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Published in:
Synthesis

DOI:
10.1055/s-0036-1590946

Publication date:
2018

Synthesis E. M. M. Abdelraheem et al. Paper

Concise Synthesis of Macrocycles by Multicomponent Reactions

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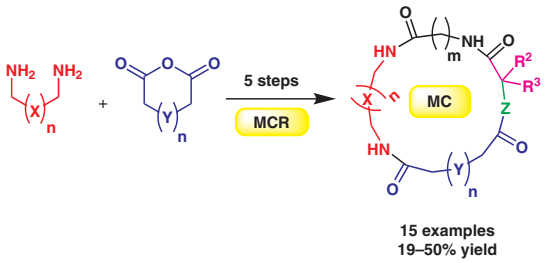


Received: 21.07.2017
Accepted after revision: 08.10.2017
Published online: 10.01.2018
DOI: 10.1055/s-0036-1590946; Art ID: ss-2017-z0480-op

Abstract A short reaction pathway was devised to synthesize a library of artificial 18–27-membered macrocycles. The five-step reaction sequence involves ring opening of a cyclic anhydride with a diamine, esterification, coupling with an amino acid isocyanide, saponification, and, finally, macro-ring closure using an Ugi or, alternatively, a Passerini multicomponent reaction. Three out of the five steps allow for the versatile introduction of linker elements, side chains, and substituents with aromatic, heteroaromatic, and aliphatic character. The versatile pathway is described for 15 different target macrocycles on a mmol scale. Artificial macrocycles have recently become of great interest due to their potential to bind to difficult post-genomic targets.

Key words macrocycles, Ugi reaction, Passerini reaction, amino acids, isocyanides

Macrocycles have recently become an emerging class of synthetic targets due to their unusual biological activities.[1–3] Moreover, their inherent properties allow macrocycles to perform a wide range of functions such as catalysis,[4,5] gelation,[6–8] and ion transport.[9,10] Naturally occurring macrocycles are clinically used as antibiotics, immunosuppressant agents, and anticancer chemotherapeutic agents.[11,12] In the drug space, macrocycles are considered to consist a novel class of compounds in between small molecules and biologics, such as monoclonal antibodies. They allow to target post-genomic targets which are difficult to address by small molecules, such as protein–protein interactions (PPIs).[12] While many ways to synthetically access macrocycles have been described, very few syntheses are useful to create libraries of sufficient size and diversity.[13–15] Therefore, the development of new synthetic methodologies that allow an improved efficient access to this important class of compounds is needed. Among these chemical methodologies are multicomponent reactions (MCRs), in which the products are formed in only one or few synthetic steps.[16–20] For instance, minimizing the time and effort and access to screening libraries of suitable size, diversity, and physicochemical properties is of major importance in early drug discovery.[21] We believe that MCRs are amongst the most powerful techniques to synthesize screening libraries, not only of small molecule scaffolds, but also macrocyclic libraries. Several groups are active in the elaboration of synthetic pathways using convergent and fast MCRs, including, for example, the use of universal aziridinealdehyde for peptidic macrocycles and unique S_nAr ring closures to form natural-product-like macrocycles (Figure 1).[22–24]

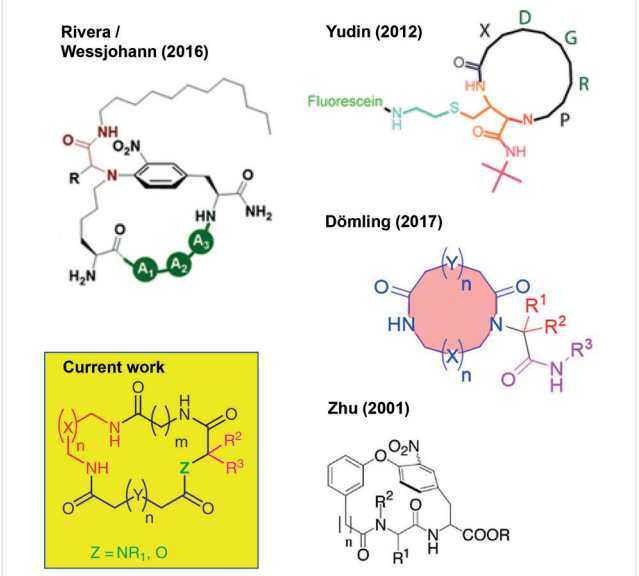
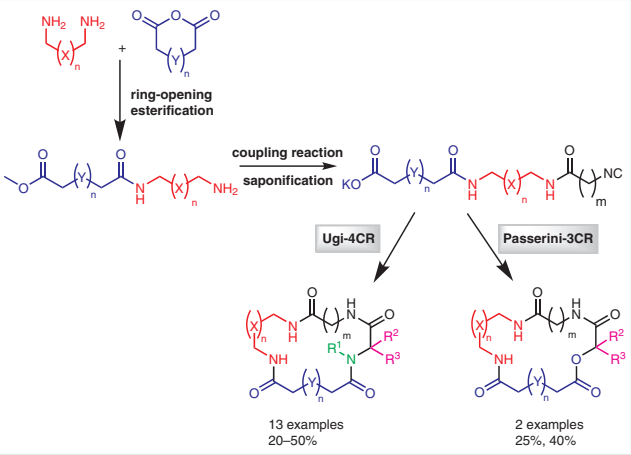


Figure 1 Some previous and the current macrocyclic scaffolds accessible by MCR chemistry

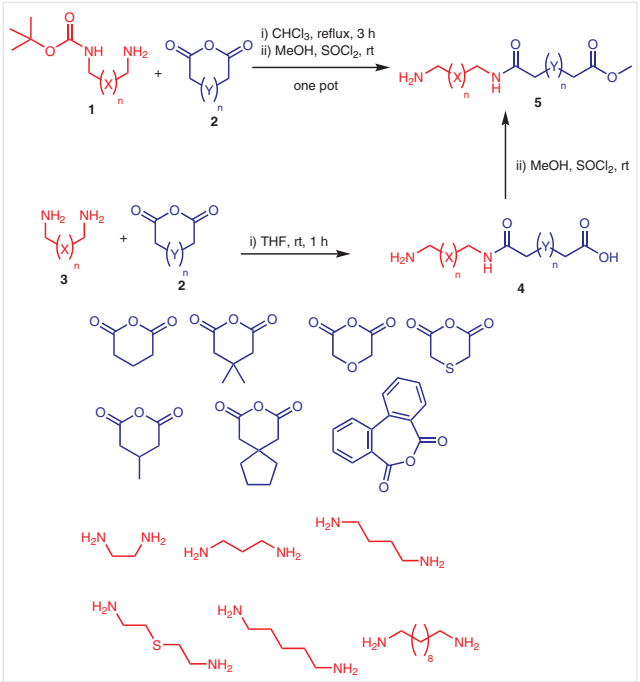
In the light of our extended research interest in MCRs[25,26] and our previous experience in the chemistry of macrocycles, we report herein the use of α-isocyano-ω-carboxylic acids for the synthesis of macrocycles via Ugi and Passerini macrocyclization reactions. The work is an extension of our recent report on macrocycles with the aim to increase the ring sizes and to provide more flexibility in

the design of the composition of the macrocycle with regard to small ring fragments, amide groups, and special distribution thereof with respect to the substituents.[16,20,27,28] The transient conformational space of macrocycles in different solvents of high and low dielectric constants seems to help passive permeation through cell membranes.[29] Therefore we believe that synthetic flexibility can ultimately lead to macrocyclic molecules not only with superior binding properties to receptors but also drug-like properties making them suitable to reach intracellular targets.

In the present synthetic strategy, we incorporated recently described synthesis and diversification elements which allow rapid and diverse assembly of the macrocycle linkers.[30] Our envisioned synthetic macrocycle pathway consists of the formation of α-amino-ω-carboxylic acids by suitable ring opening of cyclic anhydrides with diamines, amino acid derived isocyanide coupling, and, finally, macrocyclization using an Ugi or a Passerini ring closure (Scheme 1).



Scheme 1 Synthetic macrocycle pathway



Scheme 2 Synthesis of amino acid ester from commercial starting materials

We started our study by optimizing the conditions for the first step in our protocol, the synthesis of amino acid esters (Scheme 2), by employing the ring-opening reaction of a cyclic anhydride with a Boc-protected alkyl diamine in $CHCl_3$, followed by deprotection and esterification in a one-pot reaction, by changing the solvent to methanol. The synthesis can be easily performed in parallel by using suitable metal block heaters, thus leading to a manifold of products (SI movie). The reaction was easily scalable and has been performed on a 5 mmol scale.

Table 1 Structures and Yields of Amino Acid, Ester, and Coupling Products

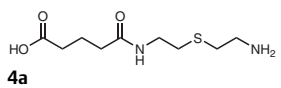
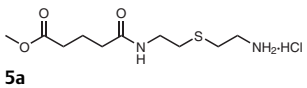
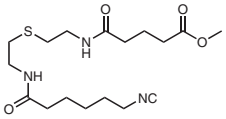
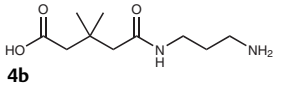
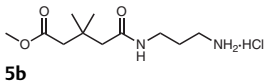
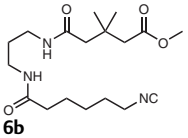
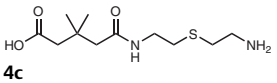
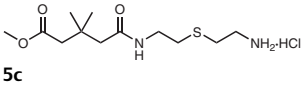
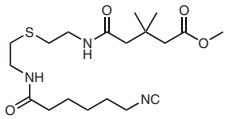
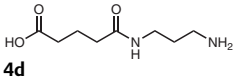
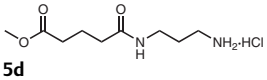
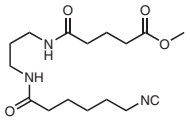
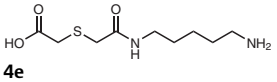
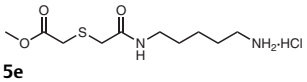
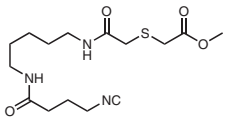
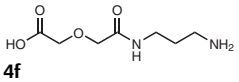
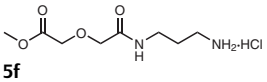
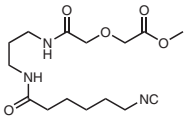
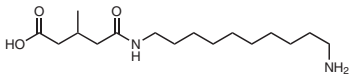
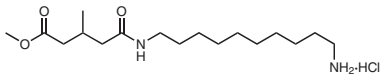
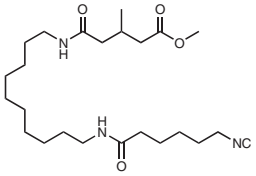
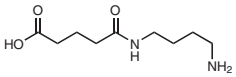
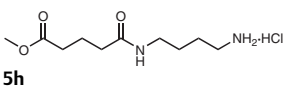
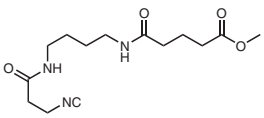
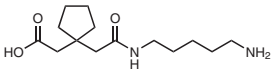
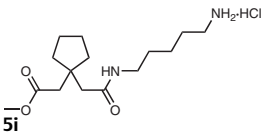
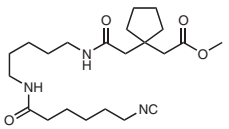
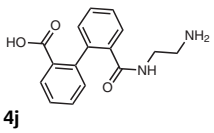
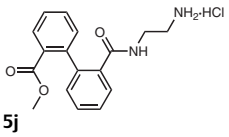
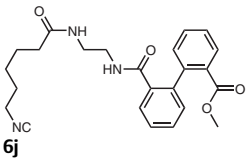
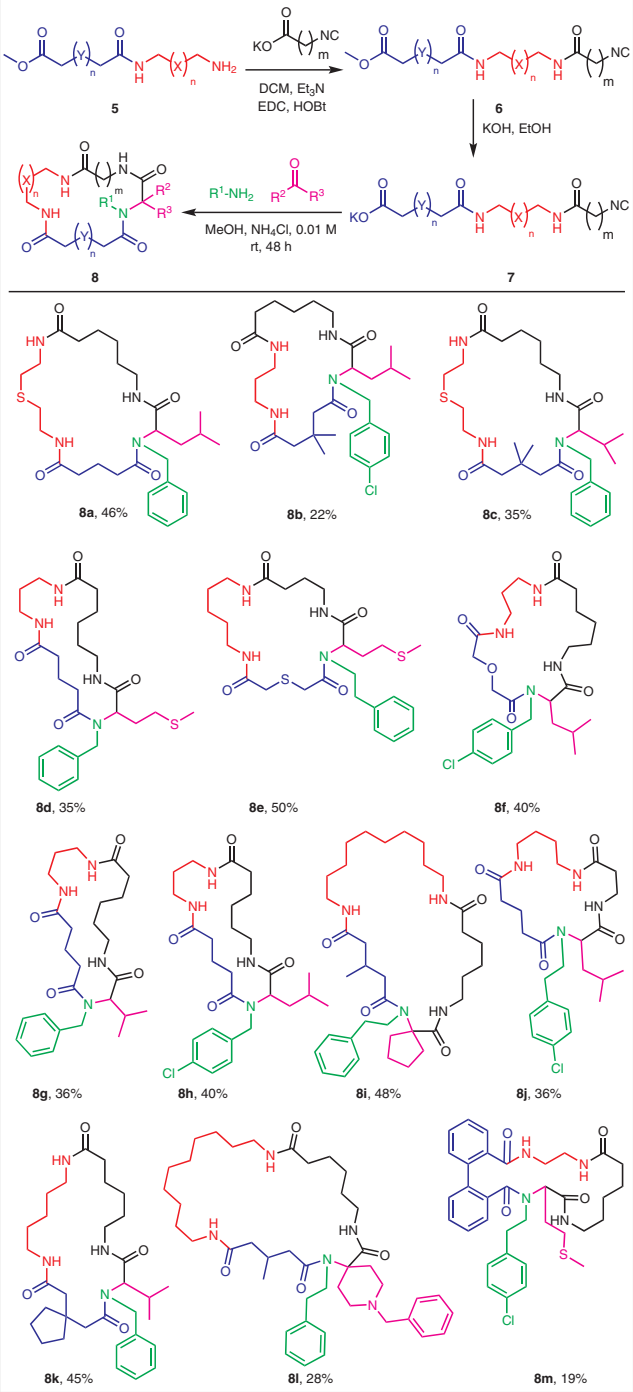
Entry	Amino acid product **4**	Yield (%)[a]	Ester product **5**	Yield (%)[a]	Coupling product **6**	Yield (%)[a]
1	 **4a**	65	 **5a**	75	 **6a**	40
2	 **4b**	77	 **5b**	83	 **6b**	63

Table 1 (continued)

Entry	Amino acid product **4**	Yield (%)[a]	Ester product **5**	Yield (%)[a]	Coupling product **6**	Yield (%)[a]
3	 **4c**	64	 **5c**	70	 **6c**	78
4	 **4d**	55	 **5d**	73	 **6d**	55
5	 **4e**	80	 **5e**	88	 **6e**	64
6	 **4f**	60	 **5f**	78	 **6f**	71
7	 **4g**	93	 **5g**	90	 **6g**	62
8	 **4h**	50	 **5h**	86	 **6h**	56
9	 **4i**	70	 **5i**	75	 **6i**	50
10	 **4j**	70	 **5j**	60	 **6j**	44

[a] Isolated yield.

However, in order to introduce more flexibility in the synthesis of the amino acids on a scale larger than 5 mmol and to avoid the use of halogenated solvents, we performed the ring opening reaction of cyclic anhydride with unprotected alkyl diamines in the aprotic polar solvent THF (Scheme 2). Under diluted conditions (0.1 M) at room temperature, we slowly dropped the anhydride into the diamine solution and we isolated 10 products **4** in 50–93%



Scheme 3 Ugi-4CR-derived macrocycle synthesis; macrocyclization examples (yields of products after purification)

yield (Table 1).[30] Next followed the esterification step using $SOCl_2$ (1.2 equiv) in methanol. This route permits us to introduce greater molecular diversity under mild reaction conditions, including substitution and scaffold diversity (Scheme 2).

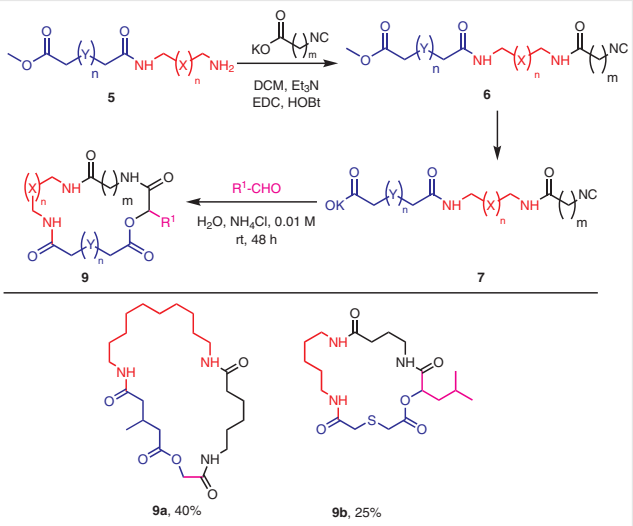
Next, the potassium salt of an isocyanide ester was coupled to amino acid ester **5** by using EDC (2.0 equiv) and HOBt hydrate (1-Hydroxybenzotriazole hydrate; 1.0 equiv) in CH_2Cl_2 to give α-isocyano-ω-carboxylate **6** in excellent yield (60–90%), followed by a saponification reaction with KOH (1.5 equiv) in ethanol (Table 1, Scheme 3).[20,28] In the coupling step, the control of solvents and temperature is of high importance. We tested various solvents, such as toluene, DMF, acetonitrile, and CH_2Cl_2 at 0 °C and at room temperature. Only after a reaction in CH_2Cl_2 at 0 °C for 12 hours followed by room temperature for another 12 hours could we isolate the product at good conversion and yield. Gratifyingly, the product could be isolated by filtration followed by a short silica column purification.

Finally, the macrocyclic ring closure by MCRs (U-4CR) with another equivalent of primary amine and an oxo component took place under optimized conditions (Scheme 3). Different solvents were screened, including EtOH, MeOH, toluene, and trifluoroethanol (TFE). The last one proved to be the optimum solvent for the reaction, but we chose MeOH as the cheapest solvent, since we had to work under highly diluted conditions. We found the NH_4Cl additive necessary for freeing the carboxylic acid from the potassium salt of the α-isocyano-ω-carboxylic **7**. Hence, the optimized conditions for the synthesis of macrocycles consisted of stirring of the reagents (1 equiv each) and NH_4Cl (1.5 equiv) in MeOH (0.01 M) as the solvent at room temperature for 48 hours (Scheme 3).

Instead of the Ugi (U-4CR), we also performed a Passerini (P-3CR) macro-ring closure, which led smoothly to depsipeptide derivatives (Scheme 4). We noted earlier that the classical aprotic nonpolar solvents usually employed in the P-3CR (Et_2O, THF, CH_2Cl_2) did not promote macrocyclization.[16] However, we found that the unusual Passerini reaction solvent water at a 0.01 M dilution leads to product formation. We speculate that the solvent is needed to solubilize the poorly soluble carboxylate in addition to the additive used.

To investigate the substrate scope and limitations we synthesized a total of 15 examples according to Schemes 2 and 3. The last step of the macrocycle synthesis was performed by using several commercially available aliphatic, aromatic, and heterocyclic oxo components as aldehydes and ketones. Also, substituted aromatic amines have been used for the Ugi reaction to afford macrocycle derivatives in moderate yields (20–46%) after purification by column chromatography.

A mechanistic rationalization for the Ugi cyclization reaction is provided in Scheme 5. It is conceivable that the initial event is the condensation of the carbonyl and amino group to form the Schiff base. Next, nucleophilic addition of the terminal carbon of the α-isocyano-ω-carboxylic anion adds to the iminium anion of the Schiff base, followed by an intramolecular nucleophilic addition of the carboxylic acid



Scheme 4 Passerini-3CR-derived macrocycle synthesis; macrocyclization examples (yields of products after purification)

anion onto the nitrilium ion, yielding the so-called α-adduct intermediate. This undergoes a Mumm rearrangement with transfer of the acyl group from the oxygen to the nitrogen. All reaction steps are reversible, except the Mumm rearrangement, which drives the whole reaction sequence.

In conclusion, we have introduced a very mild, straightforward, sequential, rapid, and highly diverse macrocycle synthesis pathway via MCRs. The artificial macrocyclic scaffolds were formed by ring closure via Ugi-4CR or Passerini-3CR of α-isocyano-ω-carboxylic acids. The overall sequence used here to introduce different ring sizes and side chain variations by using readily available starting materials comprise of only five synthesis steps. Currently, libraries of such macrocyclic derivatives are screened in our laboratory for biological activity.

NMR spectra were recorded with a Bruker Avance 500 spectrometer (^{1}H NMR, 500 MHz; ^{13}C NMR, 126 MHz). Chemical shifts for 13C NMR signals are reported in ppm relative to the solvent peak. TLC was performed with Fluka precoated silica gel plates (0.20 mm thick, particle size 25 µm). Flash chromatography was performed with a Teledyne ISCO Combiflash Rf, using RediSep Rf normal-phase silica flash columns (silica gel 60 Å, 230–400 mesh). Reagents were available from commercial suppliers and used without any purification unless otherwise noted. Other reagents were purchased from Sigma Aldrich, ABCR, Acros, and AK Scientific and were used without further purification. Electrospray ionization mass spectra (ESI-MS) were recorded with a Waters Investigator Semi-prep 15 SFC-MS instrument.

α,ω-Amino Carboxylic Acids; General Procedure A

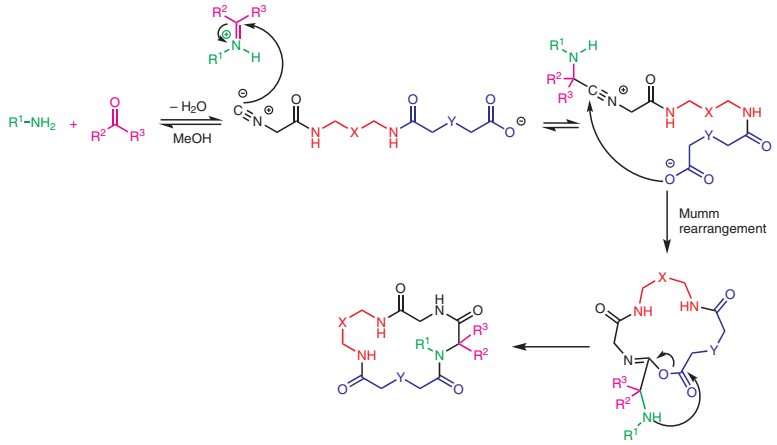
Diamine **1** (5.0 mmol) was dissolved in THF (30 mL), and then a solution of the anhydride (5.0 mmol) in THF (20 mL) was added dropwise over 30 min. The reaction mixture was further stirred for 1 h. The solvents were removed under vacuum. The crude mixture was purified by flash column chromatography (silica gel, CH_2Cl_2–MeOH, 1:9) to afford the product.

Esterification Reaction; General Procedure B

The amino acid (3.0 mmol) was dissolved in MeOH (30 mL) in a flask with a magnetic stirring bar. Thionyl chloride (3.2 mmol) was added dropwise with cooling in an ice bath. The reaction mixture was stirred overnight. The solvent was removed under vacuum, the crude which gave the pure product was dried, and the ester was subjected directly to the next step.

Coupling Reactions; General Procedure C

A suspension of the amino ester derivative (2.0 mmol), the potassium isocyanide derivative (2.2 equiv), and triethylamine (3 equiv) in CH_2Cl_2 (20 mL) was stirred for 10 min at 0 °C. Then HOBt hydrate (1 equiv) and EDC (2 equiv) were added to the mixture, and the reaction mixture was stirred for 12 h at 0 °C, followed by 12 h at rt The insoluble materials were filtered off and the filtrate was evaporated. The residue was purified by manual column chromatography (silica gel, PE–EtOAc, 2:8).



Scheme 5 Possible mechanism for the formation of the macrocycle by the Ugi reaction

Saponification Reactions; General Procedure D

The isocyanide ester (1.0 mmol) was dissolved in EtOH (1 mL), and KOH (1.5 mmol) was added. The reaction mixture was stirred at rt After consumption of the starting material indicated by TLC, the solvent was removed under vacuum and the potassium salt was subjected directly to the next step.

Macrocyclization via Ugi Reaction; General Procedure E

A mixture of the aldehyde (1.0 mmol) and the amine (1.0 mmol) was stirred at rt for 30 min. Then a solution of the α-isocyano-ω-carboxylic acid salt (1.0 mmol) and ammonium chloride (1.5 mmol) in MeOH (0.01 M, 100 mL) were added to the reaction mixture, which was then stirred further at rt for 48 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, CH_2Cl_2–MeOH, 9:1).

Macrocyclization via Passerini Reaction; General Procedure F

A mixture of the α-isocyano-ω-carboxylic acid (1.0 mmol) and ammonium chloride (1.5 mmol) in H_2O (0.01 M, 100 mL) was stirred at rt for 30 min. Then the aldehyde or ketone (1.0 mmol) was added to the mixture, which was further stirred for 72 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, CH_2Cl_2–MeOH, 9:1).

5-({2-[(2-Aminoethyl)sulfanyl]ethyl}amino)-5-oxopentanoic Acid (4a)

Prepared according to procedure A and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 1:9).

Yield: 0.761 g (65%); 5 mmol scale; white solid; mp 142–144 °C.

^{1}H NMR (500 MHz, D_2O): δ = 3.32 (t, *J* = 6.6 Hz, 2 H), 3.12 (t, *J* = 6.7 Hz, 2 H), 2.77 (t, *J* = 6.7 Hz, 2 H), 2.64 (t, *J* = 6.5 Hz, 2 H), 2.23–2.11 (m, 4 H), 1.81–1.66 (m, 2 H).

^{13}C NMR (126 MHz, D_2O): δ = 181.3, 176.4, 38.3, 38.3, 35.7, 35.2, 30.2, 28.1, 21.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{19}N_2O_3S$: 235.11109; found: 235.11095.

5-[(3-aminopropyl)amino-3,3-dimethyl-5-oxopentanoic Acid (4b)

Prepared according to procedure A and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 1:9).

Yield: 0.832 g (77%); 5 mmol scale; white solid; mp 162–164 °C.

^{1}H NMR (500 MHz, D_2O): δ = 3.03 (s, 2 H), 2.68 (s, 2 H), 2.22 (t, *J* = 7.5 Hz, 2 H), 2.17–2.12 (m, 2 H), 1.79–1.74 (m, 2 H), 0.91 (s, 6 H).

^{13}C NMR (126 MHz, D_2O): δ = 181.5, 177.3, 46.5, 46.2, 45.8, 35.9, 35.0, 34.3, 22.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{21}N_2O_3$: 217.15467; found: 217.1545.

5-({2-[(2-Aminoethyl)sulfanyl]ethyl}amino)-3,3-dimethyl-5-oxopentanoic Acid (4c)

Prepared according to procedure A and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 1:9).

Yield: 0.838 g (64%); 5 mmol scale; yellow oil.

^{1}H NMR (500 MHz, D_2O): δ = 3.43 (t, *J* = 6.6 Hz, 2 H), 3.14 (t, *J* = 6.6 Hz, 1 H), 3.09 (t, *J* = 6.6 Hz, 1 H), 2.83 (dd, *J* = 15.8, 6.6 Hz, 2 H), 2.75 (t, *J* = 6.5 Hz, 2 H), 2.28 (s, 2 H), 2.21 (s, 2 H), 1.06 (s, 6 H).

^{13}C NMR (126 MHz, D_2O): δ = 181.2, 175.1, 49.8, 47.7, 38.3, 32.8, 30.3, 29.8, 29.23, 27.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{23}N_2O_3S$: 263.1424; found: 263.1422.

5-[(3-Aminopropyl)amino]-5-oxopentanoic Acid (4d)

Prepared according to procedure A and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 1:9).

Yield: 0.517 g (55%); 5 mmol scale; white solid; mp 150–152 °C.

^{1}H NMR (500 MHz, D_2O): δ = 3.18 (t, *J* = 6.7 Hz, 2 H), 2.97–2.83 (m, 2 H), 2.16 (t, *J* = 7.5 Hz, 2 H), 2.09 (t, *J* = 7.5 Hz, 2 H), 1.83–1.67 (m, 4 H).

^{13}C NMR (126 MHz, D_2O): δ = 182.2, 176.7, 36.9, 36.4, 35.9, 35.3, 26.6, 22.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{17}N_2O_3$: 189.1234; found: 189.1234.

2-({2-[(5-Aminopentyl)amino]-2-oxoethyl}sulfanyl)acetic Acid (4e)

Prepared according to procedure A and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 1:9).

Yield: 0.936 g (80%); 5 mmol scale; white solid; mp 140–142 °C.

^{1}H NMR (500 MHz, D_2O): δ = 3.18 (s, 2 H), 3.15 (s, 2 H), 3.13 (t, *J* = 6.8 Hz, 2 H), 2.89 (t, *J* = 7.5 Hz, 2 H), 1.62–1.52 (m, 2 H), 1.51–1.42 (m, 2 H), 1.33–1.24 (m, 2 H).

^{13}C NMR (126 MHz, D_2O): δ = 176.7, 172.0, 39.3, 36.9, 35.6, 27.7, 26.3, 22.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{19}N_2O_3S$: 235.1111; found: 235.1111.

2-{2-[(3-Aminopropyl)amino]-2-oxoethoxy}acetic Acid (4f)

Prepared according to procedure A and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 1:9).

Yield: 0.570 g (60%); 5 mmol scale; white solid; mp 145–147 °C.

^{1}H NMR (500 MHz, D_2O): δ = 3.99 (s, 2 H), 3.90 (s, 2 H), 3.27 (t, *J* = 6.7 Hz, 2 H), 2.93 (t, *J* = 8.5, 6.8 Hz, 2 H), 1.89–1.77 (m, 2 H).

^{13}C NMR (126 MHz, D_2O): δ = 177.4, 172.9, 70.4, 69.5, 36.9, 35.6, 26.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_7H_{15}N_2O_4$: 191.1026; found: 191.1027.

5-[(10-Aminodecyl)amino]-3-methyl-5-oxopentanoic Acid (4g)

Prepared according to procedure A and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 1:9).

Yield: 1.39 g (93%); 5 mmol scale; white solid; mp 174–176 °C.

^{1}H NMR (500 MHz, D_2O): δ = 3.07 (t, *J* = 6.7 Hz, 2 H), 2.87 (t, *J* = 7.6 Hz, 2 H), 2.23–2.07 (m, 3 H), 2.04–1.86 (m, 2 H), 1.54 (p, *J* = 7.3 Hz, 2 H), 1.39 (p, *J* = 6.7 Hz, 2 H), 1.20 (d, *J* = 15.2 Hz, 12 H), 0.83 (d, *J* = 5.6 Hz, 3 H).

^{13}C NMR (126 MHz, D_2O): δ = 181.6, 175.4, 44.6, 43.2, 39.5, 39.2, 29.1, 28.4, 28.2, 28.1, 26.6, 25.8, 25.5, 18.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{33}N_2O_3$: 301.2486; found: 301.2484.

5-[(4-Aminobutyl)amino]-5-oxopentanoic Acid (4h)

Prepared according to procedure A and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 1:9).

Yield: 0.505 g (50%); 5 mmol scale; white solid; mp 159–160 °C.

^{1}H NMR (500 MHz, D_2O): δ = 3.06 (t, *J* = 13.1, 6.8 Hz, 2 H), 2.87 (t, *J* = 7.6 Hz, 2 H), 2.37–2.34 (m, 4 H), 1.60–1.51 (m, 2 H), 1.47–1.36 (m, 2 H), 1.32–1.23 (m, 2 H).

^{13}C NMR (126 MHz, D_2O): δ = 180.3, 175.5, 39.3, 38.8, 32.5, 32.1, 27.7, 26.3, 22.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{19}N_2O_3$: 203.139; found: 203.139.

2-(1-{2-[(5-Aminopentyl)amino]-2-oxoethyl}cyclopentyl)acetic Acid (4i)

Prepared according to procedure A and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 1:9).

Yield: 0.945 g (70%); 5 mmol scale; brown oil.

^{1}H NMR (500 MHz, D_2O): δ = 3.10 (t, *J* = 6.8 Hz, 2 H), 2.93–2.83 (m, 2 H), 2.25 (s, 2 H), 2.18 (s, 2 H), 1.61–1.50 (m, 6 H), 1.50–1.40 (m, 6 H), 1.36–1.24 (m, 2 H).

^{13}C NMR (126 MHz, D_2O): δ = 180.9, 175.1, 45.8, 44.3, 43.9, 39.3, 38.7, 37.3, 27.8, 26.3, 23.4, 23.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{27}N_2O_3$: 271.2016; found: 271.2014.

2′-[(2-Aminoethyl)carbamoyl]-[1,1′-biphenyl]-2-carboxylic acid (4j)

Prepared according to procedure A and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 1:9).

Yield: 0.994 g (70%); 5 mmol scale; white solid; mp 169–171 °C.

^{1}H NMR (500 MHz, D_2O): δ = 7.86 (dd, *J* = 34.1, 8.3, 1.3 Hz, 2 H), 7.56 (dd, *J* = 18.4, 7.1, 1.4 Hz, 2 H), 7.45–7.40 (m, 2 H), 7.40–7.37 (m, 2 H), 3.25 (t, *J* = 6.2 Hz, 2 H), 2.66 (t, *J* = 6.2 Hz, 2 H).

^{13}C NMR (126 MHz, D_2O): δ = 176.8, 173.0, 136.8, 134.1, 133.3, 131.6, 131.4, 130.0, 129.8, 127.7, 127.4, 125.8, 125.7, 125.0, 42.4, 39.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{17}N_2O_3$: 285.1234; found: 285.1232.

Methyl 5-({2-[(2-Aminoethyl)sulfanyl]ethyl}amino)-5-oxopentanoate Hydrochloride (5a)

Prepared according to procedure B.

Yield: 0.639 g (75%); 3 mmol scale; white solid; mp 200 °C (decomp).

^{1}H NMR (500 MHz, MeOD): δ = 3.48 (s, 3 H), 3.23 (t, *J* = 6.8 Hz, 2 H), 2.98 (t, *J* = 6.9 Hz, 2 H), 2.67 (t, *J* = 6.8 Hz, 2 H), 2.53 (t, *J* = 6.8 Hz, 2 H), 2.24–2.17 (m, 2 H), 2.11 (t, *J* = 7.5 Hz, 2 H), 1.77–1.67 (m, 2 H).

^{13}C NMR (126 MHz, MeOD): δ = 175.9, 175.2, 49.9, 39.9, 35.8, 33.9, 31.8, 29.6, 22.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{21}N_2O_3S$: 249.1267; found: 249.1266.

Methyl 5-[(3-Aminopropyl)amino]-3,3-dimethyl-5-oxopentanoate Hydrochloride (5b)

Prepared according to procedure B.

Yield: 0.662 g (83%); 3 mmol scale; white solid; mp 185 °C (decomp).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.42 (s, 2 H), 3.56 (s, 3 H), 3.13–3.03 (m, 2 H), 2.80–2.69 (m, 2 H), 2.36 (s, 2 H), 2.11 (s, 2 H), 1.74–1.62 (m, 2 H), 1.00 (s, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 171.9, 170.8, 51.1, 46.5, 44.9, 36.7, 35.5, 32.5, 27.4, 27.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{23}N_2O_3$: 231.1703; found: 231.1702.

Methyl 5-({2-[(2-Aminoethyl)sulfanyl]ethyl}amino)-3,3-dimethyl-5-oxopentanoate Hydrochloride (5c)

Prepared according to procedure B.

Yield: 0.655 g (70%); 3 mmol scale; white solid; mp 186 °C (decomp).

^{1}H NMR (500 MHz, MeOD): δ = 3.62 (s, 3 H), 3.18 (t, *J* = 6.9 Hz, 2 H), 2.99–2.87 (m, 2 H), 2.38 (s, 2 H), 2.23 (s, 2 H), 1.71–1.60 (m, 2 H), 1.60–1.51 (m, 2 H), 1.06 (s, 6 H).

^{13}C NMR (126 MHz, MeOD): δ = 175.1, 174.3, 50.0, 47.9, 46.3, 38.5, 36.9, 34.1, 28.9, 28.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{25}N_2O_3S$: 277.1580; found: 277.1579.

Methyl 5-[(3-aminopropyl)amino]-5-oxopentanoate Hydrochloride (5d)

Prepared according to procedure B.

Yield: 0.521 g (73%); 3 mmol scale; white solid; mp 200 °C (decomp).

^{1}H NMR (500 MHz, MeOD): δ = 3.61 (s, 3 H), 3.27–3.25 (m, 2 H), 2.89 (t, *J* = 7.4 Hz, 2 H), 2.37–2.27 (m, 2 H), 2.23 (t, *J* = 7.5 Hz, 2 H), 1.91–1.82 (m, 2 H), 1.84–1.75 (m, 2 H).

^{13}C NMR (126 MHz, MeOD): δ = 174.9, 173.8, 48.5, 36.8, 35.5, 34.4, 32.5, 27.3, 20.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{19}N_2O_3$: 203.139; found: 203.139.

Methyl 2-({2-[(5-Aminopentyl)amino]-2-oxoethyl}sulfanyl)acetate Hydrochloride (5e)

Prepared according to procedure B.

Yield: 0.749 g (88%); 3 mmol scale; white solid; mp 198 °C (decomp).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.12 (t, *J* = 5.3 Hz, 1 H), 3.63 (s, 3 H), 3.45 (s, 2 H), 3.20 (s, 2 H), 3.06–3.00 (m, 2 H), 2.76–2.70 (m, 2 H), 1.61–1.49 (m, 2 H), 1.39 (m, 2 H), 1.30 (m, 2 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 170.68, 168.68, 52.53, 39.05, 38.89, 35.14, 33.59, 28.78, 27.00, 23.60.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{21}N_2O_3S$: 249.1267; found: 249.1265.

Methyl 2-{2-[(3-Aminopropyl)amino]-2-oxoethoxy}acetate hydrochloride (5f)

Prepared according to procedure B.

Yield: 0.562 g (78%); 3 mmol scale; white solid; mp 200 °C (decomp).

^{1}H NMR (500 MHz, MeOD): δ = 4.25 (s, 2 H), 4.08 (s, 2 H), 3.74 (s, 3 H), 3.36 (t, *J* = 6.6 Hz, 2 H), 2.96 (t, *J* = 7.4 Hz, 2 H), 1.93–1.79 (m, 2 H).

^{13}C NMR (126 MHz, MeOD) δ = 175.2, 171.5, 69.9, 67.7, 50.4, 36.8, 35.1, 27.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{17}N_2O_4$: 205.1183; found: 205.1183.

Methyl 5-[(10-Aminodecyl)amino]-3-methyl-5-oxopentanoate Hydrochloride (5g)

Prepared according to procedure B.

Yield: 0.945 g (90%); 3 mmol scale; white solid; mp 182 °C (decomp).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.10 (s, 2 H), 7.91 (t, J = 5.3 Hz, 1 H), 3.58 (s, 3 H), 3.09–2.94 (m, 2 H), 2.81–2.66 (m, 2 H), 2.34 (dd, J = 14.9 Hz, 5.4 Hz, 1 H), 2.25 (d, J = 6.7 Hz, 1 H), 2.17–2.03 (m, 2 H), 1.97 (dd, J = 13.8 Hz, 7.9 Hz, 1 H), 1.63–1.48 (m, 2 H), 1.44–1.34 (m, 2 H), 1.33–1.19 (m, 12 H), 0.87 (d, J = 6.6 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.9, 171.1, 51.6, 42.5, 40.7, 39.1, 38.8, 29.6, 29.3, 29.2, 29.1, 29.0, 28.0, 27.4, 26.8, 26.3, 19.8.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{17}H_{35}N_2O_3$: 315.2642; found: 315.2638.

Methyl 5-[(4-Aminobutyl)amino]-5-oxopentanoate Hydrochloride (5h)

Prepared according to procedure B.

Yield: 0.650 g (86%); 3 mmol scale; white solid; mp 200 °C (decomp).

^{1}H NMR (500 MHz, MeOD): δ = 3.68 (s, 3 H), 3.35–3.31 (m, 2 H), 3.26 (t, J = 6.8 Hz, 2 H), 3.04–2.93 (m, 2 H), 2.44–2.37 (m, 2 H), 2.31 (t, J = 7.5 Hz, 2 H), 1.98–1.87 (m, 2 H), 1.81–1.67 (m, 1 H), 1.66–1.59 (m, 1 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 173.5, 171.9, 51.7, 38.9, 38.2, 34.8, 33.2, 26.6, 24.9, 21.1.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{10}H_{21}N_2O_3$: 217.1547; found: 217.1546.

Methyl 2-(1-{2-[(5-Aminopentyl)amino]-2-oxoethyl}cyclopentyl)acetate Hydrochloride (5i)

Prepared according to procedure B.

Yield: 0.72 g (75%); 3 mmol scale; white solid; mp 200 °C (decomp).

^{1}H NMR (500 MHz, DMSO): δ = 8.10 (s, 2 H), 7.87 (s, 1 H), 3.54 (s, 3 H), 2.98 (d, J = 5.2 Hz, 2 H), 2.75–2.68 (m, 2 H), 2.49 (s, 2 H), 2.20 (s, 2 H), 1.58–1.51 (m, 8 H), 1.48–1.43 (m, 2 H), 1.39–1.33 (m, 2 H), 1.32–1.24 (m, 2 H).

^{13}C NMR (126 MHz, DMSO): δ = 172.7, 171.1, 51.0, 43.1, 43.4, 43.0, 38.6, 38.0, 37.1, 28.6, 26.6, 23.6, 23.3.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{29}N_2O_3$: 285.2173; found: 285.2171.

Methyl 2′-[(2-Aminoethyl)carbamoyl]-[1,1′-biphenyl]-2-carboxylate Hydrochloride (5j)

Prepared according to procedure B.

Yield: 0.601 g (60%); 3 mmol scale; white solid; mp 187 °C (decomp).

^{1}H NMR (500 MHz, MeOD): δ = 7.84 (d, J = 7.8 Hz, 1 H), 7.59 (d, J = 7.6 Hz, 2 H), 7.57–7.49 (m, 1 H), 7.48–7.42 (m, 2 H), 7.31 (d, J = 7.6 Hz, 1 H), 7.23 (d, J = 7.6 Hz, 1 H), 3.63 (s, 3 H), 3.33 (dd, J = 8.4 Hz, 4.8 Hz, 2 H), 2.86–2.79 (m, 2 H).

^{13}C NMR (126 MHz, MeOD): δ = 170.0, 167.4, 139.7, 138.4, 133.3, 129.8, 129.2, 129.0, 128.3, 128.1, 127.7, 125.9, 125.7, 125.3, 49.9, 37.6, 35.5.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{17}H_{19}N_2O_3$: 299.1390; found: 299.1388.

Methyl 5-[(2-{[2-(6-Isocyanohexanamido)ethyl]sulfanyl}ethyl)amino]-5-oxopentanoate (6a)

Prepared according to procedure C and purified by manual column chromatography (silica gel, PE–EtOAc, 2:8).

Yield: 0.296 g (40%); 2 mmol scale; yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.80 (s, 1 H), 6.66 (s, 1 H), 3.70–3.58 (m, 5 H), 3.45–3.40 (m, 4 H), 2.69–2.64 (m, 4 H), 2.39–2.34 (m, 2 H), 2.32–2.18 (m, 4 H), 1.96–1.92 (m, 2 H), 1.76–1.59 (m, 4 H), 1.54–1.41 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.0, 170.3, 169.6, 155.7, 71.0, 68.6, 52.1, 41.4, 36.3, 35.8, 35.7, 29.5, 28.8, 25.9, 24.7.

HRMS (ESI): m/z [M + 2H]$^+$ calcd for $C_{17}H_{31}N_3O_4S$: 373.28495; found: 373.28468.

Methyl 5-{[3-(6-Isocyanohexanamido)propyl]amino}-3,3-dimethyl-5-oxopentanoate (6b)

Prepared according to procedure C and purified by manual column chromatography (silica gel, PE–EtOAc, 2:8).

Yield: 0.445 g (63%); 2 mmol scale; yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.91 (s, 1 H), 6.73 (s, 1 H), 3.67 (s, 3 H), 3.38 (ddd, J = 6.5 Hz, 4.9 Hz, 1.7, 2 H), 3.25 (td, J = 12.4 Hz, 6.2 Hz, 4 H), 2.36 (s, 2 H), 2.25 (s, 2 H), 2.21 (t, J = 7.5 Hz, 2 H), 1.74–1.57 (m, 6 H), 1.52–1.40 (m, 2 H), 1.06 (d, J = 19.5 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 173.3, 172.9, 172.0, 51.5, 47.3, 44.9, 41.4, 36.3, 35.8, 35.7, 33.4, 29.8, 28.8, 28.5, 25.9, 24.7.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{32}N_2O_4$: 354.2387; found: 354.2385.

Methyl 5-[(2-{[2-(6-Isocyanohexanamido)ethyl]sulfanyl}ethyl)amino]-3,3-dimethyl-5-oxopentanoate (6c)

Prepared according to procedure C and purified by manual column chromatography (silica gel, PE–EtOAc, 2:8).

Yield: 0.622 g (78%); 2 mmol scale; yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.69 (s, 3 H), 3.67 (d, J = 6.0 Hz, 1 H), 3.61–3.58 (m, 4 H), 3.57–3.53 (m, 4 H), 3.52 (d, J = 7.0 Hz, 1 H), 3.45 (q, J = 5.1 Hz, 4 H), 2.48 (t, J = 5.9 Hz, 2 H), 2.38 (s, 2 H), 2.27 (s, 2 H), 1.20 (t, J = 7.0 Hz, 2 H), 1.09 (s, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.3, 173.0, 172.0, 155.7, 51.5, 47.3, 44.9, 41.4, 36.3, 35.8, 35.7, 33.4, 29.8, 28.8, 28.5, 25.9, 24.7.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{34}N_3O_4S$: 400.22645; found: 400.22596.

Methyl 5-{[3-(6-Isocyanohexanamido)propyl]amino}-5-oxopentanoate (6d)

Prepared according to procedure C and purified by manual column chromatography (silica gel, PE–EtOAc, 2:8).

Yield: 0.357 g (55%); 2 mmol scale; yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.45 (s, 1 H), 6.41 (s, 1 H), 3.68 (d, J = 2.0 Hz, 3 H), 3.45–3.37 (m, 2 H), 3.33–3.22 (m, 4 H), 2.39 (t, J = 7.2 Hz, 2 H), 2.31–2.20 (m, 4 H), 2.03–1.92 (m, 2 H), 1.77–1.66 (m, 4 H), 1.66–1.59 (m, 2 H), 1.55–1.44 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 173.8, 173.6, 173.1, 161.7, 51.6, 41.6, 37.8, 36.3, 36.0, 35.5, 33.2, 29.6, 29.0, 26.3, 25.2, 21.0.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{16}H_{27}N_3O_4$: 326.20743; found: 326.20743.

Methyl 2-[(2-{[5-(4-Isocyanobutanamido)pentyl]amino}-2-oxoethyl)sulfanyl]acetate (6e)

Prepared according to procedure C and purified by manual column chromatography (silica gel, PE–EtOAc, 2:8).

Yield: 0.439 g (64%); 2 mmol scale; yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.99 (s, 1 H), 6.31 (s, 1 H), 3.72 (s, 3 H), 3.52–3.43 (m, 2 H), 3.32 (s, 2 H), 3.30 (s, 2 H), 3.28–3.18 (m, 4 H), 2.35 (t, *J* = 7.1 Hz, 2 H), 2.03–1.94 (m, 2 H), 1.57–1.48 (m, 4 H), 1.38–1.30 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.3, 170.5, 168.4, 156.0, 52.7, 41.1, 39.4, 39.2, 36.3, 34.2, 32.2, 29.0, 28.8, 24.7, 23.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{26}N_3O_4S$: 344.1639; found: 344.1636.

Methyl 2-(2-{[3-(6-Isocyanohexanamido)propyl]amino}-2-oxoethoxy)acetate (6f)

Prepared according to procedure C and purified by manual column chromatography (silica gel, PE–EtOAc, 2:8).

Yield: 0.464 g (71%); 2 mmol scale; yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.24 (m, 1 H), 6.70 (t, *J* = 5.8 Hz, 1 H), 4.17 (s, 2 H), 4.05 (s, 2 H), 3.74 (s, 3 H), 3.39–3.34 (m, 2 H), 3.35–3.30 (m, 2 H), 3.26–3.21 (m, 2 H), 2.19 (t, *J* = 7.5 Hz, 2 H), 1.74–1.61 (m, 6 H), 1.47–1.38 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 173.1, 170.3, 169.8, 155.7, 71.1, 68.6, 52.1, 36.3, 35.8, 35.7, 29.5, 28.8, 25.9, 24.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{25}N_3O_5$: 328.18670; found: 328.18642.

Methyl 5-{[10-(6-Isocyanohexanamido)decyl]amino}-3-methyl-5-oxopentanoate (6g)

Prepared according to procedure C and purified by manual column chromatography (silica gel, PE–EtOAc, 2:8).

Yield: 0.541 g (62%); 2 mmol scale; yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.98 (s, 1 H), 5.92 (s, 1 H), 3.65 (s, 3 H), 3.46–3.30 (m, 2 H), 3.27–3.13 (m, 4 H), 2.50–2.32 (m, 2 H), 2.29–2.12 (m, 4 H), 2.06 (dd, *J* = 13.8 Hz, 7.3 Hz, 1 H), 1.75–1.58 (m, 4 H), 1.54–1.38 (m, 6 H), 1.35–1.19 (m, 12 H), 0.99 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.1, 172.5, 171.6, 155.7, 51.5, 43.1, 41.4, 40.5, 39.5, 39.4, 39.3, 36.3, 29.6, 29.3, 29.1, 28.8, 28.2, 26.8, 26.0, 24.8, 19.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{44}N_2O_4$: 438.3326; found: 438.3325.

Methyl 5-{[4-(3-Isocyanopropanamido)butyl]amino}-5-oxopentanoate (6h)

Prepared according to procedure C and purified by manual column chromatography (silica gel, PE–EtOAc, 2:8).

Yield: 0.333 g (56%); 2 mmol scale; yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.95 (m, 1 H), 3.67 (s, 3 H), 3.35–3.23 (m, 4 H), 2.58 (t, *J* = 6.6 Hz, 1 H), 2.50–2.43 (m, 2 H), 2.43–2.35 (m, 2 H), 2.29–2.20 (m, 2 H), 2.02–1.91 (m, 2 H), 1.59–1.50 (m, 4 H), 1.29–1.20 (m, 1 H), 0.90–0.83 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.3, 172.6, 172.3, 161.5, 51.7, 39.1, 39.0, 38.8, 37.1, 35.5, 33.1, 27.1, 26.6, 20.9.

HRMS (ESI): *m*/*z* [M + 2H]$^+$ calcd for $C_{14}H_{25}N_3O_4$: 299.18599; found: 299.18593.

Methyl 2-[1-(2-{[5-(6-isocyanohexanamido)pentyl]amino}-2-oxoethyl)cyclopentyl]acetate (6i)

Prepared according to procedure C and purified by manual column chromatography (silica gel, PE–EtOAc, 2:8).

Yield: 0.407 g (50%); 2 mmol scale; yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.85 (s, 1 H), 3.69 (s, 3 H), 3.46–3.33 (m, 2 H), 3.28–3.15 (m, 4 H), 2.43 (s, 2 H), 2.30 (s, 2 H), 2.19 (t, *J* = 7.4 Hz, 1 H), 1.71–1.64 (m, 8 H), 1.54–1.47 (m, 12 H), 1.39–1.31 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.8, 172.6, 171.7, 155.7, 51.6, 44.4, 42.0, 41.4, 39.2, 38.8, 38.2, 36.2, 29.3, 28.9, 28.8, 27.4, 26.0, 24.7, 24.0, 23.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{38}N_3O_4$: 408.28568; found: 408.28513.

Methyl 2′-{[2-(6-Isocyanohexanamido)ethyl]carbamoyl}-[1,1′-biphenyl]-2-carboxylate (6j)

Prepared according to procedure C and purified by manual column chromatography (silica gel, PE–EtOAc, 2:8).

Yield: 0.370 g (44%); 2 mmol scale; yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84 (dd, *J* = 7.6 Hz, 1.5 Hz, 1 H), 7.62–7.58 (m, 1 H), 7.53–7.43 (m, 2 H), 7.40 (dd, *J* = 5.7 Hz, 3.3 Hz, 2 H), 7.24 (dd, *J* = 7.4 Hz, 1.3 Hz, 1 H), 7.13–7.01 (m, 1 H), 6.78 (t, *J* = 6.0 Hz, 1 H), 6.24 (t, *J* = 5.0 Hz, 1 H), 3.71 (s, 3 H), 3.41–3.32 (m, 2 H), 3.33–3.23 (m, 1 H), 3.15–3.04 (m, 1 H), 3.04–2.93 (m, 1 H), 2.90–2.80 (m, 1 H), 2.07 (t, *J* = 7.5 Hz, 2 H), 1.70–1.54 (m, 4 H), 1.48–1.35 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.8, 170.5, 169.1, 155.8, 141.5, 138.9, 135.6, 131.6, 130.7, 130.5, 129.7, 129.3, 129.2, 127.9, 127.9, 127.6, 52.6, 41.4, 40.1, 39.3, 36.0, 28.8, 25.9, 24.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{28}N_3O_4$: 422.2074; found: 422.2071.

10-Benzyl-11-isobutyl-1-thia-4,10,13,20-tetraazacyclodocosane-5,9,12,19-tetraone (8a)

Prepared according to procedure E and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 9:1).

Yield: 0.244 g (46%); 1 mmol scale; colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.31 (m, 2 H), 7.30–7.28 (m, 1 H), 7.17 (d, *J* = 7.6 Hz, 2 H), 7.13 (t, *J* = 5.3 Hz, 1 H), 6.73–6.64 (m, 1 H), 6.34 (t, *J* = 5.9 Hz, 1 H), 5.04–4.95 (m, 1 H), 4.59 (d, *J* = 4.1 Hz, 2 H), 3.57–3.38 (m, 6 H), 3.01–2.90 (m, 1 H), 2.75–2.71 (m, 2 H), 2.63 (t, *J* = 6.0 Hz, 2 H), 2.50 (m, 1 H), 2.35–2.24 (m, 3 H), 2.24–2.13 (m, 1 H), 2.06–1.99 (m, 1 H), 1.98–1.84 (m, 2 H), 1.70–1.63 (m, 2 H), 1.50 (m, 3 H), 1.37–1.27 (m, 3 H), 0.84 (d, *J* = 6.6 Hz, 3 H), 0.79 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.2, 173.9, 173.5, 171.0, 137.7, 129.0, 127.6, 126.2, 59.8, 56.5, 48.8, 39.0, 38.9, 36.8, 36.6, 35.5, 33.4, 33.2, 32.8, 29.0, 26.6, 25.7, 25.4, 23.1, 22.4, 21.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{45}N_4O_4S$: 533.3156; found: 533.3155.

4-(4-Chlorobenzyl)-3-isobutyl-7,7-dimethyl-1,4,10,14-tetraazacycloicosane-2,5,9,15-tetraone (8b)

Prepared according to procedure E and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 9:1).

Yield: 0.120 g (22%); 1 mmol scale; colorless oil; rotamers are observed and the major was used.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61 (t, *J* = 5.6 Hz, 1 H), 7.25 (d, *J* = 8.5 Hz, 2 H), 7.09 (d, *J* = 8.4 Hz, 2 H), 6.99 (t, *J* = 5.3 Hz, 1 H), 5.99 (t, *J* = 6.0 Hz, 1 H), 5.26–5.17 (m, 1 H), 4.62 (d, *J* = 17.8 Hz, 1 H), 4.51 (d, *J* = 17.8 Hz, 1 H), 3.44–3.34 (m, 1 H), 3.30–3.24 (m, 2 H), 3.18–3.09 (m, 2 H), 3.04–2.97 (m, 1 H), 2.77 (d, *J* = 12.7 Hz, 1 H), 2.46 (d, *J* = 15.1 Hz, 1 H), 2.24–2.19 (m, 3 H), 1.94 (d, *J* = 12.7 Hz, 1 H), 1.82–1.76 (m, 1 H), 1.69–1.61 (m, 4 H), 1.53–1.47 (m, 2 H), 1.46–1.41 (m, 2 H), 1.39–1.33 (m, 2 H), 1.03 (s, 3 H), 0.96 (s, 3 H), 0.88 (dd, *J* = 6.2 Hz, 2.3 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 174.4, 173.4, 172.4, 170.4, 136.1, 133.2, 128.9, 127.7, 59.2, 48.0, 47.1, 42.0, 38.6, 37.5, 36.4, 36.2, 35.6, 34.4, 30.0, 29.6, 29.2, 27.7, 25.6, 25.2, 24.0, 23.0, 22.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{46}N_4O_4Cl$: 549.3202; found: 549.3206.

10-Benzyl-11-isopropyl-7,7-dimethyl-1-thia-4,10,13,20-tetraazacyclodocosane-5,9,12,19-tetraone (8c)

Prepared according to procedure E and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 9:1).

Yield: 0.191 g (35%); 1 mmol scale; colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.96 (s, 1 H), 7.32 (t, *J* = 7.4 Hz, 2 H), 7.27 (d, *J* = 7.2 Hz, 1 H), 7.10 (d, *J* = 7.4 Hz, 2 H), 6.69 (s, 1 H), 6.34 (t, *J* = 5.5 Hz, 1 H), 4.76 (d, *J* = 17.4 Hz, 1 H), 4.69 (d, *J* = 17.4 Hz, 1 H), 4.59 (s, 1 H), 3.68–3.58 (m, 1 H), 3.56–3.43 (m, 2 H), 3.43–3.30 (m, 2 H), 3.20–3.07 (m, 2 H), 2.80–2.66 (m, 5 H), 2.49–2.42 (m, 1 H), 2.39 (s, 2 H), 2.30–2.24 (m, 2 H), 1.77–1.68 (m, 2 H), 1.50–1.44 (m, 2 H), 1.43–1.37 (m, 2 H), 1.08 (s, 3 H), 1.04 (s, 3 H), 0.98 (d, *J* = 6.4 Hz, 3 H), 0.89 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.2, 173.5, 171.9, 169.6, 137.2, 128.7, 127.4, 126.0, 62.2, 49.3, 47.4, 42.5, 38.9, 38.8, 38.2, 36.2, 34.7, 31.7, 31.4, 29.5, 29.1, 28.3, 26.9, 26.3, 24.7, 19.9, 19.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{47}N_4O_4S$: 547.3313; found: 547.3315.

4-Benzyl-3-[2-(methylsulfanyl)ethyl]-1,4,10,14-tetraazacycloicosane-2,5,9,15-tetraone (8d)

Prepared according to procedure E and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 9:1).

Yield 0.176 g (35%); 1 mmol scale; colorless oil; rotamers are observed (1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (t, *J* = 7.5 Hz, 3 H), 7.27 (t, *J* = 4.4 Hz, 3 H), 7.20 (d, *J* = 7.5 Hz, 2 H), 7.04 (t, *J* = 5.8 Hz, 1 H), 6.76 (t, *J* = 6.3 Hz, 1 H), 6.57–6.45 (m, 2 H), 5.10 (t, *J* = 7.2 Hz, 1 H), 4.86 (d, *J* = 15.3 Hz, 1 H), 4.70 (d, *J* = 17.4 Hz, 2 H), 4.49 (d, *J* = 17.5 Hz, 1 H), 4.34 (d, *J* = 15.3 Hz, 1 H), 4.20–4.09 (m, 1 H), 3.45–3.17 (m, 11 H), 3.20–3.07 (m, 2 H), 3.07–2.96 (m, 1 H), 2.93–2.84 (m, 1 H), 2.57–2.48 (m, 2 H), 2.48–2.30 (m, 9 H), 2.29–2.20 (m, 6 H), 2.19–2.06 (m, 3 H), 2.03 (s, 3 H), 1.99 (s, 3 H), 1.98–1.92 (m, 2 H), 1.86–1.74 (m, 2 H), 1.72–1.60 (m, 8 H), 1.58–1.47 (m, 4 H), 1.47–1.32 (m, 4 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 174.5, 174.3, 173.9, 173.6, 173.4, 173.3, 170.2, 169.4, 138.8, 137.2, 128.9, 128.3, 127.7, 127.5, 126.9, 126.3, 59.3, 57.2, 49.3, 46.9, 39.2, 39.0, 36.4, 36.3, 35.9, 35.5, 35.1, 33.5, 32.5, 32.4, 31.1, 30.5, 29.7, 29.4, 29.3, 28.5, 28.3, 28.1, 26.1, 25.9, 24.8, 24.7, 23.3, 21.6, 21.3, 21.0, 15.2, 14.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{41}N_4O_4S$: 505.2843; found: 505.2847.

5-[2-(Methylsulfanyl)ethyl]-4-phenethyl-1-thia-4,7,12,18-tetraazacycloicosane-3,6,11,19-tetraone (8e)

Prepared according to procedure E and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 9:1).

Yield: 0.268 g (50%); 1 mmol scale; yellow oil; a mixture of rotamers is observed.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.19 (s, 1 H), 7.29 (q, *J* = 6.8, 6.3 Hz, 3 H), 7.22 (d, *J* = 7.5 Hz, 2 H), 7.20–7.15 (m, 5 H), 7.14 (s, 1 H), 6.87 (s, 1 H), 6.60 (s, 1 H), 6.16 (t, *J* = 5.6 Hz, 1 H), 4.63 (t, *J* = 7.0 Hz, 1 H), 4.60–4.55 (m, 1 H), 3.83 (d, *J* = 14.2 Hz, 1 H), 3.68–3.60 (m, 1 H), 3.59–3.49 (m, 3 H), 3.48–3.33 (m, 5 H), 3.33–3.22 (m, 7 H), 3.23–3.08 (m, 6 H), 3.08–2.97 (m, 2 H), 2.98–2.82 (m, 2 H), 2.80–2.69 (m, 1 H), 2.61–2.40 (m, 6 H), 2.40–2.26 (m, 1 H), 2.26–2.14 (m, 5 H), 2.08 (s, 4 H), 2.06 (s, 2 H), 1.90–1.68 (m, 5 H), 1.57–1.44 (m, 7 H), 1.41–1.32 (m, 3 H), 1.30–1.18 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.4, 173.2, 170.3, 170.2, 170.1, 169.7, 169.1, 168.7, 139.1, 137.6, 128.9, 128.8, 128.7, 128.6, 127.1, 126.5, 59.7, 59.0, 49.9, 47.0, 39.2, 39.1, 38.9, 38.8, 38.5, 38.0, 37.3, 35.9, 35.1, 35.0, 34.4, 33.8, 33.7, 33.2, 31.0, 30.5, 29.1, 28.4, 28.1, 27.9, 26.8, 26.0, 24.7, 23.3, 22.6, 15.4, 15.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{41}N_4O_4S_2$: 537.2564; found: 537.2565.

4-(4-Chlorobenzyl)-5-isobutyl-1-oxa-4,7,14,18-tetraazacycloicosane-3,6,13,19-tetraone (8f)

Prepared according to procedure E and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 9:1).

Yield: 0.209 g (40%); 1 mmol scale; colorless oil; rotamers are observed and the major was used.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.43 (s, 1 H), 7.30 (d, *J* = 8.4 Hz, 1 H), 7.24 (d, *J* = 8.4 Hz, 1 H), 7.21 (d, *J* = 8.4 Hz, 1 H), 7.10 (d, *J* = 8.3 Hz, 1 H), 6.99 (s, *J* = 5.0 Hz, 1 H), 5.89 (t, *J* = 5.8 Hz, 1 H), 5.08 (t, *J* = 7.3 Hz, 1 H), 4.58–4.51 (m, 2 H), 4.19 (d, *J* = 14.9 Hz, 1 H), 4.16–4.09 (m, 2 H), 3.84 (d, *J* = 15.6 Hz, 1 H), 3.62–3.52 (m, 1 H), 3.46–3.38 (m, 1 H), 3.36–3.29 (m, 2 H), 3.27–3.14 (m, 2 H), 2.28–2.18 (m, 2 H), 1.88–1.80 (m, 1 H), 1.76–1.68 (m, 2 H), 1.68–1.60 (m, 2 H), 1.54–1.44 (m, 2 H), 1.44–1.36 (m, 4 H), 0.89 (t, *J* = 5.7 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.6, 171.1, 170.1, 169.7, 135.4, 133.5, 129.1, 127.3, 72.3, 70.5, 56.4, 46.8, 38.0, 37.5, 36.7, 35.7, 35.3, 29.4, 27.6, 25.3, 25.2, 23.4, 22.9, 22.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{40}N_4O_5Cl$: 523.2682; found: 523.2683.

4-Benzyl-3-isopropyl-1,4,10,14-tetraazacycloicosane-2,5,9,15-tetraone (8g)

Prepared according to procedure E and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 9:1).

Yield: 0.169 g (36%); 1 mmol scale; brown oil; rotamers are observed and the major was used.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 7.4 Hz, 1 H), 7.25 (t, *J* = 8.5 Hz, 2 H), 7.17 (d, *J* = 7.4 Hz, 2 H), 7.10 (s, 1 H), 6.83 (s, 1 H), 6.27 (s, 1 H), 4.69 (d, *J* = 17.1 Hz, 1 H), 4.58 (d, *J* = 17.1 Hz, 1 H), 4.29 (s, 1 H), 3.56–3.45 (m, 1 H), 3.44–3.11 (m, 4 H), 3.10–2.93 (m, 1 H), 2.76 (s, 1 H), 2.55–2.46 (m, 1 H), 2.46–2.35 (m, 2 H), 2.34–2.21 (m, 3 H), 2.20–2.02 (m, 2 H), 1.94–1.82 (m, 2 H), 1.74–1.46 (m, 4 H), 1.45–1.30 (m, 2 H), 0.96 (d, *J* = 6.4 Hz, 3 H), 0.81 (dd, *J* = 13.1 Hz, 6.7 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.2, 174.4, 173.9, 170.4, 137.1, 128.7, 127.5, 126.6, 67.0, 50.3, 40.7, 40.0, 39.7, 38.7, 36.1, 35.6, 32.9, 28.4, 26.8, 26.3, 24.4, 21.8, 19.9, 19.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{41}N_4O_4$: 473.3970; found: 473.2965.

4-(4-Chlorobenzyl)-3-isobutyl-1,4,10,14-tetraazacycloicosane-2,5,9,15-tetraone (8h)

Prepared according to procedure E and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 9:1).

Yield: 0.208 g (40%); 1 mmol scale; colorless oil; rotamers are observed and the major was used.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.30 (m, 1 H), 7.29 (d, *J* = 2.8 Hz, 1 H), 7.22 (d, *J* = 2.0 Hz, 2 H), 7.13 (d, *J* = 8.2 Hz, 1 H), 6.33–6.20 (m, 1 H), 4.81–4.60 (m, 1 H), 4.56–4.42 (m, 1 H), 3.50–3.37 (m, 2 H), 3.35–3.25 (m, 2 H), 3.26–3.11 (m, 2 H), 3.12–3.04 (m, 1 H), 2.47–2.35 (m, 2 H), 2.34–2.23 (m, 3 H), 2.22–2.15 (m, 2 H), 2.10–2.00 (m, 1 H), 2.01–1.92 (m, 1 H), 1.93–1.82 (m, 1 H), 1.71–1.59 (m, 4 H), 1.56–1.49 (m, 2 H), 1.47–1.33 (m, 4 H), 0.90 (d, *J* = 6.5 Hz, 3 H), 0.86 (d, *J* = 6.6 Hz, 2 H), 0.79 (d, *J* = 6.6 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 174.5, 173.8, 173.3, 170.7, 137.7, 133.0, 128.8, 128.1, 64.1, 59.0, 48.0, 39.5, 39.0, 36.2, 35.8, 35.4, 32.4, 29.5, 28.5, 26.0, 25.2, 24.6, 22.7, 22.5, 21.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{42}N_4O_4Cl$: 521.2889; found: 521.2891.

9-Methyl-6-phenethyl-6,12,23,30-tetraazaspiro[4.26]hentriacontane-7,11,24,31-tetraone (8i)

Prepared according to procedure E and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 9:1).

Yield: 0.292 g (48%); 1 mmol scale; colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (t, *J* = 7.4 Hz, 2 H), 7.27 (d, *J* = 7.4 Hz, 1 H), 7.22 (d, *J* = 7.3 Hz, 2 H), 6.69 (s, 1 H), 6.34 (s, 1 H), 5.95 (s, 1 H), 3.68–3.56 (m, 2 H), 3.32–3.18 (m, 5 H), 2.95 (t, *J* = 8.3, 2 H), 2.67 (s, 1 H), 2.48 (s, 1 H), 2.46–2.40 (m, 1 H), 2.33–2.26 (m, 2 H), 2.21–2.17 (m, 2 H), 2.15–2.09 (m, 1 H), 1.99–1.83 (m, 4 H), 1.81–1.72 (m, 4 H), 1.69–1.64 (m, 2 H), 1.54–1.48 (m, 5 H), 1.39–1.26 (m, 15 H), 1.07 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 174.6, 173.8, 173.1, 172.1, 138.1, 128.9, 128.6, 126.9, 73.1, 48.1, 42.8, 40.5, 39.5, 39.2, 39.0, 37.3, 36.7, 36.4, 36.3, 29.7, 29.1, 29.0, 28.8, 28.2, 28.1, 27.8, 26.4, 26.0, 25.7, 25.5, 23.5, 20.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{36}H_{59}N_4O_4$: 611.4531; found: 611.4531.

1-(4-Chlorophenethyl)-2-isobutyl-1,4,8,13-tetraazacyclooctadecane-3,7,14,18-tetraone (8j)

Prepared according to procedure E and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 9:1).

Yield: 0.182g (36%); 1 mmol scale; yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.38 (m, 1 H), 7.35 (t, *J* = 5.4 Hz, 1 H), 7.31–7.28 (m, 2 H), 7.12 (d, *J* = 8.3 Hz, 2 H), 6.11 (t, *J* = 6.1 Hz, 1 H), 5.10 (s, 1 H), 3.62–3.53 (m, 2 H), 3.45–3.38 (m, 3 H), 3.18–3.11 (m, 1 H), 3.11–3.02 (m, 1 H), 2.85–2.76 (m, 1 H), 2.75–2.67 (m, 1 H), 2.58–2.51 (m, 1 H), 2.49–2.42 (m, 3 H), 2.37–2.29 (m, 2 H), 2.15–2.04 (m, 2 H), 1.93–1.84 (m, 1 H), 1.71–1.64 (m, 1 H), 1.62–1.44 (m, 6 H), 0.95 (d, *J* = 6.7 Hz, 3 H), 0.93 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.7, 173.3, 172.5, 171.7, 136.2, 132.6, 130.0, 129.00, 55.3, 47.0, 38.7, 38.4, 36.8, 35.5, 34.4, 31.5, 27.8, 24.8, 24.5, 23.0, 22.2, 21.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{40}N_4O_4Cl$: 507.2733; found: 507.2733.

8-Benzyl-9-isopropyl-8,11,18,24-tetraazaspiro[4.21]hexacosane-7,10,17,25-tetraone (8k)

Prepared according to procedure E and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 9:1).

Yield: 0.249 g (45%); 1 mmol scale; colorless oil; a mixture of rotamers is observed and the major was used.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.53 (s, 1 H), 7.32 (t, *J* = 7.5 Hz, 2 H), 7.27–7.20 (m, 1 H), 7.18 (t, *J* = 7.4 Hz, 1 H), 7.12 (d, *J* = 7.7 Hz, 2 H), 7.05 (s, 1 H), 5.92 (t, *J* = 5.5 Hz, 1 H), 4.80 (d, *J* = 17.0 Hz, 1 H), 4.66 (d, *J* = 17.3 Hz, 1 H), 3.51–3.35 (m, 1 H), 3.29–3.22 (m, 3 H), 3.18–3.12 (m, 1 H), 2.70 (dd, *J* = 24.1 Hz, 13.6 Hz, 1 H), 2.49–2.41 (m, 2 H), 2.39–2.26 (m, 2 H), 2.24–2.14 (m, 2 H), 1.97 (d, *J* = 14.5 Hz, 1 H), 1.82–1.76 (m, 1 H), 1.74–1.68 (m, 2 H), 1.68–1.60 (m, 3 H), 1.59–1.52 (m, 7 H), 1.49–1.45 (m, 2 H), 1.45–1.39 (m, 3 H), 1.38–1.31 (m, 1 H), 1.29–1.23 (m, 1 H), 0.98 (d, *J* = 6.6 Hz, 3 H), 0.88 (d, *J* = 6.6 Hz, 2 H), 0.81 (d, *J* = 6.8 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.2, 173.2, 172.1, 169.8, 137.4, 128.7, 127.7, 126.1, 66.8, 49.5, 45.4, 44.8, 40.9, 39.5, 38.9, 38.7, 38.6, 38.4, 38.2, 36.1, 28.5, 28.4, 28.1, 27.1, 26.0, 24.1, 23.9, 23.4, 19.9, 19.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{51}N_4O_4$: 555.3905; found: 555.3904.

3-Benzyl-10-methyl-7-phenethyl-3,7,13,24,31-pentaazaspiro[5.26]dotriacontane-8,12,25,32-tetraone (8l)

Prepared according to procedure E and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 9:1).

Yield: 0.200 g (28%); 1 mmol scale; brown oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 6.8 Hz, 2 H), 7.41–7.35 (m, 3 H), 7.31 (d, *J* = 7.3 Hz, 2 H), 7.27–7.21 (m, 4 H), 6.91 (s, 1 H), 6.35 (t, *J* = 5.6 Hz, 1 H), 6.15 (t, *J* = 5.7 Hz, 1 H), 3.86 (s, 2 H), 3.78–3.64 (m, 1 H), 3.60–3.53 (m, 1 H), 3.42–3.33 (m, 1 H), 3.32–3.05 (m, 10 H), 3.01–2.93 (m, 2 H), 2.87–2.79 (m, 1 H), 2.72–2.65 (m, 1 H), 2.62–2.53 (m, 1 H), 2.44–2.38 (m, 2 H), 2.31–2.21 (m, 2 H), 2.20–2.10 (m, 2 H), 1.66–1.57 (m, 2 H), 1.53–1.42 (m, 6 H), 1.36–1.24 (m, 14 H), 1.02 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.8, 173.6, 173.2, 172.2, 138.0, 130.4, 128.8, 128.8, 127.9, 126.8, 61.9, 61.5, 50.2, 49.5, 46.5, 42.4, 40.7, 39.3, 39.1, 38.9, 37.1, 36.5, 31.3, 30.9, 29.0, 28.9, 28.7, 28.3, 27.9, 27.8, 27.5, 27.4, 26.5, 26.4, 26.3, 25.8, 25.5, 20.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{43}H_{66}N_5O_4$: 716.5109; found: 716.5114.

6-(4-Chlorophenethyl)-7-[2-(methylsulfanyl)ethyl}-6,7,9,10,11,12,13,14,16,17,18,19-dodecahydrodibenzo[*f*,*h*][1,4,11,14]tetraazacycloicosine-5,8,15,20-tetraone (8m)

Prepared according to procedure E and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 9:1).

Yield: 0.123 g (19%); 1 mmol scale; brown oil; a mixture of rotamers is observed and the major was used.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (s, 1 H), 7.71 (dd, *J* = 7.7, 1.4 Hz, 1 H), 7.52–7.46 (m, 2 H), 7.42 (dd, *J* = 7.6, 1.4 Hz, 2 H), 7.35 (dd, *J* = 7.7, 1.3 Hz, 1 H), 7.33–7.30 (m, 2 H), 7.09–7.07 (m, 2 H), 7.02–6.99 (m, 1 H), 6.86–6.75 (m, 1 H), 5.00 (s, 1 H), 4.20 (d, *J* = 8.4 Hz, 1 H), 3.88–3.79 (m, 1 H), 3.67–3.57 (m, 2 H), 3.47 (dd, *J* = 12.6, 6.5 Hz, 2 H), 3.14–3.04 (m, 3 H), 2.95–2.85 (m, 2 H), 2.28–2.19 (m, 3 H), 2.15–2.10 (m, 3 H), 2.05 (s, 3 H), 1.89–1.80 (m, 1 H), 1.74–1.66 (m, 1 H), 1.60–1.54 (m, 2 H), 1.50–1.44 (m, 1 H), 1.19–1.08 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.3, 172.9, 170.0, 169.1, 139.1, 137.3, 136.3, 135.8, 135.2, 133.0, 130.9, 130.5, 130.2, 129.8, 129.3, 129.0, 128.8, 128.5, 128.2, 127.8, 127.7, 124.6, 62.7, 54.0, 39.7, 39.3, 38.6, 36.9, 34.3, 30.4, 27.8, 25.6, 25.1, 24.6, 15.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{35}H_{42}N_4O_4ClS$: 649.2610; found: 649.2613.

25-Methyl-1-oxa-4,11,22-triazacycloheptacosane-3,10,23,27-tetraone (9a)

Prepared according to procedure F and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 9:1).

Yield: 0.181 g (40%); 1 mmol scale; white solid; mp 143–145 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.47 (t, *J* = 5.4 Hz, 1 H), 6.44 (t, *J* = 5.6 Hz, 1 H), 5.89 (t, *J* = 5.8 Hz, 1 H), 4.66 (d, *J* = 15.2 Hz, 1 H), 4.56 (d, *J* = 15.2 Hz, 1 H), 3.37–3.17 (m, 6 H), 2.57–2.46 (m, 1 H), 2.46–2.41 (m, 2 H), 2.31–2.24 (m, 1 H), 2.24–2.17 (m, 3 H), 1.72–1.63 (m, 2 H), 1.64–1.55 (m, 2 H), 1.55–1.45 (m, 4 H), 1.41–1.34 (m, 2 H), 1.34–1.24 (m, 12 H), 1.11 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.1, 171.9, 171.5, 167.6, 62.5, 42.6, 40.3, 39.4, 39.0, 38.9, 36.7, 29.3, 29.1, 28.8, 28.6, 28.5, 28.4, 28.3, 28.2, 26.4, 26.2, 25.8, 25.3, 20.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{44}N_3O_5$: 454.3275; found: 454.3274.

20-Isobutyl-1-oxa-4-thia-7,13,18-triazacycloicosane-2,6,14,19-tetraone (9b)

Prepared according to procedure F and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 9:1).

Yield: 0.103 g (25%); 1 mmol scale; white solid; mp 133–135 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 5.9 Hz, 1 H), 6.90 (s, 1 H), 6.25 (s, 1 H), 5.20 (dd, *J* = 9.2, 3.9 Hz, 1 H), 3.49 (s, 1 H), 3.44 (s, 1 H), 3.39 (d, *J* = 2.2 Hz, 2 H), 3.37–3.29 (m, 4 H), 3.26–3.21 (m, 1 H), 2.29 (t, *J* = 6.5 Hz, 2 H), 1.91–1.84 (m, 3 H), 1.81–1.74 (m, 3 H), 1.64–1.55 (m, 4 H), 1.45–1.39 (m, 2 H), 0.98 (d, *J* = 5.9 Hz, 3 H), 0.96 (d, *J* = 2.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.3, 170.5, 169.1, 168.7, 73.9, 40.9, 39.0, 38.9, 38.8, 35.9, 33.9, 33.5, 28.2, 28.2, 25.0, 24.6, 23.2, 23.1, 21.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{34}N_3O_5S$: 416.2214; found: 416.2212.

Funding Information

The work was financially supported by NIH 2R01GM097082-05, the Innovative Medicines Initiative (grant agreement No.115489), the European Union's Seventh Framework Programme (FP7/2007-2013), EFPIA companies' in-kind contribution, the European Union's Horizon 2020 Research and Innovation Programme under MSC ITN 'Accelerated Early Stage Drug Discovery' (No 675555), and CoFund ALERT (No 665250). E.M.M.A. was supported by the Egyptian government.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590946.

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