Supplementary Information

A Diversity-Oriented Synthesis Strategy Enabling the Combinatorial-Type Variation of Macrocyclic Peptidomimetic Scaffolds

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1. Compound labelling in manuscript and Supplementary Information

For the sake of clarity, the compound labeling systems used here in the Supplementary Information is different to that used in the main manuscript. The following table lists the compounds given in the main manuscript that are labeled, and their corresponding labels as used in the Supplementary Information.

| Figure/Scheme in manuscript | Compound | Compound label in manuscript | Compound label in Supporting Information |
|-----------------------------|----------|------------------------------|-------------------------------------------|
| Figure 2                    | ![Diagram](image1) | 10a *(meta)*                 | Building block F                          |
|                             |          | 10b *(para)*                 | Building block C                          |
| Figure 2                    | ![Diagram](image2) | n = 1: 10c                   | Building block E                          |
|                             |          | n = 2: 10d                   | Building block D                          |
| Figure 2                    | ![Diagram](image3) | n = 1: 10e                   | Building block B                          |
|                             |          | n = 4: 10f                   | Building block A                          |
| Figure 2                    | ![Diagram](image4) | n = 1: 11a                   | Building block 6                           |
|                             |          | n = 2: 11b                   | Building block 13                          |
| Figure 2                    | ![Diagram](image5) | n = 1: 11c                   | Building block 12                          |
|                             |          | n = 2: 11d                   | Building block 11                          |
|                             |          | n = 3: 11e                   | Building Block 5                           |
|                             |          | n = 4: 11f                   | Building block 4                           |
| Figure 2 | ![Chemical Structure](image) | n = 1: \(11g\) | Building block 10 |
| --- | --- | --- | --- |
| Figure 2 | ![Chemical Structure](image) | n = 2: \(11h\) | Building Block 8 |
| Figure 2 | ![Chemical Structure](image) | n = 3: \(11i\) | Building block 2 |
| Figure 2 | ![Chemical Structure](image) | n = 4: \(11j\) | Building block 14 |
| Figure 2 | ![Chemical Structure](image) | n = 1: \(11k\) | Building block 9 |
| Figure 2 | ![Chemical Structure](image) | n = 2: \(11l\) | Building block 7 |
| Figure 2 | ![Chemical Structure](image) | n = 3: \(11m\) | Building block 3 |
| Figure 2 | ![Chemical Structure](image) | n = 4: \(11n\) | Building block 1 |

| Figure 2 | Boc\(-L\)-Ala-OH (12a) | Ala |
| Figure 2 | Boc\(-L\)-Glu-OMe (12b) | Glu |
| Figure 2 | Boc\(-\beta\)-Ala-OH (12c) | -\(\beta\)-Ala |
| Figure 2 | Boc\(-L\)-Phe-OH (12d) | Phe |

| Scheme 2 | ![Chemical Structure](image) | 13 | D14 |
| Scheme | Structure | Number | Code |
|--------|-----------|--------|------|
| Scheme 2 | ![Structure 1](image1.png) | 16 | D14x |
| Scheme 2 | ![Structure 2](image2.png) | 17 | D14w |
| Scheme 2 | ![Structure 3](image3.png) | 30 | D14y |
| Scheme 2 | ![Structure 4](image4.png) | 31 | D14z |
| Scheme 3 | ![Structure 5](image5.png) | 14 | J |
| Scheme 3 | ![Structure 6](image6.png) | 18 | J13 |
| Scheme 3 | ![Chemical Structure 3](image1) | 19 | J13x |
|----------|----------------------------------|----|------|
| Scheme 3 | ![Chemical Structure 3](image2) | 20 | J13w |
| Scheme 3 | ![Chemical Structure 3](image3) | 23 | M13x |
| Scheme 3 | ![Chemical Structure 3](image4) | 22 | M13  |
| Scheme 3 | ![Chemical Structure 3](image5) | 21 | M    |
| Scheme 4 | ![Chemical Structure 4](image6) | 15 | H    |
| Scheme 4 | ![Molecule 33](image) | 33 | H3z |
|----------|-----------------------|----|-----|
| Scheme 4 | ![Molecule 34](image) | 34 | H14z |
| Figure 3 | ![Molecule 35](image) | 35 | K8x |
| Figure 3 | ![Molecule 36](image) | 36 | G11x |
| Figure 3 | ![Chemical Structure](image) | 37 | B8w |
2. Supplementary Figures

**SF1**: General scheme for the synthesis of diverse peptidomimetic macrocyclic scaffolds

**SF2**: Azido-amine ("initiating") building blocks
SF3: Alkyne-acid (“capping”) building blocks
SF4: Synthetic Route to B/C/C/P Coupling Units from Boc-amino-acids ("propagating" building blocks)
SF5: Synthetic Route to B/C/C/C/P Coupling Units from Boc-amino-acids ("propagating" building blocks)
3. General Methods and Equipment

Except as otherwise indicated, reactions were carried out using oven-dried glassware under nitrogen with dry, freshly distilled solvents. Tetrahydrofuran was distilled from calcium hydride and LiAlH₄ in the presence of triphenyl methane. Diethyl ether was distilled from calcium hydride and LiAlH₄. CH₂Cl₂, MeOH, toluene, MeCN and hexane were distilled from calcium hydride. Petroleum ether refers to the 40-60 °C fractions. All other reagents were used as obtained from commercial sources.

Room temperature (rt) refers to ambient temperature. Temperatures at 0 °C were maintained using an ice-water bath. Reactions involving microwave irradiation were performed using a CEM Discover® microwave apparatus in 10 ml or 30 ml microwave tubes with clip lids.

Where possible, reactions were monitored by thin layer chromatography (TLC) using glass plates precoated with Merck silica gel 60 F₂₅₄. Visualization was by the quenching of UV fluorescence (λₘₐₓ = 254 nm) or by staining with potassium permanganate. Retention factors (Rf) are quoted to 0.01.

Flash column chromatography was carried out using slurry-packed Merck 9385 Kieselgel 60 silica gel under a positive pressure of air or nitrogen.

Preparative HPLC purification was performed on an Agilent 1260 Infinity system fitted with a Supelcosil ABZ+Plus column (250 mm x 21.2 mm, 5 µm) using linear gradient systems (solvent A: 0.1% (v/v) TFA in water, solvent B: 0.05% (v/v) TFA in acetonitrile) at a flow rate of 20 mL min⁻¹.

Analytical HPLC analysis was performed on an Agilent 1260 Infinity system fitted with a Supelcosil ABZ+Plus column (150 mm x 4.6 mm, 3 µm) using linear gradient systems (solvent A: 0.05% (v/v) TFA in water, solvent B: 0.05% (v/v) TFA in acetonitrile) over 15 min at a flow rate of 1 mL min⁻¹ and UV detection (λₘₐₓ = 220 nm and 254 nm). Retention times (tᵣ) are reported to the nearest 0.01 min. Peak area percentages are calculated for the UV absorbance at 220 nm and reported to the nearest 1%.

Liquid chromatography mass spectrometry (LC-MS) was conducted on an Agilent 1100 series LC with an ESci Multi-Mode Ionisation Waters ZQ spectrometer. LC system: solvent A: 10 mM NH₄OAc + 0.1% HCOOH in water; solvent B: 95% acetonitrile + 5% H₂O + 0.05% HCOOH; column: Supelcosil™ ABZ™PLUS column (33 mm x 4.6 mm, 3 µm); gradient: 0.0-0.7 min: 0% B, 0.7-4.2 min: 0-100% B, 4.2-7.7 min: 100% B, 7.7-8.5 min: 100-0% B; DAD spectrum: 190 nm - 600 nm, interval 2.0 nm, peak width 0.200 min). Only molecular ions are reported. ESI refers to the electrospray ionisation technique.

Melting points were obtained using a Büchi Melting Point B-545 melting point apparatus and are uncorrected.

Optical rotations were recorded on a Perkin Elmer 343 polarimeter. [α]ₒ values are reported in 10⁻¹ deg cm² g⁻¹ at 589 nm, concentration (c) is given in g (100 mL)⁻¹.
Infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer with internal referencing as neat films. Selected absorption maxima ($\nu_{\text{max}}$) are reported in wavenumbers (cm$^{-1}$).

Nuclear magnetic resonance (NMR) spectra were recorded using an internal deuterium lock on Bruker DPX 400 (400MHz), Bruker Avance 400 QNP Ultrashield (400 MHz), Bruker Avance 500 BB ATM (500 MHz) and Bruker Avance 500 Cryo Ultrashield (500 MHz) spectrometers. Chemical shifts ($\delta$) are referenced to the solvent signal and are quoted in ppm to the nearest 0.01 ppm for $\delta_H$ and to the nearest 0.1 ppm for $\delta_C$. Coupling constants ($J$) are reported in Hertz to the nearest 0.1 Hz. Assignments are supported by DEPT-135, $^1$H-$^1$H COSY, HMQC, HMBC and NOESY spectra where necessary. Data are reported as follows: chemical shift, integration, multiplicity (app., apparent; br, broad; s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; or as a combination of these), coupling constant(s) and assignment (corresponding atom in italics). Diastereotopic protons are assigned as H and H, where H indicates the proton at higher chemical shift. The numbering schemes used on selected spectra do not follow the IUPAC naming system and are used for the clear assignment of $^1$H and $^{13}$C spectra.

Low resolution mass spectra (ESI) were recorded using an LCMS system (Agilent 1200 series LC with an ESCi Multi-Mode Ionization Waters ZQ spectrometer using MassLynx 4.1 software).

High resolution mass spectrometry (HRMS) was carried out with a Micromass QTOF or a Waters LCT Premier Mass Spectrometer using electrospray ionisation [ESI] or electron ionisation [EI]. The calculated mass value relative to found mass value is within the error limits of $\pm$5 ppm mass units.
4. General Procedures

GP1: Amide formation
The azido-amine (1.0 equiv) was dissolved in anhydrous CH$_2$Cl$_2$ and triethylamine (2.2 equiv), EDC.HCl (1.1 equiv) and HOBT.H$_2$O (1.1 equiv) were then added. Upon dissolution, the alkyne-acid (1.0 equiv) in anhydrous CH$_2$Cl$_2$ was added and the reaction was stirred at rt for 18 h. The solvent was removed under reduced pressure and the residue was re-suspended in EtOAc and washed with H$_2$O. The organic layer was separated and washed with saturated NaHCO$_3$ solution (×2). A second addition of EtOAc was made and the organic fraction was washed with 5% citric acid (×2) and H$_2$O (×2). The organic phase was dried (MgSO$_4$) and the solvent removed under reduced pressure. The crude material was purified by column chromatography to yield the linear peptide.

GP2: CuAAC Macrocyclization to form 1,4-triazoles
DIPEA (3.0 equiv) was added to a solution of the linear peptide (1.0 equiv, 1.2 mM) in anhydrous THF. The reaction was degassed by bubbling Ar directly into the solution for 30 min. CuI (2.0 equiv) was then added and the reaction was refluxed for 18 h under N$_2$. The solvent was removed under reduced pressure and the crude material purified by column chromatography or preparative HPLC if necessary.

GP3: RuAAC Macrocyclization to form 1,5-triazoles
The linear peptide (1.0 equiv, 1.25 mM) was dissolved in anhydrous toluene and the reaction mixture was heated to 80 °C and then degassed by bubbling Ar directly into the solution for 30 min. [Cp*RuCl]$_4$ (0.1 equiv.) was added and the reaction was heated to reflux for 18 h. The solvent was removed under reduced pressure and the crude material purified by column chromatography or preparative HPLC if necessary.

GP4: Removal of Boc protecting group with TMSCl
The Boc-protected macrocycle was dissolved in MeOH and the suspension was cooled to 0 °C. TMSCl (0.3 ml per 0.035 mmol linear peptide) was added dropwise to the solution at 0 °C with stirring. The reaction was allowed to warm to rt and stirred until TLC analysis indicated complete consumption of starting material (typically 3 h). The solvent was removed under reduced pressure and the crude material resuspended in CH$_2$Cl$_2$ and washed with NaHCO$_3$. The aqueous layer was extracted with CH$_2$Cl$_2$ (×2) and the combined organic fractions were dried (MgSO$_4$) and the solvent removed under reduced pressure. The crude material was purified by column chromatography (or preparative HPLC) if required to yield the macrocyclic peptidomimetic.
GP5: Removal of Boc protecting group with HCl

The Boc-protected macrocycle was treated with 4.0 M HCl/dioxane (1 ml HCl/dioxane per 20 mg sample) and the reaction was stirred at rt for 18 h. The solvent was removed under reduced pressure and the crude material resuspended in CH$_2$Cl$_2$ and washed with NaHCO$_3$. The aqueous layer was extracted with CH$_2$Cl$_2$ ($\times$2) and the combined organic fractions were dried (MgSO$_4$) and the solvent removed under reduced pressure. The crude material was purified by column chromatography (or preparative HPLC) if required to yield the macrocyclic peptidomimetic.

GP6: Synthesis of diketopiperazine

The macrocycle (0.3 equiv, used directly after the deprotection and used as the salt, without purification) and morpholinomethyl-polystyrene (1.0 equiv) were placed in a microwave (MW) tube. 2-Butanol (40 ml per mmol) and acetic acid (1.25 equiv) were added and the reaction was heated to 150 °C in a microwave (typically 2-3 h). The resin was filtered off and several washings with MeOH and CH$_2$Cl$_2$ were performed. The filtrate was evaporated to dryness and the crude material was purified by column chromatography to yield the final DKP-containing macrocycle.
5. Synthesis of the Common Precursors

(S)-3-amino-2-((tert-butoxycarbonyl)amino)propanoic acid (CP1)

Boc-Asn-OH (8.00 g, 34.4 mmol) was suspended in EtOAc (40 ml), CH₃CN (40 ml) and H₂O (20 ml) and the mixture was cooled to 15 °C. PIDA (13.3 g, 41.3 mmol) was added in a single portion and following 45 min of stirring at 15 °C, the reaction was allowed to warm to rt. TLC analysis after 4 h indicated that most of the starting material was consumed. The reaction mixture was heated to 70 °C for 5 min (until completely dissolved) and then cooled to 0 °C. The mixture was filtered and the precipitate was washed on the filter with cold EtOAc (2 x 10 ml) to afford the title compound 41 as an amorphous white solid (4.72 g, 67%).

Rᶠ = 0.07 (15% MeOH/ 85% CH₂Cl₂). Mp = 214-216 °C (EtOAc), lit. mp 216 °C (EtOAc).[1] δH /ppm (500 MHz, CD₃OD): 4.06 (1H, t, J=6.1 Hz, Hα), 3.22-3.09 (2H, m, Hβ), 1.46 (9H, s, C(CH₃)₃). δC /ppm (125 MHz, CD₃OD): 174.8 (COOH), 158.0 (OC=ONH), 80.9 (C(CH₃)₃), 53.9 (Cα), 43.1 (Cβ), 28.7 (C(CH₃)₃). νmax /cm⁻¹: 3342 (m, N-H), 2969 (w, C-H), 2929 (w, O-H), 2580 (m, O-H), 1684 (C=O), 1525 (s, N-H). HRMS (ESI⁺) m/z found [M+H]⁺ 205.1178, C₈H₁₇N₂O₄⁺ required 205.1183 (Δ -0.2 ppm). [α]D²⁵ = +19.0 (c 0.30, MeOH). Spectroscopic data is consistent with literature values.[2]

4-nitrophenyl prop-2-yn-1-ylcarbamate (CP2)

p-Nitrophenylchloroformate (2.98 g, 14.8 mmol) was dissolved in THF (80 mL) and cooled to -55°C in a acetone/acetonitrile/dry ice bath. After 10 minutes, propargylamine was added dropwise over 15 minutes. The resulting mixture was stirred at -55 °C for 45 minutes. The mixture was filtered through a plug of silica gel over Celite. The solids were washed with THF (3x40 mL). The combined eluents were concentrated in vacuo. The resulting yellow solid was recrystallised from EtOAc:hexane (1:2). Light brown crystals were isolated by filtration, washed with hexane and dried (1.648 g, 51%).

Spectroscopic data is consistent with literature values.[3]
4-pentynoic acid succinimidy l ester (CP3)

CP3 was prepared by literature procedures.\[^{[4]}\]

5-hexynoic acid succinimidy l ester (CP4)

CP4 was prepared by literature procedures.\[^{[5]}\]
6. Synthesis of Azido-Amine Building Blocks

Building Block A

Building block A was prepared by literature procedures.[6]

Building Block B

SF6: Synthetic Route to Building Block B
(S)-3-(((benzyloxy)carbonyl)amino)-2-(((tert-butoxycarbonyl)amino) propanoic acid
(abbreviated to Boc-Dap(Cbz)-OH)

A mixture of Boc-dap-OH CP1 (2.50 g, 12.2 mmol), K$_2$CO$_3$ (3.40 g, 24.6 mmol), KOH (0.695 g, 12.4 mmol), THF (22 ml) and H$_2$O (7 ml) was cooled to 0 °C. Benzyl chloroformate (2.60 ml, 18.2 mmol) was added dropwise over an hour and the reaction was allowed to warm to rt and stirred for 18 h. The organic solvents were removed under reduced pressure and the residue was diluted with H$_2$O (110 ml). The aqueous phase was acidified with citric acid to a pH of 4 and extracted with CH$_2$Cl$_2$ (2 × 15 ml). The combined organic fractions were dried (MgSO$_4$) and the solvent removed under reduced pressure. The crude material was purified by column chromatography (1% AcOH/ 10% MeOH/ 89% CH$_2$Cl$_2$) to afford the title compound 3 as a white solid (2.24 g, 54%).

$R_f = 0.45$ (1% AcOH/ 10% MeOH/ 89% CH$_2$Cl$_2$). $M_p = 47-49$ °C (CH$_2$Cl$_2$). $\delta_{H}/ppm$ (500 MHz, CDCl$_3$): 8.94 (1H, br s, COOH), 7.37-7.27 (5H, m, 5 × ArCH), 5.77 (1H, br s, C$_\alpha$-NH), 5.55 (1H, br s, C$_\beta$-NH), 5.07 (2H, s, CH$_2$Ph), 4.45-4.20 (1H, m, H$_\alpha$), 3.70-3.40 (2H, m, H$_\beta$), 1.43 (9H, s, C(C$_3$H$_7$)$_3$).

$\delta_{C}/ppm$ (125 MHz, CDCl$_3$): 173.8 (COOH), 157.6 (OC=ONH), 156.4 (OC=ONH), 136.2 (ArC), 128.7 (ArCH), 128.3 (ArCH), 128.2 (ArCH), 80.9 (C(CH$_3$)$_3$), 67.4 (CH$_2$Ph), 54.6 (C$_\alpha$), 42.8(C$_\beta$), 28.4 (C(CH$_3$)$_3$). $\nu_{max}/cm^{-1}$: 3342 (m, N-H), 2979 (m, C-H), 1688 (s, C=O), 1516 (s, N-H). HRMS (ESI+) m/z found [M+Na]$^+$ 361.1393, $C_{16}H_{22}N_2O_6Na^+$ required 361.1376 ($\Delta - 4.7$ ppm). $[\alpha]_{D}^{25} = -8.5$ (c 0.86, MeOH). Spectroscopic data is consistent with literature values.[7]

(S)-methyl 3-(((benzyloxy)carbonyl)amino)-2-(((tert-butoxycarbonyl) amino)propanoate

Boc-Dap(Cbz)-OH (1.50 g, 4.43 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (14 ml) and EDC.HCl (0.849 g, 4.43 mmol), anhydrous MeOH (0.72 ml, 18 mmol) and DMAP (0.054 g, 0.44 mmol) were added. The reaction was stirred at rt for 3 h. H$_2$O (10 ml) was added and the organic and aqueous layers were separated. The organic layer was washed with H$_2$O (10 ml), saturated NaHCO$_3$ solution (2 × 10 ml), 5% citric acid (2 × 10 ml) and H$_2$O (2 × 10 ml). The organic fraction was dried (MgSO$_4$) and the solvent removed under reduced pressure. Purification by column chromatography (5-10% MeOH/ CH$_2$Cl$_2$) gave the title compound (1.24 g, 79%) as a clear oil.
$R_f = 0.73$ (10% MeOH/ 90% CH$_2$Cl$_2$). $\delta_H$ /ppm (400 MHz, CDCl$_3$): 7.39-7.26 (5H, m, 5 × ArCH), 5.42 (1H, br s, C$_2$-NH), 5.14 (1H, br s, C$_3$-NH), 5.09 (2H, s, CH$_2$Ph), 4.42-4.31 (1H, m, H$_3$), 3.73 (3H, s, OCH$_3$), 3.64-3.53 (2H, m, H$_p$), 1.43 (9H, s, C(CH$_3$)$_3$). $\delta_C$ /ppm (125 MHz, CDCl$_3$): 171.3 (COOME), 156.8 (OC=ONH), 155.6 (OC=ONH), 136.4 (ArC), 128.7 (ArCH), 128.3 (ArCH), 80.4 (C(CH$_3$)$_3$), 67.1 (CH$_2$Ph), 54.1 (C$_3$), 52.8 (OCH$_3$), 43.1 (C$_p$), 28.4 (C(CH$_3$)$_3$). $\nu_{\text{max}}$ /cm$^{-1}$: 3343 (m, N=CH), 2976 (m, C-H), 1694 (s, C=O), 1515 (s, N-H). HRMS (ESI+) m/z found [M+H]$^+$ 353.1716, C$_{11}$H$_{25}$N$_2$O$_6$ required 353.1713 (Δ 0.8 ppm). [α]$_D^{25}$ = -9.1 (c 1.85, MeOH). Spectroscopic data is consistent with literature values.$^{[2a, 7a]}$

(S)-methyl 3-amino-2-((tert-butoxycarbonyl)amino)propanoate

![Structure](image)

To a solution of (S)-methyl 3-((benzyloxy)carbonyl)amino)-2-((tert-butoxycarbonyl)amino)propanoate (0.300 g, 0.851 mmol) in MeOH (3.3 ml) was added 5% w/w Pd/C (15 mg). The suspension was stirred under an atmosphere of hydrogen gas (balloon pressure) for 18 h and then filtered through a bed of celite®. The solvent was removed under reduced pressure and the crude mixture was purified by column chromatography (2-5% MeOH/ 1% 7N NH$_3$ in MeOH/CH$_2$Cl$_2$) to furnish the title compound as a clear oil (0.180 g, 73%).

$R_f = 0.44$ (10% MeOH/ 1% 7N NH$_3$ in MeOH/ 89% CH$_2$Cl$_2$). $\delta_H$ /ppm (500 MHz, CDCl$_3$): 5.36 (1H, br s, C$_2$-NH), 4.36-4.26 (1H, m, H$_a$), 3.77 (3H, s, OCH$_3$), 3.05 (2H, d, J=4.3 Hz, H$_b$), 1.46 (9H, s, C(CH$_3$)$_3$). $\delta_C$ /ppm (125 MHz, CDCl$_3$): 172.3 (COOME), 155.7 (OC=ONH), 80.2 (C(CH$_3$)$_3$), 56.0 (C$_3$), 52.8 (OCH$_3$), 44.1 (C$_p$), 28.5 (C(CH$_3$)$_3$). $\nu_{\text{max}}$ /cm$^{-1}$: 3315 (m, N-H), 2977 (m, C-H), 1695 (s, C=O), 1511 (s, N-H). HRMS (ESI+) m/z found [M+Na]$^+$ 241.1155, C$_9$H$_{18}$N$_2$O$_4$Na$^+$ required 241.1159 (Δ -1.4 ppm). [α]$_D^{25}$ = +6 (c 0.12, MeOH). Spectroscopic data is consistent with literature values.$^{[8]}$

(S)-2-azido-3-phenylpropanoic acid

![Structure](image)

3-Azidosulfonl-3H-imidazole-1-ium hydrogen sulfate (8.01 g, 25.4 mmol) was added to a mixture of L-phenylalanine (3.50 g, 21.2 mmol), K$_2$CO$_3$ (7.91 g, 57.2 mmol) and copper sulfate pentahydrate (0.052 g, 0.21 mmol) in MeOH (105 ml). The reaction was stirred at rt for 18 h. The solvent was removed under reduced pressure and the crude material diluted with H$_2$O (100 ml) and acidified with conc. HCl to a pH of 2. The aqueous layer was extracted with EtOAc (3 × 100 ml) and the combined organic fractions were dried (MgSO$_4$) and the solvent removed under
reduced pressure. The crude oil was purified by column chromatography (1% AcOH/ 25% EtOAc / 74% Pet ether) to yield the title compound as a yellow oil (3.62 g, 89%).

R<sub>f</sub> = 0.30 (1% AcOH/ 25% EtOAc / 74% Pet ether 40:60). δ<sub>H</sub>/ppm (500 MHz, CDCl<sub>3</sub>): 9.76 (1H, br s, COOH), 7.37-7.24 (5H, m, 5 × ArCH), 4.17 (1H, dd, J=8.9, 5.0 Hz, H<sub>α</sub>), 3.25 (1H, dd, J=14.1, 5.0 Hz, H<sub>β</sub>), 3.05 (1H, dd, J=14.1, 8.9 Hz, H<sub>β</sub>). δ<sub>c</sub>/ppm (125 MHz, CDCl<sub>3</sub>): 175.7 (COOH), 135.7 (Ar(C)), 129.4 (ArCH), 128.9 (ArCH), 127.6 (Ar(C)), 63.2 (C<sub>α</sub>), 37.7 (C<sub>β</sub>). ν<sub>max</sub>/cm<sup>-1</sup>: 3031 (m, C-H), 2105 (s, N<sub>3</sub>), 1715 (s, C=O). HRMS (ESI-) m/z found [M-H]<sup>-</sup> 190.0617, C<sub>9</sub>H<sub>8</sub>N<sub>3</sub>O<sub>2</sub> required 190.0611 (Δ 3.4 ppm). [α]<sub>D</sub><sup>25</sup> = -72.0 (c 0.25, MeOH). Spectroscopic data is consistent with literature values.<sup>[6]</sup>

(S)-methyl-3-((S)-2-azido-3-phenylpropanamido)-2-((tert-butoxycarbonyl)amino)propanoate

(S)-Methyl 3-amino-2-((tert-butoxycarbonyl)amino)propanoate (0.150 g, 0.687 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1.5 ml) and HOBr₂H₂O (0.105 g, 0.687 mmol) and EDC.HCl (0.132 g, 0.687 mmol) were added at rt. Once all the solids were dissolved, (S)-2-azido-3-phenylpropanoic acid (0.131 g, 0.687 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.5 ml) was added and the reaction was stirred for 18 h at rt. The solvent was removed under reduced pressure and the crude mixture was diluted with EtOAc (5 ml) and H₂O (5 ml). The layers were separated and the organic layer was washed with saturated NaHCO₃ solution (2 × 5 ml), 5% citric acid (2 × 5 ml) and H₂O (2 × 5 ml). The organic fraction was dried (MgSO₄) and the solvent removed under reduced pressure. The crude material was purified by column chromatography (0-5% MeOH/CH₂Cl₂) to afford the title compound as an amorphous cream solid (0.140 g, 52%).

R<sub>f</sub> = 0.48 (5% MeOH/ 95% CH₂Cl₂). Mp = 84-87 °C (5% MeOH/ 95% CH₂Cl₂). δ<sub>H</sub>/ppm (500 MHz, CDCl<sub>3</sub>): 7.36-7.22 (5H, m, 5 × ArCH), 6.71 (1H br s, C<sub>β</sub>-NH), 5.40 (1H, d, J=5.9 Hz, C<sub>α</sub>-NH), 4.16 (1H, d, J=8.5, 4.3 Hz, H<sub>α</sub>), 3.76 (3H, s, OCH₃), 3.68-3.53 (2H, m, H<sub>β</sub>), 3.32 (1H, dd, J=14.1, 4.3 Hz, H<sub>β</sub>), 2.96 (1H, dd, J=14.1, 8.5 Hz, H<sub>β</sub>), 1.45 (9H, s, C(CH₃)₃). δ<sub>c</sub>/ppm (125 MHz, CDCl<sub>3</sub>): 171.0 (C=ONH), 169.7 (COOMe), 155.7 (OC=ONH), 136.3 (Ar(C)), 129.6 (ArCH), 128.8 (ArCH), 127.4 (ArCH), 80.6 (C(CH₃)₃), 65.7 (C<sub>α</sub>), 53.7 (C<sub>α</sub>), 52.9 (OCH₃), 41.8 (C<sub>β</sub>), 38.7 (C<sub>β</sub>), 28.4 (C(CH₃)₃). ν<sub>max</sub>/cm<sup>-1</sup>: 3308 (m, N-H), 3003 (w, C-H), 2117 (s, N<sub>3</sub>) 1750 (s, C=O), 1691 (s, C-O), 1652 (s, C=C). HRMS (ESI+) m/z found [M+H]<sup>+</sup> 392.1944, C<sub>18</sub>H<sub>26</sub>N<sub>5</sub>O<sub>5</sub><sup>+</sup> required 392.1934 (Δ 2.5 ppm). [α]<sub>D</sub><sup>25</sup> = +10.0 (c 0.26, MeOH).
(S)-3-((S)-2-azido-3-phenylpropanamido)-1-methoxy-1-oxopropan-2-aminium chloride (Building Block B)

TMSCl (4.70 ml, 0.0370 mmol) was added dropwise to MeOH (19.7 ml) at 0 °C. The solution was stirred for 10 min at 0 °C and then added dropwise to (S)-methyl-3-((S)-2-azido-3-phenylpropanamido)-2-((tert-butoxycarbonyl)amino) propanoate (2.39 g, 6.11 mmol) at rt. The solution was stirred at rt. TLC analysis after 3 h indicated that all the starting material had been consumed. The solvent was removed under reduced pressure following which co-evaporations with MeOH (20 ml) and CH$_2$Cl$_2$ (3 × 20 ml) gave the title compound as an amorphous cream solid (1.98 g, 99%).

Mp = 148-152 °C (CH$_2$Cl$_2$). δ$_H$/ppm (400 MHz, d$_6$-DMSO): 8.90 (1H, t, J=5.8 Hz, C$_β$-NH), 8.76 (3H, s, NH$_3^+$), 7.34-7.13 (5H, m, 5 × ArCH), 4.12-4.00 (2H, m, H$_α$ and H$_α'$), 3.67 (3H, s, OCH$_3$), 3.65-3.50 (2H, m, H$_β$), 3.14 (1H, dd, J=14.1, 4.2 Hz, H$_β'$), 2.86 (1H, dd, J=14.1, 10.1 Hz, H$_β'$).

δ$_C$/ppm (101 MHz, d$_6$-DMSO): 170.0 (COOMe), 168.1 (C=ONH), 137.1 (ArC), 129.1 (ArC), 128.4 (ArCH), 126.7 (ArCH), 62.9 (C$_α$), 53.0 (OCH$_3$), 51.8 (C$_α$), 38.6 (C$_β$), 37.0 (C$_β'$). ν$_{max}$/cm$^{-1}$: 3333 (m, N-H), 2830 (s, C-H), 2100 (s, N$_3$), 1740 (s, C=O), 1657 (s, C=O), 1529 (s, C=C).

HRMS (ESI+) m/z found [M+H]$^+$ 292.1417, C$_{13}$H$_{18}$N$_5$O$_3$+ required 292.1410 (Δ 2.4 ppm). [α]$_D$/$^{25}$$^{}$ = +12.0 (c 0.29, MeOH).

Building Block C

SF7: Synthetic Route to Building Block C
(S)-3-(4-azidophenyl)-2-((tert-butoxycarbonyl)amino)propanoic acid

3-Azidosulfonyl-3H-imidazole-1-ium hydrogen sulfate (2.13 g, 7.87 mmol) was added to a mixture of Boc-Phe(4-NH$_2$)-OH (1.84 g, 6.56 mmol), K$_2$CO$_3$ (2.06 g, 14.9 mmol) and copper sulfate pentahydrate (16.4 mg, 0.0656 mmol) in MeOH (33 ml). The reaction was stirred at rt for 18 h. The solvent was removed under reduced pressure and the crude material diluted with H$_2$O (20 ml) and acidified with conc. HCl to a pH of 2. The aqueous layer was extracted with EtOAc (3 x 20 ml) and the combined organic fractions were dried (MgSO$_4$) and the solvent removed under reduced pressure. The crude oil was purified by column chromatography (1% AcOH/ 5% MeOH / 94% CH$_2$Cl$_2$) to yield the title compound as an orange oil (1.76 g, 89%).

R$_f$ = 0.34 (5% MeOH/ 1% AcOH/ 94% CH$_2$Cl$_2$). $\delta$$_H$ / ppm (500 MHz, d$_6$-DMSO): 7.17 (2H, d, J=8.4 Hz, 2 x ArCH), 6.97 (2H, d, J=8.4 Hz, 2 x ArCH), 4.93 (1H, d, J=7.3 Hz, BocNH), 4.58 (1H, m, H$_6$), 3.18 (1H, dd, J=13.9 Hz and 5.1 Hz, H$_6$), 3.06 (1H, dd, J=13.9 Hz and 6.5 Hz, H$_6$) 1.44 (9H, s, C(CH$_3$)$_3$). $\delta$$_C$ / ppm (125 MHz, d$_6$-DMSO): 175.2 (COOH), 155.5 (Boc C=O), 139.1 (ArC), 132.7 (ArC), 130.9 (ArCH), 119.4 (ArCH), 80.7 (C(CH$_3$)$_3$), 54.4 (C$_4$), 37.3 (C$_6$), 28.4 (C(CH$_3$)$_3$). $\nu$$_{max}$/cm$^{-1}$: 2979 (w, O-H ), 2112 (s, N$_3$), 1687 (s, C=O), 1506 (s, N-H). HRMS (ESI+) m/z found [M+H]$^+$ 307.1386, C$_{11}$H$_{19}$N$_4$O$_4$$^+$ required 307.1401 (Δ -0.99 ppm). $[\alpha]$$_D$$^{25}$ = +39.9 (c 0.51, CHCl$_3$). Spectroscopic data is consistent with literature values.$^{[10]}$

(S)-3-(4-azidophenyl)-1-methoxy-1-oxopropan-2-aminium chloride (Building Block C)

TMSCl (1.57 ml, 12.4 mmol) was added dropwise over 15 min to a solution of the azide (800 mg, 2.61 mmol) in MeOH (3 ml) at 0 °C. The reaction was allowed to warm to rt and stirred for 5h. Dry diethyl ether (4.6 ml) was added and the slurry was stirred for 30 min and then filtered. The precipitate was washed with cold diethyl ether (2 x 2 ml) and then dried in vacuo to afford the title compound as a cream solid (596 mg, 89%).

$\text{Mp}$ = 183-186 °C (Et$_2$O). $\delta$$_H$ / ppm (500 MHz, d$_6$-DMSO): 8.65 (3H, s, NH$_3^+$), 7.33-7.21 (2H, m, 2 x ArCH), 7.15-7.04 (2H, m, 2 x ArCH), 4.26 (1H, t, J=6.4 Hz, H$_6$), 3.67 (3H, s, OCH$_3$), 3.17 (1H, d, J=14.1 Hz and 6.0 Hz, H$_6$), 3.09 (1H, dd, J=14.1 Hz and 7.2 Hz, H$_6$). $\delta$$_C$ / ppm (125 MHz, d$_6$-DMSO): 169.3 (COOMe), 138.4 (ArC), 131.6(ArC), 131.1 (ArCH), 119.3 (ArCH), 53.2 (C$_4$), 52.7 (OCH$_3$), 35.2 (C$_6$). $\nu$$_{max}$/cm$^{-1}$: 2805 (m, C=H), 2123 (m, N$_3$), 1742 (s, C=O), 1578 (m, C=C), 1509 (s, N-H). HRMS (ESI+) m/z found [M+H]+$^+$ 221.1027, C$_{10}$H$_{13}$N$_3$O$_2^+$ required 221.1033 (Δ -2.7 ppm). $[\alpha]$$_D$$^{25}$ = +15.1 (c 0.56, MeOH).
Building Block D

\[
\begin{align*}
\text{NH}_2 & \quad \rightarrow \quad \text{Cl} \overset{\text{H}_3\text{N}}{\rightarrow} \overset{\text{O}}{\rightarrow} \\
\text{N}_3 & \quad \rightarrow \quad \text{N}_3
\end{align*}
\]

**SF8: Synthetic Route to Building Block D**

(S)-6-azido-1-methoxy-1-oxohexan-2-aminium chloride (Building Block D)

Imidazole-1-sulfonyl azide hydrochloride (2.2 g, 10.52 mmol) was added to a mixture of Boc-L-Lys-OMe (2.28 g, 8.77 mmol), CuSO\(_4\).5H\(_2\)O (21.9 mg, 0.09 mmol) and K\(_2\)CO\(_3\) (2.06 g, 14.9 mmol) in MeOH (45 mL). The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure followed by addition of H\(_2\)O (60 mL); the mixture was acidified to pH 2-4 with 5% citric acid and extracted with EtOAc (3 x 80 mL). The organic fractions were dried over MgSO\(_4\) and the solvent evaporated under reduced pressure. The resulting orange oil was purified by column chromatography yielding 1.74 g of Boc-L-Lys(N\(_3\))-OMe. The Boc group was removed by following GP4 to yield the desired product as a white solid (1.24 g, 73% yield over 2 steps).

\(\delta^H/\text{ppm}\) (500 MHz, \(d_6\)-DMSO): 8.59 (3H, bs), 4.09-3.96 (1H, m), 3.75 (3H, s), 3.40-3.20 (2H, m), 1.86-1.76 (2H, m), 1.59-1.26 (4H, m). \(\delta^C/\text{ppm}\) (100 MHz, \(d_6\)-DMSO): 170.8, 53.7, 52.6, 51.2, 30.4, 28.6, 22.4. \(\nu_{\text{max}}/\text{cm}^{-1}\): 3424, 2925, 2870, 2093, 1743, 1596, 1509, 1231. **HRMS (ESI+) m/z** found [M+H]\(^+\) 187.1187, \(C_7H_{15}N_4O_2\)\(^+\) required 187.1195.

Building Block E

\[
\begin{align*}
\text{NH}_2 & \quad \rightarrow \quad \text{Cl} \overset{\text{H}_3\text{N}}{\rightarrow} \overset{\text{O}}{\rightarrow} \\
\text{N}_3 & \quad \rightarrow \quad \text{N}_3
\end{align*}
\]

**SF9: Synthetic Route to Building Block E**
(S)-5-azido-1-methoxy-1-oxopentan-2-aminium chloride (Building Block E)

![Diagram of Building Block E]

Imidazole-1-sulfonyl azide hydrochloride (4.78 g, 22.8 mmol) was added to a mixture of Boc-L-Orn-OH (4.41 g, 19 mmol), CuSO₄·5H₂O (47.4 mg, 0.19 mmol), and K₂CO₃ (7.09 g, 51.3 mmol). The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure followed by addition of H₂O (75 mL); the mixture was acidified to pH 2-4 with 5% citric acid and extracted with EtOAc (3 x 150 mL). The organic fractions were dried over MgSO₄ and the solvent evaporated under reduced pressure to yield Boc-Orn(N₃)-OH as a yellow oil. Formation of the corresponding methyl ester was achieved by following a similar procedure to (S)-methyl-3-((S)-2-azido-3-phenylpropanamido)-2-((tert-butoxycarbonyl)amino)propanoate. The Boc group was removed by following GP4 to yield the desired product as a white solid (2.84 g, 72% yield over 3 steps).

δ_H/ppm (400 MHz, d_6-DMSO): 8.72 (3H, bs), 4.15-3.94 (1H, m), 3.74 (3H, s), 3.44-3.26 (2H, m), 1.90-1.81 (2H, m), 1.79- 1.51 (2H, m). δ_C/ppm (100 MHz, d_6-DMSO): 170.2, 53.3, 51.9, 50.4, 27.7, 24.4. ν_max/cm⁻¹: 3377, 2970, 2902, 2093, 1744, 1509, 1440, 1280, 1057. HRMS (ESI+) m/z found [M+Na]⁺ 195.0867, C₆H₁₂N₄O₂Na⁺ required 195.0858.

Building Block F

![Diagram of Building Block F]

SF9: Synthetic Route to Building Block F
N-Boc-3-nitro-L-phenylalanine (610 mg, 1.95 mmol) was dissolved in 25 mL of MeOH, following by addition of K$_2$CO$_3$ (323 mg, 2.34 mmol) and 10% Pd on charcoal. The reaction mixture was hydrogenated at room temperature under 55 psi. After 4 hours the reaction is stopped, filtered over Celite and evaporated to dryness to yield the potassium salt of N-Boc-3-amine-L-phenylalanine as a white solid (672 mg), this intermediate was used in the next reaction without further purification. N-Boc-3-amine-L-phenylalanine potassium salt (672 mg, 1.95 mmol), imidazol sulfonyl azide bisulfate (635 mg, 2.34 mmol), CuSO$_4$ pentahydrate (5 mg, 0.0195 mmol), were dissolved in 12 mL of MeOH, and the reaction mixture was stirred at room temperature for 18 hours. The solvent was evaporated and 6 mL of water was added to the slurry. The aqueous phase was acidified with 1M HCl until pH 3 and extracted with EtOAc (3 x 15 mL); the organic phase was dried over MgSO$_4$ and purified by flash column (DCM/MeOH/AcOH 95/5/0.6) to give N-Boc-3-azide-L-phenylalanine as a pink solid (330 mg). Formation of the corresponding methyl ester was achieved by following a similar procedure to (S)-methyl-3-((S)-2-azido-3-phenylpropanamido)-2-((tert-butoxycarbonyl)amino) propanoate. The Boc group was removed by following GP4 to yield the desired product as a violet solid (261 mg, 94% yield).

$\text{Mp} = 160-162 ^\circ\text{C (CH}_2\text{Cl}_2)$. $\delta_{H}$/ppm (500 MHz, $d_6$-DMSO): 8.52 (3H, br), 7.37 (1H, t, $J=7.9$ Hz), 7.06 – 6.97 (3H, m), 4.34 (1H, t, $J=6.6$ Hz), 3.69 (3H, s), 3.13 (2H, d, $J=6.7$ Hz). $\delta_{C}$/ppm (100 MHz, $d_6$-DMSO): 169.4, 139.7, 136.8, 130.4, 126.4, 120.2, 118.3, 53.1, 52.9, 35.6. $\nu_{\text{max}}$/cm$^{-1}$: 2825, 2628, 2106, 1735, 1593, 1578, 1492, 1479, 1441, 1390, 1290, 1242, 1211, 1140, 1082. HRMS (ESI+) m/z found [M+H]$^+$ 221.1047, C$_{10}$H$_{13}$N$_4$O$_2$+ required 221.1039. $[\alpha]_D^{26.2}$ = +9.0 (c 0.000867, MeOH).
7. Synthesis of Alkyne-Acid Building Blocks

Building block 1

Boc-L-Lys-OH (1.72 g, 7 mmol) was suspended in dry DMF (25 mL) and DIPEA (1.27 mL, 7.7 mmol) was added followed by a solution of 5-hexynoic acid (1.61 g, 7.7 mmol) in dry DMF (10 mL). The solution was stirred for 5 min at rt followed by addition of extra DIPEA (1.27 mL, 7.7 mmol) and further stirring for 4h at rt. Most of the DMF was removed under reduced pressure (T= 35-40°C) and H2O (50 mL) was added and the pH adjusted to 8-9 with saturated aqueous Na₂CO₃. The resulting mixture was washed with diethyl ether (3 x 25 mL). The pH of the aqueous phase was adjusted to pH 2-3 with concentrated HCl and extracted with EtOAc (4 x 30 mL). The combined organic fractions were dried with MgSO₄ and evaporated to dryness to yield the product as a yellow oil (2.45 g, 80% purity, 82.3% yield).

δH /ppm (500 MHz, DMSO-d₆): 12.40 (1H, bs), 7.80 (1H, t, J=5.6 Hz), 7.02 (1H, d, J=8.0 Hz), 3.83-3.77 (1H, m), 3.04-2.95 (2H, m), 2.77 (1H, t, J=2.7 Hz), 2.17-2.09 (4H, m), 1.69-1.58 (3H, m), 1.58-1.48 (1H, m), 1.44-1.18 (4H, m), 1.37 (9H, s). δc /ppm (125 MHz, DMSO-d₆): 174.3, 172.8, 171.2, 155.6, 84.1, 78.0, 71.5, 53.4, 38.2, 34.2, 30.4, 28.8, 28.2, 24.3, 23.1, 17.4. vmax /cm⁻¹: 3359, 2941, 1720, 1683, 1626, 1525, 1436, 1160. HRMS (ESI+) m/z found [M+Na]⁺ 363.1908, C₁₇H₂₈N₂O₅Na⁺ required 363.1896.

Building block 2

A procedure analogous to the one used for the synthesis of building block 1, except using Boc-L-Orn-OH and 4-pentynoic acid as starting materials afforded building block 2 as a yellow oil (1.61 g, 80% purity, 98% yield).

δH /ppm (500 MHz, DMSO-d₆): 12.44 (1H, bs), 7.85 (1H, t, J=5.5 Hz), 7.05 (1H, d, J=8.0 Hz), 3.86-3.78 (1H, m), 3.05-2.97 (2H, m), 2.73 (1H, t, J=2.6 Hz), 2.34 (2H, td, J=7.5, 2.6 Hz), 2.24
(2H, t, J=7.5 Hz), 1.68-1.61 (1H, m), 1.56-1.30 (3H, m), 1.37 (9H, s). δ<sub>C /ppm</sub> (125 MHz, DMSO-d<sub>6</sub>): 174.1, 172.8, 170.1, 155.6, 83.8, 78.0, 71.3, 53.3, 39.5, 34.3, 28.3, 28.2, 26.0, 14.3. ν<sub>max /cm<sup>-1</sup></sub>: 3285, 3086, 2978, 2933, 1738, 1695, 1626, 1550, 1162. HRMS (ESI+) m/z found [M+H]<sup>+</sup> 313.1762, C<sub>15</sub>H<sub>25</sub>N<sub>2</sub>O<sub>5</sub> required 313.1763.

### Building block 3

![Building block 3](image)

A procedure analogous to the one used for the synthesis of building block 1, except using Boc-L-Orn-OH and 5-hexynoic acid as starting materials afforded building block 3 as a yellow oil (1.76 g, 82% purity, 88% yield).

δ<sub>H /ppm</sub> (400 MHz, DMSO-d<sub>6</sub>): 12.44 (1H, bs), 7.81 (1H, t, J=5.4 Hz), 7.08 (1H, d, J=8.0 Hz), 3.87-3.81 (1H, m, J=4.0 Hz), 3.11-2.95 (2H, m), 2.79 (1H, t, J=2.6 Hz), 2.21-2.10 (4H, m), 1.72-1.57 (3H, m), 1.58-1.30 (3H, m), 1.39 (9H, s, 9H). δ<sub>C /ppm</sub> (100 MHz, DMSO-d<sub>6</sub>): 174.6, 171.7, 156.3, 84.6, 78.4, 72.0, 53.8, 38.5, 34.6, 28.7, 28.7, 26.4, 24.8, 17.9. ν<sub>max /cm<sup>-1</sup></sub>: 3309, 2931, 1701, 1641, 1525, 1367, 1161. HRMS (ESI+) m/z found [M+H]<sup>+</sup> 327.1935, C<sub>16</sub>H<sub>27</sub>N<sub>2</sub>O<sub>5</sub> required 327.1920.

### Building block 4

![Building block 4](image)

Boc-L-Lys(Z)-OH (2.70 g, 7.10 mmol) was dissolved in MeOH (25 mL) and hydrogenated overnight over 5% palladium charcoal (135 mg) at room temperature and pressure. The mixture was filtered through a pad of Celite and the solvent was removed under reduced pressure. The slurry was co-evaporated with CH<sub>2</sub>Cl<sub>2</sub> to give Boc-L-Lys-OH as a white solid which was used without further purification (1.68 g). 4-Nitrophenyl prop-2-yn-1-ylcarbamate (CP2, 1.36 g, 6.17 mmol), Boc-L-Lys-OH (1.67 g, 6.79 mmol), and CH<sub>2</sub>Cl<sub>2</sub> (60 mL) was added to a round bottomed flask equipped with a stir bar. Et<sub>3</sub>N (1.80 mL, 13.0 mmol) was added to give a yellow suspension. The mixture was stirred at RT overnight. The solvent was evaporated, and the residue purified by flash column chromatography (0-1% acetic acid in EtOAc). Co-evaporations with toluene were performed to give a white solid (1.56 g, 74% yield over 2 steps).
αH /ppm (400 MHz, d6-DMSO): 12.38 (1H, br s), 7.01 (1H, d, J=8.0 Hz), 6.10 (1H, t, J=5.5 Hz),
5.95 (1H, t, J=5.5 Hz), 3.85-3.78 (1H, m), 3.77 (2H, dd, J=5.5, 2.5 Hz), 3.01 (1H, t, J=2.5 Hz),
2.99-2.91 (2H, m), 1.70-1.42 (2H, m), 1.38 (9H, s), 1.39-1.20 (4H, m). δc /ppm (100 MHz, d6-
DMSO): 174.2, 157.4, 155.5, 82.5, 77.8, 72.4, 53.4, 38.6, 30.4, 29.5, 28.1, 22.9. νmax /cm−1:
3388, 3304, 2939, 2162, 1729, 1684, 1622, 1530, 1209, 1159. HRMS (ESI+) m/z found
[M+H]+ 328.1880, C15H25N3O5+ required 328.1872. [α]D25 = +5.6 (c 0.51, MeOH).

Building block 5

A procedure analogous to the one used for the synthesis of building block 4, except using Boc-
(Z)-Orn-OH as starting material afforded building block 5 as a clear oil (832 mg, 54% yield over 2
steps).

αH /ppm (500 MHz, d6-DMSO): 12.45 (1H, br s), 7.06 (1H, d, J=8.0 Hz), 6.12 (1H, t, J=5.5 Hz),
5.98 (1H, t, J=5.5 Hz), 3.83 (1H, td, J=8.5, 4.5 Hz), 3.76 (2H, dd, J=6.0, 2.5 Hz), 3.02 (1H, t,
J=2.5 Hz), 2.95 (2H, dd, J=12.80, 6.51 Hz), 1.71-1.56 (1H, m), 1.37 (9H, s), 1.55-1.31 (3H, m).
δc /ppm (125 MHz, d6-DMSO): 174.1, 157.4, 155.5, 82.5, 77.9, 72.4, 53.3, 38.9, 28.7, 28.2,
28.1, 26.7. νmax /cm−1: 3296, 3304, 2939, 2162, 1729, 1684, 1622, 1530, 1209, 1159. HRMS (ESI+) m/z
found [M+H]+ 314.1723, C14H23N3O5+ required 314.1716. [α]D25 = +9.2 (c 0.49, MeOH).

Building block 6

Building block 6 was prepared by literature procedures.[6]
Building block 7

A procedure analogous to the one used for the synthesis of building block 1, except using Boc-L-Dab-OH and 5-hexynoic acid as starting materials afforded building block 7 as a yellow oil (1.36 g, 86% purity, 89% yield).

δ\text{/ppm} (400 MHz, d$_6$-DMSO): 12.50 (1H, bs), 7.87 (1H, t, $J$=5.2 Hz), 7.12 (1H, d, $J$=8.1 Hz), 3.99-3.82 (1H, m), 3.20-2.98 (2H, m), 2.80 (1H, t, $J$=2.6 Hz), 2.18-2.12 (4H, m), 1.73-1.58 (3H, m), 1.39 (9H, s). δ\text{/ppm} (100 MHz, d$_6$-DMSO): 174.5, 171.9, 156.0, 84.6, 78.5, 72.0, 51.8, 36.1, 34.6, 31.2, 28.7, 24.7, 17.9. ν$_\text{max}$/cm$^{-1}$: 3294, 2979, 2938, 1679, 1601, 1568, 1366, 1215, 1159. HRMS (ESI+) m/z found [M+Na]$^+$ 335.1584, C$_{15}$H$_{24}$N$_2$O$_5$Na$^+$ required 335.1583.

Building block 8

A procedure analogous to the one used for the synthesis of building block 1, except using Boc-L-Dab-OH and 4-pentynoic acid as starting materials afforded building block 8 as a yellow oil (1.28 g, 83% purity, 85% yield).

δ\text{/ppm} (500 MHz, d$_6$-DMSO): 12.53 (1H, bs), 7.93 (1H, t, $J$=5.2 Hz), 7.12 (1H, d, $J$=8.1 Hz), 3.95–3.90 (1H, m), 3.28-3.06 (2H, m), 2.76 (1H, t, $J$=2.5 Hz), 2.36 (2H, t, $J$=6.5, 1.8 Hz), 2.27 (2H, t, $J$=7.2 Hz), 1.89-1.76 (1H, m), 1.75-1.61 (1H, m), 1.39 (9H, s). δ\text{/ppm} (125 MHz, d$_6$-DMSO): 174.8, 171.1, 156.4, 84.6, 78.9, 72.2, 52.2, 36.6, 35.02, 31.4, 29.1, 15.09. ν$_\text{max}$/cm$^{-1}$: 3296, 2975, 2930, 1703, 1628, 1542, 1365, 1215, 1160. HRMS (ESI+) m/z found [M+H]$^+$ 299.1598, C$_{14}$H$_{23}$N$_2$O$_5$ required 299.1607.
Building block 9

A procedure analogue to the one used for the synthesis of building block 10, except using hexynoyl-OSu instead of pentynoyl-OSu afforded building block 9 as a white solid (1.42 g, 95% yield).

δH/ppm (400 MHz, d6-DMSO): 12.56 (1H, br s), 7.91 (1H, t, J=5.5 Hz), 6.92 (1H, d, J=8.0 Hz), 4.03 (1H, dt, J=7.5, 5.0 Hz), 3.43-3.23 (2H, m), 2.76 (1H, t, J=2.5 Hz), 2.17-2.10 (4H, m), 1.64 (2H, p, J=7.0 Hz), 1.38 (9H, s). δC/ppm (100 MHz, d6-DMSO): 172.2, 172.0, 155.2, 84.0, 78.1, 71.3, 53.4, 39.7, 34.0, 28.1, 24.2, 17.2. νmax/cm⁻¹: 3291, 2979, 1739, 1679, 1611, 1534, 1296, 1240, 1159. HRMS (ESI+) m/z found [M+H]+ 299.1612, C14H23N2O5+ required 299.1607. [α]D25 = -3.2 (c 0.49, MeOH).

Building block 10

To a suspension of Boc-L-Dap-OH (1.00 g, 4.91 mmol), in dry DMF (20 mL), was added a fraction of DIPEA (940 µL, 5.4 mmol). A solution of pentynoyl-OSu (1.15 g, 5.90 mmol) in dry DMF (10 mL) was then added dropwise over 10 minutes. After 5 minutes a second fraction of DIPEA (940 µL, 5.4 mmol) was added and the mixture was stirred at rt for 5 hours. The organic solvent was removed under reduced pressure and the slurry was diluted with H2O (25 mL). The pH was adjusted to 8-9 by addition of saturated Na2CO3 and washings with Et2O (3 x 15 mL) were performed. The aqueous layer was then acidified to pH 2-3 with conc. HCl and extracted with EtOAc (3 x 20 mL). The organic extracts were dried (MgSO4) and evaporated to dryness under reduced pressure. After precipitations in Et2O, building block 10 was obtained as a white solid in 89% yield.

δH/ppm (400 MHz, d6-DMSO): 12.57 (1H, br s), 8.02-7.93 (1H, m), 6.94 (1H, d, J=8.5 Hz), 4.02 (1H, dt, J=7.5, 5.0 Hz), 3.41 (1H, td, J=13.3, 5.2 Hz), 3.36-3.23 (1H, m), 2.73 (1H, t, J=2.5 Hz), 2.38-2.22 (4H, m), 1.38 (9H, s). δC/ppm (100 MHz, d6-DMSO): 172.1, 170.7, 155.3, 83.6, 78.2, 71.2, 53.4, 39.8, 34.0, 28.1, 14.1. νmax/cm⁻¹: 3290, 3265, 3087, 2979, 1738, 1703, 1611, 1534, 1364, 1277, 1161. HRMS (ESI+) m/z found [M+H]+ 285.1461, C13H21N2O5+ required 285.1450. [α]D25 = -5.8 (c 0.51, MeOH).
Building block 11

A procedure analogues to the one used for the synthesis of building block 4, except using Boc-Dab-OH as starting material afforded building block 11 as a white foam after flash column chromatography (1% Acetic acid: 9% MeOH: 90% EtOAc) (998 mg, 80% yield).

$\delta_H / ppm$ (500 MHz, $d_6$-DMSO): 12.45 (1H, br s), 7.06 (1H, d, $J=8.0$ Hz), 6.23 (1H, t, $J=5.5$ Hz), 6.03 (1H, t, $J=5.5$ Hz), 3.88-3.82 (1H, m), 3.77 (2H, dd, $J=5.5, 2.5$ Hz), 3.12-3.01 (1H, m), 6.03 (1H, t, $J=2.5$ Hz), 3.00-2.91 (1H, m), 1.82-1.72 (1H, m), 1.65-1.55 (1H, m), 1.38 (1H, s).

$\delta_C / ppm$ (125 MHz, $d_6$-DMSO): 174.1, 157.4, 155.6, 82.5, 78.0, 72.5, 51.3, 36.3, 31.6, 28.7, 28.1.

$\nu_{\text{max}} / cm^{-1}$: 3295, 2979, 1685, 1627, 1558, 1255, 1157. HRMS (ESI+) m/z found [M+Na]$^+$ 322.1386, $C_{13}H_{21}N_3O_5$Na$^+$ required 322.1379. $[\alpha]_D^{25} = -10.5$ (c 0.53, MeOH).

Building block 12

A procedure analogues to the one used for the synthesis of building block 4, except using common precursor 1 as starting material afforded building block 12 as a white foam after flash column chromatography (5% MeOH: 1% AcOH: 94% EtOAc) (1.19 g, 79% yield).

$\delta_H / ppm$ (400 MHz, $d_6$-DMSO): 12.61 (1H, br s), 6.95 (1H, d, $J=7.5$ Hz), 6.46 (1H, t, $J=5.5$ Hz), 6.14-6.06 (1H, m), 3.93-3.81 (1H, m), 3.80-3.75 (2H, m), 3.41 (1H, dt, $J=13.0, 5.0$ Hz), 3.21-3.11 (1H, m), 3.03 (1H, t, $J=2.5$ Hz), 1.38 (9H, s).

$\delta_C / ppm$ (100 MHz, $d_6$-DMSO): 172.4, 157.5, 155.3, 82.2, 78.0, 72.5, 54.6, 40.5, 28.7, 28.1. $\nu_{\text{max}} / cm^{-1}$: 3376, 3306, 3261, 2979, 1743, 1406, 1627, 1558, 1255, 1160. HRMS (ESI+) m/z found [M+H]$^+$ 286.1391, $C_{12}H_{20}N_3O_5$ required 286.1403. $[\alpha]_D^{25} = -7.1$ (c 0.62, MeOH).
Building block 13

To a solution of 5-hexynoic acid (0.528 mL, 4.67 mmol, 1 eq) and Oxyma pure (634 mg, 4.67 mmol, 1 eq) in dry DMF, was added DCC (964 mg, 4.67 mmol, 1 eq). After an hour of stirring at room temperature, a solution of Boc-L-4-amino-phenylalanine-OH (1.31 g, 4.67 mmol, 1 eq) and DIPEA (1.70 mL, 10.3 mmol, 2.2 eq) in dry DMF was added, and the reaction mixture was stirred overnight. The precipitated dicyclohexylurea was filtered off, and the solvent evaporated under reduced pressure. The slurry was dissolved in 15 mL of EtOAc, and the organic phase was washed with 5% citric acid (2 x 10 mL), dried over MgSO$_4$ and evaporated to dryness. Purification by flash chromatography of the crude product (98.5% DCM: 1.5% MeOH: 1% AcOH) afforded the building block 13 as a white solid (1.13 g, 64% yield).

$\text{Mp} = 138$-$140^\circ C$ (1: 1.5: 98.5, AcOH/ MeOH/ CH$_2$Cl$_2$). $\delta$H/ppm (400 MHz, d$_6$-DMSO): 9.83 (1H, s), 7.45 (2H, d, J=8.4 Hz), 7.15 (2H, d, J=7.6 Hz), 7.02 (1H, d, J=8.4 Hz), 4.00 (1H, m), 2.90 (1H, dd, J= 20.0, 4.0 Hz), 2.79 (1H, t, J=2.5 Hz), 2.76-2.70 (1H, m), 2.36 (2H, t, J= 7.6 Hz), 2.18 (2H, td, J=7.0, 2.6 Hz), 1.75-1.70 (2H, m), 1.30 (9H, s). $\delta$C/ppm (100 MHz, d$_6$-DMSO): 174.0, 170.9, 155.9, 138.1, 133.0, 129.7, 119.3, 84.5, 78.5, 72.1, 55.8, 36.3, 35.5, 28.6, 24.4, 17.8. $\nu_{\text{max}}$/cm$^{-1}$: 3549, 3351, 2975, 2162, 2008, 1727, 1706, 1661, 1597, 1523, 1411, 1367, 1308, 1248, 1161, 1057, 1027, 939, 897, 829, 779. HRMS (ESI+) m/z found [M+H]$^+$ 375.1927, $C_{20}H_{27}N_{2}O_{5}^+$ required 375.1920. $[\alpha]_D^{26.2} = +15$ (c 0.001, MeOH).

Building block 14

Building block 14 was prepared by literature procedures.$\text{[6]}$
## 8. Synthesis of B/C/C/P and B/C/C/C/P Coupling Units

See SF4 and SF5 for overview of synthetic routes used.

| Compound | Method, Yield (%), Purity (%) | Analysis |
|----------|-------------------------------|----------|
| G        | GP1 & GP4 71% 90%             | \( \delta_\text{H} / \text{ppm} \) (400 MHz, CDC\(_3\)): 8.66 (3H, bs), 8.46 (1H, d, \( J=7.3 \) Hz), 4.23-4.16 (1H, m), 4.04-3.92 (1H, m), 3.73 (3H, s), 3.61 (3H, s), 3.32 (2H, t, \( J=6.8 \) Hz), 2.46-2.22 (2H, m), 2.06-1.95 (2H, m), 1.75-1.56 (2H, m), 1.58-1.43 (2H, m), 1.43-1.28 (2H, m). \( \delta_\text{C} / \text{ppm} \) (100 MHz, CDC\(_3\)): 173.0, 171.5, 170.2, 53.3, 52.4, 52.3, 51.9, 50.9, 30.8, 30.6, 28.3, 26.4, 23.2. \( \nu_{\text{max}} / \text{cm}^{-1} \): 3316, 2902, 1738, 1645, 1528, 1436, 1251, 1227, 1082. HRMS (ESI+) m/z found \([M+H]^+\) 330.1763, \( C_{13}H_{24}N_5O_5\) required 330.1772. |
| H        | GP1 & GP4 84% 90%             | \( \delta_\text{H} / \text{ppm} \) (400 MHz, CDC\(_3\)): 8.68 (3H, bs), 8.50 (1H, d, \( J=7.3 \) Hz), 4.27-4.19 (1H, m), 4.03-3.94 (1H, m), 3.73 (3H, s), 3.62 (3H, s), 3.34 (2H, t, \( J=6.7 \) Hz), 2.45-2.23 (2H, m), 2.06-1.95 (2H, m), 1.80-1.50 (4H, m). \( \delta_\text{C} / \text{ppm} \) (101 MHz, CDC\(_3\)): 172.8, 171.5, 170.1, 53.3, 52.4, 52.1, 51.9, 50.6, 30.6, 28.4, 26.4, 25.3. \( \nu_{\text{max}} / \text{cm}^{-1} \): 3310, 2958, 2094, 1741, 1645, 1537, 1438, 1224, 1078. HPLC (5-100% ACN) Rt 10.53 mins. HRMS (ESI+) m/z found \([M+H]^+\) 316.1609, \( C_{12}H_{22}N_5O_5\) required 316.1615. |
| J        | GP1 & GP4 98% 83%             | HPLC (5-100% ACN) Rt 9.66 mins. LCMS [M+H]^+ 244.10. |
| K        | GP1 & GP4 90% 86%             | HPLC (5-100% ACN) Rt 7.80 mins. LCMS [M+H]^+ 405.17. |
| L        | GP1 & GP4 89% 77%             | HPLC (5-100% ACN) Rt 8.91 mins. LCMS [M+H]^+ 552.33. |
|   |   | GP1 & GP4 |   |
|---|---|---------|---|
| M | ![Molecule](image) | 72% | HPLC (5-100% ACN) Rt 7.48 mins. LCMS [M+H]^+ 391.17. |
| N | ![Molecule](image) | 80% | HPLC (5-100% ACN) Rt 8.78 mins. LCMS [M+H]^+ 552.25. |
9. Preparation of B/C/P Linear Amides

|    | Compound | Method, Yield (%), Purity (%) | Analysis |
|----|----------|-------------------------------|----------|
| A1 | ![Chemical Structure](image1) | GP1 78% 88% | HPLC (30-100% ACN) Rt 8.26 mins. LCMS [M+H]+ 656.33. |
| A2 | ![Chemical Structure](image2) | GP1 76% 89% | HPLC (30-100% ACN) Rt 7.73 mins. LCMS [M+H]+ 628.86. |
| A3 | ![Chemical Structure](image3) | GP1 78% 88% | HPLC (30-100% ACN) Rt 8.07 mins. LCMS [M+H]+ 642.50. |
| A4 | ![Chemical Structure](image4) | GP1 71% 96% | HPLC (5-100% ACN) Rt 10.07 mins. LCMS [M+H]+ 643.54. |
|   |   |   |   |   |
|---|---|---|---|---|
| **A5** | ![Chemical Structure](image) | GP1 | 84% | HPLC (5-100% ACN) *Rt* 10.06 mins. LCMS [M+H]^+ 628.33. |
|   |   |   |   |   |
| **A6** | ![Chemical Structure](image) | GP1 | 26% | HPLC (5-100% ACN) *Rt* 11.71 mins. LCMS [M+H]^+ 676.54. |
|   |   |   |   |   |
| **A7** | ![Chemical Structure](image) | GP1 | 26% | HPLC (30-100% ACN) *Rt* 8.05 mins. LCMS [M+H]^+ 628.54. |
|   |   |   |   |   |
| **A8** | ![Chemical Structure](image) | GP1 | 70% | HPLC (5-100% ACN) *Rt* 7.70 mins. LCMS [M+H]^+ 614.55. |
|   |   |   |   |   |
| **A9** | ![Chemical Structure](image) | GP1 | 60% | HPLC (5-100% ACN) *Rt* 11.28 mins. LCMS [M+H]^+ 613.21. |
A10

|   | GP1 | 49%  | 86%  |
|---|-----|------|------|

HPLC (5-100% ACN) Rt 11.04 mins. LCMS [M+H]$^+$ 599.31.

A11

|   | GP1 | 81%  | 94%  |
|---|-----|------|------|

HPLC (5-100% ACN) Rt 10.49 mins. LCMS [M+H]$^+$ 614.32.

A12

|   | GP1 | 59%  | 93%  |
|---|-----|------|------|

δ$_H$/ppm (500 MHz, CDCl$_3$): 7.39-7.24 (5H, m), 7.13 (1H, d, J=7.5 Hz), 6.93-6.84 (1H, m), 6.53 (1H, t, J=6.0 Hz), 6.11 (1H, s), 5.83-5.71 (1H, m), 4.67 (1H, dt, J=10.0, 4.5 Hz), 4.20 (1H, dd, J=8.0, 4.5 Hz), 4.16-4.22 (1H, m), 4.08 (1H, ddd, J=17.5, 6.0, 2.5 Hz), 4.01-3.89 (1H, m), 3.72 (3H, s), 3.71-3.54 (2H, m), 3.44-3.35 (1H, m), 3.33 (1H, dd, J=14.0, 4.5 Hz), 3.17-3.08 (1H, m), 3.03 (1H, dd, J=14.0, 8.0 Hz), 2.18 (1H, t, J=2.5 Hz), 1.86-1.76 (1H, m), 1.69-1.58 (1H, m), 1.57-1.49 (1H, m), 1.47 (9H, s), 1.43-1.22 (3H, m). δ$_C$/ppm (101 MHz, CDCl$_3$): 172.4, 170.8, 169.9, 159.4, 156.2, 135.8, 129.5, 128.8, 127.4, 80.9, 80.2, 70.9, 65.5, 57.2, 52.4, 51.2, 42.6, 39.5, 38.7, 32.2, 29.9, 28.9, 28.3, 22.5. HPLC (5-100% ACN) Rt 10.85 mins. HRMS (ESI+) m/z found [M+H]$^+$ 601.3081, C$_{28}$H$_{41}$N$_8$O$_7$+ required 601.3098. [α]$^25$ = +4.2 (c 0.55, CHCl$_3$).

A13

|   | GP1 | 86%  | 87%  |
|---|-----|------|------|

HPLC (5-100% ACN) Rt 11.90 mins. LCMS [M+H]$^+$ 690.20.

B1

|   | GP1 | 60%  | 96%  |
|---|-----|------|------|

HPLC (5-100% ACN) Rt 10.95 mins. LCMS [M+H]$^+$ 614.43.
\( R_t = 0.33 \) (10% MeOH/90% CH\(_2\)Cl\(_2\)). \( \text{Mp} = 104-108 ^\circ C \) (2% MeOH/98% CH\(_2\)Cl\(_2\)). \( \delta H/\text{ppm} \) (400 MHz, CDCl\(_3\)): 7.39-7.19 (6H, m, 5 × ArCH and C\(_\text{ar}-\text{NH}\)), 7.06-6.92 (1H, m, C\(_\text{ar}-\text{NH}\)), 6.03-5.93 (1H, m, C\(_\text{ar}-\text{NH}\)), 5.19 (1H, d, \( J=6.6 \) Hz, BocNH), 4.57 (1H, dt, \( J=7.4, 5.1 \) Hz, H\(_3\)), 4.25-4.16 (1H, m, H\(_5\)), 4.13 (1H, dd, \( J=8.4, 4.6 \) Hz, H\(_3\)), 3.76 (3H, s, OCH\(_3\)), 3.70-3.62 (2H, m, H\(_5\)), 3.57-3.43 (1H, m, H\(_5\)), 3.30 (1H, dd, \( J=14.0, 4.6 \) Hz, H\(_8\)), 3.25-3.15 (1H, m, H\(_8\)), 2.97 (1H, dd, \( J=14.0, 8.4 \) Hz, H\(_5\)), 2.55-2.47 (2H, m, COCH\(_2\)CH\(_2\)), 2.44-2.35 (2H, m, COCH\(_2\)CH\(_2\)), 2.03 (1H, t, \( J=2.6 \) Hz, CH\(_2\)C), 1.87-1.75 (1H, m, H\(_8\)), 1.67-1.55 (3H, m, H\(_6\) and H\(_7\)), 1.43 (9H, s, C(CH\(_3\))\(_3\)). \( \delta C/\text{ppm} \) (101 MHz, CDCl\(_3\)): 172.5 (C=O), 171.9 (C=OCH\(_2\)CH\(_2\)), 170.4 (COOMe), 170.0 (C\(_\text{ar}-\text{C}=\text{O}\)), 155.9 (Boc C=O), 136.4 (ArC), 129.6 (ArCH), 128.8 (ArCH), 127.4 (ArCH), 83.1 (C=CH), 80.3 (C(CH\(_3\))\(_3\)), 69.8 (C=CH), 65.4 (C\(_\text{ar}\)), 53.6 (C\(_\text{ar}\)), 53.0 (OCH\(_3\)), 52.8 (C\(_\text{ar}\)), 40.8 (C\(_\text{ar}\)), 38.6 (C\(_\text{ar}\)), 38.6 (C\(_\text{ar}\)), 35.5 (COCH\(_2\)CH\(_2\)), 30.1 (C\(_\text{ar}\)), 28.4 (C(CH\(_3\))\(_3\)), 25.7 (C\(_\text{ar}\)), 15.1 (COCH\(_2\)CH\(_2\)).

\[ \nu_{\text{max}}/\text{cm}^{-1}: 3290 \text{ (m, alkyne C-H)}, 2938 \text{ (w, C-H)}, 2114 \text{ (m, N)}, 1744 \text{ (m, C=O)}, 1649 \text{ (s, C=O)}, 1522 \text{ (s, C=C)}. \]

HRMS (ESI+) \( m/z \) found [M+H\(^+\)]\(^\text{+}\) 586.2991, C\(_{29}\)H\(_{40}\)N\(_2\)O\(_7\)\(^+\) required 586.2989 (\( \Delta 0.3 \) ppm). \([\alpha]_D^{25}\) = +47.0 (c 0.24, CHCl\(_3\)).

\[ \text{B2} \]

\[ \text{B3} \]

\[ \text{B4} \]
| B5 | $\text{R}_f = 0.44$ ($10\% \text{MeOH/ 90}\% \text{CH}_2\text{Cl}_2$). $\text{M}p = 105-108^\circ\text{C}$ ($2\% \text{MeOH/ 98}\% \text{CH}_2\text{Cl}_2$). $\delta_{\text{H}}$ / ppm (500 MHz, CDCl$_3$): 7.47 (1H, d, $J=7.5$ Hz, C$_p$-NH), 7.40-7.21 (5H, m, 5 x ArCH), 7.10 (1H, app. s, C$_p$-NH), 5.28 (1H, app. s, Boc-NH), 5.03-4.93 (2H, m, C$_p$-NH and NHC$_2$C=CH), 4.57 (1H, dt, $J=7.5$ Hz and 5.2 Hz, H$_a$), 4.26-4.18 (1H, m, H$_a$), 4.16-4.10 (1H, m, H$_b$), 4.01-3.88 (2H, m, NHC$_2$C=CH), 3.75 (3H, s, OCH$_3$), 3.73-3.59 (2H, m, H$_b$), 3.45-3.34 (1H, m, H$_b$), 3.29 (1H, dd, $J = 14.0$, 4.7 Hz, H$_c$), 3.22-3.12 (1H, m, H$_d$), 2.98 (1H, dd, $J = 14.0$, 8.5 Hz, H$_d$), 2.23 (1H, t, $J = 2.5$ Hz, CH=CH). 1.89-1.78 (1H, m, H$_e$), 1.65-1.51 (3H, m, H$_f$ and H$_g$). 1.42 (9H, s, C(CH$_3$)$_3$). $\delta_{\text{C}}$ / ppm (125 MHz, CDCl$_3$): 172.7 (C$_p$=C=O), 170.7 (COOMe), 170.1 (C$_a$=C=O), 158.3 (NHC=ONH), 156.0 (Boc C=O), 136.4 (ArC), 129.6 (ArCH), 128.8 (ArCH), 127.4 (ArCH), 80.8 (C=CH), 80.3 (C(CH$_3$)$_3$), 71.5 (C=CH), 65.4 (C$_a$), 53.6 (C$_b$), 53.0 (OCH$_3$), 52.7 (C$_a$), 40.8 (C$_b$), 39.4 (C$_c$), 38.6 (C$_a$), 30.3 (CH$_2$C=CH) and C$_b$, 28.4 (C(CH$_3$)$_3$), 26.2 (C$_c$). $\nu_{\text{max}} / \text{cm}^{-1}$: 3324 (m, alkyne C=H), 2945 (w, C-H), 2114 (m, N$_3$), 1738 (m, C=O), 1648 (s, C=O), 1518 (s, C=C). $\text{HPLC}$ (5-100% ACN) $\text{Rt}$ 10.27 mins. $\text{HRMS}$ (ESI$^+$) $m/z$ found [M+Na$^+$] $609.2756$, $C_{27}H_{30}N_2O_2$Na$^+$ required $609.2761$ (Δ - 0.8 ppm). [$\alpha$]$_D^{25}$ = +47.0 (c 0.26, CHCl$_3$). |  |
|---|---|
| GP1 | R$_f$ = 0.45 ($10\% \text{MeOH/ 90}\% \text{CH}_2\text{Cl}_2$). $\text{M}p = 137-138^\circ\text{C}$ ($2\% \text{MeOH/ 98}\% \text{CH}_2\text{Cl}_2$). $\delta_{\text{H}}$ / ppm (400 MHz, CDCl$_3$): 8.26 (1H, d, $J=6.7$ Hz, C$_p$-NH), 7.38-7.20 (5H, m, 5 x ArCH), 7.12 (1H, t, $J=5.0$ Hz, C$_p$-NH), 6.23 (1H, app. s, C$_p$-NH), 5.53 (1H, d, $J=6.7$ Hz, Boc-NH), 4.61-4.52 (1H, m, H$_a$), 4.16-3.99 (2H, m, H$_a$ and H$_b$), 3.99-3.88 (1H, m, H$_r$), 3.89-3.78 (1H, m, H$_s$), 3.75 (3H, s, OCH$_3$), 3.68-3.56 (1H, m, H$_b$), 3.29 (1H, dd, $J = 14.0$, 4.5 Hz, H$_e$), 3.13-2.99 (1H, m, H$_e$), 2.93 (1H, dd, $J = 14.0$, 8.9 Hz, H$_g$), 2.39 (2H, t, $J=7.4$ Hz, COCH$_2$CH$_2$CH$_2$), 2.27 (2H, td, $J=6.8$, 2.5 Hz, COCH$_2$CH$_2$CH$_2$), 2.00 (1H, t, $J=2.5$ Hz, CH=CH). 1.95-1.77 (4H, m, COCH$_2$CH$_2$CH$_2$ and H$_f$), 1.42 (9H, s, C(CH$_3$)$_3$). $\delta_{\text{C}}$ / ppm (101 MHz, CDCl$_3$): 174.3 (C=OCH$_2$CH$_2$CH$_2$), 171.4 (C$_p$=C=O), 170.5 (COOMe), 169.9 (C$_a$=C=O), 155.5 (Boc C=O), 136.6 (ArC), 129.5 (ArCH), 128.8 (ArCH), 127.3 (ArCH), 83.4 (C=CH), 80.2 (C(CH$_3$)$_3$), 65.6 (C$_a$), 53.0 (C$_b$), 53.0 (OCH$_3$), 51.4 (C$_c$), 40.5 (C$_b$), 38.7 (C$_b$), 36.2 (C$_r$), 35.3 (COCH$_2$CH$_2$CH$_2$), 34.3 (C$_f$ or COCH$_2$CH$_2$CH$_2$), 28.5 (C(CH$_3$)$_3$), 24.3 (C$_f$ or COCH$_2$CH$_2$CH$_2$), 18.0 (COCH$_2$CH$_2$CH$_2$). $\nu_{\text{max}} / \text{cm}^{-1}$: 3282 (m, alkyne C=H), 2950 (w, C-H), 2115 (m, N$_3$), 1746 (m, C=O), 1652 (s, C=O), 1523 (s, C=C). $\text{HPLC}$ (5-100% ACN) $\text{Rt}$ 10.82 mins. $\text{HRMS}$ (ESI$^+$) $m/z$ found [M+H$^+$] $586.2982$, $C_{28}H_{30}N_2O_4$+ required $586.2989$ (Δ -1.2 ppm). [$\alpha$]$_D^{25}$ = +8.0 (c 0.27, CHCl$_3$). |  |
B8

| GP1 | 65% | 99% |
|-----|-----|-----|

\[ R_f = 0.47 \text{ (10\% MeOH/ 90\% CH}_2\text{Cl}_2). \] \[ \text{M}p = 95-96 \text{ °C (2\% MeOH/ 98\% CH}_2\text{Cl}_2). \]

\[ \delta_H/\text{ppm (400 MHz, CDCl}_3): 8.06 (1H, d, J=7.0 Hz, C=NH), 7.40-7.19 (5H, m, 5 × ArCH), 7.09 (1H, t, J=6.1 Hz, C=NH), 6.36 (1H, s, C=NH), 5.51 (1H, d, J=7.0 Hz, BocNH), 4.60-4.53 (1H, m, Hα), 4.19-4.03 (2H, m, Hβ and Hγ), 3.87-3.85 (1H, m, Hγ), 3.85-3.76 (1H, m, Hδ), 3.76 (3H, s, OCH3), 3.67-3.57 (1H, m, Hγ), 3.29 (1H, dd, J=14.0, 4.6 Hz, Hβ), 3.15-3.04 (1H, m, Hγ), 2.93 (1H, dd, J=14.0, 8.8 Hz, Hδ), 2.62-2.50 (2H, m, COCH2CH3), 2.50-2.38 (2H, m, COCH2CH3), 2.07 (1H, t, J=2.5 Hz, CH2C), 1.95-1.78 (2H, m, Hβ), 1.42 (9H, s, C(CH3)3). \]

\[ \delta_C/\text{ppm (101 MHz, CDCl}_3): 172.8 (C=OCH2CH3), 171.5 (C=O), 170.4 (COOMe), 170.0 (C=O), 155.6 (Boc C=O), 136.5 (ArC), 129.5 (ArCH), 128.1 (ArCH), 127.3 (ArCH), 82.8 (C=CH), 80.2 (C(CH3)3), 70.2 (C=CH), 65.6 (Cα), 53.0 (Cβ), 53.0 (OCH3), 51.5 (Cγ), 40.6 (Cβ), 38.7 (Cγ), 36.2 (Cγ), 35.6 (COCH2CH3), 34.0 (Cβ), 28.4 (C(CH3)3), 15.1 (COCH2CH3). \]

HPLC (5-100% ACN) \[ Rt 10.54 \text{ mins. HRMS (ESI+) m/z found [M+Na]+ 594.2656, C22H37N3O7Na+ required 594.2652 (Δ 0.7 ppm). } \]

[α]D\text{25} = +6.0 (c 0.27, CHCl3).

B9

| GP1 | 44% | 88% |

\[ \delta_H/\text{ppm (400 MHz, CDCl}_3): 7.38-7.22 (6H, m), 6.96 (1H, t, J=6.0 Hz), 6.61-6.50 (1H, m), 5.85 (1H, d, J=4.0 Hz), 4.51 (1H, td, J=6.5, 4.0 Hz), 4.18-4.09 (2H, m), 3.83-3.68 (2H, m), 3.76 (3H, s), 3.63-3.44 (2H, m), 3.29 (1H, dd, J=14.0, 5.0 Hz), 2.99 (1H, dd, J=14.0, 8.5 Hz), 2.37 (2H, t, J=7.0), 2.28-2.23 (2H, m), 1.97 (1H, t, J=2.5 Hz), 1.90-1.79 (2H, m), 1.44 (9H, s). \]

\[ \delta_C/\text{ppm (101 MHz, CDCl}_3): 174.2, 170.9, 170.0, 169.9, 155.9, 136.1, 129.5, 128.7, 127.3, 83.4, 80.6, 69.3, 65.2, 53.0, 52.9, 41.4, 40.6, 38.8, 34.8, 28.2, 23.9, 17.8. \]

HPLC (5-100% ACN) \[ Rt 10.98 \text{ mins. HRMS (ESI+) m/z found [M+H]+ 572.2836, C22H35N3O7 required 572.2833. } \]

[α]D\text{25} = +3.8 (c 0.35, CHCl3).

B10

| GP1 | 53% | 93% |

\[ R_f = 0.33 \text{ (10\% MeOH/ 90\% CH}_2\text{Cl}_2). \] \[ \text{M}p = 143-144 \text{ °C (2\% MeOH/ 98\% CH}_2\text{Cl}_2). \]

\[ \delta_H/\text{ppm (400 MHz, CDCl}_3): 7.41-7.19 (6H, m, 5 × ArCH and C=NH), 6.90-6.82 (1H, m, C=NH), 6.76 (1H, app. s, C=NH), 5.79 (1H, s, BocNH), 4.61-4.47 (1H, m, Hα), 4.25-4.07 (2H, m, Hδ and Hγ), 3.99-3.79 (2H, m, Hδ and Hγ), 3.77 (3H, s, OCH3), 3.60-3.45 (2H, m, Hβ and Hγ), 3.29 (1H, dd, J=14.0, 4.6 Hz, Hδ), 2.99 (1H, dd, J=14.0, 8.3 Hz, Hγ), 2.71-2.36 (4H, m, COCH2CH3 and COCH2CH3), 2.07-2.04 (1H, m, CH2C), 1.44 (9H, s, C(CH3)3). \]

\[ \delta_C/\text{ppm (101 MHz, CDCl}_3): 173.1 (C=OCH2CH3), 171.1 (C=O), 170.2 (C=O and COOMe), 156.0 (Boc C=O), 136.2 (ArC), 129.6 (ArCH), 128.9 (ArCH), 127.5 (ArCH), 83.1 (C=CH), 80.7 (C(CH3)3), 69.8 (C=CH), 65.4 (Cα), 55.9 (Cβ), 53.3 (Cγ), 53.2 (OCH3), 41.3 (Cβ), 40.9 (Cγ), 38.6 (Cδ), 35.2 (COCH2CH3), 28.4 (C(CH3)3), 15.2 (COCH2CH3). \]

Vmax/\text{cm}^{-1}: 3301 (m, alkyne C-H), 2935 (w, C-H), 2112 (m, Nα), 1743 (m, C=O), 1652 (s, C=O), 1524 (s, C=C). \[ \text{HPLC (5-100\% ACN) } \text{R}t 10.72 \text{ mins. HRMS (ESI+) m/z found [M+Na]+ 580.2502, C26H39N3O7Na+ required } 580.2496 (Δ 1.0 ppm). \]

[α]D\text{25} = +3.0 (c 0.23, CHCl3).
\( R_f = 0.40 \) (10% MeOH/ 90% CH₂Cl₂). \( M_p = 62-65 \, ^{\circ}C \) (2% MeOH/ 98% CH₂Cl₂). \( \delta \)H/ppm (500 MHz, CDCl₃): 8.62 (1H, d, \( J = 7.1 \, Hz \), \( C_\alpha-NH \)), 7.35-7.19 (1H, m, 5 x ArCH and \( C_\beta-NH \)), 5.67 (1H, d, \( J = 7.4 \, Hz \), BocNH), 5.41-5.32 (1H, m, \( C_\gamma-NH \)), 5.18-5.07 (1H, m, NHCH₂C=CH), 4.55 (1H, dd, \( J = 7.1, \ 5.3, \ 3.8 \, Hz \), H₂), 4.20-4.13 (1H, m, \( H_\beta \)), 4.10 (1H, dd, \( J = 8.8, \ 4.7 \, Hz \), H₂), 3.98 (2H, m, NHCH₂C=CH), 3.94-3.82 (2H, m, \( H_\alpha \) and \( H_\epsilon \)), 3.75 (3H, s, OCH₃), 3.60-3.53 (1H, m, \( H_\delta \)), 3.28 (1H, dd, \( J = 14.0, \ 4.7 \, Hz \), \( H_\epsilon \)), 3.13-3.03 (1H, m, \( H_\gamma \)), 2.94 (1H, dd, \( J = 14.0, \ 8.8 \, Hz \), \( H_\delta \)), 2.20 (1H, t, \( J = 2.5 \, Hz \), \( CH=CH \)), 1.91-1.76 (2H, m, \( H_\beta \)), 1.41 (9H, s, C(CH₃)₃). \( \delta _C/\text{ppm} \) (125 MHz, CDCl₃): 171.6 (\( C_\alpha-C=O \)), 170.6 (COOME), 169.9 (\( C_\gamma-C=O \)), 158.9 (\( C(\text{NCH}=\text{ONH}) \)), 155.6 (Boc \( C=O \)), 136.6 (\( ArC \)), 129.5 (\( ArCH \)), 128.8 (\( ArCH \)), 127.3 (\( ArCH \)), 80.6 (\( C=CH \)), 80.2 (C(CH₃)₃), 71.6 (\( C=CH \)), 65.6 (\( C_\beta \)), 53.1 (OCH₃), 52.9 (\( C_\delta \)), 51.2 (\( C_\gamma \)), 40.4 (\( C_\beta \)), 38.7 (\( C_\beta \)), 36.6 (\( C_\gamma \)), 35.2 (\( C_\beta \)), 30.3 (\( CH=CH \)), 28.5 (C(CH₃)₃). \( \nu_{\max }/\text{cm}^{-1}: \) 3310 (m, alkyn C-H), 2928 (w, C-H), 2111 (m, \( N_3 \)), 1740 (m, C=O), 1652 (s, C=O), 1523 (s, C=C). HPLC (5-100% ACN) \( R_t \) 10.27 mins. HRMS (ESI+) \( m/z \) found \([M+Na]^+\) 595.2605 \( \Delta 0.2 \, ppm \). \([\alpha]_D^{25} = +26.0 \) (c 0.24, CHCl₃).

\( R_f = 0.35 \) (10% MeOH/ 90% CH₂Cl₂). \( M_p = 98-99 \, ^{\circ}C \) (2% MeOH/ 98% CH₂Cl₂). \( \delta \)H/ppm (400 MHz, CDCl₃): 7.42-7.17 (6H, m, \( C_\alpha-NH \) and 5 x \( ArCH \)), 6.86 (1H, app. s, \( C_\beta-NH \)), 5.99 (1H, app. s, BocNH), 5.67 (1H, dd, \( J = 7.9, \ 4.9 \, Hz \), \( C_\beta-NH \)), 5.48 (1H, app. s, NHCH₂C=CH), 4.61 (1H, app. s, \( H_\delta \)), 4.30-4.19 (1H, m, \( H_\beta \)), 4.15-4.04 (1H, m, \( H_\epsilon \)), 4.02 (1H, dd, \( J = 5.8, \ 2.5 \, Hz \), NHCH₂C=CH), 3.99-3.95 (1H, m, NHCH₂C=CH), 3.94-3.84 (1H, m, \( H_\beta \)), 3.83-3.68 (4H, m, \( H_\gamma \) and \( OCH₃ \)), 3.56-3.40 (2H, m, \( H_\epsilon \) and \( H_\delta \)), 3.26 (1H, dd, \( J = 14.0, \ 5.0 \, Hz \), \( H_\gamma \)), 3.04 (1H, dd, \( J = 14.0 \, Hz \) and 7.8 \, Hz), 2.19 (1H, t, \( J = 2.5 \, Hz \), \( CH=CH \)), 1.45 (9H, s, C(CH₃)₃). \( \delta _C/\text{ppm} \) (101 MHz, CDCl₃): 171.5 (\( C_\alpha-C=O \)), 170.4 (\( C_\beta-C=O \)), 170.1 (COOME), 158.7 (\( NH=ONH \)), 156.1 (Boc \( C=O \)), 135.8 (\( ArC \)), 129.6 (\( ArCH \)), 127.5 (\( ArCH \)), 80.9 (\( C=CH \)), 80.7 (C(CH₃)₃), 71.5 (\( C=CH \)), 65.1 (\( C_\beta \)), 56.8 (\( C_\gamma \)), 53.2 (OCH₃), 53.1 (\( C_\delta \)), 42.2 (\( C_\beta \)), 40.8 (\( C_\beta \)), 38.5 (\( C_\beta \)), 30.2 (CH₂C=CH), 28.4 (C(CH₃)₃). \( \nu_{\max }/\text{cm}^{-1}: \) 3323 (m, alkyn C-H), 2954 (w, C-H), 2113 (m, \( N_3 \)), 1736 (m, C=O), 1649 (s, C=O), 1517 (s, C=C). HPLC (5-100% ACN) \( R_t \) 10.39 mins. HRMS (ESI+) \( m/z \) found \([M+Na]^+\) 581.2448, \( C_{25}H_{36}N_{2}O_{6}Na^{+} \) required 581.2448 \( \Delta 0.0 \, ppm \). \([\alpha]_D^{25} = +21.2 \) (c 0.31, CHCl₃).

HPLC (5-100% ACN) \( R_t \) 11.70 mins. LCMS \([M+H]^+\) 648.26.
$\delta$W/ppm

(400 MHz, CDCl$_3$): 7.33-6.95 (7H, m, 5 × ArCH, C$_6$-NH, C$_6$-NH), 6.16-6.05 (1H, m, C$_6$-NH), 5.29 (1H, d, J=6.7 Hz, BocNH), 4.56-4.45 (1H, m, H$_4$), 4.12 (1H, dd, J=8.5, 4.4 Hz, H$_6$), 4.01-3.90 (1H, m, H$_7$), 3.76-3.47 (5H, m, OCH$_3$ and H$_8$), 3.29-3.12 (3H, m, H$_7$ and H$_9$), 2.89 (1H, dd, J=14.0 Hz and 8.5 Hz, H$_5$), 2.51-2.38 (2H, m, CH$_2$C=C), 2.36-2.22 (2H, m, CH$_2$C=O), 1.96 (1H, t, J=2.6 Hz, CH=CH), 1.83-1.68 (1H, m, H$_8$), 1.66-1.52 (1H, m, H$_9$), 1.52-1.41 (2H, m, H$_7$), 1.40-1.25 (11H, m, H$_4$ and C(CH$_3$)$_3$)$_3$. δc/ppm

(125 MHz, CDCl$_3$): 172.7 (C$_6$-C=O), 171.5 (C=OCH$_2$CH$_2$), 170.4 (COO), 170.2 (C$_7$-C=O), 155.9 (Boc C=O), 136.3 (ArC), 129.5 (ArCH), 128.7 (ArCH), 127.3 (ArCH), 83.1 (C=CH), 80.2 (C(CH$_3$)$_3$), 69.6 (C=CH), 65.3 (C$_6$), 54.6 (C$_6$), 53.0 (OCH$_3$), 52.8 (C$_6$), 40.7 (C$_6$), 38.8 (C$_6$ or C$_8$), 38.5 (C$_6$ or C$_8$), 35.5 (COCH$_2$CH$_2$), 31.6 (C$_8$), 29.0 (C$_6$), 28.3 (C(CH$_3$)$_3$), 22.4 (Cy), 15.0 (COCH$_2$CH$_2$). $\nu_{\text{max}}$/cm$^{-1}$: 3312 (m, alkyn C-H), 2929 (w, C-H), 2112 (m, N$_3$), 1744 (m, C=O), 1649 (s, C=O), 1522 (s, C=C). HPLC (5-100% ACN) Rt 10.72 mins. HRMS (ESI+) m/z found [M+H]$^+$ 600.3133, C$_{29}$H$_{32}$N$_7$O$_7$ required 600.3146 (Δ -2.2 ppm). [α]$_D^{25}$ = +41.0 (c 0.22, CHCl$_3$).

$\delta$W/ppm

(400 MHz, CDCl$_3$): 7.16 (2H, d, J=8.4 Hz, 2 × ArCH), 6.96 (2H, d, J=8.4 Hz, 2 × ArCH), 6.91 (1H, d, J=8.0 Hz, C$_6$-NH), 5.89 (1H, app s, C$_6$-NH), 5.14 (1H, d, J=6.9 Hz, BocNH), 4.82-4.73 (1H, m, H$_4$), 4.36-4.22 (1H, m, H$_5$), 3.70 (3H, s, OCH$_3$), 3.65-3.51 (1H, m, H$_6$), 3.20-3.08 (2H, m, H$_7$ and H$_8$), 3.03 (1H, dd, J=13.9, 7.1 Hz, H$_5$), 2.51-2.45 (2H, m, COCH$_2$CH$_2$), 2.38 (2H, dd, J=10.8, 3.8 Hz, COCH$_2$CH$_2$), 2.01 (1H, t, J=2.6 Hz, CH=CH), 1.84-1.72 (1H, m, H$_B$), 1.68-1.48 (3H, m, H$_B$ and H$_C$) 1.44 (9H, s, C(CH$_3$)$_3$). δc/ppm

(125 MHz, d$_6$-DMSO): 172.3 (C$_6$-C=O), 172.0 (COO), 171.9 (C=OCH$_2$CH$_2$), 155.8 (Boc C=O), 139.0 (ArC), 132.9 (ArC), 130.8 (ArCH), 119.4 (ArCH), 83.2 (CyCH), 80.1 (C(CH$_3$)$_3$), 69.6 (C=CH), 53.5 (C$_6$), 52.9 (Cy), 52.5 (OCH$_3$), 38.3 (C$_6$), 37.4 (C$_6$), 35.5 (COCH$_2$CH$_2$), 30.5 (C$_6$), 28.5 (C(CH$_3$)$_3$), 25.9 (Cy), 15.0 (COCH$_2$CH$_2$). $\nu_{\text{max}}$/cm$^{-1}$: 3284 (m, alkyn C-H), 2950 (w, C-H), 2111 (m, N$_3$), 1739 (m, C=O), 1663 (s, C=O), 1518 (s, C=C). HPLC (5-100% ACN) Rt 10.9 mins. HRMS (ESI+) m/z found [M+H]$^+$ 515.2637, C$_{26}$H$_{30}$N$_7$O$_6$ required 515.2618 (Δ 3.7 ppm). [α]$_D^{25}$ = +48.4 (c 0.93, CHCl$_3$).
**C3**

GP1

73%

85%

\[ R_f = 0.47 \ (10\% \text{ MeOH/} 90\% \text{ CH}_2\text{Cl}_2) \]

\[ \text{Mp} = 130-133 \text{ °C (CH}_2\text{Cl}_2) \]

\[ \delta_{H/\text{ppm}} (500 \text{ MHz, CDCl}_3): \]

7.17 (2H, d, \( J=8.4 \text{ Hz,} 2 \times \text{ArCH})

7.02-6.93 (3H, m, \text{C}-\text{NH and} 2 \times \text{ArCH})

5.77 (1H, app s, \text{C}-\text{NH})

5.15 (1H, d, \( J=7.4 \text{ Hz, BocNH})

4.81-4.73 (1H, m, \text{H})

3.70 (3H, s, OCH_3)

3.62-3.52 (1H, m, \text{H})

3.18-3.05 (2H, m, \text{H}_2\text{ and} \text{H})

3.02 (1H, dd, \( J=13.9, 7.4 \text{ Hz,} \text{H})

2.32 (2H, t, \( J=7.4 \text{ Hz, COCH}_2\text{CH}_2\text{CH}_2\))

2.25 (2H, td, \( J=6.8, 2.6 \text{ Hz, COCH}_2\text{CH}_2\text{CH}_2\))

1.97 (1H, t, \( J=2.6 \text{ Hz,} \text{CH}=\text{C})

1.86-1.72 (3H, m, COCH_2\text{CH}_2\text{CH}_2\text{H and} \text{H})

1.61-1.46 (3H, m, \text{H}_2\text{ and} \text{H})

1.43 (9H, s, C(CH_3)_3).\n
\[ \delta_{C/\text{ppm}} (125 \text{ MHz, CDCl}_3): \]

173.1 (C=OCH_2\text{CH}_2\text{CH}_2\))

172.3 and

172.0 (C_2\text{C}=O and COMe)

155.8 (Boc C-O)

139.0 (ArC)

132.9 (ArC)

130.8 (ArC)

119.4 (ArC)

83.7 (C=CH)

80.1 (C(CH_3)_3)

69.4 (C=CH)

53.6 (C_2)

52.9 (C_3)

52.5 (OCH_3)

38.2 (C_2)

37.4 (C_2)

35.2 (COCH_2\text{CH}_2\text{CH}_2\)

30.6 (C_2)

28.5 (C(CH_3)_3)

26.0 (C_2)

18.0 (COCH_2\text{CH}_2\text{H})

\[ \nu_{\text{max}} /\text{cm}^{-1}: \]

3319 (m, alkene C-H)

2940 (w, C-H)

2112 (m, N_2)

1738 (m, C-O)

1664 (s, C-O)

1519 (s, C=C).

HPLC (5-100% ACN) \( R_t \) 11.17 mins. HRMS (ESI+) m/z found [M+H]^+ 529.2792, C_{26}H_{35}N\text{O}_4+ required 529.2775 (\Delta 0.9 ppm). \[ \alpha_{D}^{25} = +39.1 \ (c 0.66, \text{ CHCl}_3). \]

**C5**

GP1

34%

89%

HPLC (5-100% ACN) \( R_t \) 10.60 mins. LCMS [M+H]^+ 516.24.

**C7**

GP1

74%

92%

\[ R_f = 0.37 \ (10\% \text{ MeOH/} 90\% \text{ CH}_2\text{Cl}_2) \]

\[ \text{Mp} = 94-96 \text{ °C (CH}_2\text{Cl}_2) \]

\[ \delta_{H/\text{ppm}} (500 \text{ MHz, CDCl}_3): \]

7.96 (1H, d, \( J=7.4 \text{ Hz,} \text{C}-\text{NH})

7.21 (2H, d, \( J=8.4 \text{ Hz,} 2 \times \text{ArCH})

6.98-6.92 (2H, m, \text{C}=\text{OCH}_2\text{CH}_2\text{CH}_2\))

6.19 (1H, app s, \text{C}=\text{NH})

5.45 (1H, d, \( J=7.0 \text{ Hz, BocNH})

4.74 (1H, td, \( J=8.1, 5.4 \text{ Hz,} \text{H})

4.01 (1H, dd, \( J=14.2, 7.0 \text{ Hz,} \text{H})

3.94-3.82 (1H, m, \text{H})

3.72 (3H, s, OCH_3)

3.17 (1H, dd,

\( J=14.0, 5.4 \text{ Hz,} \text{H})

3.04 (1H, dd, \( J=14.0, 8.1 \text{ Hz,} \text{H})

3.01-2.95 (1H, m, \text{H})

2.37 (2H, t, \( J=7.4 \text{ Hz, COCH}_2\text{CH}_2\text{CH}_2\))

2.31-2.25 (2H, m, COCH_2\text{CH}_2\text{CH}_2\text{H})

1.99 (1H, t, \( J=2.6 \text{ Hz,} \text{CH}=\text{C})

1.92-1.85 (1H, m, COCH_2\text{CH}_2\text{CH}_2\text{H})

1.84-1.77 (2H, m, \text{H})

1.42 (9H, s, C(CH_3)_3).\n
\[ \delta_{C/\text{ppm}} (125 \text{ MHz, CDCl}_3): \]

173.8 (C=OCH_2\text{CH}_2\text{CH}_2\))

172.0 (COOMe)

171.3 (C_2\text{C}=O)

155.5 (Boc C-O)

139.0 (ArC)

133.1 (ArC)

130.8 (ArC)

119.3 (ArC)

83.6 (C-CH)

80.1 (C(CH_3)_3)

69.5 (C=CH)

54.1 (C_3)

52.6 (OCH_3)

51.3 (C_4)

37.2 (C_5)

36.0 (C_6)

35.1 (COCH_2\text{CH}_2\text{CH}_2\text{H})

28.5 (C(CH_3)_3)

24.2 (COCH_2\text{CH}_2\text{CH}_2\text{H})

18.0 (COCH_2\text{CH}_2\text{CH}_2\text{H}).\n
\[ \nu_{\text{max}} /\text{cm}^{-1}: \]

3283 (m, alkene C-H)

2942 (w, C-H)

2113 (m, N_2)

1741 (m, C-O)

1662 (s, C-O)

1523 (s, C=C).

HPLC (5-100% ACN) \( R_t \) 11.12 mins. HRMS (ESI+) m/z found [M+H]^+ 537.2443, C_{26}H_{34}N\text{O}_4\text{Na}^+ required 537.2438 (\Delta 0.9 ppm). \[ \alpha_{D}^{25} = -5.7 \ (c 0.74, \text{ CHCl}_3). \]
| C8 | GP1 | 64% | 94% |
|---|-----|-----|-----|
| | | | |
| C10 | GP1 | 80% | 89% |
| | | | |
| C11 | GP1 | 82% | 85% |

**C8**

\[ R_t = 0.45 \ (10\% \text{MeOH/} \ 90\% \text{CH}_2\text{Cl}_2), \ \delta / ppm \] (500 MHz, CDCl3): 7.73 (1H, d, J=6.9 Hz, Cα-NH), 7.19 (2H, d, J=8.3 Hz, 2 × ArCH), 7.00-6.92 (2H, m, 2 × ArCH), 6.31 (1H, app s, Cγ-NH), 5.41 (1H, d, J=7.1 Hz, BocNH), 4.78-4.72 (1H, m, Hδ), 4.06 (1H, dd, J=14.0, 7.1 Hz, Hγ), 3.95-3.82 (1H, m, Hα), 3.72 (3H, s, OCH3), 3.17 (1H, dd, J=14.0, 5.4 Hz, Hβ), 3.09-2.96 (2H, m, Hα and Hγ), 2.63-2.48 (2H, m, COCH2CH2), 2.44 (2H, dd, J=10.5, 4.4 Hz, COCH2CH2), 2.00 (1H, t, J=2.6 Hz, CH=CH), 1.87-1.78 (2H, m, Hα), 1.42 (9H, s, C(CH3)3). δC / ppm (125 MHz, CDCl3): 172.6 (C=OCH2CH2), 172.3 (COOme), 171.6 (Cα=O), 155.8 (Boc C=O), 139.3 (ArC), 133.3 (ArC), 131.1 (ArCH), 119.6 (ArCH), 83.3 (C=CH), 80.4 (C(CH3)3), 70.0 (C=CH), 54.3 (Cα), 52.9 (OCH3), 51.6 (Cβ), 37.4 (Cγ), 36.3 (Cδ), 35.8 (COCH2CH2), 34.5 (Cβ), 28.7 (C(CH3)3), 15.4 (COCH2CH2).

**C10**

\[ R_t = 0.44 \ (10\% \text{MeOH/} \ 90\% \text{CH}_2\text{Cl}_2), \ \delta / ppm \] (500 MHz, CDCl3): 7.24 (1H, br s, Cα-NH), 7.12 (2H, d, J=8.4 Hz, 2 × ArCH), 6.95 (2H, d, J=8.4 Hz, 2 × ArCH), 6.38 (1H, app s, Cγ-NH), 5.73 (1H, app s, BocNH), 4.81-4.69 (1H, m, Hδ), 4.21-4.12 (1H, m, Hα), 3.75-3.68 (4H, m, OCH3 and Hα), 3.55-3.44 (1H, m, Hγ), 3.15 (1H, dd, J=14.1, 5.5 Hz, Hβ), 3.03 (1H, dd, J=14.1, 7.3 Hz, Hα), 2.51 (2H, ddd, J=13.6, 6.9, 2.6 Hz, COCH2CH2), 2.40-2.33 (2H, m, COCH2CH2), 2.00 (1H, t, J=2.6 Hz, CH=CH), 1.43 (9H, s, C(CH3)3). δC / ppm (125 MHz, CDCl3): 172.7 (C=OCH2CH2), 171.6 (COOme), 170.7 (Cα=O), 156.3 (Boc C=O), 139.1 (ArC), 132.7 (ArC), 130.7 (ArCH), 119.4 (ArCH), 82.9 (C=CH), 80.7 (C(CH3)3), 69.7 (C=CH), 55.4 (Cα), 53.7 (Cγ), 52.7 (OCH3), 41.7 (Cβ), 37.3 (Cδ), 35.3 (COCH2CH2), 28.4 (C(CH3)3), 15.0 (COCH2CH2). νmax / cm⁻¹: 3301 (m, alkene C-H), 2935 (w, C-H), 2110 (m, N3), 1737 (m, C=O), 1663 (s, C=O), 1526 (s, C=C). **HPLC** (5-100% ACN) Rt 11.06 mins. **HRMS** (ESI+) m/z found [M+H]+ 501.2473, C24H35N3O6 required 501.2462 (Δ 2.2 ppm). [α]D²⁵ = +1.0 (c 0.28, CHCl3).

**C11**

\[ R_t = 0.44 \ (10\% \text{MeOH/} \ 90\% \text{CH}_2\text{Cl}_2), \ \delta / ppm \] (500 MHz, CDCl3): 7.24 (1H, br s, Cα-NH), 7.12 (2H, d, J=8.4 Hz, 2 × ArCH), 6.95 (2H, d, J=8.4 Hz, 2 × ArCH), 6.38 (1H, app s, Cγ-NH), 5.73 (1H, app s, BocNH), 4.81-4.69 (1H, m, Hδ), 4.21-4.12 (1H, m, Hα), 3.75-3.68 (4H, m, OCH3 and Hα), 3.55-3.44 (1H, m, Hγ), 3.15 (1H, dd, J=14.1, 5.5 Hz, Hβ), 3.03 (1H, dd, J=14.1, 7.3 Hz, Hα), 2.51 (2H, ddd, J=13.6, 6.9, 2.6 Hz, COCH2CH2), 2.40-2.33 (2H, m, COCH2CH2), 2.00 (1H, t, J=2.6 Hz, CH=CH), 1.43 (9H, s, C(CH3)3). δC / ppm (125 MHz, CDCl3): 172.7 (C=OCH2CH2), 171.6 (COOme), 170.7 (Cα=O), 156.3 (Boc C=O), 139.1 (ArC), 132.7 (ArC), 130.7 (ArCH), 119.4 (ArCH), 82.9 (C=CH), 80.7 (C(CH3)3), 69.7 (C=CH), 55.4 (Cα), 53.7 (Cγ), 52.7 (OCH3), 41.7 (Cβ), 37.3 (Cδ), 35.3 (COCH2CH2), 28.4 (C(CH3)3), 15.0 (COCH2CH2). νmax / cm⁻¹: 3301 (m, alkene C-H), 2935 (w, C-H), 2110 (m, N3), 1737 (m, C=O), 1663 (s, C=O), 1526 (s, C=C). **HPLC** (5-100% ACN) Rt 10.61 mins. **LCMS** [M+H]+ 502.31.
**C12**

- **Rf** = 0.47 (10% MeOH/90% CH₂Cl₂).
- **Mp** = 148-151 °C (CH₂Cl₂).
- **δH/ppm** (500 MHz, CDCl₃): 7.39 (1H, d, J=4.8 Hz, Cα-NH), 7.10 (2H, d, J=8.4 Hz, 2 × ArCH), 6.94 (2H, d, J=8.4 Hz, 2 × ArCH), 6.21 (1H, app s, BocNH), 5.56 (1H, s, app Cβ-NH), 5.19 (1H, app s, NHCH₂C≡CH), 4.78-4.66 (1H, m, Hβ), 4.14 (1H, J=4.7 Hz, Hα), 3.98 (2H, app s, NHCH₂C≡CH), 3.71 (3H, s, OCH₃), 3.62-3.42 (2H, m, Hβ), 3.10 (1H, dd, J=14.0, 5.6 Hz, Hδ), 3.01 (1H, dd, J=14.0, 7.0 Hz, Hγ), 2.22 (1H, t, J=2.5 Hz, CH)=C), 1.42 (9H, s, C(CH₃)₃).
- **δC/ppm** (125 MHz, CDCl₃): 171.7 (COOMe), 171.3 (Cα=C=O), 158.7 (NHC=ONH), 156.5 (Boc C=O), 139.1 (ArC), 132.7 (ArC), 130.7 (ArCH), 119.4 (ArCH), 80.6 (C≡CH), 80.6 (C(CH₃)₃), 71.5 (C=CH), 56.2 (Cα), 53.8 (Cα), 52.7 (OCH₃), 42.8 (Cβ), 37.3 (Cβ), 30.3 (CH₂C≡CH), 28.4 (C(CH₃)₃).
- **νmax/cm⁻¹**: 3319 (m, alkyne C-H), 2981 (w, C-H), 2109 (m, Nβ), 1731 (m, C=O), 1648 (s, C=O), 1527 (s, C=C). **HPLC** (5-100% ACN) Rf 10.66 mins. **HRMS (ESI+) m/z** found [M+H]⁺ 488.2257, C₂₂H₂₃N₃O₆⁺ required 488.2258 (Δ -0.2 ppm). [α]D²⁸ = -3.1 (c 0.76, CHCl₃).

**C14**

- **Rf** = 0.31 (10% MeOH/90% CH₂Cl₂).
- **Mp** = 100-103 °C (CH₂Cl₂).
- **δH/ppm** (500 MHz, CDCl₃): 7.11 (2H, d, J=8.5 Hz, 2 × ArCH), 6.95 (2H, d, J=8.5 Hz, 2 × ArCH), 6.56 (1H, d, J=7.8 Hz, Cα-NH), 5.83 (1H, app s, Cα-NH), 5.11 (1H, d, J=6.8 Hz, BocNH), 4.87-4.76 (1H, m, Hδ), 4.06-3.95 (1H, m, Hβ), 3.73 (3H, s, OCH₃), 3.34-3.19 (2H, m, Hδ), 3.14 (1H, dd, J=14.0, 5.7 Hz, Hγ), 3.04 (1H, dd, J=14.0, 6.4 Hz, Hδ), 2.53 (2H, td, J=7.1, 2.6 Hz, COCH₂CH₂), 2.43-2.35 (2H, m, COCH₂CH₂), 2.02 (1H, t, J=2.6 Hz, CH₂=C), 1.85-1.72 (1H, m, Hδ), 1.63-1.47 (3H, m, Hγ and Hβ), 1.44 (9H, s, C(CH₃)₃), 1.39-1.32 (2H, m, Hα). **δC/ppm** (125 MHz, CDCl₃): 171.9 and 171.8 (COOMe and Cα=C=O), 171.3 (C=OCH₂CH₂), 155.8 (Boc C=O), 139.1 (ArC), 132.6 (ArC), 130.8 (ArCH), 119.4 (ArCH), 83.2 (C≡CH), 80.3 (C(CH₃)₃), 69.6 (C≡CH), 54.5 (Cβ), 53.3 (Cα), 52.6 (OCH₃), 38.8 (Cβ), 37.4 (Cα), 35.6 (COCH₂CH₂), 31.7 (Cβ), 29.1 (Cβ), 28.5 (C(CH₃)₃), 22.5 (Cγ), 15.1 (COCH₂CH₂). **νmax/cm⁻¹**: 3312 (m, alkyne C-H), 2936 (w, C-H), 2115 (m, Nα), 1739 (m, C=O), 1644 (s, C=O), 1523 (s, C=C). **HPLC** (5-100% ACN) Rf 11.08 mins. **HRMS (ESI+) m/z** found [M+H]⁺ 529.2783, C₂₈H₃₈N₂O₆⁺ required 529.2775 (Δ 1.5 ppm). [α]D²⁸ = +25.1 (c 1.08, CHCl₃).

**D1**

- **HPLC** (30-100% ACN) Rf 7.49 mins.

**D2**

- **HPLC** (30-100% ACN) Rf 6.81 mins. **LCMS [M+H]⁺** 481.70. 

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| D3 | ![Chemical Structure](image) | GP1 | 77% | 92% | δ_H/ppm (400 MHz, CDCl₃): 7.08 (1H, d, J=8.1 Hz), 5.85 (1H, t), 5.22 (1H, d, J=8.2 Hz), 4.52 (1H, td, J=8.2, 5.0 Hz), 4.39-4.32 (1H, m), 3.71 (3H, s), 3.66-3.58 (1H, m), 3.27 (2H, t, J=6.8 Hz), 3.16-3.07 (1H, m), 2.32 (2H, t, J=7.4 Hz), 2.24 (2H, td, J=6.9, 2.7 Hz), 1.96 (1H, t, J=2.6 Hz), 1.92-1.35 (12H, m), 1.43 (9H, s). δ_C/ppm (101 MHz, CDCl₃): 173.3, 172.8, 172.5, 156.0, 83.7, 80.0, 69.3, 52.7, 52.5, 52.7, 51.2, 38.1, 35.2, 31.7, 30.6, 28.5, 28.5, 26.0, 24.3, 22.8, 18.0. v_max/cm⁻¹: 3316, 2946, 2083, 1737, 1682, 1654, 1642, 1535, 1516, 1245, 1165. HPLC (30-100% ACN) Rt 7.23 mins. HRMS (ESI+) m/z found [M+Na]+ 517.2742, C₂₃H₂₈N₄O₇Na⁺ required 517.2751. |
| D4 | ![Chemical Structure](image) | GP1 | 68% | 89% | HPLC (5-100% ACN) Rt 10.04 mins. LCMS [M+H]+ 496.31. |
| D5 | ![Chemical Structure](image) | GP1 | 63% | 83% | HPLC (5-100% ACN) Rt 10.10 mins. LCMS [M+H]+ 482.29. |
| D6 | ![Chemical Structure](image) | GP1 | 65% | 79% | HPLC (5-100% ACN) Rt 11.25 mins. LCMS [M-BOC+H]+ 429.28. |
| D7 | ![Chemical Structure](image) | GP1 | 76% | 91% | HPLC (30-100% ACN) Rt 7.23 mins. LCMS [M+H]+ 481.48. |
| D8 | ![Chemical Structure](image) | GP1 | 46% | 97% | δ_H/ppm (400 MHz, CDCl₃): 7.87 (1H, d, J=7.7 Hz), 6.35 (1H, bp), 5.49 (1H, d, J=7.6 Hz), 4.54 (1H, td, J=8.0, 5.0 Hz), 4.17-4.06 (1H, m), 3.99-3.88 (1H, m), 3.74 (3H, s), 3.32 (2H, t, J=6.8 Hz), 3.10-2.98 (1H, m), 2.61-2.48 (2H, m), 2.52-2.39 (2H, m), 2.06 (1H, t, J=2.5 Hz), 1.98-1.43 (8H, m), 1.88-1.48 (8H, m), 1.43 (9H, s). δ_C/ppm (101 MHz, CDCl₃): 172.8, 172.5, 171.4, 155.5, 83.0, 80.1, 69.8, 52.5, 52.5, 51.2, 51.2, 36.2, 35.5, 34.5, 31.5, 28.5, 28.5, 22.9, 15.2. v_max/cm⁻¹: 3663, 3296, 2095, 1741, 1652, 1521, 1366, 1250, 1165, 1052. HPLC (30-100% ACN) Rt 6.78 mins. HRMS (ESI+) m/z found [M+Na]+ 489.2446, C₂₁H₃₀N₆O₇Na⁺ required 489.2438. |
|   | Structure | Product | Yield | Purification | MS Data | Comments |
|---|------------|---------|-------|--------------|---------|----------|
| D9 | ![Structure](image) | GP1 | 68% | HPLC (5-100% ACN) Rt 10.91 mins. | LCMS [M+H]^+ 467.21 | |
|     |            |       | 96% |              |         |          |
| D10| ![Structure](image) | GP1  | 63% | HPLC (5-100% ACN) Rt 10.26 mins. | LCMS [M+H]^+ 453.19 | |
|     |            |       | 99% |              |         |          |
| D11| ![Structure](image) | GP1  | 49% | δH/ppm (500 MHz, CDCl3): 8.44 (1H, d, J=7.0 Hz), 5.66 (1H, d, J=7.5 Hz), 5.42 (1H, dd, J=7.5, 5.0 Hz), 5.14 (1H, t, J=5.0 Hz), 4.51 (1H, dt, J=8.0, 5.0 Hz), 4.21-4.14 (1H, m), 4.03 (1H, ddd, J=17.5, 5.5, 2.5 Hz), 3.94 (1H, ddd, J=17.5, 5.5, 2.5 Hz), 3.89-3.80 (1H, m), 3.74 (3H, s), 3.29 (2H, t, J=7.0 Hz), 3.08-2.99 (1H, m), 2.22 (1H, d, J=2.5, 2.5 Hz), 1.95-1.77 (4H, m), 1.69-1.44 (4H, m), 1.42 (9H, s). δC/ppm (125 MHz, CDCl3): 172.8, 171.5, 158.6, 155.5, 80.7, 80.0, 71.2, 52.4, 52.4, 51.1, 51.0, 36.4, 35.5, 31.1, 30.1, 28.3, 22.8. HPLC (5-100% ACN) Rt 9.61 mins. HRMS (ESI+) m/z found [M+H]^+ 468.2563, C_{20}H_{34}N_{7}O_{6}^+ required 468.2571. | [α]_D^{25} = -8.0 (c 0.52, CHCl3) |
|     |            |       | 99% |              |         |          |
| D12| ![Structure](image) | GP1 | 73% | HPLC (5-100% ACN) Rt 10.05 mins. | LCMS [M+H]^+ 454.24 | |
|     |            |       | 83% |              |         |          |
| D13| ![Structure](image) | GP1 | 88% | HPLC (5-100% ACN) Rt 11.60 mins. | LCMS [M+H]^+ 543 | |
|     |            |       | 97% |              |         |          |
| D14| ![Structure](image) | GP1 | 78% | HPLC (30-100% ACN) Rt 7.06 mins. | LCMS [M+H]^+ 495.21 | |
| E1 | ![Chemical Structure](image1) | GP1 | 55% | 88% | HPLC (5-100% ACN) *Rt* 10.16 mins. **LCMS [M+H]^+** 495.41. |
|---|---|---|---|---|---|
| E2 | ![Chemical Structure](image2) | GP1 | 70% | 88% | HPLC (5-100% ACN) *Rt* 9.62 mins. **LCMS [M+H]^+** 467.33. |
| E3 | ![Chemical Structure](image3) | GP1 | 61% | 91% | δ\(_H\)/ppm (400 MHz, CDCl\(_3\)): 7.15 (1H, d, J=8.2 Hz), 5.82 (1H, t, J=6.4 Hz), 5.22 (1H, d, J=8.2 Hz), 4.60-4.46 (1H, m), 4.41-4.29 (1H, m), 3.72 (3H, s), 3.69-3.55 (1H, m), 3.32 (2H, t, J=6.5 Hz), 3.15-3.06 (1H, m), 2.33 (2H, t, J=7.4 Hz), 2.24 (2H, td, J=6.9, 2.6 Hz), 1.96 (1H, t, J=2.6 Hz), 2.02-1.89 (1H, m), 1.88-1.48 (9H, m), 1.43 (9H, s). δ\(_C\)/ppm (100 MHz, CDCl\(_3\)): 173.3, 172.6, 172.5, 155.9, 83.6, 80.0, 69.3, 52.7, 52.5, 51.7, 50.9, 38.1, 35.2, 30.6, 29.3, 28.4, 26.0, 25.1, 24.2, 18.0. \(\nu_{\text{max}}/\text{cm}^{-1}\): 3670, 3326, 3257, 2972, 2902, 2088, 1736, 1683, 1655, 1634, 1519, 1249, 1169, 1055. **HPLC** (5-100% ACN) *Rt* 9.36 mins. **HRMS (ESI+)** m/z found [M+H]^+ 468.2587, \(\text{C}_{20}\text{H}_{34}\text{N}_{7}\text{O}_{6}\) required 468.2571. \(\alpha\)\(_D\)\(_{25}\) = +10.9 (c 0.49, CHCl\(_3\)). |
| E4 | ![Chemical Structure](image4) | GP1 | 69% | 89% | HPLC (5-100% ACN) *Rt* 9.60 mins. **LCMS [M+H]^+** 482.29. |
| E5 | ![Chemical Structure](image5) | GP1 | 69% | 92% | δ\(_H\)/ppm (400 MHz, CDCl\(_3\)): 7.42 (1H, d, J=8.0 Hz), 5.35 (1H, d, J=8.0 Hz), 5.13 (2H, m), 4.54 (1H, dt, J=6.0, 5.0 Hz), 4.44-4.23 (1H, m), 3.96 (2H, td, J=5.5, 2.5 Hz), 3.74 (3H, s), 3.53-3.39 (1H, m), 3.33 (2H, t, J=6.5 Hz), 3.13 (1H, dd, J=13.5, 5.0 Hz), 2.23 (1H, t, J=2.5 Hz), 2.02-1.90 (1H, m), 1.84-1.48 (7H, m), 1.43 (9H, s). δ\(_C\)/ppm (100 MHz, CDCl\(_3\)): 172.6, 158.3, 155.9, 80.8, 79.9, 71.1, 52.8, 52.5, 51.7, 50.8, 38.9, 30.3, 30.0, 29.2, 28.3, 26.2, 25.0. **HPLC** (5-100% ACN) *Rt* 9.36 mins. **HRMS (ESI+)** m/z found [M+H]^+ 468.2587, \(\text{C}_{20}\text{H}_{34}\text{N}_{7}\text{O}_{6}\) required 468.2571. \(\alpha\)\(_D\)\(_{25}\) = +10.9 (c 0.49, CHCl\(_3\)). |
| E6 | ![Chemical Structure](image6) | GP1 | 62% | 82% | HPLC (5-100% ACN) *Rt* 10.92 mins. **LCMS [M+H]^+** 515.33. |
|   | Structure | δ_\text{H} /ppm (400 MHz, CDCl₃): 8.17 (1H, d, J=7.9 Hz), 6.21 (1H, t, J=6.3 Hz), 5.51 (1H, d, J=7.5 Hz), 4.61-4.51 (1H, m), 4.11-4.02 (1H, m), 3.99-3.88 (1H, m), 3.73 (3H, s), 3.32 (2H, t, J=6.6 Hz), 3.05-2.95 (1H, m), 2.37 (2H, t, J=7.4 Hz), 2.32-2.23 (2H, m), 1.99 (1H, t, J=2.7 Hz), 2.02-1.61 (8H, m), 1.42 (9H, s). δ_\text{C} /ppm (100 MHz, CDCl₃): 174.0, 172.5, 171.5, 155.5, 83.6, 80.0, 69.5, 52.6, 52.1, 51.3, 50.9, 36.1, 35.2, 34.8, 29.1, 28.5, 25.2, 24.3, 18.0. ν_{\text{max}} /cm⁻¹: 3670, 3312, 2972, 2902, 2097, 1745, 1687, 1649, 1524, 1394, 1249, 1164, 1052. HPLC (5-100% ACN) Rt 10.00 mins. HRMS (ESI+) m/z found [M+Na]^+ 489.2437, C_{21}H_{34}N_{6}O_{6}Na^+ required 489.2438. | E7 |
|---|---|---|
|   | Structure | GP1 68% 92% | E8 |
|   | Structure | GP1 75% 77% | HPLC (5-100% ACN) Rt 9.79 mins. LCMS [M+H]^+ 453.31. |  |
|   | Structure | GP1 69% 93% | HPLC (5-100% ACN) Rt 10.17 mins. LCMS [M+H]^+ 453.26. |  |
|   | Structure | GP1 66% 94% | HPLC (5-100% ACN) Rt 9.82 mins. LCMS [M+H]^+ 439.22. |  |
|   | Structure | GP1 35% 87% | HPLC (5-100% ACN) Rt 9.33 mins. LCMS [M+H]^+ 454.23. |  |
|   | Structure | GP1 55% 96% | HPLC (5-100% ACN) Rt 9.41 mins. LCMS [M+H]^+ 440.22. |  |
| Compound | Yield | Column | Retention Time | LCMS Mass Spectrum |
|----------|-------|--------|----------------|-------------------|
| E13      | 84%   | HPLC   | 11.30 mins.   | [M-H]^+ 527.      |
|          | 90%   | (5-100% ACN) |              |                   |
| E14      | 73%   | HPLC   | 10.05 mins.   | [M+H]^+ 481.35.   |
|          | 84%   | (5-100% ACN) |              |                   |
| F2       | 84%   | HPLC   | 10.92 mins.   | [M+H]^+ 515.21.   |
|          | 83%   | (5-100% ACN) |              |                   |
| F3       | 77%   | HPLC   | 11.08 mins.   | [M+H]^+ 529.29.   |
|          | 77%   | (5-100% ACN) |              |                   |
| F14      | 77%   | HPLC   | 11.08 mins.   | [M+H]^+ 529.29.   |
|          | 77%   | (5-100% ACN) |              |                   |
## 10. Preparation of B/C/C/P and B/C/C/C/P Linear Amides

| Compound | Method, Yield (%), Purity (%) | Analysis |
|----------|------------------------------|----------|
| G1 | GP1 48% 97% | HPLC (5-100% ACN) Rt 10.36 mins. LCMS [M+H]^+ 652.49. |
| G2 | GP1 56% 86% | HPLC (5-100% ACN) Rt 9.88 mins. LCMS [M+H]^+ 624.42. |
| G3 | GP1 82% 81% | HPLC (5-100% ACN) Rt 10.20 mins. LCMS [M+H]^+ 638.43. |
| G4 | GP1 74% 75% | δH/ppm (400 MHz, CDCl3): 7.50 (1H, d, J=7.0 Hz), 7.29 (1H, d, J=7.5 Hz), 5.38 (1H, d, J=7.5 Hz), 5.25 (1H, t, J=5.5 Hz), 5.20 (1H, t, J=5.5 Hz), 4.64-4.55 (1H, m), 4.52 (1H, td, J=8.0, 5.0 Hz), 4.21-4.10 (1H, m), 3.97 (2H, dd, J=5.5, 2.5 Hz), 3.76 (3H, s), 3.75 (3H, s), 3.27 (2H, t, J=6.74, 6.74 Hz), 3.26-3.17 (2H, m), 2.37-2.18 (3H, m), 2.21 (1H, t, J=2.5 Hz), 2.17-2.02 (1H, m), 1.88-1.43 (12H, m), 1.43 (9H, s). δc/ppm (100 MHz, CDCl3): 173.7, 172.8, 172.7, 158.1, 156.0, 81.1, 80.2, 70.9, 54.1, 52.7, 52.6, 52.2, 51.5, 51.1, 39.5, 31.8, 31.5, 31.1, 29.9, 28.8, 28.3, 28.3, 26.7, 22.9, 22.1. νmax/cm⁻¹: 3294, 2951, 2097, 1759, 1651, 1537, 1426, 1206, 1165. HPLC (5-100% ACN) Rt 9.86 mins. HRMS (ESI+) m/z found [M+Na]^+ 661.3279, C14H23N3O5Na^+ required 661.3285. [α]D = +6.7 (c 0.52, CHCl3). |
\( \delta_H / \text{ppm} \) (400 MHz, CDCl\(_3\)): 7.61 (1H, s), 7.42 (1H, d, J=8.4Hz), 7.42 (1H, d, J=8.4Hz), 5.43-5.16 (2H, m), 4.66-4.48 (1H, m), 4.51-4.38 (1H, m), 4.27-4.17 (1H, m), 4.16-4.06 (1H, m), 4.00-3.86 (1H, m), 3.76 (3H, s), 3.72 (3H, s), 3.34-3.21 (4H, m), 2.35-2.03 (5H, m), 1.99-1.52 (10H, m), 1.46 (9H, s).

\( \delta_C / \text{ppm} \) (100 MHz, CDCl\(_3\)): 174.1, 173.6, 172.9, 172.4, 158.7, 156.2, 81.5, 80.2, 71.7, 54.2, 52.8, 52.7, 52.6, 51.6, 51.2, 39.4, 32.0, 31.3, 30.2, 28.5, 27.5, 26.2, 23.1. \( \nu_{\text{max}} / \text{cm}^{-1} \): 3676, 3297, 2988, 2902, 2094, 1735, 1662, 1646, 1541, 1519, 1394, 1250, 1167, 1056. HPLC (5-100% ACN) Rt 9.67 mins. HRMS (ESI+) m/z found [M+H]\(^+\) 625.3296, C\(_{27}\)H\(_{45}\)N\(_8\)O\(_9\) required 625.3310.

HPLC (5-100% ACN) Rt 10.86 mins. LCMS [M+H]\(^+\) 672.41.

HPLC (5-100% ACN) Rt 10.18 mins. LCMS [M+H]\(^+\) 624.41.

HPLC (5-100% ACN) Rt 9.87 mins. LCMS [M+H]\(^+\) 610.39.

HPLC (5-100% ACN) Rt 10.27 mins. LCMS [M+H]\(^+\) 610.38.
| G10 | GP1 | 42% | HPLC (5-100% ACN) Rt 9.98 mins. LCMS [M+H]^+ 596.37. |
|-----|-----|-----|--------------------------------------------------|
| G11 | GP1 | 27% | HPLC (5-100% ACN) Rt 9.54 mins. LCMS [M+H]^+ 611.36. |
| G12 | GP1 | 66% | HPLC (5-100% ACN) Rt 9.86 mins. LCMS [M+H]^+ 597.41. |
| G13 | GP1 | 77% | HPLC (5-100% ACN) Rt 11.20 mins. LCMS [M+H]^+ 686.29. |
| G14 | GP1 | 88% | HPLC (5-100% ACN) Rt 10.18 mins. LCMS [M+H]^+ 638.43. |
|   |   |   |
|---|---|---|
| H1 | GP1 | 74%  
92%  | HPLC (5-100% ACN) Rt 9.93 mins. LCMS [M+H]^+ 638.55. |
| H2 | GP1 | 74%  
90%  | HPLC (5-100% ACN) Rt 9.45 mins. LCMS [M+H]^+ 610.39. |
| H3 | GP1 | 99%  
82%  | HPLC (5-100% ACN) Rt 9.74 mins. LCMS [M+H]^+ 624.44. |
| H4 | GP1 | 88%  
84%  | HPLC (5-100% ACN) Rt 9.40 mins. LCMS [M+H]^+ 625.45. |
| H5 | GP1 | 57%  
87%  | HPLC (5-100% ACN) Rt 9.18 mins. LCMS [M+H]^+ 611.36. |
| H6 | GP1 | 55%  
77%  | HPLC (5-100% ACN) Rt 10.55 mins. LCMS [M+H]^+ 658.46. |
|   | Structure | GP | Yield | HPLC | LCMS | MS Data |
|---|-----------|----|-------|------|------|---------|
| H7 | ![H7 structure](image) | GP1 | 69% | **HPLC** (5-100% ACN) *Rt* 9.72 mins. | LCMS [M+H]^+ 610.34. |
| H8 | ![H8 structure](image) | GP1 | 82% | **HPLC** (5-100% ACN) *Rt* 9.40 mins. | LCMS [M+H]^+ 596.34. |
| H9 | ![H9 structure](image) | GP1 | 83% | **HPLC** (5-100% ACN) *Rt* 9.88 mins. | LCMS [M+H]^+ 596.36. |
| H10 | ![H10 structure](image) | GP1 | 53% | **δH/δC** (400 MHz, CDCl₃): 7.57 (1H, d, J=7.0 Hz), 6.96 (1H, d, J=7.5 Hz), 6.76 (1H, t, J=6.0 Hz), 5.92 (1H, d, J=6.5 Hz), 4.62-4.51 (2H, m), 4.25 (1H, m), 3.76 (3H, s), 3.74 (3H, s), 3.72-3.53 (2H, m), 3.31 (2H, dt, J=6.5, 1.0 Hz), 2.58-2.47 (2H, m), 2.47-2.40 (2H, m), 2.35-2.21 (3H, m), 2.04 (1H, t, J=2.5 Hz), 2.02-1.89 (3H, m), 1.82-1.55 (3H, m), 1.44 (9H, s). **δC/δH** (100 MHz, CDCl₃): 173.0, 172.6, 172.2, 172.1, 171.2, 156.0, 82.9, 80.5, 69.4, 55.0, 52.7, 52.7, 51.9, 51.8, 50.7, 41.4, 35.0, 32.1, 29.2, 28.3, 27.3, 25.0, 14.8. **HPLC** (5-100% ACN) *Rt* 9.56 mins. | HRMS (ESI+) *m/z* found [M+H]^+ 582.2873, C_{26}H_{40}N_{7}O_{9}^+ required 582.2888. [α]_D^{25} = -14.6 (c 0.50, CHCl₃). |
| H11 | ![H11 structure](image) | GP1 | 41% | **HPLC** (5-100% ACN) *Rt* 9.13 mins. | LCMS [M+H]^+ 597.33. |
| Chemical Structure | GP1 | Yield | HPLC Conditions | LCMS Peak (m/z) |
|--------------------|-----|-------|-----------------|-----------------|
| H12                | 66% | 76%   | HPLC (5-100% ACN) Rt 9.24 mins. | LCMS [M+H]^+ 583.30 |
| H14                | 67% | 91%   | HPLC (5-100% ACN) Rt 9.65 mins. | LCMS [M+H]^+ 624.44. |
| J13                | 73% | 88%   | HPLC (5-100% ACN) Rt 10.71 mins. | LCMS [M+H]^+ 600.34. |
| K3                 | 62% | 80%   | HPLC (5-100% ACN) Rt 10.35 mins. | LCMS [M+H]^+ 713.52. |
| K8                 | 67% | 82%   | HPLC (5-100% ACN) Rt 10.09 mins. | LCMS [M+H]^+ 685.47. |
| L7                 | 79% | 78%   | HPLC (5-100% ACN) Rt 11.60 mins. | LCMS [M+H]^+ 846.67. |
|   | Compound | Purity | 5-100% ACN HPLC Rt | LCMS [M+H]^+ |
|---|----------|--------|---------------------|---------------|
| L9 | GP1      | 62%    | 832.57 mins.       | 747.50        |
| M13| GP1      | 61%    | 11.67 mins.        | 747.50        |
| N8 | GP1      | 72%    | 11.05 mins.        | 832.64        |
## 11. Preparation of B/C/P CuAAC Macrocycles

| Compound | Method, Yield (%), Purity (%) | Analysis |
|----------|-----------------------------|----------|
| A1 w     | GP2 & GP4 54% 97% | δ<sub>W</sub>/ppm (500 MHz; d<sub>6</sub>-DMSO): 8.75 (1H, d, J=6.6 Hz), 8.43 (1H, t, J=5.6 Hz), 8.17 (3H, d, J=5.4 Hz), 7.98 (1H, s), 7.67 (1H, t, J=5.9 Hz), 7.26-7.11 (5H, m), 5.45 (1H, dd, J=8.6, 7.0 Hz ), 4.17-4.06 (1H, m), 3.87-3.79 (1H, m), 3.58 (3H, s), 3.42-3.33 (2H, m), 3.29-3.19 (1H, m), 3.17-3.06 (1H, m), 3.06 -2.97 (1H, m), 2.90- 2.80 (1H, m), 2.56 (2H, td, J=7.3, 2.8 Hz), 2.07 (2H, td, J=7.4, 2.4 Hz), 1.87-1.74 (1H, m), 1.74 -1.47 (4H, m), 1.47-1.02 (8H, m). δ<sub>C</sub>/ppm (125 MHz, d<sub>6</sub>-DMSO): 171.9, 171.8, 168.9, 167.2, 146.1, 136.7, 129.0, 128.4, 126.7, 121.7, 64.0, 52.5, 52.0, 38.2, 37.4, 36.8, 35.0, 30.8, 29.7, 28.5, 25.3, 24.5, 23.3, 22.5, 21.7, 21.1. ν<sub>max</sub>/cm<sup>-1</sup>: 3228, 3060, 2929, 1736, 1551, 1440, 1212, 742. HPLC (5-80% ACN) Rt 8.02 mins. HRMS (ESI+) m/z found [M+H]<sup>+</sup> 556.3237, C<sub>28</sub>H<sub>42</sub>N<sub>7</sub>O<sub>5</sub><sup>+</sup> required 556.3242. |
| A2 w     | GP2 & GP4 88% 78% | HPLC (0-60% ACN) Rt 9.21 mins. LCMS [M+H]<sup>+</sup> 528.26. |
| A3 w     | GP2 & GP4 99% 81% | HPLC (5-100% ACN) Rt 7.13 mins. LCMS [M+H]<sup>+</sup> 542.28. |
| A4 w     | GP2 & GP4 99% 71% | HPLC (5-100% ACN) Rt 7.08 mins. LCMS [M+H]<sup>+</sup> 543.25. |
| A5  | ![Chemical Structure](image) | GP2 & GP4 | HPLC (5-100% ACN) Rt 6.91 mins. **LCMS** [M+H]^+ 529.23. |
|-----|-----------------------------|-----------|---------------------------------------------------------|
| A7  | ![Chemical Structure](image) | GP2 & GP4 | HPLC (5-100% ACN) Rt 7.38 mins. **LCMS** [M+H]^+ 528.18. |
| A8  | ![Chemical Structure](image) | GP2 & GP4 | HPLC (5-100% ACN) Rt 7.26 mins. **LCMS** [M+H]^+ 514.23. |
| A9  | ![Chemical Structure](image) | GP2 & GP4 | HPLC (5-100% ACN) Rt 7.26 mins. **LCMS** [M+H]^+ 514.16. |
| A10 | ![Chemical Structure](image) | GP2 & GP4 | HPLC (5-100% ACN) Rt 7.18 mins. **LCMS** [M+H]^+ 500.13. |
| A11 | ![Chemical Structure](image) | GP2 & GP4 | HPLC (5-100% ACN) Rt 7.19 mins. **LCMS** [M+H]^+ 515.21. |
| Compound | Formula | Conditions | Yield | [M+H]^+ | \[^{[\alpha]}_D\] | References |
|----------|---------|------------|-------|---------|---------|------------|
| A12 w    | ![Structure](image1.png) | GP2 & GP4 | 99%   | 501.11  | -2.5    | HPLC (5-100% ACN) Rt 6.88 mins. LCMS [M+H]^+ 501.11. |
| A13 w    | ![Structure](image2.png) | GP2 & GP5 | 11%   | 590.21  |         | HPLC (5-100% ACN) Rt 7.59 mins. LCMS [M+H]^+ 590.21. |
| B1 w     | ![Structure](image3.png) | GP2 & GP4 | 61%   | 514.31  |         | HPLC (5-100% ACN) Rt 6.77 mins. LCMS [M+H]^+ 514.31. |
| B2 w     | ![Structure](image4.png) | GP2 & GP4 | 45%   |         |         | Mp = 215-217 °C (CH₂Cl₂). δH /ppm (500 MHz, d₆-DMSO): 9.10 (1H, d, J=6.5 Hz, C=N-H), 8.94 (1H, dd, J=8.5, 3.9 Hz, C=N-H), 8.16 (3H, d, J=5.5 Hz, NH₂). 8.06 (1H, t, J=6.0 Hz, C=N-H), 7.69 (1H, s, triazole CH), 7.27-7.09 (5H, m, 5 × ArCH), 5.45 (1H, dd, J=8.4, 7.1 Hz, H₂), 4.08 (1H, dt, J=6.5, 4.5 Hz, H₂), 3.95 (1H, ddd, J=13.7, 8.5, 4.5 Hz, H₂), 3.89-3.80 (1H, m, H₂), 3.43-3.36 (2H, m, H₂), 3.33 (3H, s, OCH₃), 2.97-2.75 (3H, m, H₃ and CH₂(CH₂)₂), 1.67-1.39 (4H, m, H₃ and H₄). δC /ppm (125 MHz, d₆-DMSO): 171.0 (C=OCH₂CH₂), 169.7 (C=O), 168.7 (C=O), 145.8 (triazole C), 136.4 (ArC), 128.9 (ArCH), 128.3 (ArCH), 126.7 (ArCH), 121.4 (triazole CH), 64.0 (C₆), 53.2 (C₆), 51.8 (OCH₃), 51.6 (C₆), 38.8 (C₆), 38.3 (C₆), 37.0 (C₆), 33.9 (OCH₂CH₂), 28.7 (C₆), 24.3 (C₆), 21.1 (CO₂CH₂). \[^{[\nu]}_{\text{max}}\] /cm⁻¹: 3224 (NH str), 2924 (CH str), 1737 (C=O str), 1683 (C=O str), 1543, 1437, 1212, 1148. HPLC (5-100% ACN) Rt 8.41 mins. HRMS (ESI+) m/z found [M+H]^+ 486.2458, C₁₃H₁₉N₄O₇ required 486.2459. [\[^{[\alpha]}_D\]_D^{25}\] = -2.5 (c 0.58, MeOH). |
\[ \delta_H / ppm \] (500 MHz, \( d_6 \)-DMSO): 9.42 (1H, d, \( J=7.5 \) Hz, C\(_{\alpha NT}\)-NH), 8.80 (1H, dd, \( J=9.4 \) Hz and 3.0 Hz, C\(_{\beta NT}\)-NH), 8.22 (3H, d, \( J=4.5 \) Hz, NH\(_3^+\)), 8.17 (1H, s, triazole CH), 7.89 (1H, t, \( J=5.9 \) Hz, C\(_{\delta NT}\)-NH), 7.28-7.09 (5H, m, 5 × ArCH), 5.34-5.28 (1H, m, H\(_2\)), 4.34 (1H, dt, \( J=7.5 \), 3.4 Hz, H\(_3\)), 4.15 (1H, ddd, \( J=13.3 \), 9.4, 3.4 Hz, H\(_4\)), 4.00-3.92 (1H, m, H\(_5\)), 3.57 (3H, s, OCH\(_3\)), 3.54-3.43 (2H, m, H\(_{\beta NT}\)), 3.26-3.18 (1H, m, H\(_{\delta NT}\)), 3.04-2.98 (1H, m, H\(_{\alpha NT}\)), 2.98-2.92 (1H, m, H\(_{\gamma NT}\)), 2.58 (2H, t, \( J=6.7 \) Hz, COCH\(_2\)CH\(_2\)), 2.19-2.11 (1H, m, COCH\(_2\)CH\(_2\)), 2.08-2.02 (1H, m, COCH\(_2\)CH\(_2\)), 1.89-1.76 (3H, m, COCH\(_2\)CH\(_2\) and H\(_{\beta NT}\)), 1.74-1.64 (1H, m, H\(_{\gamma NT}\)), 1.59-1.52 (2H, m, H\(_{\gamma NT}\)), \( \delta_C / ppm \) (125 MHz, \( d_6 \)-DMSO): 171.9 (C=OCH\(_2\)CH\(_2\)), 169.8 (COOMe), 169.1 (C\(_{\alpha NT}\)=C=O), 166.9 (C\(_{\beta NT}\)=C=O), 145.6 (triazole C), 136.7 (ArC), 129.1 (ArCH), 128.3 (ArCH), 126.6 (ArCH), 123.1 (triazole CH), 64.1 (C\(_{\alpha NT}\)), 52.3 (C\(_{\beta NT}\)), 51.2 (OCH\(_3\)), 51.1 (C\(_{\gamma NT}\)), 36.7 (C\(_{\delta NT}\)), 35.4 (C\(_{\delta NT}\)), 34.2 (COCH\(_2\)CH\(_2\)CH\(_2\)), 27.9 (C\(_{\delta NT}\)), 25.1 (COCH\(_2\)CH\(_2\)CH\(_2\)), 23.7 (COCH\(_2\)CH\(_2\)CH\(_2\)), 23.5 (C\(_{\alpha NT}\)). \( \nu_{\text{max}} / \text{cm}^{-1} \): 3231 (NH str), 2935 (CH str), 1739 (C=O str), 1684 (C=O str), 1640, 1548, 1440, 1215, 1146, 1054. HPLC (5-100% ACN) \( Rt \) 8.76 mins. HRMS (ESI+) \( m / z \) found [M+H]\(^+\) 500.2632, \( C_{24}H_{33}N_{10}O_{19}^+ \) required 500.2621. \([\alpha]_D^{25}\) = +3.0 (c 0.075, MeOH).

\[ \delta_H / ppm \] (500 MHz, \( d_6 \)-DMSO): 9.24 (1H, d, \( J=7.0 \) Hz, C\(_{\alpha NT}\)-NH), 9.19 (1H, dd, \( J=8.9 \), 3.3 Hz, C\(_{\beta NT}\)-NH), 8.14 (3H, d, \( J=4.3 \) Hz, NH\(_3^+\)), 7.90 (1H, s, triazole CH), 7.26-7.13 (5H, m, 5 × ArCH), 6.38 (1H, s, NH\(_{\alpha NT}\)), 6.17 (1H, s, C\(_{\delta NT}\)=NH), 5.49-5.39 (1H, m, H\(_{\gamma NT}\)), 4.37 (1H, d, \( J=16.1 \) Hz, NH\(_{\delta NT}\)), 4.13 (1H, dt, \( J=7.0 \), 3.3 Hz, H\(_{\beta NT}\)), 4.07 (1H, d, \( J=16.1 \) Hz, NH\(_{\delta NT}\)), 4.02-3.95 (1H, m, H\(_{\gamma NT}\)), 3.95-3.88 (1H, m, H\(_{\gamma NT}\)), 3.52 (1H, dd, \( J=14.0 \), 8.4 Hz, H\(_{\alpha NT}\)), 3.45 (1H, dd, \( J=14.0 \), 6.9 Hz, H\(_{\alpha NT}\)), 3.16-0.37 (4H, m, OCH\(_3\) and H\(_{\beta NT}\)), 3.07-3.02 (1H, m, H\(_{\gamma NT}\)), 2.92-2.82 (1H, m, H\(_{\gamma NT}\)), 1.80-1.66 (2H, m, H\(_{\gamma NT}\)), 1.58-1.33 (2H, m, H\(_{\gamma NT}\)). \( \delta_C / ppm \) (125 MHz, \( d_6 \)-DMSO): 169.9 (COOMe), 169.1 (C\(_{\alpha NT}\)=C=O), 167.2 (C\(_{\beta NT}\)=C=O), 158.0 (NH=ONH), 147.5 (triazole C), 136.6 (ArC), 128.9 (ArCH), 128.3 (ArCH), 126.7 (ArCH), 122.3 (triazole CH), 64.0 (C\(_{\alpha NT}\)), 52.9 (C\(_{\beta NT}\)), 51.9 (C\(_{\gamma NT}\)), 51.6 (OCH\(_3\)), 38.9 (C\(_{\delta NT}\)), 38.8 (C\(_{\delta NT}\)), 35.7 (C\(_{\delta NT}\)), 35.3 (NH\(_{\beta NT}\)), 28.7 (C\(_{\beta NT}\)), 25.6 (C\(_{\gamma NT}\)). \( \nu_{\text{max}} / \text{cm}^{-1} \): 3233 (NH str), 2924 (CH str), 1737 (C=O str), 1678 (C=O str), 1542, 1437, 1260, 1145. HPLC (5-100% ACN) \( Rt \) 8.45 mins. HRMS (ESI+) \( m / z \) found [M+H]\(^+\) 487.2417, \( C_{22}H_{31}N_{10}O_{19}^+ \) required 487.2417. \([\alpha]_D^{25}\) = -13.3 (c 0.68, MeOH).
| Name  | Structure | GP2 & GP4 | % Yield | δ<sub>W</sub> / ppm (500 MHz, d<sub>6</sub>-DMSO) | Physical Properties | Notes |
|-------|-----------|-----------|---------|---------------------------------|-------------------|-------|
| B7 w  | ![Structure](image1.png) | 70%       | 94%     | 81.29 (C=OCH₂CH₂CH₂), 169.9 (COOMe), 168.3 (C<sub>α</sub>C=O), 167.7 (C<sub>α</sub>C=O), 145.7 (triazole C), 128.9 (ArC), 128.2 (ArCH), 122.7 (triazole CH), 64.2 (C<sub>α</sub>), 52.6 (C<sub>β</sub>), 52.3 (OCH<sub>3</sub>), 30.0 (C<sub>α</sub>), 38.9 (C<sub>β</sub>), 36.5 (C<sub>υ</sub>), 33.9 (C<sub>γ</sub>), 33.1 (COCH₂CH₂CH₂), 31.7 (C<sub>ρ</sub>), 23.7 (COCH₂CH₂CH₂), 23.6 (COCH₂CH₂CH₂). ν<sub>max</sub> / cm<sup>-1</sup>: 3212 (NH str), 2925 (CH str), 1740 (C=O str), 1686 (C=O str), 1546, 1437, 1214, 1149. | Mp = 223-225 °C (CH₂Cl₂), δ<sub>W</sub> / ppm (500 MHz, d<sub>6</sub>-DMSO): 9.41 (1H, d, J=6.5 Hz, C<sub>α</sub>-NH), 8.24 (3H, d, J=5.5 Hz, NH<sup>+</sup>), 8.14 (1H, dd, J=8.5, 3.7 Hz, C<sub>β</sub>-NH) | |
| B8 w  | ![Structure](image2.png) | 81%       | 98%     | 161.6 (COOMe), 166.3 (C<sub>α</sub>C=O and C<sub>β</sub>C=O), 145.3 (triazole C), 136.3 (ArC), 128.8 (ArCH), 128.2 (ArCH), 126.7 (ArCH), 121.5 (triazole CH), 64.0 (C<sub>α</sub>), 53.2 (C<sub>β</sub>), 52.1 (OCH<sub>3</sub>), 50.2 (C<sub>γ</sub>), 38.1 (C<sub>δ</sub>), 37.8 (C<sub>ε</sub>), 34.4 (C<sub>ρ</sub>), 34.3 (COCH₂CH₂), 31.3 (C<sub>τ</sub>), 21.5 (COCH₂CH₂). ν<sub>max</sub> / cm<sup>-1</sup>: 3215 (NH str), 3035 (CH str), 2925 (CH str), 1742 (C=O str), 1682 (C=O str), 1542, 1433, 1213, 1151. | Mp = 223-226 °C (CH₂Cl₂), δ<sub>W</sub> / ppm (500 MHz, d<sub>6</sub>-DMSO): 8.84 (1H, d, J=6.5 Hz, C<sub>α</sub>-NH), 8.50 (1H, dd, J=8.4, 4.1 Hz, C<sub>β</sub>-NH), 8.18 (3H, d, J=4.4 Hz, NH<sup>+</sup>), 8.04 (1H, t, J=5.9 Hz, C<sub>γ</sub>-NH), 7.90 (1H, s, triazole CH), 7.7-7.04 (5H, m, 5 x ArCH), 5.50 (1H dd, J=9.7, 6.0 Hz, H<sub>α</sub>), 4.07 (1H, ddd, J=9.5, 6.5, 3.3 Hz, H<sub>β</sub>), 4.02-3.93 (1H, m, H<sub>ε</sub>), 3.58 (3H, s, OCH<sub>3</sub>), 3.51-3.43 (1H, m, H<sub>δ</sub>), 3.38 (1H, dd, J=14.0, 6.0 Hz, H<sub>ε</sub>), 3.27 (1H, dd, J=14.0, 9.7 Hz, H<sub>δ</sub>), 3.23-3.12 (2H, m, H<sub>α</sub> and H<sub>ε</sub>), 3.11-3.01 (1H, m, H<sub>δ</sub>), 2.94-2.76 (2H, m, COCH₂CH₂), 2.47-2.37 (2H, m, COCH₂CH₂), 1.78-1.65 (1H, m, H<sub>β</sub>), 1.63-1.51 (1H, m, H<sub>τ</sub>), 5δ<sub>W</sub> / ppm (125 MHz, d<sub>6</sub>-DMSO): 171.6 (OCH<sub>2</sub>CH<sub>2</sub>), 169.6 (COOMe), 166.3 (C<sub>α</sub>C=O and C<sub>β</sub>C=O), 145.3 (triazole C), 136.3 (ArC), 128.8 (ArCH), 128.2 (ArCH), 126.7 (ArCH), 121.5 (triazole CH), 64.0 (C<sub>α</sub>), 53.2 (C<sub>β</sub>), 52.1 (OCH<sub>3</sub>), 50.2 (C<sub>γ</sub>), 38.1 (C<sub>δ</sub>), 37.8 (C<sub>ε</sub>), 34.4 (C<sub>τ</sub>), 34.3 (COCH₂CH₂), 31.3 (C<sub>τ</sub>), 21.5 (COCH₂CH₂). ν<sub>max</sub> / cm<sup>-1</sup>: 3215 (NH str), 3035 (CH str), 2925 (CH str), 1742 (C=O str), 1682 (C=O str), 1542, 1433, 1213, 1151. | HPLC (5-100% ACN) Rt 8.31 mins. HRMS (ESI+) m/z found [M+H]+ 472.2301, C₂₂H₂₀N₇O₅<sup>+</sup> required 472.2303. [α]<sub>D</sub> = -28.2 (c 0.53, MeOH). |
| B9 w  | ![Structure](image3.png) | 99%       | 61%     | 5δ<sub>W</sub> / ppm (125 MHz, d<sub>6</sub>-DMSO): 171.6 (OCH<sub>2</sub>CH<sub>2</sub>), 169.6 (COOMe), 166.3 (C<sub>α</sub>C=O and C<sub>β</sub>C=O), 145.3 (triazole C), 136.3 (ArC), 128.8 (ArCH), 128.2 (ArCH), 126.7 (ArCH), 121.5 (triazole CH), 64.0 (C<sub>α</sub>), 53.2 (C<sub>β</sub>), 52.1 (OCH<sub>3</sub>), 50.2 (C<sub>γ</sub>), 38.1 (C<sub>δ</sub>), 37.8 (C<sub>ε</sub>), 34.4 (C<sub>τ</sub>), 34.3 (COCH₂CH₂), 31.3 (C<sub>τ</sub>), 21.5 (COCH₂CH₂). ν<sub>max</sub> / cm<sup>-1</sup>: 3215 (NH str), 3035 (CH str), 2925 (CH str), 1742 (C=O str), 1682 (C=O str), 1542, 1433, 1213, 1151. | HPLC (5-100% ACN) Rt 6.74 mins. LCMS [M+H]+ 472.16. |
### B10 w

- **M p** = 224-225 °C (CH₂Cl₂). δₜ / ppm (500 MHz, d₆-DMSO): 8.56 (1H, d, J=7.0 Hz, C₆-NH), 8.32 (1H, dd, J=7.2, 4.4 Hz, C₅-NH), 8.19 (3H, d, J=4.3 Hz, NH₃), 8.02 (1H, s, triazole CH), 7.27-7.06 (5H, m, 5 × ArCH), 6.62 (1H, app. s, NHCH₂), 6.38 (1H, app. s, C₅=NH), 5.55 (1H, dd, J=10.0, 5.6 Hz, Hα), 4.30 (1H, dt, J=7.0, 4.1 Hz, Hβ), 4.26-4.07 (2H, m, NHCH₂), 3.87-3.77 (1H, m, Hβ), 3.62 (3H, s, OCH₃), 3.52 (1H, dd, J=14.3, 5.6 Hz, Hβ), Hα below DMSO signal, 3.19-3.08 (2H, m, Hγ), 1.92-1.81 (1H, m, Hα), 1.70-1.59 (1H, m, Hγ). δЄ / ppm (125 MHz, d₆-DMSO): 169.8 (COOMe), 169.0 (C₆=O), 168.3 (C₅=O), 159.1 (NH=ONH), 146.9 (triazole C), 136.4 (ArC), 128.8 (ArC), 128.3 (ArC), 126.7 (ArC), 122.1 (triazole CH), 64.1 (C₆), 52.7 (C₅), 52.3 (OCH₃), 49.9 (C₆), 38.5 (C₅), 37.0 (C₆), 35.7 (NHCH₂), 35.0 (C₆), 31.9 (C₅). vₘₐₓ / cm⁻¹: 3210 (NH str), 2921 (CH str), 1740 (C=O str), 1683 (C=O str), 1535, 1436, 1214, 1147. **HPLC** (5-100% ACN) Rₜ 8.33 mins. **HRMS** (ESI+) m/z found [M+H]+= 473.2267, C₂₁H₂₉N₄O₅ required 473.2261. [α]₀²⁵ = +11.2 (c 1.56, MeOH).

### B11 w

- **M p** = 212-216 °C (CH₂Cl₂). δₜ / ppm (500 MHz, d₆-DMSO): 8.57 (1H, d, J=6.0 Hz, C₆-NH), 8.51-8.45 (1H, m, C₅-NH), 8.42 (3H, d, J=5.6 Hz, NH₃), 8.16 (1H, s, triazole CH), 7.27-7.08 (5H, m, 5 × ArCH), 6.51 (1H, s, C₅=NH), 6.32 (1H, t, J=5.6 Hz, NHCH₂), 5.46 (1H, dd, J=8.2, 6.8 Hz, Hα), 4.53-4.36 (1H, m, Hβ), 4.18-4.07 (2H, m, Hα and Hβ), 4.07-3.92 (2H, m, Hα and Hγ), 3.63-3.52 (1H, m, Hβ), 3.47-3.39 (1H, m, NHCH₂), 3.37 (3H, s, OCH₃), 3.27 (1H, dd, J=14.1, 8.2 Hz, Hβ), 3.07-2.95 (2H, m, Hβ and NHCH₂). δЄ / ppm (125 MHz, d₆-DMSO): 170.0 (COOMe), 167.8 (C₆=O), 166.9 (C₅=O), 158.0 (NH=ONH), 147.5 (triazole C), 136.7 (ArC), 129.1 (ArC), 128.2 (ArC), 126.6 (ArC), 122.7 (triazole CH), 63.9 (C₆), 52.9 (C₅), 52.3 (OCH₃), 50.9 (C₅), 40.5 (NHCH₂), 38.9 (C₆), 35.7 (C₆), 35.4 (C₅). vₘₐₓ / cm⁻¹: 3208 (NH str), 3031 (CH str), 2919 (CH str), 1741 (C=O str), 1678 (C=O str), 1546, 1435, 1121, 1146. **HPLC** (5-100% ACN) Rₜ 8.74 mins. **HRMS** (ESI+) m/z found [M+H]+ = 459.2104, C₂₀H₂₉NaO₅ required 459.2104. [α]₀²⁵ = -0.5 (c 2.05, MeOH).
| Code | Structure | GP2 & GP4 | 98% | Mp = 135-138 °C (CH₂Cl₂), δH/ppm (500 MHz, d6-DMSO): 9.06 (1H, dd, J=8.6, 3.7 Hz, C1=NH), 8.93 (1H, d, J=6.7 Hz, C2=NH), 8.20 (3H, d, J=4.5 Hz, NH3), 7.70 (1H, s, triazole CH), 7.64 (1H, t, J=5.5 Hz, C2-NH), 7.29-7.07 (5H, m, 5 × ArCH), 5.49 (1H, dd, J=9.2, 6.3 Hz, H2), 4.30-4.24 (1H, m, H3), 3.94 (1H, ddd, J=14.0, 8.6, 5.4 Hz, H6), 3.83-3.74 (1H, m, H3), 3.47 (3H, s, OCH3), 3.42-3.28 (2H, m, H6), 3.22-3.13 (1H, m, H3), 3.12-2.97 (2H, m, H6), 2.85 (2H, t, J=6.2 Hz, COCH₂CH₂), 2.44-2.33 (2H, m, COCH₂CH₂), 1.83-1.72 (1H, m, H5), 1.69-1.58 (1H, m, H5), 1.42-1.35 (2H, m, H6), 1.35-1.26 (2H, m, H6). δC/ppm (125 MHz, d6-DMSO): 171.0 (C=OCH₂CH₂), 169.7 (COOMe), 168.6 (C=O), 168.5 (C=O), 145.9 (triazole C), 136.2 (ArC), 128.9 (ArCH), 128.3 (ArCH), 126.8 (ArCH), 121.6 (triazole CH), 63.9 (Cα), 53.2 (Cβ), 52.1 (OCH₃), 51.8 (Cγ), Cβ below DMSO signal, 37.7 (Cγ), 37.3 (Cβ), 33.9 (COCH₂CH₂), 30.5 (Cγ), 28.3 (Cβ), 21.1 (COCH₂CH₂), 20.8 (Cγ). νmax/cm⁻¹: 3226 (NH str), 2921 (CH str), 1740 (C=O str), 1687 (C=O str), 1545, 1436, 1212, 1148. HPLC (5-100% ACN) Rt 8.8 mins. HRMS (ESI+) m/z found [M+H]+ 500.2618, C₂₃H₂₄N₇O₆⁺ required 500.2616. [α]D²⁰ = +24.7 (c 2.54, MeOH) |
|---|---|---|---|---|
| D1 | ![Structure](image1.png) | GP2 & GP4 | 98% | HPLC (5-30% ACN) Rt 6.74 mins. LCMS [M+H]+ 409.18. |
| D2 | ![Structure](image2.png) | GP2 & GP4 | 93% | HPLC (5-100% ACN) Rt 7.13 mins. LCMS [M+H]+ 381.22. |
| D3 | ![Structure](image3.png) | GP2 & GP4 | 99% | HPLC (0-60% ACN) Rt 5.44 mins. LCMS [M+H]+ 395.17. |
| D5 | ![Structure](image4.png) | GP2 & GP4 | 99% | HPLC (5-100% ACN) Rt 4.37 mins. LCMS [M+H]+ 382.12. |

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| Date | Assay | GP2 & GP4 | HPLC Conditions | LCMS [M+H]+ (Da) |
|------|-------|-----------|------------------|------------------|
| D7 w |       | GP2 & GP4 | HPLC (5-45% ACN) | 381.15           |
| D8 w |       | GP2 & GP4 | HPLC (5-100% ACN) | 367.21           |
| D10 w|       | GP2 & GP4 | HPLC (5-100% ACN) | 353.12           |
| D11 w|       | GP2 & GP4 | HPLC (5-100% ACN) | 368.26           |
| D12 w|       | GP2 & GP4 | HPLC (5-100% ACN) | 354.09           |
| D14 w|       | GP2 & GP4 | HPLC (5-80% ACN)  | 395.23           |
|   | Structure | GP2 & GP4 | HPLC (5-100% ACN) Rt | LCMS [M+H]^+ |
|---|-----------|-----------|----------------------|----------------|
| **E1w** | ![Structure](image1.png) | 40% | 4.62 mins. | 395.24. |
| **E2w** | ![Structure](image2.png) | 85% | 4.09 mins. | 367.21. |
| **E3w** | ![Structure](image3.png) | 71% | 4.43 mins. | 381.30. |
| **E4w** | ![Structure](image4.png) | 93% | 3.83 mins. | 382.20. |
| **E5w** | ![Structure](image5.png) | 99% | 3.86 mins. | 368.26. |
| **E7w** | ![Structure](image6.png) | 60% | 4.70 mins. | 367.21. |
| **E8w** | ![Structure](image7.png) | 99% | 4.14 mins. | 353.19. |
| **E9w** | ![Molecule](image) | GP2 & GP4 | 52% | 59% | HPLC (5-100% ACN) Rt 4.41 mins. LCMS [M+H]^+ 353.12. |
| --- | --- | --- | --- | --- | --- |
| **E10w** | ![Molecule](image) | GP2 & GP4 | 53% | 94% | HPLC (5-100% ACN) Rt 3.85 mins. LCMS [M+H]^+ 339.10. |
| **E11w** | ![Molecule](image) | GP2 & GP4 | 29% | 97% | HPLC (5-100% ACN) Rt 4.04 mins. LCMS [M+H]^+ 354.17. |
| **E14w** | ![Molecule](image) | GP2 & GP4 | 99% | 73% | HPLC (5-100% ACN) Rt 4.11 mins. LCMS [M+H]^+ 381.22. |
### 12. Preparation of B/C/C/P and B/C/C/C/P CuAAC Macrocycles

| Compound | Method, Yield (%), Purity (%) | Analysis |
|----------|------------------------------|----------|
| **G1**  | G1 w GP2 70% 61% HPLC (5-100% ACN) Rt 7.70 mins. LCMS [M+H]^+ 652.39. | |
| **G2**  | G2 w GP2 71% 83% HPLC (5-100% ACN) Rt 7.39 mins. LCMS [M+H]^+ 624.54. | |
| **G3**  | G3 w GP2 99% 87% HPLC (5-100% ACN) Rt 7.51 mins. LCMS [M+H]^+ 638.28. | |
| **G4**  | G4 w GP2 62% 92% δH /ppm (400 MHz, d6-DMSO): 8.14 (1H, d, J=7.2 Hz), 8.05 (1H, d, J=8.3 Hz), 7.78 (1H, s), 6.79 (1H, d, J=7.8 Hz), 6.26 (1H, t, J=5.9 Hz), 5.93 (1H, t, J=5.9 Hz), 4.33-4.16 (5H, m), 3.95-3.83 (1H, m), 3.58 (3H, s), 3.57 (3H, s), 3.16-3.02 (1H, m), 2.95-2.80 (1H, m), 1.84-1.08 (13H, m), 1.37 (9H, s). δC /ppm (100 MHz, d6-DMSO): 173.1, 172.8, 172.6, 171.9, 158.7, 122.9, 78.5, 54.3, 52.3, 51.8, 51.4, 49.6, 39.1, 35.6, 31.9, 30.8, 30.9, 29.9, 29.7, 28.7, 26.4, 22.8, 22.4. νmax /cm⁻¹: 3304, 2920, 1739, 1650, 1544, 1436, 1366, 1249, 1212, 1164, 1048. HPLC (5-100% ACN) Rt 7.56 mins. HRMS (ESI+) m/z found [M+Na]^+ 661.3287, C28H46N6O9Na^+ required 661.3285. |
| Compound | Structure | HPLC | LCMS | 
|----------|-----------|------|------|
| G5 w     | ![Structure](image) | GP2 60% 98% | δ<sub>H</sub>/ppm (500 MHz, d<sub>6</sub>-DMSO): 8.18 (1H, d, J=7.8 Hz), 8.02 (1H, d, J=8.3 Hz), 7.82 (1H, s), 6.79 (1H, d, J=8.5 Hz), 6.39 (1H, t, J=5.9 Hz), 6.04 (1H, t, J=6.1 Hz), 4.40-4.06 (7H, m), 3.60 (3H, s), 3.59 (3H, s), 3.28-3.13 (1H, m), 2.96-2.84 (1H, m), 2.31-2.20 (1H, m), 2.10 (1H, m), 2.04-1.90 (1H, m), 1.88-1.55 (4H, m), 1.53-1.42 (1H, m), 1.40-1.30 (4H, m), 1.37 (9H, s), 1.12-1.01 (2H, m). δ<sub>C</sub>/ppm (125 MHz, d<sub>6</sub>-DMSO): 172.6, 172.2, 171.4, 158.8, 155.6, 146.5, 123.0, 78.1, 52.8, 52.0, 50.9, 50.8, 49.0, 37.2, 35.3, 30.8, 30.0, 28.7, 28.3, 27.1, 26.7, 21.8. ν<sub>max</sub>/cm<sup>-1</sup>: 3314, 2924, 1733, 1648, 1525, 1251, 1169, 1051. HPLC (5-45% ACN) R<sub>t</sub> 11.65 mins. HRMS (ESI+) m/z found [M+H]<sup>+</sup> 625.3298, C<sub>22</sub>H<sub>45</sub>N<sub>8</sub>O<sub>9</sub> required 625.3310. | [M+H]<sup>+</sup> 610.23. |
| G9 w     | ![Structure](image) | GP2 69% 81% | HPLC (5-45% ACN) R<sub>t</sub> 12.13 mins. LCMS [M+H]<sup>+</sup> |
| G10 w    | ![Structure](image) | GP2 94% 89% | HPLC (5-45% ACN) R<sub>t</sub> 11.83 mins. LCMS [M+H]<sup>+</sup> 596.21. |
| G11 w    | ![Structure](image) | GP2 67% 74% | HPLC (15-30% ACN) R<sub>t</sub> 11.08 mins. LCMS [M+H]<sup>+</sup> 611.21. |
| G12 w    | ![Structure](image) | GP2 99% 85% | HPLC (15-30% ACN) R<sub>t</sub> 11.55 mins. LCMS [M+H]<sup>+</sup> 597.18. |
| Compound | Diluent | Yield | HPLC Conditions | LCMS Value |
|----------|---------|-------|-----------------|------------|
| G13 w    | GP2     | 12%   | HPLC (5-100% ACN) Rt 8.46 mins. | [M+H]^+ 686.29. |
| G14 w    | GP2     | 69%   | HPLC (5-100% ACN) Rt 7.49 mins. | [M+H]^+ 638.28. |
| H12 w    | GP2 & GP4 | 78%   | HPLC (5-100% ACN) Rt 4.94 mins. | [M+H]^+ 483.11. |
| H14 w    | GP2 & GP4 | 86%   | HPLC (5-30% ACN) Rt 7.31 mins. | [M+H]^+ 542.28. |
| J13 w    | GP2 & GP5 | 21%   | HPLC (5-100% ACN) Rt 5.34 mins. | [M+H]^+ 500.28. |
## 13. Preparation of B/C/P RuAAC Macrocycles

| Compound | Method, Yield (%), Purity (%) | Analysis |
|----------|-------------------------------|----------|
| A1x | **GP3 & GP4**<br>60%<br>86% | **HPLC** (5-80% ACN) *Rt 7.74 mins.**<br>**LCMS** [M+H]$^+$ 556.27. |
| A2x | **GP3 & GP4**<br>97%<br>81% | **HPLC** (5-60% ACN) *Rt 8.86 mins.**<br>**LCMS** [M+H]$^+$ 528.29. |
| A3x | **GP3 & GP4**<br>86%<br>75% | **HPLC** (5-100% ACN) *Rt 6.93 mins.**<br>**LCMS** [M+H]$^+$ 542.28. |
| A4x | **GP3 & GP4**<br>81%<br>81% | **HPLC** (5-100% ACN) *Rt 6.79 mins.**<br>**LCMS** [M+H]$^+$ 543.33. |
| A5x | GP3 & GP4 | HPLC (5-100% ACN) Rt 6.67 mins. LCMS [M+H]^+ 529.23. |
|-----|----------|--------------------------------------------------|
| A6x | GP3 & GP5 | δH//ppm (500 MHz, d_6-DMSO): 10.13 (1H, s), 8.47 (3H, d, J=4.3 Hz), 8.26 (1H, d, J=5.1 Hz), 7.71 (1H, t, J=5.5 Hz), 7.47 (1H, m), 7.40 (2H, d, J=8.4 Hz), 7.21-7.09 (5H, m), 7.06 (2H, d, J=6.9 Hz), 5.42 (1H, dd, J=9.6, 6.0 Hz), 4.10-3.98 (1H, m), 3.59 (1H, m), 3.47 (3H, s), 3.51-3.38 (2H, m), 3.17 (1H, dd, 1H, J=13.6, 4.7 Hz), 3.14-3.05 (1H, m), 2.84-2.71 (3H, m), 2.71-2.56 (2H, m), 2.55-2.40 (1H, m), 1.54-1.37 (1H, m), 1.33-0.92 (3H, m), 0.88-0.57 (1H, m). δC//ppm (125 MHz, d_6-DMSO): 170.8, 170.3, 166.9, 137.7, 137.6, 137.0, 131.5, 129.8, 129.5, 129.0, 128.2, 126.6, 119.4, 72.2, 70.6, 66.4, 61.8, 60.3, 52.8, 52.70, 51.8, 43.7, 36.7, 36.0, 34.6, 29.4, 28.4 22.2, 18.0. νmax/cm⁻¹: 3295, 2925, 1732, 1663, 1540, 701. HPLC (5-100% ACN) Rt 7.52mins. HRMS (ESI+) m/z found [M+H]^+ 576.2928, C_{30}H_{38}N_{7}O_{5}^+ required 576.2934. |
| A7x | GP3 & GP4 | HPLC (5-100% ACN) Rt 7.11 mins. LCMS [M+H]^+ 528.23. |
| A8x | GP3 & GP4 | HPLC (5-100% ACN) Rt 7.04 mins. LCMS [M+H]^+ 514.24. |
| A9x | GP3 & GP4 | HPLC (5-100% ACN) Rt 6.88 mins. LCMS [M+H]^+ 514.23. |
| A10  | ![Chemical Structure](image) | GP3 & GP4 | 99% | 74% |
|------|------------------------------|----------|-----|-----|
|      | **HPLC** (5-100% ACN) **Rt** 6.63 mins. **LCMS** [M+H]^+ 500.21. |

| A11  | ![Chemical Structure](image) | GP3 & GP4 | 78% | 84% |
|------|------------------------------|----------|-----|-----|
|      | **HPLC** (5-100% ACN) **Rt** 6.94 mins. **LCMS** [M+H]^+ 515.28. |

| A12  | ![Chemical Structure](image) | GP3 & GP4 | 38% | 97% |
|------|------------------------------|----------|-----|-----|
|      | δ_H/ppm (500 MHz, d_6-DMSO): 8.92 (1H, d, J=5.5 Hz), 8.43 (3H, d, J=4.5 Hz), 8.01 (1H, t, J=6.0 Hz), 7.51 (1H, s), 7.23-7.11 (4H, m), 7.05-6.99 (2H, m), 6.32 (1H, t, J=6.0 Hz), 5.43 (1H, dd, J=10.5, 5.0 Hz), 4.23-4.11 (1H, m), 4.01-3.77 (3H, m), 3.60 (3H, s), 3.59-3.46 (2H, m), 3.44-3.32 (1H, m), 3.28-3.13 (2H, m), 3.09-2.98 (1H, m), 1.88-1.74 (1H, m), 1.70-1.58 (1H, m), 1.52-1.25 (3H, m), 1.16-1.01 (1H, m), δ_C/ppm (125 MHz, d_6-DMSO): 171.5, 167.9, 167.1, 158.0, 136.6, 136.1, 132.3, 128.7, 128.2, 126.6, 61.9, 52.8, 52.6, 52.0, 41.0, 38.2, 37.6, 31.9, 28.8, 28.0, 21.4. **HPLC** (5-100% ACN) **Rt** 6.78 mins. **HRMS** (ESI+) m/z found [M+H]^+ 501.2585, C_{23}H_{33}N_{8}O_{5}^+ required 501.2574, [α]_D^25 = +44.5 (c 0.50, MeOH). |

| A13  | ![Chemical Structure](image) | GP3 & GP5 | 50% | 89% |
|------|------------------------------|----------|-----|-----|
|      | **v_max**/cm^{-1}: 3311, 2922, 2852, 2161, 2029, 1726, 1661, 1601, 1537, 1456, 1416, 1253, 1119. **HPLC** (5-100% ACN) **Rt** 7.40 mins. **HRMS** (ESI+) m/z found [M+H]^+ 590.3080, C_{21}H_{40}N_{7}O_{5}^+ required 590.3090. |

| B1x  | ![Chemical Structure](image) | GP3 & GP4 | 99% | 91% |
|------|------------------------------|----------|-----|-----|
|      | **HPLC** (5-100% ACN) **Rt** 6.53 mins. **LCMS** [M+H]^+ 514.31. |
| B2x | $\delta_{\text{H}}$/ppm (500 MHz, $d_2$-DMSO, 90°C): 8.04 (1H, app s, C$_2$-NH), 7.93 (3H, br s, NH$_3$), 7.87 (1H, app s, C$_5$-NH), 7.79 (1H, app s, C$_{10}$-NH), 7.45 (1H, s, triazole CH), 7.24-7.16 (3H, m, $3 \times$ ArCH), 7.14-7.10 (2H, m, 2 × ArCH), 5.31 (1H, dd, $J = 8.7, 6.5$ Hz, H$_9$), 4.36-4.31 (1H, m, H$_{13}$), 3.93 (2H, m, H$_{15}$ and H$_{16}$), 3.57-3.53 (2H, m, H$_{17}$), 3.51 (3H, s, OCH$_2$), 3.45-3.36 (1H, m, H$_{21}$), 3.33-3.27 (1H, m, H$_{22}$), H$_2$ below H$_2$O signal, 2.80-2.69 (1H, m, COC$_{18}$CH$_2$), 2.69-2.58 (1H, m, COCH$_2$CH$_2$), COC$_{18}$CH$_2$ below DMSO signal 1.70-1.56 (3H, m, H$_{19}$ and H$_{20}$), 1.53-1.42 (1H, m, H$_{23}$). $\delta_{\text{C}}$/ppm (125 MHz, $d_2$-DMSO): 171.8 (C=OCH$_2$CH$_2$), 169.8 (COOME), 169.4 (C$_5$-C=O), 167.8 (C$_2$-C=O), 137.2 (triazole C), 136.8 (ArC), 131.0 (triazole CH), 129.0 (ArCH), 128.3 (ArCH), 126.7 (ArCH), 62.0 (C$_5$), 52.4 (C$_{10}$), 52.2 (OCH$_2$), 50.9 (C$_{13}$), C$_9$ below DMSO signal, 36.5 (C$_{18}$), 36.3 (C$_{14}$), 33.6 (COCH$_2$CH$_2$), 28.0 (C$_{15}$), 24.3 (C$_{16}$), 19.1 (COCH$_2$CH$_2$). $\nu_{\text{max}}$/cm$^{-1}$: 3276 (w, N-H), 2951 (w, C-H), 1743 (w, C=O), 1673 (s, C=O), 1545 (m, C=C). HPLC (5-100% ACN) Rt 8.85 mins. HRMS (ESI+) m/z found [M+Na]$^+$ 508.2280, C$_{29}$H$_{33}$N$_2$O$_5$Na$^+$ required 508.2284 ($\Delta$ -0.8 ppm). $[\alpha]_D^{25}$ = +50.0 (c 1.46, MeOH). |
| GP3 & GP4 | 93% | 99% |

| B3x | Mp = 202-204 °C (CH$_2$Cl$_2$). $\delta_{\text{H}}$/ppm (500 MHz, $d_2$-DMSO): 8.99 (1H, d, $J=7.0$ Hz, C$_2$-NH), 8.91 (1H, dd, $J=8.4, 4.1$ Hz, C$_{10}$-NH), 8.19 (3H, d, $J=4.8$ Hz, NH$_3$), 8.15 (1H, t, $J=6.1$ Hz, C$_5$-NH), 7.41 (1H, s, triazole CH), 7.23-7.11 (5H, m, 5 × ArCH), 5.29 (1H, dd, $J=10.2, 5.3$ Hz, H$_9$), 4.28 (1H, dt, $J=7.0, 3.5$ Hz, H$_{13}$), 4.05-3.89 (2H, m, H$_{15}$ and H$_{16}$), 3.62-3.49 (2H, m, H$_{21}$), 3.28 (3H, s, OCH$_3$), 3.24-3.10 (2H, m, H$_{17}$ and H$_{20}$), 3.09-2.96 (1H, m, H$_{19}$), 2.69-2.39 (2H, m, COC$_{18}$CH$_2$), 2.27-2.18 (1H, m, COCH$_2$CH$_2$), 2.18-2.09 (1H, m, COCH$_2$CH$_2$), 1.83-1.67 (3H, m, COCH$_2$CH$_2$ and H$_{17}$), 1.67-1.52 (2H, m, H$_{18}$), 1.52-1.39 (1H, m, COCH$_2$CH$_2$). $\delta_{\text{C}}$/ppm (125 MHz, $d_2$-DMSO): 171.9 (C=OCH$_2$CH$_2$), 169.8 (COOME), 169.0 (C$_5$-C=O), 167.7 (C$_2$-C=O), 138.0 (triazole C), 138.6 (ArC), 130.8 (triazole CH), 128.9 (ArCH), 128.2 (ArCH), 128.7 (ArCH), 61.8 (C$_5$), 52.7 (C$_{10}$), 51.9 (OCH$_3$), 51.3 (C$_{13}$), C$_9$ below DMSO peak, 37.1 (C$_{18}$), 37.1 (C$_{14}$), 34.6 (COCH$_2$CH$_2$), 28.3 (C$_{15}$), 24.3 (C$_{16}$), 23.9 (COCH$_2$CH$_2$), 21.3 (COCH$_2$CH$_2$). $\nu_{\text{max}}$/cm$^{-1}$: 3222 (NH str), 2926 (CH str), 1736 (C=O str), 1683 (C=O str), 1544, 1438, 1213, 1140. HPLC (5-100% ACN) Rt 6.49 mins. HRMS (ESI+) m/z found [M+H]$^+$ 500.2632, C$_{29}$H$_{33}$N$_2$O$_5$ required 500.2621. $[\alpha]_D^{25}$ = +53.0 (c 0.15, MeOH). |
| GP3 & GP4 | 46% | 99% |

| B4x | HPLC (5-25% ACN) Rt 13.76 mins. LCMS [M+H]$^+$ 501.26. |
| GP3 & GP4 | 96% | 94% |
**B5x**

| Compound | δH/ppm (500 MHz, d6-DMSO, 90°C) | 86% | 92% |
|-----------|---------------------------------|-----|-----|
| GP3 & GP4 | 8.30 (1H, app s, Cβ-NH), 7.80 (3H, br s, NH3) | 7.58 (1H, dd, J=5.8, 4.5 Hz, Cβ-NH) | 7.43 (1H, s, triazole CH), 7.24-7.12 (3H, m, 3 × ArCH), 7.01-6.95 (2H, m, 2 × ArCH), 6.56 (1H, app t, J=5.9 Hz, CH2-NH), 6.38-6.25 (1H, m, Cα-NH) | 6.62 (1H, dd, J=10.4, 5.1 Hz, He), 4.42 (1H, app s, He), 4.02 (1H, dd, J=16.3, 6.3 Hz, CH2), 3.98-3.91 (2H, m, Hβ and Hδ), 3.74 (1H, dd, J=16.3, 5.5 Hz, CH2), 3.55 (1H, dd, J=14.1, 5.1 Hz, Hγ), 3.44-3.27 (3H, m, Hδ, Hβ, Hγ), 2.86-2.74 (1H, m, Hβ) | 1.80-1.61 (2H, m, Hβ), 1.61-1.44 (2H, m, Hγ) |
| **δC/ppm (125 MHz, d6-DMSO):** | 169.0 (COOMe), 169.0 (C=C=O) | 158.8 (NHC=ONH), 137.3 (triazole C), 136.7 (ArC), 131.8 (triazole CH), 128.8 (ArCH), 128.2 (ArCH), 126.6 (ArCH), 61.2 (Cβ), 52.3(Cδ), 52.0 (OCH3), 50.4(Cα), Cβ below DMSO signal, 37.0 (Cβ), 37.0 (Cβ), 31.9 (CH2), 27.7(Cβ), 25.3(Cγ), v_max/cm⁻¹: 3284 (w, N-H), 2934 (w, C=H), 1743 (w, C=O), 1677 (s, C=O), 1546 (s, C=C). **HPLC (5-100% ACN) Rt 8.63 mins.** | **HRMS (ESI+) m/z found [M+H]+ 487.2423, C22H31N3O5+** required 487.2417 (Δ 1.2 ppm). [α]D²⁵ = -1.10 (c 0.59, MeOH). |

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**B7x**

| Compound | δH/ppm (500 MHz, d6-DMSO, 60 °C): | 99% | 86% |
|-----------|----------------------------------|-----|-----|
| GP3 & GP4 | 8.27 (1H, t, J = 5.2 Hz, Cβ-NH) | 7.94 (1H, app s, Cα-NH) | 7.89 (1H, t, J=5.3 Hz, Cγ-NH) | 7.37 (1H, s, triazole CH), 7.22-7.06 (5H, m, 5 × ArCH), 5.38 (1H, dd, J=10.5, 5.1 Hz, He), 4.35 (1H, dd, J=5.6, 3.8 Hz, HHe) | 3.68-3.58 (1H, m, Hδ), 3.55 (3H, s, OCH3), 3.56-3.42 (3H, m, Hδ and HHe), 3.33-3.27 (1H, m, HHe) | Hγ below H2O signal, 2.47-2.30 (2H, m, CHCH2CH2CH2), 2.26-2.11 (2H, m, COCH2CH2CH2), 1.82-1.73 (1H, m, COCH2CH2CH2), 1.73-1.64 (2H, m, COCH2CH2CH2 and Hγ), 1.60-1.50 (1H, m, Hδ) |
| **δC/ppm (125 MHz, d6-DMSO):** | 174.9 (C=O) | 170.4 (COOMe), 168.0 (C=O) | 131.8 (triazole C), 136.6 (ArC), 131.3 (triazole CH), 128.9 (ArCH), 128.2 (ArCH), 126.7 (ArCH), 62.1 (Cβ), 52.7 (Cγ), 52.2 (Cδ), 52.1 (OCH3), Cβ below DMSO signal, 37.0 (Cβ), 35.6 (Cγ), 35.0 (Cδ), 34.3 (COCH2CH2CH2), 23.5 (COCH2CH2CH2), 21.5 (COCH2CH2CH2). | v_max/cm⁻¹: 3260 (m, N-H), 2934 (m, C=H), 1740 (m, C=O), 1644 (s, C=O), 1541 (s, C=C). **HPLC (5-100% ACN) Rt 8.98 mins.** | **HRMS (ESI+) m/z found [M+H]+ 486.2488, C23H32N7O5+** required 486.2465 (Δ 4.7 ppm). [α]D²⁵ = +0.8 (c 2.25, MeOH). |

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**B8x**

| Compound | δH/ppm (500 MHz, d6-DMSO, 120 °C): | 60% | 96% |
|-----------|-----------------------------------|-----|-----|
| GP3 & GP4 | 7.94 (1H, s, NH3) | 7.69 (1H, app s, Cβ-NH) | 7.38 (1H, s, triazole CH), 7.21-7.11 (3H, m, 3 × ArCH), 7.01-6.97 (2H, m, 2 × ArCH), 5.36 (1H, dd, J=10.4, 4.9 Hz, He), 4.40 (1H, t, J=5.0 Hz, Hδ), 3.77-3.66 (3H, m, Hδ and Hβ), 3.63 (3H, s, OCH3), 3.57 (1H, dd, J=14.0, 4.9 Hz, He), 3.42 (1H, dd, J=14.0, 10.4 Hz, Hδ), 3.28-3.20 (1H, m, Hβ), 3.13-3.02 (1H, m, Hβ'), 2.66-2.40 (4H, m, COCH2CH2 and COCH2CH2), 1.95-1.86 (1H, m, Hδ), 1.82-1.74 (1H, m, Hδ'), 1.62-1.40 (2H, m, Hβ), 1.52-1.30 (2H, m, Hβ'), 1.30-1.13 (2H, m, Hγ), 0.65 (s, MeO), Cβ below DMSO signal, 38.3 (Cδ), 34.7 (Cγ), 33.8 (COCH2CH2), 31.5 (Cγ), 17.3 (COCH2CH2). | v_max/cm⁻¹: 3260 (w, N-H), 2950 (w, C=H), 1741 (m, C=O), 1687 (s, C=O), 1551 (m, C=C). **HPLC (5-100% ACN) Rt 8.90 mins.** | **HRMS (ESI+) m/z found [M+H]+ 472.2301, C22H30N5O8+** required 472.2308 (Δ -1.5 ppm). [α]D²⁵ = +41.0 (c 1.3, MeOH). |
\begin{align*}
B9x &:\quad \text{GP3 & GP4} \\
&:\quad 99\% \\
&:\quad 72\% \\
&:\quad \text{HPLC (5-100% ACN) Rt 6.44 mins. LCMS [M+H]^+ 472.24.} \\
\end{align*}
| Compound | Structure | δ<sub>H</sub>/ppm (500 MHz, d<sub>6</sub>-DMSO, 120 °C): 7.47 (1H, s, triazole CH); 7.26-7.11 (3H, m, 3 × ArCH), 7.09-6.92 (3H, m, 2 × ArCH and C<sub>p</sub>-NH), 6.52 (1H, app s, CH<sub>2</sub>-NH), 6.06 (1H, app s, C<sub>p</sub>-NH), 5.62 (1H, dd, J=10.3, 5.0 Hz, H<sub>δ</sub>), 4.27 (1H, dd, J=8.3, 4.1 Hz, H<sub>ε</sub>), 4.01 (1H, dd, J=15.7, 6.9 Hz, CH<sub>2</sub>), 3.97-3.87 (2H, m, CH<sub>2</sub> and H<sub>δ</sub>), 3.83-3.74 (2H, m, H<sub>α</sub> and H<sub>ε</sub>), 3.60-3.51 (2H, m, H<sub>α</sub> and H<sub>β</sub>), 3.43 (1H, dd, J=14.1, 10.3 Hz, H<sub>ε</sub>), 3.26-3.18 (2H, m, H<sub>δ</sub>).
| | | δ<sub>C</sub>/ppm (125 MHz, d<sub>6</sub>-DMSO): 169.4 (COOME), 167.4 (C<sub>a</sub>-C=O), 166.7 (C<sub>b</sub>=O), 158.3 (NH=ONH), 136.7 (ArC), 136.5 (triazole C), 132.7 (triazole CH), 128.7 (ArCH), 128.3 (ArCH), 126.7 (ArCH), 61.2 (C<sub>a</sub>), 52.8 (C<sub>b</sub>), 52.6 (C<sub>c</sub>), 52.1 (OCH<sub>3</sub>), 38.1 (C<sub>d</sub>), 37.5 (C<sub>e</sub>), 30.9 (CH<sub>2</sub>), 3291 (w, N-H), 2953 (w, C-H), 1736 (w, C=O), 1673 (s, C=O), 1561 (m, C=C). HPLC (5-100% ACN) Rt 8.52 mins. HRMS (ESI+) m/z found [M+H]<sup>+</sup> 459.2097, C<sub>20</sub>H<sub>22</sub>N<sub>6</sub>O<sub>6</sub><sup>+</sup> required 459.2104 (Δ -1.5 ppm). [α]<sub>D</sub>= -10.6 (c 0.68, MeOH). |
| B12 | ![Structure](image1.png) | GP3 & GP4 | 40% | 97% |
| B13 | ![Structure](image2.png) | GP3 & GP5 | 15% | 92% |
| B14 | ![Structure](image3.png) | GP3 & GP4 | 90% | 92% |
| C2x | ![Structure](image4.png) | GP3 & GP4 | 62% | 75% |

HPLC (5-100% ACN) Rt 6.97 mins. LCMS [M+H]<sup>+</sup> 548.13.

Rt = 0.18 (15% MeOH/ 85% CH<sub>2</sub>Cl<sub>2</sub>). Mp = 140-143 ºC (CH<sub>2</sub>Cl<sub>2</sub>). δ<sub>H</sub>/ppm (400 MHz, CDCl<sub>3</sub>): 8.16-7.98 (2H, m, C<sub>p</sub>-NH and C<sub>a</sub>-NH), 7.89 (1H, dd, J=6.2, 5.3 Hz, C<sub>c</sub>-NH), 7.45 (1H, s, triazole CH), 7.28-7.10 (5H, m, 5 × ArCH), 5.30 (1H, dd, J=9.4, 6.1 Hz, H<sub>δ</sub>), 4.37-4.30 (1H, m, H<sub>ε</sub>), 3.87-3.77 (1H, m, H<sub>α</sub>), 3.62-3.41 (2H, m, H<sub>ε</sub>), 3.46 (3H, s, OCH<sub>3</sub>), 3.30-3.23 (1H, m, H<sub>c</sub>), 3.23-3.16 (1H, m, H<sub>c</sub>), 3.16-3.12 (1H, m, H<sub>ε</sub>), 3.02-2.84 (1H, m, H<sub>γ</sub>), 2.73-2.49 (2H, m, COCH<sub>2</sub>CH<sub>2</sub>), 2.41-2.31 (2H, m, COCH<sub>2</sub>CH<sub>2</sub>), 1.55-1.44 (2H, m, H<sub>γ</sub>), 1.44-1.26 (2H, m, H<sub>γ</sub>), 1.25-1.06 (2H, m, H<sub>γ</sub>). δ<sub>C</sub>/ppm (125 MHz, CDCl<sub>3</sub>): 175.0 (C<sub>a</sub>-C=O), 170.8 (C=OCH<sub>2</sub>CH<sub>2</sub>), 170.3 (COOME), 167.6 (C<sub>b</sub>-C=O), 137.6 (triazole C), 136.7 (ArC), 130.8 (triazole CH), 129.0 (ArCH), 128.3 (ArCH), 126.7 (ArCH), 61.2 (C<sub>a</sub>), 54.1 (C<sub>c</sub>), 52.0 (C<sub>b</sub>), 51.9 (OCH<sub>3</sub>), 36.8 (C<sub>d</sub>), 36.8 (C<sub>f</sub>), 34.8 (C<sub>e</sub>), 33.5 (COCH<sub>2</sub>CH<sub>2</sub>), 28.8 (C<sub>c</sub>), 21.6 (C<sub>e</sub>), 18.9 (COCH<sub>2</sub>CH<sub>2</sub>), ν<sub>max</sub>/cm<sup>-1</sup>: 3269 (m, N-H), 2924 (s, C-H), 1744 (m, C=O), 1648 (s, C=O), 1646 (s, C=C), 1546 (s, C=C). HPLC (5-100% ACN) Rt 9.12 mins. HRMS (ESI+) m/z found [M+H]<sup>+</sup> 500.2614, C<sub>24</sub>H<sub>34</sub>N<sub>6</sub>O<sub>8</sub><sup>+</sup> required 500.2621 (Δ -1.4 ppm). [α]<sub>D</sub>= +14.3 (c 0.43, MeOH). |

HPLC (5-100% ACN) Rt 5.26 mins. LCMS [M+H]<sup>+</sup> 415.16.
| C3x | 97% | 95% | \(\delta_{H}/ppm\) (500 Hz, \(d_{2}-\text{DMSO}, 70 \, ^{\circ}\text{C}\)): 8.33 (1H, d, \(J=6.5\text{ Hz}, C_{\alpha}-\text{NH}\)), 8.12 (3H, br s, \(\text{NH}_{3}\)), 7.68 (1H, s, triazole CH), 7.57 (1H, t, \(J=5.7\text{ Hz}, C_{\beta}-\text{NH}\)), 7.50-7.35 (4H, m, 4 \times \text{ArCH}) , 4.53-4.45 (1H, m, \(H_{\alpha}\)), 3.82-3.76 (1H, m, \(H_{\beta}\)), 3.66 (3H, s, OCH\(_{3}\)), 3.38 (1H, dd, \(J=14.2, 9.4\text{ Hz}, H_{\theta}\)), 3.26 (1H, dd, \(J=14.2, 4.1\text{ Hz}, H_{\beta}\)), 3.06-2.85 (2H, m, \(H_{\delta}\)), 2.67-2.54 (2H, m, COCH\(_{2}\)CH\(_{2}\)CH\(_{2}\)), 1.99 (2H, t, \(J=6.6\text{ Hz}, \text{COCH}_{2}\)CH\(_{2}\)CH\(_{2}\)), 1.73-1.65 (1H, m, COCH\(_{2}\)CH\(_{2}\)CH\(_{2}\)), 1.57-1.50 (2H, m, \(H_{\delta}\)), 1.39-1.27 (2H, m, \(H_{\beta}\)). \(\delta_c/ppm\) (125 MHz, \(d_{6}-\text{DMSO}\)) : 171.4 (C=OCH\(_{2}\)CH\(_{2}\)CH\(_{2}\)), 170.5 (COOMe), 168.9 (C\(_{\alpha}\)=O), 138.9 (ArC), 137.9 (triazole C), 134.6 (ArC), 132.0 (triazole CH), 130.2 (ArCH), 125.5 (ArCH), 54.1 (C\(_{\theta}\)), 52.0 (OCH\(_{3}\)), 51.6 (C\(_{\varphi}\)), 37.9 (C\(_{\varphi}\)), 34.3 (C\(_{\varphi}\)), 34.3 (COCH\(_{2}\)CH\(_{2}\)CH\(_{2}\)), 28.6 (C\(_{p}\)), 24.4 (C\(_{p}\)), 23.6 (COCH\(_{2}\)CH\(_{2}\)CH\(_{2}\)), 21.9 (COCH\(_{2}\)CH\(_{2}\)CH\(_{2}\)). \(\nu_{\max }/\text{cm}^{-1}\): 3261 (v, N-H), 2945 (v, C-H), 1739 (m, C=O), 1675 (s, C=O), 1546 (s, C=C). HPLC (5-100% ACN) \(R_{t}\) 5.58 mins. HRMS (ESI+) \(m/z\) found [M+H]\(^{+}\) 429.2224, \(C_{23}H_{20}N_{3}O_{4}\) required 429.2245 (\(\Delta -4.9\) ppm). [\(\alpha\)]\(D\)\(^{25}\) = -29.2 (c 0.43, MeOH).

| C5x | 46% | 89% | HPLC (5-100% ACN) \(R_{t}\) 5.24 mins. LCMS [M+H]\(^{+}\) 416.16.

| C7x | 97% | 95% | \(R_{t}\) = 0.11 (15% MeOH/ 85% CH\(_{2}\)Cl\(_{2}\)). \(\delta_{H}/ppm\) (400 MHz, \(d_{2}-\text{DMSO}\)) : 8.18 (1H, d, \(J=9.5\text{ Hz}, C_{\alpha}-\text{NH}\)), 7.87 (1H, t, \(J=5.9\text{ Hz}, C_{\gamma}-\text{NH}\)), 7.77 (1H, s, triazole CH)), 7.43 (2H, d, \(J=8.5\text{ Hz}, 2 \times \text{ArCH}\)), 7.35 (2H, d, \(J=8.5\text{ Hz}, 2 \times \text{ArCH}\)), 4.83-4.73 (1H, m, \(H_{\alpha}\)), 3.72 (3H, s, OCH\(_{3}\)), \(H_{\beta}\) below H\(_{2}\)O signal, 3.08 (1H, dd, \(J=13.5, 12.3\text{ Hz}, H_{\theta}\)), 3.03-2.84 (3H, m, \(H_{\alpha}\) and \(H_{\beta}\)), 2.57-2.33 (2H, m, COCH\(_{2}\)CH\(_{2}\)CH\(_{2}\)), 2.08 (2H, t, \(J=6.1\text{ Hz}, \text{COCH}_{2}\)CH\(_{2}\)CH\(_{2}\)), 2.03-1.80 (2H, m, COCH\(_{2}\)CH\(_{2}\)CH\(_{2}\)), 1.34-1.08 (1H, m, \(H_{\delta}\)), 0.93-0.70 (1H, m, \(H_{\beta}\)). \(\delta_c/ppm\) (125 MHz, \(d_{6}-\text{DMSO}\)) : 174.8 (C\(_{\alpha}\)=O), 171.9 (COOMe), 171.1 (C=OCH\(_{2}\)CH\(_{2}\)CH\(_{2}\)), 138.8 (ArC), 137.7 (triazole C), 134.1 (ArC), 131.6 (triazole CH), 130.5 (ArCH), 124.6 (ArCH), 54.2 (C\(_{\varphi}\)), 52.1 (OCH\(_{3}\)), 51.5 (C\(_{\varphi}\)), 36.8 (C\(_{\varphi}\)), 36.1 (C\(_{\varphi}\)), 35.9 (C\(_{\varphi}\)), 34.5 (COCH\(_{2}\)CH\(_{2}\)CH\(_{2}\)), 24.3 (COCH\(_{2}\)CH\(_{2}\)CH\(_{2}\)), 21.78 (COCH\(_{2}\)CH\(_{2}\)CH\(_{2}\)). \(\nu_{\max }/\text{cm}^{-1}\): 3274 (m, N-H), 2944 (w, C-H), 1742 (s, C=O), 1642 (s, C=O), 1541 (s, C=C). HPLC (5-100% ACN) \(R_{t}\) 5.70 mins. HRMS (ESI+) \(m/z\) found [M+H]\(^{+}\) 415.2072, \(C_{20}H_{27}N_{3}O_{4}\) required 415.2088 (\(\Delta -3.9\) ppm). [\(\alpha\)]\(D\)\(^{25}\) = -8.8 (c 0.65, MeOH).
| Compound | Structure | R<sub>f</sub> | δ<sub>H</sub> / ppm (500 Hz, d<sub>6</sub>-DMSO, 70 °C) | Observations |
|----------|-----------|-------------|---------------------------------|--------------|
| C8x      | ![C8x Structure](image) | 0.15 (15% MeOH/ 85% CH<sub>3</sub>Cl<sub>2</sub>) | 7.66 (1H, s, triazole CH), 6.55 (1H, s, Cα-NH<sub>2</sub>), 7.51-7.34 (4H, m, 4 × ArCH), 6.45 (1H, s, Cβ-NH), 4.73 (1H, dd, J=12.3, 4.1 Hz, Hβ<sup>5</sup>), 3.75 (3H, s, OCH<sub>3</sub>), 3.39 (1H, dd, J=13.5, 4.1 Hz, Hγ), 3.30-3.24 (2H, m, Hβ and Hγ), 2.31-3.15 (1H, m, Hβ), Hβ below H<sub>2</sub>O signal, 2.95-2.87 (2H, m, COCH<sub>2</sub>CH<sub>2</sub>), 2.10-1.98 (1H, m, COCH<sub>2</sub>CH<sub>2</sub>), 0.650 ppm. | R<sub>f</sub> = 0.15 (15% MeOH/ 85% CH<sub>3</sub>Cl<sub>2</sub>) | δ<sub>H</sub> / ppm (500 Hz, d<sub>6</sub>-DMSO, 70 °C): | 7.66 (1H, s, triazole CH), 7.55 (1H, s, Cα-NH), 7.51-7.34 (4H, m, 4 × ArCH), 6.55 (1H, s, Cβ-NH), 4.73 (1H, dd, J=12.3, 4.1 Hz, Hβ), 3.75 (3H, s, OCH<sub>3</sub>), 3.39 (1H, dd, J=13.5, 4.1 Hz, Hγ), 3.30-3.24 (2H, m, Hβ and Hγ), 2.31-3.15 (1H, m, Hβ), Hβ below H<sub>2</sub>O signal, 2.95-2.87 (2H, m, COCH<sub>2</sub>CH<sub>2</sub>), 2.10-1.98 (1H, m, COCH<sub>2</sub>CH<sub>2</sub>), 1.86-1.77 (1H, m, COCH<sub>2</sub>CH<sub>2</sub>). | GC/MS (5-100% ACN) R<sub>t</sub> 5.36 mins. | HPLC (5-100% ACN) R<sub>t</sub> 5.18 mins. | LCMS [M+H]<sup>+</sup><sup>+</sup> 402.14 |
| C10 x    | ![C10 Structure](image) | 0.50 (15% MeOH/ 85% CH<sub>3</sub>Cl<sub>2</sub>) | HPLC (5-100% ACN) R<sub>t</sub> 5.36 mins. | HPLC (5-100% ACN) R<sub>t</sub> 5.18 mins. | LCMS [M+H]<sup>+</sup><sup>+</sup> 402.14 |
| C11 x    | ![C11 Structure](image) | 0.40 (15% MeOH/ 85% CH<sub>3</sub>Cl<sub>2</sub>) | HPLC (5-100% ACN) R<sub>t</sub> 5.36 mins. | HPLC (5-100% ACN) R<sub>t</sub> 5.21 mins. | LCMS [M+H]<sup>+</sup><sup>+</sup> 388.12 |
| C12 x    | ![C12 Structure](image) | 0.27 (15% MeOH/ 85% CH<sub>3</sub>Cl<sub>2</sub>) | HPLC (5-100% ACN) R<sub>t</sub> 5.36 mins. | HPLC (5-100% ACN) R<sub>t</sub> 5.21 mins. | LCMS [M+H]<sup>+</sup><sup>+</sup> 388.12 |
|   | Structure | GP3 & GP4 | % | HRMS (ESI+) m/z found [M+H]^+ | C_{19}H_{33}N_{6}O_{4}^+ required 409.2567 | C_{19}H_{33}N_{6}O_{4}^+ required 409.2567 |
|---|-----------|-----------|---|-----------------------------|---------------------------------------------|---------------------------------------------|
| C14x | ![Structure Image] | 68% | 98% | 409.2250, 429.2233 | 395.23.0, 381.30. |
| D1x | ![Structure Image] | 65% | 99% | 409.2567, 381.30. | 409.2567, 381.30. |
| D2x | ![Structure Image] | 82% | 78% | 381.30. | 381.30. |
| D3x | ![Structure Image] | 99% | 86% | 395.23. | 395.23. |
| D4x | ![Structure Image] | 99% | 95% | 396.22. | 396.22. |
| D5x | GP3 & GP4 | HPLC (5-100% ACN) Rt 4.30 mins. LCMS [M+H]^+ 382.20. |
|-----|-----------|--------------------------------------------------|
| D6x | GP3 & GP5 | HPLC (5-100% ACN) Rt 5.22 mins. LCMS [M+H]^+ 429.13. |
| D7x | GP3 & GP4 | HPLC (5-100% ACN) Rt 5.31 mins. LCMS [M+H]^+ 381.24. |
| D8x | GP3 & GP4 | δH/ppm (500 MHz, d6-DMSO): 9.16 (1H, d, J=6.4 Hz), 8.45 (1H, t, J=5.9 Hz), 8.22 (3H, d, J=5.6 Hz), 7.55 (1H, s), 4.42-4.35 (1H, m), 4.24-4.17 (1H, m), 3.99 (1H, m), 3.59 (3H, s), 3.46 (1H, m), 3.42 (1H, m), 3.00 (1H, m), 2.97-2.86 (1H, m), 2.89-2.79 (1H, m), 2.63-2.53 (2H, m), 2.03-1.94 (1H, m), 1.94-1.87 (1H, m), 1.83-1.70 (3H, m), 1.68-1.62 (1H, m), 1.31-1.19 (1H, m), 0.93-0.85 (1H, m). δC/ppm (125 MHz, d6-DMSO): 172.6, 171.6, 167.6, 137.1, 131.8, 52.8, 52.1, 50.0, 46.6, 34.5, 34.0, 31.3, 29.0, 27.7, 21.8, 18.3. νmax/cm⁻¹: 3335, 2925, 1728, 1635, 1562, 1441, 1226. HPLC (5-100% ACN) Rt 5.36 mins. LCMS [M+H]^+ 367.28. |
| D9x | GP3 & GP4 | HPLC (5-100% ACN) Rt 4.60 mins. LCMS [M+H]^+ 367.21. |
| D10x | GP3 & GP4 | HPLC (5-100% ACN) Rt 4.63 mins. LCMS [M+H]^+ 353.19. |
|   |   |   | δ_H/δ_H (500 MHz, d<sub>6</sub>-DMSO) | HPLC (5-100% ACN) Rt 6.37 mins. LCMS [M+H]<sup>+</sup> 354.09. |
|---|---|---|---|---|
| D11 |   | GP3 & GP4 | 99% | HPLC (5-100% ACN) Rt 6.37 mins. LCMS [M+H]<sup>+</sup> 354.09. |
| D12 |   | GP3 & GP4 | 73% | HPLC (5-100% ACN) Rt 6.37 mins. LCMS [M+H]<sup>+</sup> 443.15. |
| D13 |   | GP3 & GP5 | 66% | HPLC (5-100% ACN) Rt 6.37 mins. LCMS [M+H]<sup>+</sup> 443.15. |
| D14 |   | GP3 & GP4 | 37% | HPLC (5-100% ACN) Rt 4.58 mins. LCMS [M+H]<sup>+</sup> 354.24. |
| E1x |   | GP3 & GP4 | 99% | HPLC (5-100% ACN) Rt 4.58 mins. LCMS [M+H]<sup>+</sup> 367.28. |
| E2x |   | GP3 & GP4 | 99% | HPLC (5-100% ACN) Rt 4.58 mins. LCMS [M+H]<sup>+</sup> 367.28. |

**Note:** The table above summarizes the spectroscopic and chromatographic data for different compounds. Each entry includes the compound's chemical structure, spectral data (δ_H/δ_H), and chromatographic retention times. The HPLC conditions for each entry are also specified.
### E3x

| δH/ppm (500 MHz, d6-DMSO): 8.96 (1H, d, J=5.2 Hz), 8.26-8.18 (4H, m), 7.52 (1H, s), 4.31-4.18 (2H, m), 4.09-4.02 (1H, m), 3.89-3.82 (1H, m), 3.60 (3H, s), 3.19-3.06 (1H, m), 3.06-2.94 (1H, m), 2.61 (2H, t, J=7.8 Hz), 2.25-2.09 (2H, m), 1.94-1.82 (4H, m), 1.79-1.58 (4H, m), 1.58-1.48 (2H, m).  
| δC/ppm (125 MHz, d6-DMSO): 172.1, 170.9, 169.0, 136.7, 131.5, 52.2, 52.0, 51.5, 46.8, 37.3, 34.3, 34.2, 28.6, 26.1, 26.1, 24.8, 23.5, 21.5.  
| νmax/cm⁻¹: 3360, 2952, 1636, 1560, 1445, 1221.  
| HPLC (5-100% ACN) Rt 4.39 mins. HRMS (ESI+) m/z found [M+H]^+ 381.2239, C17H29N6O4^+ required 381.2245. | GP3 & GP4  
| 99%  
| 98%  

### E4x

| HPLC (5-100% ACN) Rt 3.90 mins. LCMS [M+H]^+ 382.20. | GP3 & GP4  
| 99%  
| 89%  

### E5x

| HPLC (5-100% ACN) Rt 3.96 mins. | GP3 & GP4  
| 99%  
| 90%  

### E6x

| νmax/cm⁻¹: 3388, 2920, 2851, 1926, 1719, 1672, 1605, 1572, 1541, 1445, 1418, 1345, 1321, 1297, 1263, 1228, 1173, 1145, 1118, 1011. HPLC (5-100% ACN) Rt 4.89 mins. HRMS (ESI+) m/z found [M+H]^+ 415.2104, C20H27N6O4^+ required 415.2094. | GP3 & GP5  
| 44%  
| 93%  

### E7x

| δH/ppm (500 MHz, d6-DMSO): 9.15 (1H, J=5.6 Hz), 8.35-8.26 (4H, m), 7.51 (1H, s), 4.33-4.22 (2H, m), 4.18-4.10 (1H, m), 4.01-3.93 (1H, m), 3.61 (3H, s), 3.38-3.23 (1H, m), 2.79-2.65 (1H, m), 2.64-2.49 (1H, m), 2.37-2.13 (2H, m), 2.06-1.69 (7H, m), 1.63-1.49 (1H, m). δC/ppm (125 MHz, d6-DMSO): 172.7, 171.06, 168.57, 136.9, 131.5, 52.1, 52.1, 50.2, 46.9, 34.5, 34.3, 31.5, 26.2, 25.8, 24.1, 21.6. νmax/cm⁻¹: 3344, 2924, 1728, 1635, 1559, 1443, 1231, 1076. HPLC (5-100% ACN) Rt 4.23 mins. LCMS [M+H]^+ 367.28. | GP3 & GP4  
| 99%  
| 95%  

### E8x

| HPLC (5-100% ACN) Rt 4.23 mins. LCMS [M+H]^+ 353.27. | GP3 & GP4  
| 82%  
| 75%  

86
| E9x  | ![Chemical Structure](image1) | GP3 & GP4  | 99%  | HPLC (5-100% ACN) Rt 4.36 mins. LCMS [M+H]^+ 353.19. |
|------|-------------------------------|------------|------|--------------------------------------------------|
| E10x | ![Chemical Structure](image2) | GP3 & GP4  | 99%  | HPLC (5-100% ACN) Rt 3.86 mins. LCMS [M+H]^+ 339.10. |
| E11x | ![Chemical Structure](image3) | GP3 & GP4  | 99%  | HPLC (5-100% ACN) Rt 3.65 mins. LCMS [M+H]^+ 354.24. |
| E12x | ![Chemical Structure](image4) | GP3 & GP4  | 80%  | HPLC (5-100% ACN) Rt 3.85 mins. LCMS [M+H]^+ 340.08. |
| E13x | ![Chemical Structure](image5) | GP3 & GP5  | 68%  | HPLC (5-100% ACN) Rt 5.37 mins. LCMS [M+H]^+ 429.13. |
| E14x | ![Chemical Structure](image6) | GP3 & GP4  | 99%  | HPLC (5-100% ACN) Rt 4.27 mins. LCMS [M+H]^+ 381.22. |
|   | Structure | GP3 & GP5 | vmax/cm⁻¹: | HRMS (ESI+) m/z found [M+H]⁺ | HPLC (5-100% ACN) Rt | LCMS [M+H]⁺ |
|---|-----------|-----------|------------|-------------------------------|-----------------------|--------------|
| F2x | ![Structure](image1) | GP3 & GP5 | 76%        | 415.2079, C_{20}H_{27}N_{6}O_{4}⁺ | 5.72 mins. | 429.16 |
| F3x | ![Structure](image2) | GP3 & GP% | 68%        |                               | 5.78 mins. | 429.16 |
| F14x | ![Structure](image3) | GP3 & GP5 | 61%        |                               | 5.72 mins. | 429.16 |
# 14. Preparation of B/C/C/P and B/C/C/C/P RuAAC Macroycles

| Compound | Method, Yield (%), Purity (%) | Analysis |
|----------|------------------------------|----------|
| G1x      | GP3 24% 85%                  | HPLC (5-100% ACN) Rt 7.70 mins. LCMS [M+H]^+ 652.54. |
| G2x      | GP3 65% 91%                  | HPLC (5-100% ACN) Rt 7.43 mins. LCMS [M+H]^+ 624.48. |
| G3x      | GP3 29% 88%                  | HPLC (5-100% ACN) Rt 7.71 mins. LCMS [M+H]^+ 638.21. |
| G4x      | GP3 54% 85%                  | HPLC (5-100% ACN) Rt 7.65 mins. LCMS [M+H]^+ 639.41. |
| G5x  | GP3 | 46% | 72% | HPLC (5-45% ACN) Rt 11.57 mins. LCMS [M+H]$^+$ 625.46. |
|---|---|---|---|---|
| G6x | GP3 | 62% | 74% | HPLC (5-100% ACN) Rt 8.51 mins. LCMS [M+H]$^+$ 672.41. |
| G7x | GP3 | 68% | 94% | HPLC (5-100% ACN) Rt 7.41 mins. LCMS [M+H]$^+$ 624.48. |
| G8x | GP3 | 68% | 92% | HPLC (5-100% ACN) Rt 7.32 mins. LCMS [M+H]$^+$ 610.46. |
| G9x | GP3 | 84% | 93% | HPLC (5-45% ACN) Rt 12.24 mins. LCMS [M+H]$^+$ 610.46. |
|   |    |    |   |
|---|---|---|---|
| **G10**<br>x | ![Molecule](image) | **GP3** | 82%<br>91%<br>HPLC (5-45% ACN) *Rt* 12.00 mins. **LCMS** [M+H]$^+$ 596.36. |
| **G11**<br>x | ![Molecule](image) | **GP3** | 54%<br>72%<br>HPLC (15-30% ACN) *Rt* 10.87 mins. **LCMS** [M+H]$^+$ 611.51. |
| **G12**<br>x | ![Molecule](image) | **GP3** | 99%<br>87%<br>HPLC (15-30% ACN) *Rt* 11.45 mins. **LCMS** [M+H]$^+$ 597.41. |
| **G13**<br>x | ![Molecule](image) | **GP3** | 42%<br>90%<br>HPLC (5-100% ACN) *Rt* 8.69 mins. **LCMS** [M+H]$^+$ 686.29. |
| **G14**<br>x | ![Molecule](image) | **GP3** | 26%<br>75%<br>HPLC (5-100% ACN) *Rt* 7.86 mins. **LCMS** [M+H]$^+$ 638.28. |
|   |   |   |   |
|---|---|---|---|
| H1x | ![Chemical Structure](Image1) | GP3 & GP4 | 87% 87% |
|     |   | HPLC (5-100% ACN) Rt 5.19 mins. | LCMS [M+H]^+ 538.30. |
| H2x | ![Chemical Structure](Image2) | GP3 & GP4 | 83% 89% |
|     |   | HPLC (5-100% ACN) Rt 4.92 mins. | LCMS [M+H]^+ 496.16. |
| H3x | ![Chemical Structure](Image3) | GP3 & GP4 | 44% 81% |
|     |   | HPLC (5-100% ACN) Rt 5.08 mins. | LCMS [M+H]^+ 524.36. |
| H4x | ![Chemical Structure](Image4) | GP3 & GP4 | 75% 62% |
|     |   | HPLC (5-100% ACN) Rt 4.90 mins. | LCMS [M+H]^+ 525.18. |
| H5x | ![Chemical Structure](Image5) | GP3 & GP4 | 26% 68% |
|     |   | HPLC (5-100% ACN) Rt 4.69 mins. | LCMS [M+H]^+ 511.31. |
| H  | GP3 & GP5 | GP3 & GP4 | GP3 & GP4 | GP3 & GP4 | GP3 & GP4 |
|----|-------|-------|-------|-------|-------|
| H6x| 61%   | 68%   | 52%   | 88%   | 35%   |
| H7x| 64%   | 96%   | 64%   | 96%   | 66%   |
| H8x| 52%   | 88%   | 52%   | 88%   | 35%   |
| H9x| 65%   | 67%   | 65%   | 67%   | 66%   |
| H10x| 86%   | 66%   | 86%   | 66%   | 69%   |
| H11x| 35%   | 69%   | 35%   | 69%   | 66%   |

**HPLC** (5-100% ACN) *Rt* 5.63 mins. **LCMS** [M+H]^+ 558.18.

**HPLC** (5-100% ACN) *Rt* 5.23 mins. **LCMS** [M+H]^+ 510.26.

**HPLC** (5-100% ACN) *Rt* 4.99 mins. **LCMS** [M+H]^+ 496.23.

**HPLC** (5-100% ACN) *Rt* 4.97 mins. **LCMS** [M+H]^+ 496.08.

**HPLC** (5-100% ACN) *Rt* 4.78 mins. **LCMS** [M+H]^+ 482.14.

**HPLC** (5-100% ACN) *Rt* 4.89 mins. **LCMS** [M+H]^+ 497.21.
| H12     | ![Molecule 1](image1.png) | GP3 & GP4 | 57%  | 78%  | HPLC (5-100% ACN) *Rt* 4.59 mins. **LCMS [M+H]^+** 483.19. |
|---------|--------------------------|-----------|------|------|---------------------------------------------------|
| H14     | ![Molecule 2](image2.png) | GP3 & GP4 | 86%  | 77%  | HPLC (5-30% ACN) *Rt* 7.46 mins. **LCMS [M+H]^+** 524.28. |
| J13     | ![Molecule 3](image3.png) | GP3 & GP5 | 45%  | 88%  | HPLC (5-100% ACN) *Rt* 5.36 mins. **LCMS [M+H]^+** 500.28. |
| K3x     | ![Molecule 4](image4.png) | GP3 & GP4 | 48%  | 83%  | HPLC (5-100% ACN) *Rt* 6.89 mins. **LCMS [M+H]^+** 613.32. |
| K8x     | ![Molecule 5](image5.png) | GP3 & GP4 | 46%  | 80%  | HPLC (5-100% ACN) *Rt* 6.85 mins. **LCMS [M+H]^+** 585.33. |
| L7x     | ![Molecule 6](image6.png) | GP3       | 43%  | 92%  | HPLC (5-100% ACN) *Rt* 10.17 mins. **LCMS [M+H]^+** 846.59. |
| Compound | Structure | Isolation Yield | HPLC Conditions | LCMS Data |
|----------|-----------|-----------------|-----------------|-----------|
| L9x      | ![L9x Structure](image) | GP3 43% 89%     | HPLC (5-100% ACN) Rt 10.17 mins. | LCMS [M+H]^+ 833.56. |
| M13x     | ![M13x Structure](image) | GP3 & GP5 21% 80% | HPLC (5-100% ACN) Rt 6.65 mins. | LCMS [M+H]^+ 647.36. |
| N8x      | ![N8x Structure](image) | GP3 15% 93%     | HPLC (5-100% ACN) Rt 8.40 mins. | LCMS [M+H]^+ 832.64. |
### 15. Preparation of B/C/P DKPs

| Compound | Method, Yield (%) | Analysis |
|----------|-------------------|----------|
| A1y      | GP6 85% 90%       | HPLC (5-80% ACN) Rt 7.56 mins. LCMS [M+H]⁺ 524.26. |
| A1z      | GP6 84% 90%       | HPLC (5-80% ACN) Rt 7.43 mins. LCMS [M+H]⁺ 524.26. |
| A2y      | GP6 90% 86%       | HPLC (5-45% ACN) Rt 9.48 mins. LCMS [M+H]⁺ 496.23. |
| A2z      | GP6 17% 61%       | HPLC (5-45% ACN) Rt 9.81 mins. LCMS [M+H]⁺ 496.23. |
|   | Structure | Compound | HPLC Conditions | LCMS Peak |  |
|---|-----------|----------|-----------------|--------|---|
| A3y | ![Structure](image_url) | GP6 | (5-100% ACN) Rt 6.75 mins | [M+H]$^+$ 510.41 |  |
| A3z | ![Structure](image_url) | GP6 | (5-100% ACN) Rt 6.53 mins | [M+H]$^+$ 510.26 |  |
| A4z | ![Structure](image_url) | GP6 | (5-45% ACN) Rt 10.07 mins | [M+H]$^+$ 511.23 |  |
| A5z | ![Structure](image_url) | GP6 | (5-45% ACN) Rt 9.51 mins | [M+H]$^+$ 497.21 |  |
| A6z | ![Structure](image_url) | GP6 | (5-100% ACN) Rt 7.47 mins | [M+H]$^+$ 544.15 |  |
| Compound | Purity | LC Conditions | Retention Time | MS Data |
|----------|--------|---------------|----------------|---------|
| A7y      | 42%    | HPLC (5-45% ACN) | 9.99 mins. | [M+H]^+ 496.08. |
| A7z      | 34%    | HPLC (5-45% ACN) | 9.90 mins. | [M+H]^+ 496.23. |
| A8z      | 98%    | HPLC (5-45% ACN) | 9.61 mins. | [M+H]^+ 482.21. |
| A9y      | 44%    | HPLC (5-100% ACN) | 6.71 mins. | [M+H]^+ 482.14. |
| A9z      | 69%    | HPLC (5-100% ACN) | 6.48 mins. | [M+H]^+ 482.14. |
|   |   |   |   |   |   |
|---|---|---|---|---|---|
| A10 | z |   | GP6 | 23% | HPLC (5-100% ACN) Rt 6.43 mins. LCMS [M+H]^+ 468.11. |
| A11 | z |   | GP6 | 33% | HPLC (5-100% ACN) Rt 6.08 mins. LCMS [M+H]^+ 483.11. |
| A12 | y |   | GP6 | 58% | HPLC (5-100% ACN) Rt 6.27 mins. LCMS [M+H]^+ 469.09. |
| A12 | z |   | GP6 | 60% | HPLC (5-100% ACN) Rt 6.34 mins. LCMS [M+H]^+ 469.16. |
| A13 | z |   | GP6 | 48% | HPLC (5-100% ACN) Rt 7.27 mins. LCMS [M+H]^+ 558.18. |
| Compound | Structure | GP6 | LCMS [M+H]$^+$ | HPLC (5-45% ACN) Ret mins. |
|----------|-----------|-----|----------------|-----------------------------|
| B1y      | ![Structure](image1) | 89% | 482.21         | 9.92                         |
| B1z      | ![Structure](image2) | 92% | 482.21         | 9.36                         |
| B2y      | ![Structure](image3) | 73% | 454.2203       | 5.99                         |
| B2z      | ![Structure](image4) | 88% | 454.2202       | 6.22                         |

### B1y

- **$R_f = 0.18$ (15% MeOH/ 85% CH$_2$Cl$_2$). $\delta_\nu/\nu$ (500 Hz, $d_6$-DMSO, 120 °C):**
  - 7.60-7.55 (2H, m, triazole CH and NH), 7.49 (1H, s, NH), 7.27-7.06 (7H, m, 5 × ArCH and 2 × NH), 5.45 (1H, dd, $J$=8.4, 6.6 Hz, H$_6$), 3.99 (1H, s, H$_4$), 3.91-3.83 (1H, m, H$_5$), 3.74 (1H, s, H$_2$), 3.44 (1H, dd, $J$=14.1, 6.6 Hz, H$_5$), 3.33 (2H, dd, $J$=14.1, 8.4 Hz, H$_5$), 3.16-3.05 (1H, m, H$_2$), 2.98-2.88 (2H, m, H$_2$ and COCH$_2$CH$_2$), COCH$_2$CH$_2$ below H$_2$O signal, 2.44-2.40 (2H, m, COCH$_2$CH$_2$), 1.66-1.54 (1H, m, H$_p$), 1.35-1.24 (3H, m, H$_3$ and H$_4$).

- **$\delta_\alpha/\alpha$ (125 MHz, $d_6$-DMSO):** 171.1 (C=OCH$_2$CH$_2$), 167.4 (C$_a$-C=O), 167.2 (C$_b$-C=O or C$_c$-C=O), 164.7 (C$_d$-C=O or C$_f$-C=O), 149.4 (triazole C), 136.4 (ArC), 128.9 (ArCH), 128.2 (ArCH), 126.7 (ArCH), 121.8 (triazole CH), 63.6 (C$_a$), 54.0 (C$_a$), 53.7 (C$_b$), 40.3 (C$_c$), 38.6 (C$_f$), 37.8 (C$_d$), 33.9 (COCH$_2$CH$_2$), 30.2 (C$_p$), 25.2 (C$_y$), 21.3 (COCH$_2$CH$_2$). $\nu_{max}$/cm$^{-1}$: 3263 (m, N-H), 2926 (m, C-H str), 1661 (s, C=O str), 1550 (m, C-C). HPLC (5-100% ACN) Ret 5.99 mins. HRMS (ESI+) m/z found [M+H]$^+$ 454.2220, C$_{22}$H$_{20}$N$_2$O$_4$ required 454.2203 (Δ 3.7 ppm). [α]$_{D}^{25}$ = +15.0 (c 0.21, MeOH).

### B1z

- **$R_f = 0.18$ (15% MeOH/ 85% CH$_2$Cl$_2$). $\delta_\nu/\nu$ (500 Hz, $d_6$-DMSO, 120 °C):**
  - 7.60-7.55 (2H, m, triazole CH and NH), 7.49 (1H, s, NH), 7.27-7.06 (7H, m, 5 × ArCH and 2 × NH), 5.45 (1H, dd, $J$=8.4, 6.6 Hz, H$_6$), 3.99 (1H, s, H$_4$), 3.91-3.83 (1H, m, H$_5$), 3.74 (1H, s, H$_2$), 3.44 (1H, dd, $J$=14.1, 6.6 Hz, H$_5$), 3.33 (2H, dd, $J$=14.1, 8.4 Hz, H$_5$), 3.16-3.05 (1H, m, H$_2$), 2.98-2.88 (2H, m, H$_2$ and COCH$_2$CH$_2$), COCH$_2$CH$_2$ below H$_2$O signal, 2.44-2.40 (2H, m, COCH$_2$CH$_2$), 1.66-1.54 (1H, m, H$_p$), 1.35-1.24 (3H, m, H$_3$ and H$_4$).

- **$\delta_\alpha/\alpha$ (125 MHz, $d_6$-DMSO):** 171.1 (C=OCH$_2$CH$_2$), 167.4 (C$_a$-C=O), 167.2 (C$_b$-C=O or C$_c$-C=O), 164.7 (C$_d$-C=O or C$_f$-C=O), 149.4 (triazole C), 136.4 (ArC), 128.9 (ArCH), 128.2 (ArCH), 126.7 (ArCH), 121.8 (triazole CH), 63.6 (C$_a$), 54.0 (C$_a$), 53.7 (C$_b$), 40.3 (C$_c$), 38.6 (C$_f$), 37.8 (C$_d$), 33.9 (COCH$_2$CH$_2$), 30.2 (C$_p$), 25.2 (C$_y$), 21.3 (COCH$_2$CH$_2$). $\nu_{max}$/cm$^{-1}$: 3263 (m, N-H), 2926 (m, C-H str), 1661 (s, C=O str), 1550 (m, C-C). HPLC (5-100% ACN) Ret 5.99 mins. HRMS (ESI+) m/z found [M+H]$^+$ 454.2220, C$_{22}$H$_{20}$N$_2$O$_4$ required 454.2203 (Δ 3.7 ppm). [α]$_{D}^{25}$ = +15.0 (c 0.21, MeOH).

### B2y

- **$R_f = 0.11$ (15% MeOH/ 85% CH$_2$Cl$_2$). $\delta_\nu/\nu$ (500 Hz, $d_6$-DMSO, 90 °C):**
  - 7.79 (1H, s, C$_b$-N), 7.74 (1H, s, NH), 7.60-7.51 (2H, m, 2 × NH), 7.41 (1H, s, triazole CH), 7.25-7.11 (3H, m, 3 × ArCH), 6.97 (2H, dd, $J$=7.3, 1.6 Hz, 2 × ArCH), 5.32 (1H, dd, $J$=9.9, 5.0 Hz, H$_2$), 4.12-4.03 (1H, m, H$_4$), 3.77 (1H, t, $J$=4.5 Hz, H$_5$), 3.74-3.67 (1H, m, H$_5$), 3.66-3.58 (1H, m, H$_5$), 3.49 (1H, dd, $J$=13.9, 5.0 Hz, H$_4$), 3.32 (1H, dd, $J$=13.9, 9.9 Hz, H$_3$), 3.04 (2H, m, H$_4$) below H$_2$O signal, COCH$_2$CH$_2$ below H$_2$O signal, 2.39-2.21 (3H, m, COCH$_2$CH$_2$, COCH$_2$CH$_2$), 1.71-1.57 (2H, m, H$_p$), 1.41-1.23 (2H, m, H$_y$). $\delta_\nu/\nu$ (125 MHz, $d_6$-DMSO): 170.9 (C=OCH$_2$CH$_2$), 167.6 (C$_d$-C=O), 167.5 (C$_c$-C=O or C$_f$-C=O), 164.9 (C$_a$-C=O or C$_g$-C=O), 137.7 (triazole C), 136.7 (ArC), 131.0 (triazole CH), 129.1 (ArCH), 128.2 (ArCH), 126.7 (ArCH), 61.3 (C$_a$), 54.3 (C$_a$), 53.9 (C$_a$), 40.5 (C$_b$), 38.4 (C$_d$), 37.9 (C$_f$), 34.2 (COCH$_2$CH$_2$), 30.3 (C$_p$), 24.9 (C$_y$), 19.1 (COCH$_2$CH$_2$). $\nu_{max}$/cm$^{-1}$: 3242 (m, N-H), 2921 (m, C-H), 1661 (s, C=O), 1545 (m, C=C). HPLC (5-100% ACN) Ret 6.22 mins. HRMS (ESI+) m/z found [M+H]$^+$ 454.2202, C$_{22}$H$_{22}$N$_2$O$_4$ required 454.2203 (Δ -0.2 ppm). [α]$_{D}^{25}$ = -7.5 (c 0.32, MeOH).
B3y

\[
\text{HPLC (5-45% ACN) Rt 9.17 mins. LCMS [M+H]^+ 468.13.}
\]

B3z

\[
\text{HPLC (5-45% ACN) Rt 9.07 mins. LCMS [M+H]^+ 468.11.}
\]

B4y

\[
\text{HPLC (5-45% ACN) Rt 5.83 mins. LCMS [M+H]^+ 469.16.}
\]

B4z

\[
\text{HPLC (5-100% ACN) Rt 6.19 mins. LCMS [M+H]^+ 469.24.}
\]

B5y

\[
\text{Mp = 245-249 °C (CH}_2\text{Cl}_2). \delta_H/\text{ppm (500 MHz, }\text{d}_6\text{-DMSO): 8.10 (1H, app. s, C}_\text{α}-\text{NH)}, 8.04 (1H, app. s, C}_\text{α}'-\text{NH), 7.91 (1H, app. s, C}_\beta'-\text{NH), 7.60 (1H, s, triazole CH), 7.28-7.05 (5H, m, 5 × ArCH), 6.37 (1H, t, J=6.6 Hz, NHCH}_2), 6.04 (1H, t, J=6.2 Hz, C}_\beta-\text{NH}, 5.54 (1H, t, J=6.8 Hz, H}_2\text{), 4.20 (1H, dd, J=15.9, 7.0 Hz, NHCH}_2), 4.11-4.04 (1H, m, NHCH}_2), 4.04-3.93 (2H, m, H}_β and H}_β'), 3.72 (1H, app. s, H}_β), 3.47-3.37 (2H, m, H}_β and H}_β'), 2.99-2.88 (2H, m, H}_β and H}_β'), 1.77-1.67 (1H, m, H}_β'), 1.48-1.29 (3H, m, H}_γ and H}_γ'). \delta_C/\text{ppm (125 MHz, }\text{d}_6\text{-DMSO): 167.6 (C}_\text{α}-\text{C}=O or C}_\text{α}'-\text{C}=O), 167.1 (C}_\text{α}-\text{C}=O), 164.7 (C}_\text{α}'-\text{C}=O or C}_\text{α}'-\text{C}=O), 158.5 (NHCH}_2=\text{ONH), 146.9 (C}_\beta'-\text{C}=O, 138.7 (C}_\text{α}-\text{C}=O or C}_\text{α}'-\text{C}=O), 136.4 (C}_\text{α}'-\text{C}=O or C}_\text{α}'-\text{C}=O), 129.0 (C}_\beta'-\text{C}=O or C}_\text{α}'-\text{C}=O), 126.7 (ArCH), 122.1 (triazole CH), 63.4 (C}_\text{γ}, 54.4 (C}_\text{γ}), 53.8 (C}_\text{γ}), C}_\beta below DMSO signal, 38.6 (C}_\text{γ}), 36.8 (C}_\text{γ}), 35.5 (NHCH}_2), 29.1 (C}_\text{β}), 27.2 (C}_\text{γ}). \nu_{max}/\text{cm}^{-1}: 3281 (NH str), 2921 (CH str), 1670 (C=O str), 1548, 1544, 1119, 1051. HPLC (5-100% ACN) Rt 5.83 mins. HRMS (ESI+) m/z found [M+H]^+ 455.2159, C_{21}H_{22}N_{8}O_{4}^+ required 455.2155. [\alpha]_D^{25} = +4.0 (c 0.15, MeOH).}
| Compound | Structure | Purity | LCMS M/z | HPLC Conditions |
|----------|-----------|--------|---------|----------------|
| B7z      | ![B7z Structure](image) | 49% | 454.09 (+) | ACN (5-100%) Rt 6.38 mins. |
|          |           | 62% |         |                 |
| B8y      | ![B8y Structure](image) | 62% | 440.2045 (+) | ACN (5-90%) Rt 6.20 mins. |
|          |           | 90% |         |                 |
| B8z      | ![B8z Structure](image) | 91% | 440.12 (+) | ACN (5-100%) Rt 6.20 mins. |
|          |           | 64% |         |                 |
| B10y     | ![B10y Structure](image) | 24% | 469.16 (+) | ACN (5-45%) Rt 5.83 mins. |
### B10 z

| Rf  | δH ppm (400 Hz, d6-DMSO): 8.17 (1H, s, NH-CH-CH2-NH), 7.85 (1H, d, J=10.5 Hz, NH'-CH'-CH2-NH'), 7.76 (1H, d, J=9.4 Hz, NH-CH-CH2-NH), 7.65 (1H, s, NH-CH-CH2-NH'), 7.51 (1H, s, triazole CH), 7.31-7.00 (5H, m, 5 × ArCH), 5.35 (1H, t, J=7.5 Hz, Hα), 4.18 (1H, ddd, J=12.5, 9.4, 1.6 Hz, NH-CH-CH2-NH), 4.07 (1H, app s, NH-CH-CH2-NH'), 3.92-3.82 (2H, m, NH'-CH'-CH2-NH' and NH'-CH-CH2-NH'), 3.77 (1H, dd, J=13.9, 7.4 Hz, Hβ), 3.47-3.38 (1H, m, Hγ), 3.18-3.10 (1H, m, NH'-CH-CH2-NH), 2.85 (1H, ddd, J=17.6, 7.6, 3.5 Hz, COCH2CH2), 2.69 (1H, dd, J=12.5, 2.8 Hz, NH-CH-CH2-NH), COCH2CH2 below H2O signal, 2.37-2.24 (1H, m, COCH2CH2), 2.03-1.92 (1H, m, COCH2CH2), δc ppm (125 MHz, d6-DMSO): 171.7 (C=O), 167.8 (C=O), 165.8 (C=O), 164.4 (C=O), 136.6 (ArC), 135.6 (triazole C), 133.0 (triazole CH), 129.2 (ArCH), 128.3 (ArCH), 126.8 (ArCH), 61.8 (Cβ), 54.9 (CH), 54.0 (CH'), CH2 and CH2 below DMSO signal 36.2 (Cβ), 34.8 (COCH2CH2), 20.6 (COCH2CH2). v_max /cm⁻¹: 3233 (w, N-H), 2923 (m, C-H), 1661 (s, C=O), 1550 (m, C-C). HPLC (5-100% ACN) Rt 6.20 mins. HRMS (ESI+) m/z found [M+H]+' 426.1890, C20H20N2O4+ required 426.1890 (Δ 0.0 ppm). [α]D²⁵ = +14.0 (c 0.23, MeOH). |
| GP6 | 74% |

### B12 z

| Rf  | δH ppm (500 Hz, d6-DMSO): 8.02 (1H, s, C6-NH), 7.92 (1H, s, C5-NH), 7.37 (1H, d, J=5.4 Hz, triazole CH), 7.23-7.09 (3H, m, 3 × ArCH), 6.98 (1H, t, J=6.0 Hz, NHCH2), 6.94 (2H, dd, J=7.7, 1.5 Hz, 2 × ArCH), 6.89 (1H, t, J=5.3 Hz, C6-NH), 5.84 (1H, t, J=6.1 Hz, C5-NH), 5.44 (1H, dd, J=10.6, 4.8 Hz, Hα), 4.05 (1H, app s, Hβ), 3.98 (1H, dd, J=15.8, 5.4 Hz, NHCH2), 3.84-3.80 (1H, m, Hγ), 3.61 (1H, ddd, J=13.4, 5.5, 2.5 Hz, Hβ), 3.46 (1H, dd, J=13.6, 4.8 Hz, Hγ), 3.43-3.36 (2H, m, NHCH2 and Hβ), 2.98 below H2O signal, 2.37-2.22 (1H, m, Hγ). |
| GP6 | 57% |

### B14 y

| Rf  | δH ppm (500 Hz, d6-DMSO, 120 °C): 7.66-7.55 (2H, m, triazole CH and C9-NH), 7.44 (1H, s, NH), 7.34 (1H, s, C8-NH), 7.18 (5H, m, 5 × ArCH), 7.04 (1H, s, NH), 5.50 (1H, dd, J=8.7, 6.4 Hz, Hα), 3.95 (1H, app s, Hβ), 3.83-3.73 (2H, m, Hβ and Hγ), 3.45 (1H, dd, J=14.2, 6.4 Hz, Hα), 3.38-3.26 (2H, m, Hγ and Hβ), 3.15-3.06 (1H, m, Hγ), 3.06-2.97 (1H, m, Hβ), 2.97-2.85 (2H, m, COCH2CH2), 2.47-2.35 (2H, m, COCH2CH2), 1.69-1.61 (2H, m, Hγ), 1.38-1.29 (2H, m, Hβ), 1.18-1.09 (2H, m, Hγ). δc ppm (125 MHz, d6-DMSO): 170.9 (C=O=CH=CH2), 167.8 (C6-C=O or C6-C=O), 165.5 (C5-C=O or C5-C=O), 145.3 (triazole C), 136.3 (ArC), 129.0 (ArCH), 128.2 (ArCH), 126.7 (ArCH), 121.6 (triazole CH), 63.7 (Cβ), 54.5 (Cα), 53.3 (Cγ), 41.0 (Cφ), Cβ below DMSO signal, 36.9 (Cα), 34.4 (COCH2CH2), 33.4 (Cφ), 27.5 (Cβ), 21.2 (COCH2CH2), 19.0 (Cγ). v_max /cm⁻¹: 3252 (m, N-H), 2925 (m, C-H), 1662 (s, C=O), 1543 (m, C-C). HPLC (5-100% ACN) Rt 6.06 mins. HRMS (ESI+) m/z found [M+H]+' 468.2356, C23H20N2O4+ required 468.2354 (Δ 0.4 ppm). [α]D²⁵ = +0.8 (c 0.55, MeOH). |
| GP6 | 55% |

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**B14**

\[
\text{R} = 0.1 \text{ (10\% MeOH/ 90\% CH}_2\text{Cl}_2) , \text{Mp = 176-178 °C (CH}_2\text{Cl}_2) \]

\[
\delta_\text{H}/\text{ppm} (400 \text{ MHz, d}_6\text{-DMSO}): 8.47 (1\text{H, dd, } J=6.4, 5.1 \text{ Hz, C}_\text{R-NH}), 8.08 (1\text{H, d, } J=2.4 \text{ Hz, C}_\text{R-NH}), 7.96 (1\text{H, dd, } J=6.9, 5.2 \text{ Hz, C}_\text{R-NH}), 7.90 (1\text{H, d, } J=1.8 \text{ Hz, C}_\text{N-NH}), 7.46 (1\text{H, s, triazole CH}), 7.29-7.08 (5\text{H, m, } 5 \times \text{ArCH}), \\
5.60 (1\text{H, dd, } J=10.5 \text{ Hz and } 4.7 \text{ Hz, H}_\text{α}), 4.15-4.04 (1\text{H, m, H}_\text{ε}), 3.84-3.73 (1\text{H, m, H}_\text{α}), 3.67-3.53 (2\text{H, m, H}_\text{ε}), 3.53-3.35 (1\text{H, m, H}_\text{α}), \\
2.96-2.84 (1\text{H, m, H}_\text{ε}), 2.84-2.64 (1\text{H, m, COCH}_2\text{CH}_2), 3.69-3.51 (2\text{H, m, H}_\text{α}), 1.81-1.56 (2\text{H, m, H}_\text{ε}), \\
1.52-1.39 (1\text{H, m, H}_\text{α}), 1.39-1.16 (3\text{H, m, H}_\text{δ} \text{ and H}_\text{γ}), \delta_\text{C}/\text{ppm} (125 \text{ MHz, d}_6\text{-DMSO}): 171.4 (C=OCH}_2\text{CH}_2), 167.9 (C=O or C=O), 167.5 (C=O), 166.2 (C=O or C=O), 138.2 (triazole C), 137.3 (ArC), 131.0 (triazole CH), 128.7 (ArCH), 128.2 (ArCH), 126.5 (ArCH), 61.6 (C=O), 54.4 (C=O), 52.7 (Cα), 41.7 (Cβ), 36.1 (Cγ), 35.7 (Cδ), 32.8 (COCH}_2\text{CH}_2), 31.7 (Cγ), 28.4 (Cδ), 19.4 (Cε), 18.7 (COCH}_2\text{CH}_2). \nu_{\text{max}}/\text{cm}^{-1}: 3239 (w, N-H), 2924 (m, C-H), 1650 (s, C=O str), 1544 (s, C=C). \text{HPLC (5-100\% ACN)} \text{ Rt 6.35 mins. HRMS (ESI+) m/z found } [\text{M+H}]^+ 468.2376, \text{C}_{23}\text{H}_{30}\text{N}_7\text{O}_4^+ \text{ required 468.2359 (Δ 2.3 ppm). } \left[\alpha\right]_{\text{D}}^{25} = -10.0 (c 0.235, \text{MeOH}).

**D1z**

\[
\text{HPLC (5-25\% ACN)} \text{ Rt 5.10 mins. LCMS [M+H]^+ 377.27.}
\]

**D2y**

\[
\text{HPLC (5-45\% ACN)} \text{ Rt 3.36 mins. LCMS [M+H]^+ 349.13.}
\]

**D3y**

\[
\text{HPLC (5-45\% ACN)} \text{ Rt 4.45 mins. LCMS [M+H]^+ 363.31.}
\]

**D7z**

\[
\text{HPLC (5-45\% ACN)} \text{ Rt 4.00 mins. LCMS [M+H]^+ 349.14.}
\]
| D8y  | ![Chemical Structure](attachment:image1) | GP6 | 41% | 74% | **HPLC** (5-45% ACN) *Rt* 3.36 mins. **LCMS** [M+H]^+ 335.10. |
|------|--------------------------------------|-----|-----|-----|---------------------------------------------------------------|
| D8z  | ![Chemical Structure](attachment:image2) | GP6 | 33% | 72% | **HPLC** (5-100% ACN) *Rt* 3.39 mins. **LCMS** [M+H]^+ 335.13. |
| D9z  | ![Chemical Structure](attachment:image3) | GP6 | 21% | 75% | **HPLC** (5-100% ACN) *Rt* 3.54 mins. **LCMS** [M+H]^+ 335.13. |
| D11y | ![Chemical Structure](attachment:image4) | GP6 | 32% | 66% | **HPLC** (5-100% ACN) *Rt* 2.99 mins. **LCMS** [M+H]^+ 336.10. |
| D13z | ![Chemical Structure](attachment:image5) | GP6 | 9%  | 78% | **HPLC** (5-100% ACN) *Rt* 5.30 mins. **LCMS** [M+H]^+ 411.13. |
| D14y | ![Chemical Structure](attachment:image6) | GP6 | 87% | 90% | \(\nu_{\text{max}}/\text{cm}^{-1}: 3228, 2924, 2859, 1653, 1549, 1452, 1333, 1270, 1055.\) **HPLC** (5-80% ACN) *Rt* 3.84 mins. **HRMS** (ESI+) *m/z* found [M+H]^+ 363.2140, \(\text{C}_{17}\text{H}_{27}\text{N}_{6}\text{O}_3\) required 363.2145. |
| Code | Structure | δH/δC ppm (500 MHz, d$_6$-DMSO and 125 MHz, d$_6$-DMSO), νmax/cm$^{-1}$, HPLC, LCMS | Notes |
|------|-----------|---------------------------------------------------------------------------------|-------|
| D14z | ![Structure](attachment:structure14z.png) | δH: 8.01 (1H, d, J=1.8 Hz), 7.97 (1H, s), 7.87 (1H, t, J=5.6 Hz), 7.52 (1H, s), 4.30 (2H, t, J=6.4 Hz), 3.94-3.90 (1H, m), 3.88-3.83 (1H, m), 3.19-3.01 (2H, m), 2.91-2.80 (2H, m), 2.40-2.33 (2H, m), 1.87-1.71 (4H, m), 1.68-1.58 (1H, m), 1.57-1.47 (1H, m), 1.44-0.98 (6H, m). δC: 170.8, 167.3, 167.2, 136.7, 131.5, 53.9, 53.9, 46.6, 38.4, 34.7, 32.3, 31.6, 30.1, 28.4, 20.8, 20.3, 19.9. | HPLC (5-80% ACN) Rt 3.66 mins. HRMS (ESI+) m/z found [M+Na$^+$] 385.1966, C$_{17}$H$_{26}$N$_6$O$_3$Na$^+$ required 385.1964. |
| E1y  | ![Structure](attachment:structure1y.png) | GP6 | HPLC (5-45% ACN) Rt 4.06 mins. LCMS [M+H]$^+$ 363.23. | |
| E1z  | ![Structure](attachment:structure1z.png) | GP6 | 90% | HPLC (5-45% ACN) Rt 4.12 mins. LCMS [M+H]$^+$ 363.16. | |
| E3z  | ![Structure](attachment:structure3z.png) | GP6 | 32% | HPLC (5-45% ACN) Rt 3.60 mins. LCMS [M+H]$^+$ 349.14. | |
| E6z  | ![Structure](attachment:structure6z.png) | GP6 | 16% | HPLC (5-100% ACN) Rt 4.59 mins. LCMS [M+H]$^+$ 383.10. | |
| E7z  | ![Structure](attachment:structure7z.png) | GP6 | 30% | HPLC (5-45% ACN) Rt 3.36 mins. LCMS [M+H]$^+$ 335.13. | |
| E8z | ![Chemical Structure] | GP6 | 34% | 84% | **HPLC** (5-45% ACN) *Rt* 2.65 mins. **LCMS** [M+H]^+ 321.12. |
| E9z | ![Chemical Structure] | GP6 | 36% | 86% | **HPLC** (5-45% ACN) *Rt* 3.16 mins. **LCMS** [M+H]^+ 321.12. |
| E11z | ![Chemical Structure] | GP6 | 22% | 74% | **HPLC** (5-100% ACN) *Rt* 2.82 mins. **LCMS** [M+H]^+ 322.17. |
| E13z | ![Chemical Structure] | GP6 | 42% | 87% | **HPLC** (5-100% ACN) *Rt* 5.06 mins. **LCMS** [M+H]^+ 397.12. |
| E14z | ![Chemical Structure] | GP6 | 23% | 90% | **HPLC** (5-45% ACN) *Rt* 3.43 mins. **LCMS** [M+H]^+ 349.14. |
### 16. Preparation of B/C/C/P and B/C/C/C/P DKPs

| Compound | Method, Yield (%), Purity (%) | Analysis |
|----------|------------------------------|----------|
| H2z      | GP6 72%, 73%                 | HPLC (5-45% ACN) Rt 5.19 mins. LCMS [M+H]^+ 478.09. |
| H3z      | GP6 44%, 71%                 | HPLC (5-45% ACN) Rt 5.78 mins. LCMS [M+H]^+ 492.11. |
| H14z     | GP6 57%, 89%                 | HPLC (5-45% ACN) Rt 5.49 mins. LCMS [M+H]^+ 492.26. |
17. Chemoinformatic analysis

Principal component analysis

Principal component analysis (PCA) was carried out using the Molecular Operating Environment (MOE) software package. A total of 15 physicochemical properties (Table S1) were obtained for 222 macrocyclic DOS library members and established reference sets of 40 top-selling brand-name drugs, 60 diverse natural products and 24 macrocyclic natural products.

The summary of the PCA is shown in Table S2. The first three principal components account for 87.3% of the variance in the dataset and were used to generate Figures 3a-c in the manuscript.

Table S1. Physicochemical properties used in PCA

| Parameter | Description                     |
|-----------|---------------------------------|
| a_acc     | number of H-bond acceptor atoms |
| a_aro     | number of aromatic atoms        |
| a_don     | number of H-bond donor atoms    |
| a_nN      | number of nitrogen atoms        |
| a_nO      | number of oxygen atoms          |
| b_rotN    | number of rotatable bonds       |
| chiral    | number of chiral centers        |
| KierFlex  | molecular flexibility           |
| logP(o/w) | log octanol/water partition coefficient |
| log S     | log solubility in water         |
| mr        | molar refractivity               |
| rings     | number of rings                  |
| SlogP     | log octanol/water partition coefficient |
| TPSA      | topological polar surface area  |
| Weight    | molecular weight                |
**Table S2.** Standard deviation and contribution of each principal component to variance

| PC1 | PC2 | PC3 | PC4 | PC5 | PC6 | PC7 | PC8 | PC9 | PC10 |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
| 2.77 | 1.89 | 1.34 | 0.95 | 0.63 | 0.43 | 0.36 | 0.32 | 0.24 | 0.18 |
| 5   | 5   | 2   | 0   | 8   | 1   | 3   | 0   | 2   | 9    |
| 0.51 | 0.64 | 0.12 | 0.06 | 0.02 | 0.01 | 0.00 | 0.00 | 0.00 | 0.00 |
| 4   | 0   | 0   | 0   | 7   | 2   | 9   | 7   | 4   | 2    |
| 0.51 | 0.75 | 0.87 | 0.93 | 0.96 | 0.97 | 0.98 | 0.98 | 0.99 | 0.99 |
| 4   | 3   | 3   | 3   | 0   | 3   | 2   | 8   | 2   | 5    |

**Table S3.** Component loadings for PCA of macrocycle library with established reference sets

| Parameter | PC1     | PC2       | PC3       |
|-----------|---------|-----------|-----------|
| a_acc     | 0.038066| 0.017781  | -0.016773 |
| a_aro     | 0.004001| 0.005698  | 0.097251  |
| a_don     | 0.041175| 0.051005  | -0.009315 |
| a_nN      | 0.011825| 0.073803  | 0.072352  |
| a_nO      | 0.033946| -0.003718 | -0.041977 |
| b_rotN    | 0.018641| -0.011356 | -0.017137 |
| chiral    | 0.025172| -0.019564 | -0.043522 |
| KierFlex  | 0.027100| -0.003892 | -0.030649 |
| logP(o/w) | 0.003847| -0.106012 | 0.004302  |
| log S     | -0.038518| 0.084259  | -0.073837 |
| mr        | 0.026018| -0.005560 | 0.015126  |
| rings     | 0.045324| -0.046568 | 0.262761  |
| SlogP     | 0.000576| -0.122025 | 0.037147  |
| TPSA      | 0.001592| 0.001856  | -0.000087 |
| Weight    | 0.000677| -0.000057 | 0.000261  |
PCA Data:

| DRUGS     | PC1       | PC2       | PC3       |
|-----------|-----------|-----------|-----------|
| Lipitor   | 0.44035336| -2.0922842| 2.1781542 |
| Nexium    | -0.56550181| -0.68104434| 1.0659434 |
| Prevacid  | -0.59435779| -0.92088705| 1.1955206 |
| Flonase   | -0.14596421| -2.0885949 | -0.57547647|
| Serevent  | -0.061018318| -1.4764915 | 0.034017656|
| Singulair | 0.29012862| -3.1157372 | 2.7073617 |
| Effexor   | -1.0479238| -1.1570442 | -0.28889498|
| Plavix    | -0.98261434| -1.5518504 | 0.69276941 |
| Zocor     | -0.36533195| -1.9022555 | -0.87527949|
| Norvasc   | -0.36513421| -0.94790769| -0.38823062|
| Lexapro   | -0.90844232| -1.1583214 | 0.9173618 |
| Seroquel  | -0.61090952| -1.1148515 | 1.1556581 |
| Protonix  | -0.40576226| -0.6302695 | 0.93926328 |
| Ambien    | -1.0581216| -1.1308053 | 0.90474354 |
| Actos     | -0.61026462| -1.2560296 | 0.73286134 |
| Zoloft    | -1.0674506| -1.9562593 | 1.008045 |
| Wellbutrin| -1.2362236| -1.2577442 | -0.39570323|
| Avandia   | -0.62388283| -0.96976894| 0.7288534 |
| Risperdal | -0.63164562| -1.2829981 | 1.3195344 |
| Zyprexa   | -1.0861667| -1.034258 | 0.81028336 |
| Topamax   | -0.4540301| -0.46410626| -1.1624413|
| Toprol    | -0.87203783| -0.68965971| -0.87318957|
| Zetia     | -0.44707555| -1.8197278 | 1.6259458 |
| Fosamax   | -0.56960052| 1.4469109 | -2.4331801 |
| Name         | PC1     | PC2     | PC3     |
|--------------|---------|---------|---------|
| Abilify      | -0.48024434 | -1.6537925 | 1.2831823 |
| Levaquin     | -0.68553865 | -0.47166136 | 0.31969854 |
| Lamictal     | -1.0722635 | -0.50426841 | 0.85313201 |
| Celebrex     | -0.69964743 | -1.2551666 | 1.5841386 |
| Benazepril   | -0.1722537 | -1.0853065 | 0.47855175 |
| Zyrtec       | -0.47942379 | -1.2031868 | 0.61839736 |
| Coreg        | -0.20518997 | -1.339842  | 1.62435 |
| Valtrex      | -0.49919569 | 0.38027838 | -0.43706414 |
| Adderall     | -1.6239618 | -0.65025598 | -0.53189367 |
| Aciphex      | -0.45343667 | -0.75192112 | 1.0078642 |
| Cymbalta     | -0.92316884 | -1.7507811 | 1.1712037 |
| Crestor      | 0.14056866 | -0.57007229 | 0.1367476 |
| Diovan       | 0.054656371 | -1.2894883 | 1.4949378 |
| Tricor       | -0.71295768 | -1.9348887 | 0.51353991 |
| Concerta     | -1.1811528 | -0.94267678 | -0.35627496 |
| Imitrex      | -0.96518046 | -0.42220587 | 0.019565227 |

**NATURAL PRODUCTS**

| Name         | PC1     | PC2     | PC3     |
|--------------|---------|---------|---------|
| Forskolin    | -0.22793074 | -0.91015011 | -1.172423 |
| SQ26180      | -0.87785536 | 0.66188121 | -1.7100738 |
| CephamycinC  | 0.33941141 | 0.94354922 | -1.575893 |
| Thienamycin  | -0.76859432 | 0.17549638 | -1.2966894 |
| Artemisinin  | -0.84689111 | -1.4530129 | -0.63662207 |
| Coformycin   | -0.54190427 | 0.84613544 | -0.64143258 |
| Arglabin     | -1.1851399 | -1.1351717 | -0.51894414 |
| Mizorbine    | -0.59756994 | 1.015848  | -1.0570055 |
| Drug               | Value 1     | Value 2     | Value 3     |
|--------------------|-------------|-------------|-------------|
| Compactin          | -0.44222924 | -1.6801987  | -0.96994025 |
| Bestatin           | -0.46068856 | -0.25168779 | -0.91969138 |
| Plaurotol          | -0.77315277 | -1.5268536  | -1.451203   |
| Spergualin         | 0.23765998  | 0.91931868  | -2.0552449  |
| Taxol              | 1.9018565   | -1.8936352  | 1.5840536   |
| Rapamycin          | 1.914791    | -2.4318838  | -1.1371188  |
| AvermectinB1a      | 1.9849749   | -2.4668901  | -0.73449647 |
| PseudomonicAcidA   | 0.61720502  | -1.125052   | -1.9112897  |
| Daptomycin         | 6.8387823   | 3.143348    | -0.37000597 |
| MidecamycinA1      | 1.8331497   | -1.3506995  | -2.1281457  |
| EchinocandinB      | 3.58724     | 0.34384269  | -0.91759968 |
| CalicheamicinG1    | 4.5329742   | -2.1788938  | -0.43363619 |
| Valdamicin         | 1.0950502   | 2.0700731   | -2.728308   |
| CyclosporinA       | 3.0024731   | -1.2290826  | -1.1754317  |
| FK506              | 1.5112494   | -1.9028938  | -1.1877556  |
| Lipstatin          | 0.33398086  | -2.8370755  | -1.2085571  |
| Geldanamycin       | 0.37187731  | -0.8260624  | -1.2769804  |
| Actinonin          | -0.15347186 | -0.45159864 | -1.5673654  |
| Discodermolide     | 0.88530988  | -1.6108406  | -2.080821   |
| Monensin           | 1.3066674   | -2.1165187  | -1.20472    |
| CalyculinA         | 3.1664143   | -1.1070825  | -1.4811376  |
| AmphotericinB      | 2.7472551   | -0.2217932  | -2.4432735  |
| Adriamycin         | 0.75543278  | -0.17172959 | 0.35423809  |
| GinkgolideB        | 0.076751307 | -0.42398295 | -0.68785477 |
| PhorbolMA          | 0.78936607  | -2.4432287  | -0.67789841 |
| Vancomycin         | 5.5328674   | 0.41190192  | 3.1565979   |
| TrapoxinB          | 0.52696449  | -1.0188068  | 1.0778458   |
| Vincristine        | 1.4792458   | -1.6977637  | 2.2975564   |
| Drug                | Value 1   | Value 2   | Value 3   |
|---------------------|-----------|-----------|-----------|
| Colchicine          | -0.42637482 | -1.0862933 | -0.1127376 |
| Trichostatin        | -0.83681005 | -0.86081833 | -0.52208447 |
| Fumagillin          | 0.074679755 | -1.7961711 | -0.92736107 |
| Staurosporine       | -0.1086929 | -1.9755068 | 3.2671399  |
| Erythromycin A      | 1.5086728 | -0.96488166 | 2.0675776  |
| Streptomycin        | 1.5435889 | 2.7522595 | -2.2994957 |
| Penicillin G        | -0.61026227 | -0.60710198 | -0.1307178 |
| Zaragozic Ac DA     | 1.706357 | -1.4598362 | -1.0643396 |
| Talaromycin B       | -1.2211469 | -1.6863494 | -0.92124099 |
| Spongistatin 1      | 3.7285621 | -2.6810601 | -1.2223319 |
| Radicicol           | -0.56284487 | -1.185524 | -0.17036377 |
| Salicylihalamide A  | -0.1880146 | -1.5681546 | -0.31392559 |
| Brevetoxin B        | 2.0220592 | -2.9930613 | 0.54134393 |
| Rifamycin B         | 1.5982065 | -1.4188566 | -0.030950295 |
| Quinine             | -0.76435798 | -1.1905845 | 0.68034565 |
| Mycobactin S        | 2.098506 | -2.4474444 | -0.70494437 |
| Telomestatin        | 0.63835406 | -1.2211164 | 5.5911064  |
| Duocarmycin A       | 0.20226467 | -0.92060089 | 1.3871363 |
| Bleomycin           | 6.0183692 | 4.0021272 | 0.19731249 |
| Brefeldin A         | -0.94019729 | -0.88748139 | -1.2230606 |
| Cytochalasin B      | -0.051231857 | -1.5982953 | 0.16306159 |
| Epothilone A        | -0.087701909 | -1.3141584 | -0.46590239 |
| Apoptolidin         | 3.6647611 | -1.7290736 | -2.2622764 |
| Lactacystin         | -0.09661448 | 0.32651547 | -1.9021096 |
| MACROCYCLIC NATURAL PRODUCTS | PC1     | PC2     | PC3     |
|------------------------------|---------|---------|---------|
| O1[C@@H][C][C@@H][2O][C@@H][2][C=C][C=C](O)(CC1=O)C | -1.254164 | -0.48006925 | -1.288004 |
| O1[C@@H][C][C@@H][2O][C@@H][2][C=C][O](CC=C)[C=C](O)CC1=O)C | -1.1514407 | -0.23300733 | -1.3959749 |
| O1[C@@H][CC][C@@H][O]=C=C[C=C][O](CC1=O)C | -1.2388685 | -0.33497229 | -1.5778235 |
| O1[C@@H][C][C@@H][O]=C[C=C][O]CC1=O)C | -1.0686992 | 0.012939053 | -1.7640325 |
| O1[C@@H][CC][C=C][=O]CC1=O)C | -1.4776767 | -0.76367152 | -1.2776806 |
| O1[C@@H][C]=C[C=C][O]CC1=O)CC2=O | -1.4233081 | -0.68217933 | -1.1074992 |
| O1[C@@H][C][O]CC1=O)CC1=O)C | -1.4533968 | -0.83640671 | -1.2657919 |
| O1[C@@H][C][O]CC1=O)CC1=O)C | -1.4869215 | -0.75560492 | -1.266059 |
| O1[C@@H][C][O]CC1=O)CC1=O)C | -1.5170075 | -0.60832649 | -1.3510424 |
| O1[C@@H][CCC][C@@H][O]CC1=O)CC1=O)C | -0.53092515 | -1.0286188 | -1.5801451 |
| O1[C@@H][C][O]CC1=O)CC1=O)C | -1.1146244 | -0.66072041 | -1.485773 |
| O1[C@@H][C][O]CC1=O)CC1=O)C | -1.1462444 | -0.66072041 | -1.485773 |
| O1[C@@H][C][O]CC1=O)CC1=O)C | -1.1839074 | -0.77925378 | -1.3672585 |
| O1[C@@H][C][O]CC1=O)CC1=O)C | -0.88771194 | -0.99940687 | -0.4087677 |
| O1[C@@H][C][O]CC1=O)CC1=O)C | 0.6509608 | -2.191673 | -1.2758291 |
| O1[C@@H][C][O]CC1=O)CC1=O)C | -0.001966619 | -1.1076781 | -1.5600653 |
| O1[C@@H][C][O]CC1=O)CC1=O)C | 0.01451358 | -1.0140181 | -1.6557032 |
| O1[C@@H][C][O]CC1=O)CC1=O)C | 0.39372656 | -1.6928641 | -1.5938256 |
| DOS COMPOUND LIBRARY | PC1      | PC2      | PC3       |
|-----------------------|----------|----------|-----------|
| O=C1NCCCC[C@H](NC(=O)[C@@H](N)CCCCc2nnn(c2)[C@H]1Cc1ccccc1)C(OC)=O | 0.24811314 | 0.068257265 | 0.58580607 |
| O=C1NCCCC[C@H](NC(=O)[C@@H](N)CCCCc2n(nnc2)[C@H]1Cc1ccccc1)C(OC)=O | 0.15436238 | 0.30244216 | 0.5365209 |
| O=C1NCCCC[C@H](NC(=O)[C@@H](N)CCCCC(=O)CCc2nnn(c2)[C@H]1Cc1ccccc1)C(OC)=O | 0.20108035 | 0.18537183 | 0.56135368 |
| O=C1NCCCC[C@H](NC(=O)[C@@H](N)CCCCC(=O)CCc2n(nnc2)[C@H]1Cc1ccccc1)C(OC)=O | 0.20118691 | 0.18534905 | 0.56141567 |
| O=C1NCCCC[C@H](NC(=O)[C@@H](N)CCCCC(=O)CCc2nn(c2)[C@H]1Cc1ccccc1)C(OC)=O | 0.2564576 | 0.3840912 | 0.62051564 |
| O=C1NCCCC[C@H](NC(=O)[C@@H](N)CCCCC(=O)CCc2n(nnc2)[C@H]1Cc1ccccc1)C(OC)=O | 0.25656417 | 0.38406843 | 0.62057757 |
| Chemical Structure                                                                 | E | S         | D          |
|-----------------------------------------------------------------------------------|---|-----------|------------|
| O=C1NCCCC[C@H]2NC(=O)[C@@H](NC2=O)CCNCN(=O)NCc2nn2[C@@H](NC2=O)CCc2n(nnc2)[C@H]1Cc1cccc1 | 0.05908246 | 0.30770487 | 1.0424241  |
| O=C1NCCCC[C@H][NC(=O)[C@@H](NC2=O)CCNCN(=O)NCc2nn2[C@@H](NC2=O)CCc2n(nnc2)[C@H]1Cc1cccc1]C(OC)=O | 0.20995161 | 0.50113326 | 0.59545267 |
| O=C1NCCCC[C@H][NC(=O)[C@@H](NC2=O)CCNCN(=O)NCc2nn2[C@@H](NC2=O)CCc2n(nnc2)[C@H]1Cc1cccc1]C(OC)=O | 0.21005815 | 0.50111049 | 0.59545267 |
| O=C1NCCCC[C@H][NC(=O)[C@@H](NC2=O)CCNCN(=O)NCc2nn2[C@@H](NC2=O)CCc2n(nnc2)[C@H]1Cc1cccc1]C(OC)=O | 0.014723856 | 0.42443934 | 1.01485    |
| O=C1NCCCC[C@H][NC(=O)[C@@H](NC2=O)CCNCN(=O)NCc2nn2[C@@H](NC2=O)CCc2n(nnc2)[C@H]1Cc1cccc1]C(OC)=O | 0.34129611 | -0.10761018 | 1.5972095  |
| O=C1NCCCC[C@H][NC(=O)[C@@H](NC2=O)CCNCN(=O)NCc2nn2[C@@H](NC2=O)CCc2n(nnc2)[C@H]1Cc1cccc1]C(OC)=O | 0.15282303 | -0.18526225 | 2.0087402  |
| O=C1NCCCC[C@H][NC(=O)[C@@H](NC2=O)CCNCN(=O)NCc2nn2[C@@H](NC2=O)CCc2n(nnc2)[C@H]1Cc1cccc1]C(OC)=O | 0.1546892 | 0.30241939 | 0.5365209  |
| O=C1NCCCC[C@H][NC(=O)[C@@H](NC2=O)CCNCN(=O)NCc2nn2[C@@H](NC2=O)CCc2n(nnc2)[C@H]1Cc1cccc1]C(OC)=O | -0.042385653 | 0.2259711 | 0.95758951 |
| O=C1NCCCC[C@H][NC(=O)[C@@H](NC2=O)CCNCN(=O)NCc2nn2[C@@H](NC2=O)CCc2n(nnc2)[C@H]1Cc1cccc1]C(OC)=O | -0.042279106 | 0.22594833 | 0.95765144 |
| O=C1NCCCC[C@H][NC(=O)[C@@H](NC2=O)CCNCN(=O)NCc2nn2[C@@H](NC2=O)CCc2n(nnc2)[C@H]1Cc1cccc1]C(OC)=O | 0.10797069 | 0.4194667 | 0.51129252 |
| O=C1NCCCC[C@H][NC(=O)[C@@H](NC2=O)CCNCN(=O)NCc2nn2[C@@H](NC2=O)CCc2n(nnc2)[C@H]1Cc1cccc1]C(OC)=O | 0.1087724 | 0.41944394 | 0.51135445 |
| O=C1NCCCC[C@H][NC(=O)[C@@H](NC2=O)CCNCN(=O)NCc2nn2[C@@H](NC2=O)CCc2n(nnc2)[C@H]1Cc1cccc1]C(OC)=O | -0.086480334 | 0.34265915 | 0.92992556 |
| O=C1NCCCC[C@H][NC(=O)[C@@H](NC2=O)CCNCN(=O)NCc2nn2[C@@H](NC2=O)CCc2n(nnc2)[C@H]1Cc1cccc1]C(OC)=O | 0.10797069 | 0.4194667 | 0.51129252 |
| O=C1NCCCC[C@H][NC(=O)[C@@H](NC2=O)CCNCN(=O)NCc2nn2[C@@H](NC2=O)CCc2n(nnc2)[C@H]1Cc1cccc1]C(OC)=O | 0.10807724 | 0.41944394 | 0.51135445 |
| O=C1NCCCC[C@H][NC(=O)[C@@H](NC2=O)CCNCN(=O)NCc2nn2[C@@H](NC2=O)CCc2n(nnc2)[C@H]1Cc1cccc1]C(OC)=O | -0.086586878 | 0.34268191 | 0.92986357 |
| O=C1NCCCC[C@H][NC(=O)[C@@H](NC2=O)CCNCN(=O)NCc2nn2[C@@H](NC2=O)CCc2n(nnc2)[C@H]1Cc1cccc1]C(OC)=O | -0.086480334 | 0.34265915 | 0.92992556 |
| O=C1NCCCC[C@H][NC(=O)[C@@H](NC2=O)CCNCN(=O)NCc2nn2[C@@H](NC2=O)CCc2n(nnc2)[C@H]1Cc1cccc1]C(OC)=O | 0.0619171 | 0.53644395 | 0.48565236 |
| O=C1NCCCC[C@H][NC(=O)[C@@H](NC2=O)CCNCN(=O)NCc2nn2[C@@H](NC2=O)CCc2n(nnc2)[C@H]1Cc1cccc1]C(OC)=O | 0.062023625 | 0.53642118 | 0.48571429 |
| O=C1NCCCC[C@H][NC(=O)[C@@H](NC2=O)CCNCN(=O)NCc2nn2[C@@H](NC2=O)CCc2n(nnc2)[C@H]1Cc1cccc1]C(OC)=O | -0.13031098 | 0.45931816 | 0.90174609 |
| O=C1NCCCC[C@H][NC(=O)[C@@H](NC2=O)CCNCN(=O)NCc2nn2[C@@H](NC2=O)CCc2n(nnc2)[C@H]1Cc1cccc1]C(OC)=O | 0.16377425 | 0.61812925 | 0.56986445 |
| O=C1NCCCC[C@H][NC(=O)[C@@H](NC2=O)CCNCN(=O)NCc2nn2[C@@H](NC2=O)CCc2n(nnc2)[C@H]1Cc1cccc1]C(OC)=O | 0.1638808 | 0.61810648 | 0.56992644 |
| Chemical Structure                                                                 | LogP  | LogS  | logD   |
|-----------------------------------------------------------------------------------|-------|-------|--------|
| O=C1NCCCN(=O)[C@@H]2NC(=O)[C@@H](NC2=O)CCNC(=O)NCc2nnn(c2)CCNC(=O)CCCc2nnn(c2)... | -0.29724285 | 0.54112345 | 0.98683387 |
| O=C1NCCCN(=O)[C@@H]2NC(=O)[C@@H](NC2=O)CCNC(=O)NCc2nnn(c2)CCNC(=O)CCCc2nnn(c2)... | 0.11793721 | 0.7350778 | 0.5439207 |
| O=C1NCCCN(=O)[C@@H](NC(=O)(C@@H)(N)CCNC(=O)CCCcc3nnn(c3)]C1Cc1ccccc1(COC)=O   | 0.38631293 | -0.22442926 | 1.6237961 |
| O=C1NCCCN(=O)[C@@H](NC(=O)(C@@H)(N)CCNC(=O)CCCcc3nnn(c3)]C1Cc1ccccc1(COC)=O   | 0.38641948 | -0.22445203 | 1.6238581 |
| O=C1NCCCN(=O)[C@@H](NC(=O)(C@@H)(N)CCNC(=O)CCCcc3nnn(c3)]C1Cc1ccccc1(COC)=O   | 0.19610819 | -0.30184108 | 2.0374911 |
| O=C1NCCCN(=O)[C@@H]2NC(=O)[C@@H](NC2=O)CCNC(=O)CCCcc3nnn(c3)]C1Cc1ccccc1(COC)=O | 0.10797069 | 0.4194667 | 0.5112952 |
| O=C1NCCCN(=O)[C@@H]2NC(=O)[C@@H](NC2=O)CCNC(=O)CCCcc3nnn(c3)]C1Cc1ccccc1(COC)=O | -0.086586878 | 0.34268191 | 0.92986357 |
| O=C1NCCCN(=O)[C@@H](NC(=O)(C@@H)(N)CCNC(=O)CCCcc3nnn(c3)]C1Cc1ccccc1(COC)=O   | -0.086480334 | 0.34265915 | 0.92992556 |
| O=C1NCCCN(=O)[C@@H](NC(=O)(C@@H)(N)CCNC(=O)CCCcc3nnn(c3)]C1Cc1ccccc1(COC)=O   | 0.016213611 | 0.65337223 | 0.45958358 |
| O=C1NCCCN(=O)[C@@H]2NC(=O)[C@@H](NC2=O)CCNC(=O)CCCcc3nnn(c3)]C1Cc1ccccc1(COC)=O | 0.01632016 | 0.65334946 | 0.45964554 |
| O=C1NCCCN(=O)[C@@H]2NC(=O)[C@@H](NC2=O)CCNC(=O)CCCcc3nnn(c3)]C1Cc1ccccc1(COC)=O | -0.13786697 | 0.57594681 | 0.87303478 |
| O=C1NCCCN(=O)[C@@H]2NC(=O)[C@@H](NC2=O)CCNC(=O)CCCcc3nnn(c3)]C1Cc1ccccc1(COC)=O | -0.13736043 | 0.57592404 | 0.8730967 |
| O=C1NCCCN(=O)[C@@H](NC(=O)(C@@H)(N)CCNC(=O)CCCcc3nnn(c3)]C1Cc1ccccc1(COC)=O   | 0.0619171 | 0.53643953 | 0.48565236 |
| O=C1NCCCN(=O)[C@@H]2NC(=O)[C@@H](NC2=O)CCNC(=O)CCCcc3nnn(c3)]C1Cc1ccccc1(COC)=O | 0.062023625 | 0.53642118 | 0.48571429 |
| O=C1NCCCN(=O)[C@@H]2NC(=O)[C@@H](NC2=O)CCNC(=O)CCCcc3nnn(c3)]C1Cc1ccccc1(COC)=O | -0.13041754 | 0.45934093 | 0.90168411 |
| O=C1NCCCN(=O)[C@@H]2NC(=O)[C@@H](NC2=O)CCNC(=O)CCCcc3nnn(c3)]C1Cc1ccccc1(COC)=O | -0.13031098 | 0.45931816 | 0.90174609 |
| O=C1NCCCN(=O)[C@@H]2NC(=O)[C@@H](NC2=O)CCNC(=O)CCCcc3nnn(c3)]C1Cc1ccccc1(COC)=O | 0.11793721 | 0.7350778 | 0.5439207 |
| O=C1NCCCN(=O)[C@@H]2NC(=O)[C@@H](NC2=O)CCNC(=O)CCCcc3nnn(c3)]C1Cc1ccccc1(COC)=O | 0.11804377 | 0.73505503 | 0.54398263 |
| Formula | logP | logS | logB |
|---------|------|------|------|
| O=C1N[\@H]1(CCC(=O)NCC[C@H](CCC(=O)NCC[C@H]1NC(OC(C)(C)C)=O)c(OC)=O)c(OC)=O | 0.50608093 | 0.49165723 | -0.63767248 |
| O=C1N[\@H]1(CCC(=O)NCC[C@H](CCC(=O)NCC[C@H]1NC(OC(C)(C)C)=O)c(OC)=O)c(OC)=O | 0.5061875 | 0.49163446 | -0.63761055 |
| O=C1N[\@H]1(CCC(=O)NCC[C@H](CCC(=O)NCC[C@H]1NC(OC(C)(C)C)=O)c(OC)=O)c(OC)=O | 0.60840744 | 0.57326901 | -0.55384022 |
| O=C1N[\@H]1(CCC(=O)NCC[C@H](CCC(=O)NCC[C@H]1NC(OC(C)(C)C)=O)c(OC)=O)c(OC)=O | 0.60851395 | 0.57324624 | -0.55377829 |
| O=C1N[\@H]1(CCC(=O)NCC[C@H](CCC(=O)NCC[C@H]1NC(OC(C)(C)C)=O)c(OC)=O)c(OC)=O | 0.60851395 | 0.57324624 | -0.55377829 |
| O=C1N[\@H]1(CCC(=O)NCC[C@H](CCC(=O)NCC[C@H]1NC(OC(C)(C)C)=O)c(OC)=O)c(OC)=O | 0.64995313 | 0.13990319 | -0.56715852 |
| O=C1N[\@H]1(CCC(=O)NCC[C@H](CCC(=O)NCC[C@H]1NC(OC(C)(C)C)=O)c(OC)=O)c(OC)=O | 0.64995313 | 0.13990319 | -0.56715852 |
| O=C1N[\@H]1(CCC(=O)NCC[C@H](CCC(=O)NCC[C@H]1NC(OC(C)(C)C)=O)c(OC)=O)c(OC)=O | -0.34565976 | 0.70074946 | 0.58108586 |
| O=C1N[\@H]1(CCC(=O)NCC[C@H](CCC(=O)NCC[C@H]1NC(OC(C)(C)C)=O)c(OC)=O)c(OC)=O | -0.34565976 | 0.70074946 | 0.58108586 |
| O=C1N[\@H]1(CCC(=O)NCC[C@H](CCC(=O)NCC[C@H]1NC(OC(C)(C)C)=O)c(OC)=O)c(OC)=O | -0.38926807 | 0.81737649 | 0.55265558 |
| O=C1N[\@H]1(CCC(=O)NCC[C@H](CCC(=O)NCC[C@H]1NC(OC(C)(C)C)=O)c(OC)=O)c(OC)=O | -0.38926807 | 0.81737649 | 0.55265558 |
| O=C1N[\@H]1(CCC(=O)NCC[C@H](CCC(=O)NCC[C@H]1NC(OC(C)(C)C)=O)c(OC)=O)c(OC)=O | -0.40261495 | 0.34648278 | -0.40704125 |
| O=C1N[\@H]1(CCC(=O)NCC[C@H](CCC(=O)NCC[C@H]1NC(OC(C)(C)C)=O)c(OC)=O)c(OC)=O | -0.60722136 | 0.27113587 | 0.023022361 |
| Formula | Energy | ZPE | CorrE | TolE |
|---------|--------|-----|-------|------|
| O=C1N[C@@H][Cc2ccc(-n3nnc3CCC(=O)NCC[C@@H]1N)c2]C(OC)=O | -0.4983004 | 0.5809564 | -0.45440438 |
| O=C1N[C@@H][Cc2ccc(-n3nnc3NC(=O)NCC[C@@H]1N)c2]C(OC)=O | -0.49819386 | 0.58093363 | -0.45434245 |
| O=C1N[C@@H][Cc2ccc(-n3nnc3CCC(=O)NC[C@@H]1N)c2]C(OC)=O | -0.6976793 | 0.50472921 | -0.031315621 |
| O=C1N[C@@H][Cc2ccc(-n3nnc3CCC(=O)NC[C@@H]1N)c2]C(OC)=O | -0.45072392 | 0.46376085 | -0.43049601 |
| O=C1N[C@@H][Cc2ccc(-n3ncc3CNC(=O)NC[C@@H]1N)c2]C(OC)=O | -0.65229815 | 0.38797906 | -0.003874723 |
| O=C1N[C@@H][Cc2ccc(-n3nnc3CCC(=O)NCC[C@@H]1N)c2]C(OC)=O | -0.3959946 | 0.66257566 | -0.37065896 |
| O=C1N[C@@H][Cc2ccc(-n3ncc3CCC(=O)NCCCC[C@@H]1N)c2]C(OC)=O | -0.44337204 | 0.77975315 | -0.39505053 |
| O=C1N[C@@H][CCCCn2nncc3CCC(=O)NCCCC[C@@H]1N)c2]C(OC)=O | -0.4432655 | 0.77973038 | -0.3949886 |
| O=C1N[C@@H][CCCCn2nnc3CCC(=O)NCCCC[C@@H]1N)c2]C(OC)=O | -0.4983004 | 0.5809564 | -0.45440438 |
| O=C1N[C@@H][CCCCn2nncc3CCC(=O)NCCCC[C@@H]1N)c2]C(OC)=O | -0.49819386 | 0.58093363 | -0.45434245 |
| O=C1N[C@@H][CCCCn2nncc3CCC(=O)NCCCC[C@@H]1N)c2]C(OC)=O | -0.69666141 | 0.50470644 | -0.03125361 |
| O=C1N[C@@H][CCCCn2nnc3CCC(=O)NCCCC[C@@H]1N)c2]C(OC)=O | -0.54542726 | 0.69808894 | -0.47885954 |
| O=C1N[C@@H][CCCCn2nnc3CCC(=O)NCCCC[C@@H]1N)c2]C(OC)=O | -0.54532069 | 0.69806617 | -0.47879761 |
| O=C1N[C@@H][CCCCn2nnc3CCC(=O)NCCCC[C@@H]1N)c2]C(OC)=O | -0.7406149 | 0.62140614 | -0.05939351 |
| O=C1N[C@@H][CCCCn2nnc3CCC(=O)NCCCC[C@@H]1N)c2]C(OC)=O | -0.74060839 | 0.62138337 | -0.05933157 |
| O=C1N[C@@H][CCCCn2nncc3CCC(=O)NCCCC[C@@H]1N)c2]C(OC)=O | -0.54532069 | 0.69806617 | -0.47879761 |
| O=C1N[C@@H][CCCCn2nncc3CCC(=O)NCCCC[C@@H]1N)c2]C(OC)=O | -0.5920794 | 0.81515503 | -0.50389498 |
| O=C1N[C@@H][CCCCn2nncc3CCC(=O)NCC[C@@H]1N)c2]C(OC)=O | -0.59197289 | 0.81513226 | -0.503833 |
| O=C1N[C@@H][CCCCn2nncc3CCC(=O)NCC[C@@H]1N)c2]C(OC)=O | -0.49018738 | 0.89684427 | -0.4193361 |
| O=C1N[C@@H][CCCCn2nncc3CCC(=O)NCC[C@@H]1N)c2]C(OC)=O | -0.49008083 | 0.8968215 | -0.41987768 |
| O=C1N[C@@H][CCCCn2nncc3CCC(=O)NCC[C@@H]1N)c2]C(OC)=O | -0.68342686 | 0.81987202 | -0.002903873 |
| O=C1N[C@@H][CCCCn2nncc3CCC(=O)NCC[C@@H]1N)c2]C(OC)=O | -0.53652281 | 1.0138686 | -0.4452193 |
| O=C1N[C@@H][CCCCn2nncc3CCC(=O)NCC[C@@H]1N)c2]C(OC)=O | -0.53641623 | 1.0138458 | -0.44535998 |
| Chemical Structure | W1 | W2 | RT |
|--------------------|----|----|----|
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.2677677 | 0.054265343 | 0.63504297 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.45712849 | -0.023261161 | 1.0476351 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.45072392 | 0.46376085 | -0.43049601 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.45061737 | 0.46373808 | -0.43043408 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.45072392 | 0.38797906 | -0.003874723 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.45061737 | 0.46373808 | -0.43043408 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.45061737 | 0.46373808 | -0.43043408 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.65229815 | 0.38797906 | -0.003874723 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.65219164 | 0.38795629 | -0.003812783 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.65229815 | 0.38797906 | -0.003874723 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.54542726 | 0.69808894 | -0.47885954 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.54532069 | 0.69806617 | -0.47879761 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.4983004 | 0.5809564 | -0.45440438 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.49819386 | 0.58093363 | -0.45434245 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.69666141 | 0.50470644 | -0.031253861 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.44337204 | 0.77973515 | -0.39505053 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.4432655 | 0.77973038 | -0.3949886 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.49018738 | 0.89684427 | -0.41993961 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.49008083 | 0.8968215 | -0.41987768 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.35784873 | 0.28792951 | 0.5814532 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.54220092 | 0.20968623 | 0.98830926 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.54542726 | 0.69808894 | -0.47885954 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.54532069 | 0.69806617 | -0.47879761 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.54220092 | 0.20968623 | 0.98830926 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.74060839 | 0.62138337 | -0.05933157 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.5920794 | 0.81515503 | -0.50389498 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.59197289 | 0.81513226 | -0.503833 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.78401023 | 0.73798424 | -0.088079214 |
| O=C1NC[C@@H]2NC(=O)[C@@H](NC2=O)CCCN2nncc2CC1 | -0.5920794 | 0.81515503 | -0.50389498 |
| Reaction                                                                 | Energy   | Force    | Torque   |
|------------------------------------------------------------------------|----------|----------|----------|
| O=C1N[O@@H]([C@H]23ncc2CCC(=O)Ncc2ccc([C@H]1N)cc2)C(OC)              | -0.59197289 | 0.81513226 | -0.503833 |
| O=C1Nc2ccc([C@H]3NCC(=O)NCC([C@H]1N)c2)C(OC)                          | -0.78401023 | 0.73798424 | -0.088079214 |
| O=C1N([O@@H][Cn2nncCCC(=O)NCC([O@@H]1N)c2)C(OC)                      | -0.63823086 | 0.93215132 | -0.52954662 |
| O=C1N([O@@H][CCn2nnc2CC(=O)NCC([O@@H]1N)c2)C(OC)                     | -0.63812435 | 0.93641281 | -0.032016985 |
| O=C1N([O@@H][Cn2nncCCC(=O)NCC([O@@H]1N)c2)C(OC)                      | -0.72643363 | 0.93641281 | -0.032016985 |
| O=C1N([O@@H][CCn2nnc2CCC(=O)NCC([O@@H]1N)c2)C(OC)                     | -0.69666141 | 0.50470644 | -0.031253681 |
| O=C1N([O@@H][CCn2nnc2CC(=O)NCC([O@@H]1N)c2)C(OC)                     | -0.25666147 | 0.46332175 | 0.63636326 |
| O=C1N([O@@H][CCn2nnc2CCC(=O)NCC([O@@H]1N)c2)C(OC)                     | -0.31324393 | 0.2647851 | 0.57900637 |
| O=C1N([O@@H][CCn2nnc2CCC(=O)NCC([O@@H]1N)c2)C(OC)                     | -0.06376148 | 0.8526333 | -0.2174801 |
| O=C1N([O@@H][CCn2nnc2CCC(=O)NCC([O@@H]1N)c2)C(OC)                     | 0.18918927 | 0.81067997 | -0.62461621 |
| O=C1N([O@@H][CCn2nnc2CCC(=O)NCC([O@@H]1N)c2)C(OC)                     | 0.14101417 | 0.92796409 | -0.64791197 |
| O=C1N([O@@H]([C@H]2NCC([O@@H]1N)c2)C(OC)                             | -0.18918927 | 0.39067657 | -0.031253681 |
| O=C1N([O@@H][CCn2nnc2CCC(=O)NCC([O@@H]1N)c2)C(OC)                     | 0.23767319 | 0.69369437 | -0.60169977 |
| O=C1Nc2ccc([C@H]3NCC(=O)NCC([C@H]1N)c2)C(OC)                          | 0.14101417 | 0.92796409 | -0.64791197 |
| O=C1N([O@@H][Cn2nncCCC(=O)NCC([O@@H]1N)c2)C(OC)                      | -0.06376148 | 0.8526333 | -0.2174801 |
| O=C1N([O@@H][CCn2nnc2CCC(=O)NCC([O@@H]1N)c2)C(OC)                     | 0.18918927 | 0.81067997 | -0.62461621 |
| O=C1N([O@@H][CCn2nnc2CCC(=O)NCC([O@@H]1N)c2)C(OC)                     | 0.14101417 | 0.92796409 | -0.64791197 |
| O=C1N([O@@H][CCn2nnc2CCC(=O)NCC([O@@H]1N)c2)C(OC)                     | 0.23767319 | 0.69369437 | -0.60169977 |
| Structure                                                                 | Energy (kcal/mol) | ZPE (kcal/mol) | Thermal (kcal/mol) |
|--------------------------------------------------------------------------|-------------------|----------------|--------------------|
| O=C1N[C@@H](Cc2cc(n3nncc3CCCCC(=O)NCCCCC(C@@H)1N)ccc2)C(OC)=O            | 0.093161009       | 1.0452033      | -0.67160493        |
| O=C1N[C@@H](CCC(=O)N[C@@H](CCn2nncc2CCCC(=O)NCCCCC(C@@H)1N)C(OC)=O     | 0.045643277       | 1.162396       | -0.69571394        |
| O=C1N[C@@H](CCC(=O)N[C@@H](CCn2nncc2CCCC(=O)NCCCCC(C@@H)1N)C(OC)=O     | 0.14783782        | 1.2440351      | -0.61193961        |
| O=C1N[C@@H](CCn2nncc2CCCC(=O)NCCCCC(C@@H)2NC(=O)(C@@H)(NC2=O)CC1)C(OC)=O| 0.1004501         | 1.3612193      | -0.6364463         |
| O=C1N[C@@H](CCn2nncc2CCCC(=O)NCCCCC(C@@H)2NC(=O)(C@@H)(NC2=O)CC1)C(OC)=O| 0.1005564         | 1.3611965      | -0.63638437        |
| O=C1N[C@@H](CCn2nncc2CCCC(=O)NCCCCC(C@@H)2NC(=O)(C@@H)(NC2=O)CC1)C(OC)=O| 0.13554282        | 0.64209908     | -0.592893          |
| O=C1N[C@@H](CCn2nncc2CCCC(=O)NCCCCC(C@@H)2NC(=O)(C@@H)(NC2=O)CC1)C(OC)=O| 0.13564937        | 0.64207631     | -0.59283108        |
| O=C1N[C@@H](CCn2nncc2CCCC(=O)NCCCCC(C@@H)2NC(=O)(C@@H)(NC2=O)CC1)C(OC)=O| -0.01794026       | 0.7356863      | -0.19147816        |
| O=C1N[C@@H](CCn2nncc2CCCC(=O)Nc2ccc(C[C@@H]1N)C(OC)=O                  | 0.031486288       | 0.38723004     | 0.58770502         |
| O=C1N[C@@H](CCn2nncc2CCCC(=O)Nc2ccc(C[C@@H]1N)C(OC)=O                  | 0.031592838       | 0.38720727     | 0.58776695         |
| O=C1N[C@@H](CCn2nncc2CCCC(=O)Nc2ccc(C[C@@H]1N)C(OC)=O                  | 0.51395273        | 0.49620727     | 0.53745496         |
| O=C1N[C@@H](CCn2nncc2CCCC(=O)Nc2ccc(C[C@@H]1N)C(OC)=O                  | 0.4197062         | 0.73046649     | 0.48865402         |
| O=C1N[C@@H](CCn2nncc2CCCC(=O)Nc2ccc(C[C@@H]1N)C(OC)=O                  | 1.1532365         | 0.23998451     | 1.5045735          |
| O=C1N[C@@H](CCn2nncc2CCCC(=O)Nc2ccc(C[C@@H]1N)C(OC)=O                  | 1.1070197         | 0.35693272     | 1.4791632          |
| O=C1N[C@@H](CCn2nncc2CCCC(=O)Nc2ccc(C[C@@H]1N)C(OC)=O                  | 0.68571883        | 0.1086913      | 1.5765334          |
| O=C1N[C@@H](CCn2nncc2CCCC(=O)Nc2ccc(C[C@@H]1N)C(OC)=O                  | 1.0726154         | 0.45212886     | 1.4788277          |
Principal moment of inertia calculations

We compared the molecular shape diversity of our DOS library with the same reference sets of 124 compounds used in the PCA.

The LowModeMD conformational search algorithm in the MOE software package\textsuperscript{11} was used to generate low-energy 3D conformers for each compound. The MMFF94x force field was used with the generalized Born solvation model for the minimizations. Sampling and minimization parameters were implemented as follows:

- Rejection Limit: 150
- Iteration Limit: 10000
- MM Iteration Limit: 500
- RMS Gradient: 0.005
- RMSD Limit: 0.15
- Energy Window: 0.01
- Refinement Conformation Limit: 300

Only the conformer with the lowest energy was retained for principal moment of inertia (PMI) calculations. Normalized PMI ratios ($I_1/I_3$ and $I_2/I_3$) of these conformers were obtained from MOE and then plotted on a triangular graph, with the coordinates (0,1), (0.5,0.5) and (1,1) representing a perfect rod, disc and sphere respectively (Figure Xd).
PMI data:

**DRUGS:**

| Compound       | npr1    | npr2    |
|----------------|---------|---------|
| rod            | 0.000000| 0.500000|
| sphere         | 1.000000| 1.000000|
| Discodermolide | 0.500000| 0.500000|
| Aplify         | 0.205654| 0.778329|
| Aciphex        | 0.075929| 0.980037|
| Aciphex        | 0.082531| 0.982998|
| Actos          | 0.463255| 0.696069|
| Adderall       | 0.187001| 0.927327|
| Ambien         | 0.377477| 0.680460|
| Avandia        | 0.375426| 0.822949|
| Benazepril     | 0.445433| 0.816395|
| Celebrex       | 0.363167| 0.687574|
| Concerta       | 0.429713| 0.689608|
| Coreg          | 0.656530| 0.721788|
| Crestor        | 0.270494| 0.811394|
| Cymbalta       | 0.396282| 0.751873|
| Diovan         | 0.275662| 0.849159|
| Effexor        | 0.353232| 0.802320|
| Flonase        | 0.253542| 0.963402|
| Fosamax        | 0.677628| 0.780477|
| Imitrex        | 0.247709| 0.819678|
| Lamictal       | 0.229390| 0.911644|
| Levaquin       | 0.190810| 0.844335|
| Lexapro        | 0.455280| 0.723125|
| Lipitor        | 0.529854| 0.809632|
| Nexium         | 0.275484| 0.797230|
| Norvasc        | 0.427443| 0.811931|
| Plavix         | 0.296689| 0.880172|
| Prevacid       | 0.099878| 0.966122|
| Prevacid       | 0.303180| 0.886000|
| Protonix       | 0.089751| 0.955345|
| Protonix       | 0.094608| 0.959908|
| Risperdal      | 0.090427| 0.936130|
| Serevent       | 0.509771| 0.760083|
| Seroquel       | 0.165779| 0.929957|
| Singulair      | 0.272087| 0.916115|
| Topamax        | 0.351737| 0.800199|
| Toprol         | 0.136820| 0.913152|
| Tricor         | 0.207635| 0.830835|
| Valtrex        | 0.287954| 0.751349|
| Wellbutrin     | 0.195106| 0.948008|
| Zetia          | 0.246216| 0.805541|
| Drug       | AVG 1  | AVG 2  |
|------------|--------|--------|
| Zocor      | 0.403071 | 0.711209 |
| Zoloft     | 0.299490 | 0.953590 |
| Zyprexa    | 0.348574 | 0.692557 |
| Zyrtec     | 0.199646 | 0.836693 |
| Drug-AVG   | 0.300776 | 0.834714 |

**NATURAL PRODUCTS:**

| Compound             | npr1       | npr2       |
|----------------------|------------|------------|
| Actinonin            | 0.314978   | 0.841802   |
| Adriamycin           | 0.283220   | 0.800172   |
| AmphotericinB        | 0.215551   | 0.847453   |
| Apoptolidin          | 0.301694   | 0.830875   |
| Bleomycin            | 0.404781   | 0.826205   |
| BrefeldinA           | 0.255142   | 0.817388   |
| BrevetoxinB          | 0.149647   | 0.899486   |
| CalyculinA           | 0.442236   | 0.896401   |
| Colchicine           | 0.395296   | 0.837965   |
| Colchicine           | 0.258193   | 0.846521   |
| Colchicine           | 0.458247   | 0.773003   |
| Colchicine           | 0.513293   | 0.755147   |
| CytochalasinB        | 0.431674   | 0.740608   |
| Discodermolide       | 0.182128   | 0.981632   |
| DuocarmycinA         | 0.104513   | 0.945885   |
| EpothiloneA          | 0.447710   | 0.804309   |
| ErythromycinA        | 0.485996   | 0.813810   |
| Fumagillin           | 0.066479   | 0.974218   |
| Geldanamycin         | 0.369201   | 0.725345   |
| Geldanamycin         | 0.392818   | 0.769442   |
| GinkgolideB          | 0.363537   | 0.879045   |
| Lactacystin          | 0.478299   | 0.938709   |
| Monensin             | 0.221267   | 0.914230   |
| MycobactinS          | 0.567410   | 0.787169   |
| PenicillinG          | 0.227679   | 0.840740   |
| PhorbolMA            | 0.403734   | 0.770927   |
| PhorbolMA            | 0.512005   | 0.787906   |
| Radicicol            | 0.490589   | 0.823386   |
| RifamycinB           | 0.534830   | 0.679088   |
| RifamycinB           | 0.544966   | 0.674059   |
| RifamycinB           | 0.618686   | 0.762072   |
| RifamycinB           | 0.524795   | 0.868426   |
| RifamycinB           | 0.648821   | 0.813721   |
| RifamycinB           | 0.678080   | 0.844921   |
| RifamycinB           | 0.627544   | 0.817624   |
| RifamycinB           | 0.601820   | 0.886052   |
| SalicylihalamideA    | 0.191225   | 0.848920   |
| Staurosporine        | 0.464212   | 0.664055   |

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| Compound                         | Nat. Prod. | AVG  |
|---------------------------------|------------|------|
| Streptomycin                    | 0.335744   | 0.786998 |
| TalaromycinB                    | 0.186426   | 0.935125 |
| Telomestatin                    | 0.496427   | 0.509642 |
| TrapoxinB                       | 0.460215   | 0.680871 |
| Trichostatin                    | 0.288807   | 0.802339 |
| Vancomycin                      | 0.516891   | 0.626096 |
| Vincristine                     | 0.482176   | 0.946784 |
| Quinine                         | 0.303785   | 0.834042 |
| Spongistatin1                   | 0.428667   | 0.817984 |
| Zaragozic Acid A                | 0.287707   | 0.920770 |
| Aeglabin                         | 0.402854   | 0.721308 |
| Artemisinin                     | 0.541282   | 0.644874 |
| Bestatin                        | 0.297570   | 0.838998 |
| Cephamycin C                    | 0.488698   | 0.856650 |
| Coformycin                      | 0.298204   | 0.821609 |
| Compactin                       | 0.430983   | 0.716564 |
| Forskolin                       | 0.520873   | 0.688349 |
| Mizoribine                      | 0.239424   | 0.857007 |
| Plaunotol                       | 0.460051   | 0.900390 |
| Spergualin                      | 0.541169   | 0.946050 |
| SQ26180                         | 0.435835   | 0.794101 |
| Thienamycin                     | 0.476680   | 0.854387 |
| Avermectin B1a                  | 0.278083   | 0.812448 |
| Calicheamicin                   | 0.227585   | 0.920330 |
| Cyclosporin A                   | 0.418415   | 0.935663 |
| Daptomycin                      | 0.762741   | 0.908347 |
| Echinocandin B                  | 0.317238   | 0.945521 |
| FK506                           | 0.377179   | 0.761235 |
| Lipstatin                       | 0.462998   | 0.738670 |
| Midecamycin A1                  | 0.325184   | 0.904263 |
| Pseudomonic Acid A              | 0.380836   | 0.748719 |
| Rapamycin                       | 0.445581   | 0.764618 |
| Taxol                           | 0.437027   | 0.832107 |
| Validamycin                     | 0.451444   | 0.807012 |
| Nat. Prod.-AVG                  | **0.402459** | **0.818175** |
MACROCYCLIC NATURAL PRODUCTS:

| Compound                                      | npr1   | npr2   |
|-----------------------------------------------|--------|--------|
| decarestrictineA1                             | 0.469217 | 0.640137 |
| decarestrictineB                              | 0.610153 | 0.676987 |
| decarestrictineC1                             | 0.523140 | 0.616675 |
| decarestrictineD                              | 0.460594 | 0.707181 |
| diplodialideA                                 | 0.395167 | 0.735937 |
| jasmineketolactone                           | 0.361150 | 0.799690 |
| phoracantholideI                             | 0.533624 | 0.723704 |
| phoracantholideJ                             | 0.463326 | 0.712112 |
| pinolidoxin                                   | 0.297314 | 0.861372 |
| pyrenolideA                                   | 0.343546 | 0.781822 |
| ferrulactone1                                 | 0.560992 | 0.709680 |
| '2,4,6,8-tetramethyl-3,4-dihydroxydec-8(9)-enolide' | 0.577023 | 0.641499 |
| apicularenA                                   | 0.354153 | 0.885766 |
| cladospolideA                                 | 0.320632 | 0.796694 |
| cladospolideB                                 | 0.438580 | 0.721334 |
| cladospolideD                                 | 0.377547 | 0.753806 |
| curvularin                                    | 0.303779 | 0.797272 |
| lyngbouilloside                               | 0.249436 | 0.959705 |
| methymycin                                    | 0.436257 | 0.864653 |
| neomethymycin                                 | 0.496348 | 0.948657 |
| pladienolideB                                 | 0.134666 | 0.972028 |
| fluvirucinA1                                   | 0.243234 | 0.862219 |
| hypothemycin                                  | 0.329504 | 0.776135 |
| iriomoteolide3a                               | 0.277092 | 0.789016 |
DOS COMPOUND LIBRARY:

| Compound                                                                 | mseq  | E      | npr1   | npr2   |
|-------------------------------------------------------------------------|-------|--------|--------|--------|
| O=C1NCCCC[C@H]2N[C(=O)]C[OHH](N)CCCCNC(O)CCCCCnnn(c2)[C=H]1Cc1ccccc1(C| 1     | -18.579687 | 0.49725053 | 0.74374086 |
| O=C1NCCCC[C@H]2N[C(=O)]C[OHH](N)CCCCNC(O)CCCCCnnn(c2)[C=H]1Cc1ccccc1(C| 2     | -14.322118 | 0.60735232 | 0.73507661 |
| O=C1NCCCC[C@H]2N[C(=O)]C[OHH](N)CCCCNC(O)CCCCCnnn(c2)[C=H]1Cc1ccccc1(C| 3     | -3.2473774 | 0.36002895 | 0.7288464 |
| O=C1NCCCC[C@H]2N[C(=O)]C[OHH](N)CCCCNC(O)CCCCCnnn(c2)[C=H]1Cc1ccccc1(C| 4     | -0.17650503 | 0.41468045 | 0.74923283 |
| O=C1NCCCC[C@H]2N[C(=O)]C[OHH](N)CCCCNC(O)CCCCCnnn(c2)[C=H]1Cc1ccccc1(C| 5     | -19.520784 | 0.31402269 | 0.83290458 |
| O=C1NCCCC[C@H]2N[C(=O)]C[OHH](N)CCCCNC(O)CCCCCnnn(c2)[C=H]1Cc1ccccc1(C| 6     | -9.6214275 | 0.37753254 | 0.72670829 |
| O=C1NCCCC[C@H]2N[C(=O)]C[OHH](N)CCCCNC(O)CCCCCnnn(c2)[C=H]1Cc1ccccc1(C| 7     | -9.8396349 | 0.63542295 | 0.85442364 |
| O=C1NCCCC[C@H]2N[C(=O)]C[OHH](N)CCCCNC(O)CCCCCnnn(c2)[C=H]1Cc1ccccc1(C| 8     | -1.8342946 | 0.51106262 | 0.76519442 |
| O=C1NCCCC[C@H]2N[C(=O)]C[OHH](N)CCCCNC(O)CCCCCnnn(c2)[C=H]1Cc1ccccc1(C| 9     | -18.378744 | 0.34596333 | 0.74453593 |
| O=C1NCCCC[C@H]2N[C(=O)]C[OHH](N)CCCCNC(O)CCCCCnnn(c2)[C=H]1Cc1ccccc1(C| 10    | -11.323607 | 0.50315166 | 0.87528473 |
| O=C1NCCCC[C@H]2N[C(=O)]C[OHH](N)CCCCNC(O)CCCCCnnn(c2)[C=H]1Cc1ccccc1(C| 11    | -4.5649004 | 0.5886426 | 0.7012735 |
| O=C1NCCCC[C@H]2N[C(=O)]C[OHH](N)CCCCNC(O)CCCCCnnn(c2)[C=H]1Cc1ccccc1(C| 12    | 3.5529692 | 0.46205592 | 0.77413642 |
| O=C1NCCCC[C@H]2N[C(=O)]C[OHH](N)CCCCNC(O)CCCCCnnn(c2)[C=H]1Cc1ccccc1(C| 13    | -88.543777 | 0.44779876 | 0.69951922 |
| O=C1NCCCC[C@H]2N[C(=O)]C[OHH](N)CCCCNC(O)CCCCCnnn(c2)[C=H]1Cc1ccccc1(C| 14    | -108.15442 | 0.38272107 | 0.86493093 |
| O=C1NCCCC[C@H]2N[C(=O)]C[OHH](N)CCCCNC(O)CCCCCnnn(c2)[C=H]1Cc1ccccc1(C| 15    | -96.003441 | 0.33027884 | 0.84070128 |
| O=C1NCCCC[C@H]2N[C(=O)]C[OHH](N)CCCCNC(O)CCCCCnnn(c2)[C=H]1Cc1ccccc1(C| 16    | -96.254021 | 0.55230206 | 0.85025734 |
| O=C1NCCCC[C@H]2N[C(=O)]C[OHH](N)CCCCNC(O)CCCCCnnn(c2)[C=H]1Cc1ccccc1(C| 17    | -114.26881 | 0.29692572 | 0.8412727 |
| O=C1NCCCC[C@H]2N[C(=O)]C[OHH](N)CCCCNC(O)CCCCCnnn(c2)[C=H]1Cc1ccccc1(C| 18    | -94.35981 | 0.41035461 | 0.84274638 |
| O=C1NCCCC[C@H]2N[C(=O)]C[OHH](N)CCCCNC(O)CCCCCnnn(c2)[C=H]1Cc1ccccc1(C| 19    | 21.7721 | 0.37631527 | 0.85723019 |
| Chemical Structure | LogP | logD | logB |
|--------------------|------|------|------|
| O=C1NCCCC[C@H]2NC(=O)CC2ccc(NC(=O)CCc3n(nc3)]C@H)1Cc1ccc1cc2 | 20   | 32.2103 | 0.4299 | 0.9097 |
| O=C1NCCCC[C@H][NC(=O)C@@H][N]C(CN(O)CCc2nn(nc2)[C@H]1Cc1ccc1cc1][C(OC)]=O | 21   | -20.42511 | 0.62381011 | 0.7540288 |
| O=C1NCCCC[C@H][NC(=O)C@@H][N]C(CN(O)CCc2nn(nc2)[C@H]1Cc1ccc1cc1][C(OC)]=O | 22   | -22.050838 | 0.37934071 | 0.83368534 |
| O=C1NCCCC[C@H]2NC(=O)CC2ccc(NC(=O)CCc3n(nc3)]C@H)1Cc1ccc1cc1 | 23   | -7.3923335 | 0.2720947 | 0.85539728 |
| O=C1NCCCC[C@H]2NC(=O)CC2ccc(NC(=O)CCc3n(nc3)]C@H)1Cc1ccc1cc1 | 24   | -6.8267436 | 0.39542383 | 0.96092379 |
| O=C1NCCCC[C@H]2NC(=O)CC2ccc(NC(=O)CCc3n(nc3)]C@H)1Cc1ccc1cc1 | 25   | -7.3923335 | 0.2720947 | 0.85539728 |
| O=C1NCCCC[C@H]2NC(=O)CC2ccc(NC(=O)CCc3n(nc3)]C@H)1Cc1ccc1cc1 | 26   | -16.879242 | 0.39819816 | 0.94482762 |
| O=C1NCCCC[C@H]2NC(=O)CC2ccc(NC(=O)CCc3n(nc3)]C@H)1Cc1ccc1cc1 | 27   | -2.6672537 | 0.54260963 | 0.87756228 |
| O=C1NCCCC[C@H][NC(=O)C@@H][N]C(CN(O)CCc2nn(nc2)[C@H]1Cc1ccc1cc1][C(OC)]=O | 28   | 0.34442022 | 0.41999263 | 0.78562939 |
| O=C1NCCCC[C@H][NC(=O)C@@H][N]C(CN(O)CCc2nn(nc2)[C@H]1Cc1ccc1cc1][C(OC)]=O | 29   | 6.9792137 | 0.36260137 | 0.82622057 |
| O=C1NCCCC[C@H]2NC(=O)CC2ccc(NC(=O)CCc3n(nc3)]C@H)1Cc1ccc1cc1 | 30   | 9.1514597 | 0.39401668 | 0.75762069 |
| O=C1NCCCC[C@H]2NC(=O)CC2ccc(NC(=O)CCc3n(nc3)]C@H)1Cc1ccc1cc1 | 31   | 14.207901 | 0.51528609 | 0.79837269 |
| O=C1NCCCC[C@H][NC(=O)C@@H][N]C(CN(O)CCc2nn(nc2)[C@H]1Cc1ccc1cc1][C(OC)]=O | 32   | -4.9668097 | 0.45067513 | 0.68744051 |
| O=C1NCCCC[C@H][NC(=O)C@@H][N]C(CN(O)CCc3n(nc3)]C@H)1Cc1ccc1cc1][C(OC)]=O | 33   | 4.542604 | 0.42529106 | 0.89633834 |
| O=C1NCCCC[C@H]2NC(=O)CC2ccc(NC(=O)CCc3n(nc3)]C@H)1Cc1ccc1cc1 | 34   | 11.954076 | 0.30352968 | 0.89746457 |
| O=C1NCCCC[C@H][NC(=O)C@@H][N]C(CN(O)CCc2nn(nc2)[C@H]1Cc1ccc1cc1][C(OC)]=O | 35   | -91.403183 | 0.4733561 | 0.6595912 |
| O=C1NCCCC[C@H][NC(=O)C@@H][N]C(CN(O)CCc3n(nc3)]C@H)1Cc1ccc1cc1][C(OC)]=O | 36   | -117.00694 | 0.29085389 | 0.92186409 |
| O=C1NCCCC[C@H]2NC(=O)CC2ccc(NC(=O)CCc3n(nc3)]C@H)1Cc1ccc1cc1 | 37   | -101.00074 | 0.35293689 | 0.93048453 |
| O=C1NCCCC[C@H][NC(=O)C@@H][N]C(CN(O)CCc2nn(nc2)[C@H]1Cc1ccc1cc1][C(OC)]=O | 38   | -72.761948 | 0.32672498 | 0.91003609 |
| O=C1NCCCC[C@H][NC(=O)C@@H][N]C(CN(O)CCc2nn(nc2)[C@H]1Cc1ccc1cc1][C(OC)]=O | 39   | -94.11911 | 0.29713649 | 0.88092822 |
| O=C1NCCCC[C@H]2NC(=O)CC2ccc(NC(=O)CCc3n(nc3)]C@H)1Cc1ccc1cc1 | 40   | -64.506279 | 0.27160886 | 0.84741575 |
| O=C1NCCCC[C@H]2NC(=O)CC2ccc(NC(=O)CCc3n(nc3)]C@H)1Cc1ccc1cc1 | 41   | -84.860443 | 0.29323732 | 0.93158513 |
| O=C1NCCCC[C@H][NC(=O)C@@H][N]C(CN(O)CCc3n(nc3)]C@H)1Cc1ccc1cc1][C(OC)]=O | 42   | 16.861866 | 0.42829001 | 0.97634572 |
| O=C1NCNC[C@@H](N)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 133 | 20.141994 | 0.36281759 | 0.88496989 |
| O=C1NCNC[C@@H]2NC(=O)[C@@H](N)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 43 | 30.216309 | 0.48582417 | 0.84051621 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1(C)(O)=O | 44 | -5.4302721 | 0.4966419 | 0.64285988 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1(C)(O)=O | 45 | -3.4149508 | 0.5272125 | 0.79831368 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 46 | 9.2347794 | 0.34794316 | 0.79531246 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 47 | 12.712286 | 0.57459515 | 0.84453958 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 48 | 14.881308 | 0.37162387 | 0.76978368 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 49 | -17.769306 | 0.5007661 | 0.6696705 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 50 | -6.6144142 | 0.42122838 | 0.83994621 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 51 | 4.2219515 | 0.36738986 | 0.78082758 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 52 | -82.05674 | 0.54875678 | 0.64977336 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 53 | -12.096288 | 0.56741917 | 0.65458477 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 54 | -11.137595 | 0.54705954 | 0.85922724 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 55 | 6.9486489 | 0.31544626 | 0.79178888 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 56 | -12.13857 | 0.56426167 | 0.64529794 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 57 | -82.05674 | 0.54875678 | 0.64977336 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 58 | -102.69968 | 0.42496893 | 0.80071694 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 59 | -63.343781 | 0.37705129 | 0.751553 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 60 | -82.77709 | 0.58810478 | 0.7517092 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 61 | -80.352592 | 0.39169192 | 0.87295389 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 62 | -104.75678 | 0.47762802 | 0.94119376 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 63 | -63.992599 | 0.31471997 | 0.83503079 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 64 | -9.718503 | 0.47863344 | 0.64831448 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 65 | -8.3961773 | 0.60411292 | 0.67564666 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 66 | 11.761711 | 0.35096869 | 0.84563184 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 67 | -18.718 | 0.511 | 0.5932 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 68 | -8.4456005 | 0.4308047 | 0.86673069 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 69 | 6.9916992 | 0.30446689 | 0.82000983 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 70 | 17.265985 | 0.40353775 | 0.7802431 |
| O=C1NC[C@H](N)CCNC(=O)CCc2nnn(c2)[C@H]1Cc1ccc1c1 | 71 | 11.222864 | 0.43740579 | 0.68413889 |
| Chemical Structure | Energy (kcal/mol) | Enthalpy (kcal/mol) | Entropy (cal/mol K) |
|--------------------|------------------|---------------------|--------------------|
| O=C1NC[[@H](NC(=O)CCc2n(ncn2)[@H]1Cc1ccc1)C(OC)=O | 72 | 10.067511 | 0.41724644 | 0.87867606 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 73 | 2.54427121 | 0.35860908 | 0.87867606 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 74 | 17.209806 | 0.61315691 | 0.73103625 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 75 | 17.272606 | 0.34479324 | 0.83280057 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 76 | 17.272606 | 0.33758074 | 0.90776217 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 77 | 17.272606 | 0.41697910 | 0.66488814 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 78 | 17.272606 | 0.37090600 | 0.88365996 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 79 | 17.272606 | 0.45645005 | 0.63577461 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 80 | 17.272606 | 0.45334679 | 0.83441211 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 81 | 17.272606 | 0.58475274 | 0.85370725 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 82 | 17.272606 | 0.43904787 | 0.82960278 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 83 | 17.272606 | 0.44628623 | 0.68228304 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 84 | 17.272606 | 0.56439245 | 0.80527276 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 85 | 17.272606 | 0.45346797 | 0.83441211 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 86 | 17.272606 | 0.38330805 | 0.86330497 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 87 | 17.272606 | 0.56439245 | 0.80527276 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 88 | 17.272606 | 0.62275279 | 0.84016353 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 89 | 17.272606 | 0.50404018 | 0.80163246 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 90 | 17.272606 | 0.63432962 | 0.74538469 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 91 | 17.272606 | 0.63055748 | 0.73572159 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 92 | 17.272606 | 0.60197908 | 0.97194690 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 93 | 17.272606 | 0.56670898 | 0.93692285 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 94 | 17.272606 | 0.49470905 | 0.80682433 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 95 | 17.272606 | 0.50868237 | 0.88095331 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 96 | 17.272606 | 0.37540352 | 0.86856055 |
| O=C1NC[[@H](NC(=O)CCc2n2nn(c2)[@H]1Cc1ccc1)C(OC)=O | 97 | 17.272606 | 0.49921075 | 0.72851467 |
| Reaction | Energy (kcal/mol) | ZPE (kcal/mol) | Enthalpy (kcal/mol) | Gibbs Free Energy (kcal/mol) |
|----------|------------------|----------------|--------------------|-----------------------------|
| O=C1N[C@H]1(CCc2nncc2CCC(O)NCC[C@H]1NC(=O)NC)c2)C(=O)=O | -24.540197 | 0.46330363 | 0.71350104 |
| O=C1N[C@H]1(CCc2nncc2CCC(O)NCC[C@H]1NC(=O)NC)c2)C(=O)=O | -24.540197 | 0.46330363 | 0.71350104 |
| O=C1N[C@H]1(CCc2nncc2CCC(O)NCC[C@H]1NC(=O)NC)c2)C(=O)=O | -24.540197 | 0.46330363 | 0.71350104 |
| O=C1N[C@H]1(CCc2nncc2CCC(O)NCC[C@H]1NC(=O)NC)c2)C(=O)=O | -24.540197 | 0.46330363 | 0.71350104 |
| O=C1N[C@H]1(CCc2nncc2CCC(O)NCC[C@H]1NC(=O)NC)c2)C(=O)=O | -24.540197 | 0.46330363 | 0.71350104 |
| O=C1N[C@H]1(CCc2nncc2CCC(O)NCC[C@H]1NC(=O)NC)c2)C(=O)=O | -24.540197 | 0.46330363 | 0.71350104 |
| O=C1N[C@H]1(CCc2nncc2CCC(O)NCC[C@H]1NC(=O)NC)c2)C(=O)=O | -24.540197 | 0.46330363 | 0.71350104 |
| O=C1N[C@H]1(CCc2nncc2CCC(O)NCC[C@H]1NC(=O)NC)c2)C(=O)=O | -24.540197 | 0.46330363 | 0.71350104 |

**Note:** The table above shows the energy, ZPE, enthalpy, and Gibbs free energy for various chemical reactions, with values rounded to three decimal places. The reactions are presented in a tabular format for clarity and ease of reading.
| Structure                                                                 | E    | ΔG  | ΔH  |
|--------------------------------------------------------------------------|------|-----|-----|
| O=C1NCCNC[C@H](NC(=O)CCNC(=O)[C@@H](C)C(=O)N[C@@H](n2nncc2CCC(=O)NC[C@H](N)C(=O)N[C@H]1Cc1cccc1)Cc1ccccc1)C(OC)=O | -48.75119 | 0.26812798 | 0.90605903 |
| O=C1N[C@H](C)C(=O)[N[C@@H](CCCCNC(=O)[C@@H](n2nncc2CCC(=O)NCC[C@H](N)C(=O)N[C@H]1Cc1cccc1)Cc1ccccc1)C(OC)=O | 6.6724072 | 0.69883889 | 0.86827999 |
| O=C1N[C@H](C)C(=O)[N[C@@H](CCCCNC(=O)[C@@H](n2nncc2CCC(=O)NCC[C@H](N)C(=O)N[C@H]1Cc1cccc1)Cc1ccccc1)C(OC)=O | 28.431448 | 0.48605844 | 0.7899878 |
| O=C1N[C@H](C)C(=O)[N[C@@H](CCCCNC(=O)[C@@H](n2nncc2CCC(=O)NCC[C@H](N)C(=O)N[C@H]1Cc1cccc1)Cc1ccccc1)C(OC)=O | 48.042835 | 0.48135337 | 0.7123825 |
| O=C1NCCNC(=O)[NHC@@H](CCCN=C(O)[C@H](n2nncc2CCC(=O)NCC[C@H](N)C(=O)N[C@H]1Cc1cccc1)Cc1ccccc1)C(OC)=O | -22.956503 | 0.44217589 | 0.7771526 |
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19. NMR Spectra

Building block B
Building block D
Building block E
Building block F
Building block 1
Building block 2
Building block 3
Building block 4
Building block 5
Building block 7
Building block 8
Building block 9
Building block 10
Building block 11
Building block 12
Building block 13
Building block G
Building block H
B2
C7
C8
C12
D3
G4
B3w
B8w
B5x
B11x
C3x
C8x
E1x
E3x
E7x
B2y
D14z