT = 21.4 min) gave title compound **116m** and its diastereomer (RT = 20.9 min) in a ratio of 4.6 : 1 and a combined yield of 24 % (10.1 mg, 7.01 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.88 (dd, J = 5.2, 1.5 Hz, 2H), 8.16 (d, J = 9.3 Hz, 2H), 7.96 (d, J = 4.5 Hz, 2H), 7.59 (dd, J = 9.3, 2.5 Hz, 2H), 7.55 (s, 2H),

7.29 (s, 2H), 7.22 – 7.17 (m, 4H), 7.17 – 7.12 (m, 2H), 7.07 – 7.02 (m, 4H), 5.06 (hept, J = 5.9 Hz, 2H), 4.14 (d, J = 8.3 Hz, 2H), 3.92 (t, J = 7.9 Hz, 2H), 3.84 – 3.79 (m, 2H), 3.73 (dd, J = 11.5, 6.8 Hz, 2H), 3.60 (t, J = 7.2 Hz, 2H), 3.52 (t, J = 12.2 Hz, 2H), 3.36 – 3.29 (m, 4H), 3.27 (dd, J = 13.7, 7.2 Hz, 2H), 2.70 (ddt, J = 13.3, 8.0, 2.5 Hz, 2H), 2.64 (s, 2H), 2.41 (td, J = 11.0, 7.2 Hz, 2H), 1.92 (s, 2H), 1.85 – 1.78 (m, 2H), 1.65 (ddd, J = 14.4, 10.5, 3.9 Hz, 2H), 1.38 (dd, J = 6.0, 4.7 Hz, 12H), 1.33 – 1.28 (m, 2H), 1.26 – 1.21 (m, 2H), 1.21 – 1.16 (m, 2H), 1.09 – 1.03 (m, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.45, 176.33, 168.77, 158.93, 145.04, 144.23, 140.19, 138.96, 138.91, 128.92, 128.03, 127.36, 127.13, 125.85, 123.87, 120.10, 103.45, 71.61, 69.74, 63.82, 63.56, 58.91, 49.83, 49.76, 48.49, 47.81, 34.91, 33.17, 23.54, 21.66, 21.16, 19.01, 16.75, 16.27.

HRMS (ESI): $C_{72}H_{77}O_{10}N_8$ $[M+H]^+$; calculated: 1213.57572, found: 1213.57673.

$[\alpha]_{20}^{D}$ = + 25 ° (c = 1, MeCN).

116n, QD6*i*Pr-1-Methyl-1-(2-Fluorophenyl)ethyl-S; 117e, QD6*i*Pr-1-Methyl-1-(2-Fluorophenyl)ethyl-A

116n and **117e** were prepared from aldehyde **113b** according to General Procedure 6. Preparative HPLC (15 – 55 % MeCN; RT = 21.7 min) gave title compound **116n** and its diastereomer **117e** (RT = 23.3 min) in a ratio of 1.5 : 1 and a combined yield of 25 % (11.0 mg, 7.43 µmol).

116n, QD6*i*Pr-1-Methyl-1-(2-Fluorophenyl)ethyl-S

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.82 (dd, J = 5.1, 1.4 Hz, 2H), 8.13 (dd, J = 9.2, 1.2 Hz, 2H), 7.90 – 7.85 (m, 2H), 7.57 (dd, J = 9.3, 2.4 Hz, 2H), 7.53 (s, 2H), 7.30 (s, 2H), 7.25 – 7.17 (m, 4H), 7.05 (td, J = 7.6, 1.3 Hz, 2H), 7.01 (ddd, J = 12.8, 8.2, 1.3 Hz, 2H), 5.04 (hept, J = 6.1 Hz, 2H), 4.06 (d, J = 8.1 Hz, 2H), 3.82 – 3.76 (m, 4H), 3.63 (dd, J = 11.7, 7.1 Hz, 2H), 3.53 (ddd, J = 12.9, 10.9, 1.7 Hz, 2H), 3.45 (t, J = 7.4 Hz, 2H), 3.31 – 3.24 (m, 4H), 3.21 (ddd, J = 13.9, 7.2, 2.3 Hz, 2H), 2.64 – 2.59 (m, 2H), 2.52 (s, 2H), 2.16 (td, J = 11.2, 7.2 Hz, 2H), 1.79 – 1.71 (m, 2H), 1.68 (s, 6H), 1.66 – 1.63 (m, 2H), 1.62 (s, 6H), 1.62 – 1.56 (m, 2H), 1.38 (dd, J = 9.7, 6.0 Hz, 12H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.14, 176.07, 168.78, 160.85, 159.46, 158.66, 158.64, 144.85, 144.80, 144.20, 144.13, 139.89, 139.84, 133.00, 132.94, 129.49, 129.44,

128.73, 128.68, 127.32, 127.30, 126.98, 126.61, 126.57, 124.81, 124.79, 120.04, 116.49, 116.36, 103.52, 71.51, 69.36, 64.15, 63.81, 60.58, 59.05, 50.70, 49.79, 48.16, 47.73, 33.40, 27.07, 26.55, 23.51, 23.25, 21.69, 21.22, 18.81.

HRMS (ESI): $C_{72}H_{79}O_{10}N_8F_2$ $[M+H]^+$; calculated: 1253.58817, found: 1253.58961.

$[\alpha]_{20}^{D}$ = + 49 ° (c = 1, MeCN).

117e, QD6*i*Pr-1-Methyl-1-(2-Fluorophenyl)ethyl-A

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.82 (d, J = 4.8 Hz, 1H), 8.67 (d, J = 4.9 Hz, 1H), 8.10 (dd, J = 12.9, 9.2 Hz, 2H), 7.66 (d, J = 4.7 Hz, 1H), 7.55 – 7.50 (m, 3H), 7.48 (d, J = 2.6 Hz, 1H), 7.45 (d, J = 2.5 Hz, 1H), 7.42 (t, J = 5.5 Hz, 2H), 7.32 – 7.29 (m, 2H), 7.27 (td, J = 8.3, 1.7 Hz, 1H), 7.23 – 7.16 (m, 2H), 7.07 (td, J = 7.5, 1.3 Hz, 2H), 7.01 (ddd, J = 12.8, 8.2, 1.3 Hz, 1H), 5.05 – 4.97 (m, 2H), 4.12 (d, J = 8.4 Hz, 1H), 3.99 (d, J = 8.3 Hz, 1H), 3.79 – 3.70 (m, 4H), 3.61 – 3.50 (m, 6H), 3.37 (ddd, J = 14.1, 7.3, 2.4 Hz, 1H), 3.35 – 3.25 (m, 4H), 3.14 (dd, J = 10.0, 7.2 Hz, 1H), 2.56 (s, 2H), 2.53 – 2.48 (m, 1H), 2.32 – 2.20 (m, 3H), 1.97 (d, J = 4.8 Hz, 6H), 1.92 – 1.86 (m, 1H), 1.81 – 1.77 (m, 1H), 1.75 (s, 3H), 1.74 – 1.70 (m, 2H), 1.68 (s, 3H), 1.54 (ddd, J = 14.0, 11.0, 3.8 Hz, 1H), 1.44 (td, J = 12.4, 10.8, 7.4 Hz, 1H), 1.40 – 1.36 (m, 12H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 177.24, 176.48, 176.11, 169.25, 169.15, 161.30, 161.10, 159.84, 159.55, 158.39, 158.34, 145.69, 133.70, 133.64, 129.93, 129.77, 129.72, 129.49, 129.44, 127.76, 127.39, 126.70, 126.64, 125.95, 125.42, 124.81, 119.31, 116.40, 103.39, 71.78, 71.40, 71.38, 70.14, 65.41, 64.25, 63.98, 63.93, 60.68, 60.43, 58.72, 58.26, 52.32, 52.17, 50.39, 50.08, 49.94, 48.93, 48.24, 48.14, 38.19, 33.84, 27.12, 27.02, 26.69, 23.48, 23.36, 23.22, 23.15, 21.73, 21.62, 21.33, 19.31, 19.04.

HRMS (ESI): $C_{72}H_{79}O_{10}N_8F_2$ $[M+H]^+$; calculated: 1253.58817, found: 1253.58956.

$[\alpha]_{20}^{D}$ = + 25 ° (c = 0.3, MeCN).

116o, QD6*i*Pr-1-(2-chlorophenyl)cyclopropyl-S; 117f, QD6*i*Pr-1-(2-chlorophenyl)cyclopropyl-A

116o and **117f** was prepared from aldehyde **113b** according to General Procedure 6. Preparative HPLC (15 – 60 % MeCN; RT = 20.5 min) gave title compound **116o** and its

diastereomer **117f** (RT = 21.8 min) in a ratio of 1 : 1.64 and a combined yield of 29 % (12.6 mg, 8.34 µmol).

116o, QD6*i*Pr-1-(2-chlorophenyl)cyclopropyl-S

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.86 (d, J = 5.1 Hz, 2H), 8.20 (d, J = 9.2 Hz, 2H), 7.90 (d, J = 5.1 Hz, 2H), 7.62 (dd, J = 9.3, 2.5 Hz, 2H), 7.57 – 7.51 (m, 4H), 7.27 – 7.24 (m, 4H), 7.16 (td, J = 7.6, 1.7 Hz, 2H), 7.08 (td, J = 7.6, 1.3 Hz, 2H), 5.07 (hept, J = 6.0 Hz, 2H), 3.99 (d, J = 8.3 Hz, 2H), 3.81 (dd, J = 10.3, 8.2 Hz, 2H), 3.72 (t, J = 8.0 Hz, 2H), 3.59 (dd, J = 11.6, 6.8 Hz, 2H), 3.49 – 3.44 (m, 2H), 3.43 (t, J = 7.3 Hz, 2H), 3.35 – 3.27 (m, 4H), 3.18 (ddd, J = 13.8, 7.3, 2.5 Hz, 2H), 2.63 (ddt, J = 13.4, 7.7, 2.5 Hz, 2H), 2.59 (s, 2H), 2.37 (td, J = 11.2, 7.2 Hz, 2H), 1.93 – 1.89 (m, 2H), 1.86 – 1.79 (m, 2H), 1.63 (ddd, J = 14.5, 10.7, 4.0 Hz, 2H), 1.47 – 1.42 (m, 2H), 1.40 (dd, J = 9.2, 6.0 Hz, 12H), 1.28 – 1.19 (m, 4H), 1.14 – 1.07 (m, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 175.94, 175.84, 168.76, 158.81, 144.61, 144.58, 139.54, 136.65, 135.33, 134.98, 130.33, 130.20, 128.46, 127.13, 126.91, 126.87, 120.11, 103.61, 71.60, 69.60, 63.86, 63.54, 59.02, 49.89, 49.83, 48.41, 47.78, 35.53, 32.96, 23.57, 23.51, 21.71, 21.28, 18.98, 14.27, 14.19.

HRMS (ESI): $C_{72}H_{75}O_{10}N_8Cl_2$ $[M+H]^+$; calculated: 1281.49777, found: 1281.49949.

$[\alpha]_{20}^{D}$ = + 39 ° (c = 0.5, MeCN).

117f, QD6*i*Pr-1-(2-chlorophenyl)cyclopropyl-A

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.89 (d, J = 4.9 Hz, 1H), 8.84 (d, J = 4.9 Hz, 1H), 8.16 (d, J = 9.3 Hz, 1H), 8.12 (d, J = 9.2 Hz, 1H), 7.85 (dd, J = 7.6, 2.1 Hz, 1H), 7.66 – 7.61 (m, 2H), 7.59 – 7.52 (m, 3H), 7.50 – 7.45 (m, 3H), 7.39 – 7.32 (m, 2H), 7.30 – 7.25 (m, 2H), 7.18 (td, J = 7.6, 1.8 Hz, 1H), 7.12 (td, J = 7.6, 1.4 Hz, 1H), 7.07 (s, 1H), 5.05 (h, J = 6.1 Hz, 1H), 5.01 (h, J = 6.0 Hz, 1H), 3.95 (d, J = 8.6 Hz, 1H), 3.85 (d, J = 8.4 Hz, 1H), 3.81 – 3.75 (m, 2H), 3.57 (dd, J = 11.5, 6.8 Hz, 1H), 3.54 (dd, J = 8.7, 7.8 Hz, 1H), 3.53 – 3.43 (m, 5H), 3.42 (dd, J = 7.8, 6.8 Hz, 1H), 3.38 – 3.23 (m, 5H), 3.10 (dd, J = 10.0, 7.3 Hz, 1H), 2.64 (s, 1H), 2.59 (s, 1H), 2.48 – 2.39 (m, 2H), 2.31 – 2.25 (m, 1H), 2.25 – 2.18 (m, 1H), 1.98 – 1.87 (m, 2H), 1.82 (tdt, J = 12.7, 6.9, 3.3 Hz, 2H), 1.80 – 1.75 (m, 1H), 1.71 (ddd, J = 10.4, 7.4, 5.6 Hz, 1H),

1.57 (td, J = 10.4, 5.4 Hz, 1H), 1.54 – 1.50 (m, 1H), 1.50 – 1.48 (m, 1H), 1.48 – 1.43 (m, 1H), 1.41 – 1.37 (m, 13H), 1.35 – 1.24 (m, 2H), 1.15 (ddd, J = 9.0, 7.6, 4.9 Hz, 1H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.87, 176.18, 175.88, 175.86, 169.15, 169.10, 158.45, 158.37, 145.79, 145.75, 143.06, 142.41, 141.37, 141.35, 137.29, 136.74, 135.41, 135.38, 135.14, 134.80, 130.49, 130.40, 130.37, 130.23, 129.90, 129.87, 127.36, 126.96, 126.74, 126.70, 126.09, 126.00, 119.32, 118.72, 103.38, 103.36, 71.81, 71.43, 71.39, 70.11, 65.04, 63.81, 63.61, 63.58, 58.69, 58.29, 52.02, 51.87, 50.35, 49.94, 49.34, 48.86, 48.23, 48.09, 38.23, 36.09, 35.53, 33.40, 23.69, 23.41, 23.26, 23.18, 21.77, 21.65, 21.32, 19.35, 19.09, 14.46, 14.16, 13.38, 13.31.

HRMS (ESI): $C_{72}H_{75}O_{10}N_8Cl_2$ $[M+H]^+$; calculated: 1281.49777, found: 1281.49949.

$[\alpha]_{20}^{D}$ = + 16 ° (c = 0.5, MeCN).

5.10.14 Macrocycles from aldehyde 113c

118a, QD6cBu-H-S

118a was prepared from aldehyde **113c** according to General Procedure 6. Preparative HPLC (0 – 25 % MeCN; RT = 27.0 min) gave title compound **118a** and its diastereomer in a ratio of 3.3:1 and a combined yield of 15 % (4.3 mg, 4.28 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.84 (d, J = 5.0 Hz, 2H), 8.13 (d, J = 9.2 Hz, 2H), 7.88 (d, J = 5.0 Hz, 2H), 7.58 (dd, J = 9.3, 2.5 Hz, 2H), 7.36 (d, J = 2.5 Hz, 2H), 7.19 (s, 2H), 5.06 (p, J = 7.1 Hz, 2H), 4.01 (d, J = 8.2 Hz, 2H), 3.89 (t, J = 7.7 Hz, 2H), 3.80 (dd, J = 10.3, 8.2 Hz, 2H), 3.63 (dd, J = 11.3, 7.1 Hz, 2H), 3.60 (t, J = 7.2 Hz, 2H), 3.47 (ddd, J = 13.1, 10.8, 1.7 Hz, 2H), 3.33 – 3.29 (m, 4H), 3.25 (ddd, J = 13.8, 7.1, 2.7 Hz, 2H), 2.73 – 2.67 (m, 2H), 2.61 – 2.51 (m, 6H), 2.44 (td, J = 11.1, 7.1 Hz, 2H), 2.14 (pd, J = 10.4, 7.1 Hz, 4H), 1.91 (d, J = 3.2 Hz, 2H), 1.89 – 1.79 (m, 4H), 1.79 – 1.72 (m, 2H), 1.69 (ddd, J = 14.2, 10.5, 3.7 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 177.44, 176.95, 168.60, 157.82, 145.18, 143.70, 140.05, 128.85, 126.66, 125.36, 120.26, 103.29, 72.38, 69.39, 63.39, 63.20, 58.95, 51.72, 49.79, 49.42, 48.22, 32.76, 30.29, 30.09, 23.39, 23.26, 18.81, 13.17.

HRMS (ESI): $C_{56}H_{61}O_{10}N_8$ $[M+H]^+$; calculated: 1005.45052, found: 1005.45090.

$[\alpha]_{20}^{D}$ = + 35 ° (c = 0.3, MeCN).

118b, QD6cBu-Me-S

118b was prepared from aldehyde **113c** according to General Procedure 6. Preparative HPLC (10 – 40 % MeCN; RT = 19.7 min) gave title compound **118b** and its diastereomer (RT = 21.9 min) in a ratio of 12:1 and a combined yield of 24 % (8.8 mg, 7.0 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.84 (d, J = 4.8 Hz, 2H), 8.12 (d, J = 9.2 Hz, 2H), 7.84 (d, J = 4.8 Hz, 2H), 7.54 (dd, J = 9.3, 2.6 Hz, 2H), 7.35 (d, J = 2.6 Hz, 2H), 7.23 (s, 2H), 5.08 (p, J = 7.0 Hz, 2H), 4.02 (d, J = 8.0 Hz, 2H), 3.89 (t, J = 7.7 Hz, 2H), 3.79 (dd, J = 10.4, 8.1 Hz, 2H), 3.65 (dd, J = 11.7, 7.0 Hz, 2H), 3.57 (t, J = 7.2 Hz, 2H), 3.46 (ddd, J = 12.9, 10.9, 1.7 Hz, 2H), 3.39 – 3.29 (m, 4H), 3.26 (ddd, J = 13.8, 7.1, 2.5 Hz, 2H), 2.71 (td, J = 10.3, 4.7 Hz, 2H), 2.67 (s, 6H), 2.64 (s, 2H), 2.56 (dp, J = 14.0, 3.4 Hz, 4H), 2.40 (td, J = 11.2, 7.2 Hz, 2H), 2.19 – 2.10 (m, 4H), 1.91 (d, J = 3.1 Hz, 2H), 1.89 – 1.81 (m, 4H), 1.79 – 1.72 (m, 2H), 1.68 (ddd, J = 14.6, 10.8, 3.9 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.38, 176.12, 168.68, 157.70, 146.23, 142.55, 141.74, 130.21, 126.59, 124.86, 120.19, 103.20, 72.39, 69.56, 63.61, 63.44, 59.18, 50.70, 49.90, 48.45, 48.36, 33.01, 30.53, 30.21, 25.02, 23.64, 23.47, 18.98, 13.34.

HRMS (ESI): $C_{58}H_{65}O_{10}N_8$ $[M+H]^+$; calculated: 1033.48182, found: 1033.48198.

$[\alpha]_{20}^{D}$ = + 27 ° (c = 0.3, MeCN).

118c, QD6cBu-Et-S

118c was prepared from aldehyde **113c** according to General Procedure 6. Preparative HPLC (15 – 45 % MeCN; RT = 18.2 min) gave title compound **118c** and its diastereomer (RT = 20.4 min) in a ratio of 5:1 and a combined yield of 25 % (9.30 mg, 7.22 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.89 (d, J = 5.1 Hz, 2H), 8.17 (d, J = 9.3 Hz, 2H), 7.94 (d, J = 5.0 Hz, 2H), 7.59 (dd, J = 9.3, 2.5 Hz, 2H), 7.41 (d, J = 2.6 Hz, 2H), 7.28 (s, 2H), 5.10 (p, J = 7.0 Hz, 2H), 4.06 (d, J = 8.2 Hz, 2H), 3.88 (t, J = 7.8 Hz, 2H), 3.80 (dd, J = 10.4, 8.1 Hz, 2H), 3.67 (dd, J = 11.6, 6.9 Hz, 2H), 3.56 (t, J = 7.2 Hz, 2H), 3.48 (ddd, J = 13.0, 10.9, 1.7 Hz, 2H), 3.38 – 3.29 (m, 4H), 3.25 (dqd, J = 14.5, 7.1, 2.2 Hz, 6H), 2.71 (ddt, J =

13.2, 7.6, 2.4 Hz, 2H), 2.64 (s, 2H), 2.60 – 2.54 (m, 4H), 2.42 (td, J = 11.0, 6.9 Hz, 2H), 2.15 (ddtd, J = 29.2, 12.0, 9.9, 7.0 Hz, 4H), 1.92 (d, J = 3.2 Hz, 2H), 1.90 – 1.81 (m, 4H), 1.75 (dtt, J = 11.0, 9.8, 8.2 Hz, 2H), 1.67 (ddd, J = 14.5, 10.4, 3.7 Hz, 2H), 0.92 (dd, J = 7.2 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.15, 176.03, 168.67, 158.12, 145.03, 144.31, 139.96, 128.79, 126.94, 125.83, 120.32, 103.33, 72.52, 69.56, 63.60, 63.40, 59.00, 50.47, 49.91, 48.44, 48.30, 34.33, 33.03, 30.49, 30.12, 23.62, 23.51, 19.02, 13.30, 12.74.

HRMS (ESI): $C_{60}H_{69}O_{10}N_8$ $[M+H]^+$; calculated: 1061.51312, found: 1061.51328.

$[\alpha]_{20}^{D}$ = + 29 ° (c = 0.5, MeCN).

118d, QD6cBu-*n*Pr-S

118d was prepared from aldehyde **113c** according to General Procedure 6. Preparative HPLC (15 – 45 % MeCN; RT = 21.6 min) gave title compound **118d** and its diastereomer (RT = 23.6 min) in a ratio of 5.6 : 1 and a combined yield of 20 % (7.6 mg, 5.78 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.87 (d, J = 5.0 Hz, 2H), 8.16 (d, J = 9.3 Hz, 2H), 7.91 (d, J = 5.0 Hz, 2H), 7.58 (dd, J = 9.3, 2.5 Hz, 2H), 7.39 (d, J = 2.6 Hz, 2H), 7.26 (s, 2H), 5.09 (p, J = 7.1 Hz, 2H), 4.06 (d, J = 8.2 Hz, 2H), 3.89 (t, J = 7.8 Hz, 2H), 3.82 – 3.76 (m, 2H), 3.67 (dd, J = 11.6, 6.9 Hz, 2H), 3.57 (t, J = 7.2 Hz, 2H), 3.48 (ddd, J = 13.7, 10.9, 1.7 Hz, 2H), 3.38 – 3.28 (m, 4H), 3.25 (ddd, J = 13.8, 7.1, 2.6 Hz, 2H), 3.17 (t, J = 7.3 Hz, 4H), 2.70 (ddt, J = 13.1, 7.5, 2.4 Hz, 2H), 2.64 (s, 2H), 2.60 – 2.53 (m, 4H), 2.39 (td, J = 11.1, 7.0 Hz, 2H), 2.21 – 2.08 (m, 4H), 1.94 – 1.89 (m, 2H), 1.91 – 1.79 (m, 4H), 1.79 – 1.70 (m, 2H), 1.67 (ddd, J = 14.5, 10.6, 3.8 Hz, 2H), 1.40 – 1.30 (m, 4H), 0.72 (dd, J = 7.5 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.38, 176.18, 168.65, 158.00, 145.37, 143.79, 140.47, 129.20, 126.83, 125.55, 120.25, 103.29, 72.49, 69.55, 63.60, 63.40, 59.04, 50.35, 49.91, 48.47, 48.18, 41.01, 33.13, 30.50, 30.14, 23.61, 23.51, 21.22, 19.03, 13.31, 11.15.

HRMS (ESI): $C_{62}H_{73}O_{10}N_8$ $[M+H]^+$; calculated: 1089.54442, found: 1089.54466.

$[\alpha]_{20}^{D}$ = + 24 ° (c = 0.5, MeCN).

118e, QD6cBu-*i*Pr-S

118e was prepared from aldehyde **113c** according to General Procedure 6. Preparative HPLC (15 – 45 % MeCN; RT = 21.6 min) gave title compound **118e** and its diastereomer (RT = 23.7 min) in a ratio of 4 : 1 and a combined yield of 21 % (8.2 mg, 6.23 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.87 (d, J = 5.0 Hz, 2H), 8.16 (d, J = 9.2 Hz, 2H), 7.90 (d, J = 5.0 Hz, 2H), 7.57 (dd, J = 9.3, 2.5 Hz, 2H), 7.38 (d, J = 2.6 Hz, 2H), 7.26 (s, 2H), 5.09 (p, J = 7.0 Hz, 2H), 4.07 – 4.00 (m, 4H), 3.82 – 3.77 (m, 4H), 3.65 (dd, J = 11.7, 6.8 Hz, 2H), 3.52 – 3.45 (m, 4H), 3.38 – 3.28 (m, 4H), 3.25 (ddd, J = 13.8, 7.2, 2.7 Hz, 2H), 2.69 (ddt, J = 13.0, 7.5, 2.4 Hz, 2H), 2.63 (s, 2H), 2.59 – 2.54 (m, 4H), 2.42 (td, J = 11.2, 7.1 Hz, 2H), 2.20 – 2.09 (m, 4H), 1.92 (d, J = 14.5 Hz, 2H), 1.89 – 1.80 (m, 4H), 1.79 – 1.71 (m, 2H), 1.66 (ddd, J = 14.5, 10.6, 3.9 Hz, 2H), 1.13 (dd, J = 16.2, 6.9 Hz, 12H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.26, 176.13, 168.76, 157.98, 145.41, 143.67, 140.56, 129.26, 126.83, 125.50, 120.24, 103.30, 72.48, 69.59, 63.71, 63.49, 59.04, 50.19, 49.94, 48.52, 47.96, 44.53, 33.02, 30.51, 30.15, 23.60, 23.52, 19.08, 19.05, 18.73, 13.31.

HRMS (ESI): $C_{62}H_{73}O_{10}N_8$ $[M+H]^+$; calculated: 1089.54442, found: 1089.54471.

$[\alpha]_{20}^{D}$ = + 24 ° (c = 0.5, MeCN).

118f, QD6cBu-*t*Bu-S

118f was prepared from aldehyde **113c** according to General Procedure 6. Preparative HPLC (15 – 45 % MeCN; RT = 24.4 min) gave title compound **118f** and its diastereomer (RT = 27.2 min) in a ratio of 3.6 : 1 and a combined yield of 20 % (7.60 mg, 5.66 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.87 (d, J = 5.0 Hz, 2H), 8.15 (d, J = 9.2 Hz, 2H), 7.89 (d, J = 5.0 Hz, 2H), 7.57 (dd, J = 9.3, 2.5 Hz, 2H), 7.40 (d, J = 2.6 Hz, 2H), 7.28 (s, 2H), 5.09 (p, J = 7.0 Hz, 2H), 4.02 (d, J = 8.0 Hz, 2H), 3.80 (dd, J = 10.5, 8.1 Hz, 2H), 3.68 (t, J = 7.8 Hz, 2H), 3.63 (dd, J = 11.7, 6.9 Hz, 2H), 3.50 (ddd, J = 13.8, 10.8, 1.7 Hz, 2H), 3.38 (t, J = 7.3 Hz, 2H), 3.37 – 3.27 (m, 4H), 3.24 (ddd, J = 13.7, 7.1, 2.6 Hz, 2H), 2.67 (ddt, J = 13.1, 7.6, 2.3 Hz, 2H), 2.63 (s, 2H), 2.59 – 2.54 (m, 4H), 2.35 (td, J = 11.2, 7.1 Hz, 2H), 2.20 – 2.09 (m, 4H), 1.92 – 1.79 (m, 6H), 1.79 – 1.71 (m, 2H), 1.65 (td, J = 12.5, 10.6, 3.9 Hz, 2H), 1.31 (s, 18H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 177.00, 176.96, 168.86, 157.99, 145.28, 143.91, 140.39, 129.06, 126.90, 125.57, 120.23, 103.42, 72.51, 69.49, 64.17, 63.85, 59.07, 58.89, 50.44, 49.94, 48.46, 47.95, 33.25, 30.52, 30.17, 27.89, 23.58, 23.39, 19.04, 13.31.

HRMS (ESI): $C_{64}H_{77}O_{10}N_8$ $[M+H]^+$; calculated: 1117.57572, found: 1117.57647.

$[\alpha]_{20}^{D}$ = + 25 ° (c = 0.5, MeCN).

118g, QD6cBu-Cyclohexyl-S

118g was prepared from aldehyde **113c** according to General Procedure 6. Preparative HPLC (20 – 60 % MeCN; RT = 18.5 min) gave title compound **118g** and its diastereomer (RT = 20.4 min) in a ratio of 7.5 : 1 and a combined yield of 10 % (3.70 mg, 2.65 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.83 (d, J = 4.8 Hz, 2H), 8.13 (d, J = 9.2 Hz, 2H), 7.81 (dd, J = 4.8, 0.7 Hz, 2H), 7.54 (dd, J = 9.2, 2.5 Hz, 2H), 7.34 (d, J = 2.6 Hz, 2H), 7.21 (s, 2H), 5.07 (p, J = 7.1 Hz, 2H), 4.02 (d, J = 8.3 Hz, 2H), 3.82 – 3.75 (m, 4H), 3.67 – 3.59 (m, 4H), 3.51 – 3.47 (m, 2H), 3.48 – 3.43 (m, 2H), 3.35 (tt, J = 11.1, 3.4 Hz, 2H), 3.30 (ddd, J = 13.1, 10.7, 7.4 Hz, 2H), 3.24 (ddd, J = 13.6, 7.1, 2.7 Hz, 2H), 2.72 – 2.65 (m, 2H), 2.63 (s, 2H), 2.60 – 2.54 (m, 4H), 2.40 (td, J = 11.1, 7.1 Hz, 2H), 2.19 – 2.10 (m, 4H), 1.93 – 1.89 (m, 2H), 1.88 – 1.71 (m, 10H), 1.70 – 1.63 (m, 6H), 1.53 – 1.48 (m, 2H), 1.46 – 1.40 (m, 4H), 1.14 (qt, J = 13.5, 3.7 Hz, 4H), 0.98 (qt, J = 13.2, 3.6 Hz, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.23, 176.04, 168.78, 157.66, 146.30, 142.30, 141.90, 130.31, 126.57, 124.78, 120.13, 103.24, 72.40, 69.58, 63.71, 63.51, 59.15, 52.51, 50.15, 49.95, 48.52, 47.90, 33.00, 30.54, 30.23, 29.20, 28.84, 25.95, 25.37, 23.59, 23.50, 19.08, 13.33.

HRMS (ESI): $C_{68}H_{81}O_{10}N_8$ $[M+H]^+$; calculated: 1169.60702, found: 1169.60741.

$[\alpha]_{20}^{D}$ = + 25 ° (c = 0.2, MeCN).

118h, QD6cBu-(R)-1-Cyclohexylethyl-S

118h was prepared from aldehyde **113c** according to General Procedure 6. Preparative HPLC (20 – 60 % MeCN; RT = 22.6 min) gave title compound **118h** and its diastereomer (RT = 25.2 min) in a ratio of 2.5 : 1 and a combined yield of 15 % (6.10 mg, 4.20 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.86 (d, J = 5.0 Hz, 2H), 8.15 (d, J = 9.3 Hz, 2H), 7.88 (d, J = 4.9 Hz, 2H), 7.57 (dd, J = 9.3, 2.5 Hz, 2H), 7.37 (d, J = 2.6 Hz, 2H), 7.24 (s, 2H), 5.08 (p, J = 7.0 Hz, 2H), 4.04 (d, J = 8.3 Hz, 2H), 3.83 (t, J = 7.9 Hz, 2H), 3.81 – 3.76 (m, 2H), 3.64 (dd, J = 11.6, 6.8 Hz, 2H), 3.58 – 3.52 (m, 4H), 3.54 – 3.47 (m, 2H), 3.38 – 3.27 (m, 4H), 3.23 (ddd, J = 13.7, 7.2, 2.6 Hz, 2H), 2.71 – 2.65 (m, 2H), 2.64 (s, 2H), 2.60 – 2.53 (m, 4H), 2.38 (td, J = 11.2, 7.2 Hz, 2H), 2.14 (ddtd, J = 22.3, 12.3, 10.0, 7.5 Hz, 4H), 1.92 – 1.88 (m, 2H), 1.88 – 1.80 (m, 4H), 1.78 – 1.71 (m, 2H), 1.69 – 1.60 (m, 8H), 1.58 – 1.50 (m, 4H), 1.44 – 1.39 (m, 2H), 1.15 – 1.09 (m, 2H), 1.08 (d, J = 7.0 Hz, 6H), 1.07 – 0.98 (m, 4H), 0.78 – 0.70 (m, 2H), 0.65 – 0.55 (m, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.51, 176.27, 168.61, 157.96, 145.48, 143.55, 140.68, 129.35, 126.80, 125.45, 120.20, 103.34, 72.50, 69.54, 63.79, 63.51, 59.07, 53.96, 49.96, 49.85, 48.61, 47.66, 39.34, 33.18, 30.51, 30.43, 30.31, 30.17, 26.31, 26.02, 23.57, 23.54, 19.08, 15.30, 13.32.

HRMS (ESI): $C_{72}H_{89}O_{10}N_8$ $[M+H]^+$; calculated: 1225.66962, found: 1225.66943.

$[\alpha]_{20}^{D}$ = + 21 ° (c = 0.3, MeCN).

118i, QD6cBu-Ph -S

118i was prepared from aldehyde **113c** according to General Procedure 6. Preparative HPLC (0 – 40 % MeCN; RT = 27.1 min) gave title compound **118i** and its diastereomer (RT = 29.1 min) in a ratio of 6 : 1 and a combined yield of 27 % (10.9 mg, 7.88 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.86 (d, J = 5.0 Hz, 2H), 8.12 (d, J = 9.2 Hz, 2H), 7.95 (d, J = 5.0 Hz, 2H), 7.55 (dd, J = 9.3, 2.5 Hz, 2H), 7.40 (d, J = 2.6 Hz, 2H), 7.37 (dd, J = 8.3, 6.7 Hz, 4H), 7.35 – 7.30 (m, 2H), 7.29 (s, 2H), 7.12 – 7.07 (m, 4H), 5.09 (p, J = 7.0 Hz, 2H), 4.23 (d, J = 8.3 Hz, 2H), 4.07 (t, J = 7.9 Hz, 2H), 3.86 – 3.79 (m, 4H), 3.78 (t, J = 7.1 Hz, 2H), 3.53 (ddd, J = 13.0, 10.9, 1.7 Hz, 2H), 3.38 (ddd, J = 13.8, 7.1, 2.5 Hz, 2H), 3.36 – 3.28 (m, 4H), 2.78 (ddt, J = 13.1, 8.0, 2.4 Hz, 2H), 2.65 (s, 2H), 2.60 – 2.50 (m, 6H), 2.13 (ddtd, J = 26.1, 12.1, 10.0, 7.3 Hz, 4H), 1.94 – 1.89 (m, 2H), 1.90 – 1.79 (m, 4H), 1.75 (dtd, J = 10.9, 9.7, 8.2 Hz, 2H), 1.74 – 1.68 (m, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 175.57, 175.50, 168.91, 158.07, 145.05, 144.16, 140.01, 132.59, 129.61, 129.41, 128.82, 127.44, 126.92, 125.73, 120.32, 103.35, 72.51, 69.85, 63.98, 63.88, 58.98, 50.84, 49.91, 48.82, 48.47, 33.02, 30.49, 30.13, 23.62, 19.13, 13.32.

HRMS (ESI): $C_{68}H_{69}O_{10}N_8$ $[M+H]^+$; calculated: 1157.51312, found: 1157.51383.

$[\alpha]_{20}^{D}$ = + 11 ° (c = 0.5, MeCN).

118j, QD6cBu-4-Fluorophenyl-S

118j was prepared from aldehyde **113c** according to General Procedure 6. Preparative HPLC (20 – 60 % MeCN; RT = 16.2 min) gave title compound **118j** and its diastereomer (RT = 17.9 min) in a ratio of 5.5 : 1 and a combined yield of 31 % (12.8 mg, 9.02 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.87 (d, J = 5.2 Hz, 2H), 8.14 (d, J = 9.3 Hz, 2H), 7.98 (d, J = 5.1 Hz, 2H), 7.58 (dd, J = 9.3, 2.5 Hz, 2H), 7.42 (d, J = 2.6 Hz, 2H), 7.30 (s, 2H), 7.15 – 7.08 (m, 8H), 5.09 (p, J = 7.0 Hz, 2H), 4.23 (d, J = 8.3 Hz, 2H), 4.07 (t, J = 7.9 Hz, 2H), 3.86 – 3.79 (m, 4H), 3.80 – 3.76 (m, 2H), 3.52 (ddd, J = 12.9, 10.9, 1.7 Hz, 2H), 3.38 (ddd, J = 13.7, 7.2, 2.3 Hz, 2H), 3.37 – 3.29 (m, 4H), 2.77 (ddt, J = 12.8, 8.0, 2.3 Hz, 2H), 2.64 (s, 2H), 2.60 – 2.54 (m, 4H), 2.54 – 2.49 (m, 2H), 2.19 – 2.08 (m, 4H), 1.91 (dt, J = 9.9, 3.2 Hz, 2H), 1.89 – 1.80 (m, 4H), 1.75 (ddt, J = 11.0, 9.5, 8.2 Hz, 2H), 1.72 – 1.67 (m, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 174.95, 174.85, 168.28, 162.83, 161.43, 157.61, 144.13, 144.05, 138.80, 128.93, 128.88, 128.01, 127.99, 127.74, 126.41, 125.44, 119.74, 115.96, 115.83, 102.79, 71.95, 69.24, 63.36, 63.25, 58.31, 50.21, 49.30, 48.20, 47.83, 32.38, 29.86, 29.50, 23.00, 18.49, 12.69.

HRMS (ESI): $C_{68}H_{67}O_{10}N_8F_2$ $[M+H]^+$; calculated: 1193.49427, found: 1193.49379.

$[\alpha]_{20}^{D}$ = + 33 ° (c = 1, MeCN).

118k, QD6cBu-(S)-1-Phenylethyl-S

118k was prepared from aldehyde **113c** according to General Procedure 6. Preparative HPLC (20 – 50 % MeCN; RT = 19.3 min) gave title compound **118k** and its diastereomer (RT = 21.0 min) in a ratio of 2.5 : 1 and a combined yield of 13 % (5.30 mg, 3.63 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.83 (d, J = 4.9 Hz, 2H), 8.11 (d, J = 9.2 Hz, 2H), 7.82 (d, J = 4.8 Hz, 2H), 7.52 (dd, J = 9.2, 2.5 Hz, 2H), 7.33 (d, J = 2.6 Hz,

2H), 7.25 – 7.16 (m, 12H), 5.08 (qt, J = 7.0, 3.3 Hz, 4H), 4.08 (d, J = 8.2 Hz, 2H), 3.91 (t, J = 7.9 Hz, 2H), 3.82 – 3.75 (m, 2H), 3.68 (dd, J = 11.6, 6.8 Hz, 2H), 3.54 – 3.48 (m, 4H), 3.37 – 3.24 (m, 6H), 2.68 (ddt, J = 13.3, 7.7, 2.3 Hz, 2H), 2.60 (s, 2H), 2.59 – 2.54 (m, 4H), 2.41 (td, J = 11.1, 7.1 Hz, 2H), 2.20 – 2.09 (m, 4H), 1.92 – 1.84 (m, 2H), 1.84 – 1.78 (m, 2H), 1.78 – 1.71 (m, 4H), 1.63 (ddd, J = 14.4, 10.6, 3.9 Hz, 2H), 1.58 (d, J = 7.2 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.16, 175.94, 168.71, 157.67, 146.36, 142.24, 141.98, 140.00, 130.40, 128.85, 127.96, 127.35, 126.51, 124.78, 120.05, 103.14, 72.39, 69.69, 63.75, 63.53, 59.11, 50.79, 50.12, 49.95, 48.64, 47.93, 33.23, 30.54, 30.22, 23.57, 23.49, 19.07, 16.99, 13.34.

HRMS (ESI): $C_{72}H_{77}O_{10}N_8$ $[M+H]^+$; calculated: 1213.57572, found: 1213.57548.

$[\alpha]_{20}^{D}$ = - 2 ° (c = 0.3, MeCN).

118l, QD6cBu-(R)-1-Phenylethyl-S

118l was prepared from aldehyde **113c** according to General Procedure 6. Preparative HPLC (20 – 60 % MeCN; RT = 18.8 min) gave title compound **118l** and its diastereomer in a ratio of 5 : 1 and a combined yield of 24 % (9.0 mg, 7.42 µmol).

^{1}H NMR (600 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.80 (d, J = 4.8 Hz, 2H), 8.10 (d, J = 9.2 Hz, 2H), 7.78 (dd, J = 4.9, 0.7 Hz, 2H), 7.51 (dd, J = 9.2, 2.5 Hz, 2H), 7.32 (d, J = 2.6 Hz, 2H), 7.27 – 7.16 (m, 12H), 5.13 (q, J = 7.2 Hz, 2H), 5.06 (p, J = 7.1 Hz, 2H), 4.07 (d, J = 8.3 Hz, 2H), 3.82 (t, J = 7.9 Hz, 2H), 3.81 – 3.75 (m, 2H), 3.67 (dd, J = 11.6, 6.8 Hz, 2H), 3.58 (t, J = 7.2 Hz, 2H), 3.49 (ddd, J = 14.3, 10.8, 1.7 Hz, 2H), 3.36 – 3.23 (m, 6H), 2.71 – 2.64 (m, 2H), 2.62 (s, 2H), 2.60 – 2.52 (m, 4H), 2.34 (td, J = 11.0, 7.0 Hz, 2H), 2.20 – 2.07 (m, 4H), 1.89 – 1.79 (m, 6H), 1.79 – 1.71 (m, 2H), 1.68 – 1.60 (m, 2H), 1.51 (d, J = 7.2 Hz, 6H).

^{13}C NMR (151 MHz, CD_3CN:D_2O [10:1]) δ 176.13, 175.87, 168.79, 157.55, 146.54, 142.32, 141.86, 140.19, 130.64, 128.91, 127.96, 127.25, 126.47, 124.56, 119.96, 103.15, 72.35, 69.75, 63.85, 63.62, 59.11, 50.52, 50.08, 49.93, 48.63, 48.03, 33.16, 30.56, 30.22, 23.56, 23.53, 19.11, 16.40, 13.33.

HRMS (ESI): $C_{72}H_{77}O_{10}N_8$ $[M+H]^+$; calculated: 1213.57572, found: 1213.57587.

$[\alpha]_{20}^{D}$ = + 39 ° (c = 0.3, MeCN).

118m, QD6cBu-1-Methyl-1-(2-Fluorophenyl)ethyl-S

118m was prepared from aldehyde **113c** according to General Procedure 6. Preparative HPLC (20 – 60 % MeCN; RT = 19.5 min) gave title compound **118m** and its diastereomer (RT = 21.4 min) in a ratio of 2 : 1 and a combined yield of 10 % (4.00 mg, 2.66 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.81 (d, J = 5.0 Hz, 2H), 8.12 (d, J = 9.2 Hz, 2H), 7.82 (d, J = 4.9 Hz, 2H), 7.55 (dd, J = 9.2, 2.5 Hz, 2H), 7.36 (d, J = 2.6 Hz, 2H), 7.26 (s, 2H), 7.24 – 7.18 (m, 4H), 7.05 (td, J = 7.6, 1.3 Hz, 2H), 7.01 (ddd, J = 12.8, 8.2, 1.3 Hz, 2H), 5.08 (p, J = 7.0 Hz, 2H), 4.04 (d, J = 7.9 Hz, 2H), 3.77 (td, J = 8.1, 2.9 Hz, 4H), 3.62 (dd, J = 11.7, 7.0 Hz, 2H), 3.53 (ddd, J = 13.8, 10.8, 1.7 Hz, 2H), 3.44 (t, J = 7.4 Hz, 2H), 3.29 (dddd, J = 26.9, 13.2, 6.3, 3.6 Hz, 4H), 3.23 (ddd, J = 13.8, 7.2, 2.6 Hz, 2H), 2.62 (ddt, J = 13.1, 7.7, 2.3 Hz, 2H), 2.57 (dddd, J = 9.7, 8.5, 4.3, 2.6 Hz, 4H), 2.52 (s, 2H), 2.19 – 2.10 (m, 6H), 1.91 – 1.85 (m, 2H), 1.78 – 1.72 (m, 4H), 1.67 (s, 6H), 1.66 – 1.63 (m, 2H), 1.62 (s, 6H), 1.61 – 1.58 (m, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.11, 176.00, 168.79, 160.87, 159.48, 157.84, 145.65, 143.23, 141.01, 133.03, 132.97, 129.54, 129.52, 129.47, 127.34, 127.32, 126.74, 125.26, 124.84, 124.82, 120.11, 116.50, 116.37, 103.38, 72.47, 69.38, 64.18, 63.85, 60.59, 59.12, 50.71, 49.90, 48.32, 47.77, 33.43, 30.52, 30.22, 27.10, 26.56, 23.52, 23.25, 18.93, 13.33.

HRMS (ESI): $C_{74}H_{79}O_{10}N_8F_2$ $[M+H]^+$; calculated: 1277.58817, found: 1277.58829.

$[\alpha]_{20}^{D}$ = + 33 ° (c = 0.3, MeCN).

5.10.15 Macrocycles prepared from aldehyde 113d

107b, QD2Ph-Me-S

107b was prepared from aldehyde **113d** according to General Procedure 6. Preparative HPLC (15 – 45 % MeCN; RT = 24.3 min) gave title compound **107b** and its diastereomer (RT = 27.1 min) in a ratio of 11 : 1 and a combined yield of 45 % (17.2 mg, 12.9 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.30 (s, 2H), 8.26 – 8.22 (m, 6H), 7.73 (d, J = 2.6 Hz, 2H), 7.63 – 7.58 (m, 8H), 7.53 (s, 2H), 4.15 (d, J = 8.2 Hz, 2H), 4.10 (s, 6H), 4.03 (t, J = 7.8 Hz, 2H), 3.87 – 3.83 (m, 2H), 3.83 – 3.79 (m, 2H), 3.61 (t, J = 7.1 Hz, 2H),

3.47 (t, J = 12.2 Hz, 2H), 3.44 – 3.39 (m, 2H), 3.39 – 3.36 (m, 2H), 3.29 (ddd, J = 13.2, 11.0, 7.1 Hz, 2H), 2.86 – 2.81 (m, 2H), 2.67 (s, 8H), 2.45 (td, J = 11.2, 7.1 Hz, 2H), 1.93 – 1.90 (m, 2H), 1.85 – 1.79 (m, 2H), 1.66 (td, J = 12.6, 10.9, 3.8 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.39, 176.23, 168.56, 160.45, 153.99, 144.22, 141.63, 137.18, 131.28, 129.85, 129.71, 128.85, 125.79, 125.42, 118.80, 102.34, 70.23, 63.91, 63.66, 59.02, 57.75, 50.64, 49.57, 48.46, 33.28, 25.09, 23.84, 23.75, 19.21.

HRMS (ESI): $C_{64}H_{65}O_{10}N_8$ $[M+H]^+$; calculated: 1105.48182, found: 1105.48432.

$[\alpha]_{20}^{D}$ = + 65 ° (c = 0.5, MeCN).

107b, QD2Ph-*i*Pr-S

107c was prepared from aldehyde **113d** according to General Procedure 6. Preparative HPLC (15 – 65 % MeCN; RT = 20.1 min) gave title compound **107c** and its diastereomer (RT = 21 min) in a ratio of 2.1 : 1 and a yield of 26 % (10.4 mg, 7.49 µmol; yield from **107c** exclusively).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.24 (s, 2H), 8.23 – 8.18 (m, 6H), 7.64 – 7.55 (m, 8H), 7.48 (t, J = 2.2 Hz, 2H), 7.28 (s, 2H), 4.08 (d, J = 8.3 Hz, 2H), 4.04 (s, 6H), 4.04 – 3.98 (m, 2H), 3.90 – 3.85 (m, 2H), 3.87 – 3.82 (m, 2H), 3.74 (dd, J = 11.7, 6.8 Hz, 2H), 3.54 – 3.47 (m, 4H), 3.44 (ddt, J = 14.1, 11.4, 3.1 Hz, 2H), 3.36 – 3.26 (m, 4H), 2.77 (ddt, J = 13.0, 7.5, 2.3 Hz, 2H), 2.64 (s, 2H), 2.45 (td, J = 10.9, 6.8 Hz, 2H), 1.92 (s, 2H), 1.82 (dddd, J = 18.4, 9.4, 4.8, 1.7 Hz, 2H), 1.65 (ddd, J = 14.3, 10.4, 3.8 Hz, 2H), 1.12 (t, J = 6.5 Hz, 12H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.29, 176.09, 168.80, 160.00, 154.35, 142.78, 142.52, 137.97, 130.86, 130.53, 129.68, 128.53, 125.32, 124.73, 117.74, 101.54, 70.09, 63.84, 63.65, 59.00, 56.87, 50.42, 49.74, 48.59, 48.07, 44.50, 33.10, 23.64, 23.55, 19.11, 19.07, 18.67.

HRMS (ESI): $C_{68}H_{73}O_{10}N_8$ $[M+H]^+$; calculated: 1161.54442, found: 1161.54526.

$[\alpha]_{20}^{D}$ = + 51 ° (c = 0.5, MeCN).

107d, QD2Ph-*t*Bu-S

107d was prepared from aldehyde **113d** according to General Procedure 6. Preparative HPLC (20 – 65 % MeCN; RT = 20.5 min) gave title compound **107d** and its diastereomer (RT = 22.9 min) in a ratio of 1.6 : 1 and a combined yield of 46 % (18.6 mg, 13.1 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.25 – 8.22 (m, 4H), 8.20 (s, 2H), 8.16 (d, J = 9.2 Hz, 2H), 7.59 (t, J = 7.4 Hz, 4H), 7.54 (ddd, J = 11.7, 7.2, 1.9 Hz, 4H), 7.46 (d, J = 2.6 Hz, 2H), 7.29 (s, 2H), 4.06 (d, J = 8.1 Hz, 2H), 4.03 (s, 6H), 3.86 – 3.81 (m, 2H), 3.76 (t, J = 7.8 Hz, 2H), 3.71 (dd, J = 11.7, 6.9 Hz, 2H), 3.52 (ddd, J = 13.1, 11.0, 1.7 Hz, 2H), 3.45 – 3.41 (m, 2H), 3.40 (t, J = 7.2 Hz, 2H), 3.35 – 3.31 (m, 2H), 3.31 – 3.26 (m, 2H), 2.74 (ddt, J = 13.0, 7.8, 2.3 Hz, 2H), 2.65 (s, 2H), 2.36 (td, J = 11.1, 7.0 Hz, 2H), 1.92 – 1.86 (m, 2H), 1.84 – 1.77 (m, 2H), 1.62 (ddd, J = 14.5, 10.7, 3.9 Hz, 2H), 1.30 (s, 18H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.96, 176.93, 168.92, 159.80, 154.69, 143.70, 141.83, 139.01, 131.55, 130.50, 129.64, 128.36, 125.21, 124.20, 118.04, 101.49, 70.08, 64.41, 64.13, 59.17, 58.87, 56.82, 50.80, 49.77, 48.60, 48.15, 33.51, 27.95, 23.71, 23.49, 19.07.

HRMS (ESI): $C_{70}H_{77}O_{10}N_8$ $[M+H]^+$; calculated: 1189.57572, found: 1189.57534.

$[\alpha]_{20}^{D}$ = + 45 ° (c = 0.5, MeCN).

107e, QD2Ph-Neopentyl-S

107e was prepared from aldehyde **113d** according to General Procedure 6. Preparative HPLC (20 – 60 % MeCN; RT = 23.5 min) gave title compound **107e** and its diastereomer (RT = 25.8 min) in a ratio of 1:1.48 and a combined yield of 43 % (17.9 mg, 12.4 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.20 (d, J = 0.8 Hz, 2H), 8.19 – 8.14 (m, 6H), 7.60 – 7.55 (m, 4H), 7.57 – 7.51 (m, 4H), 7.44 (d, J = 2.4 Hz, 2H), 7.27 (s, 2H), 4.09 (d, J = 8.0 Hz, 2H), 4.03 (s, 6H), 4.01 (d, J = 7.9 Hz, 2H), 3.85 (dd, J = 10.6, 7.8 Hz, 2H), 3.73 (dd, J = 11.6, 7.1 Hz, 2H), 3.62 (t, J = 7.3 Hz, 2H), 3.54 (ddd, J = 13.0, 10.8, 1.7 Hz, 2H), 3.43 (ddt, J = 13.8, 11.0, 3.0 Hz, 2H), 3.33 – 3.26 (m, 4H), 3.06 (s, 4H), 2.82 – 2.75 (m, 2H), 2.71 (s, 2H), 2.33 (td, J = 11.0, 7.0 Hz, 2H), 1.90 (ddt, J = 13.8, 10.6, 3.1 Hz, 2H), 1.86 – 1.78 (m, 2H), 1.69 – 1.62 (m, 2H), 0.72 (s, 18H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.92, 176.48, 168.47, 159.79, 154.72, 143.51, 141.86, 138.89, 131.40, 130.46, 129.60, 128.32, 125.15, 124.20, 117.92, 101.44, 69.98, 63.78, 63.54, 59.25, 56.79, 50.48, 50.47, 49.64, 48.58, 48.01, 33.69, 33.55, 27.87, 23.69, 23.45, 18.99.

HRMS (ESI): $C_{72}H_{81}O_{10}N_8$ $[M+H]^+$; calculated: 1217.60702, found: 1217.60673.

$[\alpha]_{20}^{D}$ = + 35 ° (c = 0.6, MeCN).

107f, QD2Ph-Cyclohexyl-S

107f was prepared from aldehyde **113d** according to General Procedure 6. Preparative HPLC (25 – 70 % MeCN; RT = 19.8 min) gave title compound **107f** and its diastereomer (RT = 21.9 min) in a ratio of 2:1 and a combined yield of 51 % (21.6 mg, 14.7 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.26 (s, 2H), 8.25 – 8.20 (m, 6H), 7.66 (d, J = 2.6 Hz, 2H), 7.64 – 7.56 (m, 8H), 7.48 (s, 2H), 4.11 (d, J = 8.3 Hz, 2H), 4.09 (s, 6H), 3.89 (t, J = 7.9 Hz, 2H), 3.83 (dd, J = 10.4, 8.2 Hz, 2H), 3.76 (dd, J = 11.6, 6.7 Hz, 2H), 3.63 (tt, J = 12.2, 3.8 Hz, 2H), 3.51 (t, J = 7.1 Hz, 2H), 3.48 (t, J = 12.3 Hz, 2H), 3.42 (ddt, J = 14.2, 11.5, 3.1 Hz, 2H), 3.34 (ddd, J = 13.6, 7.1, 2.7 Hz, 2H), 3.29 (ddd, J = 13.2, 11.0, 7.1 Hz, 2H), 2.79 – 2.73 (m, 2H), 2.64 (s, 2H), 2.45 (q, J = 10.8 Hz, 2H), 1.93 – 1.88 (m, 2H), 1.84 – 1.75 (m, 6H), 1.62 (td, J = 12.0, 10.4, 4.1 Hz, 6H), 1.47 (d, J = 11.8 Hz, 2H), 1.43 (d, J = 12.0 Hz, 4H), 1.12 (q, J = 12.3, 11.4 Hz, 4H), 0.96 (q, J = 12.3, 11.7 Hz, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.35, 176.24, 168.82, 160.29, 154.19, 143.53, 142.22, 137.71, 131.08, 130.23, 129.80, 128.75, 125.64, 125.11, 102.14, 70.21, 64.01, 63.79, 59.00, 57.53, 52.55, 50.36, 49.67, 48.61, 48.04, 33.29, 29.39, 28.84, 26.03, 25.45, 23.79, 23.76, 19.24.

HRMS (ESI): $C_{74}H_{81}O_{10}N_8$ $[M+H]^+$; calculated: 1241.60875, found: 1241.60702.

$[\alpha]_{20}^{D}$ = + 83 ° (c = 0.5, MeCN).

107g, QD2Ph-Cyclohexylmethyl-S

107g was prepared from aldehyde **113d** according to General Procedure 6. Preparative HPLC (20 –70 % MeCN; RT = 21.2 min) gave title compound **107g** and its diastereomer (RT = 24.3 min) in a ratio of 2.9:1 and a combined yield of 47 % (20.1 mg, 13.4 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.21 – 8.17 (m, 6H), 8.16 (d, J = 9.2 Hz, 2H), 7.60 – 7.57 (m, 4H), 7.56 – 7.52 (m, 4H), 7.41 (d, J = 2.7 Hz, 2H), 7.22 (s, 2H), 4.06 (d, J = 8.2 Hz, 2H), 4.03 (s, 6H), 3.98 (t, J = 7.8 Hz, 2H), 3.87 – 3.82 (m, 2H), 3.72 (dd, J = 11.7, 7.0 Hz, 2H), 3.61 (t, J = 7.2 Hz, 2H), 3.50 (ddd, J = 13.1, 10.6, 1.7 Hz, 2H), 3.44 (ddt, J = 14.1, 11.4, 3.3 Hz, 2H), 3.30 (dtd, J = 13.2, 7.0, 4.0 Hz, 4H), 3.03 (qd, J = 13.4, 7.2 Hz, 4H), 2.81 – 2.75 (m, 2H), 2.67 (s, 2H), 2.42 – 2.35 (m, 2H), 1.93 – 1.89 (m, 2H), 1.85 – 1.79 (m, 2H), 1.69 – 1.63 (m, 2H), 1.57 – 1.44 (m, 10H), 1.36 (ttt, J = 10.9, 7.1, 3.5 Hz, 2H), 1.08 – 0.99 (m, 6H), 0.76 – 0.67 (m, 4H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.53, 176.17, 168.63, 159.65, 154.79, 143.87, 141.36, 139.12, 131.72, 130.35, 129.56, 128.21, 125.02, 123.94, 118.02, 101.37, 70.02, 63.70, 63.52, 59.19, 56.73, 50.53, 49.74, 48.54, 48.21, 45.60, 36.49, 33.26, 30.88, 30.82, 26.34, 25.91, 25.86, 23.60, 23.46, 18.98.

HRMS (ESI): $C_{76}H_{85}O_{10}N_8$ $[M+H]^+$; calculated: 1269.63832, found: 1269.64023.

$[\alpha]_{20}^{D}$ = + 37 ° (c = 0.15, MeCN).

107h, QD2Ph-(cis)-Myrthanyl-S

107h was prepared from aldehyde **113d** according to General Procedure 6. Preparative HPLC (35 – 85 % MeCN; RT = 18.2 min) gave title compound **107h** and its diastereomer (RT = 21.8 min) in a ratio of 1.25 : 1 and a combined yield of 38 % (17.4 mg, 11.0 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.22 – 8.17 (m, 6H), 8.16 (d, J = 9.2 Hz, 2H), 7.58 (t, J = 7.5 Hz, 4H), 7.57 – 7.51 (m, 4H), 7.45 (d, J = 2.7 Hz, 2H), 7.25 (s, 2H), 4.06 (d, J = 8.1 Hz, 2H), 4.03 (s, 6H), 3.98 (t, J = 7.8 Hz, 2H), 3.88 – 3.83 (m, 2H), 3.73 (dd, J = 11.6, 7.1 Hz, 2H), 3.60 (t, J = 7.2 Hz, 2H), 3.53 (t, J = 12.2 Hz, 2H), 3.44 (tt, J = 11.1, 3.2 Hz, 2H), 3.34 – 3.27 (m, 4H), 3.25 (dd, J = 13.4, 8.9 Hz, 2H), 3.18 (dd, J = 13.3, 7.0 Hz, 2H), 2.81 – 2.76 (m, 2H), 2.69 (s, 2H), 2.35 (td, J = 11.1, 7.0 Hz, 2H), 2.23 – 2.18 (m, 2H), 2.09 (p, J = 8.0 Hz, 2H), 1.92 – 1.88 (m, 2H), 1.86 – 1.77 (m, 4H), 1.76 – 1.69 (m, 6H), 1.69 – 1.62 (m, 4H), 1.28 (qt, J = 16.4, 5.2 Hz, 2H), 0.92 (s, 6H), 0.86 (s, 6H), 0.70 (d, J = 9.6 Hz, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.57, 176.13, 168.56, 159.79, 154.72, 143.72, 141.84, 138.89, 131.45, 130.45, 129.63, 128.34, 125.17, 124.18, 117.83, 101.46, 70.08, 63.75,

63.54, 59.21, 56.81, 50.57, 49.70, 48.56, 48.21, 44.74, 43.71, 41.56, 39.51, 38.84, 33.62, 33.03, 27.57, 26.09, 23.78, 23.53, 22.69, 19.29, 19.04.

HRMS (ESI): $C_{82}H_{93}O_{10}N_8$ $[M+H]^+$; calculated: 1349.70092, found: 1349.70153.

$[\alpha]_{20}^{D}$ = + 64 ° (c = 0.5, MeCN).

107i, QD2Ph-Bn-S

107i was prepared from aldehyde **113d** according to General Procedure 6. Preparative HPLC (25 – 70 % MeCN; RT = 18.2 min) gave title compound **107i** and its diastereomer (RT = 20.1 min) in a ratio of 1.81 : 1 and a combined yield of 45 % (19.2 mg, 12.9 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.22 (s, 2H), 8.21 – 8.17 (m, 4H), 8.16 (d, J = 9.2 Hz, 2H), 7.61 – 7.52 (m, 8H), 7.46 (d, J = 2.6 Hz, 2H), 7.26 (s, 2H), 7.22 – 7.16 (m, 6H), 7.10 (dd, J = 7.6, 1.9 Hz, 4H), 4.43 (d, J = 15.1 Hz, 2H), 4.36 (d, J = 15.1 Hz, 2H), 4.12 (d, J = 8.2 Hz, 2H), 4.05 (d, J = 7.8 Hz, 2H), 4.03 (s, 6H), 3.87 – 3.81 (m, 2H), 3.77 (dd, J = 11.6, 6.9 Hz, 2H), 3.65 (t, J = 7.2 Hz, 2H), 3.52 (ddd, J = 13.0, 10.9, 1.7 Hz, 2H), 3.43 (ddt, J = 14.2, 11.6, 3.2 Hz, 2H), 3.35 (ddd, J = 13.7, 7.1, 2.9 Hz, 2H), 3.30 (ddd, J = 13.1, 11.0, 7.2 Hz, 2H), 2.80 (ddt, J = 13.2, 7.5, 2.4 Hz, 2H), 2.67 (s, 2H), 2.41 (td, J = 11.2, 7.2 Hz, 2H), 1.91 (dt, J = 10.7, 3.2 Hz, 2H), 1.84 – 1.78 (m, 2H), 1.66 (td, J = 10.3, 5.1 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.26, 175.95, 168.62, 159.86, 154.52, 143.08, 142.23, 138.45, 136.13, 131.02, 130.61, 129.62, 129.03, 128.36, 128.15, 128.13, 125.19, 124.41, 117.86, 101.43, 70.14, 63.76, 63.57, 59.07, 56.79, 50.62, 49.67, 48.57, 48.39, 42.85, 33.30, 23.64, 23.52, 19.04.

HRMS (ESI): $C_{76}H_{73}O_{10}N_8$ $[M+H]^+$; calculated: 1257.54442, found: 1257.54599.

$[\alpha]_{20}^{D}$ = +51 ° (c = 0.5, MeCN).

107j, QD2Ph-4-Fluorobenzyl-S

107j was prepared from aldehyde **113d** according to General Procedure 6. Preparative HPLC (25 – 70 % MeCN; RT = 18.9 min) gave title compound **107j** and its diastereomer (RT = 20.8 min) in a ratio of 2 : 1 and a combined yield of 40 % (17.6 mg, 11.6 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.22 – 8.18 (m, 6H), 8.15 (d, J = 9.2 Hz, 2H), 7.59 – 7.56 (m, 4H), 7.56 – 7.52 (m, 4H), 7.46 (d, J = 2.6 Hz, 2H), 7.27 (s, 2H),

7.16 – 7.09 (m, 4H), 6.92 (t, J = 8.8 Hz, 4H), 4.41 (d, J = 15.0 Hz, 2H), 4.34 (d, J = 15.0 Hz, 2H), 4.12 (d, J = 8.2 Hz, 2H), 4.04 (s, 6H), 4.02 (t, J = 7.9 Hz, 2H), 3.86 – 3.81 (m, 2H), 3.77 (dd, J = 11.6, 6.9 Hz, 2H), 3.63 (t, J = 7.2 Hz, 2H), 3.52 (ddd, J = 13.0, 10.9, 1.8 Hz, 2H), 3.43 (ddt, J = 14.0, 11.3, 3.2 Hz, 2H), 3.34 (ddd, J = 13.6, 7.1, 2.8 Hz, 2H), 3.30 (ddd, J = 13.1, 11.0, 7.2 Hz, 2H), 2.83 – 2.76 (m, 2H), 2.66 (s, 2H), 2.39 (td, J = 11.1, 7.1 Hz, 2H), 1.93 – 1.88 (m, 2H), 1.84 – 1.78 (m, 2H), 1.65 (ddd, J = 14.4, 10.7, 4.0 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.25, 175.94, 168.68, 163.32, 161.93, 159.85, 154.67, 143.56, 141.94, 138.88, 132.35, 132.33, 131.44, 130.52, 130.42, 130.37, 129.63, 128.34, 125.20, 124.28, 118.02, 115.75, 115.62, 101.43, 70.22, 63.82, 63.62, 59.13, 56.82, 50.67, 49.69, 48.62, 48.46, 42.17, 33.38, 23.71, 23.60, 19.11.

HRMS (ESI): $C_{76}H_{71}O_{10}N_8F_2$ $[M+H]^+$; calculated: 1293.52557, found: 1293.52690.

$[\alpha]_{20}^{D}$ = + 47 ° (c = 0.5, MeCN).

107k, QD2Ph-4-Cyanobenzyl-S

107j was prepared from aldehyde **113d** according to General Procedure 6. Preparative HPLC (20 – 65 % MeCN; RT = 20.4 min) gave title compound **107k** and its diastereomer (RT = 21.5 min) in a ratio of 2.2 : 1 and a combined yield of 43 % (18.9 mg, 12.3 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.21 – 8.17 (m, 6H), 8.13 (d, J = 9.2 Hz, 2H), 7.59 – 7.53 (m, 10H), 7.52 (dd, J = 9.2, 2.7 Hz, 2H), 7.44 (d, J = 2.7 Hz, 2H), 7.26 (s, 2H), 7.25 (d, J = 3.7 Hz, 4H), 4.49 (d, J = 15.7 Hz, 2H), 4.43 (d, J = 15.7 Hz, 2H), 4.15 (d, J = 8.2 Hz, 2H), 4.06 – 4.03 (m, 2H), 4.03 (s, 6H), 3.85 – 3.81 (m, 2H), 3.79 (dd, J = 11.6, 6.8 Hz, 2H), 3.67 (t, J = 7.2 Hz, 2H), 3.53 (ddd, J = 12.9, 10.8, 1.7 Hz, 2H), 3.43 (ddt, J = 14.0, 11.3, 3.1 Hz, 2H), 3.36 (ddd, J = 13.6, 7.0, 2.7 Hz, 2H), 3.30 (ddd, J = 13.1, 11.0, 7.2 Hz, 2H), 2.82 – 2.77 (m, 2H), 2.65 (s, 2H), 2.39 (td, J = 11.2, 7.1 Hz, 2H), 1.92 – 1.87 (m, 2H), 1.83 – 1.77 (m, 2H), 1.66 (ddd, J = 14.5, 10.8, 3.9 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.19, 175.87, 168.68, 159.75, 154.69, 143.73, 141.65, 141.49, 138.99, 132.96, 131.57, 130.43, 129.58, 128.84, 128.25, 125.10, 124.12, 119.13, 118.02, 111.48, 101.35, 70.28, 63.78, 63.60, 59.08, 56.76, 50.59, 49.66, 48.60, 48.46, 42.47, 33.36, 23.65, 23.56, 19.08.

HRMS (ESI): $C_{78}H_{71}O_{10}N_{10}$ $[M+H]^+$; calculated: 1307.53491, found: 1307.53556.

$[\alpha]_{20}^{D}$ = + 49 ° (c = 0.5, MeCN).

107l, QD2Ph-Piperonyl-S

107l was prepared from aldehyde **113d** according to General Procedure 6. Preparative HPLC (25 – 70 % MeCN; RT = 17.6 min) gave title compound **107l** and its diastereomer (RT = 19.2 min) in a ratio of 2.1:1 and a combined yield of 42 % (19.1 mg, 12.1 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.24 (s, 2H), 8.22 – 8.17 (m, 6H), 7.64 – 7.54 (m, 10H), 7.43 (s, 2H), 6.64 (d, J = 7.8 Hz, 2H), 6.61 – 6.57 (m, 4H), 5.85 (s, 4H), 4.33 (d, J = 14.9 Hz, 2H), 4.25 (d, J = 15.0 Hz, 2H), 4.13 (d, J = 8.2 Hz, 2H), 4.08 (s, 6H), 4.03 (t, J = 7.9 Hz, 2H), 3.86 – 3.80 (m, 2H), 3.78 (dd, J = 11.6, 6.8 Hz, 2H), 3.63 (t, J = 7.1 Hz, 2H), 3.49 (ddd, J = 12.8, 10.8, 1.7 Hz, 2H), 3.41 (ddt, J = 13.9, 11.3, 3.2 Hz, 2H), 3.36 (ddd, J = 13.6, 7.0, 2.7 Hz, 2H), 3.28 (ddd, J = 13.1, 10.9, 7.1 Hz, 2H), 2.83 – 2.77 (m, 2H), 2.67 (s, 2H), 2.40 (td, J = 11.2, 7.2 Hz, 2H), 1.94 – 1.88 (m, 2H), 1.81 (tdd, J = 13.3, 8.3, 2.3 Hz, 2H), 1.64 (ddd, J = 14.4, 10.8, 3.9 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.32, 176.07, 168.65, 160.22, 154.29, 148.25, 147.60, 143.30, 142.41, 137.92, 130.95, 130.40, 130.11, 129.75, 128.65, 125.55, 124.99, 121.88, 118.47, 108.74, 108.57, 102.01, 70.28, 63.89, 63.67, 59.05, 57.44, 50.52, 49.62, 48.64, 48.36, 42.68, 33.48, 23.78, 23.71, 19.21.

HRMS (ESI): $C_{78}H_{73}O_{14}N_8$ $[M+H]^+$; calculated: 1345.52408, found: 1345.52565.

$[\alpha]_{20}^{D}$ = + 59 ° (c = 0.5, MeCN).

107m, QD2Ph-(S)-1-Phenylethyl-S

107m was prepared from aldehyde **113d** according to General Procedure 6. Preparative HPLC (25 – 70 % MeCN; RT = 19.7 min) gave title compound **107m** and its diastereomer (RT = 21.3 min) in a ratio of 1.2 : 1 and a combined yield of 43 % (18.7 mg, 12.4 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.23 – 8.19 (m, 6H), 8.15 (d, J = 9.2 Hz, 2H), 7.59 (dd, J = 8.2, 6.5 Hz, 4H), 7.57 – 7.52 (m, 4H), 7.45 (d, J = 2.6 Hz, 2H), 7.26 (s, 2H), 7.23 – 7.14 (m, 10H), 5.07 (q, J = 7.1 Hz, 2H), 4.12 (d, J = 8.4 Hz, 2H), 4.04 (s, 6H), 3.99 (t, J = 8.0 Hz, 2H), 3.85 – 3.80 (m, 2H), 3.76 (dd, J = 11.7, 6.8 Hz, 2H), 3.57 – 3.49 (m, 4H), 3.43 (ddt, J = 14.1, 11.2, 3.2 Hz, 2H), 3.34 (ddd, J = 13.7, 7.1, 2.7 Hz, 2H), 3.29 (ddd, J = 13.2,

11.0, 7.2 Hz, 2H), 2.81 – 2.72 (m, 2H), 2.61 (s, 2H), 2.44 (td, J = 11.2, 7.1 Hz, 2H), 1.92 – 1.86 (m, 2H), 1.83 – 1.75 (m, 2H), 1.62 (td, J = 12.6, 10.7, 3.9 Hz, 2H), 1.57 (dd, J = 7.3, 1.8 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.22, 175.99, 168.81, 159.81, 154.71, 143.60, 141.82, 140.00, 138.93, 131.47, 130.48, 129.62, 128.82, 128.35, 127.96, 127.40, 125.15, 124.22, 118.05, 101.39, 70.20, 63.86, 63.68, 59.09, 56.80, 50.77, 50.40, 49.74, 48.67, 48.05, 33.32, 23.65, 23.54, 19.09, 16.99.

HRMS (ESI): $C_{78}H_{77}O_{10}N_8$ $[M+H]^+$; calculated: 1285.57572, found: 1285.57684.

$[\alpha]_{20}^{D}$ = + 24 ° (c = 0.5, MeCN).

107n, QD2Ph-(R)-1-Phenylethyl-S

107n was prepared from aldehyde **113d** according to General Procedure 6. Preparative HPLC (20 – 60 % MeCN; RT = 24.9 min) gave title compound **107n** and its diastereomer (RT = 27.3 min) in a ratio of 1:1.13 and a combined yield of 41 % (17.8 mg, 11.8 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.21 – 8.17 (m, 6H), 8.14 (d, J = 9.2 Hz, 2H), 7.59 – 7.54 (m, 4H), 7.56 – 7.51 (m, 4H), 7.43 (d, J = 2.6 Hz, 2H), 7.24 (s, 2H), 7.22 – 7.14 (m, 10H), 5.11 (q, J = 7.2 Hz, 2H), 4.12 (d, J = 8.3 Hz, 2H), 4.03 (s, 6H), 3.92 (t, J = 7.9 Hz, 2H), 3.85 – 3.81 (m, 2H), 3.75 (dd, J = 11.6, 6.7 Hz, 2H), 3.61 – 3.58 (m, 2H), 3.51 (ddd, J = 12.9, 10.9, 1.7 Hz, 2H), 3.42 (ddt, J = 14.0, 11.1, 3.2 Hz, 2H), 3.33 (ddd, J = 13.6, 7.1, 2.8 Hz, 2H), 3.28 (ddd, J = 13.1, 10.9, 7.2 Hz, 2H), 2.81 – 2.71 (m, 2H), 2.63 (s, 2H), 2.36 (td, J = 11.2, 7.1 Hz, 2H), 1.88 (tq, J = 10.6, 3.4 Hz, 2H), 1.83 – 1.77 (m, 2H), 1.63 (ddd, J = 14.4, 10.5, 3.9 Hz, 2H), 1.50 (d, J = 7.2 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.17, 175.94, 168.82, 159.71, 154.71, 143.70, 141.56, 140.23, 138.97, 131.56, 130.41, 129.56, 128.88, 128.26, 127.91, 127.22, 125.09, 124.08, 117.96, 101.39, 70.24, 63.94, 63.75, 59.09, 56.74, 50.63, 50.34, 49.74, 48.67, 48.11, 33.25, 23.61, 23.55, 19.08, 16.54.

HRMS (ESI): $C_{78}H_{77}O_{10}N_8$ $[M+H]^+$; calculated: 1285.57572, found: 1285.57740.

$[\alpha]_{20}^{D}$ = + 86 ° (c = 0.45, MeCN).

107a, QD2Ph-(R)-1-(4-Bromophenyl)ethyl-S; 108a, QD2Ph-(R)-1-(4-Bromophenyl)-A

107a and 108a were prepared from aldehyde **113d** according to General Procedure 6. Preparative HPLC (25 – 75 % MeCN 30 mL/min; RT = 21.5 min) gave title compound **107a** and its diastereomer **108a** (RT = 24.1 min) in a ratio of 1 : 1.22 and a combined yield of 40 % (19.3 mg, 11.6 µmol).

18n, QD2Ph-(R)-1-(4-Bromophenyl)ethyl-S

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.21 – 8.16 (m, 6H), 8.13 (d, J = 9.1 Hz, 2H), 7.59 – 7.50 (m, 8H), 7.45 – 7.42 (m, 2H), 7.37 – 7.32 (m, 4H), 7.24 (s, 2H), 7.12 – 7.08 (m, 4H), 5.07 (q, J = 7.2 Hz, 2H), 4.12 (d, J = 8.4 Hz, 2H), 4.03 (s, 6H), 3.94 – 3.89 (m, 2H), 3.86 – 3.80 (m, 2H), 3.75 (dd, J = 11.6, 6.7 Hz, 2H), 3.60 – 3.56 (m, 2H), 3.51 (ddd, J = 12.7, 10.8, 1.8 Hz, 2H), 3.42 (ddt, J = 13.9, 11.1, 3.2 Hz, 2H), 3.34 (ddd, J = 13.6, 7.1, 2.8 Hz, 2H), 3.28 (ddd, J = 13.1, 10.9, 7.2 Hz, 2H), 2.76 (ddt, J = 12.9, 7.5, 2.2 Hz, 2H), 2.61 (s, 2H), 2.35 (td, J = 11.1, 7.0 Hz, 2H), 1.90 – 1.83 (m, 2H), 1.83 – 1.76 (m, 2H), 1.63 (ddd, J = 14.0, 10.4, 3.8 Hz, 2H), 1.48 (d, J = 7.2 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.08, 175.86, 168.82, 159.69, 154.77, 143.89, 141.42, 139.51, 139.15, 131.80, 131.73, 130.35, 129.55, 129.46, 128.25, 125.08, 124.01, 121.26, 117.85, 101.37, 70.32, 63.93, 63.73, 59.09, 56.74, 50.30, 49.98, 49.72, 48.68, 48.10, 33.27, 23.63, 23.58, 19.10, 16.30.

HRMS (ESI): $C_{78}H_{75}O_{10}N_8Br_2$ $[M+H]^+$; calculated: 1441.39674, found: 1441.39802.

$[\alpha]_{20}^{D}$ = + 75 ° (c = 0.5, MeCN).

108a, QD2Ph-(R)-1-(4-Bromophenyl)-A

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.28 – 8.24 (m, 2H), 8.16 – 8.11 (m, 4H), 8.08 (s, 1H), 7.98 (s, 1H), 7.59 – 7.51 (m, 8H), 7.50 – 7.46 (m, 2H), 7.45 (dd, J = 12.5, 2.7 Hz, 2H), 7.40 – 7.35 (m, 2H), 7.32 – 7.27 (m, 3H), 7.20 – 7.15 (m, 3H), 5.28 (q, J = 7.2 Hz, 1H), 5.14 (q, J = 7.2 Hz, 1H), 4.17 (d, J = 8.8 Hz, 1H), 4.13 (d, J = 8.5 Hz, 1H), 4.03 (s, 6H), 3.91 – 3.86 (m, 1H), 3.83 – 3.78 (m, 1H), 3.75 – 3.67 (m, 4H), 3.58 – 3.50 (m, 4H), 3.48 – 3.42 (m, 3H), 3.31 – 3.25 (m, 2H), 3.19 (dd, J = 10.0, 7.2 Hz, 1H), 2.65 – 2.62 (m, 1H), 2.61 (s, 2H), 2.54 – 2.48 (m, 1H), 2.38 (q, J = 10.0 Hz, 1H), 2.26 (q, J = 10.5, 10.0 Hz, 1H), 1.93 – 1.86 (m, 2H), 1.83 (d, J = 7.2 Hz, 3H), 1.82 – 1.76 (m, 2H), 1.64 – 1.54 (m, 2H), 1.53 (d, J = 7.3 Hz, 3H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 177.13, 176.15, 176.13, 176.08, 169.47, 169.32, 159.71, 154.96, 154.90, 143.89, 142.15, 141.18, 139.76, 139.60, 139.08, 138.81, 131.98, 131.79, 131.61, 130.42, 129.84, 129.66, 129.62, 129.44, 128.54, 128.29, 125.12, 125.02, 124.22, 124.18, 121.55, 121.29, 117.42, 116.37, 101.49, 72.03, 70.66, 64.75, 63.94, 63.68, 63.45, 58.64, 58.50, 56.71, 52.75, 52.09, 50.26, 50.22, 50.04, 49.83, 49.68, 49.18, 48.61, 48.09, 38.61, 33.66, 23.79, 23.37, 19.48, 19.23, 16.89, 16.25.

HRMS (ESI): $C_{78}H_{75}O_{10}N_8Br_2$ $[M+H]^+$; calculated: 1441.39674, found: 1441.39789.

$[\alpha]_{20}^{D}$ = + 60 ° (c = 0.5, MeCN).

107o, QD2Ph-Phenethyl-S

107o was prepared from aldehyde **113d** according to General Procedure 6. Preparative HPLC (25 – 80 % MeCN; RT = 18.9 min) gave title compound **107o** and its diastereomer (RT = 17.0 min) in a ratio of 3.54 : 1 and a combined yield of 35 % (15.1 mg, 9.98 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.20 – 8.16 (m, 8H), 7.61 – 7.53 (m, 8H), 7.48 (d, J = 2.6 Hz, 2H), 7.30 (s, 2H), 7.27 – 7.21 (m, 6H), 7.18 – 7.13 (m, 4H), 4.05 (s, 6H), 3.98 (d, J = 7.9 Hz, 2H), 3.88 (t, J = 7.6 Hz, 2H), 3.86 – 3.82 (m, 2H), 3.66 – 3.59 (m, 4H), 3.47 (t, J = 7.3 Hz, 2H), 3.42 (ddd, J = 13.9, 7.4, 4.2 Hz, 4H), 3.34 (t, J = 12.3 Hz, 2H), 3.28 – 3.22 (m, 2H), 3.22 – 3.18 (m, 2H), 2.75 – 2.65 (m, 4H), 2.57 – 2.50 (m, 4H), 1.81 – 1.70 (m, 4H), 1.62 (ddd, J = 14.5, 11.0, 3.8 Hz, 2H), 1.48 (td, J = 11.2, 7.1 Hz, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 175.79, 175.50, 168.70, 159.79, 154.64, 143.62, 141.78, 138.82, 138.75, 131.48, 130.49, 130.01, 129.64, 129.01, 128.22, 127.14, 125.13, 124.22, 117.91, 101.43, 69.95, 63.51, 63.47, 59.08, 56.82, 51.07, 49.66, 48.46, 48.19, 40.12, 33.50, 33.31, 23.55, 23.16, 18.82.

HRMS (ESI): $C_{78}H_{77}O_{10}N_8$ $[M+H]^+$; calculated: 1285.57572, found: 1285.57534.

$[\alpha]_{20}^{D}$ = + 91 ° (c = 0.5, MeCN).

107p, QD2Ph-Homopiperonyl-S

18p was prepared from aldehyde **113d** according to General Procedure 6. Preparative HPLC (25 – 80 % MeCN; RT = 16.4 min) gave title compound **107p** and its diastereomer (RT = 17.8 min) in a ratio of 4.15 : 1 and a combined yield of 41 % (19.0 mg, 11.9 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.22 – 8.17 (m, 8H), 7.62 – 7.54 (m, 8H), 7.50 (d, J = 2.6 Hz, 2H), 7.33 (s, 2H), 6.73 (d, J = 7.9 Hz, 2H), 6.70 (d, J = 1.7 Hz, 2H), 6.58 (dd, J = 7.9, 1.7 Hz, 2H), 5.88 (d, J = 34.2 Hz, 4H), 4.05 (s, 6H), 4.03 (d, J = 8.0 Hz, 2H), 3.91 (t, J = 7.7 Hz, 2H), 3.85 (dd, J = 10.7, 7.8 Hz, 2H), 3.68 (dd, J = 11.7, 7.2 Hz, 2H), 3.54 (ddd, J = 13.5, 9.0, 6.7 Hz, 2H), 3.49 (t, J = 7.3 Hz, 2H), 3.45 (tt, J = 10.9, 3.3 Hz, 2H), 3.41 – 3.36 (m, 4H), 3.30 – 3.22 (m, 4H), 2.77 – 2.69 (m, 2H), 2.62 (ddd, J = 13.7, 6.6, 4.6 Hz, 2H), 2.57 (s, 2H), 2.44 (ddd, J = 13.6, 9.0, 7.1 Hz, 2H), 1.84 – 1.73 (m, 4H), 1.70 (td, J = 11.2, 7.1 Hz, 2H), 1.63 (ddd, J = 14.5, 11.1, 4.2 Hz, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 175.87, 175.62, 168.75, 159.94, 154.55, 148.20, 146.81, 143.31, 142.22, 138.59, 132.78, 131.20, 130.64, 129.70, 128.35, 125.27, 124.48, 122.97, 117.88, 110.30, 108.49, 101.75, 101.50, 70.04, 63.60, 63.57, 59.06, 56.88, 51.01, 49.71, 48.44, 48.35, 40.42, 33.69, 33.32, 23.83, 23.33, 18.89.

HRMS (ESI): $C_{80}H_{77}O_{14}N_8$ $[M+H]^+$; calculated: 1373.55538, found: 1373.55582.

$[\alpha]_{20}^{D}$ = + 91 ° (c = 1.0, MeCN).

107q, QD2Ph-4-(4-Fluorophenoxy)benzyl-S

18q was prepared from aldehyde **113d** according to General Procedure 6. Preparative HPLC (35 – 85 % MeCN; RT = 17.8 min) gave title compound **107q** and its diastereomer (RT = 19.6 min) in a ratio of 2.4 : 1 and a combined yield of 56 % (28.2 mg, 16.5 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.25 – 8.18 (m, 6H), 8.13 (d, J = 9.1 Hz, 2H), 7.56 (t, J = 7.5 Hz, 4H), 7.54 – 7.49 (m, 4H), 7.46 (d, J = 2.6 Hz, 2H), 7.28 (s, 2H), 7.11 – 7.06 (m, 8H), 6.94 (dd, J = 9.1, 4.5 Hz, 4H), 6.76 (d, J = 8.6 Hz, 4H), 4.41 (d, J = 15.1 Hz, 2H), 4.33 (d, J = 15.0 Hz, 2H), 4.12 (d, J = 8.2 Hz, 2H), 4.03 (s, 6H), 4.01 (d, J = 7.9 Hz, 2H), 3.83 (dd, J = 10.4, 8.1 Hz, 2H), 3.78 (dd, J = 11.6, 6.9 Hz, 2H), 3.64 (t, J = 7.2 Hz, 2H), 3.52 (ddd, J = 13.0, 10.9, 1.7 Hz, 2H), 3.42 (ddt, J = 14.0, 11.3, 3.2 Hz, 2H), 3.34 (ddd, J = 13.7, 7.2, 2.8 Hz, 2H), 3.29 (ddd, J = 13.2, 11.0, 7.1 Hz, 2H), 2.83 – 2.78 (m, 2H), 2.67 (s, 2H), 2.40 (td, J = 11.2, 7.1 Hz, 2H), 1.93 – 1.88 (m, 2H), 1.84 – 1.77 (m, 2H), 1.65 (ddd, J = 14.4, 10.7, 3.9 Hz, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.32, 176.02, 168.76, 160.32, 159.85, 158.96, 157.91, 154.81, 153.31, 153.30, 144.15, 141.59, 139.40, 135.17, 131.98, 131.13, 130.39, 130.05, 129.65, 128.31, 125.22, 124.11, 121.71, 121.67, 118.80, 117.14, 117.01, 101.44,

70.27, 63.90, 63.72, 59.25, 56.87, 50.80, 49.74, 48.70, 48.57, 42.32, 33.52, 23.83, 23.71, 19.20.

HRMS (ESI): $C_{88}H_{79}O_{12}N_8F_2$ $[M+H]^+$; calculated: 1477.57800, found: 1477.57805.

$[\alpha]_{20}^{D}$ = +34 (c = 0.5, MeCN).

5.10.16 Macrocycles from aldehyde 113e

119a, CN2Thio-Me-S

119a was prepared from aldehyde **113e** according to General Procedure 6 but using DMF as the solvent. Preparative HPLC (15 – 55 % MeCN; RT = 23.0 min) gave title compound **119a** and its diastereomer (RT = 24.92 min) in a ratio of 4.5:1 and a combined yield of 28 % (10.2 mg, 7.94 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.25 (d, J = 8.3 Hz, 2H), 8.16 (s, 2H), 8.10 (d, J = 8.2 Hz, 2H), 8.02 – 8.00 (m, 2H), 7.85 (ddd, J = 8.3, 6.8, 1.2 Hz, 2H), 7.70 (ddd, J = 8.3, 6.8, 1.3 Hz, 2H), 7.65 (dd, J = 5.0, 1.1 Hz, 2H), 7.27 (s, 2H), 7.25 (dd, J = 5.0, 3.7 Hz, 2H), 4.08 (d, J = 8.1 Hz, 2H), 4.01 (t, J = 7.7 Hz, 2H), 3.85 (dd, J = 10.8, 7.6 Hz, 2H), 3.77 (dd, J = 11.7, 7.0 Hz, 2H), 3.61 (t, J = 7.2 Hz, 2H), 3.48 – 3.44 (m, 2H), 3.44 – 3.39 (m, 2H), 3.35 (ddd, J = 13.4, 7.1, 2.7 Hz, 2H), 3.31 (ddd, J = 13.2, 11.1, 7.1 Hz, 2H), 2.88 – 2.83 (m, 2H), 2.67 (s, 2H), 2.64 (s, 6H), 2.43 (q, J = 10.6, 10.1 Hz, 2H), 1.93 – 1.91 (m, 2H), 1.87 – 1.80 (m, 2H), 1.78 – 1.71 (m, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.33, 175.88, 168.63, 152.66, 148.38, 145.12, 142.12, 131.26, 130.40, 130.13, 129.19, 128.17, 128.05, 123.83, 123.38, 116.29, 70.09, 63.62, 63.58, 59.58, 50.77, 49.83, 48.49, 48.38, 33.10, 24.99, 23.70, 23.50, 18.93.

HRMS (ESI): $C_{58}H_{57}O_8N_8S_2$ $[M+H]^+$; calculated: 1057.37353, found: 1057.37418.

$[\alpha]_{20}^{D}$ = + 9 ° (c = 0.25, MeCN).

119b, CN2Thio-Me-S

119b was prepared from aldehyde **113e** according to General Procedure 6 but using DMF as the solvent. Preparative HPLC (15 – 60 % MeCN; RT = 27.6 min) gave title compound **119b**

and its two diastereomers (RT = 29.7 min, RT = 32.2 min) in a ratio of 4 : 9.9 : 1 and a combined yield of 48 % (19.1 mg, 13.67 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.16 (d, J = 8.3 Hz, 2H), 8.14 (s, 2H), 8.09 (dd, J = 8.5, 1.2 Hz, 2H), 7.95 (dd, J = 3.7, 1.1 Hz, 2H), 7.84 (ddd, J = 8.3, 6.8, 1.2 Hz, 2H), 7.69 (ddd, J = 8.2, 6.8, 1.3 Hz, 2H), 7.63 (dd, J = 5.0, 1.1 Hz, 2H), 7.24 – 7.21 (m, 4H), 4.09 (d, J = 8.0 Hz, 2H), 4.05 (t, J = 7.7 Hz, 2H), 3.88 – 3.84 (m, 2H), 3.75 (dd, J = 11.6, 7.1 Hz, 2H), 3.64 (t, J = 7.3 Hz, 2H), 3.51 (ddd, J = 12.9, 10.7, 1.7 Hz, 2H), 3.45 – 3.40 (m, 2H), 3.33 – 3.27 (m, 4H), 3.03 (d, J = 2.7 Hz, 4H), 2.87 – 2.80 (m, 2H), 2.72 (s, 2H), 2.32 (td, J = 11.0, 6.8 Hz, 2H), 1.92 – 1.87 (m, 2H), 1.86 – 1.80 (m, 2H), 1.73 (ddd, J = 14.4, 10.6, 3.7 Hz, 2H), 0.69 (s, 18H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.23, 175.61, 167.86, 152.13, 147.90, 144.55, 141.30, 130.63, 129.70, 129.67, 128.53, 127.56, 127.38, 123.20, 122.65, 115.72, 69.39, 63.09, 62.96, 59.13, 49.92, 49.87, 49.27, 47.91, 47.47, 33.09, 32.90, 27.24, 23.11, 22.83, 18.32.

HRMS (ESI): $C_{66}H_{73}O_8N_8S_2$ $[M+H]^+$; calculated: 1169.49873, found: 1169.50025.

$[\alpha]_{20}^{D}$ = + 88 ° (c = 0.5, MeCN).

119c, CN2Thio-Bn-S

119c was prepared from aldehyde **113e** according to General Procedure 6 but using DMF as the solvent. Preparative HPLC (10 – 60 % MeCN 10 mL/min; RT = 26.56 min) gave title compound **119c** and its 3 diastereomers (RT = 28.32 min, RT = 29.79 min, RT = 31.33 min) in a ratio of 11.9 : 8.6 : 1.2 : 1 and a combined yield of 25 % (10.4 mg, 7.23 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.18 (d, J = 8.3 Hz, 2H), 8.15 (s, 2H), 8.08 (dd, J = 8.2, 1.1 Hz, 2H), 7.98 (dd, J = 3.7, 1.2 Hz, 2H), 7.83 (ddd, J = 8.3, 6.9, 1.3 Hz, 2H), 7.68 (ddd, J = 8.2, 6.8, 1.3 Hz, 2H), 7.63 (dd, J = 5.0, 1.1 Hz, 2H), 7.25 – 7.21 (m, 4H), 7.21 – 7.15 (m, 6H), 7.10 – 7.05 (m, 4H), 4.41 (d, J = 15.0 Hz, 2H), 4.33 (d, J = 15.1 Hz, 2H), 4.13 (d, J = 8.1 Hz, 2H), 4.07 (t, J = 7.8 Hz, 2H), 3.87 – 3.82 (m, 2H), 3.79 (dd, J = 11.6, 6.9 Hz, 2H), 3.68 (t, J = 7.2 Hz, 2H), 3.49 (ddd, J = 13.0, 10.9, 1.7 Hz, 2H), 3.43 (ddt, J = 14.2, 11.1, 3.2 Hz, 2H), 3.35 (ddd, J = 13.5, 7.1, 2.8 Hz, 2H), 3.30 (ddd, J = 13.2, 11.0, 7.1 Hz, 2H), 2.87 – 2.81 (m, 2H), 2.67 (s, 2H), 2.41 (td, J = 11.2, 7.1 Hz, 2H), 1.93 – 1.88 (m, 2H), 1.85 – 1.79 (m, 2H), 1.73 (ddd, J = 14.4, 10.6, 3.7 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.22, 175.73, 168.61, 152.71, 148.49, 145.22, 141.97, 136.17, 131.22, 130.33, 130.25, 129.13, 129.05, 128.14, 128.10, 127.94, 123.79, 123.25, 116.19, 70.14, 63.70, 63.62, 59.57, 50.68, 49.86, 48.51, 48.43, 42.84, 33.29, 23.68, 23.53, 18.98.

HRMS (ESI): $C_{70}H_{65}O_8N_8S_2$ $[M+H]^+$; calculated: 1209.43613, found: 1209.43640.

$[\alpha]_{20}^{D}$ = + 120 ° (c = 0.5, MeCN).

5.10.17 Macrocycles from aldehyde 113f

120a, CN2nBu-Me-S

120a was prepared from aldehyde **113f** according to General Procedure 6. Preparative HPLC (15 – 40 % MeCN; RT = 14.7 min) gave title compound **120a** and its diastereomer (RT = 16.6 min) in a ratio of 8.38:1 and a combined yield of 50 % (18.8 mg, 15.25 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.45 (d, J = 8.4 Hz, 2H), 8.23 (d, J = 8.2 Hz, 2H), 8.03 (ddd, J = 8.3, 7.0, 1.2 Hz, 2H), 7.98 (s, 2H), 7.87 (ddd, J = 8.3, 7.0, 1.2 Hz, 2H), 7.33 (s, 2H), 4.06 (d, J = 8.0 Hz, 2H), 3.94 (t, J = 7.7 Hz, 2H), 3.86 – 3.80 (m, 2H), 3.72 (dd, J = 11.7, 7.0 Hz, 2H), 3.59 (t, J = 7.2 Hz, 2H), 3.45 (dddd, J = 25.9, 14.1, 11.1, 2.5 Hz, 4H), 3.35 – 3.27 (m, 4H), 3.21 – 3.11 (m, 4H), 2.81 (ddt, J = 13.4, 7.2, 2.3 Hz, 2H), 2.66 (s, 6H), 2.65 (s, 2H), 2.42 (td, J = 11.2, 7.0 Hz, 2H), 1.97 – 1.91 (m, 2H), 1.89 – 1.80 (m, 6H), 1.76 – 1.69 (m, 2H), 1.46 – 1.37 (m, 4H), 0.94 (t, J = 7.4 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.38, 176.14, 168.63, 162.82, 147.78, 142.14, 133.58, 129.76, 124.91, 124.05, 123.94, 121.08, 69.62, 63.51, 63.39, 59.21, 50.72, 49.78, 48.43, 48.18, 36.34, 32.99, 31.72, 24.99, 23.69, 23.48, 22.64, 18.87, 13.66.

HRMS (ESI): $C_{58}H_{69}O_8N_8$ $[M+H]^+$; calculated: 1005.52329, found: 1005.52462.

$[\alpha]_{20}^{D}$ = + 124 ° (c = 1.0, MeCN).

120b, CN2nBu-*i*Pr-S

120b was prepared from aldehyde **113f** according to General Procedure 6. Preparative HPLC (10 – 55 % MeCN; RT = 17.2 min) gave title compound **120b** and its diastereomer (RT = 19.0 min) in a ratio of 2.2 : 1 and a combined yield of 40 % (14.9 mg, 11.56 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.50 – 8.41 (m, 2H), 8.28 – 8.22 (m, 2H), 8.06 – 8.01 (m, 2H), 7.99 – 7.95 (m, 2H), 7.91 – 7.85 (m, 2H), 7.35 – 7.29 (m, 2H), 4.09 – 3.99 (m, 4H), 3.88 – 3.79 (m, 4H), 3.74 – 3.67 (m, 2H), 3.51 (t, J = 7.3 Hz, 2H), 3.49 – 3.41 (m, 4H), 3.34 – 3.26 (m, 4H), 3.21 – 3.15 (m, 4H), 2.80 – 2.74 (m, 2H), 2.64 (s, 2H), 2.44 (td, J = 11.2, 7.0 Hz, 2H), 1.92 (d, J = 3.5 Hz, 2H), 1.85 (ddddd, J = 20.7, 17.9, 16.0, 10.1, 5.6 Hz, 6H), 1.69 (ddd, J = 14.5, 10.4, 3.5 Hz, 2H), 1.47 – 1.37 (m, 4H), 1.14 (d, J = 6.9 Hz, 6H), 1.11 (d, J = 6.9 Hz, 6H), 0.93 (t, J = 7.4 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.21, 176.00, 168.66, 162.77, 133.68, 129.83, 124.74, 124.08, 123.96, 121.11, 69.71, 63.64, 63.48, 59.19, 50.22, 49.83, 48.35, 47.94, 44.54, 36.31, 33.03, 31.71, 23.68, 23.53, 22.66, 19.03, 18.92, 18.73, 13.72.

HRMS (ESI): $C_{62}H_{77}O_8N_8$ $[M+H]^+$; calculated: 1061.58589, found: 1061.58564.

$[\alpha]_{20}^{D}$ = + 128 ° (c = 0.5, MeCN).

120c, CN2nBu-*t*Bu-S

120c was prepared from aldehyde **113f** according to General Procedure 6. Preparative HPLC (15 – 60 % MeCN; RT = 15.6 min) gave title compound **120c** and its diastereomer (RT = 17.5 min) in a ratio of 1.15:1 and a combined yield of 47 % (17.7 mg, 13.4 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.45 (d, J = 8.4 Hz, 2H), 8.24 (d, J = 8.5 Hz, 2H), 8.03 (ddd, J = 8.4, 6.9, 1.2 Hz, 2H), 7.95 (s, 2H), 7.87 (ddd, J = 8.3, 7.0, 1.2 Hz, 2H), 7.33 (s, 2H), 4.02 (d, J = 8.1 Hz, 2H), 3.83 (dd, J = 10.4, 8.1 Hz, 2H), 3.74 (t, J = 7.8 Hz, 2H), 3.68 (dd, J = 11.7, 6.9 Hz, 2H), 3.49 (t, J = 12.2 Hz, 2H), 3.46 – 3.41 (m, 2H), 3.41 – 3.39 (m, 2H), 3.33 – 3.25 (m, 4H), 3.18 (t, J = 7.8 Hz, 4H), 2.78 – 2.71 (m, 2H), 2.64 (s, 2H), 2.38 (td, J = 11.2, 7.1 Hz, 2H), 1.92 – 1.78 (m, 8H), 1.68 (ddd, J = 14.4, 10.9, 3.8 Hz, 2H), 1.42 (dtd, J = 15.7, 8.5, 7.5, 6.2 Hz, 4H), 1.31 (s, 18H), 0.94 (t, J = 7.4 Hz, 6H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.95, 176.88, 168.75, 162.77, 147.93, 141.96, 133.68, 129.84, 124.77, 124.17, 124.00, 121.13, 69.72, 64.14, 63.86, 59.28, 58.95, 50.49, 49.84, 48.37, 47.95, 36.32, 33.26, 31.72, 27.92, 23.71, 23.43, 22.70, 18.91, 13.77.

HRMS (ESI): $C_{64}H_{81}O_8N_8$ $[M+H]^+$; calculated: 1089.61719, found: 1089.61680.

$[\alpha]_{20}^{D}$ = + 131 ° (c = 0.5, MeCN).

120d, CN2nBu-Neopentyl-S

120d was prepared from aldehyde **113f** according to General Procedure 6. Preparative HPLC (20 – 70 % MeCN; RT = 13.0 min) gave title compound **120d** and its diastereomer (RT = 14.5 min) in a ratio of 1:1.9 and a combined yield of 43 % (16.7 mg, 12.4 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) 1H NMR (700 MHz,) δ 8.40 (d, J = 8.4 Hz, 2H), 8.21 (d, J = 8.4 Hz, 2H), 8.00 (ddd, J = 8.4, 6.9, 1.1 Hz, 2H), 7.92 (s, 2H), 7.85 (ddd, J = 8.3, 7.0, 1.2 Hz, 2H), 7.30 (s, 2H), 4.05 (d, J = 8.0 Hz, 2H), 3.96 (t, J = 7.8 Hz, 2H), 3.83 (dd, J = 10.8, 7.6 Hz, 2H), 3.70 (dd, J = 11.6, 7.0 Hz, 2H), 3.62 (t, J = 7.3 Hz, 2H), 3.53 – 3.47 (m, 2H), 3.42 (ddt, J = 14.0, 11.2, 3.2 Hz, 2H), 3.30 (ddd, J = 8.4 Hz, 2H), 3.26 (ddd, J = 13.6, 7.1, 2.8 Hz, 2H), 3.12 (ddd, J = 9.1, 6.9, 2.7 Hz, 4H), 3.07 (d, J = 13.3 Hz, 2H), 3.04 (d, J = 13.1 Hz, 2H), 2.78 (ddt, J = 12.7, 7.0, 2.0 Hz, 2H), 2.69 (s, 2H), 2.35 (td, J = 11.2, 7.2 Hz, 2H), 1.93 – 1.87 (m, 2H), 1.87 – 1.78 (m, 6H), 1.71 (ddd, J = 14.5, 10.5, 3.7 Hz, 2H), 1.43 (h, J = 7.4 Hz, 4H), 0.95 (t, J = 7.4 Hz, 6H), 0.73 (s, 18H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.86, 176.42, 168.42, 162.87, 146.98, 142.85, 133.27, 129.55, 125.50, 123.95, 123.87, 120.91, 69.61, 63.59, 63.41, 59.35, 50.52, 50.27, 49.77, 48.35, 47.91, 36.65, 33.57, 33.44, 31.72, 27.91, 23.70, 23.47, 22.74, 18.89, 13.70.

HRMS (ESI): $C_{66}H_{85}O_8N_8$ $[M+H]^+$; calculated: 1117.64849, found: 1117.64935.

$[\alpha]_{20}^{D}$ = +127 (c = 0.4, MeCN).

120e, CN2nBu-4-Acetylphenyl-S

120e was prepared from aldehyde **113f** according to General Procedure 6. Preparative HPLC (20 – 50 % MeCN; RT = 14.2 min) gave title compound **120e** and its 2 diastereomers (RT = 13.8 min) and (RT = 15.9 min) in a ratio of 3.25:1:1.48 and a combined yield of 58% (24.0 mg, 16.65 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.43 (d, J = 8.5 Hz, 2H), 8.19 (d, J = 8.5 Hz, 2H), 8.04 – 7.99 (m, 4H), 7.97 – 7.91 (m, 4H), 7.87 (ddd, J = 8.2, 7.1, 1.0 Hz, 2H), 7.33 (s, 2H), 7.29 – 7.22 (m, 4H), 4.25 (d, J = 8.2 Hz, 2H), 4.12 (t, J = 7.9 Hz, 2H), 3.89 (dd, J = 11.6, 6.8 Hz, 2H), 3.87 – 3.83 (m, 2H), 3.83 – 3.80 (m, 2H), 3.52 (ddd, J = 12.8, 10.8, 1.7 Hz, 2H), 3.42 (ddt, J = 13.6, 9.7, 6.8 Hz, 4H), 3.31 (ddd, J = 13.0, 11.0, 7.2 Hz, 2H), 3.19 – 3.16 (m, 4H), 2.89 – 2.81 (m, 2H), 2.66 (s, 2H), 2.58 – 2.52 (m, 2H), 2.51 (s, 6H), 1.90 (d, J = 3.0 Hz, 2H), 1.89 – 1.79 (m, 6H), 1.76 – 1.70 (m, 2H), 1.47 – 1.37 (m, 4H), 0.93 (t, J = 7.4 Hz, 6H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 198.71, 175.14, 175.08, 168.77, 162.69, 147.82, 141.81, 137.42, 136.37, 133.68, 129.83, 129.52, 127.35, 124.65, 123.99, 123.87, 120.97, 70.00, 63.95, 63.90, 59.07, 50.95, 49.81, 48.92, 48.31, 36.20, 32.93, 31.63, 26.65, 23.60, 23.55, 22.62, 18.93, 13.64.

HRMS (ESI): $C_{72}H_{77}O_{10}N_8$ $[M+H]^+$; calculated: 1213.57572, found: 1213.57688.

$[\alpha]_{20}^{D}$ = + 93 ° (c = 0.5, MeCN).

21f, CN2nBu-Bn-S

120f was prepared from aldehyde **113f** according to General Procedure 6. Preparative HPLC (20 – 50 % MeCN; RT = 17.4 min) gave title compound **120f** and its diastereomer (RT = 20.5 min) in a ratio of 1.79:1 and a combined yield of 36 % (14.1 mg, 10.8 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 8.55 (d, J = 8.4 Hz, 2H), 8.28 (dd, J = 8.6, 1.2 Hz, 2H), 7.99 (ddd, J = 8.3, 6.9, 1.2 Hz, 2H), 7.95 (s, 2H), 7.83 (ddd, J = 8.2, 6.9, 1.2 Hz, 2H), 7.39 (s, 2H), 7.26 – 7.18 (m, 6H), 7.16 – 7.12 (m, 4H), 4.44 (d, J = 14.9 Hz, 2H), 4.38 (d, J = 14.9 Hz, 2H), 4.10 (d, J = 8.1 Hz, 2H), 3.98 (t, J = 7.8 Hz, 2H), 3.80 (dd, J = 10.6, 7.8 Hz, 2H), 3.76 (dd, J = 11.6, 6.9 Hz, 2H), 3.62 (t, J = 7.2 Hz, 2H), 3.50 (ddd, J = 13.0, 10.9, 1.7 Hz, 2H), 3.41 (tt, J = 11.2, 3.1 Hz, 2H), 3.35 – 3.25 (m, 4H), 3.18 (t, J = 7.8 Hz, 4H), 2.80 (ddd, J = 14.1, 6.3, 2.9 Hz, 2H), 2.67 (s, 2H), 2.41 (td, J = 11.3, 7.2 Hz, 2H), 1.92 – 1.78 (m, 8H), 1.69 (ddd, J = 14.4, 10.7, 3.8 Hz, 2H), 1.42 (h, J = 7.4 Hz, 4H), 0.92 (t, J = 7.4 Hz, 6H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) 13C NMR (176 MHz, CD3CN) δ 176.30, 176.02, 168.75, 162.99, 147.72, 142.89, 136.48, 133.49, 129.72, 129.27, 128.48, 128.37, 125.58, 124.44, 124.23, 121.18, 69.94, 63.85, 63.73, 59.36, 50.77, 49.86, 48.56, 48.39, 43.07, 36.64, 33.56, 31.94, 31.87, 24.04, 23.88, 22.93, 22.90, 19.22, 13.91.

HRMS (ESI): $C_{70}H_{77}O_8N_8$ $[M+H]^+$; calculated: 1157.58644, found: 1157.58859.

$[\alpha]_{20}^{D}$ = + 131 ° (c = 0.5, MeCN).

120g, CN2nBu-4-Fluorobenzyl-S

120g was prepared from aldehyde **113f** according to General Procedure 6. Preparative HPLC (20 – 50 % MeCN; RT = 18.8 min) gave title compound **120g** and its diastereomer (RT = 22.2 min) in a ratio of 2.14:1 and a combined yield of 28 % (11.5 mg, 8.09 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.57 (d, J = 8.6 Hz, 2H), 8.31 (d, J = 8.5 Hz, 2H), 8.00 (ddt, J = 8.2, 6.8, 1.2 Hz, 2H), 7.96 (s, 2H), 7.83 (ddt, J = 8.2, 6.9, 1.2 Hz, 2H), 7.40 (s, 2H), 7.19 – 7.15 (m, 4H), 6.99 – 6.93 (m, 4H), 4.43 (d, J = 14.9 Hz, 2H), 4.34 (d, J = 14.9 Hz, 2H), 4.10 (d, J = 8.1 Hz, 2H), 3.96 (t, J = 7.8 Hz, 2H), 3.82 – 3.78 (m, 2H), 3.76 (dd, J = 11.6, 6.9 Hz, 2H), 3.60 (t, J = 7.2 Hz, 2H), 3.49 (ddd, J = 13.0, 10.9, 1.7 Hz, 2H), 3.41 (ddt, J = 14.1, 11.3, 3.3 Hz, 2H), 3.34 – 3.25 (m, 4H), 3.18 (dt, J = 14.4, 7.1 Hz, 4H), 2.79 (ddt, J = 13.0, 7.2, 2.2 Hz, 2H), 2.66 (s, 2H), 2.39 (td, J = 11.2, 7.0 Hz, 2H), 1.93 – 1.77 (m, 8H), 1.69 (tt, J = 10.9, 2.5 Hz, 2H), 1.45 – 1.37 (m, 4H), 0.91 (t, J = 7.4 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.25, 175.99, 168.78, 163.58, 162.99, 162.19, 147.95, 142.75, 133.59, 132.64, 130.75, 130.70, 129.78, 125.46, 124.50, 124.27, 121.23, 115.95, 115.82, 69.95, 63.86, 63.73, 59.33, 50.80, 49.84, 48.60, 48.35, 42.36, 36.55, 33.56, 31.95 (trippled), 24.06, 23.91, 22.93 (trippled), 19.23, 13.89.

HRMS (ESI): $C_{70}H_{75}O_8N_8F_2$ $[M+H]^+$; calculated: 1193.56704, found: 1193.56660.

$[\alpha]_{20}^{D}$ = + 102 ° (c = 0.5, MeCN).

120h, CN2nBu-4-Methylbenzyl-S

120h was prepared from aldehyde **113f** according to General Procedure 6. Preparative HPLC (20 – 50 % MeCN; RT = 20.04 min) gave title compound **120h** and its diastereomer (RT = 23.53 min) in a ratio of 3.38:1 and a combined yield of 42 % (17.0 mg, 12.0 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.57 (d, J = 8.5 Hz, 2H), 8.30 (d, J = 8.5 Hz, 2H), 8.02 – 7.97 (m, 2H), 7.95 (s, 2H), 7.83 (t, J = 7.7 Hz, 2H), 7.40 (s, 2H), 7.06 – 7.00 (m, 8H), 4.39 (d, J = 14.8 Hz, 2H), 4.33 (d, J = 14.8 Hz, 2H), 4.09 (d, J = 8.1 Hz, 2H), 3.96 (t, J = 7.8 Hz, 2H), 3.79 (dd, J = 10.7, 7.8 Hz, 2H), 3.75 (dd, J = 11.6, 6.9 Hz, 2H), 3.60 (t, J

= 7.2 Hz, 2H), 3.49 (ddd, J = 12.9, 10.9, 1.7 Hz, 2H), 3.41 (ddt, J = 14.1, 11.2, 3.2 Hz, 2H), 3.29 (dddd, J = 18.3, 13.2, 8.9, 4.9 Hz, 4H), 3.22 – 3.14 (m, 4H), 2.82 – 2.76 (m, 2H), 2.66 (s, 2H), 2.40 (td, J = 11.2, 7.1 Hz, 2H), 2.23 (s, 6H), 1.92 – 1.77 (m, 8H), 1.69 (ddd, J = 14.4, 10.6, 3.6 Hz, 2H), 1.42 (h, J = 7.3 Hz, 4H), 0.92 (t, J = 7.4 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.30, 176.03, 168.77, 162.98, 147.89, 142.79, 138.18, 135.25, 133.52, 129.84, 129.76, 128.55, 125.50, 124.50, 124.27, 121.24, 69.93, 63.86, 63.73, 59.35, 50.78, 49.85, 48.57, 48.35, 42.85, 36.57, 33.58, 31.97 (trippled), 24.07, 23.91, 22.95 (trippled), 20.87, 19.24, 13.91.

HRMS (ESI): $C_{72}H_{81}O_8N_8$ $[M+H]^+$; calculated: 1185.61719, found: 1185.61652.

$[\alpha]_{20}^{D}$ = + 114 ° (c = 0.5, MeCN).

120i, CN2nBu-Piperonyl-S

120i was prepared from aldehyde **113f** according to General Procedure 6. Preparative HPLC (20 – 50 % MeCN; RT = 16.7 min) gave title compound **120i** and its diastereomer (RT = 19.5 min) in a ratio of 3.25:1 and a combined yield of 40 % (16.9 mg, 11.5 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) 1H NMR (700 MHz, Acetonitrile-d3) δ 8.55 (d, J = 8.5 Hz, 2H), 8.26 (d, J = 8.5 Hz, 2H), 8.05 (ddd, J = 8.3, 7.0, 1.0 Hz, 2H), 8.02 (s, 2H), 7.91 (ddd, J = 8.2, 7.0, 1.1 Hz, 2H), 7.37 (s, 2H), 6.67 (d, J = 8.4 Hz, 2H), 6.64 – 6.60 (m, 4H), 5.86 (s, 4H), 4.33 (d, J = 14.8 Hz, 2H), 4.24 (d, J = 14.8 Hz, 2H), 4.10 (d, J = 8.1 Hz, 2H), 4.01 (t, J = 7.8 Hz, 2H), 3.83 (dd, J = 10.8, 7.5 Hz, 2H), 3.74 (dd, J = 11.6, 6.9 Hz, 2H), 3.63 (t, J = 7.2 Hz, 2H), 3.49 (ddd, J = 12.9, 10.9, 1.7 Hz, 2H), 3.43 (ddt, J = 14.2, 11.3, 3.2 Hz, 2H), 3.34 – 3.27 (m, 4H), 3.18 (ddd, J = 8.6, 7.0, 3.4 Hz, 4H), 2.84 – 2.76 (m, 2H), 2.66 (s, 2H), 2.40 (td, J = 11.1, 7.1 Hz, 2H), 1.93 – 1.89 (m, 2H), 1.88 – 1.79 (m, 6H), 1.70 (tt, J = 10.9, 2.3 Hz, 2H), 1.43 – 1.36 (m, 4H), 0.89 (t, J = 7.4 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.17, 175.92, 168.50, 162.67, 148.71, 148.16, 147.55, 141.21, 134.05, 130.12, 129.95, 124.32, 124.15, 124.03, 122.00, 121.19, 108.79, 108.52, 101.93, 69.76, 63.58, 63.43, 59.13, 50.35, 49.76, 48.36, 48.17, 42.63, 35.90, 33.16, 31.61, 23.68, 23.52, 22.61, 18.94, 13.60.

HRMS (ESI): $C_{72}H_{76}O_8N_{12}$ $[M+H]^+$; calculated: 1245.56555, found: 1245.56715.

$[\alpha]_{20}^{D}$ = + 113 ° (c = 0.5, MeCN).

120j, CN2nBu-(R)-Phenylethyl-S

21j was prepared from aldehyde **113f** according to General Procedure 6. Preparative HPLC (15 – 60 % MeCN; RT = 18.13 min) gave title compound **120j** and its diastereomer (RT = 20.2 min) in a ratio of 1 : 1.1 and a combined yield of 47 % (19.3 mg, 13.7 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.34 (d, J = 8.5 Hz, 2H), 8.16 (d, J = 8.5 Hz, 2H), 7.95 (t, J = 7.7 Hz, 2H), 7.82 (d, J = 7.6 Hz, 4H), 7.27 (s, 2H), 7.26 – 7.16 (m, 10H), 5.12 (q, J = 7.2 Hz, 2H), 4.05 (d, J = 8.2 Hz, 2H), 3.85 (t, J = 7.9 Hz, 2H), 3.81 (t, J = 9.2 Hz, 2H), 3.70 (dd, J = 11.6, 6.8 Hz, 2H), 3.58 (t, J = 7.2 Hz, 2H), 3.47 (t, J = 12.2 Hz, 2H), 3.44 – 3.37 (m, 2H), 3.33 – 3.24 (m, 4H), 3.09 – 3.05 (m, 4H), 2.77 – 2.70 (m, 2H), 2.62 (s, 2H), 2.36 (q, J = 10.0 Hz, 2H), 1.90 – 1.84 (m, 2H), 1.80 (h, J = 6.3 Hz, 6H), 1.67 (ddd, J = 14.3, 11.1, 3.9 Hz, 2H), 1.49 (d, J = 7.2 Hz, 6H), 1.37 (h, J = 7.3 Hz, 4H), 0.89 (t, J = 7.4 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.07, 175.83, 168.66, 162.88, 146.91, 142.80, 140.22, 133.27, 129.56, 128.91, 128.01, 127.36, 125.47, 123.95, 123.87, 120.88, 69.95, 63.79, 63.63, 59.23, 50.83, 50.12, 49.84, 48.47, 47.98, 36.60, 33.14, 31.62, 23.67, 23.54, 22.65, 18.96, 16.60, 13.69.

HRMS (ESI): $C_{72}H_{81}O_8N_8$ $[M+H]^+$; calculated: 1185.61719, found: 1185.61708.

$[\alpha]_{20}^{D}$ = + 120 ° (c = 1.0, MeCN).

121a, **CN2nBu-1-Methyl-1-(2-fluorophenyl)ethyl-A**

121a was prepared from aldehyde **113f** according to General Procedure 6. Preparative HPLC (15 – 55 % MeCN; RT = 22.9 min) gave title compound **121a** and its symmetrical diastereomer (RT = 20.9 min) in a ratio of 2.35 : 1 and a combined yield of 28 % (12.0 mg, 8.12 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.47 – 8.41 (m, 2H), 8.22 (ddd, J = 10.4, 8.6, 1.1 Hz, 2H), 8.04 (tdd, J = 8.4, 3.5, 1.2 Hz, 2H), 7.88 (dtd, J = 8.1, 6.9, 1.2 Hz, 2H), 7.79 (s, 1H), 7.61 (s, 1H), 7.49 (ddd, J = 9.1, 8.0, 1.8 Hz, 1H), 7.39 (s, 1H), 7.37 – 7.32 (m, 1H), 7.26 (tdd, J = 8.4, 4.9, 1.5 Hz, 2H), 7.20 – 7.16 (m, 2H), 7.12 (ddd, J = 13.1, 8.1, 1.3 Hz, 1H), 7.06 (td, J = 7.6, 1.3 Hz, 1H), 7.00 (ddd, J = 12.7, 8.2, 1.3 Hz, 1H), 4.08 (d, J = 8.3 Hz, 1H), 3.93 (d, J = 8.3 Hz, 1H), 3.85 (t, J = 9.4 Hz, 1H), 3.80 – 3.76 (m, 2H), 3.69 (dd, J = 11.6, 6.8 Hz, 1H),

3.59 (dd, J = 10.9, 7.3 Hz, 1H), 3.54 (td, J = 7.7, 6.7, 1.9 Hz, 4H), 3.50 (dd, J = 10.1, 8.3 Hz, 1H), 3.48 – 3.38 (m, 3H), 3.31 – 3.25 (m, 2H), 3.18 (dd, J = 10.1, 7.3 Hz, 1H), 3.12 (t, J = 7.8 Hz, 2H), 3.09 (s, 1H), 3.00 – 2.94 (m, 1H), 2.63 (s, 1H), 2.58 (s, 1H), 2.53 – 2.48 (m, 1H), 2.43 – 2.37 (m, 1H), 2.33 – 2.26 (m, 2H), 1.97 (d, J = 5.7 Hz, 6H), 1.91 (dd, J = 10.7, 3.1 Hz, 1H), 1.83 – 1.71 (m, 10H), 1.67 (s, 3H), 1.62 – 1.53 (m, 2H), 1.42 – 1.31 (m, 4H), 0.93 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 177.08, 176.33, 175.92, 175.83, 168.95, 168.82, 162.67, 162.38, 161.25, 161.11, 161.05, 160.85, 160.65, 159.72, 159.41, 148.60, 147.37, 141.87, 141.48, 133.89, 133.69, 133.43, 133.37, 132.85, 132.79, 129.84, 129.79, 129.61, 129.56, 129.35, 129.30, 127.42, 127.26, 127.23, 125.32, 124.63, 124.59, 124.21, 124.04, 123.96, 123.85, 123.79, 120.22, 119.62, 119.56, 116.36, 116.30, 116.23, 116.19, 116.06, 71.43, 70.02, 65.18, 64.06, 63.75, 63.67, 60.59, 60.29, 58.83, 58.38, 52.65, 52.51, 50.09, 50.00, 49.69, 48.73, 47.89, 47.85, 37.86, 36.08, 35.80, 33.51, 31.83, 31.60, 27.13, 26.92, 26.56, 26.50, 23.34, 23.26, 23.19, 22.92, 22.72, 22.48, 18.94, 18.83, 13.55, 13.50.

HRMS (ESI): $C_{74}H_{83}O_8N_8F_2$ $[M+H]^+$; calculated: 1249.62964, found: 1249.63093.

$[\alpha]_{20}^{D}$ = + 75° (c = 0.5, MeCN).

120k, CN2nBu-1-(2-Chlorophenyl)ethyl-S; 121b, CN2nBu-1-(2-Chlorophenyl)ethyl-A

120k was prepared from aldehyde **113f** according to General Procedure 6. Preparative HPLC (15 – 55 % MeCN; RT = 19.4 min) gave title compound **120k** and its diastereomer **121b**(RT = 21.3 min) in a ratio of 1 : 3.1 and a combined yield of 28 % (12.1 mg, 8.03 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.39 (d, J = 8.3 Hz, 2H), 8.24 (d, J = 8.6 Hz, 2H), 8.03 (ddd, J = 8.4, 6.9, 1.2 Hz, 2H), 7.91 – 7.83 (m, 4H), 7.56 (dd, J = 7.8, 1.7 Hz, 2H), 7.29 – 7.23 (m, 4H), 7.16 (td, J = 7.6, 1.7 Hz, 2H), 7.08 (td, J = 7.6, 1.4 Hz, 2H), 3.95 (d, J = 8.3 Hz, 2H), 3.83 (dd, J = 10.9, 7.6 Hz, 2H), 3.76 (t, J = 8.0 Hz, 2H), 3.62 (dd, J = 11.7, 6.9 Hz, 2H), 3.44 (qd, J = 9.9, 9.1, 4.6 Hz, 6H), 3.30 (ddd, J = 13.2, 11.0, 7.1 Hz, 2H), 3.25 (ddd, J = 13.9, 7.2, 2.8 Hz, 2H), 3.11 (t, J = 7.9 Hz, 4H), 2.74 – 2.67 (m, 2H), 2.61 (s, 2H), 2.40 (td, J = 11.3, 7.1 Hz, 2H), 1.92 (s, 2H), 1.87 – 1.77 (m, 6H), 1.66 (tt, J = 10.8, 2.4 Hz, 2H), 1.45 (ddd, J = 10.4, 7.7, 5.7 Hz, 2H), 1.38 (h, J = 7.3 Hz, 4H), 1.26 – 1.22 (m, 2H), 1.18 (ddd, J = 10.4, 7.7, 5.6 Hz, 2H), 1.08 (ddd, J = 10.2, 7.7, 5.6 Hz, 2H), 0.88 (t, J = 7.4 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 175.79, 175.58, 168.56, 162.92, 136.65, 135.36, 135.11, 133.22, 130.29, 130.23, 129.51, 126.91, 125.60, 123.97, 123.88, 120.90, 69.90, 63.81, 63.58, 59.27, 49.86, 48.42, 47.72, 36.67, 35.51, 32.95, 31.60, 23.67, 23.49, 22.71, 22.69, 18.90, 14.24, 14.21, 13.66.

HRMS (ESI): $C_{74}H_{79}O_8N_8Cl_2$ $[M+H]^+$; calculated: 1277.53924, found: 1277.54101.

$[\alpha]_{20}^{D}$ = + 115° (c = 0.3, MeCN).

121b, CN2nBu-1-(2-Chlorophenyl)ethyl-A

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.48 (dd, J = 17.0, 8.5 Hz, 2H), 8.31 (dd, J = 8.6, 1.1 Hz, 1H), 8.27 (dd, J = 8.5, 1.1 Hz, 1H), 8.11 (ddd, J = 8.4, 7.0, 1.1 Hz, 1H), 8.08 (ddd, J = 8.4, 6.9, 1.1 Hz, 1H), 7.95 (ddd, J = 8.3, 7.0, 1.2 Hz, 1H), 7.92 (ddd, J = 8.3, 7.0, 1.2 Hz, 1H), 7.88 (s, 1H), 7.83 (dd, J = 7.8, 1.8 Hz, 1H), 7.81 (s, 1H), 7.63 (dd, J = 7.8, 1.7 Hz, 1H), 7.42 (dd, J = 7.8, 1.4 Hz, 1H), 7.36 (s, 1H), 7.31 (td, J = 7.6, 1.4 Hz, 1H), 7.28 (ddd, J = 7.8, 5.9, 1.6 Hz, 2H), 7.20 (s, 1H), 7.17 (td, J = 7.6, 1.7 Hz, 1H), 7.10 (td, J = 7.6, 1.4 Hz, 1H), 3.90 (d, J = 8.6 Hz, 1H), 3.87 (t, J = 9.4 Hz, 1H), 3.84 – 3.78 (m, 2H), 3.55 – 3.42 (m, 9H), 3.40 – 3.17 (m, 8H), 3.14 (dd, J = 10.1, 7.3 Hz, 1H), 2.69 (s, 1H), 2.59 (s, 1H), 2.48 (ddt, J = 13.9, 8.7, 2.6 Hz, 1H), 2.47 – 2.40 (m, 2H), 2.26 (td, J = 10.8, 7.4 Hz, 1H), 1.99 – 1.85 (m, 7H), 1.82 (dddd, J = 15.9, 13.4, 7.0, 4.7 Hz, 2H), 1.66 – 1.57 (m, 3H), 1.53 (dddd, J = 11.7, 9.8, 8.6, 5.6 Hz, 3H), 1.49 – 1.43 (m, 3H), 1.32 (ddd, J = 10.2, 7.8, 6.0 Hz, 1H), 1.30 – 1.24 (m, 2H), 1.14 – 1.09 (m, 1H), 1.02 (t, J = 7.4 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.81, 176.18, 175.81, 175.76, 169.07, 168.94, 162.81, 162.53, 149.59, 148.57, 141.07, 140.92, 137.27, 136.68, 135.46, 135.39, 135.22, 134.74, 134.44, 134.35, 130.54, 130.43, 130.32, 130.29, 130.25, 127.36, 126.93, 124.37, 124.25, 124.13, 124.08, 123.98, 123.79, 120.67, 119.90, 119.66, 71.62, 70.16, 64.95, 63.83, 63.55, 63.52, 58.91, 58.52, 52.47, 52.43, 50.18, 49.90, 49.37, 48.91, 47.96, 47.91, 38.10, 35.96, 35.94, 35.78, 35.55, 33.19, 32.06, 31.88, 23.60, 23.50, 23.39, 23.16, 23.05, 22.81, 19.12, 19.05, 14.42, 14.22, 13.75, 13.71, 13.61, 13.58.

HRMS (ESI): $C_{74}H_{79}O_8N_8Cl_2$ $[M+H]^+$; calculated: 1277.53924, found: 1277.54097.

$[\alpha]_{20}^{D}$ = + 83° (c = 0.5, MeCN).

120l, CN2nBu-Phenethyl-S

120l was prepared from aldehyde **113f** according to General Procedure 6. Preparative HPLC (20 – 60 % MeCN; RT = 14.9 min) gave title compound **120l** and its diastereomer (RT = 17.7 min) in a ratio of 3.09:1 and a combined yield of 45 % (18.1 mg, 12.8 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.55 – 8.49 (m, 1H), 8.26 (d, J = 8.6 Hz, 1H), 8.05 (ddd, J = 8.4, 7.0, 1.2 Hz, 1H), 7.99 (s, 1H), 7.90 (ddd, J = 8.3, 7.0, 1.2 Hz, 1H), 7.40 (s, 1H), 7.30 – 7.22 (m, 3H), 7.17 – 7.13 (m, 2H), 4.02 (d, J = 7.9 Hz, 1H), 3.88 (t, J = 7.6 Hz, 1H), 3.82 (dd, J = 10.6, 7.8 Hz, 1H), 3.65 – 3.58 (m, 2H), 3.47 (t, J = 7.4 Hz, 1H), 3.46 – 3.40 (m, 2H), 3.33 (ddd, J = 13.1, 10.9, 1.8 Hz, 1H), 3.24 (ddd, J = 13.4, 11.0, 7.2 Hz, 1H), 3.17 (dddd, J = 22.7, 14.0, 6.3, 4.4 Hz, 3H), 2.75 – 2.68 (m, 2H), 2.57 – 2.51 (m, 2H), 1.89 – 1.81 (m, 2H), 1.81 – 1.70 (m, 2H), 1.66 (ddd, J = 14.6, 10.9, 3.8 Hz, 1H), 1.54 (td, J = 11.3, 7.1 Hz, 1H), 1.42 (tdd, J = 14.1, 10.6, 7.0 Hz, 2H), 0.93 (t, J = 7.4 Hz, 3H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 175.91, 175.56, 168.64, 162.79, 148.24, 141.84, 138.80, 133.84, 130.00, 129.96, 129.08, 127.21, 124.67, 124.26, 124.05, 121.11, 69.60, 63.37, 63.35, 59.20, 50.88, 49.80, 48.39, 48.05, 40.26, 36.20, 33.53, 33.27, 31.77, 23.66, 23.26, 22.68, 18.78, 13.73.

HRMS (ESI): $C_{72}H_{81}O_8N_8$ $[M+H]^+$; calculated: 1185.61719, found: 1185.61665. $\mathbf{[\alpha]_{20}^{D}}$ = +168 (c = 0.5, MeCN).

120m, CN2nBu-Homopiperonyl-S

120m was prepared from aldehyde **113f** according to General Procedure 6. Preparative HPLC (20 – 60 % MeCN; RT = 15.1 min) gave title compound **120m** and its diastereomer (RT = 17.3 min) in a ratio of 3.2:1 and a combined yield of 46 % (20 mg, 13.3 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.40 (d, J = 8.4 Hz, 2H), 8.16 (d, J = 8.6 Hz, 2H), 7.94 (ddt, J = 8.3, 6.9, 1.1 Hz, 2H), 7.84 (s, 2H), 7.82 – 7.76 (m, 2H), 7.29 (s, 2H), 6.67 (d, J = 7.8 Hz, 2H), 6.62 (d, J = 1.7 Hz, 2H), 6.51 (dd, J = 7.9, 1.7 Hz, 2H), 5.83 (dd, J = 15.6, 0.8 Hz, 4H), 3.93 (d, J = 7.9 Hz, 2H), 3.79 (t, J = 7.7 Hz, 2H), 3.75 (dd, J = 10.3, 8.0 Hz, 2H), 3.58 (dd, J = 11.7, 7.3 Hz, 2H), 3.46 (ddd, J = 13.4, 8.7, 6.8 Hz, 2H), 3.42 (t, J = 7.4 Hz, 2H), 3.40 – 3.35 (m, 2H), 3.32 (ddd, J = 13.5, 7.2, 4.9 Hz, 2H), 3.28 (ddd, J = 12.9, 11.0, 1.7 Hz, 2H), 3.20 – 3.14 (m, 4H), 3.11 – 3.02 (m, 4H), 2.66 (ddt, J = 13.4, 7.6, 2.5 Hz, 2H), 2.57 – 2.52

(m, 2H), 2.50 (s, 2H), 2.38 (ddd, J = 13.7, 8.8, 7.2 Hz, 2H), 1.82 – 1.64 (m, 10H), 1.63 – 1.58 (m, 2H), 1.40 – 1.30 (m, 4H), 0.87 (t, J = 7.3 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 175.82, 175.62, 168.68, 162.97, 148.29, 146.88, 133.32, 132.81, 129.60, 125.69, 124.13, 123.97, 122.96, 120.93, 110.29, 108.55, 101.83, 69.71, 63.45, 63.44, 59.29, 50.84, 49.87, 48.38, 48.19, 40.52, 36.76, 33.60, 33.32, 31.83, 31.77, 23.89, 23.38, 22.74, 22.71, 18.84, 13.82.

HRMS (ESI): $C_{74}H_{81}O_{12}N_8$ $[M+H]^+$; calculated: 1273.59685, found: 1273.59896.

$[\alpha]_{20}^{D}$ = + 149 ° (c = 0.3, MeCN).

120n, CN2nBu-(S)-2-Phenylpropyl-S

120n was prepared from aldehyde **113f** according to General Procedure 6. Preparative HPLC (20 – 70 % MeCN; RT = 14.6 min) gave title compound **120n** and its diastereomer (RT = 16.8 min) in a ratio of 1:1.36 and a combined yield of 47 % (19.5 mg, 13.5 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.50 (d, J = 8.4 Hz, 2H), 8.28 (d, J = 8.6 Hz, 2H), 8.09 (t, J = 7.8 Hz, 2H), 8.02 (s, 2H), 7.93 (t, J = 7.7 Hz, 2H), 7.35 (s, 2H), 7.25 (t, J = 7.6 Hz, 4H), 7.18 (t, J = 7.3 Hz, 2H), 7.07 (d, J = 7.6 Hz, 4H), 4.01 (d, J = 7.9 Hz, 2H), 3.91 (t, J = 7.7 Hz, 2H), 3.83 (dd, J = 11.0, 7.4 Hz, 2H), 3.63 (dd, J = 11.7, 7.1 Hz, 2H), 3.47 – 3.36 (m, 8H), 3.34 (dd, J = 13.6, 8.0 Hz, 2H), 3.29 (ddd, J = 13.4, 10.9, 7.2 Hz, 2H), 3.20 (s, 6H), 3.02 (q, J = 7.3 Hz, 2H), 2.77 – 2.70 (m, 2H), 2.55 (s, 2H), 2.04 (td, J = 12.2, 11.8, 7.0 Hz, 2H), 1.92 – 1.77 (m, 8H), 1.68 (ddd, J = 14.5, 10.9, 3.8 Hz, 2H), 1.44 (h, J = 7.3 Hz, 4H), 1.05 (d, J = 7.0 Hz, 6H), 0.94 (t, J = 7.4 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.14, 175.90, 168.34, 162.60, 148.92, 143.87, 140.93, 134.20, 130.19, 129.08, 127.80, 127.27, 124.20, 124.01, 123.91, 121.17, 69.46, 63.39, 63.26, 59.14, 50.49, 49.74, 48.07, 47.93, 45.89, 37.64, 35.77, 33.10, 31.64, 23.57, 23.26, 22.61, 19.04, 18.73, 13.62.

HRMS (ESI): $C_{74}H_{85}O_8N_8$ $[M+H]^+$; calculated: 1213.64849, found: 1213.64788.

$[\alpha]_{20}^{D}$ = +106 (c = 0.5, MeCN).

120o, CN2nBu-(R)-2-Phenylpropyl-S

120o was prepared from aldehyde **113f** according to General Procedure 6. Preparative HPLC (20 – 60 % MeCN; RT = 16.1 min) gave title compound **120o** and its 3 diastereomers (RT = 17.0 min, RT = 17.0 min, RT = 18.7 min) in a ratio of 3.7 : 1 : 1 : 1.2 and a combined yield of 35 % (14.6 mg, 10.3 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.48 (d, J = 8.5 Hz, 2H), 8.23 (d, J = 8.5 Hz, 2H), 8.01 (ddt, J = 8.2, 6.9, 1.2 Hz, 2H), 7.90 – 7.85 (m, 4H), 7.38 (s, 2H), 7.35 – 7.30 (m, 6H), 7.25 – 7.20 (m, 4H), 3.90 (d, J = 7.7 Hz, 2H), 3.82 – 3.75 (m, 4H), 3.63 (dd, J = 13.4, 11.0 Hz, 2H), 3.51 (dd, J = 11.8, 7.5 Hz, 2H), 3.43 (ddt, J = 14.3, 11.3, 3.3 Hz, 2H), 3.38 (t, J = 7.4 Hz, 2H), 3.26 (dd, J = 13.4, 5.4 Hz, 2H), 3.23 – 3.16 (m, 4H), 3.16 – 3.04 (m, 6H), 2.77 – 2.70 (m, 2H), 2.66 – 2.60 (m, 2H), 2.46 (s, 2H), 1.85 – 1.78 (m, 4H), 1.75 (tdd, J = 11.2, 7.5, 2.1 Hz, 2H), 1.66 – 1.58 (m, 4H), 1.45 – 1.35 (m, 4H), 1.10 (d, J = 7.1 Hz, 6H), 0.92 (t, J = 7.4 Hz, 6H), 0.86 (td, J = 11.3, 7.0 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 175.77, 174.95, 168.63, 162.97, 146.87, 144.14, 143.20, 133.25, 129.56, 129.14, 129.11, 127.52, 125.81, 124.10, 123.94, 120.84, 69.59, 63.45, 63.27, 59.26, 51.10, 49.82, 48.44, 47.96, 45.58, 38.93, 36.80, 33.35, 31.85, 23.61, 23.07, 22.71, 22.68, 19.32, 18.71, 13.77.

HRMS (ESI): $C_{74}H_{85}O_8N_8$ $[M+H]^+$; calculated: 1213.64849, found: 1213.64811.

$[\alpha]_{20}^{D}$ = + 171 ° (c = 0.4, MeCN).

120p, CN2nBu-4-(4-Fluorophenoxy)benzyl-S

120p was prepared from aldehyde **113f** according to General Procedure 6. Preparative HPLC (20 – 70 % MeCN; RT = 18.9 min) gave title compound **120p** and its diastereomer (RT = 20.7 min) in a ratio of 2.4:1 and a combined yield of 52 % (24.1 mg, 15.0 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.50 (d, J = 8.5 Hz, 2H), 8.26 (d, J = 8.6 Hz, 2H), 8.04 (ddd, J = 8.3, 6.9, 1.1 Hz, 2H), 8.01 (s, 2H), 7.89 (ddd, J = 8.2, 6.9, 1.2 Hz, 2H), 7.35 (s, 2H), 7.13 – 7.07 (m, 8H), 6.97 – 6.93 (m, 4H), 6.79 (d, J = 8.6 Hz, 4H), 4.40 (d, J = 14.9 Hz, 2H), 4.32 (d, J = 14.9 Hz, 2H), 4.11 (d, J = 8.1 Hz, 2H), 4.00 (t, J = 7.8 Hz, 2H), 3.83 (dd, J = 10.8, 7.5 Hz, 2H), 3.75 (dd, J = 11.6, 6.9 Hz, 2H), 3.63 (t, J = 7.2 Hz, 2H), 3.50 (ddd, J = 13.0, 10.9, 1.8 Hz, 2H), 3.46 – 3.40 (m, 2H), 3.33 – 3.27 (m, 4H), 3.18 (ddd, J = 8.5, 7.0, 2.9

Hz, 4H), 2.80 (ddt, J = 13.3, 7.7, 2.6 Hz, 2H), 2.66 (s, 2H), 2.41 (td, J = 11.2, 7.1 Hz, 2H), 1.93 – 1.88 (m, 2H), 1.87 – 1.78 (m, 6H), 1.71 (ddd, J = 14.4, 10.8, 3.8 Hz, 2H), 1.38 (hd, J = 7.0, 2.4 Hz, 4H), 0.87 (t, J = 7.4 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.18, 175.94, 168.54, 162.70, 160.23, 158.86, 157.85, 153.21, 148.65, 141.35, 134.01, 130.98, 130.41, 130.12, 130.07, 124.24, 124.05, 121.59, 121.54, 121.20, 118.36, 117.06, 116.93, 116.60, 69.73, 63.60, 63.44, 59.16, 50.48, 49.77, 48.32, 48.28, 42.27, 35.96, 33.20, 31.65, 23.73, 23.55, 22.66, 18.95, 13.66.

HRMS (ESI): $C_{82}H_{83}O_{10}N_8F_2$ $[M+H]^+$; calculated: 1377.61947, found: 1377.61925.

$[\alpha]_{20}^{D}$ = +109° (c = 1, MeCN).

5.10.18 Macrocycles from aldehyde 113g

122a, QD2Cl-Me-S

122a was prepared from aldehyde **113g** according to General Procedure B. Preparative HPLC (10 – 50 % MeCN; RT = 21.0 min) gave title compound **122a** and its diastereomer (RT = 23.1 min, was not isolated) in a ratio of 16.2 : 1 and a yield of 38 % (13.7 mg, 11.0 µmol, only **122a**).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 7.95 (d, J = 9.2 Hz, 2H), 7.75 (s, 2H), 7.51 (dd, J = 9.2, 2.6 Hz, 2H), 7.42 (d, J = 2.6 Hz, 2H), 7.17 (s, 2H), 4.00 (s, 6H), 3.97 (d, J = 8.1 Hz, 2H), 3.89 (t, J = 7.7 Hz, 2H), 3.82 – 3.78 (m, 2H), 3.66 (dd, J = 11.7, 6.9 Hz, 2H), 3.57 (t, J = 7.2 Hz, 2H), 3.48 – 3.39 (m, 4H), 3.33 – 3.24 (m, 4H), 2.75 – 2.70 (m, 2H), 2.69 (s, 6H), 2.66 (s, 2H), 2.40 (td, J = 11.2, 6.9 Hz, 2H), 1.93 – 1.91 (m, 2H), 1.83 (dddd, J = 13.5, 11.1, 7.0, 2.4 Hz, 2H), 1.71 (ddd, J = 14.4, 10.8, 3.8 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.37, 175.99, 168.57, 159.86, 148.14, 144.28, 143.42, 131.29, 125.04, 124.28, 121.01, 101.76, 69.58, 63.61, 63.44, 58.85, 56.77, 50.67, 49.67, 48.39, 48.28, 33.01, 25.00, 23.66, 23.48, 18.91.

HRMS (ESI): $C_{52}H_{55}O_{10}N_8Cl_2$ $[M+H]^+$; calculated: 1021.34127, found: 1021.34121.

$[\alpha]_{20}^{D}$ = + 83 ° (c = 1, MeCN).

122b, QD2Cl-Propargyl-S

122b was prepared from aldehyde **113g** according to General Procedure B with $Cu(NCCH_3)_4OTf$ instead of AgOTf. Preparative HPLC (15 – 45 % MeCN; RT = 26.1 min) gave title compound **122b** and its diastereomer (RT = 28.3 min) in a ratio of 3.4 : 1 and a combined yield of 37 % (13.9 mg, 10.7 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 7.96 (d, J = 9.2 Hz, 2H), 7.75 (s, 2H), 7.51 (dd, J = 9.2, 1.8 Hz, 2H), 7.41 (s, 2H), 7.16 (s, 2H), 4.05 – 3.93 (m, 14H), 3.83 – 3.77 (m, 2H), 3.69 (dd, J = 11.6, 7.0 Hz, 2H), 3.64 (t, J = 7.1 Hz, 2H), 3.49 – 3.43 (m, 2H), 3.41 (ddd, J = 11.4, 9.2, 6.4 Hz, 2H), 3.33 – 3.25 (m, 4H), 2.72 (ddt, J = 13.3, 7.6, 2.5 Hz, 2H), 2.67 (s, 2H), 2.44 (t, J = 2.5 Hz, 2H), 2.41 (td, J = 11.0, 6.8 Hz, 2H), 1.98 – 1.95 (m, 2H), 1.86 – 1.80 (m, 2H), 1.71 (ddd, J = 14.3, 10.8, 3.8 Hz, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 175.12, 174.73, 168.39, 159.87, 148.14, 144.28, 143.38, 131.31, 125.03, 124.30, 120.93, 101.74, 77.38, 72.16, 69.74, 63.67, 63.47, 58.77, 56.76, 50.59, 49.69, 48.51, 48.37, 33.08, 28.19, 23.64, 23.50, 18.96.

HRMS (ESI): $C_{56}H_{55}O_{10}N_8Cl_2$ $[M+H]^+$; calculated: 1069.34127, found: 1069.34172.

$[\alpha]_{20}^{D}$ = + 74 ° (c = 0.5, MeCN).

122c, QD2Cl-*i*Pr-S

122c was prepared from aldehyde **113g** according to General Procedure B. Preparative HPLC (10 – 50 % MeCN; RT = 25.9 min) gave title compound **122c** and its diastereomer (RT = 28.3 min) in a ratio of 3.62 : 1 and a combined yield of 50 % (18.8 mg, 14.4 µmol).

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 7.95 (dd, J = 9.2, 1.6 Hz, 2H), 7.75 (s, 2H), 7.51 (dt, J = 9.3, 2.0 Hz, 2H), 7.41 (s, 2H), 7.17 (s, 2H), 4.05 (hept, J = 7.0 Hz, 2H), 4.00 (s, 8H), 3.82 – 3.76 (m, 4H), 3.68 – 3.63 (m, 2H), 3.50 (t, J = 7.2 Hz, 2H), 3.49 – 3.44 (m, 2H), 3.41 (ddt, J = 14.1, 11.4, 3.2 Hz, 2H), 3.32 – 3.23 (m, 4H), 2.69 (ddt, J = 13.1, 7.5, 2.3 Hz, 2H), 2.64 (s, 2H), 2.43 (td, J = 10.9, 6.7 Hz, 2H), 1.93 – 1.90 (m, 2H), 1.86 – 1.79 (m, 2H), 1.68 (td, J = 12.6, 10.7, 3.8 Hz, 2H), 1.16 (d, J = 6.9 Hz, 6H), 1.14 (d, J = 7.0 Hz, 6H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 1245.33, 1244.98, 1237.76, 1228.90, 1217.17, 1213.31, 1212.37, 1200.32, 1194.03, 1193.30, 1189.94, 1170.74, 1138.60, 1132.70, 1132.49,

1127.74, 1125.70, 1119.15, 1118.67, 1117.41, 1116.87, 1113.42, 1101.95, 1092.52, 1092.44, 1088.03, 1087.88, 1087.61.

HRMS (ESI): $C_{56}H_{64}O_{10}N_8Cl_2$ $[M+H]^+$; calculated: 1077.40387, found: 1077.40388.

$[\alpha]_{20}^{D}$ = + 85 ° (c = 1, MeCN).

122d, QD2Cl-Ph-S

122d was prepared from aldehyde **113g** according to General Procedure B. Preparative HPLC (10 – 60 % MeCN; RT = 22.8 min) gave title compound **122d** and its diastereomer (RT = 24.9 min) in a ratio of 4.7 : 1 and a combined yield of 50 % (19.9 mg, 14.5 µmol).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 7.91 (d, J = 9.2 Hz, 2H), 7.76 (s, 2H), 7.47 (dd, J = 9.2, 2.6 Hz, 2H), 7.41 – 7.36 (m, 6H), 7.35 – 7.32 (m, 2H), 7.17 (s, 2H), 7.13 – 7.10 (m, 4H), 4.15 (d, J = 8.4 Hz, 2H), 4.07 (t, J = 7.9 Hz, 2H), 3.99 (s, 6H), 3.85 – 3.80 (m, 4H), 3.80 – 3.76 (m, 2H), 3.53 – 3.48 (m, 2H), 3.40 (dddt, J = 13.9, 9.8, 6.8, 3.1 Hz, 4H), 3.29 (ddd, J = 13.1, 11.1, 7.1 Hz, 2H), 2.77 (ddt, J = 13.3, 7.7, 2.4 Hz, 2H), 2.67 (s, 2H), 2.53 (td, J = 11.2, 6.8 Hz, 2H), 1.91 (d, J = 3.3 Hz, 2H), 1.85 – 1.79 (m, 2H), 1.73 (ddd, J = 14.2, 10.7, 3.8 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 175.47, 175.35, 168.81, 159.82, 148.12, 144.21, 143.24, 132.61, 131.26, 129.65, 129.63, 129.42, 127.46, 125.00, 124.21, 120.98, 101.75, 69.96, 64.01, 63.93, 58.76, 56.75, 50.86, 49.71, 48.80, 48.42, 33.01, 23.63, 23.62, 19.04.

HRMS (ESI): $C_{62}H_{59}O_{10}N_8Cl_2$ $[M+H]^+$; calculated: 1145.37257, found: 1145.37284.

$[\alpha]_{20}^{D}$ = + 49 ° (c = 1, MeCN).

122e, QD2Cl-(S)-1-Phenylethyl-S; 24a, QD2Cl-(S)-1-Phenylethyl-A

122e and **123a** were prepared from aldehyde **113g** according to General Procedure B. Preparative HPLC (20 – 60 % MeCN; RT = 23.6 min) gave title compound **122e** and its diastereomer **123a** (RT = 26.2 min) in a ratio of 2.64 : 1 and a combined yield of 41 % (16.9 mg, 11.8 µmol).

122e, QD2Cl-(S)-1-Phenylethyl-S

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 7.95 (s, 2H), 7.75 (s, 2H), 7.50 (dd, J = 9.2, 2.6 Hz, 2H), 7.42 (d, J = 2.7 Hz, 2H), 7.26 – 7.21 (m, 8H), 7.21 – 7.15 (m, 4H), 5.10 (q, J = 7.2 Hz, 2H), 4.04 (d, J = 8.3 Hz, 2H), 4.00 (s, 6H), 3.93 (t, J = 7.9 Hz, 2H), 3.77 (dd, J = 10.3, 8.2 Hz, 2H), 3.70 (dd, J = 11.6, 6.7 Hz, 2H), 3.54 – 3.51 (m, 2H), 3.51 – 3.47 (m, 2H), 3.40 (ddt, J = 14.0, 11.4, 3.2 Hz, 2H), 3.28 (tdd, J = 12.9, 6.4, 3.9 Hz, 4H), 2.68 (ddt, J = 13.2, 7.6, 2.5 Hz, 2H), 2.61 (s, 2H), 2.42 (td, J = 11.2, 7.0 Hz, 2H), 1.90 (tq, J = 10.3, 3.2 Hz, 2H), 1.79 (tdd, J = 13.5, 8.3, 2.4 Hz, 2H), 1.66 (ddd, J = 14.4, 10.4, 3.9 Hz, 2H), 1.59 (d, J = 7.2 Hz, 6H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.18, 175.84, 168.65, 159.88, 148.14, 144.28, 143.38, 140.03, 131.29, 128.83, 127.94, 127.35, 125.02, 124.32, 120.87, 101.74, 69.71, 63.77, 63.54, 58.77, 56.77, 50.76, 50.10, 49.72, 48.55, 47.87, 33.21, 23.60, 23.51, 19.01, 17.01.

HRMS (ESI): $C_{66}H_{67}O_{10}N_8Cl_2$ $[M+H]^+$; calculated: 1201.43517, found: 1201.43582.

$[\alpha]_{20}^{D}$ = 46 ° (c = 1, MeCN).

123a, QD2Cl-(S)-1-Phenylethyl-A

^{1}H NMR (700 MHz, $CD_3CN:D_2O$ [10:1], NH^+ and NH not observed) δ 7.95 (dd, J = 11.6, 9.2 Hz, 2H), 7.66 (s, 1H), 7.60 (s, 1H), 7.51 (ddd, J = 9.2, 6.6, 2.6 Hz, 2H), 7.45 (d, J = 7.5 Hz, 2H), 7.43 – 7.38 (m, 4H), 7.36 – 7.33 (m, 1H), 7.27 – 7.23 (m, 4H), 7.21 (s, 1H), 7.19 (td, J = 5.8, 2.9 Hz, 1H), 7.08 (s, 1H), 5.39 (q, J = 7.3 Hz, 1H), 5.15 (q, J = 7.2 Hz, 1H), 4.09 (d, J = 8.7 Hz, 1H), 4.05 (d, J = 8.5 Hz, 1H), 4.01 (s, 3H), 3.99 (s, 3H), 3.83 – 3.78 (m, 2H), 3.77 (dd, J = 10.8, 8.1 Hz, 1H), 3.72 (dd, J = 11.5, 6.6 Hz, 1H), 3.64 (dd, J = 10.8, 7.3 Hz, 1H), 3.60 (dd, J = 10.0, 8.5 Hz, 1H), 3.54 – 3.51 (m, 2H), 3.49 (d, J = 9.6 Hz, 2H), 3.46 – 3.40 (m, 2H), 3.38 (ddd, J = 14.1, 7.4, 2.7 Hz, 1H), 3.30 – 3.25 (m, 2H), 3.23 (dd, J = 10.0, 7.2 Hz, 1H), 2.70 (s, 1H), 2.61 – 2.56 (m, 2H), 2.47 – 2.38 (m, 2H), 2.27 (td, J = 10.8, 7.4 Hz, 1H), 1.92 (d, J = 7.3 Hz, 3H), 1.91 – 1.86 (m, 2H), 1.85 – 1.75 (m, 2H), 1.62 (d, J = 7.2 Hz, 3H), 1.59 (dq, J = 10.4, 4.9 Hz, 2H).

^{13}C NMR (176 MHz, $CD_3CN:D_2O$ [10:1]) δ 176.86, 176.35, 176.24, 175.95, 169.44, 169.39, 159.88, 159.81, 148.30, 147.97, 144.39, 143.74, 143.03, 140.62, 140.05, 135.05, 131.34, 131.31, 129.64, 129.05, 128.82, 128.64, 128.34, 127.94, 127.59, 127.44, 125.06, 124.94, 124.46, 124.30, 120.13, 119.79, 101.78, 71.60, 70.01, 64.71, 63.71, 63.52, 63.50, 58.44, 58.19,

56.74, 56.71, 52.83, 52.56, 50.83, 50.71, 50.08, 49.88, 49.73, 49.14, 48.33, 47.90, 38.37, 33.55, 23.68, 23.36, 23.34, 23.22, 19.38, 18.96, 17.01, 16.86.

HRMS (ESI): $C_{66}H_{67}O_{10}N_8Cl_2$ $[M+H]^+$; calculated: 1201.43517, found: 1201.43571.

$[\alpha]_{20}^{D}$ = + 30 ° (c = 1, MeCN).

122f, QD2Cl-(R)-1-Phenylethyl-S; 123b, QD2Cl-(R)-1-Phenylethyl-A

23f and **24b** were prepared from aldehyde **113g** according to General Procedure B. Preparative HPLC (15 – 60 % MeCN; RT = 25.4 min) gave title compound **122f** and its diastereomer **123b** (RT = 27.9 min) in a ratio of 2.1 : 1 and a combined yield of 43 % (17.9 mg, 12.5 µmol).

122f, QD2Cl-(R)-1-Phenylethyl-S

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 7.94 (d, J = 9.2 Hz, 2H), 7.73 (d, J = 0.8 Hz, 2H), 7.50 (dd, J = 9.2, 2.6 Hz, 2H), 7.40 (d, J = 2.7 Hz, 2H), 7.29 – 7.24 (m, 4H), 7.23 – 7.19 (m, 6H), 7.17 (s, 2H), 5.15 (q, J = 7.2 Hz, 2H), 4.04 (d, J = 8.3 Hz, 2H), 3.99 (s, 6H), 3.86 (t, J = 7.9 Hz, 2H), 3.81 – 3.74 (m, 2H), 3.69 (dd, J = 11.6, 6.7 Hz, 2H), 3.61 – 3.56 (m, 2H), 3.48 (ddd, J = 12.9, 10.8, 1.7 Hz, 2H), 3.40 (ddt, J = 14.1, 11.4, 3.2 Hz, 2H), 3.32 – 3.23 (m, 4H), 2.68 (ddt, J = 13.2, 7.6, 2.4 Hz, 2H), 2.63 (s, 2H), 2.35 (td, J = 10.8, 6.6 Hz, 2H), 1.91 – 1.84 (m, 2H), 1.84 – 1.77 (m, 2H), 1.67 (ddd, J = 14.4, 10.6, 3.9 Hz, 2H), 1.53 (d, J = 7.2 Hz, 6H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.17, 175.81, 168.72, 159.84, 148.12, 144.29, 143.28, 140.23, 131.32, 128.92, 127.95, 127.24, 125.01, 124.28, 120.85, 101.80, 69.79, 63.88, 63.65, 58.79, 56.76, 50.51, 50.11, 49.76, 48.60, 47.99, 33.17, 23.59, 23.55, 19.04, 16.42.

HRMS (ESI): $C_{66}H_{67}O_{10}N_8Cl_2$ $[M+H]^+$; calculated: 1201.43517, found: 1201.43661.

$[\alpha]_{20}^{D}$ = + 91 ° (c = 1, MeCN).

123b, QD2Cl-(R)-1-Phenylethyl-A

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 7.95 (dd, J = 9.2, 0.9 Hz, 2H), 7.67 (s, 1H), 7.55 (s, 1H), 7.51 (ddd, J = 9.3, 5.5, 2.6 Hz, 2H), 7.47 – 7.43 (m, 2H), 7.42 – 7.36 (m, 4H), 7.33 – 7.27 (m, 1H), 7.26 (d, J = 5.8 Hz, 4H), 7.22 (dt, J = 6.0, 3.0 Hz, 1H), 7.20 (s, 1H), 7.05 (s, 1H), 5.40 (q, J = 7.2 Hz, 1H), 5.20 (q, J = 7.2 Hz, 1H), 4.08 (d, J = 8.7 Hz, 1H), 4.06 (d, J = 8.5 Hz, 1H), 4.00 (d, J = 0.8 Hz, 6H), 3.83 – 3.77 (m, 1H), 3.77 (dd, J = 10.6, 8.3 Hz, 1H),

3.71 (dd, J = 8.7, 7.7 Hz, 1H), 3.71 – 3.65 (m, 2H), 3.61 (dd, J = 10.7, 7.3 Hz, 1H), 3.57 (dd, J = 7.7, 6.7 Hz, 1H), 3.54 – 3.46 (m, 3H), 3.47 – 3.40 (m, 2H), 3.41 – 3.36 (m, 1H), 3.30 – 3.22 (m, 2H), 3.18 (dd, J = 10.0, 7.2 Hz, 1H), 2.64 (s, 2H), 2.54 (ddt, J = 13.4, 8.5, 2.3 Hz, 1H), 2.42 (ddt, J = 13.3, 8.6, 2.3 Hz, 1H), 2.39 – 2.33 (m, 1H), 2.24 (td, J = 10.8, 7.6 Hz, 1H), 1.92 – 1.86 (m, 5H), 1.80 (tdd, J = 11.4, 8.3, 4.6 Hz, 2H), 1.64 (td, J = 12.6, 10.9, 4.3 Hz, 1H), 1.61 – 1.55 (m, 4H).

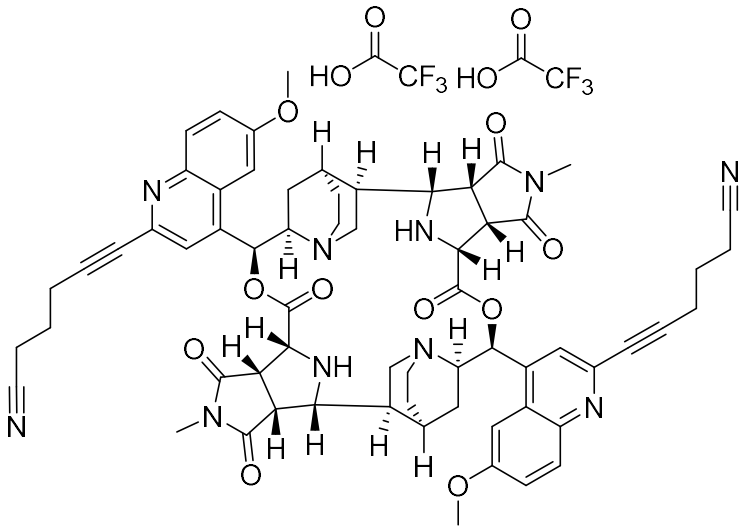
^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 177.02, 176.25, 176.11, 176.03, 169.37, 169.31, 159.83, 159.82, 148.24, 148.01, 144.43, 144.39, 143.77, 142.92, 140.45, 140.34, 131.35, 131.33, 129.07, 128.90, 128.28, 127.97, 127.73, 127.41, 125.04, 124.92, 124.38, 124.33, 120.22, 119.59, 101.86, 71.60, 70.10, 64.63, 63.77, 63.58, 63.25, 58.47, 58.23, 56.73, 52.75, 52.23, 50.75, 50.61, 50.20, 49.83, 49.64, 49.12, 48.56, 48.02, 38.47, 33.60, 23.74, 23.35, 23.29, 23.22, 19.38, 19.08, 16.87, 16.41.

HRMS (ESI): $C_{66}H_{67}O_{10}N_8Cl_2$ $[M+H]^+$; calculated: 1201.43517, found: 1201.43666.

$[\alpha]_{20}^{D}$ = + 61 ° (c = 1, MeCN).

5.10.19 Macrocycles prepared via Sonogashira coupling from macrocycle 122b

124a, QD2(bis(hex-5-ynenitrile))-Me-S



124a was prepared from **122a** (20.5 mg, 16.4 µmol) according to General Procedure 7. Preparative HPLC (5 – 40 % MeCN; RT = 25.8 min) gave title compound **124a** in 48 % (10.8 mg, 7.92 µmol) yield.

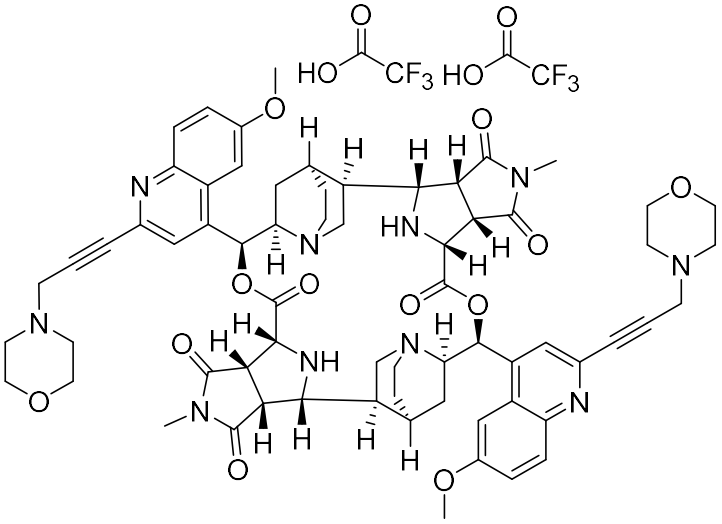
^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.00 (d, J = 9.3 Hz, 2H), 7.80 (s, 2H), 7.51 (dd, J = 9.3, 2.5 Hz, 2H), 7.39 (s, 2H), 7.17 (s, 2H), 4.01 (s, 8H), 3.91 (t, J = 7.7 Hz, 2H), 3.80 (dd, J = 10.6, 7.8 Hz, 2H), 3.67 (dd, J = 11.7, 7.0 Hz, 2H), 3.59 (t, J = 7.2 Hz, 2H), 3.49 – 3.42 (m, 2H), 3.40 (dt, J = 11.4, 3.1 Hz, 2H), 3.29 (dddd, J = 20.0, 12.6, 9.0, 4.9 Hz, 4H), 2.72 (dd, J = 10.6, 4.4 Hz, 2H), 2.70 (s, 6H), 2.69 – 2.60 (m, 10H), 2.41 (td, J = 11.2, 7.0 Hz, 2H), 1.97 (p, J = 7.1 Hz, 4H), 1.93 – 1.91 (m, 2H), 1.87 – 1.79 (m, 2H), 1.69 (ddd, J = 13.8, 10.5, 3.5 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.33, 175.97, 168.57, 160.18, 143.73, 141.03, 140.38, 131.19, 125.27, 124.33, 122.94, 120.71, 101.36, 90.90, 81.91, 69.65, 63.65, 63.48, 58.99, 56.82, 50.66, 49.64, 48.42, 48.27, 25.03, 24.54, 23.66, 23.49, 18.92, 18.56, 16.28.

HRMS (ESI): $C_{64}H_{68}O_{10}N_{10}Cl$ $[M+2H]^{2+}$; calculated: 568.25548, found: 568.25698.

$[\alpha]_{20}^{D}$ = + 84 ° (c = 0.5, MeCN).

124b, **QD2(bis(6-methoxy-2-(3-morpholinoprop-1-yn-1-yl))-Me-S**



124b was prepared from **122a** (24.2 mg, 19.4 µmol) according to General Procedure 7. Preparative HPLC (5 – 50 % MeCN; RT = 15.4 min) gave title compound **124b** in 56 % (15.5 mg, 10.9 µmol) yield.

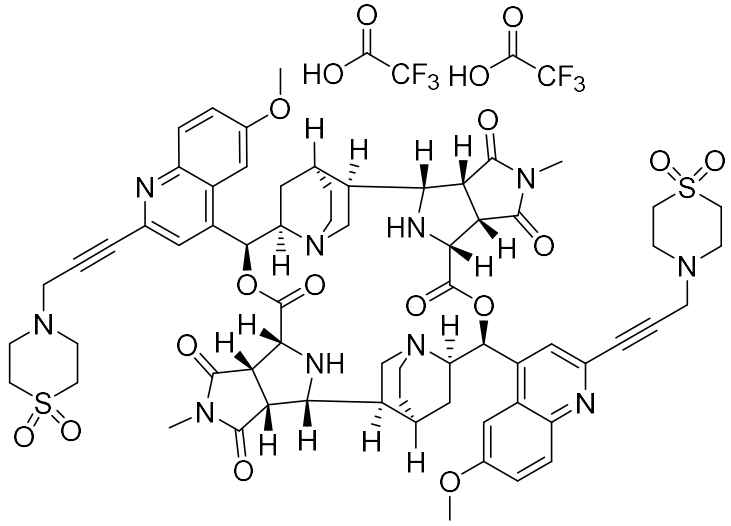
^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.01 (d, J = 9.3 Hz, 2H), 7.89 (s, 2H), 7.53 (dd, J = 9.3, 2.6 Hz, 2H), 7.40 (d, J = 2.7 Hz, 2H), 7.15 (s, 2H), 4.30 (d, J = 3.8 Hz, 4H), 4.13 (d, J = 8.1 Hz, 2H), 4.01 (s, 8H), 3.97 – 3.86 (m, 8H), 3.84 – 3.79 (m, 2H), 3.74 (dd, J = 11.7, 6.9 Hz, 2H), 3.60 (t, J = 7.2 Hz, 2H), 3.53 – 3.36 (m, 12H), 3.36 – 3.27 (m, 4H), 2.78 – 2.72 (m, 2H), 2.69 (s, 6H), 2.63 (s, 2H), 2.43 (td, J = 11.1, 7.0 Hz, 2H), 1.98 – 1.93 (m, 2H), 1.87 – 1.79 (m, 2H), 1.67 (ddd, J = 14.7, 10.8, 3.9 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.43, 176.33, 168.62, 160.61, 144.40, 140.75, 138.87, 131.97, 125.84, 124.49, 123.01, 101.27, 89.71, 77.71, 69.79, 64.36, 63.65, 63.54, 58.92, 56.87, 51.55, 50.60, 49.57, 48.35, 48.26, 46.93, 33.00, 25.02, 23.71, 23.55, 18.89.

HRMS (ESI): $C_{66}H_{76}O_{12}N_{10}Cl$ $[M+2H]^{2+}$; calculated: 600.28166, found: 600.28269.

$[\alpha]_{20}^{D}$ = + 108 ° (c = 0.5, MeCN).

124c, QD2(bis(2-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-Me-S



124c was prepared from **122a** (22.4 mg, 17.9 µmol) according to General Procedure 7. Preparative HPLC (5 – 35 % MeCN; RT = 24.6 min) gave title compound **124c** in 41 % (11.0 mg, 7.22 µmol) yield.

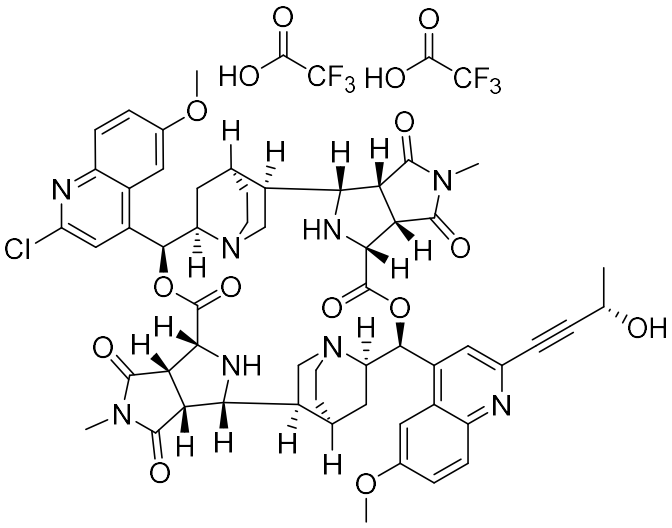
^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.00 (d, J = 9.2 Hz, 2H), 7.85 (s, 2H), 7.51 (dd, J = 9.3, 2.6 Hz, 2H), 7.38 (d, J = 2.6 Hz, 2H), 7.14 (s, 2H), 4.04 (d, J = 8.1 Hz, 2H), 4.02 – 3.99 (m, 6H), 3.95 (t, J = 7.7 Hz, 2H), 3.88 (s, 4H), 3.85 – 3.80 (m, 2H), 3.71 (dd, J = 11.7, 6.9 Hz, 2H), 3.62 (t, J = 7.2 Hz, 2H), 3.48 – 3.40 (m, 4H), 3.32 (dddd, J = 16.8, 11.0, 6.5, 3.4 Hz, 4H), 3.23 (h, J = 9.7, 9.3 Hz, 16H), 2.75 (ddt, J = 13.2, 7.8, 2.6 Hz, 2H), 2.69 (s, 6H), 2.67 (s, 2H), 2.42 (td, J = 11.0, 6.8 Hz, 2H), 1.97 – 1.95 (m, 2H), 1.86 – 1.81 (m, 2H), 1.70 (ddd, J = 14.5, 10.8, 3.8 Hz, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.49, 176.04, 168.53, 160.26, 144.12, 140.57, 139.98, 131.67, 125.39, 124.24, 123.39, 101.30, 86.78, 84.90, 69.72, 63.59, 63.46, 58.92, 56.83, 51.25, 50.83, 50.47, 49.65, 48.69, 48.54, 48.28, 47.08, 32.99, 25.01, 23.69, 23.46, 18.93.

HRMS (ESI): $C_{66}H_{75}O_{14}N_{10}S_2$ $[M+H]^+$; calculated: 1295.49001, found: 1295.49016.

$[\alpha]_{20}^{D}$ = + 98 ° (c = 0.5, MeCN).

124d, (3aS,4R,7S,8R,12S,13R,14R,14aR,17aS,18R,21S,22R,26S,27R,28R,28aR)-7-(2-chloro-6-methoxyquinolin-4-yl)-21-(2-((S)-3-hydroxybut-1-yn-1-yl)-6-methoxyquinolin-4-yl)-2,16-dimethylicosahydro-4,28:14,18-diepimino-8,12:9,13:22,26:23,27-tetramethanodipyrrolo-[3,4-j:3',4'-w][1,14]dioxa[4,17]diazacyclohexacosine-1,3,5,15,17,19(2H,16H)-hexaone



124d was prepared from **122a** (23.4 mg, 18.7 µmol) utilizing the desymmetrizing conditions of General Procedure 7. Preparative HPLC (5 – 35 % MeCN; RT = 27.5 min) gave title compound **124d** in 20 % (4.7 mg, 3.66 µmol) yield. 39 % starting material (9.2 mg, 7.3 µmol) could be recovered. Di-adduct could be observed (RT = 24.9 min).

^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+, NH and OH not observed) δ 8.00 (d, J = 9.2 Hz, 1H), 7.96 (d, J = 9.2 Hz, 1H), 7.79 (d, J = 0.7 Hz, 1H), 7.75 (d, J = 0.8 Hz, 1H), 7.51 (ddd, J = 9.2, 6.4, 2.6 Hz, 2H), 7.39 (dd, J = 13.2, 2.7 Hz, 2H), 7.18 (s, 1H), 7.16 (s, 1H), 4.74 (q, J = 6.6 Hz, 1H), 4.01 (s, 3H), 4.00 (s, 3H), 4.00 – 3.98 (m, 1H), 3.97 (d, J = 8.1 Hz, 1H), 3.89 (q, J = 7.5 Hz, 2H), 3.82 – 3.79 (m, 1H), 3.79 – 3.76 (m, 1H), 3.66 (dd, J = 11.7, 7.0 Hz, 2H), 3.59 (q, J = 7.3 Hz, 2H), 3.46 – 3.38 (m, 4H), 3.32 – 3.22 (m, 4H), 2.75 – 2.70 (m, 2H), 2.69 (s, 6H), 2.66 (s, 2H), 2.44 – 2.37 (m, 2H), 1.92 (s, 2H), 1.87 – 1.80 (m, 2H), 1.76 – 1.69 (m, 2H), 1.50 (d, J = 6.6 Hz, 3H).

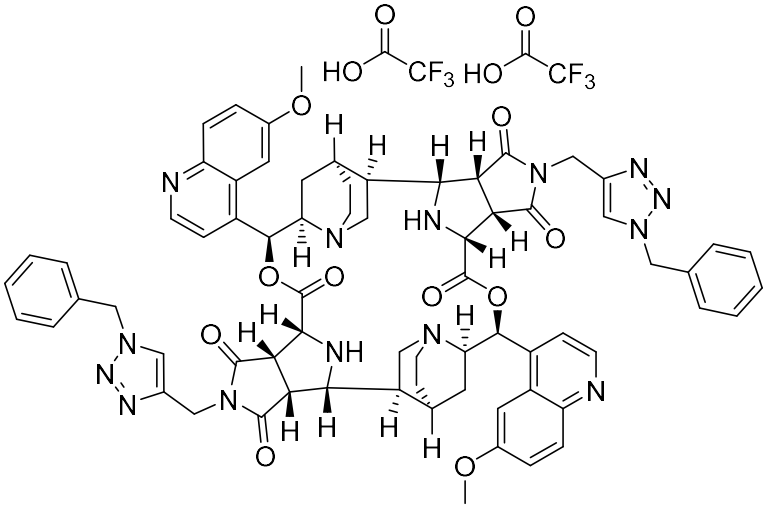
^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.38, 176.37, 176.02, 175.97, 168.71, 168.65, 160.14, 159.83, 148.15, 144.42, 144.27, 143.31, 140.58, 140.43, 131.79, 131.32, 125.27, 125.01, 124.24, 124.10, 122.69, 121.05, 101.80, 101.30, 93.09, 83.08, 69.52, 69.42, 63.65, 63.54, 63.45, 59.07, 58.89, 58.02, 56.81, 50.77, 50.75, 49.73, 48.45, 48.43, 48.31, 48.24, 32.98, 32.96, 25.03, 25.01, 24.06, 23.63, 23.60, 23.44, 18.89.

HRMS (ESI): $C_{56}H_{60}O_{11}N_8Cl$ $[M+H]^+$; calculated: 1055.40646, found: 1055.40640.

$[\alpha]_{20}^{D}$ = + 83 ° (c = 0.3, MeCN).

5.10.20 Macrocycles prepared via CuAAC from macrocycles 101ad or 102b

125, **QD-(1-benzyl-1H-1,2,3-triazol-4-yl)methyl-S**



To a solution of macrocycle **101ad** (50 mg, 40.8 µmol, 1 eq.) in tBuOH/H2O (1:1, 0.5 M) was added DIPEA (163 µmol, 4 eq.), Benzylazide (240 µmol, 6 eq.) and CuI (61.1 µmol, 1.5 eq.). The solution was stirred at 21°C and the reaction was monitored via u-HPLC. After stirring for 16 h the compound was purified via prep-HPLC (10 – 50% MeCN; RT = 17.3 min). The title compound **125** was obtained as a white solid in a yield of 40 % (24.1 mg, 16.1 µmol).

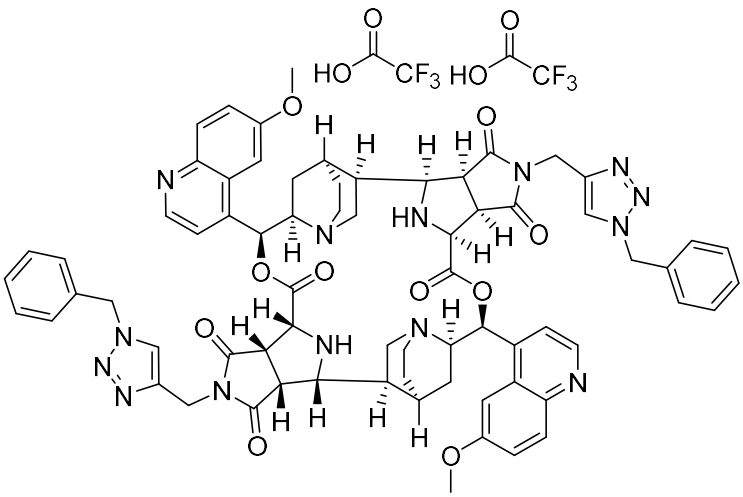
^{1}H NMR (600 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.87 (d, J = 5.1 Hz, 2H), 8.15 (d, J = 9.3 Hz, 2H), 7.92 (d, J = 5.0 Hz, 2H), 7.63 (dd, J = 9.3, 2.6 Hz, 2H), 7.60 (s, 2H), 7.51 (d, J = 2.6 Hz, 2H), 7.33 – 7.28 (m, 6H), 7.27 (s, 2H), 7.23 – 7.19 (m, 4H), 5.40 (d, J = 2.7 Hz, 4H), 4.46 (s, 4H), 4.09 (d, J = 8.0 Hz, 2H), 4.03 (s, 6H), 3.99 (dd, J = 8.0, 7.1 Hz, 2H), 3.81 (dd, J = 10.5, 8.0 Hz, 2H), 3.71 – 3.63 (m, 4H), 3.50 – 3.45 (m, 2H), 3.42 (ddt, J = 14.0, 11.5, 3.1 Hz, 2H), 3.32 – 3.22 (m, 4H), 2.71 (ddt, J = 13.1, 7.7, 2.2 Hz, 2H), 2.63 (s, 2H), 2.37 (td, J = 10.9, 7.1 Hz, 2H), 1.89 (dt, J = 10.6, 3.2 Hz, 2H), 1.84 – 1.76 (m, 2H), 1.66 (ddd, J = 14.4, 10.6, 3.9 Hz, 2H).

^{13}C NMR (151 MHz, CD_3CN:D_2O [10:1]) δ 175.79, 175.64, 168.53, 160.47, 145.24, 144.02, 142.46, 140.35, 135.94, 129.47, 129.00, 128.85, 128.64, 126.78, 125.55, 123.86, 120.14, 101.65, 69.70, 63.71, 63.49, 58.94, 56.96, 54.14, 50.53, 49.61, 48.40, 48.33, 34.51, 33.02, 23.55, 23.44, 18.87.

HRMS (ESI): $C_{70}H_{71}O_{10}N_{14}$ $[M+H]^+$; calculated: 1267.54721, found: 1267.55204.

$[\alpha]_{20}^{D}$ = + 61 ° (c = 0.5, MeCN).

126, **QD-(1-benzyl-1H-1,2,3-triazol-4-yl)methyl-A**



To a solution of macrocycle **102b** (20 mg, 16.3 µmol, 1 eq.) in *t*BuOH/H_2O (1:1, 0.5 M) was added DIPEA (65.2 µmol, 4 eq.), Benzylazide (100 µmol, 6 eq.) and CuI (61.1 µmol, 1.5 eq.). The solution was stirred at 21°C for 16 h and the compound was purified via prep-HPLC (10 – 50% MeCN; RT = 19.4 min). The title compound **126** was obtained as a white solid in a yield of 22 % (5.4 mg, 3.62 µmol).

^{1}H NMR (600 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.81 (d, J = 5.0 Hz, 1H), 8.68 (d, J = 5.0 Hz, 1H), 8.13 (dd, J = 9.3, 4.8 Hz, 2H), 7.96 (s, 1H), 7.88 (d, J = 5.0 Hz, 1H), 7.71 (d, J = 4.9 Hz, 1H), 7.64 (s, 1H), 7.61 (ddd, J = 9.3, 4.5, 2.6 Hz, 2H), 7.47 (t, J = 2.2 Hz, 2H), 7.32 – 7.17 (m, 12H), 7.09 (s, 1H), 5.59 (s, 2H), 5.44 – 5.35 (m, 2H), 4.86 – 4.76 (m, 2H), 4.49 (s, 2H), 4.12 (d, J = 8.4 Hz, 1H), 4.07 (d, J = 8.4 Hz, 1H), 4.02 (s, 6H), 3.80 (ddd, J = 15.1, 10.8, 7.4 Hz, 4H), 3.64 (td, J = 9.7, 7.7 Hz, 2H), 3.59 – 3.50 (m, 2H), 3.48 – 3.35 (m, 5H), 3.33 (dd, J = 9.6, 7.7 Hz, 1H), 3.31 – 3.23 (m, 1H), 2.76 (s, 1H), 2.54 (s, 1H), 2.53 – 2.48 (m, 1H), 2.48 – 2.43 (m, 1H), 2.38 (q, J = 11.0 Hz, 1H), 2.32 (q, J = 10.7 Hz, 1H), 1.89 (d, J = 10.7 Hz, 2H), 1.85 – 1.75 (m, 2H), 1.56 – 1.46 (m, 2H).

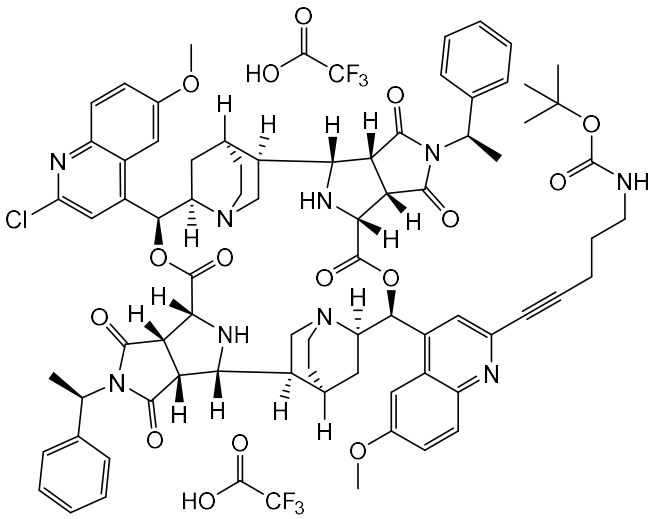
^{13}C NMR (151 MHz, CD_3CN:D_2O [10:1]) δ 176.75, 176.26, 175.89, 175.82, 169.37, 169.17, 160.33, 160.27, 145.76, 145.38, 143.41, 143.30, 142.51, 142.39, 141.25, 140.76, 136.18, 135.95, 129.48, 129.44, 129.15, 129.00, 128.98, 128.73, 128.61, 126.68, 126.65, 125.37, 125.19, 124.05, 123.70, 119.88, 101.62, 101.56, 71.76, 70.16, 65.41, 63.60, 63.58, 63.47, 58.68, 58.23, 56.88, 56.84, 54.37, 54.12, 53.35, 52.76, 50.15, 50.08, 49.73, 48.78, 48.34, 37.67, 34.45, 34.39, 33.31, 23.54, 23.41, 23.32, 23.12, 19.20, 19.15.

HRMS (ESI): $C_{70}H_{71}O_{10}N_{14}$ $[M+H]^+$; calculated: 1267.54721, found: 1267.55212.

$[\alpha]_{20}^{D}$ = + 148 ° (c = 0.35, MeCN).

5.10.21 Boc-protected pulldown probes 132, 134, 136, 138

132, QD[2'Cl-2''(C5-linker-NHBoc)]-(R)-1-Phenylethyl-S



132 was prepared from **122f** (21.4 mg, 15.0 µmol) according to General Procedure B. Preparative HPLC (20 – 65 % MeCN; RT = 24.0 min) gave title compound **132** in 28 % (6.5 mg, 4.12 µmol) yield. Startingmaterial (RT = 22.6 min) and di-adduct in 12 % (RT = 26.6 min, 3.0 mg, 1.74 µmol) were observed as well.

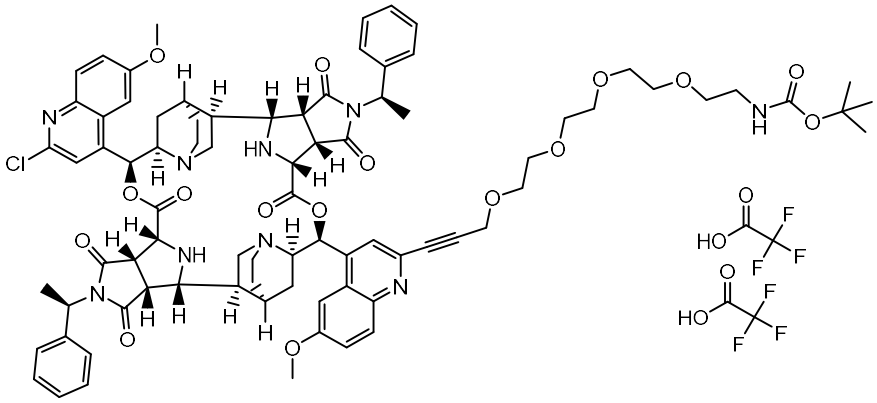
^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 7.97 (d, J = 9.2 Hz, 1H), 7.94 (d, J = 9.2 Hz, 1H), 7.75 (s, 1H), 7.72 (d, J = 0.8 Hz, 1H), 7.49 (ddd, J = 11.9, 9.2, 2.6 Hz, 2H), 7.40 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 2.5 Hz, 1H), 7.25 (dddd, J = 7.8, 6.3, 3.2, 1.5 Hz, 4H), 7.21 (ddd, J = 8.2, 4.2, 3.0 Hz, 6H), 7.17 (s, 2H), 5.15 (q, J = 7.2 Hz, 2H), 4.05 (dd, J = 13.4, 8.3 Hz, 2H), 4.00 (d, J = 2.0 Hz, 6H), 3.85 (q, J = 7.9 Hz, 2H), 3.78 (q, J = 7.9, 7.4 Hz, 2H), 3.69 (dt, J = 11.5, 7.2 Hz, 2H), 3.60 (dt, J = 14.1, 7.1 Hz, 2H), 3.48 (ddd, J = 12.6, 10.6, 1.7 Hz, 2H), 3.44 – 3.36 (m, 2H), 3.26 (dddd, J = 14.0, 10.9, 7.0, 3.0 Hz, 4H), 3.17 (tq, J = 13.6, 6.9 Hz, 2H), 2.67 (dtd, J = 13.6, 5.5, 2.9 Hz, 2H), 2.63 (s, 2H), 2.50 (t, J = 7.0 Hz, 2H), 2.35 (dp, J = 11.6, 5.1 Hz, 2H), 1.91 – 1.83 (m, 2H), 1.81 (ddt, J = 10.0, 6.2, 3.3 Hz, 2H), 1.74 (p, J = 7.1 Hz, 2H), 1.70 – 1.61 (m, 2H), 1.54 (d, J = 3.1 Hz, 3H), 1.53 (d, J = 3.1 Hz, 3H), 1.38 (s, 9H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.15, 176.12, 175.81, 175.70, 168.78, 168.73, 160.00, 159.84, 157.05, 148.10, 144.30, 144.08, 143.26, 140.89, 140.55, 140.24, 140.22, 131.43, 131.32, 128.93, 128.92, 127.96, 127.94, 127.25, 127.22, 125.08, 125.01, 124.28, 124.10, 122.68, 120.82, 101.80, 101.36, 92.09, 81.27, 79.21, 69.73, 63.91, 63.85, 63.68, 63.65, 58.95, 58.79, 56.75, 50.54, 50.53, 50.15, 50.14, 49.76, 49.74, 48.57, 48.55, 48.05, 48.01, 39.75, 33.17, 33.14, 28.91, 28.26, 23.58, 23.57, 23.55, 19.05, 19.01, 16.90, 16.49, 16.42.

HRMS (ESI): $C_{76}H_{83}O_{12}N_9Cl$ $[M+H]^+$; calculated: 1348.58442, found: 1348.58505.

$[\alpha]_{20}^{D}$ = + 98 ° (c = 0.5, MeCN).

134, QD[2'Cl-2''(PEG4-linker-NHBoc)]-(R)-1-Phenylethyl-S



134 was prepared from **122f** (25.0 mg, 17.5 µmol) according to General Procedure B. Preparative HPLC (15 – 70 % MeCN; RT = 22.2 min) gave title compound **134** in 21 % (6.4 mg, 3.71 µmol) yield. Startingmaterial and di-adduct were observed as well.

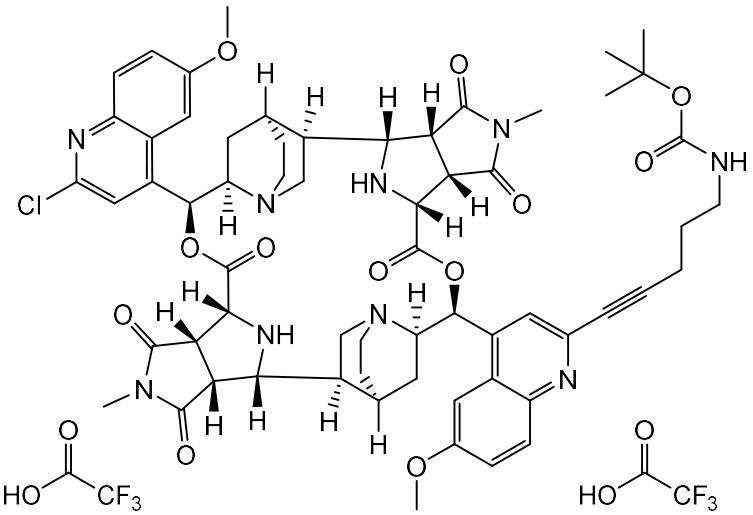
^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.00 (d, J = 9.2 Hz, 1H), 7.95 (d, J = 9.2 Hz, 1H), 7.79 (s, 1H), 7.72 (s, 1H), 7.50 (ddd, J = 9.2, 4.2, 2.6 Hz, 2H), 7.38 (dd, J = 12.4, 2.6 Hz, 2H), 7.28 – 7.23 (m, 4H), 7.23 – 7.19 (m, 6H), 7.17 (s, 1H), 7.16 (s, 1H), 5.15 (qd, J = 7.2, 3.1 Hz, 2H), 4.45 (d, J = 2.7 Hz, 2H), 4.04 (dd, J = 13.2, 8.3 Hz, 2H), 4.01 – 3.99 (m, 6H), 3.84 (dt, J = 17.6, 7.9 Hz, 2H), 3.80 – 3.74 (m, 2H), 3.72 – 3.66 (m, 4H), 3.63 – 3.52 (m, 12H), 3.47 (t, J = 12.2 Hz, 2H), 3.43 (t, J = 5.6 Hz, 2H), 3.41 – 3.37 (m, 2H), 3.30 – 3.22 (m, 4H), 3.14 (t, J = 5.6 Hz, 2H), 2.68 (q, J = 8.9 Hz, 2H), 2.63 (s, 2H), 2.35 (q, J = 10.5 Hz, 2H), 1.90 – 1.85 (m, 2H), 1.84 – 1.77 (m, 2H), 1.67 (ddt, J = 15.3, 11.6, 3.1 Hz, 2H), 1.53 (dd, J = 7.3, 2.8 Hz, 6H), 1.36 (s, 9H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.15, 176.11, 175.82, 175.71, 168.82, 168.77, 160.23, 159.84, 148.11, 144.59, 144.30, 143.21, 140.42, 140.22, 140.05, 132.00, 131.34, 128.94, 128.93, 127.99, 127.97, 127.26, 127.25, 127.24, 125.35, 125.00, 124.27, 124.15, 122.48, 120.84, 101.82, 101.32, 86.40, 86.17, 79.27, 70.64, 70.59, 70.56, 70.41, 70.37, 70.19, 69.83, 63.93, 63.86, 63.67, 63.65, 58.92, 58.81, 56.78, 56.76, 50.54, 50.17, 50.15, 49.80, 48.62, 48.57, 48.05, 48.03, 40.45, 33.14, 28.23, 23.57, 23.54, 19.03, 16.43, 16.42.

HRMS (ESI): $C_{82}H_{95}O_{16}N_9Cl$ $[M+H]^+$; calculated: 1496.66330, found: 1496.65798.

$[\alpha]_{20}^{D}$ = + 88 ° (c = 0.5, MeCN).

136, QD[2'Cl-2''(C5-linker-NHBoc)]-Me-S



136 was prepared from **122a** (21.0 mg, 16.8 µmol) according to General Procedure B. Preparative HPLC (5 – 50 % MeCN; RT = 25.4 min) gave title compound **136** in 28 % (6.5 mg, 4.65 µmol) yield. Startingmaterial (RT = 23.1 min) and di-adduct (RT = 27.8 min) were observed as well.

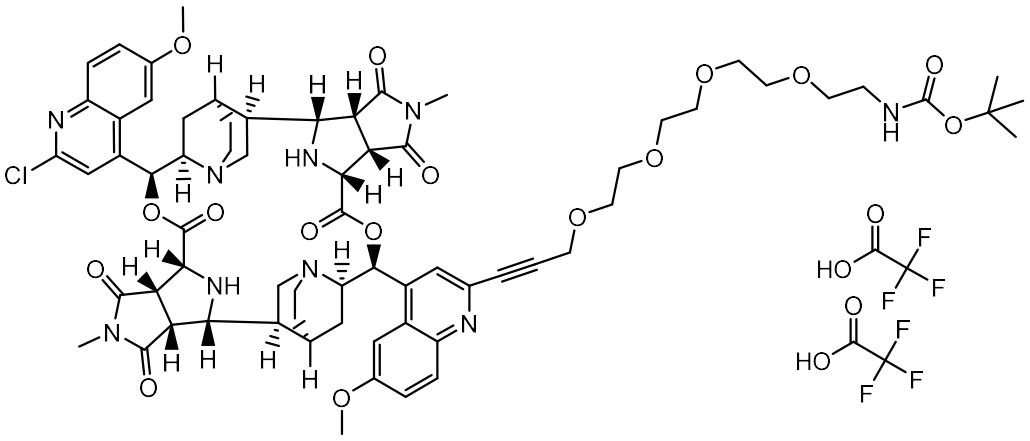
^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 7.98 (d, J = 9.2 Hz, 1H), 7.96 (d, J = 9.2 Hz, 1H), 7.77 (s, 1H), 7.74 (s, 1H), 7.53 – 7.48 (m, 2H), 7.42 – 7.39 (m, 1H), 7.37 (t, J = 2.4 Hz, 1H), 7.18 – 7.15 (m, 2H), 4.00 (d, J = 2.3 Hz, 6H), 3.99 – 3.98 (m, 1H), 3.97 (d, J = 8.1 Hz, 1H), 3.89 (q, J = 7.7 Hz, 2H), 3.79 (q, J = 9.2 Hz, 2H), 3.66 (dt, J = 11.8, 7.3 Hz, 2H), 3.60 – 3.56 (m, 2H), 3.47 – 3.38 (m, 4H), 3.33 – 3.23 (m, 4H), 3.20 (t, J = 6.9 Hz, 2H), 2.74 – 2.70 (m, 2H), 2.69 (d, J = 1.3 Hz, 6H), 2.65 (s, 2H), 2.52 (t, J = 7.0 Hz, 2H), 2.44 – 2.37 (m, 2H), 1.93 – 1.91 (m, 2H), 1.87 – 1.80 (m, 2H), 1.77 (p, J = 7.0 Hz, 2H), 1.74 – 1.67 (m, 2H), 1.38 (s, 9H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.35, 176.33, 176.00, 175.90, 168.67, 168.61, 160.02, 159.86, 157.11, 148.13, 144.29, 143.36, 140.90, 140.72, 131.32, 125.11, 125.03, 124.27, 124.11, 122.87, 121.01, 101.78, 101.33, 92.15, 81.25, 79.23, 69.52, 63.64, 63.57, 63.46, 63.45, 59.03, 58.87, 56.78, 50.75, 50.73, 49.70, 48.45, 48.28, 48.25, 39.71, 33.00, 32.97, 28.88, 28.25, 25.03, 25.02, 23.65, 23.63, 23.48, 18.90, 16.86.

HRMS (ESI): $C_{62}H_{71}O_{12}N_9Cl$ $[M+H]^+$; calculated: 1168.49052, found: 1168.49532.

$[\alpha]_{20}^{D}$ = + 78 ° (c = 0.5, MeCN).

138, QD[2'Cl-2''(PEG4-linker-NHBoc)]-Me-S



138 was prepared from **122a** (19.3 mg, 15.4 µmol) according to General Procedure B. Preparative HPLC (10 – 55 % MeCN; RT = 22.5 min) gave title compound **138** in 27 % (6.30 mg, 4.08 µmol) yield. Startingmaterial and di-adduct (RT = 25.0 min) were observed as well.

^{1}H NMR (600 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 8.01 (d, J = 9.3 Hz, 1H), 7.96 (d, J = 9.2 Hz, 1H), 7.81 (s, 1H), 7.74 (s, 1H), 7.52 (t, J = 2.7 Hz, 1H), 7.51 (t, J = 2.8 Hz, 1H), 7.40 (d, J = 2.6 Hz, 1H), 7.38 (d, J = 2.5 Hz, 1H), 7.17 (s, 1H), 7.16 (s, 1H), 4.48 (s, 2H), 4.00 (d, J = 6.0 Hz, 6H), 3.97 (dd, J = 11.3, 8.1 Hz, 2H), 3.88 (dt, J = 10.1, 7.7 Hz, 2H), 3.79 (q, J = 10.6 Hz, 2H), 3.75 – 3.72 (m, 2H), 3.68 – 3.63 (m, 4H), 3.61 – 3.52 (m, 10H), 3.47 – 3.38 (m, 6H), 3.34 – 3.21 (m, 4H), 3.15 (t, J = 5.6 Hz, 2H), 2.77 – 2.70 (m, 2H), 2.69 (d, J = 2.4 Hz, 6H), 2.66 (s, 2H), 2.40 (q, J = 9.9 Hz, 2H), 1.97 – 1.95 (m, 2H), 1.87 – 1.79 (m, 2H), 1.76 – 1.66 (m, 2H), 1.37 (s, 9H).

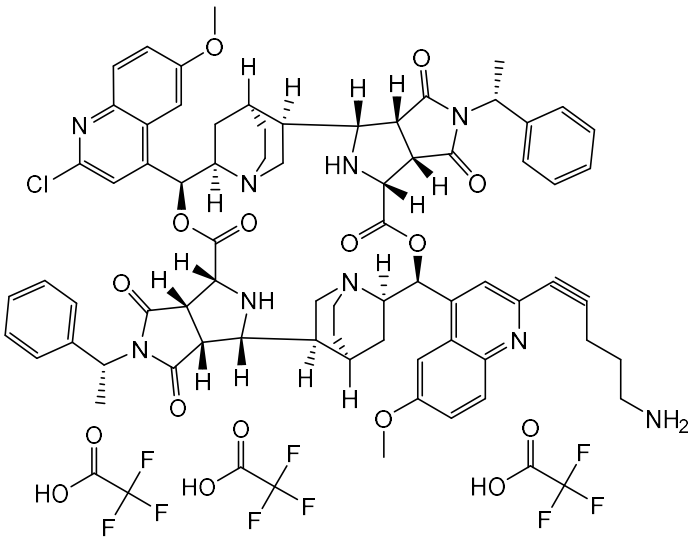
^{13}C NMR (151 MHz, CD_3CN:D_2O [10:1]) δ 176.36, 176.33, 176.00, 175.90, 168.66, 168.61, 160.25, 159.84, 156.96, 148.12, 144.50, 144.27, 143.34, 140.59, 140.02, 131.93, 131.31, 125.38, 125.01, 124.27, 124.18, 122.67, 121.00, 101.74, 101.23, 86.44, 86.10, 79.27, 70.63, 70.58, 70.54, 70.42, 70.35, 70.18, 69.86, 69.53, 63.64, 63.57, 63.45, 63.43, 59.02, 58.93, 58.86, 56.78, 56.76, 50.73, 49.68, 48.43, 48.40, 48.28, 48.24, 40.43, 32.97, 28.21, 25.03, 25.01, 23.64, 23.62, 23.46, 18.89.

HRMS (ESI): $C_{68}H_{83}O_{16}N_9Cl$ $[M+H]^+$; calculated: 1316.57003, found: 1316.56408.

$[\alpha]_{20}^{D}$ = + 89 ° (c = 0.5, MeCN).

5.10.22 Primary amine pulldown probes 133, 135, 137, 139

133, QD[2'Cl-2''(C5-linker-NH2)]-(R)-1-Phenylethyl-S



132 (5.20 mg, 3.30 µmol) in 2.7 mL CH_2Cl_2 at 0°C was added 0.3 mL TFA dropwise. The reaction was stirred for 2 h before it was warmed to 21 °C and the solvent was removed under a stream of argon. The residue was dissolved in CH_2Cl_2 the solvent was removed a stream of argon. Residual TFA was removed under reduced pressure. Title compound **133** was obtained in 99 % (5.18 mg, 3.26 µmol) yield and used without further purification.

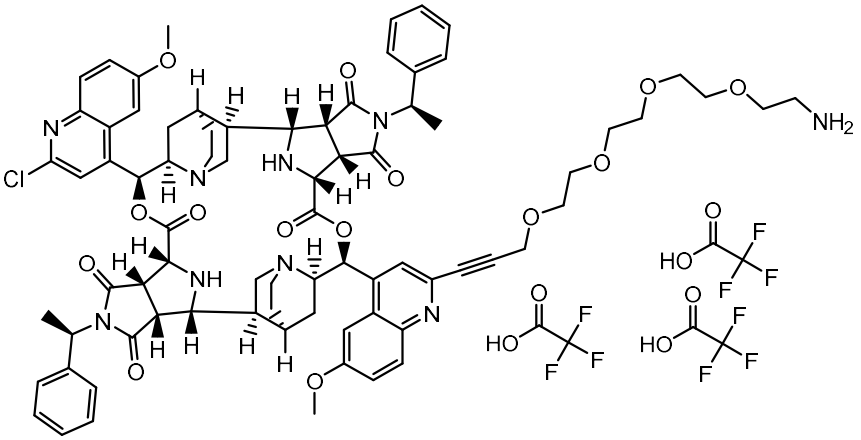
^{1}H NMR (600 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 7.96 (dd, J = 12.0, 9.2 Hz, 2H), 7.73 (d, J = 4.7 Hz, 2H), 7.50 (ddd, J = 9.0, 6.2, 2.6 Hz, 2H), 7.39 (dd, J = 5.0, 2.7 Hz, 2H), 7.28 – 7.24 (m, 4H), 7.23 – 7.18 (m, 7H), 7.16 (s, 1H), 5.15 (qd, J = 7.2, 4.3 Hz, 2H), 4.06 (dd, J = 8.7 Hz, 2H), 4.00 (d, J = 2.9 Hz, 6H), 3.83 (dt, J = 14.5, 7.9 Hz, 2H), 3.77 (dt, J = 21.6, 9.2 Hz, 2H), 3.68 (ddd, J = 11.6, 8.4, 6.7 Hz, 2H), 3.59 (t, J = 7.1 Hz, 2H), 3.51 – 3.45 (m, 2H), 3.39 (t, J = 11.7 Hz, 2H), 3.30 – 3.20 (m, 4H), 3.13 – 3.08 (m, 2H), 2.72 – 2.65 (m, 2H), 2.62 (s, 2H), 2.59 (t, J = 7.0 Hz, 2H), 2.39 – 2.29 (m, 2H), 1.99 – 1.95 (m, 2H), 1.90 – 1.84 (m, 2H), 1.83 – 1.77 (m, 2H), 1.70 – 1.62 (m, 2H), 1.53 (d, J = 7.3 Hz, 6H).

^{13}C NMR (151 MHz, CD_3CN:D_2O [10:1]) δ 176.17, 176.15, 175.84, 168.88, 168.80, 160.07, 159.82, 148.10, 144.29, 143.22, 140.71, 140.64, 140.20, 140.18, 131.47, 131.32, 128.93, 128.92, 127.96, 127.24, 127.21, 125.20, 124.98, 124.27, 124.19, 122.30, 120.80, 101.79, 90.20, 81.94, 69.69, 63.93, 63.79, 63.62, 59.01, 58.79, 56.75, 56.74, 50.51, 50.46, 50.15, 49.77, 48.58, 48.52, 48.04, 48.02, 39.08, 33.14, 33.11, 26.13, 23.53, 19.01, 16.66, 16.40, 16.37.

HRMS (ESI): $C_{71}H_{75}O_{10}N_9Cl$ $[M+H]^+$; calculated: 1248.53199, found: 1248.53234.

$[\alpha]_{20}^{D}$ = + 84 ° (c = 0.33, MeCN).

135, QD[2'Cl-2''(PEG4-linker-NH2)]-(R)-1-Phenylethyl-S



134 (5.1mg, 2.96 µmol) in 2.7 mL CH_2Cl_2 at 0°C was added 0.3 mL TFA dropwise. The reaction was stirred for 2 h before it was warmed to 21 °C and the solvent was removed under a stream of argon. The residue was dissolved in CH_2Cl_2 the solvent was removed a stream of argon. Residual TFA was removed under reduced pressure. Title compound **135** was obtained in quantitative yield (5.11 mg, 2.94 µmol) and used without further purification.

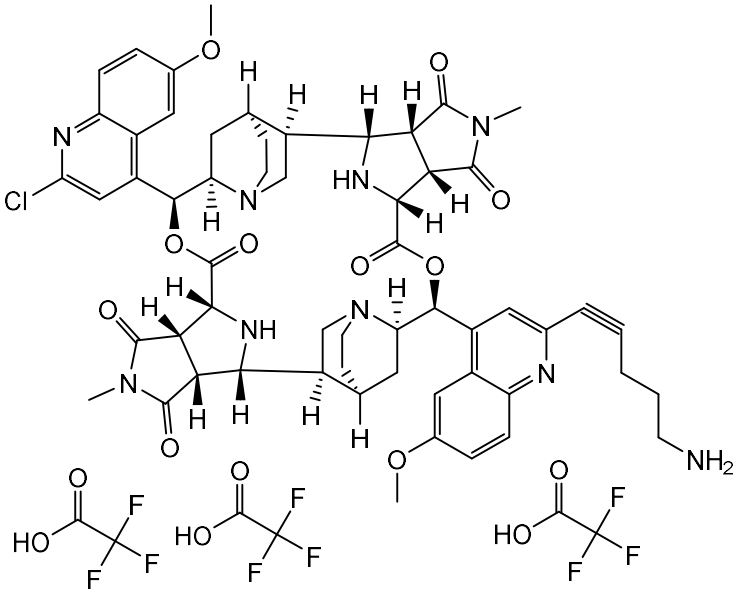
^{1}H NMR (600 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 7.98 (d, J = 9.2 Hz, 1H), 7.95 (d, J = 9.2 Hz, 1H), 7.79 (s, 1H), 7.72 (s, 1H), 7.51 (d, J = 2.5 Hz, 1H), 7.50 (d, J = 2.5 Hz, 1H), 7.41 – 7.39 (m, 2H), 7.25 (ddt, J = 8.4, 7.0, 1.3 Hz, 4H), 7.23 – 7.19 (m, 7H), 7.17 (s, 1H), 5.15 (p, J = 7.2 Hz, 2H), 4.47 (s, 2H), 4.06 (dd, J = 10.2, 8.3 Hz, 2H), 4.00 (d, J = 8.2 Hz, 6H), 3.85 (dd, J = 8.3, 7.6 Hz, 1H), 3.82 (t, J = 7.9 Hz, 1H), 3.80 – 3.75 (m, 2H), 3.73 (td, J = 3.9, 2.1 Hz, 2H), 3.69 (ddd, J = 11.5, 6.6, 3.0 Hz, 2H), 3.67 – 3.64 (m, 2H), 3.63 – 3.62 (m, 2H), 3.62 – 3.57 (m, 10H), 3.50 – 3.46 (m, 2H), 3.44 – 3.36 (m, 2H), 3.30 – 3.22 (m, 4H), 3.10 (t, J = 5.0 Hz, 2H), 2.72 – 2.65 (m, 2H), 2.63 (s, 2H), 2.34 (td, J = 11.3, 5.8 Hz, 2H), 1.90 – 1.85 (m, 2H), 1.83 – 1.77 (m, 2H), 1.70 – 1.62 (m, 2H), 1.53 (dd, J = 7.2, 2.9 Hz, 6H).

^{13}C NMR (151 MHz, CD_3CN:D_2O [10:1]) δ 176.18, 176.15, 175.84, 175.80, 168.83, 168.76, 160.31, 159.86, 148.10, 144.50, 144.31, 143.28, 140.70, 140.22, 140.21, 139.90, 131.82, 131.32, 128.94, 128.93, 127.97, 127.25, 127.23, 125.47, 125.01, 124.32, 124.30, 122.43, 120.81, 101.83, 101.36, 86.24, 86.18, 70.49, 70.44, 70.37, 70.22, 70.12, 69.87, 69.74, 66.81, 63.94, 63.85, 63.66, 63.64, 58.94, 58.79, 56.82, 56.78, 50.53, 50.51, 50.15, 50.12, 49.77, 49.73, 48.60, 48.56, 48.04, 48.01, 39.88, 33.18, 33.16, 23.56, 19.04, 16.42.

HRMS (ESI): $C_{77}H_{87}O_{14}N_9Cl$ $[M+H]^+$; calculated: 1396.60555, found: 1396.61166.

$[\alpha]_{20}^{D}$ = + 71° (c = 0.25, MeCN).

137, QD[2'Cl-2''(C5-linker-NH2)]-Me-S



Carbamate **136** (5.30 mg, 3.79 µmol) in 2.7 mL CH_2Cl_2 at 0°C was added 0.3 mL TFA dropwise. The reaction was stirred for 2 h before it was warmed to 21 °C and the solvent was removed under a stream of argon. The residue was dissolved in CH_2Cl_2 the solvent was removed a stream of argon. Residual TFA was removed under reduced pressure. Title compound **137** was obtained in 96 % (5.14 mg, 3.64 µmol) yield and used without further purification.

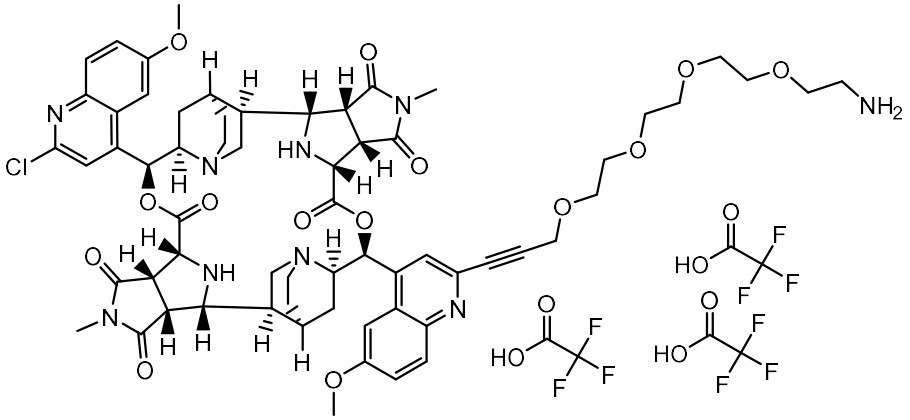
^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 7.97 (dd, J = 16.8, 9.3 Hz, 2H), 7.76 (dd, J = 14.7, 0.8 Hz, 2H), 7.51 (ddd, J = 9.2, 6.4, 2.6 Hz, 2H), 7.40 (dd, J = 11.6, 2.7 Hz, 2H), 7.17 (d, J = 4.1 Hz, 2H), 4.06 – 4.01 (m, 2H), 4.00 (d, J = 3.5 Hz, 6H), 3.90 (q, J = 7.5 Hz, 2H), 3.83 – 3.74 (m, 2H), 3.68 (dd, J = 11.7, 7.0 Hz, 2H), 3.59 (t, J = 7.2 Hz, 2H), 3.48 – 3.37 (m, 5H), 3.34 – 3.22 (m, 5H), 3.15 – 3.10 (m, 2H), 2.76 – 2.71 (m, 2H), 2.69 (d, J = 1.9 Hz, 6H), 2.65 (s, 2H), 2.62 (t, J = 6.9 Hz, 2H), 2.40 (td, J = 11.0, 6.8 Hz, 2H), 1.98 (dt, J = 14.5, 7.0 Hz, 2H), 1.84 (tdd, J = 12.6, 7.2, 3.1 Hz, 2H), 1.75 – 1.66 (m, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) δ 176.43, 176.11, 176.06, 168.73, 168.67, 160.11, 159.86, 148.17, 144.28, 144.18, 143.39, 140.88, 140.67, 131.42, 131.31, 125.25, 125.04, 124.27, 124.20, 122.66, 121.03, 101.78, 90.39, 81.91, 69.51, 63.66, 63.56, 63.46, 63.45, 59.06, 58.89, 57.16, 56.81, 56.79, 50.75, 50.74, 49.69, 49.65, 48.45, 48.28, 48.25, 39.13, 33.01, 33.00, 26.12, 25.03, 25.01, 23.66, 23.50, 18.90, 16.68.

HRMS (ESI): $C_{57}H_{63}O_{10}N_9Cl$ $[M+H]^+$; calculated: 1068.43809, found: 1068.44208.

$[\alpha]_{20}^{D}$ = + 79 ° (c = 0.5, MeCN).

139, QD[2'Cl-2''(PEG4-linker-NH2)]-Me-S



138 (3.10 mg, 2.01 µmol) in 2.7 mL CH_2Cl_2 at 0°C was added 0.3 mL TFA dropwise. The reaction was stirred for 2 h before it was warmed to 21 °C and the solvent was removed under a stream of argon. The residue was dissolved in CH_2Cl_2 the solvent was removed a stream of argon. Residual TFA was removed under reduced pressure.. Title compound **139**was obtained in 99 % (3.08 mg, 1.98 µmol) yield and used without further purification.

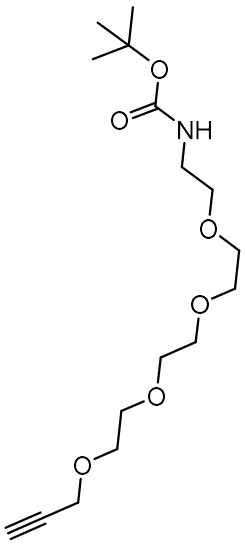
^{1}H NMR (700 MHz, CD_3CN:D_2O [10:1], NH^+ and NH not observed) δ 7.99 (d, J = 9.3 Hz, 1H), 7.96 (d, J = 9.3 Hz, 1H), 7.81 (d, J = 0.8 Hz, 1H), 7.74 (d, J = 0.8 Hz, 1H), 7.53 (d, J = 2.6 Hz, 1H), 7.51 (d, J = 2.6 Hz, 1H), 7.40 (dd, J = 4.3, 2.7 Hz, 2H), 7.18 (s, 1H), 7.16 (s, 1H), 4.49 (s, 2H), 4.01 (d, J = 8.1 Hz, 6H), 4.00 – 3.97 (m, 2H), 3.90 (t, J = 6.9 Hz, 1H), 3.88 – 3.85 (m, 1H), 3.82 – 3.77 (m, 2H), 3.77 – 3.74 (m, 2H), 3.69 – 3.63 (m, 6H), 3.61 (d, J = 3.2 Hz, 8H), 3.58 (t, J = 7.2 Hz, 2H), 3.47 – 3.38 (m, 4H), 3.28 (dtdd, J = 16.6, 13.0, 7.3, 2.2 Hz, 4H), 3.10 (t, J = 5.0 Hz, 2H), 2.72 (dd, J = 8.6, 5.4 Hz, 2H), 2.69 (d, J = 4.6 Hz, 6H), 2.65 (s, 2H), 2.40 (q, J = 10.0 Hz, 2H), 1.93 – 1.91 (m, 2H), 1.87 – 1.80 (m, 2H), 1.76 – 1.67 (m, 2H).

^{13}C NMR (176 MHz, CD_3CN:D_2O [10:1]) 13C NMR (176 MHz, ACN_D2O) δ 176.40, 176.38, 176.03, 168.68, 168.63, 160.32, 159.87, 148.13, 144.47, 144.29, 143.37, 140.78, 139.94, 131.81, 131.32, 125.49, 125.03, 124.29, 121.01, 101.79, 86.26, 86.17, 70.49, 70.44, 70.37, 70.23, 70.12, 69.90, 69.51, 66.81, 63.66, 63.59, 63.46, 63.45, 59.04, 58.96, 56.85, 56.80, 50.75, 50.72, 49.71, 49.67, 48.45, 48.42, 48.29, 39.89, 33.01, 32.99, 25.04, 25.02, 23.65, 23.48, 18.91.

HRMS (ESI): $C_{63}H_{75}O_{14}N_9Cl$ $[M+H]^+$; calculated: 1216.51165, found: 1216.51555.

$[\alpha]_{20}^{D}$ = + 77 ° (c = 0.3, MeCN).

145, tert-butyl (3,6,9,12-tetraoxapentadec-14-yn-1-yl)carbamate



3,6,9,12-tetraoxapentadec-14-yn-1-amine (500 mg, 2.16 mmol) in CH_2Cl_2 (4 ml) at 0 °C was added a solution of Boc_2O (520 mg, 2.38 mmol)in CH_2Cl_2 2 ml. FCC (7:3 EtOAc:cyclohexane, Rf = 0.32) gave title compound **145** as a colorless oil in 81 % (577 mg, 1.74 mmol) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (s, 1H), 4.09 (d, J = 2.4 Hz, 2H), 3.62 – 3.48 (m, 12H), 3.43 (dd, J = 5.6, 4.8 Hz, 2H), 3.20 (t, J = 5.2 Hz, 2H), 2.32 (t, J = 2.4 Hz, 1H), 1.33 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.11, 79.78, 79.31, 74.65, 70.76, 70.73, 70.68, 70.56, 70.40, 70.36, 69.24, 58.53, 40.55, 28.56.

6 List of Abbreviations

Abbreviation	Full Phrase
A	
Ac	acetyl group
Ac_2O	acetic anhydride
AIBN	azobisisobutyronitrile
ATG	autophagy-related gene
B	
BAF	Bafilomycin
BBr_3	boron trifluoride etherate
BIOS	biology-oriented synthesis
Boc	*tert*-butyloxycarbonyl group
C	
cBu	cyclobutyl
CN	cinchonine
COMAS	Compound Management and Screening Center
CQ	chloroquine
CtD	complexity-to-diversity
CuAAC	copper(I)-catalyzed azide-alkyne cycloaddition

Abbreviation	Full Phrase
D	
d.r.	distereomeric ratio
DCC	N,N'-dicyclohexylcarbodiimide
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMPA	2,2-dimethoxy-2-phenylacetophenone
DMSO	dimethylsuloxide
DOS	diversity-oriented synthesis
DPPA	diphenylphosphoryl azide
E	
EBSS	Earl's balanced salt solution
EC_{50}	half maximal effective concentration
eGFP	enhanced green fluorescent protein
eq.	equivalents
ESI	electrospray ionization
et al.	et alia (Latin, "and others")
F	
FBDD	fragment-based drug design
FDA	Food and Drug Administration
H	
(u)HPLC	(ultra-) high pressure liquid chromatography
HRMS	high resolution mass spectrometry
HTS	high-throughput screening

Abbreviation	Full Phrase
I	
IC_{50}	half maximal inhibitory concentration
L	
LC3	microtubule-associated proteins 1A/1B light chain 3B
M	
M	molar
*m*CPBA	*meta*-chloroperoxybenzoic acid
MeCN	acetonitrile
mTOR	mammalian target of rapamycin
N	
n.d.	not determined
nBu, nPr	unbranched butyl/propyl
NHS	N-hydroxy succinyl
NMR	Nuclear magnetic resonance spectroscopy
NOESY	Nuclear Overhauser effect spectroscopy
NP	natural product
O	
OAc	acetoxy group
OTf	trilate
P	
P450	
PBS	Phosphate buffered saline
PNP	pseudo-natural product
PPh_3	triphenylphosphine
PPI	protein-protein interaction

Abbreviation	Full Phrase
Q	
QCD	quincoridine
QD	quinidine
QN	quinine
R	
Rapa	Rapamycin
S	
SAM	*S*-adenosyl methionine
SAR	structure activity relationship
SCONP	structural classification of natural products
T	
Tan	Tantalosin-I
*t*Bu	*tert*-butyl
TFA	trifluoroacetate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
Tor	Torin-1

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Angew. Chemie - Int. Ed. **2020**, *59*, 5721–5729.

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