Macrocyclization of \(\omega\)-Isocyanoaldehydes and Towards the Total Synthesis of Jamaicensamide A

Présentée le 18 juin 2021

Faculté des sciences de base
Laboratoire de synthèse et produits naturels
Programme doctoral en chimie et génie chimique

pour l'obtention du grade de Docteur ès Sciences

par

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Acknowledgements

First of all, I would like to thank Prof. Nicolai Cramer for acceptance to be the president of my thesis jury. I also sincerely thank Prof. Rodolfo Lavilla and Prof. Laurent El Kaïm for having accepted to be part of the jury. Finally, I thank Prof. Jérôme Waser for being a part of the jury member and for the quality of his teaching within the Doctoral School.

I wish to express my deepest gratitude and sincere appreciation to my advisor, Prof. Jieping Zhu, for offering me a PhD position in the Laboratory of Synthesis and Natural Products (LSPN) at EPFL. I appreciated in his valuable instruction, expert guidance and excellent suggestion. Thank you very much to push and encourage me a lot throughout this four years.

I would like to thank Dr. Qian Wang for her support and suggestion about the chemistry. Also, thank you very much for the correction on the supporting information.

Special acknowledgments go to Monique Borcard-Sacco, the secretary of LSPN. I am very grateful on your administrative support. I also would like to thank Anne Lene Odegaard for the monitoring of the deadlines and the requirements of my doctoral studies within the Doctoral School. Thank you also to the team of the chemical store, the teams of the NMR, mass, X-ray services.

I am grateful to the Development and Promotion of Science and Technology Talents Project (DPST) for a scholarship and the Office of Educational Affairs (OEA) in Paris to take care of me during my study.

Moreover, I would like to thank all the members of LSPN, especially, Dr. Cyril Piemontesi who is my collaborator on the first project. He also taught and suggested me a lot on the chemistry task. I would also like to thank Bastien Delayre on the translation of my English abstract to French.

Finally, I would like to thank my family and friends including the Thai community in Switzerland for their love and encouragement. I also thank them all for their kindness and valuable advice. Everything will be always kept in my mind.
Abstract

In the first chapter of this thesis, the macrocyclization of a new type of bifunctional substrates, \( \omega \)-isocyanoaldehyde derivatives, is described. Ten different \( \omega \)-isocyanoaldehydes in terms of different ring sizes and functional groups were prepared. They were smoothly proceeded under the simple multicomponent reactions including Passerini reaction, Ugi reaction and modified Ugi reaction. A wide range of 9- to 22-membered macrocyclic lactams were obtained in low to excellent yields with up to four bonds were formed in a single step.

In the second chapter, synthetic studies towards the total synthesis of cyclic peptide jamaicensamide A are presented. We applied our strategy to cyclize the advanced intermediate containing \( \omega \)-isocyanoaldehyde into the cyclic peptide in one-pot procedure. The precursors for the preparation of \( \omega \)-isocyanoaldehydes with different functional groups and protecting groups were prepared. The derived 24-membered cyclic peptides were formed in good yields. The study on the deprotection of protecting groups is still on-going to complete the total synthesis of jamaicensamide A.

Keywords

macrocyclization, \( \omega \)-isocyanoaldehyde, multicomponent reactions (MCRs), total synthesis, cyclic peptide, jamaicensamide A
Résumé

Dans le premier chapitre de cette thèse est décrite la macrocyclisation d’un nouveau type de substrats bifonctionnels, les dérivés de \( \omega \)-isocyanoaldehyde. Dix différents substrats de tailles de cycles variable et aborant différents groupements fonctionnels ont été préparés. Ces substrats ont réagit lors de réactions multicomposants de type Passerini, Ugi, ainsi qu’une version modifiée de Ugi. Un large spectre de lactames macrocycliques (de 9 à 22 chaînons) a été obtenus avec des rendements allant de faibles à excellents. Jusqu’à quatre liaisons ont été formés lors de cette synthèse monotope.

Le deuxième chapitre de cette thèse est consacré à nos études visant à accomplir la synthèse totale du peptide cyclique jamaicensamide A. La stratégie de cyclisation d’un substrat avancé transformant un \( \omega \)-isocyanoaldehyde en peptide cyclique a été appliquée avec succès de façon monotope. Les précurseurs nécessaires à la préparation du substrat contenant le \( \omega \)-isocyanoaldehydes ont été préparés avec différents groupements fonctionnels et protecteurs. Les peptides cycliques à 24 chaînons ont été formés avec de bons rendements. Les études de la déprotection finale de l’ensemble des groupements protecteurs sont en cours dans l’objectif de terminer la synthèse totale de jamaicensamide A.

Mots-clés

Macrocyclisation, \( \omega \)-isocyanoaldehyde, reactions multicomposants (MRC), synthèse totale, peptide cyclique, jamaicensamide A
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Chapter 1

Macrocyclization of $\omega$-Isocyanooaldehydes

1.1 Introduction

1.1.1 Bioactive macro lactams

A wide variety of macro lactams have been isolated from natural sources. Many of them showed interesting biological activities (Figure 1).\(^1\) Vicenistatin, a 20-membered macrocyclic lactam isolated from the culture broth of *Streptomyces* sp. HC34, exhibited antitumor activity.\(^2\) Leinamycin also showed potent antitumor activity against tumor cell lines that were resistant to anticancer drugs.\(^3\) The polyene macro lactam salinilactam was first isolated from marine Actinomycete *Salinispora tropica*.\(^4\) A *Streptomyces* strain produced BE-14106 which inhibited the growth of leukemia cell lines and displayed antimicrobial activity.\(^5\) A 22-membered macro lactam, aureoverticilactam, from the marine Actinomycete *Streptomyces aureoverticillatus* showed cytotoxicity against various tumor cell lines.\(^6\) An antibiotic Fluvirucin B1 exhibited potent inhibitory activity against influenza A.\(^7\) Hitachimycin, a 19-membered macro lactam possessing a $\beta$-phenylalanine, exhibited antitumor activity.\(^8\) Cremimycin, another example of 19-membered macro lactam, showed broad antimicrobial activities against Gram-positive bacteria as well as MRSA.\(^9\) A potent antiproliferative silvalactam was produced by *Streptomyces* strain.\(^10\)

1.1.2 Macrocyclizations of bifunctional substrates

Because of the biological activities of macrocyclic lactams, many methods have been developed for their synthesis. One of the most interest of our group is the macrocyclization using the chemistry of multicomponent reactions (MCRs), especially the Passerini and Ugi reactions. To construct the macrocycles in one step, bifunctional substrates have been used. Six theoretical possibilities of the bifunctional substrates for macrocyclizations through the Ugi reaction was represented in Figure 2.\(^11\)
Figure 1. Structures of bioactive macrolactams.

Figure 2. Six possibilities of bifunctional substrates for macrocyclizations via the Ugi reaction.
The most widely explored bifunctional substrate is the tethering of carboxylic acid and amine (ω-amino acid) (Figure 2, A). In 2017, Dömling and coworkers applied the Ugi-4-center 3-component reaction for the ω-amino acids (3 for instance) to afford various 8- to 19-membered macrocycles in low to good yields (Scheme 1, A). In the same year, they reported the synthesis of medium-sized rings by using the same strategy. 8- to 11-membered cyclic products were obtained in 22-65% yields (Scheme 1, B). ω-Amino acids 3 and 9 were prepared from the condensation of cyclic anhydrides 1 and 7 with alkyl diamines 2 and 8, respectively.

Scheme 1. The synthesis of macrocycles and medium-sized rings from ω-amino acids.

The ω-amino acids were applied for the macrocyclizations of peptides. Side chain-to-side chain peptide macrocyclization precursor 13 for the Ugi reaction was reacted with cyclohexyl isocyanide (14) and paraformaldehyde in MeOH for 72 hours. Macrocycle 15 was obtained in 59% yield (Scheme 2, A). In addition, the Ugi reaction of the peptide 16 for the side chain-to-termini peptide macrocyclization yielded macrocycle 17 in 60% (Scheme 2, B).
Sequential Ugi reaction was applied for the synthesis of cyclic pentadepsipeptoids. An example was depicted in Scheme 3. The first Ugi 4-component reaction using methyl isocyanooacetate (18), N-Boc-glycine (19), benzylamine (20) and paraformaldehyde, followed by hydrolysis provided peptoid 21. A Passerini reaction of acid 21 with tert-butyl isocyanooacetate (22) and isobutyraldehyde (23) gave acyclic depsipeptoid 24 in quantitative yield. The ω-amino acid 24 was subjected to the Ugi three-component four-center reaction (U-3C4CR), affording cyclic pentadepsipeptoid 25 in moderate yield.\(^\text{15}\)

Scheme 2. Macrocyclizations of peptide side chains by the Ugi reaction.

Cyclopeptoid 31 was also synthesized by the consecutive Ugi reactions. For the last Ugi reaction of ω-amino acid derived from 30, pseudo-high-dilution conditions was applied to avoid oligomerization (Scheme 4).\textsuperscript{16}

![Scheme 4. Synthesis of cyclopeptoid 31.](image)

Yudin and coworkers reported the macrocyclizations of linear peptides enabled by amphoteric amino aldehydes (33). The nucleophilic center at the α-position of the amphoteric amino aldehyde is responsible for the Mumm rearrangement instead of the amino group of the ω-amino acid 32. 9- to 18-membered cyclic peptides were produced in good yields (Scheme 5).\textsuperscript{17}

![Scheme 5. The Ugi reaction of linear peptides and amphoteric amino aldehydes.](image)

α-Isocyno-ω-carboxylic acid (Figure 2, B), a type of the bifunctional substrates, is also investigated for the macrocyclizations. A few research groups have studied on this type of substrate. In
2015, Dömling reported the macrocyclizations of $\alpha$-isocyano-$\omega$-carboxylic acid 40. The cyclic Ugi products were obtained in 34-45% yields (Scheme 6).¹⁸

![Scheme 6. An example of cyclic Ugi products derived from $\alpha$-isocyano-$\omega$-carboxylic acid 40.](image1)

In order to introduce more complexity and flexibility, the overall macrocycle was achieved by the union of two orthogonal MCRs. The first Ugi 4-component reaction was applied to provide a suitable substrate for the second multicomponent reaction. The tetrazole ring (46) was constructed via the first Ugi tetrazole synthesis by using TMSN$_3$ as the source of HN$_3$. After the intramolecular Ugi reaction of 49, macrolactam 50 was obtained in 36% (Scheme 7).¹⁸

![Scheme 7. An example of macrocycles synthesis using the union of two MCRs.](image2)

In 2016, Dömling and coworkers used the same strategy for the synthesis of macrocyclic depsipeptides. Yields of the first linear Ugi products (53 for instance) were moderate to excellent. On the other hand, the macrocyclization process gave the cyclic depsipeptides (57 for instance) in low yields (20-36%) (Scheme 8).¹⁹
Recently, Dömling group introduced $\alpha$-isocyano-$\omega$-amines (Figure 2, C), a type of bifunctional substrates, for the macrocyclization. For example, $\alpha$-isocyano-$\omega$-amine 59 was prepared from the amidation of isocynoester 43 and 1,3-diaminopropane (58). The Ugi reaction of 59 with isovaleraldehyde (60) and 2-phenylacetic acid (61) produced the macrolactam 62 in 74%.\textsuperscript{11} In addition, Ugi tetrazole 63 was obtained in 40\% from the reaction of 59 with isobutyraldehyde (23) and TMSN$_3$ (45) (Scheme 9).\textsuperscript{20}

In 1999, Zhang and coworkers introduced the bifunctional starting materials containing aldehyde and carboxylic acid (Figure 2, D) for the synthesis of medium-sized lactams. 5- to 8-membered rings were investigated and 8-membered ring lactams were produced in low yields (19-42\%), presumably due to the difficulties of forming that 8-membered ring (Scheme 10).\textsuperscript{21}
Scheme 10. 8-membered ring lactam form the Ugi reaction of aldehyde tethering acid substrate.

In 2012, Saxena group used the alcohol/formamide (68) as the substrates for the intramolecular Ugi reaction to synthesized 5- to 8-membered lactams via the sequential procedure. The sequence was the Parikh-Doering oxidation of primary alcohol, dehydration of formamide followed by Ugi reaction. The synthesized 5- to 8-membered rings were obtained in moderate to good yields (Scheme 11).\(^22\)

\[\text{Scheme 11. Sequential procedure for the synthesis of medium-sized lactams.}\]

1.1.3 Synthesis of (+)-peganumine A

In 2016, our group reported the enantioselective synthesis of (+)-peganumine A (72). The octacyclic structure of 72 was constructed through the enantioselective Pictet-Spengler reaction of two achiral building blocks (73 and 74) (Scheme 12).\(^23\)

\[\text{Scheme 12. Retrosynthesis of the (+)-peganumine A.}\]
Moreover, a single-step preparation of tetracyclic α-ketoamide 74 was achieved by hydroxylamine-mediated intramolecular oxidative coupling of ω-isocyanoo-γ-oxoaldehyde 75 (Scheme 14).

From this report, we realized that the macrocyclization of a new type of the bifunctional substrates, ω-isocyanooaldehyde (Figure 2, F), could be applied to other substrates to provide a wide range of macrocyclic lactams which displayed various biological activities (Figure 1).
1. Results

1.2 Synthesis of starting materials

The indole-containing compounds was the first type of substrates that was tried for the macrocyclization. It was prepared from tryptamine as follows in Scheme 15. The primary aliphatic amine of tryptamine (81) was formylated chemoselectively with ethyl formate under reflux conditions to give 82 as brown oil. Without further purification, the indolic nitrogen of compound 82 was protected with Boc₂O in the present of DMAP in DMF to afford compound 83 in 75% yield (over 2 steps). To prepare the material for the Liebeskind–Srogl cross-coupling reaction, stannylated indole 84 was furnished in 75% yield by C2-lithiation of 83 using TMPLi followed by quenching with tributyltin chloride. The other coupling partner is thioester derivative. Four thioesters (85-88) were prepared in one step in 73-84% yields from alkenyl acids and thiophenol (Scheme 16). The Liebeskind–Srogl cross-coupling reaction was performed under the optimized conditions: [Pd₂dba] (10 mol%), AsPh₃ (10 mol%), copper(I) diphenylphosphinate (CuDPP, 2.0 equiv) in 3:1 hexanes:THF (c 0.067 M) at room temperature for 6 h. The coupling products (89-92) were obtained in 63-71% yields. The coupling reaction between 84 and S-phenyl 4-oxobutanethioate was performed and the corresponding product (93) was obtained in low yield (37%). As the ozonolysis of alkene 89 gave trace amount of aldehyde 93, two-step conversion of alkene moiety to aldehyde was performed. The sequential dihydroxylation and oxidative cleavage of compounds 89-92 gave the aldehydes 93-96 in 82-95% yields. To obtain the ω-isocyanooaldehydes, dehydration of N-formamides 93-96 by using POCl₃ and NEt₃ afforded compounds 97-100, which were used directly for the macrocyllization reactions.

Scheme 15. The synthesis of indole-containing ω-isocyanooaldehydes 97-100.
The alkyl-substituted indole derivatives were the next target. 9- and 15-membered ring precursors were prepared from 83. The C–H functionalization via palladium-catalyzed alkenylation at C2 of indole 83 with acrolein (105) afforded unsaturated aldehyde 106 in 56% yield. Hydrogenation of 106 in CH2Cl2 at room temperature for 6 h gave the corresponding aldehyde 107 and alcohol 108 in 35% and 60%, respectively. The N-formamide 107 was converted to isonitrile 109 which was ready for the 9-membered ring cyclization. For the primary alcohol 108, it was alkylated with 6-bromo-1-hexene (110) and the alkylated product was isolated in 35%. The alkene 111 was converted to aldehyde 112 through dihydroxylation-oxidative cleavage process in 66% followed by the dehydration of N-formamide group to give isonitrile 113 for the 15-membered ring macrocyclization (Scheme 17).


Scheme 17. The synthesis of indole-containing ω-isocynoaldehydes 109 and 113.
To provide the phenol-containing precursors, the synthesis began with the amide formation of methyl salicylate (114) with 1,3-diamino propane (58), yielding N-(3-aminopropyl)-2-hydroxybenzamide (115) which was used directly for the next step without purification. The formylation of crude primary amine 115 with ethyl formate at reflux temperature afforded phenol 116 in 52% (over 2 steps) and the diamide compound which was formed in the first reaction was also isolated in 31% (Scheme 18, A). Phenol 116 was alkylated with two different alkyl bromides, 6-bromo-1-hexene (110) and 6-((6-bromohexyl)oxy)hex-1-ene (119). Alkyl bromide 119 was obtained in 14% from the nucleophilic substitution reaction of 1,6-dibromohexane (117) and hex-5-en-1-ol (118) (Scheme 18, B). The alkylated products (121 and 122) were obtained in good yields. The conversion of terminal alkenes under the dihydroxylation-oxidative cleavage process yielded the corresponding aldehydes 123 in 90% and 124 in 69%. The phenol-containing precursors for the cyclization reaction were obtained from the dehydration of N-formamides 125 and 126 (Scheme 18, C).

Scheme 18. The synthesis of phenol-containing precursors.

A benzamide precursor 133 for 14-membered ring cyclization was prepared from methyl anthranilate (127). 4-Pentenoic acid (101) was underwent mild decarboxylation in the present of CDI to generate a carbonyl imidazole intermediate which was reacted with methyl anthranilate (127) at reflux conditions to give amide 128. The N-H of amide should be protected in order to avoid the hemiaminal formation with the terminal aldehyde functional group. Therefore, the crude of amide 128 was used directly for the N-benzylation step to afford the benzyl-protected amide 129 in 34% yield (over 2 steps).
The condensation of ester 129 and 1,3-diaminopropane (58) followed by the formylation of corresponding primary amino group yielded compound 131 in 73%. Aldehyde 132 was formed in 61% from a two-step procedure and the \( \omega \)-isocyanaldehyde 133 was obtained after the dehydration of \( N \)-formamide group (Scheme 19).

**Scheme 19. The synthesis of benzamide precursor for the 14-membered ring cyclization.**

A \( m \)-cyclophane precursor was obtained using the similar strategy of 125 (Scheme 20). Methyl 3-hydroxybenzoate (134) was subjected to a condensation reaction with 1,3-diaminopropane (58) at 110 \( ^\circ \)C, followed by the formylation of the present primary amine (135) with ethyl formate to give phenol 136. The alkylation of 136 with 6-bromo-1-hexene (110) yielded 137 in 56% (over 3 steps). Conversion of terminal alkene 137 to aldehyde 138 was accomplished in 76% and the dehydration of \( N \)-formamide furnished the precursor of \( m \)-cyclophane 139.
Scheme 20. The synthesis of m-cyclophane precursor.

A p-cyclophane precursor was prepared using the methyl 4-hydroxybenzoate (140) as starting material (Scheme 21). The alkylation of 140 with 6-bromo-1-hexene (110) yielded 141 in 97%. Hydrolysis of methyl ester 141 under the basic conditions, followed by the coupling reaction between the corresponding carboxylic acid (142) with N-(3-aminopropyl)formamide (143) at room temperature, affording the coupling product 144 in 87%. Conversion of terminal alkene 144 to aldehyde 145 was accomplished in 78% under 2 steps and the dehydration of N-formamide furnished the precursor of p-cyclophane 146.

Scheme 21. The synthesis of m-cyclophane precursor.
1.2.2 Macrocyclization

Having some starting materials in hand, the cyclization reactions were investigated (Scheme 22).

Scheme 22. Outline of multicomponent reactions for macrocyclizations of ω-isocyanooaldehydes.

An indole-containing ω-isocyanog-γ-oxoaldehyde 97 was selected as the first substrate. Various cyclization reactions were performed with 97 in 0.05 mmol scale (Figure 3). A Passerini 3-center-2-component reaction of 97 with trifluoroacetic acid in the present of pyridine in dichloromethane (c 0.01 M, 5 days) at room temperature afforded tetracycle 147 in 51%. The reaction underwent through a 10-membered macrolactam 153 and the tetracycle 154 was formed via the transannular cyclization. After hydrolysis under the basic conditions, α-hydroxy macrolactam 147 was furnished (Scheme 23). The first intermediate (153) or its hydrolyzed adduct could not be determined due to the rapid transannular cyclization process under the acidic conditions even in silica gel (SiO₂) and CDCl₃. This Passerini reaction could be scalable and 59% yield of 147 was obtained with 0.58 mmol scale of starting material 97. Other carboxylic acids were applied for the Passerini reaction of 97. A reaction with acetic acid (1.3 equiv) gave the tetracyclic product 148 in 62% (0.05 mmol scale). The yield dropped a bit when the reaction was performed with 1.14 mmol of 97. A Passerini reaction with benzoic acid gave the tetracycle 149 in moderate yield (55%). An example of Ugi 4-center-3-component reaction of 97 was performed with benzylamine (1.2 equiv) and acetic acid (1.5 equiv) to provide 150 in 89% yield. Finally, the oxidative Ugi reaction for the α-ketoamide synthesis was performed with N-methylhydroxylamine hydrochloride and acetic acid in MeOH (c 0.01 M) in the presence of 4 Å molecular sieves and NaHCO₃. After filtration and direct purification, 3-(methy lamino)pyridine-2(1H)-one derivative 151 was obtained in 89% yield. On the other hand, α-ketoamide product 152 was obtained in 79% yield after quenching the reaction with 2 M HCl. The formation of pyridinone ring started with the Ugi 4-center-
3-component reaction of 97 gave 10-membered ring intermediate 155. The $\beta$-elimination of 155 afforded the $\alpha$-iminolactam 156, which underwent tautomerization to furnish the observed product 151. The $\alpha$-ketoamide 152 could be formed from 156 via the hydrolysis under the acidic conditions (Scheme 24).

![Molecular structures](image)

**Figure 3. Tetracycle products obtained from $\omega$-isocyano-$\gamma$-oxoaldehyde 97.**

*The reaction was performed in 0.58 mmol. †The reaction was performed in 1.14 mmol.

![Scheme 23](image)

**Scheme 23. The formation of tetracyclic $\alpha$-hydroxy lactam 147.**
Scheme 24. The formation of 3-(methylamino)pyridine-2(1H)-one derivative 151 and α-ketoamide 152.

The cyclization reactions of indole-containing ω-isocyano-γ-oxoaldehyde 98 which extended with one more methylene group gave the 11-membered macrolactams in moderate to good yields (Figure 4). Notably, no transannular cyclized product was formed. Three Passerini reactions were performed with different carboxylic acid derivatives. The reaction with TFA in the present of pyridine gave the α-hydroxy macrolactam 157 in 68% yield. Compound 158 was isolated in 72% after performing the reaction of 98 with acetic acid (1.3 equiv) at room temperature for 3 days. N-(tert-Butoxycarbonyl)glycine (19) was also used as an example of carboxylic acids and cyclized product 159 was obtained in 78%. The Ugi 4-center-3-component reaction of 98 afforded Ugi product 160 in 61%.

Figure 4. 11-membered macrolactams from the macrocyclization of 98.

The precursor for 12-membered ring cyclization (99) was subjected to four reactions. The Passerini reaction with TFA afforded the α-hydroxy lactam 161 in excellent yield (92%). Two Passerini reactions which 99 was performed with acetic acid and N-(tert-Butoxycarbonyl)glycine (19) gave the same activity. 85% of compounds 162 and 163 were obtained in high yields. While, the Ugi reaction of 99 gave the α-amino lactam 164 in moderate yield (57%) (Figure 5).
Next, the cyclizations of 13-membered ring precursor 100 were then explored. The α-hydroxy lactam 165 was obtained in 83% yield. The other two Passerini reactions of 100 gave the corresponding cyclized products 166 and 167 in 62% and 73%, respectively. The Ugi product 168 was obtained in moderate yield (54%). The α-ketoamide 169 was obtained in 60% yield under the oxidative Ugi conditions (Figure 6). The structure of compound 159 is confirmed by X-ray crystallography (Figure 7).
The 9-membered medium-sized ring precursor 109 was subjected to three Passerini reactions, one Ugi reaction and one Ugi tetrazole reaction (Figure 8). The Passerini reaction with TFA in the present of pyridine gave the hydroxyl-containing lactam 170 in 44%. The other two ester-containing products 171 and 172 were also obtained in moderate yields (50% and 55%, respectively). The Ugi 4-center-3-component reaction of 109 with benzylamine (20) and acetic acid yielded the corresponding α-amino 9-membered lactam (173) in 43%. Compound 109 was subjected to the Ugi tetrazole reaction together with 4-aminobenzonitrile (175) and trimethylsilyl azide (45) (as a convenient source for hydrazoic acid). The reaction was performed in MeOH (c 0.1 M) at room temperature for 2 days and the tetrazole product 174 was obtained in 35% yield. The formation of tetrazole 174 was described in Scheme 25. The imine formation between aldehyde 109 and 4-aminobenzonitrile (175) gives imine intermediate 176. The intramolecular nucleophilic attack of isocyano group to the imine affords cyclic nitrilium intermediate 177. This intermediate is then trapped with hydrazoic acid which is generated in situ from TMSN₃ in the present of MeOH to give intermediate 178. Finally, the intramolecular cyclization forms the tetrazole ring and yields the Ugi tetrazole product 174.

Figure 7. The X-ray structure of compound 159.

Figure 8. 9-membered cycles from the cyclization of 109.
The precursor of 15-membered macrocyclic ring system (113) was investigated (Figure 9). The Passerini reactions gave the cyclized products in moderate yields. The α-hydroxy lactam 179 was obtained in 51% and products (180 and 181) derived from acetic acid and N-(tert-butoxycarbonyl)glycine (19) were isolated in 52% and 58%, respectively. The Ugi product 182 was obtained in 30% after 113 was reacted with benzylamine (20) and acetic acid in CH₂Cl₂ (c 0.01 M) at room temperature for 4 days. Low yield (23%) of Ugi tetrazole product 183 was afforded after reacting 113 with aniline (184) and TMSN₃ (45) in MeOH (c 0.1 M) at room temperature for 1 day.
The phenyl-based substrates were then explored, starting with a precursor containing phenol moiety. The phenyl-based ω-isocyanaldehyde 125, a precursor for 15-membered macrocycles, was subjected to various cyclization reactions (Figure 10). The Passerini reaction with TFA and pyridine gave the hydrolyzed product 185 in 84%. The 15-membered macrolactam with the acetoxy group (186) was obtained in 91% from the Passerini reaction of 125 and acetic acid. The other Passerini reaction with protected glycine (19) gave the excellent yield of product 187 (95%). The Ugi 4-center-3-component reaction of 125 occurred smoothly to afford the Ugi product 188 in 97%. However, the Ugi tetrazole product 189 was obtained in moderate yield (43%) after reacting 125 with aniline (184) and TMSN₃ (45) in MeOH (c 0.1 M) at room temperature for 4 days. The structure of compound 189 is confirmed by X-ray crystallography (Figure 11). The Ugi 4-center-3-component reaction with N-hydroxysuccinimide (192) as the acid component instead of carboxylic acid derivatives was performed.³³ The α-hydrazino macrolactam 190 was obtained in low yield (22%). The reaction mechanism related to normal Ugi reaction (Scheme 26). The imine 193 is first formed from the condensation of aldehyde 125 with benzylamine (20). The intramolecular nucleophilic addition of isocyanato group to imine which is activated by ZnCl₂ takes place to give nitrilium intermediate 195. Intermediate 195 is trapped with hydroxamate anion 196 followed by the Mumm-like rearrangement to form the N-N bond and give the α-hydrazino macrolactam 190. The oxidative Ugi reaction of the ω-isocyanaldehyde 125 gave the α-ketoamide 191 in 71% yield.

![Figure 10. 15-membered cycles from the phenyl-based ω-isocyanaldehyde 125.](image-url)
According to the X-ray structure of compound 189 (Figure 11), there is a hydrogen-bonding between the amide NH and the phenol oxygen. The pre-organization of the \( \omega \)-isocyanoaldehyde 125 (Scheme 27, A) could lower the conformational freedom of the side chains to give products in the better yields than the other indole-series 15-membered rings in Figure 9 which lacked of this interaction.

Scheme 26. The formation of \( \alpha \)-hydrazino macrolactam 190.

Scheme 27. Possible conformational pre-organization for the phenol based substrates.
The phenol-containing precursor 126 was then investigated. 22-membered macrocycles were obtained in moderate to good yields (Figure 12). The Passerini reaction of 126 with TFA and pyridine yielded the α-hydroxy lactam 198 in 71%. Acetate 199 and glycinate 200 products were afforded in 85% and 80% yields, respectively. The Ugi reaction of 126 with benzylamine (20) and acetic acid gave the macrocycle 201 in 78% yield. The tetrazole product 202 was produced in 53% yield after subjecting precursor 126 in the Ugi tetrazole conditions. The oxidative Ugi reaction of the ω-isocyanooaldehyde 126 gave the α-ketoamide 203 in 68% yield. The possible pre-organization of substrate 126 could explain the high yields observed. Additional hydrogen-bond could occur with the NH of the amide and the ether oxygen (Scheme 27, B).

Figure 12. 22-membered rings derived from the phenyl-based ω-isocyanooaldehyde 126.

The cyclization reactions of benzamide precursor 133 were performed. Three Passerini products were obtained in moderate to excellent yields. The reaction with TFA in the present of pyridine gave the hydroxylated product 204 in 66%. The Passerini reaction with acetic acid was completed in 2.5 days and gave product 205 in 77% yield. The Passerini reaction with N-(tert-butoxycarbonyl)glycine (19) was performed with the same reaction time and the 14-membered lactam 206 was isolated in 93% yield. The Ugi 4-center-3-component reaction of 133 yielded the Ugi product 207 in moderate yield (56%). Two tetrazole Ugi reaction of 133 with aniline (184) and 4-aminobenzonitrile (175) were performed and the corresponding products were obtained in low yields (28% and 24%, respectively) (Figure 13).
The \( m \)-cyclophane precursor 139 was subjected to a Passerini reaction with acetic acid (1.3 equiv) in \( \text{CH}_2\text{Cl}_2 \) (\( c = 0.01 \text{ M} \)). The reaction was allowed to stir at room temperature for 5 days. After the purification, the desired cyclized product 210 was isolated in 9\% together with the cyclodimer 211 in 26\%. To reduce the cyclodimerization, the reaction was performed in the lower concentration (0.001 M of \( \text{CH}_2\text{Cl}_2 \)) with an increase amount of acetic acid (5.0 equiv) and the reaction gave low conversion after 5 days. To improve the conversion, a new batch of this Passerini reaction was performed in \( \text{CH}_2\text{Cl}_2 \) (\( c = 0.002 \text{ M} \)). After 7 days, the desired 16-membered \( m \)-cyclophane 210 was produced in 20\% and the cyclodimer 211 was obtained in the lower yield (12\%) (Scheme 28).

Scheme 28. The cyclization of \( m \)-cyclophane precursor 139.

Finally, under the Passerini reaction of precursor 146, the \( p \)-cyclophane 212 was isolated in 61\% without the formation of dimer product (Scheme 29).
Scheme 29. The cyclization of \( p \)-cyclophane precursor 146.

The higher yield obtained for 212 compared to the apparently less strained \( m \)-cyclophane 210 could be attributed to the transannular interaction between the ortho proton with the macrocycle ring which did not exist in the \( p \)-cyclophane 212 (Figure 14).

Figure 14. Optimized (DFT, 6-31G(1)d, B3LYP) geometry of the obtained \( m \)- and \( p \)-cyclophanes.
1.3 Conclusion

The macrocyclizations of a new type of bifunctional substrates, $\omega$-isocyanoaldehyde derivatives, smoothly proceeded under the Passerini and Ugi reactions. Ten $\omega$-isocyanoaldehydes with different ring sizes and functional groups were prepared. 9- to 22-membered macrocyclic lactams were obtained in low to excellent yields (Figure 14). In our investigation, Passerini reaction gave the higher yield than the Ugi reaction. The pre-organization of the phenol-tethered substrates by intramolecular hydrogen bonding could lower the conformational freedom of the side chains to give products in the better yields than that of indole series.

![Figure 15. Examples of obtained macrocycles.](image-url)
Chapter 2
Towards the Total Synthesis of Jamaicensamide A

2.1 Introduction

As the macrocyclizations of the $\omega$-isocyanooldehydes were accomplished, we would like to apply our strategy for the total synthesis of a natural product.

2.1.1 Cyclic $\alpha$-ketoamides

Natural cyclic $\alpha$-ketoamides have shown interesting biological activities. They have been isolated from many natural sources including sponges, bacteria, fungi and ascidians. Examples of natural cyclic $\alpha$-ketoamides were depicted in Figure 16. A series of cyclotheonamides A-E5 have been isolated from marine sponges. They showed significant serine protease inhibitor and thrombin inhibitor.$^{34-37}$ A series of keramamides showed cytotoxic activity towards many cell lines. They were isolated from Okinawan marine sponge Theonella swinhoei.$^{38-42}$ Oriamide$^{43}$ and cyclotheonellazoles A–C$^{44}$ showed similar core structure. These four compounds were also isolated from marine sponge Theonella swinhoei and acted as potent protease inhibitors. Calyxamides A and B, showing moderate cytotoxicity against murine leukemia P388 cell-line, were isolated from a marine sponge Discodermia calyx in 2012.$^{45}$ Antifungal discobahamins A and B were isolated in 1994 from a Bahamian marine sponge Discodermia sp.$^{46}$ They showed the similar core structure to the cytotoxic orbiculamide A which was isolated from a marine sponge Theonella sp in 1991.$^{47}$ Jahnellamides A and B were isolated from myxobacterium Jahnella sp in 2013.$^{48}$ Eurystats A and B were isolated in 1991 from the bacteria Streptomyces eurythermus R353-21 which was collected from a soil sample in India.$^{49}$ Scleritodermin A was isolated from lithistid sponge Scleritoderma nodosum. It inhibited tubulin polymerization and showed cytotoxic activity against human tumor cell lines.$^{50}$
Figure 16. Examples of cyclic α-ketoamides.
2.1.2 Jamaicensamide A

The 24-membered cyclic peptide jamaicensamide A (201) (Figure 17) was selected as the target molecule for the total synthesis. This new cyclic peptide was isolated from the Bahamian sponge *Plakina jamaicensis* by the group of Professor Tadeusz F. Molinski in 2016. It composed of six amino acids, a thiazole-homologated amino acid, and an α-keto amide group which was expected to be formed under our strategy. As it was obtained in very low amount, 33 µg, and no biological activities were reported, we would like to study the total synthesis of this molecule by applying our strategy to confirm the structure of this molecule and to obtain more amount that useful for the biological activities study.
2.2 Results

2.2.1 Retrosynthesis

Our retrosynthesis started by the disconnection of the side chain B which can be prepared from L-isoleucine and L-2-aminobutyric acid. The macrocycle C was expected to form by using our macrocyclization method on the ω-isocyanoaldehyde precursor D. This sensitive precursor D can be formed from E by the reduction of Weinreb amide or ester to aldehyde and the dehydration of formyl group to isocyanide. Further disconnection of pentapeptide E showed that it can be prepared from the amide coupling reactions between the small amino acids including L-ornithine, L-proline, L-norvaline and 5-hydroxy-L-tryptophan together with the thiazole F (Scheme 30).

Scheme 30. Retrosynthesis of jamaicensamide A.
2.2.2 Synthesis

Some precursors E1-E3 for the formation of ω-isocyanaldehyde D were designed with different reduced groups on the L-norvaline and protecting groups on the 5-hydroxy-L-tryptophan (Figure 18). E1 was selected to study first.

![Figure 18. Precursors to prepare ω-isocyanaldehydes D.](image)

Our total synthesis started with the formation of thiazole fragment F (Scheme 31). The peptide coupling reaction between L-serine methyl ester (214) and Boc protected L-alanine (215) in 15.0 mmol scale gave 91% yield of product. The TBS protection of the primary alcohol 216 gave good yield. The transformation of amide 217 using Lawesson’s reagent gave 79% yield of thioamide 218. Deprotection of TBS yielded primary alcohol 219 in 90% which was ready for the thiazole formation. Ring formation by using DEAD and PPh3 followed by the oxidation using BrCCl3 and DBU gave the thiazole product 220 in 89% yield over two steps. Note that, when DAST was used as the reagent for the thiazoline formation, oxazoline was found as the major product while Burgess reagent gave the thiazoline compound in low conversion (Table 1). The Boc protecting group of thiazole 220 was converted to formyl group under two step synthesis. The DIBAL reduction converted the methyl ester group of 222 to aldehyde which was ready for the HWE reaction. The reaction of corresponding aldehyde 223 with the trimethyl phosphonoacetate gave the α,β-unsaturated ester in 70% over two steps. Finally, the hydrolysis of methyl ester gave the α,β-unsaturated carboxylic acid substituted thiazole 225 (fragment F) in good yield.
Scheme 31. Synthesis of thiazole F (route 1).

Table 1. Thiazoline formation of 219 with different reagent.

<table>
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<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DAST, K$_2$CO$_3$, CH$_2$Cl$_2$, -78 °C to rt</td>
<td>219a (20%) and 219b (77%)</td>
</tr>
<tr>
<td>2</td>
<td>Burgess reagent (1.1 eq), THF, 0 °C to rt</td>
<td>low conversion and no production of 219b</td>
</tr>
<tr>
<td>3</td>
<td>Burgess reagent (2.0 eq), CH$_2$Cl$_2$, 0 °C to rt</td>
<td>low conversion and no production of 219b</td>
</tr>
<tr>
<td>4</td>
<td>Burgess reagent (1.2 eq), THF, reflux</td>
<td>219a (37%)</td>
</tr>
<tr>
<td>5</td>
<td>DEAD, PPh$_3$, THF, rt</td>
<td>full conversion and no production of 219b</td>
</tr>
</tbody>
</table>
As the previous route was quite long to form the thiazole ring (220), we therefore change to another route (Scheme 32). This route started with the Boc protection of L-alanine (226) followed by the amide and thioamide formations respectively to yield the thioamide 228 in 73% over three steps. Under the modified Hantzsch thiazole synthesis, the thiazole 220 was obtained in 77% in one step.

Scheme 32. New route for the synthesis of thiazole ring.

The other 4 different amino acids were prepared for the coupling reactions. The esterification with methanol and SOCl₂ of L-proline and 5-hydroxy-L-tryptophan gave quantitative yield. Both amino groups of L-ornithine were protected. Treatment of L-ornithine with CuSO₄ and NaOH allowed the α-amino acid to form a copper dimer. Addition of CbzCl and K₂CO₃ to protect the terminal amino group afforded complex 234. Then, decomposition of dimer using EDTA and NaOH led to free α-amino acid 235 which was used directly for the N-Boc protection to furnish the desired ornithine derivative 236 in 50% yield over three steps. Finally, the Weinreb amide of L-norvaline was prepared through a three-step procedure. Boc protection followed by the Weinreb amide formation gave 239 in 83% over two steps. The deprotection of Boc under the acidic conditions gave 240 in quantitative yield (Scheme 33).
Scheme 33. Synthesis of the starting amino acid derivatives.

With all amino acid fragments and thiazole F in hands, the coupling reactions of these five fragments were performed starting with the amide formation of 5-hydroxy-L-tryptophan methyl ester (232) and thiazole fragment F (225) afforded coupling product in 83% yield. The methyl ester of 241 was hydrolysed using LiOH in THF/H₂O to give the carboxylic acid 242 in quantitative yield (Scheme 34). Meanwhile, the L-proline methyl ester (230) was coupled with the protected L-ornithine 236 to yield 243 in 89%. After the hydrolysis of 243, the coupling reaction of corresponding carboxylic acid 244 and Weinreb amide 240 was performed and the tripeptide product 245 was obtained in 86% yield. Hydrogenolysis of Cbz protecting group gave free amino compound 246 which was a coupling partner of dipeptide 242 to obtain the final pentapeptide E1 (247) in moderate yield (Scheme 35).
Scheme 34. Coupling reaction between compound 232 and fragment F.

Scheme 35. Preparation of pentapeptide E1.
A small-scale reduction/dehydration of precursor \( \textbf{E1} \) (0.1 mmol) accomplished the \( \omega \)-isocyanoaldehyde \( \textbf{D1} \) (249) in good yield. The crude \( \textbf{D1} \) was used directly without further purification to test the macrocyclization reaction (Scheme 36). Interestingly, the Passerini reaction with AcOH and TFA/pyridine gave the corresponding 24-membered rings in pleasant yields (Scheme 37). With 0.01 mmol scale, the macrocyclization of \( \textbf{D1} \) with AcOH (2.0 equiv) in THF (0.01 M) for 4 days gave the cyclized product in 28%. The hydrolyzed compound 248 which was formed from the remaining starting material during the workup process was isolated in 44%. Adding more AcOH into the reaction with prolong the reaction time improved the yield to 49%. The Passerini reaction of \( \textbf{D1} \) with TFA (6.0 equiv) and pyridine (12.0 equiv) gave the \( \alpha \)-hydroxy lactam 251 in 51% together with the hydrolyzed product in 31%.

Unfortunately, the reduction of the Weinreb amide \( \textbf{E1} \) to get the aldehyde 248 by using LAH and DIBAL as reducing agents in the bigger scale gave un reproducible results. The over reduction at formyl group was observed. Therefore, compound \( \textbf{E2} \) (Figure 18) was chosen to be the next precursor to prepare the reactive intermediate \( \textbf{D1} \).

Scheme 36. Preparation of \( \omega \)-isocyanoaldehyde \( \textbf{D1} \).
To prepare the precursor E2, Weinreb amide 245 was used as the starting material. It was reduced by LAH to give the corresponding aldehyde 252 which was directly protected with ethylene glycol under the acidic conditions to give compound 253 in 72% over two steps. The Cbz protecting group was cleaved by hydrogenolysis and the corresponding free amine (254) was coupled with carboxylic acid 242 to give pentapeptide 255 (precursor E2) in moderate yield. Deprotection of the 1,3-dioxolane ring under the mild acidic conditions gave compound 248 in 60% yield (Scheme 38).

The α-hydroxy lactam 251 was prepared in the bigger scale in order to have sufficient amount for the next step. The oxidation of α-hydroxyamide to the α-ketoamide was investigated. With different oxidation conditions including DMP, PCC, Swern oxidation, giving complex mixture. On the other hand, MnO₂ oxidation gave no reaction. The presence of unprotected 5-hydroxy indole ring might cause the complex mixture results. Thus, compound E3 (Figure 18) with the TIPS protection on the hydroxyl group of the indole ring was prepared. The functional group on L-norvaline was converted to methyl ester instead of Weinreb amide as it is easier to prepare.
Scheme 38. Preparation of precursor E2.

The esterification of 5-hydroxy-L-tryptophan (231) followed by the Boc protection of amino group gave compound 257 which was used directly for the TIPS protection to give the protected tryptophan 258 in 65% yield over three steps. The Boc group was cleaved under the acidic conditions to give compound 259 which was coupled with fragment F (225) to give the coupling product (260) in 65% yield. Saponification of the methyl ester 260 gave the corresponding carboxylic acid 261 in quantitative yield.

Scheme 39. Preparation of precursor E3.
To complete the synthesis of precursor E3, L-norvaline (237) was converted to methyl ester and coupled with dipeptide 244 to give tripeptide 263 in good yield. Hydrogenolysis of Cbz protecting group gave pure free amine 264 which was coupled with coupling partner 261 to give precursor E3 (265) in 69% yield (Scheme 40).

Scheme 40. Preparation of precursor E3 (cont).

The reduction of methyl ester 265 to the corresponding aldehyde 266 or primary alcohol 267 was investigated (Table 2). The DIBAL reduction was very slow and no desired products were observed (entry 1). Reduction with NaBH₄ upto 30 equiv to give the full conversion of substrate and yield the primary alcohol 267 in 91% (entry 2). LiBH₄ in 20 equiv gave the same result as NaBH₄ (entries 3 and 4). Surprisingly, LiAlH₄ in 3.0 equiv could stop at the first reduction to give the corresponding aldehyde 266 as a major product (entries 5 and 6). The reduction of compound 265 (4.2 mmol) with LiAlH₄ (3.0 equiv) in THF for 24 hours gave the desired aldehyde 266 in 72% together with alcohol 267 in 13%. Note that, the primary alcohol 267 could be converted to the aldehyde 266 by the DMP oxidation.

With the proper amount of aldehyde 266 in hands, we turn our interest to the optimization of the macrocyclization conditions (Table 3). The reaction of the ω-isocynoaldehyde 267 in the presence of TFA and pyridine was used as the model substrate, giving cyclic α-hydroxyamide 268 as product. With different solvents including CH₂Cl₂, CHCl₃, THF, dioxane, toluene and MeOH, CH₂Cl₂ gave the best yield (entries 1-6). The amount of reagents were tested and the reaction with 6.0 equiv of TFA and 12.0 equiv of pyridine gave the best result (entries 7-11). The concentration of 0.02 M gave the best yield. With higher concentration, the reaction produced other products (entries 12-17).
Table 2. The reduction of methyl ester of 265.

<table>
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<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
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<tbody>
<tr>
<td>1</td>
<td>DIBAL (2 to 10 equiv), THF, -78 °C</td>
<td>low conversion, both 266 and 267 were not observed</td>
</tr>
<tr>
<td>2</td>
<td>NaBH₄ (30 equiv), THF, 0 °C to rt</td>
<td>full conversion to give 267 in 91%</td>
</tr>
<tr>
<td>3</td>
<td>LiBH₄ (10 equiv), THF, 0 °C to rt</td>
<td>50% conversion to 267</td>
</tr>
<tr>
<td>4</td>
<td>LiBH₄ (20 equiv), 1:1 THF/MeOH, 0 °C to rt</td>
<td>full conversion to give 267</td>
</tr>
<tr>
<td>5</td>
<td>LiAlH₄ (5 equiv), THF, 0 °C to rt</td>
<td>full conversion to give 267</td>
</tr>
<tr>
<td>6</td>
<td>LiAlH₄ (3 equiv), THF, 0 °C to rt</td>
<td>full conversion to give 266 as major product</td>
</tr>
</tbody>
</table>

The cyclic α-hydroxyamide 268 containing the TIPS protecting group was tested for the oxidation reaction to give the corresponding α-hydroxy amide 269. The results were shown in Table 4. The DMP oxidation in THF at room temperature could not complete the conversion of starting material, only 20% of product were obtained (entry 1). The PCC oxidation gave lower yield than DMP oxidation (entry 2). Swern oxidation and Parikh-Doering oxidation gave the complex mixture (entries 3 and 4). On the other hand, IBX oxidation in DMSO gave no reaction. The DMP oxidation was selected for further optimization. With high loading of DMP in the reaction, the higher yields were observed (entries 6-9). Running the reaction at higher temperature (60 °C) was help to accelerate the reaction to the completion and gave the product in good yield (entry 10).

The side chain acid 277 was prepared for the coupling reaction with the macrocycle 269. It was prepared from L-2-aminobutyric acid (271) and L-isoleucine (273) (Scheme 41). The diazotization of L-isoleucine converted the α-amino acid to α-hydroxy acid (274) in 75% yield with the retention of configuration. The present hydroxyl group was protected with TBS to give carboxylic acid 275 in good yield. It was coupled with the L-2-Aminobutyric acid methyl ester hydrochloride (272) to give compound 276 in 83% yield. The hydrolysis of methyl ester to carboxylic acid 277 was obtained in quantitative yield.
Table 3. Optimization of macrocyclization conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv of TFA/pyridine</th>
<th>Solvent</th>
<th>Concentration [M]</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6/12</td>
<td>CH₂Cl₂</td>
<td>0.01</td>
<td>268 (59%) and 266 (28%) were isolated</td>
</tr>
<tr>
<td>2</td>
<td>6/12</td>
<td>CHCl₃</td>
<td>0.01</td>
<td>268 (55%) and 266 (28%) were isolated.</td>
</tr>
<tr>
<td>3</td>
<td>6/12</td>
<td>THF</td>
<td>0.01</td>
<td>268 (52%) and 266 (32%) were isolated.</td>
</tr>
<tr>
<td>4</td>
<td>6/12</td>
<td>dioxane</td>
<td>0.01</td>
<td>268 (47%) and 266 (33%) were isolated.</td>
</tr>
<tr>
<td>5</td>
<td>6/12</td>
<td>toluene</td>
<td>0.01</td>
<td>slow conversion</td>
</tr>
<tr>
<td>6</td>
<td>6/12</td>
<td>MeOH</td>
<td>0.01</td>
<td>slow conversion</td>
</tr>
<tr>
<td>7</td>
<td>2/4</td>
<td>CH₂Cl₂</td>
<td>0.01</td>
<td>slow conversion</td>
</tr>
<tr>
<td>8</td>
<td>3/6</td>
<td>CH₂Cl₂</td>
<td>0.01</td>
<td>slow conversion</td>
</tr>
<tr>
<td>9</td>
<td>5/10</td>
<td>CH₂Cl₂</td>
<td>0.01</td>
<td>268 (52%) and 266 (32%) were isolated</td>
</tr>
<tr>
<td>10</td>
<td>8/16</td>
<td>CH₂Cl₂</td>
<td>0.01</td>
<td>268 (52%) and 266 (30%) were isolated</td>
</tr>
<tr>
<td>11</td>
<td>10/20</td>
<td>CH₂Cl₂</td>
<td>0.01</td>
<td>268 (40%) and 266 (43%) were isolated</td>
</tr>
<tr>
<td>12</td>
<td>6/12</td>
<td>CH₂Cl₂</td>
<td>0.02</td>
<td>268 (63%) and 266 (25%) were isolated</td>
</tr>
<tr>
<td>13</td>
<td>6/12</td>
<td>CH₂Cl₂</td>
<td>0.03</td>
<td>268 + 266 + other product</td>
</tr>
<tr>
<td>14</td>
<td>6/12</td>
<td>CH₂Cl₂</td>
<td>0.05</td>
<td>268 + 266 + other product</td>
</tr>
<tr>
<td>15</td>
<td>6/12</td>
<td>CH₂Cl₂</td>
<td>0.1</td>
<td>268 + 266 + other product</td>
</tr>
<tr>
<td>16</td>
<td>6/12</td>
<td>CH₂Cl₂</td>
<td>0.005</td>
<td>slow conversion</td>
</tr>
<tr>
<td>17</td>
<td>6/12</td>
<td>CH₂Cl₂</td>
<td>0.001</td>
<td>slow conversion</td>
</tr>
</tbody>
</table>
### Table 4. Optimization of the oxidation conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMP (1.5 equiv), THF, 0 °C to rt, 24 h</td>
<td>not complete, 20% of product was obtained</td>
</tr>
<tr>
<td>2</td>
<td>PCC (1.5 equiv), THF, 0 °C to rt, 24 h</td>
<td>not complete, 12% of product was obtained</td>
</tr>
<tr>
<td>3</td>
<td>Swern oxidation, 24 h</td>
<td>not complete, complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>Parikh-Doering oxidation, 24 h</td>
<td>not complete, complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>IBX (1.5 equiv), DMSO, 0 °C to rt, 24 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td>DMP (2.0 equiv), THF, 0 °C to rt, 24 h</td>
<td>not complete, 20% of product was obtained</td>
</tr>
<tr>
<td>7</td>
<td>DMP (4.0 equiv), THF, 0 °C to rt, 24 h</td>
<td>not complete, 26% of product was obtained</td>
</tr>
<tr>
<td>8</td>
<td>DMP (6.0 equiv), THF, 0 °C to rt, 24 h</td>
<td>not complete, 41% of product was obtained</td>
</tr>
<tr>
<td>9</td>
<td>DMP (10.0 equiv), THF, 0 °C to rt, 24 h</td>
<td>full conversion, 79% of product was obtained</td>
</tr>
<tr>
<td>10</td>
<td>DMP (5.0 equiv), THF, 60 °C, 24 h</td>
<td>full conversion, 72% of product was obtained</td>
</tr>
</tbody>
</table>

![Scheme 41. Preparation of side chain carboxylic acid 277.](image)
To connect the side chain carboxylic acid 277 to the cyclic peptide 269, the deprotection of Boc using HCl in dioxane smoothly gave amine salt 270 which was directly coupled with the freshly prepared carboxylic acid 277 to give the protected jamaicensamide A (278) in 81% yield (Scheme 42). Attempts to deprotect TIPS and TBS protecting groups with various conditions failed to give the target molecule. Deprotection using the fluorine sources including TBAF, TASF, HF-pyridine, HF-NEt₃, CsF and KF gave the complex mixture. No desired product was observed. Deprotection under the strong acidic conditions also gave the same results.

Scheme 42. Coupling reaction of side chain acid with macrocycle.

We also prepared the cyclic compound with a milder silyl protecting group, TBS, (compound 279) to try the deprotection in the last step. The structure was shown in Figure 19. The synthetic route was similar to compound 278. The deprotection of this compound is still on going.

Figure 19. The TBS protected jamaicensamide A.
We also decided to change the protecting groups that having the different deprotection process to the silyl enol ethers. The allyl group is the good choice because its deprotection conditions based on the palladium chemistry. The structure of this compound (280) was depicted in Figure 20. The synthetic route was similar to compound 278.

![Figure 20. The allyl protected jamaicensamidem A.](image)

Various deprotection conditions were employed to cleave the allyl groups. Most of conditions using the palladium in catalytic amount gave no reaction. This molecule contained many amide groups together with a $\alpha$-ketoamide which could be problematic for the palladium to selective coordinate with the allyl groups instead of the amide bonds. Higher loading of palladium did not help, the starting material started to decomposed. Some of reactions were shown in Table 5.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh)$_3$ (10-50 mol%), morpholine, CH$_2$:Cl$_2$, H$_2$:O, rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>10% Pd/C, 10% KOH in MeOH, rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>10% Pd/C, PTSA, MeOH, rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$ (10 mol% to 1.1 equiv), PPh$_3$, HCOOH, rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PPh)$_3$ (10 mol% to 1.1 equiv), K$_2$CO$_3$, MeOH, rt</td>
<td>no reaction</td>
</tr>
</tbody>
</table>
Table 5. Deprotection of allyl groups (cont).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Pd(PPh₃)₄ (1.1 equiv), morpholine, CH₂Cl₂, H₂O, rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>7</td>
<td>Pd(PPh₃)₄ (2.0 equiv), morpholine, CH₂Cl₂, H₂O, rt</td>
<td>start to decompose</td>
</tr>
<tr>
<td>8</td>
<td>Pd(PPh₃)₄ (10 mol%), morpholine, CH₂Cl₂, H₂O, reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>9</td>
<td>Pd(PPh₃)₄ (1.1 equiv), morpholine, CH₂Cl₂, H₂O, reflux</td>
<td>start to decompose</td>
</tr>
<tr>
<td>10</td>
<td>Pd(PPh₃)₄ (1.1 equiv), K₂CO₃, MeOH, reflux</td>
<td>start to decompose</td>
</tr>
<tr>
<td>11</td>
<td>Pd(PPh₃)₄ (2 mol%), NaBH₄ (2.0 equiv), THF, 0 °C to rt</td>
<td>complex mixture</td>
</tr>
<tr>
<td>12</td>
<td>Pd(PPh₃)₂Cl₂ (10 mol%), NaBH₄ (2.0 equiv), THF, 0 °C to rt</td>
<td>complex mixture</td>
</tr>
<tr>
<td>13</td>
<td>Pd(OH)₂/C (10 mol%), MeOH or 2PrOH or 2BuOH, rt or reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>14</td>
<td>Pd(PPh₃)₄ (5-20 mol%), 1,3-dimethylbarbituric acid (2.0 equiv), MeOH, rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>15</td>
<td>Pd(PPh₃)₄ (1.0 equiv), 1,3-dimethylbarbituric acid (2.0 equiv), MeOH, rt</td>
<td>start to decompose</td>
</tr>
</tbody>
</table>
2.3 Conclusion

To apply our strategy on the macrocyclization of $\omega$-isocyanaldehyde in the total synthesis of a natural product. The 24-membered cyclic peptide jamaicensamide A was selected to be studied. The construction of a reactive precursor $\omega$-isocyanaldehyde $\textbf{D}$ was prepared through the peptide coupling reactions between L-norvaline, L-proline, L-ornithine, 5-hydroxy-L-tryptophan and a thiazole fragment $\textbf{F}$. The $\omega$-isocyanaldehyde $\textbf{D}$ smoothly underwent the Passerini reaction to afford the cyclic peptide in satisfactory yield. To complete the total synthesis of jamaicensamide A, the last step deprotection of protecting groups have to be further investigated.

Scheme 43. Outline for the total synthesis of jamaicensamide A.
Chapter 3  
Supporting Information

3.1 General Information

Reagents and solvents were purchased from commercial sources. More sensitive compounds were stored in a desiccator or glove-box if required. Reagents were used without further purification unless otherwise noted.

All reactions were performed under argon (or nitrogen) and stirring unless otherwise noted. When needed, glassware was dried in an oven (T°>100 °C) or under vacuum with a heat gun (T°>200 °C).

When solvents are indicated as dry they were either purchased as such, distilled prior to use or were dried by a passage through a column of anhydrous alumina or copper using a Puresolv MD 5 from Innovative Technology Inc., based on the Grubbs’ design.

Flash column chromatography was performed using Silicycle SiliaFlash® P60 230-400 mesh. Reactions were monitored using Merck Kieselgel 60F254 aluminium plates. TLCs were visualized by UV fluorescence (254 nm) then one of the following: KMnO₄, 2,4-dinitrophenol solution.

NMR spectra were recorded on a Brüker AvanceIII-400, Brüker Avance-400 or Brüker DPX-400 spectrometer at room temperature, ¹H frequency is at 400.13 MHz, ¹³C frequency is at 100.62 MHz. Chemical shifts (δ) were reported in parts per million (ppm) relative to residual solvent peaks rounded to the nearest 0.01 for proton and 0.1 for carbon (ref: CHCl₃ [¹H: 7.26, ¹³C: 77.16 ppm]). Coupling constants (J) were reported in Hz to the nearest 0.1 Hz. Peak multiplicity was indicated as follows s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Attribution of peaks was done using the multiplicities and integrals of the peaks.

IR spectra were recorded in a Jasco FT/IR-4100 spectrometer outfitted with a PIKE technology MIRacleTM ATR accessory as neat films compressed onto a Zinc Selenide window or a Perkin Elmer Spectrum BX FT-IR. The spectra are reported in cm⁻¹. Abbreviations used are: w (weak), m (medium), s (strong) and br (broad).

Mass spectra were determined with a Waters ACQUITY H-class UPLC/MS ACQ-SQD by electron ionization (EI positive and negative) or a Finnigan TSQ7000 by electrospray ionization (ESI+). The
accurate masses were done by the mass spectrometry service of the EPFL by ESI-TOF using a QTOF Ultima from Waters.
3.2 Macrocyclization of \(\omega\)-Isocyanoaldehydes

3.2.1 Synthesis of starting materials

Compound 84 was prepared in three steps from tryptamine (81).

**tert-Butyl 3-(2-formamidoethyl)-1H-indole-1-carboxylate (83)**

A solution of tryptamine (81) (8.01 g, 50 mmol, 1.0 equiv) in dry ethyl formate (30 mL, 1.67 M) was heated to reflux and stirred for 21 h. The solution was cooled to room temperature and evaporated to dryness to give 82 as brown oil which was used for the next step without any purification.

To a solution of crude 82 (50 mmol, 1.0 equiv) and DMAP (152.7 mg, 1.25 mmol, 0.025 equiv) in dry DMF (150 mL) was added a solution of Boc\(_2\)O (10.9 g, 50 mmol, 1.0 equiv) in dry DMF (50 mL) dropwise. The resulting solution was stirred at room temperature for 24 h. After completion of the reaction, water was added and the mixture was extracted with EtOAc. The combined organic layers were washed with water (3 times) and brine, dried over Na\(_2\)SO\(_4\), filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO\(_2\), 2% to 5% MeOH/CH\(_2\)Cl\(_2\)) to yield 83 in 75% yield (10.75 g, 37.3 mmol) as yellow solid.

The spectral data were in accordance with those reported in the literature.\(^{23}\)

**tert-Butyl 3-(2-formamidoethyl)-2-(tributylstannyl)-1H-indole-1-carboxylate (84)**

To a solution of tetramethylpiperidine (6.6 mL, 39.1 mmol, 2.3 equiv) in dry THF (70 mL) was added \(n\)-BuLi (2.2 M, 19.3 mL, 42.5 mmol, 2.5 equiv) dropwise at -78 °C. After stirring at -78 °C for 10 minutes, a solution of 83 (4.90 g, 17.0 mmol, 1.0 equiv) in dry THF (15 mL) was added dropwise and the solution was stirred at -78 °C for 1 h. After that time, Bu\(_3\)SnCl (13.8 mL, 51.0 mmol, 3.0 equiv) was added dropwise and the resulting solution was stirred at -78 °C for 1 h. The mixture was quenched with water at -78 °C and allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na\(_2\)SO\(_4\), filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO\(_2\), 5% to 30% EtOAc/PE + 3% NEt\(_3\)) to yield 84 in 75% yield (7.41 g, 12.8 mmol) as yellowish viscous oil.
1H NMR (400 MHz, CD$_3$OD) δ 8.04 (s, 1H), 7.94 (d, $J = 7.7$ Hz, 1H), 7.60 (d, $J = 7.0$ Hz, 1H), 7.27 – 7.17 (m, 2H), 3.42 (t, $J = 7.7$ Hz, 2H), 2.96 (t, $J = 7.6$ Hz, 2H), 1.71 (s, 9H), 1.59 – 1.47 (m, 6H), 1.39 – 1.30 (m, 6H), 1.16 – 1.11 (m, 6H), 0.88 (t, $J = 7.3$ Hz, 9H).

13C NMR (101 MHz, CD$_3$OD) δ 163.7, 153.9, 140.2, 138.8, 133.5, 130.6, 124.9, 123.4, 119.4, 116.4, 85.4, 40.4, 39.0, 30.4, 28.5, 28.4, 14.1, 14.0.

The spectral data were in accordance with those reported in the literature.

**Synthesis of 5-hexenoic acid (102)**

According to a reported procedure,$^{34}$ to a suspension of NaH (60% dispersion in mineral oil, 440.0 mg, 11.0 mL, 1.1 equiv) in dry THF (40 mL) was added diethyl malonate (S2) (1.67 mL, 11.0 mmol, 1.1 equiv) dropwise at 0 °C. The mixture was stirred at 0 °C for 15 min, then at room temperature for 30 min before being cooled again to 0 °C. A solution of 4-bromo-1-butene (S1) (1.35 g, 10.0 mmol, 1.0 equiv) in dry THF (10 mL) was added dropwise. The resulting mixture was allowed to warm to room temperature and was heated to reflux for 20 h. After completion, the mixture was allowed to cool to room temperature and quenched with water. The layers were separated and the aqueous layer was extracted with Et$_2$O. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO$_2$, 5% Et$_2$O/PE) to yield S3 in 86% yield (1.85 g, 8.63 mmol) as colorless oil ($R_f = 0.27$ (10% Et$_2$O/PE)).

1H NMR (400 MHz, CDCl$_3$) δ 5.77 (ddt, $J = 16.9$, 10.1, 6.6 Hz, 1H), 5.09 – 4.97 (m, 2H), 4.19 (q, $J = 7.1$ Hz, 1H), 3.35 (t, $J = 7.3$ Hz, 1H), 2.13 – 2.07 (m, $J = 6.9$ Hz, 2H), 2.02 – 1.97 (m, $J = 7.3$ Hz, 2H), 1.26 (t, $J = 7.1$ Hz, 6H).

13C NMR (101 MHz, CDCl$_3$) δ 169.6, 137.0, 116.1, 61.5, 51.4, 31.4, 28.0, 14.2.

5-Hexenoic acid (102)

According to a reported procedure,$^{27}$ to a solution of diester S3 (1.71 g, 8.0 mmol, 1.0 equiv) in EtOH (40 mL) was added 10% aqueous NaOH (9.6 mL). After heating the mixture to reflux for 6 h, the mixture was allowed to cool to room temperature and EtOH was removed. The aqueous layer was acidified with 2 M HCl to pH~1 and extracted with Et$_2$O. The combined organic layers were washed with brine, dried
over Na$_2$SO$_4$, filtered and evaporated to dryness to give the diacid intermediate. The crude diacid was dissolved in DMSO (10 mL) and the resulting solution was stirred at 120 °C for 4 h. The mixture was allowed to cool to room temperature, diluted with Et$_2$O, and washed with brine (3 times). The organic layers were dried over Na$_2$SO$_4$, filtered and evaporated to dryness to afford 102 in 95% yield (868.6 mg, 7.61 mmol) as colorless liquid.

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.93 (br s, 1H), 5.78 (ddt, $J = 16.9$, 10.3, 6.7 Hz, 1H), 5.09 – 4.96 (m, 2H), 2.37 (t, $J = 7.5$ Hz, 2H), 2.12 (q, $J = 7.1$ Hz, 2H), 1.75 (p, $J = 7.5$ Hz, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 180.1, 137.6, 115.7, 33.4, 33.1, 23.9.

**Synthesis of 6-heptenoic acid (103)**

6-Heptenenitrile (S4)

According to a reported procedure, to a solution of potassium cyanide (716.3 mg, 11.0 mmol, 2.2 equiv) in DMSO (40 mL) was added a solution of 6-bromo-1-hexene (110) (815.3 mg, 5.0 mmol, 1.0 equiv) in DMSO (10 mL). The resulting solution was stirred at 100 °C for 3 h. The mixture was allowed to cool to room temperature, quenched with water and extracted with Et$_2$O. The combined organic layers were washed with water (3 times) and brine, dried over Na$_2$SO$_4$, filtered and evaporated to dryness to give S4 in 96% yield (522.5 mg, 4.79 mmol) as colorless liquid.

$^1$H NMR (400 MHz, CDCl$_3$) δ 5.77 (ddt, $J = 16.9$, 10.2, 6.7 Hz, 1H), 5.07 – 4.94 (m, 2H), 2.34 (t, $J = 7.0$ Hz, 2H), 2.09 (qt, $J = 6.9$, 1.4 Hz, 2H), 1.71 – 1.63 (m, 2H), 1.59 – 1.51 (m, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 137.7, 119.8, 115.5, 32.9, 27.8, 24.8, 17.1.

6-Heptenoic acid (103)

According to a reported procedure, to a solution of nitrile S4 (409.4 mg, 3.75 mmol, 1.0 equiv) in EtOH (19 mL) was added 10% aqueous NaOH (4.5 mL). After heating the mixture to reflux overnight, the mixture was allowed to cool to room temperature and EtOH was removed. The aqueous layer was acidified with 2 M HCl to pH~1 and extracted with Et$_2$O. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered and evaporated to dryness to give 103 in 90% yield (430.7 mg, 3.36 mmol) as colorless liquid.
1H NMR (400 MHz, CDCl3) δ 5.79 (ddt, J = 16.9, 10.1, 6.6 Hz, 1H), 5.01 (dq, J = 17.2, 1.8 Hz, 1H), 4.96 (dq, J = 10.1, 1.5 Hz, 1H), 2.36 (t, J = 7.5 Hz, 2H), 2.08 (qt, J = 7.2, 1.5 Hz, 2H), 1.69 – 1.62 (m, 2H), 1.49 – 1.41 (m, 2H).

13C NMR (101 MHz, CDCl3) δ 180.0, 138.4, 114.9, 34.0, 33.5, 28.4, 24.2.

Synthesis of 7-octenoic acid (104)

Diethyl 2-(hex-5-en-1-yl)malonate (S5)

To a suspension of NaH (60% dispersion in mineral oil, 220.0 mg, 5.5 mL, 1.1 equiv) in dry THF (10 mL) was added diethyl malonate (S2) (0.84 mL, 5.5 mmol, 1.1 equiv) dropwise at 0 °C. The mixture was stirred at 0 °C for 15 min, then at room temperature for 30 min before being cooled again to 0 °C. A solution of 6-bromo-1-hexene (110) (0.67 mL, 5.0 mmol, 1.0 equiv) in dry THF (10 mL) was added dropwise. The resulting mixture was allowed to warm to room temperature and was heated to reflux for 15 h. After completion, the mixture was allowed to cool to room temperature and quenched with water. The layers were separated and the aqueous layer was extracted with Et2O. The combined organic layers were washed with brine, dried over Na2SO4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO2, 5% Et2O/PE) to yield S5 in 76% yield (923.4 mg, 3.81 mmol) as colorless oil (Rf = 0.29 (10% Et2O/PE)).

1H NMR (400 MHz, CDCl3) δ 5.78 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 4.99 (dq, J = 17.2, 1.7 Hz, 1H), 4.93 (ddt, J = 10.2, 2.2, 1.2 Hz, 1H), 4.19 (qd, J = 7.1, 0.9 Hz, 4H), 3.31 (t, J = 7.5 Hz, 1H), 2.08 – 2.01 (m, 2H), 1.92 – 1.86 (m, 2H), 1.46 – 1.39 (m, 2H), 1.38 – 1.31 (m, 2H), 1.26 (t, J = 7.1 Hz, 6H).

13C NMR (101 MHz, CDCl3) δ 169.7, 138.7, 114.7, 61.4, 52.2, 33.5, 28.7, 28.6, 26.9, 14.2.

7-Octenoic acid (104)

To a solution of diester S5 (654.5 mg, 2.7 mmol, 1.0 equiv) in EtOH (13.5 mL) was added 10% aqueous NaOH (3.3 mL). After heating the mixture to reflux overnight, the mixture was allowed to cool to room temperature and EtOH was removed. The aqueous layer was acidified with 2 M HCl to pH~1 and extracted with Et2O. The combined organic layers were washed with brine, dried over Na2SO4, filtered and evaporated to dryness to give the diacid intermediate. The crude diacid was dissolved in DMSO (6 mL) and the resulting solution was stirred at 120 °C for 4 h. The mixture was allowed to cool to room
temperature, diluted with Et₂O, and washed with brine (3 times). The organic layers were dried over Na₂SO₄, filtered and evaporated to dryness to afford 104 in quantitative yield (387.0 mg, 2.72 mmol) as colorless liquid.

¹H NMR (400 MHz, CDCl₃) δ 5.80 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.00 (dt, J = 17.1, 1.8 Hz, 1H), 4.94 (d, J = 10.2 Hz, 1H), 2.36 (t, J = 7.5 Hz, 2H), 2.05 (q, J = 7.0 Hz, 2H), 1.65 (p, J = 7.4 Hz, 2H), 1.43 – 1.36 (m, 4H).

¹³C NMR (101 MHz, CDCl₃) δ 179.7, 138.9, 114.6, 34.0, 33.7, 28.6, 24.7.

General procedure for the synthesis of the thioesters

To a solution of the carboxylic acid (1.0 equiv) in dry CH₂Cl₂ (0.3 M) was added trifluoroacetic anhydride (TFAA) (1.0 equiv). The solution was stirred at room temperature for 2 h and thiophenol was then added. The resulting solution was stirred at 50 °C for 21 h. The mixture was allowed to cool to room temperature and quenched with saturated NaHCO₃. The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO₂) to afford the thioester product.

S-Phenyl pent-4-enethioate (85)

Yield: 84%, Rₐ = 0.47 (5% Et₂O/PE)

¹H NMR (400 MHz, CDCl₃) δ 7.42 (s, 5H), 5.85 (ddt, J = 16.8, 10.2, 6.5 Hz, 1H), 5.11 (dq, J = 17.1, 1.6 Hz, 1H), 5.06 (dq, J = 10.2, 1.4 Hz, 1H), 2.77 (t, J = 7.2 Hz, 2H), 2.51 – 2.44 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 196.8, 136.1, 134.6, 129.5, 129.3, 127.8, 116.1, 42.9, 29.5.

HRMS (ESI/QTOF) m/z: [M + H]⁺ calcd for C₁₁H₁₁OS⁺ 193.0682; found 193.0684.
**S-Phenyl hex-5-enethioate (86)**

Yield: 80%, Eluent: 2% Et₂O/PE, Rₖ = 0.47 (5% Et₂O/PE)

$^1$H NMR (400 MHz, CDCl₃) δ 7.41 (s, 5H), 5.79 (ddt, $J = 17.0$, 10.2, 6.7 Hz, 1H), 5.13 – 4.94 (m, 2H), 2.67 (t, $J = 7.5$ Hz, 2H), 2.14 (q, $J = 7.1$ Hz, 2H), 1.82 (p, $J = 7.4$ Hz, 2H).

$^{13}$C NMR (101 MHz, CDCl₃) δ 197.5, 137.6, 134.6, 129.5, 129.3, 128.0, 115.8, 43.0, 33.0, 24.8.

HRMS (ESI/QTOF) m/z: [M + H]$^+$ calcd for C₁₂H₁₅OS$^+$ 207.0838; found 207.0841.

IR: ν (cm$^{-1}$) 3072, 2925, 1702, 1477, 1438, 993, 912, 742, 719, 686.

**S-Phenyl hept-6-enethioate (87)**

Yield: 74%, Eluent: 2% Et₂O/PE, Rₖ = 0.50 (5% Et₂O/PE)

$^1$H NMR (400 MHz, CDCl₃) δ 7.41 (s, 5H), 5.80 (ddt, $J = 16.9$, 10.1, 6.6 Hz, 1H), 5.02 (dd, $J = 17.2$, 1.7 Hz, 1H), 4.97 (d, $J = 10.2$ Hz, 1H), 2.67 (t, $J = 7.4$ Hz, 2H), 2.09 (q, $J = 7.1$ Hz, 2H), 1.74 (p, $J = 7.5$ Hz, 2H), 1.47 (p, $J = 7.7$ Hz, 2H).

$^{13}$C NMR (101 MHz, CDCl₃) δ 197.6, 138.4, 134.6, 129.5, 129.3, 128.0, 115.0, 43.7, 33.5, 28.3, 25.2.

HRMS (ESI/QTOF) m/z: [M + Na]$^+$ calcd for C₁₃H₁₆NaOS$^+$ 243.0814; found 243.0821.

IR: ν (cm$^{-1}$) 3075, 2928, 2858, 1703, 1474, 1438, 990, 905, 740, 686.

**S-Phenyl oct-7-enethioate (88)**

Yield: 73%, Eluent: 2% Et₂O/PE, Rₖ = 0.50 (5% Et₂O/PE)

$^1$H NMR (400 MHz, CDCl₃) δ 7.41 (s, 5H), 5.81 (ddt, $J = 16.9$, 10.2, 6.7 Hz, 1H), 5.01 (dq, $J = 17.2$, 1.7 Hz, 1H), 4.95 (ddt, $J = 10.1$, 2.3, 1.2 Hz, 1H), 2.66 (t, $J = 7.5$ Hz, 2H), 2.06 (q, $J = 6.7$ Hz, 2H), 1.73 (p, $J = 7.3$ Hz, 2H), 1.47 – 1.35 (m, 4H).

$^{13}$C NMR (101 MHz, CDCl₃) δ 197.6, 138.9, 134.6, 129.4, 129.3, 128.0, 114.6, 43.8, 33.6, 28.6, 28.5, 25.6.

HRMS (ESI/QTOF) m/z: [M + Na]$^+$ calcd for C₁₄H₁₈NaOS$^+$ 257.0971; found 257.0974.
General procedure A: synthesis of the C2 acylated tryptamine derivatives

A mixture of 84 (1.1 equiv), the thioester (1.0 equiv), Pd$_2$dba$_3$ (0.1 equiv), AsPh$_3$ (0.1 equiv) and CuDPP (2.0 equiv) in dry degassed 3:1 hexanes/THF (0.067 M) was stirred at room temperature for 6 h. After completion of reaction, the mixture was filtered through a pad of Celite (rinsed with EtOAc). The filtrate was washed with 2 M HCl, 10% NH$_4$OH and brine, dried over Na$_2$SO$_4$, filtered and evaporated to dryness. Purification of the crude mixture by column chromatography (SiO$_2$) afforded the desired compound.

**tert-Butyl 3-(2-formamidoethyl)-2-(pent-4-enoyl)-1H-indole-1-carboxylate (89)**

Yield: 71%, Eluent: 1:1 EtOAc/PE, $R_f = 0.30$ (2:1 EtOAc/PE)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.15 (s, 1H), 8.02 (dt, $J = 8.4, 0.9$ Hz, 1H), 7.59 (dt, $J = 7.8, 1.0$ Hz, 1H), 7.45 (ddd, $J = 8.4, 7.2, 1.2$ Hz, 1H), 7.32 (ddd, $J = 8.0, 7.2, 1.0$ Hz, 1H), 7.13 (br s, 1H), 5.80 (ddt, $J = 16.8, 10.2, 6.5$ Hz, 1H), 5.02 (apparent dq, $J = 17.1, 1.7$ Hz, 1H), 4.97 (apparent dq, $J = 10.2, 1.4$ Hz, 1H), 3.59 – 3.55 (m, 2H), 2.89 – 2.83 (m, 4H), 2.47 – 2.41 (m, 2H), 1.68 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 198.3, 162.0, 150.2, 136.9, 136.4, 136.3, 129.0, 127.5, 124.0, 122.6, 120.5, 116.0, 115.8, 85.9, 42.9, 38.5, 29.3, 28.3, 23.2.

HRMS (ESI/QTOF) $m/z$: [M + Na]$^+$ calcd for C$_{23}$H$_{28}$N$_2$NaO$_4$ $^+$ 393.1785; found 393.1779.

IR: $\nu$ (cm$^{-1}$) 3304, 2979, 2931, 1725, 1676, 1450, 1369, 1323, 1231, 1146, 839, 749.
**tert-Butyl 3-(2-formamidoethyl)-2-(hex-5-enoyl)-1H-indole-1-carboxylate (90)**

Yield: 66%, Eluent: 1:1 EtOAc/PE, R₇ = 0.32 (1:1 EtOAc/PE)

$^1$H NMR (400 MHz, CDCl₃) δ 8.15 (s, 1H), 8.02 (d, $J = 8.4$ Hz, 1H), 7.59 (d, $J = 7.8$ Hz, 1H), 7.44 (ddd, $J = 8.3$, 7.4, 1.2 Hz, 1H), 7.32 (t, $J = 7.5$ Hz, 1H), 7.11 (br s, 1H), 5.76 (ddt, $J = 17.0$, 10.1, 6.7 Hz, 1H), 5.03 – 4.93 (m, 2H), 3.60 – 3.54 (m, 2H), 2.88 (t, $J = 6.5$ Hz, 2H), 2.74 (t, $J = 7.6$ Hz, 2H), 2.10 (q, $J = 7.1$ Hz, 2H), 1.78 (p, $J = 7.4$ Hz, 2H), 1.68 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl₃) δ 198.9, 161.9, 150.1, 137.8, 136.5, 136.2, 128.9, 127.3, 123.9, 122.2, 120.4, 115.9, 115.7, 85.8, 43.1, 38.3, 33.3, 28.3, 24.1, 23.1.

HRMS (nanochip-ESI/LTQ-Orbitrap) $m/z$: [M + Na]$^+$ calcld for C$_{22}$H$_{28}$N$_2$O$_4$Na + 407.1941; found 407.1936.

IR: ν (cm$^{-1}$) 3298, 2976, 2931, 1727, 1672, 1450, 1369, 1321, 1231, 1143, 834, 767, 749.

**tert-Butyl 3-(2-formamidoethyl)-2-(hept-6-enoyl)-1H-indole-1-carboxylate (91)**

Yield: 68%, Eluent: 2:1 EtOAc/PE, R₇ = 0.34 (2:1 EtOAc/PE)

$^1$H NMR (400 MHz, CDCl₃) δ 8.15 (s, 1H), 8.02 (d, $J = 8.4$ Hz, 1H), 7.59 (d, $J = 7.8$ Hz, 1H), 7.44 (t, $J = 7.9$ Hz, 1H), 7.31 (t, $J = 7.6$ Hz, 1H), 7.12 (br s, 1H), 5.76 (ddt, $J = 16.6$, 10.7, 5.3 Hz, 1H), 5.01 – 4.91 (m, 2H), 3.59 – 3.54 (m, 2H), 2.88 (t, $J = 5.8$ Hz, 2H), 2.74 (t, $J = 7.6$ Hz, 2H), 2.05 (q, $J = 7.0$ Hz, 2H), 1.70 – 1.65 (m, 2H), 1.67 (s, 9H), 1.42 (p, $J = 7.5$ Hz, 2H).

$^{13}$C NMR (101 MHz, CDCl₃) δ 198.9, 161.8, 150.0, 138.4, 136.4, 136.1, 128.9, 127.3, 123.8, 122.1, 120.4, 115.8, 114.9, 85.7, 43.6, 38.3, 33.5, 28.5, 28.2, 24.5, 23.1.

HRMS (nanochip-ESI/LTQ-Orbitrap) $m/z$: [M + Na]$^+$ calcld for C$_{23}$H$_{30}$N$_2$NaO$_4$ + 421.2098; found 421.2090.
IR: $\nu$ (cm$^{-1}$) 1727, 1679, 1367, 1321, 1228, 1143, 746.

tert-Butyl 3-(2-formamidoethyl)-2-(oct-7-enoyl)-1H-indole-1-carboxylate (92)

Yield: 63%, Eluent: 1:1 EtOAc/PE, $R_f = 0.55$ (1:1 EtOAc/PE)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.15 (s, 1H), 8.02 (d, $J = 8.4$ Hz, 1H), 7.59 (d, $J = 7.8$ Hz, 1H), 7.44 (t, $J = 7.8$ Hz, 1H), 7.31 (t, $J = 7.5$ Hz, 1H), 7.16 (brs, 1H), 5.76 (ddt, $J = 16.9, 10.1, 6.6$ Hz, 1H), 4.97 (dq, $J = 17.1, 1.9$ Hz, 1H), 4.92 (dd, $J = 10.2, 1.2$ Hz, 1H), 3.59 – 3.55 (m, 2H), 2.88 (t, $J = 6.5$ Hz, 2H), 2.73 (t, $J = 7.6$ Hz, 2H), 2.03 (q, $J = 6.9$ Hz, 2H), 1.67 (s, 9H), 1.66 – 1.62 (m, 2H), 1.43 – 1.28 (m, 4H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 199.1, 161.9, 150.1, 138.8, 136.5, 136.1, 128.9, 127.3, 123.8, 122.1, 120.4, 115.8, 114.6, 85.7, 43.7, 38.3, 33.6, 28.8, 28.7, 28.2, 24.9, 23.1.

HRMS (nanochip-ESI/LTQ-Orbitrap) $m/z$: [M + Na]$^+$ calcd for C$_{24}$H$_{32}$N$_2$NaO$_4$ + 435.2254; found 435.2245.

IR: $\nu$ (cm$^{-1}$) 3311, 2976, 2931, 2856, 1727, 1682, 1450, 1369, 1318, 1255, 1231, 1143, 749.

General procedure B: conversion of the alkenes to the aldehydes$^{27}$

To a solution of the alkene (1.0 equiv) in 3:1 acetone/H$_2$O (0.13 M) was added K$_2$OsO$_4$·2H$_2$O (0.05 equiv) and NMO (2.0 equiv). The resulting mixture was stirred at room temperature for 5 h. Acetone was removed and the mixture was extracted with CH$_2$Cl$_2$. The combined organic layer was washed with brine, dried over Na$_2$SO$_4$, filtered and evaporated to dryness to give the crude diol. The crude diol was dissolved in 4:1 THF/H$_2$O (0.13 M). NaIO$_4$ (2.0 equiv) was added and the resulting mixture was stirred at room temperature for 1 h. The mixture was filtered through a pad of Celite (rinsed with CH$_2$Cl$_2$) and the filtrate was washed with brine, dried over Na$_2$SO$_4$, filtered and evaporated to dryness. Purification of the crude mixture by column chromatography (SiO$_2$) afforded the desired compound.
**tert-Butyl 3-(2-formamidoethyl)-2-(4-oxobutanoyl)-1H-indole-1-carboxylate (93)**

Yield: 93%, Eluent: 3% MeOH/CH₂Cl₂, Rᵣ = 0.32 (5% MeOH/CH₂Cl₂)

¹H NMR (400 MHz, CDCl₃) δ 9.87 (s, 1H), 8.13 (s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.44 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 6.87 (br s, 1H), 3.58 (q, J = 5.6 Hz, 2H), 3.09 (t, J = 6.3 Hz, 2H), 2.95 (t, J = 6.3 Hz, 2H), 2.92 (t, J = 6.1 Hz, 2H), 1.68 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 200.6, 196.7, 161.8, 150.3, 136.1, 136.0, 129.1, 127.4, 123.9, 122.9, 120.6, 115.9, 85.9, 38.7, 38.2, 35.7, 28.3, 23.1.

HRMS (ESI/QTOF) m/z: [M + Na]⁺ calcld for C₂₀H₂₄N₂O₅Na + 395.1577; found 395.1576.

IR: ν (cm⁻¹) 3319, 2979, 2934, 1718, 1676, 1450, 1387, 1369, 1321, 1143, 1086, 1028, 836, 767, 752.

**tert-Butyl 3-(2-formamidoethyl)-2-(5-oxopentanoyl)-1H-indole-1-carboxylate (94)**

Yield: 95%, Eluent: 2% to 5% MeOH/CH₂Cl₂, Rᵣ = 0.29 (5% MeOH/CH₂Cl₂)

¹H NMR (400 MHz, CDCl₃) δ 9.79 (t, J = 1.3 Hz, 1H), 8.14 (s, 1H), 7.98 (dt, J = 8.4, 0.9 Hz, 1H), 7.59 (dt, J = 7.8, 1.0 Hz, 1H), 7.43 (ddd, J = 8.4, 7.2, 1.3 Hz, 1H), 7.31 (ddd, J = 8.0, 7.3, 1.0 Hz, 1H), 6.98 (br s, 1H), 3.59 – 3.54 (m, 2H), 2.92 – 2.84 (m, 2H), 2.79 (t, J = 7.1 Hz, 2H), 2.59 (td, J = 7.0, 1.3 Hz, 2H), 2.05 (p, J = 7.0 Hz, 2H), 1.68 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 201.9, 197.9, 161.8, 150.2, 136.3, 136.0, 128.9, 127.3, 123.9, 122.2, 120.4, 115.9, 85.9, 42.8, 42.4, 38.3, 38.2, 28.3, 23.2, 17.0.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + Na]⁺ calcld for C₂₁H₂₆N₂NaO₅⁺ 409.1734; found 409.1727.

IR: ν (cm⁻¹) 1718, 1679, 1359, 1321, 1139, 755.
**tert-Butyl 3-(2-formamidoethyl)-2-(6-oxohexanoyl)-1H-indole-1-carboxylate (95)**

Yield: 83%, Eluent: 2% to 5% MeOH/CH₂Cl₂, Rf = 0.26 (5% MeOH/CH₂Cl₂)

1H NMR (400 MHz, CDCl₃) δ 9.76 (t, J = 1.5 Hz, 1H), 8.14 (s, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.44 (t, J = 7.7 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.07 (br s, 1H), 3.56 (q, J = 5.1 Hz, 2H), 2.88 (t, J = 6.3 Hz, 2H), 2.76 (t, J = 7.0 Hz, 2H), 1.75 – 1.62 (m, 4H), 1.68 (s, 9H).

13C NMR (101 MHz, CDCl₃) δ 202.2, 198.3, 161.9, 150.1, 136.3, 128.9, 127.3, 123.9, 122.3, 120.4, 115.8, 85.8, 43.7, 43.3, 38.3, 28.2, 24.4, 23.1, 21.7.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + Na]⁺ calcd for C₂₂H₂₈N₂NaO₅⁺ 423.1890; found 423.1881.

IR: ν (cm⁻¹) 1718, 1679, 1367, 1324, 1143, 755.

**tert-Butyl 3-(2-formamidoethyl)-2-(7-oxoheptanoyl)-1H-indole-1-carboxylate (96)**

Yield: 82%, Eluent: 2% MeOH/CH₂Cl₂, Rf = 0.34 (5% MeOH/CH₂Cl₂)

1H NMR (400 MHz, CDCl₃) δ 9.74 (t, J = 1.7 Hz, 1H), 8.14 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.04 (br s, 1H), 3.55 (q, J = 6.2 Hz, 2H), 2.87 (t, J = 6.2 Hz, 2H), 2.74 (t, J = 7.6 Hz, 2H), 2.43 (td, J = 7.2, 1.6 Hz, 2H), 1.77 – 1.68 (m, 2H), 1.67 (s, 9H), 1.66 – 1.58 (m, 2H), 1.41 – 1.33 (m, 2H).

13C NMR (101 MHz, CDCl₃) δ 202.5, 198.7, 161.9, 150.1, 136.4, 136.1, 128.9, 127.3, 123.8, 122.2, 120.4, 115.8, 85.8, 43.7, 43.4, 38.3, 28.7, 28.2, 24.7, 23.1, 21.8.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + Na]⁺ calcd for C₂₃H₃₀N₂NaO₅⁺ 437.2047; found 437.2038.
General procedure C: dehydration of the formamides to the isocyanides

To a solution of the formamide (1.0 equiv) in dry CH$_2$Cl$_2$ (0.3 M) was added NEt$_3$ (5.0 equiv) and POCl$_3$ (1.5 equiv) dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 3 h. After completion of reaction, the mixture was quenched with saturated Na$_2$CO$_3$ at -78 °C, allowed to warm to room temperature and extracted with Et$_2$O. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered and evaporated to dryness to provide the ω-isocyanoaldehyde which was used for the next step without further purification.

**tert-Butyl 3-(2-isocyanoethyl)-2-(4-oxobutanoyl)-1H-indole-1-carboxylate (97)**

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.86 (t, $J$ = 0.7 Hz, 1H), 8.01 (dt, $J$ = 8.4, 0.9 Hz, 1H), 7.64 (dt, $J$ = 7.9, 1.1 Hz, 1H), 7.45 (ddd, $J$ = 8.4, 7.2, 1.3 Hz, 1H), 7.34 (ddd, $J$ = 8.1, 7.3, 1.0 Hz, 1H), 3.72 (t, $J$ = 7.2 Hz, 2H), 3.12 – 3.08 (m, 4H), 2.95 (t, $J$ = 6.4 Hz, 2H), 1.67 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 200.6, 195.6, 157.2 (t, $J$ = 5.4 Hz), 150.1, 136.2, 136.0, 129.1, 127.3, 123.9, 120.8, 120.4, 115.9, 85.9, 42.3 (t, $J$ = 6.6 Hz), 38.6, 35.9, 28.2, 24.7.

HRMS (ESI/QTOF) $m/z$: [M + H]$^+$ calcd for C$_{20}$H$_{23}$N$_2$O$_4$ 355.1652; found 355.1653.

IR: $\nu$ (cm$^{-1}$) 2976, 2922, 2142, 1727, 1682, 1454, 1366, 1323, 1258, 1237, 1143, 1079, 752.
** tert-Butyl 3-(2-isocyanoethyl)-2-(5-oxopentanoyl)-1H-indole-1-carboxylate (98)**

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.79 (t, $J = 1.3$ Hz, 1H), 8.00 (dt, $J = 8.5$, 0.9 Hz, 1H), 7.61 (dt, $J = 7.9$, 1.0 Hz, 1H), 7.44 (ddd, $J = 8.5$, 7.2, 1.3 Hz, 1H), 7.33 (ddd, $J = 8.0$, 7.2, 1.0 Hz, 1H), 3.72 (t, $J = 7.1$ Hz, 2H), 3.07 (t, $J = 7.1$ Hz, 2H), 2.81 (t, $J = 7.2$ Hz, 2H), 2.59 (td, $J = 7.0$, 1.3 Hz, 2H), 2.06 (p, $J = 7.1$ Hz, 2H), 1.67 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 202.0, 196.7, 157.2, 150.1, 136.6, 135.8, 128.9, 127.2, 123.9, 120.2, 120.0, 115.9, 85.9, 42.9, 42.6, 42.3 (t, $J = 6.2$ Hz), 28.2, 24.8, 16.9.

HRMS (ESI/QTOF) $m/z$: [M + Na]$^+$ calcd for C$_{21}$H$_{24}$N$_2$NaO$_4$ 391.1628; found 391.1629.

IR: ν (cm$^{-1}$) 2979, 2929, 2146, 1722, 1689, 1450, 1394, 1369, 1321, 1257, 1236, 1143, 1079, 750.

** tert-Butyl 3-(2-isocyanoethyl)-2-(6-oxohexanoyl)-1H-indole-1-carboxylate (99)**

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.77 (s, 1H), 8.03 (d, $J = 8.4$ Hz, 1H), 7.62 (d, $J = 7.9$ Hz, 1H), 7.44 (t, $J = 7.8$ Hz, 1H), 7.33 (t, $J = 7.5$ Hz, 1H), 3.72 (t, $J = 7.1$ Hz, 2H), 3.07 (t, $J = 7.2$ Hz, 2H), 2.78 (t, $J = 6.9$ Hz, 2H), 2.48 (t, $J = 6.8$ Hz, 2H), 1.77 – 1.70 (m, 2H), 1.67 (s, 9H), 1.20 (t, $J = 7.2$ Hz, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 202.3, 197.1, 157.2, 150.0, 136.6, 135.9, 128.9, 127.2, 123.9, 120.2, 120.1, 115.9, 85.9, 46.2, 43.8, 43.6, 42.3 (t, $J = 5.7$ Hz), 28.2, 24.9, 24.2, 21.7.

HRMS (QTOF) $m/z$: [M + Na]$^+$ calcd for C$_{22}$H$_{26}$N$_2$NaO$_4$ 405.1790; found 405.1790.

IR: ν (cm$^{-1}$) 2979, 2931, 2146, 1727, 1685, 1454, 1367, 1321, 1257, 1236, 1147, 1078, 750.
**tert-Butyl 3-(2-isocyanoethyl)-2-(7-oxoheptanoyl)-1H-indole-1-carboxylate (100)**

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.75 (s, 1H), 8.03 (d, \(J = 8.4\) Hz, 1H), 7.62 (d, \(J = 7.8\) Hz, 1H), 7.44 (t, \(J = 7.8\) Hz, 1H), 7.33 (t, \(J = 7.5\) Hz, 1H), 3.72 (t, \(J = 7.1\) Hz, 2H), 3.07 (t, \(J = 7.2\) Hz, 2H), 2.75 (t, \(J = 7.6\) Hz, 2H), 2.44 (t, \(J = 7.3\) Hz, 2H), 1.73 – 1.60 (m, 4H), 1.66 (s, 9H), 1.43 – 1.35 (m, 2H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 202.6, 197.4, 157.0, 150.0, 136.6, 135.9, 128.9, 127.2, 123.8, 120.2, 120.1, 115.8, 85.8, 45.9, 43.8, 43.7, 42.3 (t, \(J = 5.9\) Hz), 28.8, 28.2, 24.9, 24.5, 21.9.

HRMS (nanochip-ESI/LTQ-Orbitrap) \(m/z\): [M + Na]\(^+\) calcd for C\(_{23}\)H\(_{28}\)N\(_2\)NaO\(_4\) 419.1941; found 419.1933.

IR: \(\nu\) (cm\(^{-1}\)) 2979, 2937, 2275, 1727, 1681, 1517, 1455, 1367, 1321, 1261, 1147, 1008, 755, 719.

**tert-Butyl (E)-3-(2-formamidoethyl)-2-(3-oxoprop-1-en-1-yl)-1H-indole-1-carboxylate (106)**

According to a reported procedure,\(^3\)\(^6\) acrolein (105) (2.1 mL, 32.0 mmol, 4.0 equiv), t-BuO\(_2\)Bz (2.1 mL, 11.2 mmol, 1.4 equiv) and Pd(OAc)\(_2\) (179.6 mg, 0.8 mmol, 0.1 equiv) were added to a solution of 83 in dioxane (12 mL) and AcOH (4 mL). The resulting mixture was stirred at 70 °C for 24 h. The mixture was allowed to cool to room temperature, neutralized with saturated NaHCO\(_3\) and filtered through a pad of Celite (rinsed with EtOAc). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na\(_2\)SO\(_4\), filtered and evaporated to dryness. The crude product was purified by flash column chromatography (1% to 2% MeOH/CH\(_2\)Cl\(_2\)) to afford compound 106 in 56% yield (1.53 g, 4.46 mmol) as yellow solid (\(R_f = 0.39\) (5% MeOH/CH\(_2\)Cl\(_2\))).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) Major rotamer: \(\delta\) 9.71 (d, \(J = 7.7\) Hz, 1H), 8.18 (s, 1H), 8.09 (d, \(J = 8.5\) Hz, 1H), 7.99 (d, \(J = 16.1\) Hz, 1H), 7.73 (d, \(J = 7.8\) Hz, 1H), 7.39 (t, \(J = 7.7\) Hz, 1H), 7.30 (t, \(J = 7.5\) Hz, 1H), 6.46 (dd, \(J = 16.2, 7.7\) Hz, 1H), 6.20 (br s, 1H), 3.56 (q, \(J = 7.1\) Hz, 2H), 3.08 (t, \(J = 7.5\) Hz, 2H), 1.68 (s, 9H).
\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) Major rotamer: \(\delta 193.9, 161.7, 150.4, 143.8, 136.8, 131.8, 129.9, 129.6, 126.9, 123.7, 122.8, 120.1, 115.9, 85.3, 38.3, 28.3, 25.4.\)

HRMS (ESI/QTOF) \(m/z\): [M + Na]\(^+\) calcd for C\(_{19}\)H\(_{22}\)N\(_2\)NaO\(_4\)\(^+\) 365.1472; found 365.1470.

IR: \(\nu (\text{cm}^{-1})\) 1724, 1673, 1616, 1550, 1455, 1357, 1321, 1228, 1143, 1120, 746.

According to a reported procedure,\(^6\) to a solution of the unsaturated aldehyde 106 (684.8 mg, 2.0 mmol, 1.0 equiv) in dry CH\(_2\)Cl\(_2\) (20 mL) was added 10% Pd/C (94.0 mg). The resulting mixture was stirred under H\(_2\) balloon (1 atm) at room temperature for 6 h. The mixture was filtered through a pad of Celite (rinsed with CH\(_2\)Cl\(_2\)) and the filtrate was evaporated to dryness. The crude mixture was purified by flash column chromatography (2% to 3% MeOH/CH\(_2\)Cl\(_2\)) to afford compound 107 in 35% yield (239.4 mg, 0.70 mmol) as yellowish oil together with compound 108 in 60% yield (412.5 mg, 1.20 mmol) as yellowish oil.

**tert-Butyl 3-(2-formamidoethyl)-2-(3-oxopropyl)-1H-indole-1-carboxylate (107)**

Yield: 35%, Eluent: 2% to 3% MeOH/CH\(_2\)Cl\(_2\), \(R_f = 0.37\) (5% MeOH/CH\(_2\)Cl\(_2\))

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 9.83 (t, J = 1.1 \text{ Hz}, 1\text{H}), 8.15 (s, 1\text{H}), 8.05 (dd, J = 7.3, 1.3 \text{ Hz}, 1\text{H}), 7.60 – 7.48 (m, 1\text{H}), 7.32 – 7.21 (m, 2\text{H}), 5.71 (br s, 1\text{H}), 3.54 (q, J = 6.8 \text{ Hz}, 2\text{H}), 3.33 (t, J = 7.3 \text{ Hz}, 2\text{H}), 2.96 (t, J = 7.1 \text{ Hz}, 2\text{H}), 2.84 (td, J = 7.3, 1.2 \text{ Hz}, 2\text{H}), 1.68 (s, 9\text{H}).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 201.3, 161.3, 150.3, 136.3, 135.8, 129.4, 124.1, 122.9, 118.2, 115.9, 115.8, 84.2, 44.2, 38.1, 28.2, 24.1, 19.4.

HRMS (ESI/QTOF) \(m/z\): [M + Na]\(^+\) calcd for C\(_{19}\)H\(_{22}\)N\(_2\)NaO\(_4\)\(^+\) 367.1628; found 367.1629.

IR: \(\nu (\text{cm}^{-1})\) 2977, 2931, 1722, 1660, 1454, 1367, 1324, 1249, 1224, 1159, 1132, 730.
**tert-Butyl 3-(2-formamidoethyl)-2-(3-hydroxypropyl)-1H-indole-1-carboxylate (108)**

Yield: 60%, Eluent: 2% to 3% MeOH/CH$_2$Cl$_2$, $R_f = 0.37$ (5% MeOH/CH$_2$Cl$_2$)

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.14 (s, 1H), 8.07 (d, $J = 7.9$ Hz, 1H), 7.49 (d, $J = 6.9$ Hz, 1H), 7.28 – 7.21 (m, 2H), 5.86 (br s, 1H), 3.69 (t, $J = 5.9$ Hz, 2H), 3.56 (q, $J = 7.2$ Hz, 2H), 3.17 (t, $J = 7.3$ Hz, 2H), 2.96 (t, $J = 7.4$ Hz, 2H), 2.29 (br s, 1H), 1.90 (p, $J = 6.6$ Hz, 2H), 1.69 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 161.6, 150.7, 138.3, 136.0, 129.7, 123.9, 122.9, 118.1, 115.9, 115.5, 84.2, 61.8, 38.4, 33.2, 28.4, 24.4, 22.9.

HRMS (ESI/QTOF) $m/z$: [M + Na]$^+$ calcd for C$_{19}$H$_{26}$N$_2$NaO$_4$ 369.1785; found 369.1784.

IR: ν (cm$^{-1}$) 3853, 3729, 3704, 3367, 1727, 1668, 1454, 1363, 1160, 1132, 752.

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**tert-Butyl 3-(2-isocyanooethyl)-2-(3-oxopropyl)-1H-indole-1-carboxylate (109)**

Prepared according to general procedure C from compound 107 (218.9 mg, 0.64 mmol).

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.84 (s, 1H), 8.07 (d, $J = 7.8$ Hz, 1H), 7.41 (dd, $J = 6.8$, 1.4 Hz, 1H), 7.29 (td, $J = 7.3$, 1.4 Hz, 1H), 7.26 – 7.24 (m, 1H), 3.63 (t, $J = 7.1$ Hz, 2H), 3.36 (t, $J = 7.2$ Hz, 2H), 3.15 (t, $J = 7.1$ Hz, 2H), 2.91 (t, $J = 7.3$ Hz, 2H), 1.69 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 201.1, 156.9, 150.3, 137.4, 136.0, 128.8, 124.3, 123.0, 117.7, 116.1, 114.2, 84.5, 45.8, 44.6, 28.3, 24.7, 19.4.

HRMS (ESI/QTOF) $m/z$: [M + Na]$^+$ calcd for C$_{19}$H$_{22}$N$_2$NaO$_3$ 349.1528; found 349.1525.

IR: ν (cm$^{-1}$) 2979, 2146, 1724, 1454, 1367, 1324, 1276, 1257, 1132, 1079, 752.
tert-Butyl 3-(2-formamidoethyl)-2-(3-(hex-5-en-1-yl oxy)propyl)-1H-indole-1-carboxylate (111)

According to a reported procedure\(^3\), NaH (60% dispersion in mineral oil, 127.6 mg, 3.19 mmol, 1.1 equiv) was added to a solution of primary alcohol 108 (1.00 g, 2.90 mmol, 1.0 equiv) in dry DMF (10 mL) at 0 °C. After stirring at the same temperature for 30 min, a solution of 6-bromo-1-hexene (110) (520.2 mg, 3.19 mmol, 1.1 equiv) in dry DMF (4.5 mL) was added dropwise at 0 °C. The resulting mixture was allowed to warm to room temperature and stir for 15 h. The mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with water (3 times) and brine, dried over Na\(_2\)SO\(_4\), filtered and evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO\(_2\), 2% MeOH/CH\(_2\)Cl\(_2\)) to afford compound 111 in 35% yield (438.2 mg, 1.02 mmol) as yellowish oil (R\(_f\) = 0.35 (5% MeOH/CH\(_2\)Cl\(_2\))).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 8.09 (d, J = 1.6 Hz, 1H), 7.55 (dt, J = 7.8, 0.9 Hz, 1H), 7.28 (dt, J = 8.2, 1.0 Hz, 1H), 7.17 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.09 (ddd, J = 7.9, 7.0, 1.0 Hz, 1H), 5.86 – 5.72 (m, 2H), 5.05 – 4.96 (m, 2H), 4.12 (t, J = 6.2 Hz, 2H), 4.07 (t, J = 7.6 Hz, 2H), 3.56 (q, J = 6.7 Hz, 2H), 2.96 (t, J = 7.0 Hz, 2H), 2.89 – 2.83 (m, 2H), 2.14 – 2.08 (m, 2H), 1.98 – 1.90 (m, 2H), 1.81 – 1.72 (m, 2H), 1.53 – 1.47 (m, 2H), 1.49 (s, 9H).

\(^13\)C NMR (101 MHz, CDCl\(_3\)) δ 161.2, 153.5, 138.1, 136.2, 136.1, 127.8, 121.1, 119.2, 118.3, 115.1, 109.4, 108.0, 82.2, 66.0, 43.3, 38.8, 33.3, 29.7, 29.5, 27.8, 26.3, 24.6, 20.8.

HRMS (ESI/QTOF) \(m/z\): [M + Na]\(^+\) calcd for C\(_{25}\)H\(_{36}\)N\(_2\)O\(_4\)Na + 451.2567; found 451.2576.

IR: ν (cm\(^{-1}\)) 3853, 1737, 1675, 1276, 1251, 755.

\textit{tert-Butyl 3-(2-formamidoethyl)-2-(3-((5-oxopentyl)oxy)propyl)-1H-indole-1-carboxylate (112)}

Prepared according to general procedure B from alkene 111 (362.3 mg, 0.85 mmol) to give aldehyde 112 in 66% yield (242.6 mg, 0.56 mmol) as brown oil (R\(_f\) = 0.26 (5% MeOH/CH\(_2\)Cl\(_2\))) after purification by flash column chromatography (SiO\(_2\), 2% MeOH/CH\(_2\)Cl\(_2\)).
$^1$H NMR (400 MHz, CDCl$_3$) δ 9.74 (t, $J = 1.4$ Hz, 1H), 8.13 (d, $J = 1.2$ Hz, 1H), 7.55 (d, $J = 7.8$ Hz, 1H), 7.27 (d, $J = 8.0$ Hz, 1H), 7.18 (td, $J = 8.2$, 1.2 Hz, 1H), 7.09 (ddd, $J = 7.9$, 7.0, 1.1 Hz, 1H), 5.68 (br s, 1H), 4.12 – 4.07 (m, 4H), 3.58 (q, $J = 6.7$ Hz, 2H), 2.96 (t, $J = 6.9$ Hz, 2H), 2.85 (t, $J = 7.8$ Hz, 2H), 2.46 (td, $J = 7.1$, 1.4 Hz, 2H), 1.97 – 1.89 (m, 2H), 1.82 – 1.74 (m, 2H), 1.69 – 1.61 (m, 2H), 1.49 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 201.8, 161.3, 153.6, 136.3, 136.2, 127.9, 121.4, 119.5, 118.5, 109.4, 108.5, 82.4, 66.1, 43.5, 43.2, 38.8, 29.9, 29.6, 27.9, 24.7, 21.0, 19.5.

HRMS (nanochip-ESI/LTQ-Orbitrap) $m$/c: [M + H]$^+$ calcd for C$_{24}$H$_{35}$N$_2$O$_5$+ 431.2540; found 431.2531.

IR: ν (cm$^{-1}$) 2929, 1733, 1664, 1465, 1367, 1276, 1255, 1155, 1099, 736.

**tert-Butyl 3-(2-isocyanoethyl)-2-(3-((5-oxopentyl)oxy)propyl)-1$H$-indole-1-carboxylate (113)**

Prepared according to general procedure C from compound **112** (242.6 mg, 0.56 mmol).

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.75 (t, $J = 1.4$ Hz, 1H), 7.46 (d, $J = 7.8$ Hz, 1H), 7.27 (d, $J = 8.7$ Hz, 1H), 7.19 (ddd, $J = 8.2$, 7.0, 1.2 Hz, 1H), 7.11 (td, $J = 7.4$, 6.9, 1.1 Hz, 1H), 4.12 – 4.08 (m, 4H), 3.60 (t, $J = 7.4$ Hz, 2H), 3.14 (t, $J = 7.3$ Hz, 2H), 2.92 – 2.88 (m, 2H), 2.47 (td, $J = 7.0$, 1.4 Hz, 2H), 1.98 – 1.91 (m, 2H), 1.82 – 1.75 (m, 2H), 1.72 – 1.64 (m, 2H), 1.50 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 201.7, 156.2, 153.6, 136.8, 136.2, 127.3, 121.6, 119.6, 117.9, 109.6, 106.9, 82.4, 65.9, 43.5, 43.3, 42.2, 29.8, 29.6, 27.9, 25.4, 21.0, 19.6.

HRMS (ESI/QTOF) $m$/c: [M + Na]$^+$ calcd for C$_{26}$H$_{37}$N$_2$O$_5$Na+ 435.2254; found 435.2247.

IR: ν (cm$^{-1}$)
N-(3-Formamidopropyl)-2-hydroxybenzamide (116)

A mixture of methyl salicylate (114) (3.04 g, 20.0 mmol, 1.0 equiv) and 1,3-diaminopropane (58) (1.67 mL, 20.0 mmol, 1.0 equiv) was stirred vigorously at 110 °C for 3 h. The mixture was allowed to cool to room temperature and evaporate to dryness to give the adduct 115, which was formylated with ethyl formate (12.0 mL, 1.67 M) at 75 °C for 21 h. After cooling down to room temperature, the reaction solution was evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO$_2$, 2% to 5% MeOH/CH$_2$Cl$_2$) to afford compound 116 in 52% yield (over 2 steps) (2.31 g, 10.47 mmol) as yellowish viscous oil ($R_f = 0.19$ (5% MeOH/CH$_2$Cl$_2$)).

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.28 (s, 1H), 7.72 (br s, 1H), 7.57 (d, $J = 8.0$ Hz, 1H), 7.38 (t, $J = 7.8$ Hz, 1H), 6.96 (d, $J = 8.3$ Hz, 1H), 6.87 (t, $J = 7.6$ Hz, 1H), 6.24 (br s, 1H), 3.49 (q, $J = 6.0$ Hz, 2H), 3.42 (q, $J = 6.1$ Hz, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 170.5, 162.7, 161.6, 134.3, 126.0, 119.0, 118.5, 114.4, 35.5, 35.0, 29.5.

HRMS (nanochip-ESI/LTQ-Orbitrap) $m/z$: [M + Na]$^+$ calcld for C$_{11}$H$_{14}$N$_2$NaO$_3$ $^+$ 245.0897; found 245.0892.

IR: v (cm$^{-1}$) 3318, 1660, 1637, 1594, 1540, 1490, 1378, 1234, 755.

N-(3-Formamidopropyl)-2-(hex-5-en-1-yloxy)benzamide (121)

According to a reported procedure$^6$, to a solution of phenol 116 (881.0 mg, 4.0 mmol, 1.0 equiv) in acetone (20 mL) were added K$_2$CO$_3$ (1.11 g, 8.0 mmol, 2.0 equiv) and 6-bromo-1-hexene (110) (0.59 mL, 4.4 mmol, 1.1 equiv). The resulting mixture was heated to reflux and stirred for 14 h. The mixture was allowed to cool to room temperature and evaporated to dryness. Water was added to the residue and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na$_2$SO$_4$, filtered and evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO$_2$, 2% to 3% MeOH/CH$_2$Cl$_2$) to afford compound 121 in 94% yield (1.15 g, 3.78 mmol) as colorless viscous oil ($R_f = 0.42$ (5% MeOH/CH$_2$Cl$_2$)).
1H NMR (400 MHz, CDCl$_3$) $\delta$ 8.18 (s, 1H), 8.12 (d, $J = 7.8$ Hz, 1H), 8.12 (br s, 1H), 7.41 (t, $J = 7.8$ Hz, 1H), 7.04 (t, $J = 7.6$ Hz, 1H), 6.97 (br s, 1H), 5.79 (ddt, $J = 16.9, 9.8, 6.6$ Hz, 1H), 5.07 – 4.95 (m, 2H), 4.13 (t, $J = 6.0$ Hz, 2H), 3.52 (q, $J = 6.3$ Hz, 2H), 3.32 (q, $J = 6.3$ Hz, 2H), 2.13 (q, $J = 7.2$ Hz, 2H), 1.88 (p, $J = 6.7$ Hz, 2H), 1.73 (p, $J = 6.2$ Hz, 2H), 1.56 (p, $J = 7.5$ Hz, 2H).

13C NMR (101 MHz, CDCl$_3$) $\delta$ 166.6, 161.5, 157.0, 138.0, 133.0, 132.1, 121.3, 121.2, 115.3, 112.4, 68.9, 36.3, 34.5, 33.3, 30.0, 28.6, 25.5.

HRMS (nanochip-ESI/LTQ-Orbitrap) $m/z$: [M + H]$^+$ calcd for C$_{17}$H$_{25}$N$_2$O$_3$ 305.1860; found 305.1866.

IR: $\nu$ (cm$^{-1}$) 3853, 3731, 3031, 1641, 1523, 1294, 1234, 755.

6-((6-Bromohexyl)oxy)hex-1-ene (119)

According to a reported procedure, to a suspension of NaH (60% dispersion in mineral oil, 1.60 g, 40.0 mmol, 2.0 equiv) in dry THF (110 mL) was added a solution of 5-hexen-1-ol (118) (2.00 g, 20.0 mmol, 1.0 equiv) in dry THF (20 mL) dropwise at 0 °C. After stirring the mixture at 0 °C for 30 min, 1,6-dibromohexane (117) (3.03 mL, 20.0 mmol, 1.0 equiv) was added dropwise at 0 °C. The resulting mixture was heated to reflux for 22 h. The mixture was allowed to cool to room temperature and quench with water at 0 °C. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na$_2$SO$_4$, filtered and evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO$_2$, 20% CH$_2$Cl$_2$/PE) to afford compound 119 in 14% yield (727.63 mg, 2.76 mmol) as colorless liquid ($R_f = 0.16$ (20% CH$_2$Cl$_2$/PE)).

1H NMR (400 MHz, CDCl$_3$) $\delta$ 5.81 (ddt, $J = 16.9, 10.2, 6.6$ Hz, 1H), 5.00 (dq, $J = 17.1, 1.8$ Hz, 1H), 4.94 (dq, $J = 10.2, 1.4$ Hz, 1H), 3.43 – 3.38 (m, 6H), 2.07 (q, $J = 7.1$ Hz, 2H), 1.87 (p, $J = 6.9$ Hz, 2H), 1.61 – 1.55 (m, 4H), 1.49 – 1.33 (m, 6H).

13C NMR (101 MHz, CDCl$_3$) $\delta$ 139.0, 114.6, 70.9, 70.8, 34.1, 33.7, 32.9, 29.7, 29.4, 28.2, 25.7, 25.6.

HRMS (nanochip-ESI/LTQ-Orbitrap) $m/z$: [M + H]$^+$ calcd for C$_{12}$H$_{24}$BrO$^+$ 263.1005; found 263.1000.

IR: $\nu$ (cm$^{-1}$) 2933.2, 2857, 1637, 1455, 1436, 1116, 993, 910, 719.
According to a reported procedure, to a solution of phenol 116 (506.6 mg, 2.3 mmol, 1.0 equiv) in acetone (11.5 mL) were added K₂CO₃ (635.8 mg, 4.6 mmol, 2.0 equiv) and bromide 119 (666.0 mg, 2.53 mmol, 1.1 equiv). The resulting mixture was heated to reflux and stirred for 17 h. The mixture was allowed to cool to room temperature and evaporated to dryness. Water was added to the residue and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered and evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO₂, 2% to 3% MeOH/CH₂Cl₂) to afford compound 122 in 89% yield (825.1 mg, 2.04 mmol) as colorless viscous oil (R_f = 0.23 (5% MeOH/CH₂Cl₂)).

1H NMR (400 MHz, CDCl₃) δ 8.21 (s, 1H), 8.17 (br s, 1H), 8.15 (dd, J = 7.8, 1.9 Hz, 1H), 7.44 (ddd, J = 8.3, 7.4, 1.9 Hz, 1H), 7.07 (td, J = 7.6, 1.0 Hz, 1H), 7.00 (br s, 1H), 6.96 (d, J = 8.3 Hz, 1H), 5.80 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.00 (dq, J = 17.1, 1.7 Hz, 1H), 4.94 (ddt, J = 10.2, 2.2, 1.2 Hz, 1H), 4.14 (t, J = 6.5 Hz, 2H), 3.55 (q, J = 6.3 Hz, 2H), 3.43 – 3.38 (m, 4H), 3.35 (q, J = 6.1 Hz, 2H), 2.10 – 2.03 (m, 2H), 1.96 – 1.85 (m, 4H), 1.75 (p, J = 6.2 Hz, 2H), 1.64 – 1.55 (m, 4H), 1.51 – 1.42 (m, 4H).

13C NMR (101 MHz, CDCl₃) δ 166.8, 161.6, 157.1, 138.9, 133.2, 121.4, 121.2, 114.7, 112.4, 71.0, 70.7, 69.1, 36.3, 34.5, 33.7, 30.2, 29.9, 29.33, 29.26, 26.3, 26.1, 25.6.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + Na]^+ calcd for C₂₃H₃₆N₂NaO₄ 427.2567; found 427.2563.

IR: ν (cm⁻¹) 3855, 3602, 2931, 2859, 1643, 1525, 1230, 1106, 755.

N-(3-Formamidopropyl)-2-((5-oxopentyloxy)oxy)benzamide (123)

Prepared according to general procedure B from alkene 121 (761.0 mg, 2.5 mmol) to give aldehyde 123 in 90% yield (687.1 mg, 2.24 mmol) as yellowish oil (R_f = 0.23 (5% MeOH/CH₂Cl₂)) after purification by flash column chromatography (SiO₂, 3% to 5% MeOH/CH₂Cl₂).

1H NMR (400 MHz, CDCl₃) δ 9.83 (s, 1H), 8.21 (s, 1H), 8.16 (br dd, J = 7.8, 1.9 Hz, 2H), 7.44 (ddd, J = 8.7, 7.4, 1.9 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.95 (br d, J = 8.3 Hz, 2H), 4.15 (t, J = 5.9 Hz, 2H),
3.58 (q, \( J = 6.3 \text{ Hz}, 2\text{H} \)), 3.36 (q, \( J = 6.0 \text{ Hz}, 2\text{H} \)), 2.61 (t, \( J = 6.5 \text{ Hz}, 2\text{H} \)), 1.94 – 1.87 (m, 2H), 1.86 – 1.74 (m, 4H).

\(^{13}\text{C} \text{ NMR} (101 \text{ MHz, CDCl}_3) \delta 201.8, 166.6, 161.7, 157.0, 133.1, 132.4, 121.5, 121.4, 112.3, 68.7, 43.4, 36.5, 34.7, 30.1, 28.7, 18.8.

HRMS (nanochip-ESI/LTQ-Orbitrap) \( m/z \): [M + H]\(^+\) calcd for C\(_{16}\)H\(_{23}\)N\(_2\)O\(_4\) \( 307.1652 \); found 307.1647.

IR: \( \nu (\text{cm}^{-1}) \) 3392, 3284, 2937, 2883, 1643, 1535, 1517, 1299, 1236, 719.

\( \text{N-}(3\text{-Formamidopropyl})\text{-2-}((6\text{-}((5\text{-oxopentyl)}\text{oxy})\text{hexyl)}\text{oxy})\text{benzamide (124)} \)

Prepared according to general procedure B from alkene 122 (768.7 mg, 1.9 mmol) to give aldehyde 124 in 69% yield (532.0 mg, 1.31 mmol) as yellowish oil (\( R_f = 0.28 \) (5% MeOH/CH\(_2\)Cl\(_2\))) after purification by flash column chromatography (SiO\(_2\), 3% to 5% MeOH/CH\(_2\)Cl\(_2\)).

\(^{1}\text{H} \text{ NMR} (400 \text{ MHz, CDCl}_3) \delta 9.74 (s, 1\text{H}), 8.18 (s, 1\text{H}), 8.12 (dd, \( J = 8.0, 1.9 \text{ Hz}, 1\text{H} \)), 8.12 (brs, 1\text{H}), 7.41 (t, \( J = 7.5 \text{ Hz}, 1\text{H} \)), 7.04 (t, \( J = 7.5 \text{ Hz}, 1\text{H} \)), 6.95 (d, \( J = 8.3 \text{ Hz}, 2\text{H} \)), 4.12 (t, \( J = 6.5 \text{ Hz}, 3\text{H} \)), 3.52 (q, \( J = 6.3 \text{ Hz}, 2\text{H} \)), 3.43 – 3.31 (m, 6H), 2.44 (t, \( J = 7.1 \text{ Hz}, 3\text{H} \)), 1.87 (p, \( J = 6.6 \text{ Hz}, 3\text{H} \)), 1.78 – 1.64 (m, 4H), 1.57 (p, \( J = 6.6 \text{ Hz}, 4\text{H} \)), 1.50 – 1.40 (m, 4H).

\(^{13}\text{C} \text{ NMR} (101 \text{ MHz, CDCl}_3) \delta 202.6, 166.6, 161.6, 157.1, 133.0, 132.1, 121.3, 121.2, 112.4, 70.8, 70.4, 69.0, 43.7, 36.3, 34.5, 30.1, 29.8, 29.2, 26.2, 26.0, 19.0.

HRMS (nanochip-ESI/LTQ-Orbitrap) \( m/z \): [M + Na]\(^+\) calcd for C\(_{22}\)H\(_{34}\)N\(_2\)NaO\(_5\) \( 429.2360 \); found 429.2353.

IR: \( \nu (\text{cm}^{-1}) \) 2940, 2861, 1675, 1648, 1525, 1481, 1297, 1234, 1106, 755.

\( \text{N-}(3\text{-Isocyanopropyl})\text{-2-}((5\text{-oxopentyl)}\text{oxy})\text{benzamide (125)} \)

Prepared according to general procedure C from compound 123 (459.5 mg, 1.5 mmol).
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.84 (s, 1H), 8.19 (d, \(J = 8.1\) Hz, 1H), 8.16 (br s, 1H), 7.44 (t, \(J = 8.1\) Hz, 1H), 7.08 (t, \(J = 7.6\) Hz, 1H), 6.95 (d, \(J = 8.2\) Hz, 1H), 4.15 (t, \(J = 5.4\) Hz, 2H), 3.64 (q, \(J = 5.5\) Hz, 2H), 3.50 (t, \(J = 7.0\) Hz, 2H), 2.63 (t, \(J = 6.3\) Hz, 2H), 2.07 – 2.02 (m, 2H), 1.97 – 1.89 (m, 2H), 1.88 – 1.80 (m, 2H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 201.6, 166.0, 157.0, 156.7 (t, \(J = 5.7\) Hz), 133.1, 132.5, 121.5, 121.3, 112.2, 68.7, 43.4, 39.5 (t, \(J = 6.4\) Hz), 36.7, 29.0, 28.8, 18.8.

HRMS (nanochip-ESI/LTQ-Orbitrap) \(m/z\): [M + H]\(^+\) calcld for C\(_{16}\)H\(_{21}\)N\(_2\)O\(_3\) 289.1547; found 289.1540.

IR: \(\nu\) (cm\(^{-1}\)) 3399, 2933, 2146, 1716, 1646, 1598, 1531, 1482, 1452, 1295, 1232, 755, 719.

\(N\)-(3-Isocyanopropyl)-2-(((6-((5-oxopentyl)oxy)hexyl)oxy)benzamide (126)

Prepared according to general procedure C from compound 124 (487.8 mg, 1.2 mmol).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.76 (t, \(J = 1.7\) Hz, 1H), 8.18 (dd, \(J = 7.8, 1.9\) Hz, 1H), 8.15 (br s, 1H), 7.43 (ddd, \(J = 8.4, 7.3, 1.9\) Hz, 1H), 7.09 – 7.04 (m, 1H), 6.96 (d, \(J = 8.3\) Hz, 1H), 4.14 (t, \(J = 6.6\) Hz, 2H), 3.60 (q, \(J = 6.4\) Hz, 2H), 3.51 (tt, \(J = 6.6, 1.8\) Hz, 2H), 3.46 – 3.39 (m, 4H), 2.46 (td, \(J = 7.2, 1.7\) Hz, 2H), 2.07 – 1.99 (m, 2H), 1.95 – 1.87 (m, 2H), 1.73 – 1.58 (m, 6H), 1.54 – 1.44 (m, 4H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 202.7, 166.0, 157.1, 156.9, 133.1, 132.3, 121.4, 121.1, 112.3, 70.8, 70.4, 69.1, 43.7, 39.4, 36.6, 29.8, 29.3, 29.2, 29.1, 26.2, 26.1, 19.1.

HRMS (ESI/QTOF) \(m/z\): [M + H]\(^+\) calcld for C\(_{22}\)H\(_{33}\)N\(_2\)O\(_4\) 389.2435; found 389.2433.

IR: \(\nu\) (cm\(^{-1}\)) 3397, 2935, 2865, 2146, 1718, 1648, 1598, 1531, 1482, 1450, 1297, 1234, 1106, 1051, 757.

To a solution of 4-pentenoic acid (101) (4.00 g, 40.0 mmol, 2.0 equiv) in dry THF (10 mL) was added 1,1’-carbonyldiimidazole (CDI) (6.49 g, 40.0 mmol, 2.0 equiv) portionwise. The solution was stirred at room temperature for 30 min. A solution of methyl anthranilate (127) (3.02 g, 20.0 mmol, 1.0 equiv) in dry THF (10 mL) was added and the resulting solution was heated to reflux for 24 h. After completion
of reaction, the mixture was allowed to cool to room temperature, quenched with water and extracted with EtOAc. The combined organic layers were washed with saturated NaHCO₃ and brine, dried over Na₂SO₄, filtered and evaporated to dryness to afford methyl 2-(pent-4-enamido)benzoate (128) which was used for the next step without further purification.

To a suspension of NaH (60% dispersion in mineral oil, 880.0 mg, 22.0 mmol, 1.1 equiv) in dry DMF (100 mL) was added a solution of crude 128 in dry DMF (100 mL) dropwise at 0 °C. After stirring at 0 °C for 30 min, benzyl bromide (4.73 mL, 40.0 mmol, 2.0 equiv) was added. The resulting mixture was allowed to warm to room temperature and stir for 17 h. The mixture was quenched with water at 0 °C and extracted with EtOAc. The combined organic layers were washed with water (3 times) and brine, dried over Na₂SO₄, filtered and evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO₂, 10% to 20% EtOAc/PE) to afford compound 129 in 34% yield (over two steps) (2.17 g, 6.71 mmol) as yellowish oil (Rf = 0.29 (20% EtOAc/PE)).

Methyl 2-(pent-4-enamido)benzoate (128)

¹H NMR (400 MHz, CDCl₃) δ 11.09 (br s, 1H), 8.73 (dd, J = 8.5, 1.2 Hz, 1H), 8.02 (dd, J = 8.0, 1.7 Hz, 1H), 7.54 (ddd, J = 8.7, 7.3, 1.7 Hz, 1H), 7.07 (dd, J = 8.3, 7.3, 1.2 Hz, 1H), 5.94 – 5.83 (m, 1H), 5.11 (dq, J = 17.2, 1.5 Hz, 1H), 5.02 (dq, J = 10.3, 1.3 Hz, 1H), 3.93 (s, 3H), 2.58 – 2.47 (m, 4H).

¹³C NMR (101 MHz, CDCl₃) δ 171.5, 168.9, 141.7, 136.8, 134.8, 130.9, 122.5, 120.5, 115.8, 114.9, 52.5, 37.9, 29.5.

HRMS (ESI/QTOF) m/z: [M + Na]⁺ calcd for C₁₃H₁₅NNaO₃⁺ 256.0944; found 256.0945.

IR: ν (cm⁻¹) 3307, 2983, 2956, 1685, 1589, 1519, 1444, 1255, 1159, 1085, 912, 752, 698.

Methyl 2-(N-benzylpent-4-enamido)benzoate (129)

¹H NMR (400 MHz, CDCl₃) δ 7.96 – 7.93 (m, 1H), 7.46 – 7.38 (m, 2H), 7.26 – 7.21 (m, 3H), 7.16 – 7.14 (m, 2H), 6.89 – 6.86 (m, 1H), 5.73 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.29 (d, J = 14.3 Hz, 1H), 4.94 (dq, J = 17.3, 1.8 Hz, 1H), 4.92 – 4.87 (m, 1H), 4.31 (d, J = 14.2 Hz, 1H), 3.77 (s, 3H), 2.41 – 2.33 (m, 2H), 2.13 – 2.00 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 172.1, 166.1, 141.8, 137.8, 137.3, 133.3, 132.0, 131.3, 129.6, 129.5, 128.5, 128.4, 127.5, 115.1, 53.1, 52.7, 34.0, 29.4.

HRMS (ESI/QTOF) m/z: [M + Na]⁺ calcd for C₂₀H₂₁NNaO₃⁺ 346.1414; found 346.1417.
IR: $\nu$ (cm$^{-1}$) 3064, 2948, 1722, 1658, 1598, 1490, 1432, 1396, 1288, 1255, 1191, 1126, 1083, 914, 715, 701.

2-(N-Benzylpent-4-enamido)-N-(3-formamidopropyl)benzamide (131)

A mixture of methyl benzoate (129) (2.13 g, 6.6 mmol, 1.0 equiv) and 1,3-diaminopropane (58) (0.55 mL, 6.6 mmol, 1.0 equiv) was stirred vigorously at 110 °C for 3 h. The mixture was allowed to cool to room temperature and evaporate to dryness to give the adduct 130, which was dissolved in ethyl formate (4.0 mL, 1.67 M). The resulting solution was stirred at 75 °C for 16 h. After cooling down to room temperature, the reaction solution was evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO$_2$, 2% to 3% MeOH/CH$_2$Cl$_2$) to afford compound 131 in 73% yield (over 2 steps) (1.89 g, 4.81 mmol) as yellowish viscous oil ($R_f = 0.27$ (5% MeOH/CH$_2$Cl$_2$)).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.21 (s, 1H), 7.63 (t, $J = 3.2$ Hz, 1H), 7.40 (t, $J = 3.3$ Hz, 2H), 7.26 (d, $J = 2.1$ Hz, 3H), 7.22 – 7.16 (m, 2H), 6.93 (t, $J = 3.4$ Hz, 1H), 6.36 (s, 1H), 6.16 (br t, $J = 6.7$ Hz, 1H), 5.79 – 5.66 (m, 1H), 5.15 (d, $J = 14.1$ Hz, 1H), 4.95 (d, $J = 16.9$ Hz, 1H), 4.90 (d, $J = 10.0$ Hz, 1H), 4.65 (d, $J = 14.1$ Hz, 1H), 3.41 – 3.28 (m, 2H), 3.26 – 3.12 (m, 2H), 2.35 (q, $J = 7.4$ Hz, 2H), 2.23 (dt, $J = 14.9$, 7.2 Hz, 1H), 2.09 (dt, $J = 15.5$, 7.4 Hz, 1H), 1.67 – 1.55 (m, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 172.7, 167.6, 162.0, 139.5, 137.7, 137.2, 135.0, 131.6, 130.4, 129.7, 129.5, 128.7, 127.9, 115.3, 53.4, 36.4, 34.7, 34.1, 29.7, 29.4.

HRMS (ESI/QTOF) $m/z$: [M + Na]$^+$ calcd for C$_{23}$H$_{27}$N$_3$NaO$_3$: 416.1945; found 416.1943.

IR: $\nu$ (cm$^{-1}$) 3674, 3650, 2989, 2901, 1648, 1537, 1508, 1396, 1261, 1068, 761, 749.
2-(N-Benzyl-4-oxobutanamido)-N-(3-formamidopropyl)benzamide (132)

Prepared according to general procedure B from alkene 131 (1.89 g, 4.81 mmol) to give aldehyde 132 in 61% yield (1.17 g, 2.95 mmol) as pale brown oil (Rf = 0.39 (10% MeOH/CH2Cl2)) after purification by flash column chromatography (SiO2, 5% MeOH/CH2Cl2).

1H NMR (400 MHz, CDCl3) δ 9.78 (s, 1H), 8.21 (d, J = 1.2 Hz, 1H), 7.75 (dd, J = 7.6, 1.7 Hz, 1H), 7.41 (td, J = 7.5, 1.3 Hz, 1H), 7.34 (td, J = 7.7, 1.7 Hz, 1H), 7.24 – 7.20 (m, 4H), 7.15 – 7.09 (m, 2H), 6.81 (dd, J = 7.8, 1.3 Hz, 1H), 6.56 (br s, 1H), 5.40 (d, J = 14.1 Hz, 1H), 4.21 (d, J = 14.1 Hz, 1H), 3.48 (q, J = 6.3 Hz, 2H), 3.32 (m, 2H), 3.24 (ddd, J = 19.3, 9.9, 4.1 Hz, 1H), 2.67 (ddd, J = 19.3, 5.9, 3.7 Hz, 1H), 2.41 (ddd, J = 16.8, 9.9, 3.7 Hz, 1H), 2.24 (ddd, J = 16.8, 5.9, 4.0 Hz, 1H), 1.78 (p, J = 6.2 Hz, 2H).

13C NMR (101 MHz, CDCl3) δ 202.6, 171.0, 167.4, 156.7 (t, J = 5.2 Hz), 138.1, 136.4, 134.6, 131.3, 131.1, 130.3, 129.5, 129.0, 128.6, 127.9, 53.0, 39.6 (t, J = 6.5 Hz), 39.4, 37.5, 29.2, 27.8.

HRMS (ESI/QTOF) m/z: [M + Na]+ calcd for C22H25N3NaO4 418.1737; found 418.1738.

IR: ν (cm−1) 3289, 3067, 2934, 2861, 1640, 1444, 1387, 1302, 1264, 776, 727, 700.

2-(N-Benzyl-4-oxobutanamido)-N-(3-isocyanopropyl)benzamide (133)

Prepared according to general procedure C from compound 132 (593.2 mg, 1.5 mmol).

1H NMR (400 MHz, CDCl3) δ 9.78 (s, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.24 – 7.18 (m, 4H), 7.13 - 7.10 (m, 2H), 6.79 (d, J = 7.8 Hz, 1H), 5.36 (d, J = 13.9 Hz, 1H), 4.22 (d, J = 13.9 Hz, 1H), 3.63 - 3.51 (m, 2H), 3.48 (t, J = 6.5 Hz, 2H), 3.24 (ddd, J = 19.3, 10.6, 2.8 Hz, 1H), 2.64 (ddd, J = 19.5, 5.8, 3.1 Hz, 1H), 2.40 (ddd, J = 17.0, 10.5, 2.9 Hz, 1H), 2.20 (dt, J = 16.9, 4.8 Hz, 1H), 2.03 (p, J = 7.2 Hz, 2H).

13C NMR (101 MHz, CDCl3) δ 202.6, 171.0, 167.4, 156.7 (t, J = 5.2 Hz), 138.1, 136.4, 134.6, 131.3, 131.1, 130.3, 129.5, 129.0, 128.6, 127.9, 53.0, 39.6 (t, J = 6.5 Hz), 39.4, 37.5, 29.2, 27.8.
HRMS (ESI/QTOF) $m/z$: [M + Na]$^+$ calcd for C$_{22}$H$_{23}$N$_3$NaO$_3$ $^+$ 400.1632; found 400.1631.

IR: $\nu$ (cm$^{-1}$) 3291, 2929, 2146, 1712, 1646, 1535, 1442, 1407, 1299, 719.

$N$-(3-Formamidopropyl)-3-(hex-5-en-1-yloxy)benzamide (137)

A mixture of methyl 3-hydroxybenzoate (134) (3.04 g, 20.0 mmol, 1.0 equiv) and 1,3-diaminopropane (58) (1.67 mL, 20.0 mmol, 1.0 equiv) was stirred vigorously at 110 °C for 3 h. The mixture was allowed to cool to room temperature and evaporate to dryness to give the adduct 135, which was formylated with ethyl formate (12.0 mL, 1.67 M) at 75 °C for 19 h. After cooling down to room temperature, the reaction solution was evaporated to dryness. A mixture of phenol 136 and diamide compound formed in the first step was obtained. To a solution of this mixture (1.1 g, 5.0 mmol, 1.0 equiv) in acetone (25 mL) were added K$_2$CO$_3$ (1.38 g, 10.0 mmol, 2.0 equiv) and 6-bromo-1-hexene (110) (0.74 mL, 5.5 mmol, 1.1 equiv). The resulting mixture was heated to reflux and stirred for 19 h. The mixture was allowed to cool to room temperature and evaporated to dryness. Water was added to the residue and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na$_2$SO$_4$, filtered and evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO$_2$, 1% to 3% MeOH/CH$_2$Cl$_2$) to afford compound 137 in 56% yield (over three steps) (851.0 mg, 2.80 mmol) as white solid ($R_f = 0.25$ (5% MeOH/CH$_2$Cl$_2$)).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.14 (s, 1H), 7.40 – 7.15 (m, 4H), 6.94 (dd, $J = 8.0$, 2.5 Hz, 1H), 6.72 (br s, 1H), 5.74 (ddt, $J = 17.0$, 10.3, 6.6 Hz, 1H), 4.95 (d, $J = 17.1$ Hz, 1H), 4.89 (d, $J = 10.2$ Hz, 1H), 3.92 (t, $J = 6.5$ Hz, 2H), 3.41 (q, $J = 6.2$ Hz, 2H), 3.29 (q, $J = 6.3$ Hz, 2H), 2.04 (q, $J = 7.3$ Hz, 2H), 1.79 – 1.58 (m, 4H), 1.48 (p, $J = 7.5$ Hz, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 168.1, 162.2, 159.4, 138.5, 135.7, 129.7, 118.8, 118.3, 114.9, 113.0, 68.0, 36.2, 34.7, 33.5, 29.6, 28.7, 25.4.

HRMS (ESI/QTOF) $m/z$: [M + Na]$^+$ calcd for C$_{17}$H$_{24}$N$_2$O$_3$ $^+$ 327.1679; found 327.1680.
IR: ν (cm$^{-1}$) 3297, 3073, 2863, 1641, 1579, 1535, 1486, 1434, 1382, 1301, 1238, 1132, 1031, 998, 910, 750, 717, 688.

For analysis of compound 136, the crude mixture can be purified by flash column chromatography (20% acetone/EtOAc) to yield the pure 136 as a colorless viscous oil ($R_f$ = 0.16 (20% acetone/EtOAc)).

$^1$H NMR (400 MHz, CD$_3$OD) δ 8.04 (s, 1H), 7.25 – 7.18 (m, 3H), 6.93 – 6.87 (m, 1H), 3.36 (t, $J = 6.8$ Hz, 2H), 3.26 (t, $J = 6.8$ Hz, 2H), 1.75 (p, $J = 6.8$ Hz, 2H).

$^{13}$C NMR (101 MHz, CD$_3$OD) δ 170.4, 164.0, 158.8, 137.1, 130.6, 119.5, 119.0, 115.2, 38.1, 36.5, 30.2.

HRMS (ESI/QTOF) $m/z$: [M + Na]$^+$ calcd for C$_{11}$H$_{14}$N$_2$NaO$_3$+$^+$ 245.0897; found 245.0896.

IR: ν (cm$^{-1}$) 3276, 3058, 2931, 2869, 1652, 1536, 1382, 1238, 719.

$N$-(3-Formamidopropyl)-3-((5-oxopentyl)oxy)benzamide (138)

Prepared according to general procedure B from alkene 137 (791.4 mg, 2.6 mmol) to give aldehyde 138 in 76% yield (608.2 mg, 1.99 mmol) as colorless oil ($R_f$ = 0.44 (10% MeOH/CH$_2$Cl$_2$)) after purification by flash column chromatography (SiO$_2$, 5% to 10% MeOH/CH$_2$Cl$_2$).

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.79 (s, 1H), 8.23 (s, 1H), 7.39 – 7.28 (m, 3H), 7.18 (br t, $J = 6.4$ Hz, 1H), 7.01 (d, $J = 7.8$ Hz, 1H), 6.59 (br s, 1H), 4.05 – 3.99 (m, 2H), 3.50 (q, $J = 6.4$ Hz, 2H), 3.38 (q, $J = 6.4$ Hz, 2H), 2.52 (br t, $J = 6.2$ Hz, 2H), 1.85 – 1.80 (m, 4H), 1.75 (p, $J = 6.4$ Hz, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 202.4, 168.0, 162.2, 159.3, 135.7, 129.8, 119.0, 118.4, 112.9, 67.7, 43.6, 36.2, 34.7, 29.7, 28.7, 18.9.

HRMS (ESI/QTOF) $m/z$: [M + Na]$^+$ calcd for C$_{16}$H$_{22}$N$_2$NaO$_4$+$^+$ 329.1472; found 329.1469.

IR: ν (cm$^{-1}$) 3299, 3066, 2938, 2869, 1720, 1643, 1577, 1536, 1482, 1434, 1386, 1295, 1238, 1132, 1027, 719, 688.
N-(3-Isocyanopropyl)-3-((5-oxopentyl)oxy)benzamide (139)

Prepared according to general procedure C from compound 138 (459.5 mg, 1.5 mmol).

1H NMR (400 MHz, CDCl₃) δ 9.73 (t, J = 1.7 Hz, 1H), 7.28 – 7.19 (m, 3H), 6.96 (dd, J = 7.7, 2.6 Hz, 1H), 6.39 (br t, J = 5.9 Hz, 1H), 3.96 (q, J = 5.0, 3.5 Hz, 2H), 3.54 (q, J = 6.4 Hz, 2H), 3.45 (t, J = 6.4 Hz, 2H), 2.52 – 2.40 (m, 2H), 2.01 – 1.94 (m, 2H), 1.79 – 1.72 (m, 4H).

13C NMR (101 MHz, CDCl₃) δ 202.4, 167.9, 159.3, 156.9, 135.6, 129.8, 118.9, 118.5, 113.0, 67.6, 43.6, 39.6, 37.3, 29.2, 28.6, 18.9.

HRMS (ESI/QTOF) m/z: [M + H]+ calcd for C₁₆H₂₁N₂O₃+ 289.1547; found 289.1542.

IR: ν (cm⁻¹) 3299, 2931, 2867, 2146, 1716, 1641, 1579, 1535, 1486, 1436, 1297, 1132, 1043, 750, 717.

N-(3-Formamidopropyl)-4-(hex-5-en-1-yloxy)benzamide (144)

Compound 142 and 143 were prepared according to a literature procedures. To a solution of acid 142 (1.08 g, 4.88 mmol, 1.0 equiv) in dry DMF (23 mL, 0.215 M) at room temperature were added amine 143 (850 mg, 4.88 mmol, 1.0 equiv), DIPEA (4.03 mL, 24.39 mmol, 5.0 equiv), EDC·HCl (1.08 g, 5.61 mmol, 1.15 equiv) and HOBt (725 mg, 5.37 mmol, 1.1 equiv). After being stirred at room temperature for 12 hours, the reaction mixture was quenched with HCl 1 M and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The residue was purified by flash column chromatography (SiO₂, PE/EtOAc 3:1) to yield the desired product 144 (87%) as a yellow oil.

1H NMR (400 MHz, CDCl₃): δ 8.23 (s, 1H), 7.78 (d, J = 8.7 Hz, 2H), 7.11 (s, 1H), 6.90 (d, J = 8.7 Hz, 2H), 6.73 (s, 1H), 5.82 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.10 – 4.92 (m, 2H), 3.99 (t, J = 6.5 Hz, 2H).
3.50 (q, J = 6.0 Hz, 2H), 3.38 (q, J = 6.2 Hz, 2H), 2.12 (q, J = 7.0 Hz, 2H), 1.89 – 1.68 (m, 4H), 1.57 (q, J = 7.5 Hz, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 168.7, 162.8, 162.2, 138.2, 132.6, 126.4, 115.1, 114.8, 68.1, 38.5, 37.6, 33.2, 28.7, 25.5.

HRMS (ESI): m/z calcd for C$_{17}$H$_{25}$N$_2$O$_3$ ([M + H]$^+$): 305.1860; found: 305.1854.

$\text{N-(3-Formamidopropyl)-4-((5-oxopentyl)oxy)benzamide (145)}$

Prepared according to general procedure B from alkene 144 to give aldehyde 145 in 78% yield as yellowish oil after purification by flash column chromatography (SiO$_2$, 5% to 10% MeOH/CH$_2$Cl$_2$).

$^1$H NMR (400 MHz, CDCl$_3$): δ 9.79 (t, J = 1.5 Hz, 1H), 8.23 (d, J = 1.6 Hz, 1H), 7.78 (d, J = 8.8 Hz, 2H), 7.12 (s, 1H), 6.90 (d, J = 8.8 Hz, 2H), 6.69 (s, 1H), 4.05 – 3.91 (m, 2H), 3.56 – 3.43 (m, 2H), 3.37 (q, J = 6.2 Hz, 2H), 2.53 (ddt, J = 6.9, 4.9, 1.7 Hz, 2H), 1.91 – 1.79 (m, 4H), 1.73 (t, J = 6.1 Hz, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 202.3, 167.8, 162.2, 161.7, 128.9, 126.4, 114.4, 67.7, 43.6, 36.1, 34.7, 29.8, 28.6, 18.9.

HRMS (ESI): m/z calcd for C$_{16}$H$_{23}$N$_2$O$_4$ ([M + H]$^+$): 307.1652; found: 307.1648.

$\text{N-(3-Isocyanopropyl)-4-((5-oxopentyl)oxy)benzamide (146)}$

Prepared according to general procedure C from compound 145.

$^1$H NMR (400 MHz, CDCl$_3$): δ 9.81 (t, J = 1.5 Hz, 1H), 7.72 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.9 Hz, 2H), 4.01 (q, J = 2.6 Hz, 2H), 3.60 (q, J = 6.5 Hz, 2H), 3.51 (tt, J = 6.6, 1.8 Hz, 2H), 2.55 (td, J = 5.2, 2.5 Hz, 2H), 2.04 (qd, J = 4.7, 2.2 Hz, 2H), 1.88 – 1.81 (m, 4H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 202.2, 167.5, 161.9, 157.0, 128.8, 126.4, 114.4, 67.7, 43.6, 39.7, 37.3, 29.3, 28.7, 18.9.
HRMS (ESI): m/z calcd for C_{16}H_{21}N_{2}O_{3} ([M + H]^{+}): 289.1547; found: 289.1551.
3.2.2 Procedures for macrocyclization reactions

General Procedure D: synthesis of the α-hydroxy lactams

Pyridine (6.0 equiv) and TFA (3.0 equiv) were added dropwise to a solution of the ω-isocyanooaldehyde (1.0 equiv) in dry CH₂Cl₂ (0.01 M) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred until the completion of reaction (1-5 days). The mixture was evaporated to dryness and the residue was dissolved in EtOAc. Saturated NaHCO₃ was added and the mixture was stirred at room temperature for 1 h. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with 2 M HCl, saturated NaHCO₃ and brine, dried over Na₂SO₄, filtered and evaporated to dryness. The crude product was purified by flash column chromatography (SiO₂) to afford the α-hydroxy lactam product.

General Procedure E: Passerini reaction of the ω-isocyanooaldehydes

To a solution of the ω-isocyanooaldehyde (1.0 equiv) in dry CH₂Cl₂ (0.01 M) was added the carboxylic acid (acetic acid or N-(tert-butoxycarbonyl)glycine or benzoic acid) (1.3 equiv). The resulting solution was stirred at room temperature until the completion of reaction (1-5 days). Saturated NaHCO₃ was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered and evaporated to dryness. The crude product was purified by flash column chromatography (SiO₂) to yield the macrocycle product.

General Procedure F: Ugi reaction of the ω-isocyanooaldehydes

To a solution of the ω-isocyanooaldehyde (1.0 equiv) in MeOH (0.01 M) was added benzylamine (1.2 equiv). After stirring at room temperature for 1 h, glacial acetic acid (1.5 equiv) was added dropwise. The resulting solution was stirred at room temperature until the completion of reaction (1-5 days). The mixture was evaporated to dryness and the residue was purified by flash column chromatography (SiO₂) to yield the macrocycle product.

General Procedure G: Ugi tetrazole reaction of the ω-isocyanooaldehydes

To a solution of the ω-isocyanooaldehyde (1.0 equiv) in MeOH (0.1 M) was added the aniline derivative (aniline or 4-aminobenzonitrile) (1.1 equiv). After stirring at room temperature for 1 h, trimethylsilyl azide (TMSN₃) (1.1 equiv) was added dropwise. The resulting solution was stirred at room temperature until the completion of reaction (1-5 days). The mixture was evaporated to dryness and the residue was purified by flash column chromatography (SiO₂) to yield the macrocycle tetrazole product.
**tert-Butyl 3-hydroxy-4-oxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (147)**

Yield: 51% (0.05 mmol scale) and 59% (0.58 mmol scale), Eluent: 1:2 EtOAc/PE, \( R_f = 0.40 \) (1:1 EtOAc/PE)

\(^1\)H NMR (400 MHz, CDCl3) \( \delta \) 7.99 (dt, \( J = 8.4, 0.9 \) Hz, 1H), 7.46 (d, \( J = 7.9 \) Hz, 1H), 7.35 (ddd, \( J = 8.5, 7.2, 1.4 \) Hz, 1H), 7.26 (td, \( J = 7.4, 1.0 \) Hz, 1H), 5.58 (dd, \( J = 7.5, 3.0 \) Hz, 1H), 4.41 (dt, \( J = 12.8, 5.2 \) Hz, 1H), 4.23 (dd, \( J = 14.5, 7.7 \) Hz, 1H), 3.88 (br s, 1H), 3.81 (ddd, \( J = 12.9, 7.3, 5.6 \) Hz, 1H), 2.93 – 2.85 (m, 2H), 2.78 (dt, \( J = 16.5, 7.6 \) Hz, 1H), 2.57 – 2.45 (m, 1H), 1.66 (s, 9H).

\(^{13}\)C NMR (101 MHz, CDCl₃) \( \delta \) 171.8, 150.6, 139.3, 129.5, 129.4, 127.6, 126.2, 123.4, 121.8, 119.2, 115.3, 103.1, 84.6, 66.4, 39.4, 28.3, 27.7, 21.3.

HRMS (nanochip-ESI/LTQ-Orbitrap) \( m/z \): \([M + Na]^+\) calcd for C₂₀H₂₂N₂NaO₄⁺ 377.1472; found 377.1470.

IR: \( \nu \) (cm\(^{-1}\)) 2958, 2915, 1729, 1691, 1448, 1369, 1311, 1251, 1051, 757.

**tert-Butyl 3-acetoxy-4-oxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (148)**

Yield: 62% (0.05 mmol scale) and 54% (1.14 mmol scale), Eluent: 1:2 EtOAc/PE, \( R_f = 0.63 \) (1:1 EtOAc/PE)

\(^1\)H NMR (400 MHz, CDCl3) \( \delta \) 7.98 (d, \( J = 8.4 \) Hz, 1H), 7.47 (d, \( J = 7.6 \) Hz, 1H), 7.35 (ddd, \( J = 8.5, 7.2, 1.4 \) Hz, 1H), 7.27 (t, \( J = 7.3 \) Hz, 1H), 5.54 (dd, \( J = 6.9, 3.5 \) Hz, 1H), 5.45 (dd, \( J = 13.3, 7.7 \) Hz, 1H), 4.40 (dt, \( J = 12.8, 5.2 \) Hz, 1H), 3.79 (ddd, \( J = 12.9, 7.7, 5.2 \) Hz, 1H), 2.98 – 2.82 (m, 2H), 2.80 – 2.60 (m, 2H), 2.21 (s, 3H), 1.67 (s, 9H).

\(^{13}\)C NMR (101 MHz, CDCl₃) \( \delta \) 170.4, 166.6, 150.6, 139.3, 129.8, 129.4, 127.7, 126.2, 123.4, 122.4, 119.3, 115.3, 101.4, 84.6, 67.9, 39.0, 28.3, 25.6, 21.4, 21.1.

HRMS (APCI/QTOF) \( m/z \): \([M + H]^+\) calcd for C₂₂H₂₅N₂O₅⁺ 397.1758; found 397.1748.

IR: \( \nu \) (cm\(^{-1}\)) 2979, 2934, 1730, 1688, 1369, 1309, 1218, 1137, 1095, 1047, 839, 734.
**tert-Butyl 3-(benzoyloxy)-4-oxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (149)**

Yield: 55% (0.05 mmol scale), Eluent: 1:3 EtOAc/PE, R_f = 0.45 (1:3 EtOAc/PE)

^1^H NMR (400 MHz, CDCl_3) δ 8.14 (d, J = 8.5, 1.5 Hz, 2H), 8.00 (d, J = 8.3 Hz, 1H), 7.57 (tt, J = 7.4, 1.4 Hz, 1H), 7.47 (dt, J = 8.5, 6.9 Hz, 3H), 7.36 (ddd, J = 8.5, 1.3 Hz, 1H), 7.27 (td, J = 7.5, 1.0 Hz, 1H), 5.70 (dd, J = 13.5, 7.6 Hz, 1H), 5.60 (dd, J = 7.1, 3.3 Hz, 1H), 4.44 (dt, J = 12.8, 5.2 Hz, 1H), 3.83 (ddd, J = 12.8, 7.9, 5.0 Hz, 1H), 3.01 – 2.74 (m, 4H), 1.68 (s, 9H).

^13^C NMR (101 MHz, CDCl_3) δ 166.6, 166.0, 150.7, 139.4, 133.4, 130.2, 129.9, 129.5, 128.5, 127.7, 126.3, 123.4, 122.4, 119.3, 115.3, 101.3, 84.6, 68.3, 39.1, 28.3, 25.8, 21.4.

HRMS (ESI/QTOF) m/z: [M + H]^+ calcd for C_{27}H_{27}N_{2}O_{5} 459.1914; found 459.1916.

IR: ν (cm\(^{-1}\)) 2979, 2925, 1725, 1688, 1454, 1369, 1116, 754, 706.

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**tert-Butyl 3-(N-benzylacetamido)-4-oxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (150)**

Yield: 89% (0.05 mmol scale), Eluent: 2% MeOH/CH_2Cl_2, R_f = 0.37 (5% MeOH/CH_2Cl_2)

^1^H NMR (400 MHz, CDCl_3) δ 7.95 (d, J = 8.3 Hz, 1H), 7.45 (d, J = 7.4 Hz, 1H), 7.40 – 7.32 (m, 3H), 7.31 – 7.22 (m, 4H), 5.44 (dd, J = 7.4, 2.9 Hz, 1H), 5.18 (dd, J = 14.8, 7.2 Hz, 1H), 4.80 (d, J = 17.9 Hz, 1H), 4.50 (d, J = 18.0 Hz, 1H), 4.40 (dt, J = 12.8, 5.4 Hz, 1H), 3.79 (ddd, J = 12.7, 7.6, 5.2 Hz, 1H), 2.86 (dd, J = 5.8, 5.2 Hz, 2H), 2.82 – 2.71 (m, 1H), 2.35 (dt, J = 16.4, 7.4 Hz, 1H), 2.18 (s, 3H), 1.62 (s, 9H).

^13^C NMR (101 MHz, CDCl_3) δ 172.6, 167.8, 150.6, 139.3, 138.0, 129.8, 129.3, 129.0, 127.7, 127.6, 126.2, 126.0, 123.4, 122.1, 119.2, 115.2, 103.1, 84.4, 55.2, 51.6, 39.2, 28.3, 24.9, 22.2, 21.4.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + H]^+ calcd for C_{29}H_{32}N_{3}O_{4} 486.2387; found 486.2390.

IR: ν (cm\(^{-1}\)) 2956, 2919, 1733, 1660, 1450, 1369, 1309, 1251, 1153, 1078, 1051, 755.
tert-Butyl 3-(methylamino)-4-oxo-6,7-dihydroindolo[2,3-a]quinolizine-12(4H)-carboxylate (151)

According to a reported procedure, a mixture of ω-isocyano-γ-oxoaldehyde 97 (35.4 mg, 0.1 mmol, 1.0 equiv), N-methylhydroxylamine hydrochloride (25.1 mg, 0.3 mmol, 3.0 equiv), NaHCO₃ (50.4 mg, 0.6 mmol, 6.0 equiv) and 4 Å molecular sieves (75 mg) in MeOH (10 mL) was stirred at room temperature for 30 min. Acetic acid (0.15 mL, 2.7 mmol, 27.0 equiv) was added and the resulting mixture was stirred at room temperature for 5 days. The mixture was filtered (rinsed with MeOH) and the filtrate was evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO₂, 2% MeOH/CH₂Cl₂ + 3% NEt₃) to afford compound 144 in 89% (32.5 mg, 0.89 mmol) as white solid (Rf = 0.65 (5% MeOH/CH₂Cl₂)).

1H NMR (400 MHz, CDCl₃) δ 8.03 (dt, J = 8.4, 0.9 Hz, 1H), 7.48 – 7.44 (m, 1H), 7.32 (ddd, J = 8.4, 7.2, 1.5 Hz, 1H), 7.26 (td, J = 7.4, 1.1 Hz, 1H), 6.44 (d, J = 7.9 Hz, 1H), 6.24 (d, J = 7.9 Hz, 1H), 5.21 (s, 1H), 4.52 (t, J = 6.3 Hz, 2H), 2.92 (t, J = 6.3 Hz, 2H), 2.89 (s, 3H), 1.64 (s, 9H).

13C NMR (101 MHz, CDCl₃) δ 157.2, 150.6, 139.3, 138.9, 131.2, 127.9, 125.5, 123.5, 123.4, 120.1, 118.7, 115.5, 107.4, 104.9, 84.5, 40.2, 30.0, 28.3, 20.6.


IR: ν (cm⁻¹) 2956, 2921, 1729, 1670, 1454, 1367, 1309, 1257, 1228, 1149, 740.

tert-Butyl 3,4-dioxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (152)

It was prepared from the same procedure as compound 144 followed by washing with 2 M HCl.

Yield: 79%, Eluent: 5% to 10% MeOH/CH₂Cl₂

**tert-Butyl 5-hydroxy-4,9-dioxo-2,3,4,5,6,7,8,9-octahydro-[1]azacycloundecino[5,4-b]indole-10 (1H)-carboxylate (157)**

Yield: 68%, Eluent: 2% MeOH/CH$_2$Cl$_2$, R$_f$ = 0.35 (5% MeOH/CH$_2$Cl$_2$)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.05 (dt, J = 8.3, 0.8 Hz, 1H), 7.55 (dt, J = 7.8, 1.0 Hz, 1H), 7.42 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 7.29 (ddd, J = 8.0, 7.3, 1.0 Hz, 1H), 6.45 (br t, J = 6.2 Hz, 1H), 4.20 (dd, J = 5.6, 2.1 Hz, 1H), 3.68 (dtd, J = 13.2, 6.0, 2.7 Hz, 1H), 3.46 – 3.32 (m, 1H), 3.04 (ddd, J = 14.9, 6.0, 2.3 Hz, 1H), 2.96 (ddd, J = 17.1, 8.9, 3.1 Hz, 1H), 2.87 – 2.80 (m, 1H), 2.12 – 1.96 (m, 3H), 1.85 – 1.75 (m, 1H), 1.59 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 199.4, 174.2, 149.7, 136.9, 135.5, 128.6, 127.2, 123.5, 122.1, 119.9, 115.5, 85.2, 70.2, 41.7, 39.7, 30.8, 28.1, 23.0, 16.0.

HRMS (LTQ-Orbitrap) m/z: [M + Na]$^+$ calculated for C$_{21}$H$_{26}$N$_2$NaO$_5$ 409.1734; found 409.1736.

IR: $\nu$ (cm$^{-1}$) 2956, 2919, 2854, 1737, 1668, 1486, 1455, 1359, 1315, 1234, 1187, 1147, 1083, 970.

**tert-Butyl 5-acetoxy-4,9-dioxo-2,3,4,5,6,7,8,9-octahydro-[1]azacycloundecino[5,4-b]indole-10(1H) -carboxylate (158)**

Yield: 72%, Eluent: 2% MeOH/CH$_2$Cl$_2$, R$_f$ = 0.35 (5% MeOH/CH$_2$Cl$_2$)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.06 (dt, J = 8.4, 0.9 Hz, 1H), 7.56 (dt, J = 7.9, 1.0 Hz, 1H), 7.43 (ddd, J = 8.4, 7.2, 1.3 Hz, 1H), 7.30 (ddd, J = 8.0, 7.2, 1.0 Hz, 1H), 6.19 (t, J = 6.4 Hz, 1H), 5.13 (t, J = 4.5 Hz, 1H), 3.80 (dtd, J = 13.5, 6.7, 3.0 Hz, 1H), 3.43 – 3.34 (m, 1H), 3.18 (ddd, J = 14.9, 9.6, 3.0 Hz, 1H), 3.04 (ddd, J = 14.8, 6.4, 2.6 Hz, 1H), 2.95 – 2.82 (m, 2H), 2.10 (s, 3H), 2.08 – 2.02 (m, 2H), 2.01 – 1.91 (m, 1H), 1.88 – 1.79 (m, 1H), 1.61 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 197.3, 169.6, 169.4, 149.8, 136.9, 135.8, 128.6, 127.0, 123.4, 121.5, 120.0, 115.5, 85.2, 72.9, 42.9, 39.3, 29.3, 28.1, 23.3, 21.1, 17.6.
HRMS (nanochip-ESI/LTQ-Orbitrap) $m/z$: [M + Na]$^+$ calcd for C$_{23}$H$_{26}$N$_2$NaO$_6$ $^+$ 451.1840; found 451.1841.

IR: $\nu$ (cm$^{-1}$) 3241, 2956, 2925, 2854, 1739, 1673, 1454, 1359, 1321, 1234, 1149, 746.

**tert-Butyl 5-(((tert-butoxycarbonyl)glycyl)oxy)-4,9-dioxo-2,3,4,5,6,7,8,9-octahydro-[1]azacycloodecino[5,4-b]indole-10(1H)-carboxylate (159)**

Yield: 78%, Eluent: 2% to 5% MeOH/CH$_2$Cl$_2$, $R_f = 0.19$ (5% MeOH/CH$_2$Cl$_2$)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.03 (d, $J = 8.4$ Hz, 1H), 7.54 (d, $J = 7.8$ Hz, 1H), 7.40 (ddd, $J = 8.4, 7.2, 1.2$ Hz, 1H), 7.28 (d, $J = 7.3$ Hz, 1H), 6.63 (br t, $J = 6.2$ Hz, 1H), 5.16 (br dd, $J = 5.9, 3.0$ Hz, 2H), 3.94 – 3.72 (m, 3H), 3.36 – 3.27 (m, 1H), 3.24 – 3.18 (m, 1H), 2.99 (dd, $J = 14.2, 4.8$ Hz, 1H), 2.87 (t, $J = 6.5$ Hz, 2H), 2.11 – 1.79 (m, 4H), 1.60 (s, 9H), 1.28 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 197.2, 169.4, 169.2, 156.2, 149.8, 136.9, 135.6, 128.7, 127.0, 123.4, 121.7, 119.9, 115.4, 85.1, 80.4, 73.7, 42.9, 42.9, 39.5, 29.0, 28.3, 28.1, 23.1, 17.7.

HRMS (nanochip-ESI/LTQ-Orbitrap) $m/z$: [M + Na]$^+$ calcd for C$_{28}$H$_{37}$N$_3$NaO$_8$ $^+$ 566.2473; found 566.2472.

IR: $\nu$ (cm$^{-1}$) 2952, 2921, 2856, 1729, 1685, 1523, 1454, 1363, 1321, 1234, 1159, 742.

**tert-Butyl 5-((N-benzylacetamido)-4,9-dioxo-2,3,4,5,6,7,8,9-octahydro-[1]azacycloodecino[5,4-b]-indole-10(1H)-carboxylate (160)**

Yield: 61%, Eluent: 2% MeOH/CH$_2$Cl$_2$, $R_f = 0.39$ (5% MeOH/CH$_2$Cl$_2$)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.02 (d, $J = 8.3$ Hz, 1H), 7.53 (d, $J = 7.8$ Hz, 1H), 7.40 – 7.31 (m, 3H), 7.28 – 7.22 (m, 2H), 7.14 (d, $J = 7.5$ Hz, 2H), 6.92 (br s, 1H), 4.91 (d, $J = 18.1$ Hz, 1H), 4.70 (d, $J =$
11.2 Hz, 1H), 4.58 (d, J = 18.2 Hz, 1H), 3.88 – 3.78 (m, 1H), 3.20 – 3.08 (m, 2H), 3.03 – 2.95 (m, 1H), 2.85 (t, J = 6.6 Hz, 2H), 2.11 – 2.00 (m, 1H), 1.84 – 1.80 (m, 4H), 1.69 – 1.62 (m, 2H), 1.58 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 197.9, 172.7, 171.3, 149.8, 138.2, 136.5, 135.6, 128.9, 128.8, 127.3, 126.9, 125.7, 123.4, 121.7, 119.8, 115.6, 85.1, 58.5, 50.0, 42.0, 39.0, 28.08, 28.05, 23.3, 22.1, 20.4.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + Na]$^+$ calcd for C$_{30}$H$_{35}$N$_3$NaO$_5$+ 540.2469; found 540.2472.

IR: ν (cm$^{-1}$) 2956, 2921, 2867, 1729, 1675, 1627, 1450, 1359, 1324, 1234, 1143, 755.

$^t$-Butyl 5-hydroxy-4,10-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-11H-[1]azacyclododecino[5,4-b]-indole-11-carboxylate (161)

Yield: 92%, Eluent: 2% MeOH/CH$_2$Cl$_2$, R$_f$ = 0.39 (5% MeOH/CH$_2$Cl$_2$)

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.10 (d, J = 8.5 Hz, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 5.92 (t, J = 6.4 Hz, 1H), 4.15 (q, J = 4.3 Hz, 1H), 3.79 (ddt, J = 41.3, 12.9, 6.7 Hz, 2H), 3.09 (t, J = 5.8 Hz, 2H), 3.01 – 2.90 (m, 1H), 2.84 – 2.70 (m, 2H), 2.05 – 1.91 (m, 1H), 1.71 – 1.59 (m, 2H), 1.63 (s, 9H), 1.56 – 1.44 (m, 2H), 1.24 – 1.13 (m, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 197.7, 173.1, 149.9, 137.1, 136.7, 128.7, 127.1, 123.7, 121.9, 120.7, 116.0, 85.7, 71.3, 42.2, 37.4, 32.4, 28.1, 24.9, 24.1, 21.8.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + Na]$^+$ calcd for C$_{22}$H$_{28}$N$_2$NaO$_5$+ 423.1890; found 423.1893.

IR: ν (cm$^{-1}$) 2956, 2919, 1729, 1675, 1454, 1369, 1321, 1234, 1143, 1078, 1051, 755.

$^t$-Butyl 5-acetoxy-4,10-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-11H-[1]azacyclododecino[5,4-b]-indole-11-carboxylate (162)
**Yield:** 85%, **Eluent:** 2% MeOH/CH₂Cl₂, Rᵢ = 0.36 (5% MeOH/CH₂Cl₂)

**¹H NMR** (400 MHz, CDCl₃) δ 8.11 (d, J = 8.3 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 6.04 (t, J = 6.4 Hz, 1H), 5.01 (t, J = 5.3 Hz, 1H), 3.92 – 3.81 (m, 1H), 3.70 – 3.60 (m, 1H), 3.17 – 3.01 (m, 2H), 2.88 – 2.71 (m, 2H), 2.00 (s, 3H), 1.95 – 1.86 (m, 1H), 1.78 – 1.58 (m, 3H), 1.61 (s, 9H), 1.51 – 1.26 (m, 2H).

**¹³C NMR** (101 MHz, CDCl₃) δ 197.7, 169.6, 168.9, 149.9, 136.7, 136.3, 128.8, 127.2, 123.7, 122.6, 120.7, 115.9, 85.7, 73.9, 43.4, 37.4, 29.6, 28.1, 24.7, 24.6, 23.0, 21.1.


**IR:** ν (cm⁻¹) 3853, 1733, 1679, 1540, 1359, 1319, 1230, 1139, 755.

**t-Jbuty 5-(((tert-butoxycarbonyl)glycyl)oxy)-4,10-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-11H-[1]-azacyclododecino[5,4-b]indole-11-carboxylate (163)**

**Yield:** 85%, **Eluent:** 2% MeOH/CH₂Cl₂, Rᵢ = 0.42 (5% MeOH/CH₂Cl₂)

**¹H NMR** (400 MHz, CDCl₃) δ 8.08 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.27 (t, J = 7.5 Hz, 1H), 6.49 (br s, 1H), 5.19 – 5.08 (m, 1H), 5.06 (t, J = 5.1 Hz, 1H), 3.95 – 3.81 (m, 1H), 3.84 – 3.65 (m, 2H), 3.67 – 3.45 (m, 1H), 3.18 – 2.96 (m, 2H), 2.87 – 2.69 (m, 2H), 2.02 – 1.82 (m, 2H), 1.78 – 1.56 (m, 2H), 1.61 (s, 9H), 1.49 – 1.32 (m, 2H), 1.32 (s, 9H).

**¹³C NMR** (101 MHz, CDCl₃) δ 197.9, 169.3, 168.8, 156.1, 149.9, 136.6, 136.2, 128.8, 127.0, 123.7, 122.5, 120.7, 115.9, 85.6, 80.3, 74.6, 43.1, 42.8, 37.7, 29.4, 28.3, 28.1, 24.7, 24.4, 22.8.

**HRMS** (nanochip-ESI/LTQ-Orbitrap) m/z; [M + Na]⁺ calcd for C₂₉H₃₈N₃NaO₈⁺ 580.2629; found 580.2632.

**IR:** ν (cm⁻¹) 3322, 2958, 2925, 1724, 1679, 1525, 1450, 1363, 1319, 1234, 1149, 1078, 1051, 757.
**tert-Butyl** 5-(N-benzylacetamido)-4,10-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-11H-[1]azacyclodecino[5,4-b]indole-11-carboxylate (164)

Yield: 57%, Eluent: 2:1 EtOAc/PE, R_f = 0.48 (5% 3:1 EtOAc/PE)

^1^H NMR (400 MHz, CDCl_3) δ 8.09 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.42 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 7.34 – 7.28 (m, 3H), 7.23 (t, J = 7.4 Hz, 1H), 7.11 (d, J = 7.2 Hz, 2H), 6.59 (br s, 1H), 4.96 (d, J = 18.3 Hz, 1H), 4.83 (dd, J = 12.6, 3.7 Hz, 1H), 4.59 (d, J = 18.2 Hz, 1H), 4.11 – 3.99 (m, 1H), 3.40 – 3.29 (m, 1H), 3.11 (ddd, J = 13.8, 10.1, 3.4 Hz, 1H), 3.05 – 2.96 (m, 2H), 2.59 (td, J = 12.3, 3.4 Hz, 1H), 1.98 – 1.89 (m, 1H), 1.86 (s, 3H), 1.77 – 1.68 (m, 1H), 1.60 (s, 9H), 1.54 – 1.47 (m, 1H), 1.42 – 1.34 (m, 1H), 1.28 – 1.23 (m, 2H).

^13^C NMR (101 MHz, CDCl_3) δ 197.4, 172.8, 170.3, 149.9, 138.3, 136.8, 136.2, 128.8, 127.2, 127.1, 125.6, 123.7, 123.0, 120.6, 116.0, 85.6, 56.3, 49.2, 43.6, 37.3, 28.11, 28.07, 24.6, 24.0, 23.9, 22.2.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + Na]^+ calcd for C_{31}H_{37}N_3NaO_5 554.2625; found 554.2616.

IR: ν (cm⁻¹) 3318, 2956, 2925, 1729, 1679, 1625, 1450, 1367, 1319, 1236, 1139, 1079, 755.

**tert-Butyl** 5-hydroxy-4,11-dioxo-2,3,4,5,6,7,8,9,10,11-decahydro-[1]azacyclotridecino[5,4-b]indole-12(1H)-carboxylate (165)

Yield: 83%, Eluent: 2% to 3% MeOH/CH_2Cl_2, R_f = 0.20 (5% MeOH/CH_2Cl_2)

^1^H NMR (400 MHz, CDCl_3) δ 8.08 (d, J = 8.6 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.36 – 7.27 (m, 1H), 6.23 (br d, J = 6.9 Hz, 1H), 4.13 (br s, 1H), 3.94 (dd, J = 13.9, 6.9, 3.2 Hz, 1H), 3.81 – 3.67 (m, 1H), 3.21 (ddd, J = 15.7, 9.4, 3.2 Hz, 1H), 3.06 (ddd, J = 15.6, 6.9, 2.9 Hz, 1H), 2.96 – 2.79 (m, 2H), 2.47 (br d, J = 4.7 Hz, 1H), 1.95 – 1.84 (m, 2H), 1.74 – 1.67 (m, 2H), 1.63 (s, 9H), 1.34 – 1.24 (m, 4H).
$^{13}$C NMR (101 MHz, CDCl$_3$) δ 198.3, 173.6, 149.9, 136.9, 136.8, 128.8, 127.1, 123.6, 122.2, 120.7, 115.8, 85.4, 71.1, 42.1, 37.9, 32.3, 28.2, 27.5, 25.2, 23.4, 21.5.

HRMS (nanochip-ESI/LTQ-Orbitrap) $m/z$: [M + Na]$^+$ calcd for C$_{23}$H$_{30}$N$_2$NaO$_5$ 437.2047; found 437.2040.

IR: ν (cm$^{-1}$) 3361, 2921, 2859, 1729, 1673, 1535, 1454, 1367, 1321, 1255, 1236, 1143, 1099, 836, 736.

tert-Butyl 5-acetoxy-4,11-dioxo-2,3,4,5,6,7,8,9,10,11-decahydro-[1]azacyclotridecino[5,4-b]indole-12(1H)-carboxylate (166)

Yield: 62%, Eluent: 1:1 to 2:1 EtOAc/PE, $R_f = 0.55$ (2:1 EtOAc/PE)

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.08 (d, $J = 8.4$ Hz, 1H), 7.63 (d, $J = 7.9$ Hz, 1H), 7.44 (t, $J = 7.8$ Hz, 1H), 7.31 (t, $J = 7.5$ Hz, 1H), 6.11 (t, $J = 6.0$ Hz, 1H), 5.05 (dd, $J = 6.5$, 3.4 Hz, 1H), 4.13 – 3.96 (m, 1H), 3.61 – 3.49 (m, 1H), 3.24 – 3.15 (m, 1H), 3.10 (ddd, $J = 15.9$, 6.3, 3.0 Hz, 1H), 2.88 (t, $J = 6.0$ Hz, 2H), 1.95 (s, 3H), 1.91 – 1.76 (m, 3H), 1.72 – 1.65 (m, 1H), 1.62 (s, 9H), 1.41 – 1.23 (m, 4H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 197.8, 169.7, 169.3, 149.9, 137.0, 136.8, 128.8, 127.2, 123.6, 122.4, 120.7, 115.7, 85.4, 73.7, 41.6, 37.6, 29.6, 28.1, 27.2, 25.1, 23.9, 22.7, 21.0.

HRMS (nanochip-ESI/LTQ-Orbitrap) $m/z$: [M + Na]$^+$ calcd for C$_{25}$H$_{32}$N$_2$NaO$_6$ 479.2153; found 479.2147.

IR: ν (cm$^{-1}$) 2958, 2915, 1739, 1675, 1375, 1319, 1234, 1147, 1078, 1051, 755.

tert-Butyl 5-(((tert-butoxycarbonyl)glycyl)oxy)-4,11-dioxo-2,3,4,5,6,7,8,9,10,11-decahydro-[1]azacyclotridecino[5,4-b]indole-12(1H)-carboxylate (167)

Yield: 73%, Eluent: 5% MeOH/CH$_2$Cl$_2$, $R_f = 0.27$ (5% MeOH/CH$_2$Cl$_2$)
1H NMR (400 MHz, CDCl₃) δ 8.06 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.42 (t, J = 7.7 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 6.56 (t, J = 6.3 Hz, 1H), 5.19 – 5.04 (m, 2H), 4.08 – 3.98 (m, 1H), 3.83 – 3.67 (m, 2H), 3.58 – 3.46 (m, 1H), 3.26 – 3.01 (m, 2H), 2.94 – 2.66 (m, 3H), 1.99 – 1.87 (m, 2H), 1.83 – 1.74 (m, 2H), 1.67 – 1.64 (m, 3H), 1.61 (s, 9H), 1.30 (s, 9H).

13C NMR (101 MHz, CDCl₃) δ 197.8, 169.7, 169.1, 156.2, 149.9, 136.8, 136.6, 128.9, 127.0, 123.6, 122.7, 120.8, 115.6, 85.3, 80.3, 74.5, 42.8, 41.8, 38.1, 29.5, 28.1, 27.3, 25.1, 23.8, 22.6.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + Na]⁺ calcd for C₃₀H₄₁N₃NaO₈ + 594.2786; found 594.2776.

IR: ν (cm⁻¹) 3322, 2952, 2925, 1727, 1679, 1529, 1450, 1363, 1324, 1234, 1149, 757.

tert-Butyl 5-(N-benzylacetamido)-4,11-dioxo-2,3,4,5,6,7,8,9,10,11-decahydro-[1]azacyclotridecino[5,4-b]indole-12(1H)-carboxylate (168)

Yield: 54%, Eluent: 2:1 to 3:1 EtOAc/PE, Rₓ = 0.52 (3:1 EtOAc/PE)

1H NMR (400 MHz, CDCl₃) δ 8.06 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 7.35 – 7.27 (m, 3H), 7.23 (t, J = 7.3 Hz, 1H), 7.11 (d, J = 7.5 Hz, 2H), 6.38 (dd, J = 8.6, 4.5 Hz, 1H), 4.92 – 4.72 (m, 2H), 4.56 (d, J = 18.2 Hz, 1H), 4.20 – 4.04 (m, 1H), 3.28 (dtt, J = 13.1, 8.5, 4.1 Hz, 1H), 3.18 – 3.04 (m, 2H), 2.98 (ddd, J = 17.1, 8.5, 4.5 Hz, 1H), 2.78 (ddd, J = 17.1, 7.1, 4.2 Hz, 1H), 1.94 (s, 3H), 1.80 – 1.73 (m, 2H), 1.62 (s, 9H), 1.41 – 1.18 (m, 6H).

13C NMR (101 MHz, CDCl₃) δ 197.4, 172.7, 170.8, 150.0, 138.3, 136.9, 136.8, 128.84, 128.80, 127.2, 127.1, 125.7, 123.6, 122.7, 120.6, 115.7, 85.2, 57.0, 48.9, 41.7, 38.0, 28.1, 28.0, 26.5, 25.2, 24.8, 23.4, 22.3.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + Na]⁺ calcd for C₃₂H₃₉N₃NaO₅ + 568.2782; found 568.2773.

IR: ν (cm⁻¹) 2956, 2921, 2865, 1733, 1679, 1625, 1454, 1363, 1321, 1255, 1234, 1139, 966, 761, 734.
**tert-Butyl 4,5,11-trioxo-2,3,4,5,6,7,8,9,10,11-decahydro-[1]azacyclotridecino[5,4-b]indole-12(1H)-carboxylate (169)**

It was prepared from the same procedure as compound 144 followed by washing with 2 M HCl.

Yield: 60%, Eluent: 2:1 PE/EtOAc

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.07 (dt, $J = 8.8$, 0.9 Hz, 1H), 7.59 (dt, $J = 7.8$, 1.1 Hz, 1H), 7.44 (ddd, $J = 8.5$, 7.2, 1.3 Hz, 1H), 7.31 (ddd, $J = 8.0$, 7.2, 1.0 Hz, 1H), 6.67 (t, $J = 6.7$ Hz, 1H), 3.82 – 3.72 (m, 2H), 3.15 – 3.05 (m, 2H), 2.79 – 2.72 (m, 2H), 2.72 – 2.63 (m, 2H), 1.84 (p, $J = 6.6$ Hz, 2H), 1.62 (s, 9H), 1.57 – 1.48 (m, 2H), 1.48 – 1.40 (m, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 202.4, 197.9, 161.4, 149.8, 136.5, 136.4, 128.7, 127.0, 123.6, 120.7, 120.3, 115.9, 85.5, 42.5, 38.0, 36.9, 28.2, 27.3, 24.6, 24.2, 23.6.

HRMS (ESI): $m/z$ calcd for C$_{23}$H$_{28}$N$_2$O$_5$ ([M + Na]$^+$): 435.1890; found: 435.1887.

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**tert-Butyl 5-hydroxy-4-oxo-2,3,4,5,6,7-hexahydroazonino[5,4-b]indole-8(1H)-carboxylate (170)**

Yield: 44%, Eluent: 2% MeOH/CH$_2$Cl$_2$, $R_f = 0.26$ (5% MeOH/CH$_2$Cl$_2$)

HRMS (ESI/QTOF) $m/z$: [M + Na]$^+$ calcd for C$_{19}$H$_{24}$N$_2$NaO$_4$ $^+$ 367.1634; found 367.1631.

IR: v (cm$^{-1}$) 2946, 1727, 1664, 1454, 1363, 1321, 1132, 755.

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**tert-Butyl 5-acetoxy-4-oxo-2,3,4,5,6,7-hexahydroazonino[5,4-b]indole-8(1H)-carboxylate (171)**

Yield: 50%, Eluent: 2% MeOH/CH$_2$Cl$_2$, $R_f = 0.42$ (5% MeOH/CH$_2$Cl$_2$)
$^{1}$H NMR (400 MHz, CD$_3$OD) δ 8.04 (d, $J = 7.8$ Hz, 1H), 7.48 (d, $J = 7.0$ Hz, 1H), 7.27 – 7.16 (m, 2H), 4.94 – 4.87 (m, 1H), 3.68 (q, $J = 12.0$ Hz, 1H), 3.63 – 3.40 (m, 1H), 3.19 – 2.89 (m, 3H), 2.81 – 2.46 (m, 2H), 2.37 (br s, 1H), 2.18 – 1.95 (m, 3H), 1.70 (s, 9H).

$^{13}$C NMR (101 MHz, CD$_3$OD) δ 174.9, 172.0, 151.8, 138.3, 137.8, 130.5, 125.1, 123.6, 118.8, 116.7, 85.0, 74.0, 41.1, 35.6, 28.5, 22.3, 20.9, 20.5.

HRMS (ESI/QTOF) $m/z$: [M + Na]$^+$ calcd for C$_{21}$H$_{26}$N$_2$NaO$_5$ 409.1734; found 409.1731.

IR: ν (cm$^{-1}$) 3853, 3729, 3704, 3600, 2362, 2339, 2318, 2167, 1729, 1536, 1517, 1455, 1359, 1319, 1228, 1132, 755.

tert-Butyl 5-((tert-butoxycarbonyl)glycyl)oxy)-4-oxo-2,3,4,5,6,7-hexahydroazonino[5,4-b]indole-8(1H)-carboxylate (172)

Yield: 55%, Eluent: 2% MeOH/CH$_2$Cl$_2$, $R_f = 0.35$ (5% MeOH/CH$_2$Cl$_2$)

HRMS (ESI/QTOF) $m/z$: [M + Na]$^+$ calcd for C$_{26}$H$_{35}$N$_3$NaO$_7$ 524.2367; found 524.2369.

IR: ν (cm$^{-1}$) 3322, 2921, 1691, 1660, 1454, 1369, 1159, 1020, 755.


tert-Butyl 5-(N-benzylacetamido)-4-oxo-2,3,4,5,6,7-hexahydroazonino[5,4-b]indole-8(1H)-carboxylate (173)

Yield: 43%, Eluent: 1% to 2% MeOH/CH$_2$Cl$_2$, $R_f = 0.16$ (5% MeOH/CH$_2$Cl$_2$)

HRMS (ESI/QTOF) $m/z$: [M + H]$^+$ calcd for C$_{28}$H$_{34}$N$_3$O$_7$ 476.2544; found 476.2543.

IR: ν (cm$^{-1}$) 2969, 2908, 1727, 1643, 1450, 1367, 1324, 1251, 1224, 1164, 1132, 1116, 1074, 1052, 757, 723.
tert-Butyl 14-((4-cyanophenyl)amino)-6,12,13,14-tetrahydrotetrazolo[1',5':1,9]azonino[5,4-b]indole-11(5H)-carboxylate (174)

Yield: 35%, Eluent: 1% MeOH/CH₂Cl₂, R_f = 0.48 (5% MeOH/CH₂Cl₂)

^1H NMR (400 MHz, CDCl₃) δ 8.18 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.35 (t, J = 7.4 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 6.23 (br s, 2H), 5.37 (br s, 1H), 5.08 (br s, 1H), 4.35 (br s, 1H), 4.15 (br s, 1H), 3.55 (br s, 2H), 2.89 (br s, 1H), 2.80 (tt, J = 13.3, 3.6 Hz, 1H), 2.32 (br s, 1H), 1.69 (s, 9H).

^13C NMR (101 MHz, CDCl₃) δ 156.3, 150.2, 148.8, 136.3, 135.7, 133.9, 128.4, 125.3, 123.5, 119.7, 117.7, 116.4, 112.9, 101.0, 85.1, 49.4, 46.0, 37.0, 28.4, 25.1, 23.4.

HRMS (ESI/QTOF) m/z: [M + Na]⁺ calcd for C₂₆H₂₇N₇NaO₂⁺ 492.2118; found 492.2118.

IR: ν (cm⁻¹) 2952, 2925, 2217, 1729, 1604, 1519, 1454, 1363, 1321, 1159, 1133, 825, 761, 746.

tert-Butyl 5-hydroxy-4-oxo-1,2,3,4,5,6,7,8,9,11,12,13-dodecahydro-14H-[1]oxa[8]azacyclopenta-decino[12,11-b]indole-14-carboxylate (179)

Yield: 51%, Eluent: 2% to 3% MeOH/CH₂Cl₂, R_f = 0.42 (5% MeOH/CH₂Cl₂)

^1H NMR (400 MHz, CDCl₃) δ 7.46 (d, J = 7.8 Hz, 1H), 7.28 (t, J = 9.4 Hz, 1H), 7.18 – 7.06 (m, 2H), 5.48 (br t, J = 6.5 Hz, 0.6H), 4.88 (br s, 0.4H), 4.36 – 4.24 (m, 1H), 4.06 – 3.81 (m, 4H), 3.79 (br s, 0.6H), 3.66 (br t, J = 6.0 Hz, 0.4H), 3.54 (dt, J = 13.5, 6.6 Hz, 0.6H), 3.42 (dq, J = 12.2, 6.0 Hz, 0.4H), 3.09 (t, J = 6.9 Hz, 1H), 3.04 – 2.91 (m, 2H), 2.85 (dq, J = 13.9, 6.6 Hz, 1H), 2.03 – 1.87 (m, 2H), 1.86 – 1.71 (m, 2H), 1.66 – 1.57 (m, 2H), 1.49 (s, 9H), 1.15 – 1.00 (m, 1.2H), 0.38 – 0.22 (m, 0.8H).

^13C NMR (101 MHz, CDCl₃) δ Major rotamer: 173.5, 153.6, 138.7, 137.8, 129.2, 121.4, 119.7, 118.0, 110.8, 109.0, 82.2, 71.8, 65.9, 42.2, 36.9, 35.0, 29.6, 27.9, 26.2, 23.1, 22.3, 18.1. Minor rotamer: 174.0,
HRMS (ESI/QTOF) \( m/z \) \([M + Na]^{+}\) calcd for C\(_{24}\)H\(_{34}\)N\(_2\)NaO\(_5\) \( 453.2360 \); found 453.2354.

IR: \( \nu \) (cm\(^{-1}\)) 3368, 2955, 2919, 2850, 1733, 1679, 1462, 1369, 1275, 1255, 1161, 797, 764, 740.

tert-Butyl 5-acetoxy-4-oxo-1,2,3,4,5,6,7,8,9,11,12,13-dodecahydro-14\(H\)-[1]oxa[8]azacyclopenta-decino[12,11-\(b\)]indole-14-carboxylate (180)

Yield: 52\%, Eluent: 2\% MeOH/CH\(_2\)Cl\(_2\), \( R_f = 0.35 \) (5\% MeOH/CH\(_2\)Cl\(_2\))

\(^1\)H NMR (400 MHz, CD\(_3\)OD) \( \delta \) 7.49 (d, \( J = 7.8 \) Hz, 1H), 7.30 (d, \( J = 8.2 \) Hz, 1H), 7.11 – 6.97 (m, 2H), 4.59 (d, \( J = 4.5 \) Hz, 0.5H), 4.51 (d, \( J = 7.2 \) Hz, 0.5H), 4.37 – 4.26 (m, 1H), 4.15 – 3.85 (m, 5H), 3.82 – 3.74 (m, 0.5H), 3.67 – 3.54 (m, 1H), 3.50 – 3.34 (m, 1.5H), 3.16 – 2.98 (m, 2.5H), 2.95 – 2.82 (m, 2.5H), 2.06 (s, 1.5H), 1.90 (s, 1.5H), 1.78 – 1.69 (m, 2H), 1.64 – 1.53 (m, 2H), 1.46 (s, 9H).

\(^{13}\)C NMR (101 MHz, CD\(_3\)OD) \( \delta \) Major rotamer: 172.0, 171.8, 155.1, 140.4, 139.5, 130.1, 122.0, 120.3, 119.4, 111.7, 110.5, 82.8, 74.9, 66.8, 42.3, 38.1, 32.2, 30.8, 28.0, 26.8, 24.4, 22.8, 20.5, 19.3. Minor rotamer: 172.1, 171.7, 155.1, 140.2, 139.5, 130.3, 121.8, 119.8, 119.4, 111.6, 110.5, 82.8, 74.8, 66.9, 43.0, 37.9, 31.8, 30.6, 28.1, 27.5, 24.0, 22.9, 20.7, 19.7.

HRMS (nanochip-ESI/LTQ-Orbitrap) \( m/z \) \([M + Na]^{+}\) calcd for C\(_{26}\)H\(_{36}\)N\(_2\)NaO\(_6\) \( 495.2466 \); found 495.2458.

IR: \( \nu \) (cm\(^{-1}\)) 2958, 2921, 1737, 1668, 1459, 1369, 1276, 1251, 1159, 1079, 1037, 755, 736.
**tert-Butyl 5-(((tert-butoxycarbonyl)glycyl)oxy)-4-oxo-1,2,3,4,5,6,7,8,9,11,12,13-dodecahydro-14H-[1]oxa[8]azacyclopentadecino[12,11-b]indole-14-carboxylate (181)**

Yield: 58%, Eluent: 2% MeOH/CH$_2$Cl$_2$, $R_f = 0.42$ (5% MeOH/CH$_2$Cl$_2$)

HRMS (nanochip-ESI/LTQ-Orbitrap) $m/z$: [M + Na]$^+$ calcd for C$_{31}$H$_{45}$N$_3$NaO$_8$ $^+$ 610.3099; found 610.3089.

IR: $\nu$ (cm$^{-1}$) 2967, 2925, 1739, 1673, 1373, 1276, 1255, 1164, 1074, 757.

**tert-Butyl 5-(N-benzylacetamido)-4-oxo-1,2,3,4,5,6,7,8,9,11,12,13-dodecahydro-14H-[1]oxa[8]azacyclopentadecino[12,11-b]indole-14-carboxylate (182)**

Yield: 30%, Eluent: 2% to 5% MeOH/CH$_2$Cl$_2$, $R_f = 0.41$ (5% MeOH/CH$_2$Cl$_2$)

HRMS (nanochip-ESI/LTQ-Orbitrap) $m/z$: [M + Na]$^+$ calcd for C$_{33}$H$_{43}$N$_3$NaO$_5$ $^+$ 584.3095; found 584.3091.

IR: $\nu$ (cm$^{-1}$) 2956, 2921, 2865, 1733, 1679, 1625, 1454, 1363, 1321, 1255, 1234, 1139, 966, 761, 734.

**tert-Butyl 4-(phenylamino)-5,6,7,8,11,12,18,19-octahydro-4H-tetrazolo[5',1':7,8][1]oxa[8]azacyclopentadecino[12,11-b]indole-13(10H)-carboxylate (183)**

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Yield: 23%, Eluent: 1% to 3% MeOH/CH₂Cl₂, Rₜ = 0.42 (5% MeOH/CH₂Cl₂)

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + Na]^+ calcd for C₃₀H₃₈N₆NaO₃⁺ 553.2898; found 553.2892.

IR: ν (cm⁻¹) 3311, 1648, 1598, 1498, 1444, 1405, 1299, 1261, 730, 692.

6-Hydroxy-3,4,5,6,9,10,11,12-octahydrobenzo[b][1]oxa[5,9]diazacyclopentadecine-7,13(2H,8H)-dione (185)

Yield: 84%, Eluent: 3% to 5% MeOH/CH₂Cl₂, Rₜ = 0.32 (10% MeOH/CH₂Cl₂)

¹H NMR (400 MHz, CD₃OD) δ 8.25 (br s, 1H), 8.14 br (s, 1H), 7.82 (dd, J = 7.7, 1.8 Hz, 1H), 7.45 (dd, J = 8.9, 7.3, 1.8 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 7.03 (t, J = 7.3 Hz, 1H), 4.26 – 4.09 (m, 3H), 3.65 – 3.55 (m, 2H), 3.51 – 3.44 (m, 1H), 3.18 – 3.07 (m, 1H), 2.00 – 1.84 (m, 4H), 1.83 – 1.71 (m, 2H), 1.69 – 1.58 (m, 1H), 1.52 – 1.43 (m, 1H).

¹³C NMR (101 MHz, CD₃OD) δ 176.9, 168.7, 158.2, 133.8, 131.6, 123.7, 121.8, 113.7, 72.5, 68.6, 37.8, 37.7, 33.6, 29.5, 29.4, 21.0.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + Na]^+ calcd for C₁₆H₂₂N₂NaO₄⁺ 329.1472; found 329.1469.

IR: ν (cm⁻¹) 2958, 2915, 1799, 1459, 1375, 1078, 1052, 755.

7,13-Dioxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydrobenzo[b][1]oxa[5,9]diazacyclopentadecin-6-yl acetate (186)

Yield: 91%, Eluent: 2% MeOH/CH₂Cl₂, Rₜ = 0.39 (5% MeOH/CH₂Cl₂)

¹H NMR (400 MHz, CDCl₃) δ 8.04 (dd, J = 7.8, 1.9 Hz, 1H), 7.87 (br t, J = 6.3 Hz, 1H), 7.38 (ddd, J = 8.3, 7.3, 1.9 Hz, 1H), 7.02 (td, J = 7.6, 1.0 Hz, 1H), 6.94 (dd, J = 8.4, 1.0 Hz, 1H), 6.73 (br t, J = 6.2 Hz, 1H), 5.19 (dd, J = 5.8, 3.2 Hz, 1H), 4.16 (t, J = 5.3 Hz, 2H), 3.73 – 3.61 (m, 2H), 3.56 – 3.49 (m, 1H), 3.42 – 3.38 (m, 2H), 3.19 – 3.15 (m, 1H).
3.22 – 3.14 (m, 1H), 2.06 (ddd, J = 14.8, 7.5, 3.3 Hz, 1H), 1.99 (s, 3H), 1.97 – 1.87 (m, 1H), 1.86 – 1.68 (m, 4H), 1.55 (p, J = 7.7 Hz, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.8, 169.5, 166.3, 156.3, 132.6, 131.7, 122.6, 121.3, 112.6, 73.9, 67.7, 38.0, 37.8, 29.8, 29.2, 28.2, 20.9, 20.5.

HRMS (nanochip-ESI/LTQ-Orbitrap) $m/z$: [M + Na]$^+$ calcd for C$_{18}$H$_{24}$N$_2$O$_5$Na$^+$ 371.1577; found 371.1574.

IR: ν (cm$^{-1}$) 2952, 2929, 1739, 1646, 1535, 1454, 1373, 1299, 1230, 755.

7,13-Dioxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydrobenzo[b][1]oxa[5,9]diazacyclopentadecin-6-yl (tert-butoxycarbonyl)glycinate (187)

Yield: 95%, Eluent: 2% to 3% MeOH/CH$_2$Cl$_2$, R$_f$ = 0.39 (5% MeOH/CH$_2$Cl$_2$)

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.98 (dd, J = 7.8, 1.9 Hz, 1H), 7.86 (br t, J = 6.3 Hz, 1H), 7.36 (ddd, J = 8.8, 7.4, 1.9 Hz, 1H), 6.99 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 5.53 (br t, J = 6.0 Hz, 1H), 5.28 (dd, J = 5.4, 2.9 Hz, 1H), 4.14 (ddd, J = 10.4, 7.4, 3.2 Hz, 1H), 4.06 (m, 1H), 3.80 (d, J = 5.6 Hz, 2H), 3.74 – 3.62 (m, 1H), 3.57 (m, 2H), 3.06 (m, 1H), 2.16 – 2.06 (m, 1H), 2.00 – 1.69 (m, 5H), 1.64 – 1.50 (m, 2H), 1.35 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.7, 169.3, 166.3, 156.6, 156.4, 132.6, 131.5, 122.5, 121.2, 112.2, 80.4, 74.6, 67.4, 43.0, 37.8, 37.2, 29.6, 29.1, 28.33, 28.28, 20.5.

HRMS (nanochip-ESI/LTQ-Orbitrap) $m/z$: [M + Na]$^+$ calcd for C$_{23}$H$_{33}$N$_3$NaO$_7$Na$^+$ 486.2211; found 486.2205.

IR: ν (cm$^{-1}$) 3407, 3313, 2948, 2925, 1751, 1712, 1648, 1535, 1454, 1369, 1297, 1234, 1160, 755.
\[ \text{N-Benzyl-N-(7,13-dioxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydrobenzo[\text{b}][1]oxa[5,9]diazacyclo-pentadecin-6-yl)acetamide (188)} \]

Yield: 97%, Eluent: 2% to 3% MeOH/CH\(_2\)Cl\(_2\), \(R_f = 0.23\) (5% MeOH/CH\(_2\)Cl\(_2\))

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.00 (dd, \(J = 7.7, 1.8\) Hz, 1H), 7.81 (br t, \(J = 7.5\) Hz, 1H), 7.38 – 7.28 (m, 3H), 7.25 (t, \(J = 7.0\) Hz, 1H), 7.18 – 7.11 (m, 3H), 6.98 (t, \(J = 8.3\) Hz, 1H), 6.87 (d, \(J = 8.3\) Hz, 1H), 4.92 (dd, \(J = 12.4, 2.8\) Hz, 1H), 4.80 (d, \(J = 18.1\) Hz, 1H), 4.61 (d, \(J = 18.1\) Hz, 1H), 4.10 – 4.00 (m, 2H), 3.80 – 3.64 (m, 2H), 3.40 (ddt, \(J = 14.0, 9.1, 4.3\) Hz, 1H), 2.98 (dq, \(J = 13.8, 4.5\) Hz, 1H), 2.23 – 2.11 (m, 1H), 2.02 (s, 3H), 1.99 – 1.88 (m, 2H), 1.82 – 1.71 (m, 1H), 1.63 – 1.35 (m, 4H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 173.0, 171.1, 166.1, 156.4, 137.8, 132.3, 128.9, 127.3, 125.6, 122.6, 121.0, 111.8, 66.5, 49.3, 37.3, 36.7, 28.6, 28.1, 27.3, 22.4, 22.3.

HRMS (nanochip-ESI/LTQ-Orbitrap) \(m/z\): [M + Na]\(^+\) calcd for C\(_{25}\)H\(_{31}\)N\(_3\)NaO\(_4\) \(460.2207\); found 460.2203.

IR: \(\nu\) (cm\(^{-1}\)) 3397, 3299, 2952, 2925, 1643, 1535, 1450, 1299, 1240, 1078, 1047, 755.

\[ \text{19-(Phenylamino)-5,6,7,8,16,17,18,19-octahydro-9H,15H-benzo[\text{b}]tetrazolo[1,5-i][1]oxa[5,9]diazacyclopentadecin-9-one (189)} \]

Yield: 43%, Eluent: 2% MeOH/CH\(_2\)Cl\(_2\), \(R_f = 0.32\) (5% MeOH/CH\(_2\)Cl\(_2\))

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.18 (dd, \(J = 7.8, 1.9\) Hz, 1H), 7.78 (t, \(J = 5.9\) Hz, 1H), 7.52 – 7.39 (m, 1H), 7.12 – 7.09 (m, 3H), 6.99 (d, \(J = 8.3\) Hz, 1H), 6.74 (t, \(J = 7.4\) Hz, 1H), 6.55 (d, \(J = 7.9\) Hz, 2H), 4.93 (t, \(J = 6.7\) Hz, 1H), 4.49 (dt, \(J = 13.4, 6.5\) Hz, 1H), 4.32 – 4.16 (m, 3H), 3.59 – 3.51 (m, 1H), 3.50 – 3.41 (m, 1H), 2.61 – 2.49 (m, 2H), 2.27 – 2.09 (m, 2H), 2.05 – 1.96 (m, 1H), 1.92 – 1.83 (m, 1H), 1.68 – 1.48 (m, 2H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 166.3, 156.5, 145.7, 133.2, 132.3, 129.6, 121.8, 121.6, 119.6, 113.9, 112.4, 68.5, 49.9, 44.6, 35.9, 34.5, 27.62, 27.57, 23.7.
HRMS (ESI/QTOF) m/z: [M + Na]+ calcd for C_{22}H_{26}N_{6}NaO_{2} 429.2009; found 429.2008.

IR: ν (cm⁻¹) 3401, 3328, 2952, 2925, 2873, 1646, 1598, 1498, 1448, 1299, 1236, 1051, 755.

6-(Benzyl(2,5-dioxopyrrolidin-1-yl)amino)-3,4,5,6,9,10,11,12-octahydrobenzo[b][1]oxa[5,9]diaza-
cyclopentadecine-7,13(2H,8H)-dione (190)

According to a reported procedure, a mixture of ω-isocyanoaldehyde 125 (28.8 mg, 0.1 mmol, 1.0 equiv), benzylamine (20) (12.0 μL, 0.11 mmol, 1.1 equiv), N-hydroxysuccinimide (182) (17.3 mg, 0.15 mmol, 1.5 equiv) and ZnCl₂ (4.1 mg, 0.03 mmol, 0.3 equiv) in toluene (1 mL) was stirred at room temperature for 3 days. The mixture was filtered (rinsed with EtOAc) and the filtrate was evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO₂, 2% to 5% MeOH/CH₂Cl₂) to afford compound 190 in 22% (10.9 mg, 0.022 mmol) as white solid (RF = 0.31 (5% MeOH/CH₂Cl₂)).

¹H NMR (400 MHz, CDCl₃) δ 8.17 (dd, J = 7.8, 1.9 Hz, 1H), 7.73 (dd, J = 8.1, 4.4 Hz, 1H), 7.50 – 7.39 (m, 3H), 7.35 (t, J = 7.4 Hz, 2H), 7.31 – 7.24 (m, 2H), 7.07 (t, J = 7.5 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 4.17 (h, J = 5.6, 5.2 Hz, 2H), 4.08 (d, J = 12.4 Hz, 1H), 4.02 – 3.94 (m, 1H), 3.82 (dd, J = 11.5, 3.6 Hz, 1H), 3.77 (d, J = 12.4 Hz, 1H), 3.36 – 3.21 (m, 2H), 3.03 – 2.95 (m, 1H), 2.92 – 2.77 (m, 4H), 2.21 – 2.12 (m, 1H), 2.03 – 1.85 (m, 3H), 1.80 – 1.65 (m, 4H).

¹³C NMR (101 MHz, CDCl₃) δ 170.6, 165.7, 156.9, 156.4, 139.1, 132.7, 132.3, 128.7, 128.6, 127.5, 121.8, 121.3, 111.8, 69.0, 54.6, 51.6, 42.8, 35.5, 32.8, 29.9, 29.5, 25.8, 23.5.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + H]+ calcd for C_{27}H_{33}N_{4}O_{5} 493.2445; found 493.2439.

IR: ν (cm⁻¹) 2956, 2925, 1712, 1643, 1450, 1378, 1240, 1078, 1051, 755.

13-Hydroxy-2,3,4,5,6,7,10,11,12,13,16,17,18,19-tetradecahydrobenzo[b][1,16]diox[5,9]diaza-
cyclodocosine-14,20(9H,15H)-dione (198)
Yield: 71%, Eluent: 3% to 5% MeOH/CH₂Cl₂, Rₜ = 0.28 (5% MeOH/CH₂Cl₂)

¹H NMR (400 MHz, CDCl₃) δ 8.21 – 8.16 (m, 2H), 7.41 (td, J = 7.8, 1.9 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 6.88 (t, J = 6.2 Hz, 1H), 4.18 – 4.09 (m, 3H), 3.86 (d, J = 5.1 Hz, 1H), 3.56 – 3.29 (m, 8H), 2.04 – 1.49 (m, 16H).

¹³C NMR (101 MHz, CDCl₃) δ 174.5, 165.8, 157.2, 132.8, 132.3, 121.7, 121.3, 112.3, 72.8, 71.1, 70.8, 69.3, 37.1, 36.5, 33.6, 30.1, 29.9, 29.6, 28.4, 26.8, 26.6, 23.5.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + Na]⁺ calcd for C₂₂H₃₄N₂NaO₅⁺ 429.2360; found 429.2356.

IR: ν (cm⁻¹) 3606, 3392, 2952, 2915, 2867, 1641, 1524, 1378, 1240, 1078, 1051, 755.

14,20-Dioxo-2,3,4,5,6,7,9,10,11,12,13,14,15,16,17,18,19,20-octadecahydrobenzo[b][1,16]dioxo[5,9]diazacyclodocosin-13-yl acetate (199)

Yield: 85%, Eluent: 2% MeOH/CH₂Cl₂, Rₜ = 0.35 (5% MeOH/CH₂Cl₂)

¹H NMR (400 MHz, CDCl₃) δ Major rotamer: 8.17 (br t, J = 5.7 Hz, 1H), 8.08 (dd, J = 7.8, 1.9 Hz, 1H), 7.33 (ddd, J = 8.8, 7.3, 1.9 Hz, 1H), 6.96 (td, J = 7.6, 1.1 Hz, 1H), 6.88 (dd, J = 8.4, 1.0 Hz, 1H), 6.41 (br t, J = 6.3 Hz, 1H), 5.11 (t, J = 5.6 Hz, 1H), 4.14 – 4.02 (m, 2H), 3.51 – 3.29 (m, 7H), 3.28 – 3.17 (m, 1H), 2.07 (s, 3H), 1.92 – 1.79 (m, 4H), 1.73 (p, J = 6.8 Hz, 2H), 1.61 – 1.36 (m, 10H).

¹³C NMR (101 MHz, CDCl₃) δ Major rotamer: 170.1, 169.8, 165.8, 157.1, 132.6, 132.1, 121.8, 121.0, 112.3, 74.2, 70.2, 70.0, 69.2, 37.0, 36.8, 31.4, 30.1, 29.6, 29.5, 29.2, 28.9, 26.4, 26.1, 21.8, 21.1.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + Na]⁺ calcd for C₂₄H₃₆N₂NaO₆⁺ 471.2466; found 471.2460.

IR: ν (cm⁻¹) 3388, 2952, 2921, 2861, 1739, 1643, 1531, 1230, 1051, 755.
14,20-Dioxo-2,3,4,5,6,7,9,10,11,12,13,14,15,16,17,18,19,20-octadecahydrobenzo[b][1,16]dioxo-[5,9]diazacyclodocosin-13-yl (tert-butoxycarbonyl)glycinate (200)

Yield: 80%, Eluent: 2% to 5% MeOH/CH$_2$Cl$_2$, $R_f$ = 0.31 (5% MeOH/CH$_2$Cl$_2$)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.28 (br t, $J$ = 5.8 Hz, 1H), 8.12 (dd, $J$ = 7.8, 1.9 Hz, 1H), 7.37 (ddd, $J$ = 8.2, 7.3, 1.9 Hz, 1H), 7.05 – 6.98 (m, 2H), 6.92 (dd, $J$ = 8.4, 1.0 Hz, 1H), 5.45 (br t, $J$ = 5.8 Hz, 1H), 5.22 (t, $J$ = 5.4 Hz, 1H), 4.17 (dt, $J$ = 9.5, 6.4 Hz, 1H), 4.08 (dt, $J$ = 9.2, 6.8 Hz, 1H), 3.97 – 3.83 (m, 2H), 3.54 – 3.19 (m, 8H), 2.06 – 1.84 (m, 4H), 1.83 – 1.71 (m, 2H), 1.58 – 1.45 (m, 10H), 1.41 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.0, 169.4, 165.8, 157.1, 156.7, 132.6, 132.1, 121.8, 120.9, 112.3, 80.5, 74.9, 70.2, 70.0, 69.2, 43.1, 37.0, 36.6, 31.3, 29.8, 29.5, 29.2, 28.9, 28.4, 26.4, 26.0, 21.9.

HRMS (nanochip-ESI/LTQ-Orbitrap) $m/z$: [M + Na]$^+$ calcd for C$_{29}$H$_{45}$N$_3$NaO$_8$ $^+$ 586.3099; found 586.3091.

IR: $\nu$ (cm$^{-1}$) 3338, 2929, 2856, 1745, 1641, 1529, 1450, 1369, 1294, 1159, 1120, 966, 757.

N-Benzyl-N-(14,20-dioxo-2,3,4,5,6,7,9,10,11,12,13,14,15,16,17,18,19,20-octadecahydrobenzo[b]-[1,16]dioxo-[5,9]diazacyclodocosin-13-yl)acetamide (201)

Yield: 78%, Eluent: 2% to 3% MeOH/CH$_2$Cl$_2$, $R_f$ = 0.34 (5% MeOH/CH$_2$Cl$_2$)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.21 – 8.15 (m, 2H), 7.40 – 7.35 (m, 1H), 7.31 (t, $J$ = 7.4 Hz, 2H), 7.23 (t, $J$ = 7.3 Hz, 1H), 7.15 (d, $J$ = 7.8 Hz, 2H), 7.02 (t, $J$ = 7.6 Hz, 1H), 6.92 (d, $J$ = 8.3 Hz, 1H), 6.70 (br t, $J$ = 6.2 Hz, 1H), 4.91 (dd, $J$ = 10.3, 4.2 Hz, 1H), 4.70 (d, $J$ = 17.6 Hz, 1H), 4.59 (d, $J$ = 18.0 Hz, 1H), 4.15 – 4.06 (m, 2H), 3.50 – 3.31 (m, 7H), 3.22 – 3.09 (m, 1H), 2.14 – 2.08 (m, 1H), 2.04 (s, 3H), 1.94 – 1.88 (m, 2H), 1.81 – 1.73 (m, 2H), 1.61 – 1.37 (m, 10H), 1.32 – 1.23 (m, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 173.0, 170.9, 165.6, 157.1, 137.8, 132.6, 132.2, 128.8, 127.3, 125.9, 121.6, 121.0, 112.2, 70.1, 70.0, 69.1, 57.9, 49.2, 37.2, 37.0, 29.9, 29.6, 29.4, 29.1, 28.4, 26.5, 26.1, 23.8, 22.4.
HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + Na]^+ calcd for C_{31}H_{43}N_{3}NaO_{5}^+ 560.3095; found 560.3084.

IR: v (cm\(^{-1}\)) 3397, 3311, 2929, 2859, 1641, 1529, 1450, 1294, 1230, 1105, 755.

4-((21-Oxo-5,6,7,8,10,11,12,13,14,15,22,23,24,25-tetradecahydro-4H,21H-benzo[b]tetrazolo[1,5-i][1,16]dioxo[5,9]diazacyclodocosin-4-yl)amino)benzonitrile (202)

Yield: 53%, Eluent: 1% to 3% MeOH/CH\(_2\)Cl\(_2\), R\(_f\) = 0.39 (5% MeOH/CH\(_2\)Cl\(_2\))

\(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 8.18 (t, J = 6.0 Hz, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.36 (d, J = 8.3 Hz, 2H), 7.05 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 8.3 Hz, 1H), 6.62 (d, J = 8.5 Hz, 2H), 4.95 (t, J = 7.0 Hz, 1H), 4.52 (t, J = 7.1 Hz, 2H), 4.16 (t, J = 5.9 Hz, 2H), 3.57 – 3.32 (m, 6H), 2.36 – 2.03 (m, 4H), 1.92 – 1.82 (m, 2H), 1.71 – 1.31 (m, 10H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) δ 166.2, 157.0, 155.4, 149.5, 134.0, 133.1, 132.1, 121.42, 121.38, 119.9, 113.0, 112.4, 100.8, 70.5, 70.2, 69.1, 49.1, 45.5, 36.7, 33.7, 30.1, 29.9, 29.3, 28.4, 26.6, 26.3, 23.5.

HRMS (ESI/QTOF) m/z: [M + Na]^+ calcd for C_{29}H_{37}N_{7}NaO_{3}^+ 554.2850; found 554.2853.

IR: v (cm\(^{-1}\)) 3600, 2952, 1770, 1604, 1041, 755, 719.

2,3,4,5,6,7,9,10,11,12,16,17,18,19-Tetradecahydrobenzo[b][1,16]dioxo[5,9]diazacyclodocosine-13,14,20(15\(H\))-trione (203)

It was prepared from the same procedure as compound 144 followed by washing with 2 M HCl.

Yield: 68%, Eluent: 2% MeOH/CH\(_2\)Cl\(_2\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 8.38 (t, J = 6.0 Hz, 1H), 8.21 (dd, J = 7.8, 1.9 Hz, 1H), 7.41 (ddd, J = 8.2, 7.3, 1.9 Hz, 1H), 7.10 (t, J = 6.3 Hz, 1H), 7.04 (ddd, J = 8.1, 7.3, 1.0 Hz, 1H), 6.95 (dd, J = 8.4, 1.1
Hz, 1H), 4.16 (t, $J = 6.8$ Hz, 2H), 3.55 – 3.28 (m, 8H), 3.10 (t, $J = 7.0$ Hz, 2H), 2.03 – 1.91 (m, 2H), 1.89 – 1.73 (m, 5H), 1.72 – 1.59 (m, 2H), 1.58 – 1.38 (m, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 199.2, 165.8, 161.0, 157.3, 132.8, 132.4, 121.4, 121.1, 112.2, 71.3, 70.8, 69.2, 37.0, 36.7, 36.5, 29.8, 29.7, 29.3, 27.9, 26.8, 26.3, 21.6.

1-Benzy-5-hydroxy-4,5,8,9,10,11-hexahydrobenzo[b][1,5,9]triazacyclotetradecine-2,6,12-(1H,3H,7H)-trione (204)

Yield: 66%, Eluent: 2% to 3% MeOH/CH$_2$Cl$_2$, $R_f = 0.29$ (5% MeOH/CH$_2$Cl$_2$)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.48 (d, $J = 8.0$ Hz, 1H), 7.45 (br s, 1H), 7.36 (t, $J = 7.6$ Hz, 1H), 7.29 – 7.23 (m, 4H), 7.23 – 7.17 (m, 2H), 6.75 (br s, 1H), 6.57 (d, $J = 7.9$ Hz, 1H), 5.67 (d, $J = 14.4$ Hz, 1H), 4.18 (d, $J = 14.4$ Hz, 2H), 3.99 – 3.88 (m, 1H), 3.68 (dt, $J = 15.5$, 8.1 Hz, 1H), 3.18 (t, $J = 12.1$ Hz, 1H), 3.12 – 3.02 (m, 1H), 2.21 – 2.07 (m, 3H), 2.01 – 1.82 (m, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.9, 174.4, 167.8, 138.2, 136.9, 136.1, 131.0, 130.3, 129.5, 129.3, 129.1, 128.6, 127.8, 71.6, 53.6, 40.7, 38.9, 32.5, 29.0, 26.9.

HRMS (ESI/QTOF) $m/z$: [M + Na]$^+$ calcld for C$_{22}$H$_{25}$N$_3$NaO$_4$ 418.1737; found 418.1744.

IR: $\nu$ (cm$^{-1}$) 3064, 3037, 1641, 1535, 1442, 1303, 1261, 1197, 790, 723.

1-Benzy-2,6,12-trioxo-1,2,3,4,5,6,7,8,9,10,11,12-dodecahydrobenzo[b][1,5,9]triazacyclotetradecin-5-y1 acetate (205)

Yield: 77%, Eluent: 2% to 3% MeOH/CH$_2$Cl$_2$, $R_f = 0.22$ (5% MeOH/CH$_2$Cl$_2$)

HRMS (ESI/QTOF) $m/z$: [M + Na]$^+$ calcld for C$_{24}$H$_{27}$N$_3$NaO$_5$ 460.1843; found 460.1840.

IR: $\nu$ (cm$^{-1}$) 2956, 2925, 1739, 1652, 1525, 1230, 755.
1-Benzyl-2,6,12-trioxo-1,2,3,4,5,6,7,8,9,10,11,12-dodecahydrobenzo[\textit{b}][1,5,9]triazacyclotetradecin-5-yl (\textit{tert}-butoxycarbonyl)glycinate (206)

Yield: 93\%, Eluent: 2\% to 3\% MeOH/CH\textsubscript{2}Cl\textsubscript{2}, \textit{R\textsubscript{f}} = 0.22 (5\% MeOH/CH\textsubscript{2}Cl\textsubscript{2})

\textsuperscript{1}H NMR (400 MHz, MeOD) \( \delta \) 7.68 (dd, \( J = 7.7, 1.5 \) Hz, 0.3H), 7.63 (dd, \( J = 7.7, 1.6 \) Hz, 0.7H), 7.47 – 7.43 (m, 1H), 7.34 – 7.20 (m, 6H), 6.68 – 6.64 (m, 1H), 5.71 – 5.67 (m, 1H), 5.23 (dd, \( J = 7.2, 3.4 \) Hz, 0.7H), 4.79 (dd, \( J = 9.5, 3.3 \) Hz, 0.3H), 4.15 – 4.09 (m, 1H), 3.95 – 3.73 (m, 3H), 3.51 – 3.33 (m, 2H), 3.24 – 3.14 (m, 1H), 2.38 – 2.29 (m, 1H), 2.22 – 2.07 (m, 2H), 1.99 – 1.86 (m, 3H), 1.45 (s, 3H), 1.42 (s, 6H).

\textsuperscript{13}C NMR (101 MHz, MeOD) \( \delta \) Major rotamer: 172.8, 171.6, 171.1, 169.7, 158.4, 140.2, 138.9, 136.5, 132.2, 131.6, 130.2, 130.1, 130.0, 129.4, 128.6, 80.6, 74.6, 54.6, 42.9, 40.6, 39.5, 29.5, 28.7, 28.5, 27.0. Minor rotamer: 172.6, 171.8, 171.0, 169.3, 158.6, 140.5, 138.9, 135.7, 132.3, 131.8, 130.2, 130.0, 130.0, 129.4, 128.5, 80.7, 75.2, 54.7, 43.2, 39.2, 37.7, 30.2, 28.7, 27.5, 26.6.

HRMS (ESI/QTOF) \( m/z \): [M + Na]\textsuperscript{+} calcd for C\textsubscript{29}H\textsubscript{36}N\textsubscript{4}NaO\textsubscript{7} 575.2476; found 575.2485.

IR: \( \nu \) (cm\textsuperscript{-1}) 3318, 2956, 2921, 2856, 1718, 1654, 1525, 1450, 1369, 1257, 1164, 707.

\textit{N-Benzyl-N-(1-benzyl-2,6,12-trioxo-1,2,3,4,5,6,7,8,9,10,11,12-dodecahydrobenzo[\textit{b}][1,5,9]triazacyclotetradecin-5-yl)acetamide} (207)

Yield: 56\%, Eluent: 2\% to 3\% MeOH/CH\textsubscript{2}Cl\textsubscript{2}, \textit{R\textsubscript{f}} = 0.23 (5\% MeOH/CH\textsubscript{2}Cl\textsubscript{2})

\textsuperscript{1}H NMR (400 MHz, DMSO- \textit{d}_6) \( \delta \) 8.34 (dd, \( J = 7.4, 3.1 \) Hz, 0.6H), 8.21 (dd, \( J = 8.0, 3.5 \) Hz, 0.4H), 8.11 (dd, \( J = 7.2, 2.5 \) Hz, 0.6H), 8.01 (dd, \( J = 8.0, 3.8 \) Hz, 0.4H), 7.56 (dd, \( J = 7.7, 1.6 \) Hz, 1H), 7.46 – 7.39 (m, 1H), 7.36 – 7.12 (m, 10H), 7.08 – 7.06 (m, 1H), 6.65 (ddd, \( J = 20.0, 7.9, 1.2 \) Hz, 1H), 5.64 (d, \( J = 15.0 \) Hz, 1H), 5.40 (d, \( J = 15.0 \) Hz, 1H), 4.94 (d, \( J = 18.7 \) Hz, 1H), 4.75 (d, \( J = 18.7 \) Hz, 1H), 4.62 – 4.40 (m, 2H), 4.09 (d, \( J = 14.9 \) Hz, 1H), 4.04 (d, \( J = 15.0 \) Hz, 1H), 3.78 – 3.54 (m, 2H), 3.05 – 2.90 (m, 1H), 2.79 – 2.72 (m, 1H), 2.40 (s, 2H), 2.34 – 2.25 (m, 1H), 2.02 – 1.94 (m, 1H), 1.81 (s, 1H), 1.77 – 1.53 (m, 4H), 1.39 – 1.32 (m, 1H).
HRMS (ESI/QTOF) m/z: [M + H]^+ calcd for C_{31}H_{35}N_{4}O_{4}: 527.2653; found 527.2644.

IR: ν (cm\(^{-1}\)) 3596, 3538, 3307, 1652, 1529, 1434, 1413, 1303, 1261, 777, 707, 686.

14-Benzyl-18-(phenylamino)-5,6,7,8,17,18-hexahydrobenzo[\(b\)]tetrazolo[1,5-\(i\)][1,5,9]triaza-
tetradecine-9,15(14\(H\),16\(H\))-dione (208)

Yield: 28%, Eluent: 1% to 3% MeOH/CH\(_2\)Cl\(_2\), R\(_f\) = 0.45 (5% MeOH/CH\(_2\)Cl\(_2\))

HRMS (ESI/QTOF) m/z: [M + H]^+ calcd for C_{28}H_{30}N_{7}O_{2}: 496.2455; found 496.2462.

IR: ν (cm\(^{-1}\)) 3311, 1648, 1598, 1498, 1444, 1405, 1299, 1261, 730, 692.

To a solution of \(ω\)-isocyanoaldehyde 139 (28.8 mg, 1.0 equiv) in dry CH\(_2\)Cl\(_2\) (50 mL, 0.002 M) was added acetic acid (28.6 \(\mu\)L, 0.5 mmol, 5.0 equiv). The resulting solution was stirred at room temperature for 7 days.
for 7 days. Saturated NaHCO₃ was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered and evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO₂) (eluent: 2% to 5% MeOH/CH₂Cl₂) to yield compound 210 in 20% (6.8 mg, 0.02 mmol) (Rf = 0.45 (5% MeOH/CH₂Cl₂)).

1H NMR (400 MHz, CDCl₃) δ 7.57 (d, J = 7.6 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.28 – 7.21 (m, 1H), 7.12 (br s, 1H), 7.06 (dd, J = 8.2, 2.3 Hz, 1H), 6.54 (s, 1H), 5.09 (t, J = 6.1 Hz, 1H), 4.28 – 4.18 (m, 2H), 3.76 – 3.68 (m, 1H), 3.61 – 3.47 (m, 2H), 3.43 – 3.35 (m, 1H), 1.98 (s, 3H), 2.04 – 1.53 (m, 8H).

13C NMR (101 MHz, CDCl₃) δ 170.9, 169.8, 167.6, 158.5, 135.8, 130.3, 121.5, 121.4, 112.3, 73.4, 68.4, 40.2, 40.0, 30.8, 29.5, 28.0, 21.8, 21.0.

HRMS m/z: [M + Na]⁺ calcd for C₁₈H₂₄N₂NaO₅⁺ 371.1577; found 371.1579.

IR: ν (cm⁻¹) 3288, 2927, 2852, 1737, 1648, 1583, 1536, 1434, 1238, 1025, 717.
Towards the Total Synthesis of Jamaicensamide A

Methyl (tert-butoxycarbonyl)-L-alanyl-L-serinate (216)

According to a reported procedure, to a solution of L-serine methyl ester hydrochloride (214) (3.03 g, 19.5 mmol, 1.3 equiv) and N-(tert-butoxycarbonyl)glycine (215) (2.84 g, 15.0 mmol, 1.0 equiv) in dry CH₂Cl₂ (100 mL) was added DIPEA (4.0 mL, 24.0 mmol, 1.6 equiv) dropwise at 0 °C. After stirring at 0 °C for 20 min, EDC·HCl (3.45 g, 18.0 mmol, 1.2 equiv) was added and the mixture was stirred at 0 °C for 20 min followed by the addition of HOBt (2.43 g, 18.0 mmol, 1.2 equiv) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 18 h. The mixture was quenched with 0.5 M HCl and the layers were separated. The aqueous layer was extracted with CH₂Cl₂. The combined organic layer was washed with H₂O and sat. aq. NH₄Cl, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO₂, 2% to 3% MeOH/CH₂Cl₂) to yield 216 in 48% yield (2.11 g, 7.26 mmol) as colorless oil (Rf = 0.42 (5% MeOH/CH₂Cl₂)).

¹H NMR (400 MHz, CDCl₃) δ 6.95 (d, J = 7.6 Hz, 1H), 5.07 (d, J = 7.1 Hz, 1H), 4.64 (dt, J = 7.3, 3.5 Hz, 1H), 4.14 (p, J = 7.0 Hz, 1H), 3.96 (dd, J = 6.6, 3.6 Hz, 2H), 3.79 (s, 3H), 1.44 (s, 9H), 1.39 (d, J = 7.0 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 173.2, 170.8, 155.7, 80.3, 62.4, 54.6, 52.4, 50.5, 28.2, 18.1.

Methyl N-((tert-butoxycarbonyl)-L-alanyl)-O-(tert-butyldimethylsilyl)-L-serinate (217)

To a solution of 216 (2.11 g, 7.26 mmol, 1.0 equiv) and DMAP (115.3 mg, 0.94 mmol, 0.13 equiv) in CH₂Cl₂ (15 mL) were added TBSCl (1.42 g, 9.44 mmol, 1.3 equiv) and NEt₃ (2.0 mL, 14.52 mmol, 2.0 equiv) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 19 h.
After completion, the mixture was quenched with sat. aq. NH₄Cl. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layer was washed with sat. aq. NH₄Cl and brine, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO₂, 15% to 20% EtOAc/PE) to yield **217** in 83% yield (2.43 g, 6.02 mmol) as white solid (Rᵋ = 0.26 (5% 20% EtOAc/PE)).

1H NMR (400 MHz, CDCl₃) δ 6.70 (d, J = 8.3 Hz, 1H), 5.01 (br s, 1H), 4.62 (dt, J = 8.3, 3.0 Hz, 1H), 4.22 (br s, 1H), 4.07 (dd, J = 10.1, 2.7 Hz, 1H), 3.81 (dd, J = 10.1, 3.2 Hz, 1H), 3.74 (s, 3H), 1.45 (s, 9H), 1.39 (d, J = 7.1 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

13C NMR (101 MHz, CDCl₃) δ 172.4, 170.6, 63.4, 54.2, 52.4, 28.3, 25.7, 18.8, 18.2, -5.5, -5.7.

**Methyl N-((S)-2-((tert-butoxycarbonyl)amino)propanethioyl)-O-(tert-butyldimethylsilyl)-L-serinate (218)**

According to a reported procedure, to a solution of **217** (2.43 g, 6.02 mmol, 1.0 equiv) in toluene (60 mL) was added Lawesson’s reagent (1.70 g, 4.21 mmol, 0.7 equiv) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred at 80 °C for 14 h. The mixture was allowed to cool to room temperature and quenched with sat. aq. NaHCO₃. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO₂, 5% to 10% EtOAc/PE) to yield **218** in 79% yield (1.99 g, 4.73 mmol) as white solid (Rᵋ = 0.26 (5% 20% EtOAc/PE)).

1H NMR (400 MHz, CDCl₃) δ 8.44 (br d, J = 5.6 Hz, 1H), 5.20 (dt, J = 7.7, 2.7 Hz, 2H), 4.50 (p, J = 7.0 Hz, 1H), 4.11 (dd, J = 10.3, 2.5 Hz, 1H), 4.03 (dd, J = 10.3, 2.9 Hz, 1H), 3.77 (s, 3H), 1.48 (d, J = 7.0 Hz, 3H), 1.44 (s, 9H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

13C NMR (101 MHz, CDCl₃) δ 205.5, 169.7, 154.9, 62.3, 59.4, 52.6, 28.3, 25.7, 22.1, 18.2, -5.50, -5.7.

**Methyl ((S)-2-((tert-butoxycarbonyl)amino)propanethioyl)-L-serinate (219)**

According to a reported procedure, to a solution of **218** (1.98 g, 4.70 mmol, 1.0 equiv) in CH₂Cl₂ (24 mL) was added TBAF (1 M in THF) (7.1 mL, 7.05 mmol, 1.5 equiv) dropwise at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 4 h. After completion, the mixture was quenched with H₂O at 0 °C. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layer was washed with sat. aq. NaHCO₃ and brine, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO₂,
40% EtOAc/PE) to yield 219 in 90% yield (1.30 g, 4.25 mmol) as yellowish viscous oil (Rf = 0.35 (50% EtOAc/PE)).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.70 (s, 1H), 5.40 – 5.15 (m, 2H), 4.45 (p, \(J = 6.6\) Hz, 1H), 4.20 (d, \(J = 11.9\) Hz, 1H), 4.02 (d, \(J = 11.4\) Hz, 1H), 3.83 (s, 3H), 1.74 (s, 1H), 1.48 (d, \(J = 6.9\) Hz, 3H), 1.42 (s, 9H).

\(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 206.5, 170.2, 156.3, 80.8, 61.4, 60.0, 59.8, 53.0, 44.2, 28.4, 24.9, 22.9, 22.3.

**Methyl (S)-2-(1-((tert-butoxycarbonyl)amino)ethyl)thiazole-4-carboxylate (220)**

To a solution of 219 (1.03 g, 3.35 mmol, 1.0 equiv) and PPh\(_3\) (878.7 mg, 3.35 mmol, 1.0 equiv) in THF (34 mL) was added DEAD (2.2 M in toluene) (1.5 mL, 3.35 mmol, 1.0 equiv) dropwise at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 17 h. After completion, the mixture was quenched with sat. aq. NH\(_4\)Cl. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with sat. aq. NaHCO\(_3\) and brine, dried over Na\(_2\)SO\(_4\), filtered and evaporated to dryness.

The crude mixture was dissolved in CH\(_2\)Cl\(_2\) (34 mL) and cooled to -10 °C. DBU (1.5 mL, 10.05 mmol, 3.0 equiv) was added dropwise and the solution was stirred at -10 °C for 10 min followed by the slow addition of bromotrichloromethane (1.0 mL, 10.05 mmol, 3.0 equiv) at the same temperature. The resulting solution was stirred at -10 °C for 2 h. The mixture was quenched with sat. aq. NaHSO\(_4\) and the layers were separated. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) and the combined organic layer was washed dried over Na\(_2\)SO\(_4\), filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO\(_2\), 20% EtOAc/PE) to yield 220 in 89% yield over two steps (850.4 mg, 2.97 mmol) as white solid (Rf = 0.44 (40% EtOAc/PE)).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.08 (s, 1H), 5.23 (br s, 1H), 5.10 – 5.07 (m, 1H), 3.92 (s, 3H), 1.60 (d, \(J = 6.9\) Hz, 3H), 1.42 (s, 9H).

\(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 175.3, 161.9, 155.0, 146.9, 127.5, 80.4, 52.5, 49.0, 28.4, 21.8.
Methyl (S)-2-(1-formamidoethyl)thiazole-4-carboxylate (222)

A solution of 220 (621.9 mg, 2.17 mmol, 1.0 equiv) in 4 M HCl in dioxane (22 mL) was stirred at room temperature for 2 h. After the completion of reaction, the mixture was evaporated to dryness. To the crude mixture in dry ethyl formate (5.2 mL, 65.1 mmol, 30.0 equiv) was added DIPEA (1.4 mL, 8.68 mmol, 4.0 equiv). The resulting mixture was heated to reflux and stirred for 16 h. The mixture was allowed to cool to room temperature and evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO₂, 2% MeOH/CH₂Cl₂) to afford compound 222 in 79% yield (368.9 mg, 1.72 mmol) as pale yellow solid (Rᵋ = 0.35 (5% MeOH/CH₂Cl₂)).

¹H NMR (400 MHz, CDCl₃) δ 8.24 (s, 1H), 8.13 (s, 1H), 6.49 (br s, 1H), 5.51 (p, J = 7.4 Hz, 1H), 3.95 (s, 3H), 1.68 (d, J = 6.9 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 172.3, 161.7, 160.5, 146.8, 127.9, 52.7, 46.2, 22.1.

Methyl (S,E)-3-(2-(1-formamidoethyl)thiazol-4-yl)acrylate (224)

To a solution of 222 (278.3 mg, 1.3 mmol, 1.0 equiv) in THF (13 mL) was added DIBAL (1.2 M in toluene) (3.3 mL, 3.9 mmol, 3.0 equiv) dropwise at -78 °C. The resulting solution was stirred at -78 °C for 4 h. MeOH was then added and the resulting solution was evaporated to dryness. The residue was dissolved in EtOAc. Sat. aq. NH₄Cl was then added and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and evaporated to dryness to give crude aldehyde 223.

To a suspension of NaH (60 % dispersion in mineral oil) (126.0 mg, 3.15 mmol, 1.5 equiv) in THF (10 mL) was added trimethyl phosphonoacetate (0.37 mL, 2.31 mmol, 1.1 equiv) dropwise at 0 °C. The mixture was allowed to warm to room temperature and stirred for 30 min before the addition of the solution of crude 223 in THF (11 mL) dropwise at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 16 h. After completion of reaction, sat. aq. NaHCO₃ was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by flash column chromatography.
(SiO₂, 30% acetone/PE) to yield 224 in 70% yield over two steps (217.3 mg, 0.90 mmol) as white solid ($R_t = 0.42$ (40% acetone/PE)).

$^1$H NMR (400 MHz, CDCl₃) δ 8.24 (s, 1H), 8.13 (s, 1H), 6.49 (br s, 1H), 5.51 (p, $J = 7.4$ Hz, 1H), 3.95 (s, 3H), 1.68 (d, $J = 6.9$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl₃) δ 172.32, 161.74, 160.47, 146.75, 127.92, 52.68, 46.16, 22.09.

(S,E)-3-(2-(1-formamidoethyl)thiazol-4-yl)acrylic acid (225)

To a solution of 224 (58.5 mg, 0.24 mmol, 1.0 equiv) in THF (2.4 mL) and H₂O (2.4 mL) was added LiOH (17.2 mL, 0.72 mmol, 3.0 equiv). The resulting solution was stirred at room temperature for 3 h. The mixture was extracted with sat. aq. NaHCO₃, the aqueous layer was acidified with 1 M HCl until pH = 4 and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered and evaporated to dryness to give 225 in quantitative yield (54.1 mg, 0.239 mmol) as white solid which was used directly for the next step without purification.

$^1$H NMR (400 MHz, MeOD) δ 8.16 (s, 1H), 7.71 (s, 1H), 7.59 (d, $J = 17.3$ Hz, 1H), 6.66 (d, $J = 15.6$ Hz, 1H), 5.39 (q, $J = 7.0$ Hz, 1H), 1.63 (d, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (101 MHz, MeOD) δ 175.5, 170.4, 163.3, 152.8, 138.0, 123.3, 121.6, 47.3, 21.1.
tert-Butyl (S)-(1-amino-1-thioxopropan-2-yl)carbamate (228)

According to a reported procedure, to a solution of L-alanine (226) (2.67 g, 30.0 mmol, 1.0 equiv) in 1,4-dioxane (67 mL) and H₂O (33 mL) were added 1 M NaOH (30 mL), Boc₂O (9.82 g, 45.0 mmol, 1.5 equiv) and NaHCO₃ (2.52 g, 30.0 mmol, 1.0 equiv) respectively at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 20 h. After completion of reaction, solvent was removed to a half of the original volume and the residue was diluted with EtOAc. The mixture was acidified with 1 M KHSO₄ until pH = 2 at 0 °C. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with H₂O and brine, dried over Na₂SO₄, filtered and evaporated to dryness to give crude (tert-butoxycarbonyl)-L-alanine (215).

According to a reported procedure, to a solution of the crude 215 in THF (150 mL) were added 4-methylmorpholine (3.6 mL, 33.0 mmol, 1.1 equiv) and isobutyl chloroformate (4.3 mL, 33.0 mmol, 1.1 equiv) respectively at -10 °C. After stirring the solution at -10 °C for 20 min, 25% ammonia (10.2 mL) was added at the same temperature. The resulting solution was allowed to warm to room temperature and stirred for 14 h. THF was removed and the residue was dissolved in EtOAc and H₂O. The pH of solution was adjusted to 3 with 1 M KHSO₄ and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with sat. aq. NaHCO₃, H₂O and brine, dried over Na₂SO₄, filtered and evaporated to dryness to give crude tert-butyl (S)-(1-amino-1-oxopropan-2-yl)carbamate (227).

According to a reported procedure, to a solution of the crude 227 in THF (300 mL) was added Lawesson’s reagent (9.10 g, 22.5 mmol, 0.75 equiv) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 16 h. After completion of reaction, the mixture was quenched with sat. aq. NaHCO₃. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with H₂O and brine, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO₂, 30% acetone/PE) to yield 228 in 73% yield over three steps (4.49 g, 22.0 mmol) as white solid (Rf = 0.42 (40% acetone/PE)).

1H NMR (400 MHz, CDCl₃) δ 8.34 (br s, 1H), 7.94 (br s, 1H), 5.47 (br s, 1H), 4.59 (p, J = 7.0 Hz, 1H), 1.45 (d, J = 6.9 Hz, 3H), 1.42 (s, 9H).

13C NMR (101 MHz, CDCl₃) δ 210.7, 155.6, 80.6, 55.2, 28.5, 22.0.

Methyl (S)-2-((tert-butoxycarbonyl)amino)ethyl)thiazole-4-carboxylate (220)

According to a reported procedure, to a solution of 228 in DME (190 mL) was added KHCO₃ (18.73 g, 187.0 mmol, 8.7 equiv) at -15 °C. After stirring at the -15 °C for 15 min, methyl bromopyruvate (7.6 mL, 71.0 mmol, 3.3 equiv) was added dropwise at -15 °C. The mixture was stirred at -15 °C for 30 min.
and then at room temperature for 30 min. A solution of TFAA (13.4 mL, 95.5 mmol, 4.44 equiv) and 2,6-lutidine (23.2 mL, 199.3 mmol, 9.27 equiv) was added dropwise at -15 °C. The resulting mixture was allowed to warm to room temperature and stirred for 18 h. After completion of reaction, DME was removed. The residue was dissolved in H₂O and extracted with CH₂Cl₂. The combined organic layers was dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO₂, 10% to 20% EtOAc/PE) to yield 220 in 77% yield (4.71 g, 16.4 mmol) as white solid (Rᵣ = 0.44 (40% EtOAc /PE)).

Methyl L-proline hydrochloride (230)

According to a reported procedure,⁶³ to a solution of L-proline (229) (2.30 g, 20.0 mmol, 1.0 equiv) in MeOH (20 mL) was added SOCl₂ (1.9 mL, 26.0 mmol, 1.3 equiv) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 16 h. After completion of reaction, the reaction mixture was evaporated to dryness to give 230 as colorless viscous oil in quantitative yield which was used directly for the next step without purification.

Methyl (S)-2-amino-3-(5-hydroxy-1H-indol-3-yl)propanoate hydrochloride (232)

According to a reported procedure,⁶⁴ to a solution of 5-Hydroxy-L-tryptophan (231) (4.40 g, 20.0 mmol, 1.0 equiv) in MeOH (67 mL) was added SOCl₂ (2.9 mL, 40.0 mmol, 2.0 equiv) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred at 40 °C for 16 h. After completion of reaction, the reaction mixture was cooled down to room temperature and evaporated to dryness to give 232 as black solid in quantitative yield which was used directly for the next step without purification.

¹H NMR (400 MHz, MeOD) δ 7.20 – 7.17 (m, 1H), 7.12 (d, J = 2.5 Hz, 1H), 6.68 (dd, J = 8.9, 2.5 Hz, 1H), 4.26 (t, J = 6.6 Hz, 1H), 3.76 (s, 3H), 3.31 – 3.24 (m, 2H).

¹³C NMR (101 MHz, MeOD) δ 170.8, 151.7, 133.1, 128.8, 126.4, 113.1, 113.0, 106.5, 54.5, 53.7, 27.6.
According to a reported procedure, to a solution of L-ornithine hydrochloride (233) (3.37 g, 20.0 mmol, 1.0 equiv) in 0.5 M NaOH (43 mL) was added a solution of CuSO₄ (1.88 g, 11.8 mmol, 0.59 equiv) in H₂O (200 mL). After stirring the resulting blue solution at room temperature for 5 h, NaHCO₃ (3.36 g, 40.0 mmol, 2.0 equiv) and CbzCl (3.84 g, 27.0 mmol, 1.35 equiv) were added at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 15 h. The blue precipitate was collected by filtration and washed with a small amount of H₂O. It was dissolved in 100 mL of 0.5 M EDTA (pH = 8) and the resulting mixture was stirred at room temperature for 14 h. After filtration, the white solid was collected and washed with a small amount of H₂O. It was suspended in 1,4-dioxane (100 mL) and H₂O (100 mL) followed by the addition of Boc₂O (7.42 g, 34.0 mmol, 1.7 equiv). The resulting mixture was basified to pH = 10 with 4 M NaOH and stirred for 15 h. After completion of reaction, MeOH (44 mL) was added and the resulting solution was stirred at room temperature for another 14 h. Organic solvents were removed, the aqueous layer was acidified until pH = 3 with 2 M HCl at 0 °C and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO₂, 2% to 10% MeOH/CH₂Cl₂) to yield 236 in 50% yield (3.67 g, 10.0 mmol) as colorless solid (Rf = 0.26 (5% MeOH/CH₂Cl₂)).

**1H NMR (400 MHz, MeOD)** δ 7.34 – 7.28 (m, 5H), 5.06 (s, 2H), 4.07 (dd, J = 8.6, 4.9 Hz, 1H), 3.13 (t, J = 6.6 Hz, 2H), 1.88 – 1.80 (m, 1H), 1.69 – 1.53 (m, 3H), 1.44 (s, 9H).

**13C NMR (101 MHz, MeOD)** δ 176.1, 158.9, 158.1, 138.4, 129.4, 128.9, 128.7, 80.5, 67.3, 54.7, 41.3, 30.1, 28.7, 27.4.

**tert-Butyl (S)-(1-(methoxy(methyl)amino)-1-oxopentan-2-yl)carbamate (239)**
According to a reported procedure, to a solution of L-norvaline (237) (2.34 g, 20.0 mmol, 1.0 equiv) in THF (20 mL) and H₂O (15 mL) was added a solution of NaOH (800 mg, 20.0 mmol, 1.0 equiv) in H₂O (5 mL) at 0 °C. After stirring at 0 °C for 10 min, Boc₂O (5.24 g, 24.0 mmol, 1.2 equiv) was added at the same temperature. The resulting solution was allowed to warm to room temperature and stirred for 14 h. The mixture was acidified with 2 M HCl until pH = 2 at 0 °C and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with H₂O and brine, dried over Na₂SO₄, filtered and evaporated to dryness.

According to a reported procedure, the residue was dissolved in CH₂Cl₂ (80 mL) and placed at 0 °C. DMAP (2.44 g, 20.0 mmol, 1.0 equiv), N,O-dimethylhydroxylamine (1.95 g, 20.0 mmol, 1.0 equiv), EDC·HCl (3.83 g, 20.0 mmol, 1.0 equiv) and 4-methylmorpholine (2.2 mL, 20.0 mmol, 1.0 equiv) were added respectively. The resulting mixture was allowed to warm to room temperature and stirred for 16 h. After completion of reaction, 2 M HCl was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂. The combined organic layer was washed with sat. aq. NaHCO₃ and brine, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO₂, 20% to 30% EtOAc/PE) to yield 239 in 83% yield (4.34 g, 16.7 mmol) as colorless oil (Rf = 0.29 (30% EtOAc/PE)).

1H NMR (400 MHz, CDCl₃) δ 5.13 (br d, J = 9.4 Hz, 1H), 4.68 (br s, 1H), 3.77 (s, 3H), 3.20 (s, 3H), 1.71 – 1.62 (m, 1H), 1.54 – 1.32 (m, 3H), 1.43 (s, 9H), 0.93 (t, J = 7.3 Hz, 3H).

13C NMR (101 MHz, CDCl₃) δ 159.8, 79.6, 61.7, 50.3, 35.3, 32.2, 28.5, 18.8, 13.9.

(S)-2-Amino-N-methoxy-N-methylpentanamide hydrochloride (240)

A solution of 239 (1.30 g, 5.0 mmol, 1.0 equiv) in 4 M HCl in dioxane (37.5 mL) was stirred at room temperature for 2 h. The mixture was then evaporated to dryness to give 240 as yellowish oil in quantitative yield which was used directly for the next step without purification.
Methyl (S)-2-((E)-3-((2-(S)-1-formamidoethyl)thiazol-4-yl)acrylamido)-3-(5-hydroxy-1H-indol-3-yl)propanoate (241)

To a solution of 232 (828.4 mg, 3.06 mmol, 1.0 equiv) and 225 (693.0 mg, 3.06 mmol, 1.0 equiv) in CH₂Cl₂ (26 mL) and DMF (4 mL) were added NEt₃ (1.3 mL, 9.18 mmol, 3.0 equiv), EDC·HCl (654.3 mg, 3.37 mmol, 1.1 equiv) and HOBt (454.8 mg, 3.37 mmol, 1.1 equiv) respectively at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 16 h. Sat. aq. NH₄Cl was added, the layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layer was washed with H₂O (6 times) and brine, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO₂, 2% to 5% MeOH/CH₂Cl₂) to yield 241 in 83% yield (1.12 g, 2.5 mmol) as colorless oil (Rf = 0.29 (5% MeOH/CH₂Cl₂)).

(S)-2-((E)-3-((2-(S)-1-Formamidoethyl)thiazol-4-yl)acrylamido)-3-(5-hydroxy-1H-indol-3-yl)propanoic acid (242)

To a solution of 241 (1.12 g, 2.54 mmol, 1.0 equiv) in MeOH (8.5 mL), THF (8.5 mL) and H₂O (8.5 mL) was added LiOH (182.5 mg, 7.6 mmol, 3.0 equiv). The resulting solution was stirred at room temperature for 4 h. The mixture was then evaporated to dryness, the residue was dissolved in H₂O and then acidified with 1 M HCl until pH = 4. The mixture was extracted with EtOAc and the combined organic layer was dried over Na₂SO₄, filtered and evaporated to dryness to give 242 in quantitative yield which was used directly for the next step without purification.
Methyl ((S)-5-(((benzyl)oxy)carbonyl)amino)-2-(((tert-butoxycarbonyl)amino)pentanoyl)-L-prolinate (243)

To a solution of 230 (2.91 g, 17.6 mmol, 1.0 equiv) and 236 (6.45 g, 17.6 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (60 mL) was added DIPEA (14.5 mL, 88.0 mmol, 5.0 equiv) dropwise at 0 °C. After stirring at 0 °C for 20 min, HOBt (4.76 g, 35.2 mmol, 2.0 equiv) was added and the mixture was stirred at the same temperature for 20 min before the addition of EDC·HCl (6.74 g, 35.2 mmol, 2.0 equiv). The resulting mixture was allowed to warm to room temperature and stirred for 20 h. After completion of reaction, 10% aq. citric acid (100 mL) was added. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layer was washed with sat. aq. NaHCO$_3$, H$_2$O and brine, dried over Na$_2$SO$_4$, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO$_2$, 1% to 2% MeOH/CH$_2$Cl$_2$) to yield 243 in 89% yield (7.44 g, 15.58 mmol) as colorless viscous oil (R$_f$ = 0.45 (5% MeOH/CH$_2$Cl$_2$)).
Benzyl tert-buty ([(S)-5-((S)-2-(((S)-1-(methoxy(methyl)amino)-1-oxopentan-2-yl)carbamoyl)pyrrolidin-1-yl)-5-oxopentane-1,4-diyl)dicarbamate (245)

To a solution of 243 (7.81 g, 16.34 mmol, 1.0 equiv) in MeOH (68 mL) at 0 °C was added the solution of NaOH in H2O (14 mL) dropwise. The resulting solution was allowed to warm to room temperature and stirred for 4 h. MeOH was evaporated and the pH of the residue was adjusted to 3 with 10% aq. citric acid. The mixture was extracted with EtOAc and the combined organic layers were washed with brine dried over Na2SO4, filtered and evaporated to dryness to give crude 244 which was used directly for the next step without purification.

To a solution of the crude 244 and 240 (3.21 g, 16.34 mmol, 1.0 equiv) in CH2Cl2 (163 mL) was added DIPEA (8.1 mL, 49.04 mmol, 3.0 equiv) at 0 °C. After stirring at 0 °C for 20 min, HOBt (2.65 g, 19.61 mmol, 1.2 equiv) and EDC·HCl (3.76 g, 19.61 mmol, 1.2 equiv) were added at the same temperature. The resulting mixture was allowed to warm to room temperature and stirred for 24 h. H2O was added and the layers were separated. The aqueous layer was extracted with CH2Cl2. The combined organic layer was dried over Na2SO4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO2, 2% MeOH/CH2Cl2) to yield 245 in 53% yield (5.26 g, 8.69 mmol) as colorless solid (Rf = 0.45 (5% MeOH/CH2Cl2)).

tert-Butyl ([(S)-5-((E)-3-(2-((S)-1-formamidoethyl)thiazol-4-yl)acrylamido)-3-(5-hydroxy-1H-indol-3-yl)propanamido)-1-((S)-2-(((S)-1-(methoxy(methyl)amino)-1-oxopentan-2-yl)carbamoyl)pyrrolidin-1-yl)-1-oxopentan-2-yl)carbamate (247)

To a solution of 245 (1.88 g, 3.11 mmol, 1.2 equiv) in MeOH (31 mL) was added 10% Pd/C (155.5 mg). The resulting mixture was stirred at room temperature under H2 balloon for 4 h. The mixture was filtered through a pad of Celite (rinsed with MeOH) and the filtrate was evaporated to dryness. The residue together with the crude 242 (2.54 mmol) was dissolved in DMF (25 mL). DIPEA (1.7 mL, 10.16 mmol, 4.0 equiv) was added dropwise at 0 °C. After stirring at 0 °C for 20 min, HOBt (686.4 mg, 5.08 mmol, 2.0 equiv) and EDC·HCl (973.8 mg, 5.08 mmol, 2.0 equiv) were added at the same temperature. The resulting mixture was allowed to warm to room temperature and stirred for 24 h. Sat. aq. NH4Cl was added and the mixture was extracted with EtOAc. The combined organic layers were washed with H2O (6 times) and brine, dried over Na2SO4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO2, 2% MeOH/CH2Cl2) to yield 247 in 52% yield (1.16 g, 1.31 mmol) as colorless solid (Rf = 0.45 (5% MeOH/CH2Cl2)).
Benzyl *tert*-butyl ((S)-5-(((S)-2-(((S)-1,3-dioxolan-2-yl)butyl)carbamoyl)pyrrolidin-1-yl)-5-oxopentane-1,4-diyl)dicarbamate (253)

To a solution of 245 (1.82 g, 3.0 mmol, 1.0 equiv) in THF (30 mL) was added LiAlH₄ (91.0 mg, 2.4 mmol, 0.8 equiv) portionwise at 0 °C. The resulting suspension was allowed to stir at 0 °C for 1 h. The mixture was quenched with 1 M HCl at 0 °C and extracted with EtOAc. The combined organic layers were washed with sat. NaHCO₃, H₂O and brine, dried over Na₂SO₄, filtered and evaporated to dryness to give crude 252 which was used directly for the next step without purification.

To a solution of crude 252 in toluene (30 mL) were added ethylene glycol (4 mL) and *p*-toluenesulfonic acid monohydrate (57.0 mg, 0.3 mmol, 0.1 equiv). The resulting solution was heated to reflux and stirred for 14 h. After completion, the mixture was allowed to cool to room temperature, sat. NaHCO₃ was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO₂, 2% MeOH/CH₂Cl₂) to yield 253 in 72% yield over two steps (1.27 g, 2.15 mmol).

tert-Butyl ((S)-1-(((S)-2-(((S)-1,3-dioxolan-2-yl)butyl)carbamoyl)pyrrolidin-1-yl)-5-(((S)-2-((E)-3-2-(((S)-1-formamidoethyl)thiazol-4-yl)acrylamido)-3-(5-hydroxy-1H-indol-3-yl)propanamido)-1-oxopentan-2-yl)carbamate (255)

To a solution of 253 (1.25 g, 2.1 mmol, 1.0 equiv) in MeOH (21 mL) was added 10% Pd/C (106.0 mg). The resulting mixture was stirred at room temperature under H₂ balloon for 4 h. The mixture was filtered through a pad of Celite (rinsed with MeOH) and the filtrate was evaporated to dryness. The residue together with the crude 242 (2.0 mmol) was dissolved in DMF (20 mL). DIPEA (1.4 mL, 8.0 mmol, 4.0
equiv) was added dropwise at 0 °C. After stirring at 0 °C for 20 min, HOBt (540.5 mg, 4.0 mmol, 2.0 equiv) and EDC·HCl (767.0 mg, 4.0 mmol, 2.0 equiv) were added at the same temperature. The resulting mixture was allowed to warm to room temperature and stirred for 24 h. Sat. aq. NH₄Cl was added and the mixture was extracted with EtOAc. The combined organic layers were washed with H₂O (6 times) and brine, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO₂, 2% to 10% MeOH/CH₂Cl₂) to yield 255 in 53% yield (919.0 mg, 1.06 mmol).

Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-((triisopropylsilyl)oxy)-1H-indol-3-yl)propanoate (258)

According to a reported procedure,⁶⁹ to a solution of 5-hydroxy-L-tryptophan (4.4 g, 20.0 mmol, 1.0 equiv) in MeOH (20 mL) was added SOCl₂ (1.9 mL, 26.0 mmol, 1.3 equiv) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred at 40 °C for 16 h. After completion of reaction, the reaction mixture was evaporated to dryness to give 256 as black solid in quantitative yield which was used directly for the next step without purification.

To a solution of crude 256 in CH₃CH (80 mL) and H₂O (20 mL) was added NaHCO₃ at 0°C to adjust the pH of the solution to 8. Boc₂O (5.24 g, 24.0 mmol, 1.2 equiv). The resulting mixture was allowed to warm to room temperature and stirred for 16 h. Sat. aq. NaHCO₃ was added and the mixture was extracted with EtOAc. The combined organic layers were washed brine, dried over Na₂SO₄, filtered and evaporated to dryness to give 257 as yellowish solid which was used directly for the next step without purification.

According to a reported procedure,⁷⁰ to a solution of crude 257 and imidazole (10.9 g, 160.0 mmol, 8.0 equiv) in DMF (40 mL) was added TIPSCI (5.1 mL, 24.0 mmol, 1.2 equiv). The resulting solution was stirred at room temperature for 16 h. Sat. aq. NaHCO₃ was added and the mixture was extracted with EtOAc. The combined organic layers were washed H₂O (6 times) and brine, dried over Na₂SO₄, filtered
and evaporated to dryness. The residue was purified by flash column chromatography (SiO₂, 2% to 3% MeOH/CH₂Cl₂) to yield 258 in 65% yield (6.38 g, 13.0 mmol).

**Methyl (S)-2-amino-3-(5-((triisopropylsilyl)oxy)-1H-indol-3-yl)propanoate (259)**

To a solution of 258 (5.89 g, 12.0 mmol, 1.0 equiv) in EtOAc (60 mL) was added concentrated HCl (20 mL). The resulting solution was stirred at room temperature for 2 h. The mixture was then evaporated to dryness to give 259 in quantitative yield which was used directly for the next step without purification.

![Chemical structure of 259 and 260](image)

**Methyl (S)-2-(((E)-3-(2-((S)-1-formamidoethyl)thiazol-4-yl)acrylamido)-3-(5-((triisopropylsilyl)oxy)-1H-indol-3-yl)propanoic acid (261)**

To a solution of crude 259 (12.0 mmol) and crude 225 (12.0 mmol) in DMF (120 mL) was added DIPEA (8.4 mL, 48.0 mmol, 4.0 equiv) dropwise at 0 °C. After stirring at 0 °C for 20 min, HOBt (3.24 g, 24.0 mmol, 2.0 equiv) and EDC·HCl (4.60 g, 24.0 mmol, 2.0 equiv) were added at the same temperature. The resulting mixture was allowed to warm to room temperature and stirred for 24 h. Sat. aq. NH₄Cl was added and the mixture was extracted with EtOAc. The combined organic layers were washed with H₂O (6 times) and brine, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO₂, 2% to 5% MeOH/CH₂Cl₂) to yield 260 in 65% yield (4.67 g, 7.80 mmol).

To a solution of 260 (4.67 g, 7.80 mmol, 1.0 equiv) in THF (39 mL) and H₂O (39 mL) was added LiOH (560.4 mg, 23.4 mmol, 3.0 equiv). The resulting solution was stirred at room temperature for 4 h. The mixture was then evaporated to dryness, the residue was dissolved in H₂O and then acidified with 1 M
HCl until pH = 4. The mixture was extracted with EtOAc and the combined organic layer was dried over Na₂SO₄, filtered and evaporated to dryness to give 261 in quantitative yield which was used directly for the next step without purification.

Methyl \((S)\)-2-(((S)-1-(((benzyloxy)carbonyl)amino)-2-((tert-butoxycarbonyl)amino)-pentanoyl)pyrrolidine-2-carboxamido)pentanoate (263)

To a solution of L-norvaline (2.34 g, 20.0 mmol, 1.0 equiv) in MeOH (20 mL) was added SOCl₂ (1.9 mL, 26.0 mmol, 1.3 equiv) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred at 40 °C for 16 h. After completion of reaction, the reaction mixture was evaporated to dryness to give 262 as colorless solid in quantitative yield which was used directly for the next step without purification.

To a solution of crude 262 (20.0 mmol) and crude 244 (20.0 mmol) in CH₂Cl₂ (200 mL) was added DIPEA (14.0 mL, 80.0 mmol, 4.0 equiv) dropwise at 0 °C. After stirring at 0 °C for 20 min, HOBt (5.40 g, 40.0 mmol, 2.0 equiv) and EDC·HCl (7.67 g, 40.0 mmol, 2.0 equiv) were added at the same temperature. The resulting mixture was allowed to warm to room temperature and stirred for 24 h. Sat. aq. NH₄Cl was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO₂, 2% to 5% MeOH/CH₂Cl₂) to yield 263 in 73% yield (8.36 g, 14.5 mmol).
Methyl (S)-2-((S)-1-((S)-2-((tert-butoxycarbonyl)amino)-5-((S)-2-((E)-3-((S)-1-formamidomethyl)thiazol-4-yl)acrylamido)-3-(5-((triisopropylsilyl)oxy)-1H-indol-3-yl)propanamido)-pentanoyl)pyrrolidine-2-carboxamido)pentanoate (265)

To a solution of 263 (4.50 g, 7.8 mmol, 1.0 equiv) in MeOH (78 mL) was added 10% Pd/C (393.7 mg). The resulting mixture was stirred at room temperature under H₂ balloon for 4 h. The mixture was filtered through a pad of Celite (rinsed with MeOH) and the filtrate was evaporated to dryness. The residue together with the crude 261 (7.8 mmol) was dissolved in DMF (78 mL). DIPEA (5.4 mL, 31.2 mmol, 4.0 equiv) was added dropwise at 0 °C. After stirring at 0 °C for 20 min, HOBt (2.11 g, 15.6 mmol, 2.0 equiv) and EDC·HCl (2.99 g, 15.6 mmol, 2.0 equiv) were added at the same temperature. The resulting mixture was allowed to warm to room temperature and stirred for 24 h. Sat. aq. NH₄Cl was added and the mixture was extracted with EtOAc. The combined organic layers were washed with H₂O (6 times) and brine, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO₂, 2% to 10% MeOH/CH₂Cl₂) to yield 265 in 69% yield (5.43 g, 5.38 mmol).

\[ \text{tert-Butyl } ((S)-5-((S)-2-((E)-3-((S)-1-formamidoethyl)thiazol-4-yl)acrylamido)-3-(5-((triisopropylsilyl)oxy)-1H-indol-3-yl)propanamido)-1-oxo-1-(((S)-2-(((S)-1-oxopentan-2-yl)carbamoyl)pyrrolidin-1-yl)pentan-2-yl)carbamate (266) \]

To a solution of 265 (4.24 g, 4.2 mmol, 1.0 equiv) in THF (42 mL) was added LiAlH₄ (478.2 mg, 12.6 mmol, 3.0 equiv) portionwise at 0 °C. The resulting suspension was allowed to warm to room temperature and stirred for 15 h. After completion, MeOH (5 mL) was added followed by the addition of sat. aq. Rochelle's salt. After stirring for 2 h, the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO₂, 2% to 10% MeOH/CH₂Cl₂) to yield 266 in 72% yield (2.94 g, 3.0 mmol).
tert-Butyl \(((S)-5-((S)-2-((E)-3-((S)-1-isocyanooethyl)thiazol-4-yl)acrylamido)-3-((5-((triisopropylsilyl)oxy)-1H-indol-3-yl)propanamido)-1-oxo-1-((S)-2-(((S)-1-oxopentan-2-yl)carbamoyl)pyrrolidin-1-yl)pentan-2-yl)carbamate (266a)\)

To a solution of 266 (1.0 equiv) in dry CH$_2$Cl$_2$ (0.3 M) was added NEt$_3$ (5.0 equiv) and POCl$_3$ (1.5 equiv) dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 3 h. After completion of reaction, the mixture was quenched with saturated Na$_2$CO$_3$ at -78 °C, allowed to warm to room temperature and extracted with Et$_2$O. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered and evaporated to dryness to provide the ω-isocyanooaldehyde which was used for the next step without further purification.

\textit{t}ert-Butyl \(((1^2Z,9^2S,2S,6S,11S,17S,20E)-2-methyl-4,5,8,10,16,19-hexaoxo-6-propyl-17-((5-((triisopropylsilyl)oxy)-1H-indol-3-yl)methyl)-3,7,15,18-tetraaza-1(2,4)-thiazola-9(2,1)-pyrrolidinacyclohenicosaphan-20-en-11-yl)carbamate (269)\)
To a solution of crude 266a (19.2 mg, 0.02 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (1 mL) were added pyridine (20 µL, 0.24 mmol, 12.0 equiv) and TFA (10 µL, 0.12 mmol, 6.0 equiv) respectively at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 4 days. The mixture was evaporated to dryness and the residue was dissolved in EtOAc. Saturated NaHCO$_3$ was added and the mixture was stirred at room temperature for 1 h. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with saturated NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO$_2$, 3% to 10% MeOH/CH$_2$Cl$_2$) to yield 268 in 63% yield (12.3 mg, 0.013 mmol).

To a solution of 268 (303.6 mg, 0.31 mmol, 1.0 equiv) in THF (31 mL) was added DMP (657.4 mg, 1.55 mmol, 5.0 equiv) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 24 h. Saturated NaHCO$_3$ was added and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na$_2$SO$_4$, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO$_2$, 3% to 10% MeOH/CH$_2$Cl$_2$) to yield 269 in 75% yield (227.2 mg, 0.23 mmol).

(2S,3S)-2-((tert-Butyldimethylsilyl)oxy)-3-methyl-N-(((S)-1-(((12Z,9S,25,6S,11S,17S,20E)-2-methyl-4,5,8,10,16,19-hexaoxo-6-propyl-17-((5-((triisopropylsilyl)oxy)-1H-indol-3-yl)methyl)-3,7,15,18-tetraaza-1(2,4)-thiazola-9(2,1)-pyrrolidinacyclohenicosaphan-20-en-11-yl)amino)-1-oxobutan-2-yl)pentanamide (278)

A solution of 269 (97.7 mg, 0.1 mmol, 1.0 equiv) in 4 M HCl in dioxane (1.0 mL) was stirred at room temperature for 1 h. The mixture was then evaporated to dryness. The residue and 277 (132.6 mg, 0.4
mmol, 4.0 equiv) were dissolved in THF (10 mL). DIPEA (0.3 mL, 1.6 mmol, 16.0 equiv) was added dropwise at 0 °C. After stirring at 0 °C for 20 min, HOBr (108.1 mg, 0.8 mmol, 8.0 equiv) and EDC·HCl (153.4 mg, 0.8 mmol, 8.0 equiv) were added at the same temperature. The resulting mixture was allowed to warm to room temperature and stirred for 24 h. Sat. aq. NH₄Cl was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO₂, 3% to 10% MeOH/CH₂Cl₂) to yield 278 in 81% yield (95.2 mg, 0.08 mmol).
References


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Swiss Federal Institute of Technology Zürich (ETH Zürich), Switzerland  
March, 2015  
Visiting Student  
Advisor: Professor Dr. Jeffrey W. Bode  
Topic: SnAP Hydrazine Reagent for the Synthesis of Oxadiazepine Derivatives

April, 2012-  
Prince of Songkla University, Hat Yai, Thailand  
2015  
Graduate Research Assistant  
Advisor: Assistant Professor Dr. Juthanat Kaeobamrung  
Topic: Cu(I)-Catalyzed Domino Synthesis of Quinazolinone Derivatives

November, 2011-  
Prince of Songkla University, Hat Yai, Thailand  
March, 2012  
Undergraduate Research Assistant  
Advisor: Dr. Juthanat Kaeobamrung  
Topic: Convenient One-pot Reaction for Fast Access to Dihydroisoxazole Derivatives via 1,3-Dipolar Cycloaddition Reactions

June-October, 2011  
Prince of Songkla University, Hat Yai, Thailand  
Undergraduate Research Assistant  
Advisor: Professor Dr. Vatcharin Rukachaisirikul  
Topic: Metabolites from the Endophytic Ascomycete Fungus PSU-PE0124
March-May, 2010 Prince of Songkla University, Hat Yai, Thailand

Undergraduate Research Assistant

Advisor: Professor Dr. Vatcharin Rukachaisirikul

Topic: Chemical Constituents from the Leaves of *Garcinia bancana*

**PERSONAL SKILL**

Skills in Organic Chemistry

- Natural products (structural elucidation, separation)
- Methodology

Technical Skills

- UV-Vis spectroscopy
- IR spectroscopy
- NMR spectroscopy
- Chromatography techniques

Computer Skills

- Microsoft Offices (Word, Excel, Powerpoint)
- ChemBioDraw
- MestRenova
- SciFinder, Reaxys

Language Skills

- Thai (native)
- English

**REFERENCES**

Professor Dr. Jieping Zhu
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