Supporting Information

14-membered Macrocyclic Ring-derived Tool Box: The Identification of Small Molecule Inhibitors of Angiogenesis and an Early Embryo Development in Zebrafish-based Assay

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[##]LC: Syngene International Pvt. Ltd. Bangalore, India

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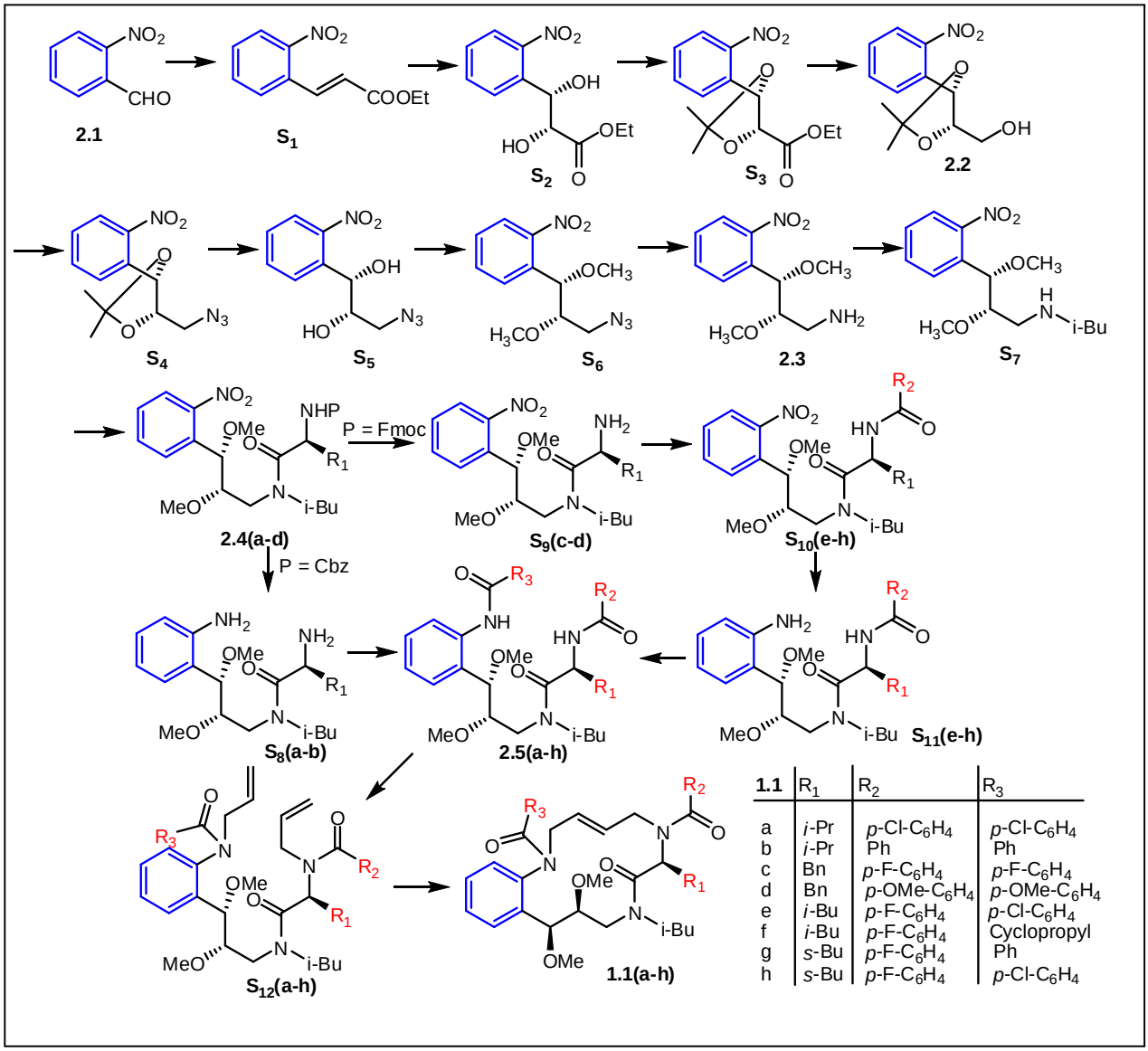
i) Abbreviations:

Aq	Aqueous
Bn	Benzyl
DBU	1,8-Diazabicyclo-[5.4.0]-undec-7-ene
DCM	Dichloromethane
DIPEA	N, N-Diisopropylethylamine
DMF	Dimethylformamide
Et	Ethyl
EtOAc	Ethyl acetate
Eq	Molar equivalent(s)
HBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium Hexafluorophosphate
Me	Methyl
NMR	Nuclear magnetic resonance
Ph	Phenyl
rt	Room temperature
TBAI	Tetrabutylammonium iodide
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

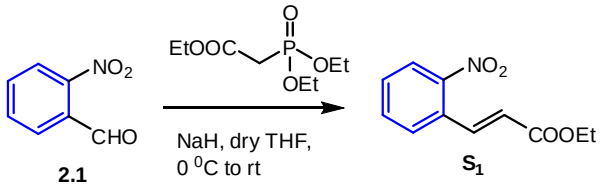
ii) General Information:

^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on Varian 400 MHz. NMR spectrometer at the frequency indicated. Where indicated, NMR peak assignments were made using COSY experiments. All chemical shifts are quoted on the δ-scale and were referenced to residual solvent as an internal standard. Combinations of the following abbreviations are used to describe NMR spectra: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. Mass spectra and LCMS were recorded using electron impact, chemical ionisation or electrospray ionisation techniques, on Agilent-6430 mass spectrometer. High-performance liquid chromatography was carried out on Agilent-1200 instrument using X-BRIDGE C-18 150×4.6mm 5µ column. Thin layer chromatography (TLC) was carried out on aluminium sheets coated with silica gel $60F_{254}$ (Merck, 1.05554) and the spots were visualized with UV light at 254 nm or alternatively by staining with aqueous basic potassium permanganate or ceric ammonium molybdate. Flash column chromatography was performed using silica gel (Merck, 60A, 230-400 Mesh). Commercially available reagents were used as supplied and some of them were distilled before use. All reactions were performed in oven dried glassware. DMF, DCM, MeOH and THF were dried immediately prior to use according to standard procedures: Dimethylformamide, Dichloromethane was distilled under N_2 from CaH_2, Methanol was distilled under N_2 over Mg and tetrahydrofuran was distilled under N_2 over Na. All solvents were removed by evaporation under reduced pressure.

iii) General Experimental procedures of Macrocycle 1.1



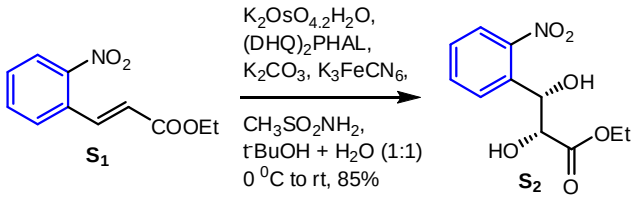
1.1	R_1	R_2	R_3
a	*i*-Pr	*p*-Cl-C_6H_4	*p*-Cl-C_6H_4
b	*i*-Pr	Ph	Ph
c	Bn	*p*-F-C_6H_4	*p*-F-C_6H_4
d	Bn	*p*-OMe-C_6H_4	*p*-OMe-C_6H_4
e	*i*-Bu	*p*-F-C_6H_4	*p*-Cl-C_6H_4
f	*i*-Bu	*p*-F-C_6H_4	Cyclopropyl
g	*s*-Bu	*p*-F-C_6H_4	Ph
h	*s*-Bu	*p*-F-C_6H_4	*p*-Cl-C_6H_4



(E)-ethyl 3-(2-nitrophenyl)acrylate (S_1):

To a suspension of 60 % NaH (2.36 g, 98.33 mmol) in dry THF (100 mL), triethyl phosphonoacetate (26 mL, 131.14 mmol) was added at 0 °C, and stirred under nitrogen atmosphere for 30 min. A solution of 2-nitro-benzaldehyde (10 g, 66 mmol) in THF was then added drop wise to the reaction mixture and allowed to stir for 2 h at 0 °C. After completion of the reaction, reaction mixture was quenched by the addition of saturated ammonium chloride solution (20 mL) and extracted with ethyl acetate (3 X 200 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography (1:19 ethyl acetate/hexanes) to give the compound **S_1** (13.5 g ,92.4% yield) as yellow liquid.

Molecular Formula: $C_{11}H_{11}NO_4$; R_f : 0.25 (1:19 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.11 (d, *J* = 15.81 Hz, 1H), 8.04 (d, *J* = 8.05 Hz, 1H), 7.70-7.61 (m, 2H), 7.59-7.50 (m, 1H), 6.37 (d, *J* = 15.81 Hz, 1H), 4.29 (q, *J* = 7.14 Hz, 2H), 1.35 (t, *J* = 7.14 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 165.7, 139.7, 133.4, 130.2, 129.0, 124.8, 123.3, 60.8, 14.2; LRMS: (ES+) m/z = 222.2 (M+1)

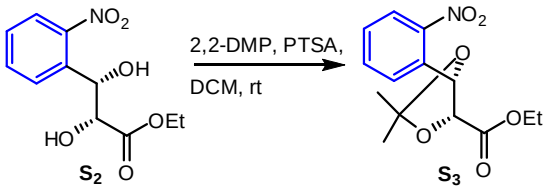


(2R,3S)-ethyl 2,3-dihydroxy-3-(2-nitrophenyl)propanoate (S_2):

To a stirred mixture of $K_3Fe(CN)_6$ (44 g, 133 mmol), K_2CO_3 (18.7 g, 135.3 mmol), $(DHQ)_2PHAL$ (520 mg, 0.67 mmol), K_2OsO_4 (60 mg, 0.18 mmol), methane sulfonamide (4.29 g, 45.19 mmol) in *t*-BuOH (300 mL) and water (300 mL), a solution of **S_1** (10 g, 45.20 mmol) in *t*-BuOH (100 mL) was added at a time at 0 °C and allowed to stir for 12 h at room temperature. After completion of the reaction, reaction mixture was quenched by the addition of solid sodium

sulfite and extracted with ethyl acetate (3 X 300 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography (3:7 ethyl acetate/hexanes) to give the compound **S_2** (9.1 g, 81% yield) as white solid.

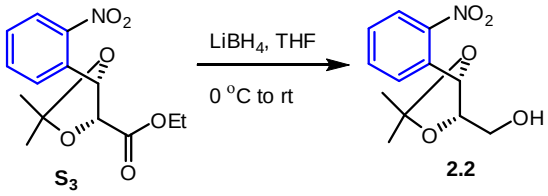
Molecular Formula: $C_{11}H_{13}NO_6$; R_f: 0.3 (3:7 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.01 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.68 (t, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 5.71 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 1H), 4.52 (dd, J_1 = 5.6 Hz, J_2 = 2.4 Hz, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.29 (d, *J* = 6.8 Hz, 1H), 3.02 (d, *J* = 5.6Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.5, 147.4, 135.9, 133.3, 129.4, 128.6, 124.4, 73.3, 69.6, 62.4, 14.0; LRMS: (ES+) m/z = 256.3 (M+1)



(4R,5S)-ethyl 2,2-dimethyl-5-(2-nitrophenyl)-1,3-dioxolane-4-carboxylate (S_3):

To a solution of the compound **S_2** (8.5 g, 33.34mmol) in dry dichloromethane (200 mL), 2,2-dimethoxy propane (8.16 mL, 66.68 mmol) and *p*-TSA (50 mg) were added. The reaction mixture was stirred at room temperature for 12 h under nitrogen atmosphere. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution, and extracted with dichloromethane (3 X 100 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography (1:9 ethyl acetate/hexanes) to give the compound **S_3** (8.8 g, 86% yield) as yellow liquid.

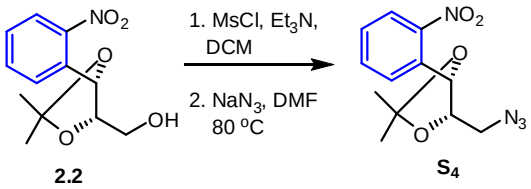
Molecular Formula: $C_{14}H_{17}NO_6$; R_f : 0.25 (1:9 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.98(d, *J* = 8.0 Hz, 1H), 7.87(d, *J* = 8.0 Hz, 1H), 7.69(t, *J* = 8.0 Hz, 1H), 7.49(t, *J* = 8.0 Hz, 1H), 5.85 (d, *J* = 7.6 Hz, 1H), 4.3 (m, 1H), 1.63 (s, 3H), 1.60 (s, 3H), 1.25(t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 169.6, 148.1, 133.6, 133.3, 129.1, 128.4, 124.6, 112.0, 81.6, 76.1, 61.7, 26.7, 25.9, 13.8; LRMS: (ES+) m/z = 296.3 (M+1)



((4S,5S)-2,2-dimethyl-5-(2-nitrophenyl)-1,3-dioxolan-4-yl)methanol (2.2):

To a solution of **S3** (8.5 g, 27.51mmol) in dry THF (150 mL), at 0 °C, $LiBH_4$ (1.2 g, 55.02 mmol) was added, and reaction mixture was allowed to stir for 24 h at room temperature. After completion of the reaction, reaction mixture was quenched by the addition of ice cold water, and extracted with ethyl acetate (3 X 100 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography (3:7 ethyl acetate/hexanes) to give the compound **2.2** (6.6 g, 94.8% yield) as yellow liquid.

Molecular Formula: $C_{12}H_{15}NO_5$; R_f: 0.3 (3:7 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.85 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 5.40 (d, *J* = 8.4 Hz, 1H), 4.00 (m, 1H), 3.90 (dd, J_1 = 12.0 Hz, J_2 = 3.2 Hz, 1H), 3.81 (dd, J_1 = 12.0 Hz, J_2 = 5.2 Hz, 1H), 1.58 (s, 3H), 1.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 149.2, 133.3, 132.9, 129.2, 128.9, 124.2, 109.7, 84.4, 74.2, 61.6, 27.1, 26.9; LRMS: (ES+) m/z = 254.2 (M+1)

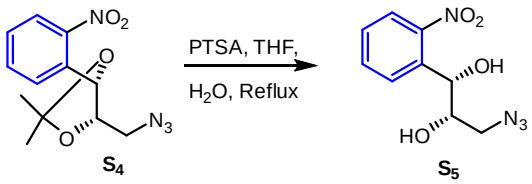


(4S,5S)-4-(azidomethyl)-2,2-dimethyl-5-(2-nitrophenyl)-1,3-dioxolane (S_4):

To a solution of **2.2** (6 g, 23.71mmol) in dry dichloromethane (150 mL), at 0 °C, Et_3N (9.98 mL, 71.13 mmol) and methane sulfonyl chloride were added, and reaction mixture was allowed to stir for 1 h at room temperature. After completion of the reaction, reaction mixture was quenched by the addition of sodium bicarbonate solution, and extracted with dichloromethane (3 X 100 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude liquid (7.5 g).

To a solution of above crude in dry DMF, NaN_3 (2.9 g, 45.2 mmol) was added, and reaction mixture was heated at 80 °C for 10 h. After completion of the reaction, reaction mixture was quenched by the addition of sodium bicarbonate solution, and extracted with dichloromethane (3 X 100 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude liquid, which was purified by column chromatography (1:4 ethyl acetate/hexanes) to give the compound **S_4** (5.3 g, 80.3% yield) as yellow liquid.

Molecular Formula: $C_{12}H_{14}N_4O_4$; R_f : 0.3 (1:9 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.89 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 5.42 (d, *J* = 8.0 Hz, 1H), 4.05 (m, 1H), 3.65 (dd, J_1 = 13.2 Hz, J_2 = 3.2 Hz, 1H), 3.52 (dd, J_1 = 13.2 Hz, J_2 = 6.0 Hz, 1H), 1.60 (s, 3H), 1.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 149.2, 133.4, 132.6, 129.2, 129.1, 124.3, 110.3, 82.9, 74.8, 51.3, 29.6, 27.0, 26.9; LRMS: (ES+) m/z = 279.3 (M+1)



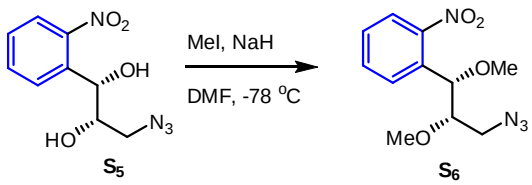
S_4 **S_5**

(1S,2S)-3-azido-1-(2-nitrophenyl)propane-1,2-diol (S_5):

To a solution of **S_4** (5.3 g, 19.06 mmol) in THF (150 mL), PTSA (9.83 g, 57.19 mmol) and water 10 mL were added, and reaction mixture was allowed to reflux for 12 h. After completion of the reaction, reaction mixture was quenched by the addition of sodium bicarbonate solution, and extracted with ethyl acetate (3 X 100 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography (3:7 ethyl acetate/hexanes) to give the compound **S_5** (4.5 g, 99% yield) as yellow liquid.

Molecular Formula: $C_9H_{10}N_4O_4$; R_f: 0.3 (3:7 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.97(m, 1H), 7.75(m, 1H), 7.64(m, 1H), 7.51(m, 1H), 5.25(m, 1H), 4.0(m, 1H), 2.90-3.56

(m, 1H) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 147.5, 136.5, 133.6, 128.8, 128.7, 124.7, 73.0, 69.1, 54.3; LRMS: (ES+) m/z = 239.1 (M+1)

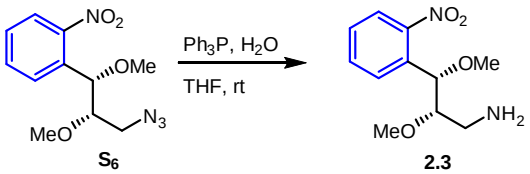


S5 **S6**

1-((1S,2S)-3-azido-1,2-dimethoxypropyl)-2-nitrobenzene (S6):

To a -78 °C solution of **NaH** (2.72 g, 113.35 mmol) and **MeI** (11.7 mL, 188.9 mmol) in DMF (150 mL) was added a solution of **S$_5$** (4.5 g, 18.89mmol) in DMF. The solution was stirred for 5 min, allowed to warm to room temperature. The solution was stirred for 1 h and then quenched by drop wise addition of NH_4Cl solution (20 mL), and extracted with ethyl acetate (3 X 100 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography (3:7 ethyl acetate/hexanes) to give the compound **S$_6$** (4.5 g, 89.5% yield) as yellow liquid.

Molecular Formula: $C_{11}H_{14}N_4O_4$; R_f : 0.3 (1:4 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.97 (d, *J* = 8.18 Hz, 1H), 7.78 (d, *J* = 7.85 Hz, 1H), 7.67 (t, *J* = 7.59 Hz, 1H), 7.49 (t, *J* = 7.74 Hz, 1H), 5.01 (d, *J* = 3.14 Hz, 1H), 3.68 (td, *J* = 7.76, 3.97 Hz, 1H), 3.39 (dd, *J* = 12.60, 7.61 Hz, 1H), 3.35-3.27 (m, 4H), 3.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 149.2, 133.6, 133.0, 129.4, 128.6, 124.5, 82.5, 77.9, 60.0, 57.8, 51.6; LRMS: (ES+) m/z = 267.3 (M+1)

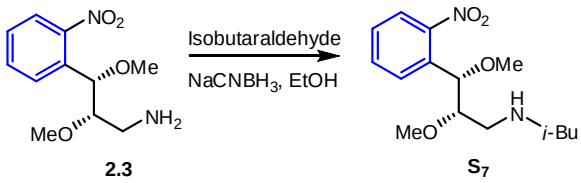


S6 **2.3**

(2S,3S)-2,3-dimethoxy-3-(2-nitrophenyl)propan-1-amine (2.3):

To a solution of the compound **S$_6$** (4.5 g, 16.90 mmol) in THF (50 mL), TPP (8.85 g, 33.38 mmol) and water (3 mL, 169 mmol) were added and stirred for 24 h. After completion of the reaction, reaction mixture was concentrated to leave a residue, which was purified by column chromatography (4:1 ethyl acetate/hexanes) to give the compound **2.3** (3.8 g, 93.6% yield) as light yellow oil.

Molecular Formula: $C_{11}H_{16}N_2O_4$; R_f (solvent system): 0.3 (ethyl acetate/hexane)

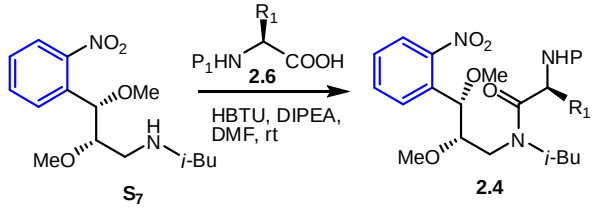


2.3 **S_7**

(2S,3S)-N-isobutyl-2,3-dimethoxy-3-(2-nitrophenyl)propan-1-amine (S_7):

To a suspension of compound **2.3** (3.0 g, 12.48 mmol) in EtOH (30 mL), isobutyraldehyde (1.24 mL, 12.48 mmol) was added and stirred for 30 min. A mixture of $NaCNBH_3$ (1.18 g, 18.72 mmol) and acetic acid (50 µL) in ethanol (5 mL) were added to the reaction mixture at 0 °C allowed to stir for 1 h. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution (5 mL), and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography (3:7 ethyl acetate/hexanes) to give the compound **S_7** (2.5 g, 67.8% yield) as light yellow oil.

Molecular Formula: $C_{15}H_{24}N_2O_4$; R_f : 0.2 (3:7 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.89 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 5.09 (d, J = 4.0 Hz, 1H), 3.61 (m, 1H), 3.30 (s, 3H), 3.28 (s, 3H), 2.66 (dd, J_1 = 12.0Hz, J_2 = 3.6 Hz, 1H), 2.54 (dd, J_1 = 12.0Hz, J_2 = 8.0 Hz, 1H), 2.36 (dd, J_1 = 6.8 Hz, J_2 = 2.4 Hz, 2H), 1.71 (m, 1H), 0.89 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 149.4, 134.3, 132.5, 129.2, 128.1, 124.1, 82.8, 78.4, 59.6, 57.9, 57.7, 49.9, 28.1, 20.5, 20.4; LRMS: (ES+) m/z = 297.4 (M+1)

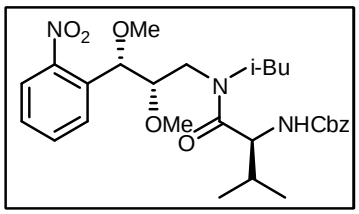


S_7 **2.4**

Compound 2.4:

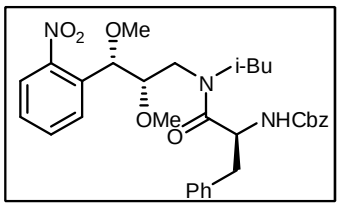
To a suspension of compound **S_7** (1 mmol) in DMF (10 mL), **2.6** (1.5 mmol), HBTU (1.5 mmol) and DIPEA (2 mmol) were added at 0 °C and allowed to stirred for 6 h. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution (10 mL), and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give the pure compound **2.4.**

Benzyl (S)-1-(((2S,3S)-2,3-dimethoxy-3-(2-nitrophenyl) propyl) (isobutyl)amino)-3-methyl-1 oxobutan-2-ylcarbamate (2.4a):



Molecular Formula: $C_{28}H_{39}N_3O_7$; R_f : 0.4 (1:4 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-88.9% (yellow liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.00 (m, 1H), 7.83 (m, 1H), 7.68 (m, 1H), 7.54-7.24 (m, 6H), 5.56 (m, 1H), 5.23-4.83 (m, 3H), 4.52 (m, 1H), 3.98-3.70 (m, 2H), 3.12 (m, 9H), 2.08-1.88 (m, 2H), 1.03-0.79 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.1, 156.3, 149.3, 149.2, 136.5, 136.5, 134.1, 133.1, 133.0, 129.4, 129.2, 128.8, 128.6, 128.5, 128.5, 128.3, 128.1, 127.9, 127.8, 127.8, 124.6, 124.4, 82.9, 81.5, 78.3, 66.6, 66.6, 60.4, 60.1, 57.6, 56.4, 55.8, 55.5, 54.1, 53.4, 48.5, 47.9, 31.4, 31.4, 28.1, 26.5, 20.1, 20.1, 19.9, 19.9, 19.8, 19.5, 16.9 ; LRMS: (ES+) m/z = 530.1 (M+1)

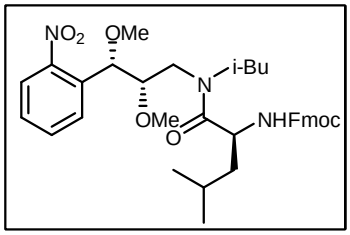
Benzyl (S)-1-(((2S,3S)-2,3-dimethoxy-3-(2-nitrophenyl) propyl) (isobutyl)amino)-1-oxo-3-phenylpropan-2-ylcarbamate (2.4b):



Molecular Formula: $C_{32}H_{39}N_3O_7$; R_f : 0.5 (1:4 ethyl acetate/hexanes) ; Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-86.0% (yellow liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.98 (d, *J* = 8.06 Hz,1H), 7.86-7.72 (m, 1H), 7.67 (t, *J* = 7.58 Hz,

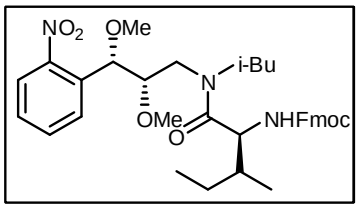
1H), 7.48 (m, 1H), 7.38-7.10 (m, 10H), 5.59 (d, *J* = 9.31 Hz, 1H), 5.16-4.74 (m, 4H), 3.84 (d, *J* = 6.79 Hz, 1H), 3.38-2.83 (m, 12H), 1.96-1.74 (m, 1H), 0.88-0.70 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.3, 172.0, 155.6, 155.5, 149.4, 149.0, 136.6, 136.5, 136.5, 136.4, 134.3, 133.5, 133.1, 133.0, 129.6, 129.3, 129.3, 129.1, 128.6, 128.4, 128.4, 128.3, 127.9, 127.8, 127.8, 126.7, 124.6, 124.4, 82.7, 81.0, 78.1, 66.6, 66.5, 60.3, 60.0, 57.8, 57.6, 56.4, 54.6, 52.1, 51.9, 48.8, 48.4, 39.6, 39.5, 28.4, 26.7, 20.2, 20.1, 19.9, 19.7; LRMS: (ES+) m/z = 578.3 (M+1)

(9H-fluoren-9-yl)methyl(S)-1-(((2S,3S)-2,3-dimethoxy-3-(2-nitro-phenyl)propyl)(isobutyl) amino)-4-methyl-1-oxopentan-2-yl carbamate (2.4c):

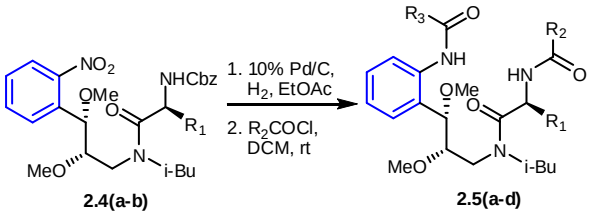


Molecular Formula: $C_{29}H_{41}N_3O_7$; R_f: 0.4 (1:4 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-85.0% (yellow liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.95 (t, *J* = 7.00 Hz, 1H), 7.79 (m, 3H), 7.71-7.55 (m, 3H), 7.46 (t, *J* = 7.33 Hz, 1H), 7.38 (t, *J* = 7.31 Hz, 2H), 7.28 (dd, *J* = 12.51, 5.22 Hz, 2H), 5.65 (d, *J* = 9.04 Hz, 1H), 5.19-4.83 (m, 1H), 4.76 (s, 1H), 4.43-4.16 (m, 3H), 4.01-3.83 (m, 1H), 3.68-3.43 (m, 1H), 3.39-3.05 (m, 8H), 2.02 (m, 1H), 1.67-1.50 (m, 1H), 1.36 (m, 1H), 1.06-0.78 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.6, 173.2, 156.1, 149.1, 143.8, 141.2, 141.2, 134.3, 133.1, 132.9, 129.4, 128.5, 128.5, 127.5, 126.9, 125.2, 124.6, 124.4, 119.8, 119.8, 82.5, 81.1, 78.2, 66.9, 60.3, 60.2, 57.7, 56.4, 53.9, 49.6, 49.3, 48.3, 47.1, 47.1, 47.0, 42.4, 28.4, 26.6, 24.6, 24.5, 23.6, 23.5, 21.4, 21.63, 20.2, 20.1, 19.9, 19.7; LRMS: (ES+) m/z = 632.1 (M+1)

(9H-fluoren-9-yl)methyl(2S,3R)-1-(((2S,3S)-2,3-dimethoxy-3-(2-nitrophenyl)propyl) (isobutyl)amino)-3-methyl-1-oxopentan-2-ylcarbamate (2.4d):



Molecular Formula: $C_{29}H_{41}N_3O_7$; R_f: 0.2 (1:9 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-85.5% (yellow liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.96 (d, *J* = 8.14 Hz, 1H), 7.79 (m, 3H), 7.71-7.55 (m, 3H), 7.53-7.23 (m, 5H), 5.64 (d, *J* = 9.35 Hz, 1H), 4.92 (d, *J* = 2.56 Hz, 1H), 4.63-4.13 (m, 4H), 3.88 (t, *J* = 7.55 Hz, 2H), 3.42-2.99 (m, 8H), 1.98 (d, *J* = 6.49 Hz, 1H), 1.86-1.47 (m, 3H), 1.02-0.75 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.2, 156.2, 149.2, 144.0, 143.8, 143.8, 141.2, 141.2, 134.1, 133.1, 133.0, 132.9, 129.4, 129.4, 128.5, 128.5, 128.4, 127.5, 127.0, 1216.9, 125.1, 125.1, 124.5, 124.4, 124.4, 119.9, 119.9, 119.8, 82.8, 82.7, 81.5, 66.9, 66.8, 60.3, 60.1, 57.8, 57.6, 56.5, 55.1, 48.1, 47.9, 47.1, 47.1, 38.3, 29.6, 28.1, 23.6, 20.1, 19.5, 15.9, 11.3; LRMS: (ES+) m/z = 632.1 (M+1)

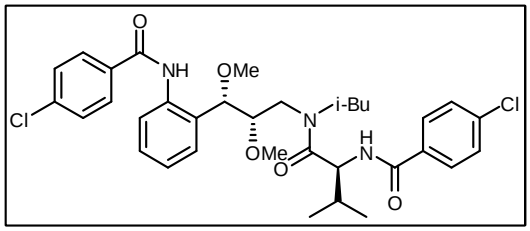


Compound 2.5(a-d):

To a suspension of compound **2.4(a-b)** (1 mmol) in ethyl acetate (10 mL), 10% Pd/C (0.2 mmol) was added and stirred the reaction mixture for 12 h under hydrogen atmosphere. After completion of the reaction, reaction mixture was passed through celite and concentrated to leave crude oil, which was subjected to the next reaction without any purification.

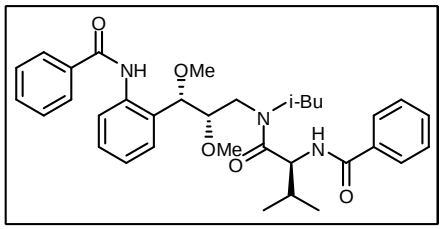
To a suspension of above compound (0.2 mmol) in DCM (10 mL), acid chloride (0.5 mmol) was added at 0 °C and allowed to stir for 10 min. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution (5 mL), concentrated, and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give pure compound **2.5(a-d).**

4-chloro-N-(2-((1S,2S)-3-((S)-2-(4-chlorobenzamido)-N-isobutyl-3-methylbutanamido)-1,2-dimethoxypropyl)phenyl)benzamide (2.5a):



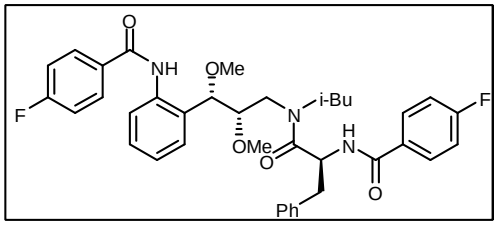
Molecular Formula: $C_{34}H_{41}Cl_2N_3O_5$; R_f : 0.5 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-85.4% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.05 (s, 1H), 8.51 (d, *J* = 8.06 Hz, 1H), 7.98-7.91 (m, 2H), 7.81-7.61 (m, 2H), 7.52-6.76 (m, 10H), 5.05 (m, 1H), 4.37 (m, 1H), 3.92-2.87 (m, 12H), 2.22-1.96 (m, 2H), 1.08-0.82 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.3, 172.1, 165.9, 165.7, 163.7, 137.7, 137.6, 137.4, 133.5, 133.3, 132.3, 132.1, 129.4, 129.2, 128.9, 128.7, 128.6, 128.6, 128.5, 128.4, 128.4, 128.3, 126.0, 123.9, 121.9, 85.9, 84.6, 83.9, 60.6, 60.2,57.2, 57.0, 56.8, 54.6, 54.5, 53.8, 49.7, 49.1, 31.7, 31.6, 28.1, 26.6, 20.2, 20.1, 20.0, 19.9, 19.5, 19.4, 17.7, 17.2; LRMS: (ES+) m/z = 642.3 (M+1)

N-(2-((1S,2S)-3-((S)-2-benzamido-N-isobutyl-3-methylbutanamido)-1,2-dimethoxy propyl)phenyl)benzamide (2.5b):



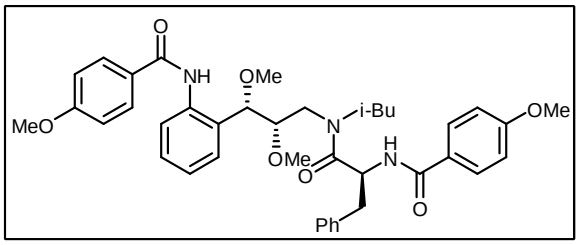
Molecular Formula: $C_{34}H_{43}N_3O_5$; R_f: 0.3(3:7 ethyl acetate/ hexanes); Yield-88.6% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.07 (s, 1H), 8.54 (d, *J* = 8.24 Hz, 1H), 8.02 (t, *J* = 7.95 Hz, 2H), 7.78 (m, 2H), 7.44 (m, 7H), 7.22-6.79 (m, 2H), 5.07 (d, *J* = 3.12 Hz, 1H), 4.40 (m, 1H), 3.91-2.91 (m, 11H), 2.11 (s, 2H), 1.08-0.82 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.5, 172.3, 167.1, 166.8, 164.9, 137.7, 135.2, 134.9, 134.0, 133.9, 131.7, 131.6, 131.5, 131.5, 129.5, 129.2, 129.0, 128.9, 128.6, 127.2, 127.1, 127.0, 126.9, 126.1, 123.8, 122.1, 85.9, 84.9, 84.0, 60.8, 60.3, 57.3, 57.1, 56.9, 54.7, 54.4, 53.8, 49.9, 49.1, 32.0, 31.9, 28.3, 26.7, 20.3, 20.1, 20.0, 19.7, 19.6, 17.7, 17.4; LRMS: (ES+) m/z = 574.3 (M+1)

4-fluoro-N-(2-((1S,2S)-3-((S)-2-(4-fluorobenzamido)-N-isobutyl-3-phenylpropanamido)-1,2-dimethoxypropyl)phenyl)benzamide (2.5c):



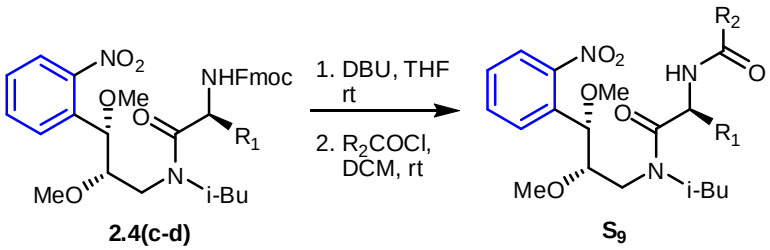
Molecular Formula: $C_{38}H_{41}F_2N_3O_5$; R_f : 0.5 (3:7 ethyl acetate/hexanes); Yield-85.4% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.94 (s, 1H), 8.42 (m, 1H), 8.10-7.90 (m, 2H), 7.69 (m, 2H), 7.46-6.69 (m, 14H), 5.44-5.25 (m, 1H), 4.43-4.23 (m, 1H), 3.86-2.95 (m, 14H), 1.98-1.76 (m, 1H), 0.97-0.72 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.6, 165.9, 165.6, 165.5, 164.2, 163.7, 163.4, 137.4, 136.4, 136.3, 131.3, 131.3, 130.9, 130.8, 129.6, 129.6, 129.5, 129.4, 129.4, 129.4, 129.3, 129.3, 129.1, 129.1, 128.9, 128.9, 128.5, 128.4, 126.9, 126.8, 126.1, 124.7, 123.8, 121.8, 1215.6, 115.5, 115.4, 115.4, 115.3, 115.2, 115.1, 114.9, 85.3, 83.9, 83.3, 60.6, 59.8, 57.2, 56.9, 56.8, 54.9, 50.8, 49.9, 49.3, 38.7, 29.5, 28.5, 26.7, 20.1, 20.0, 19.7; LRMS: (ES+) m/z = 658.1 (M+1)

N-((S)-1-(((2S,3S)-2,3-dimethoxy-3-(2-(4-methoxybenzamido)phenyl)propyl)(isobutyl) amino)-1-oxo-3-phenyl propan-2-yl)-4-methoxybenzamide (2.5d):



Molecular Formula: $C_{40}H_{47}N_3O_7$; R_f: 0.5 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-78.5% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.95 (s, 1H), 8.39 (m, 1H), 8.11-7.63 (m, 5H), 7.43-6.82 (m, 14H), 5.34 (d, *J* = 7.08 Hz, 1H), 4.45-4.25 (m, 1H), 3.92-2.98 (m, 20H), 1.95-1.71 (m, 1H), 0.82 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.8, 166.3, 16.1, 165.0, 164.5, 163.5, 162.4, 162.3, 162.2, 137.8, 137.3, 136.5, 136.4, 132.1, 129.6, 129.5, 129.3, 129.3, 129.2, 129.1, 129.0, 129.0, 128.9,

128.8, 128.8, 128.6, 128.5, 127.5, 127.1, 126.9, 126.8, 126.1, 125.9, 125.8, 124.4, 123.5, 121.9, 113.8, 113.7, 113.6, 85.3, 84.1, 83.2, 60.8, 59.9, 57.3, 56.9, 56.9, 55.4, 55.3, 54.7, 50.8, 50.5, 49.8, 49.4, 39.1, 39.0, 29.6, 28.7, 26.7, 20.1, 20.1, 20.0, 19.7; LRMS: (ES+) m/z = 682.4 (M+1)

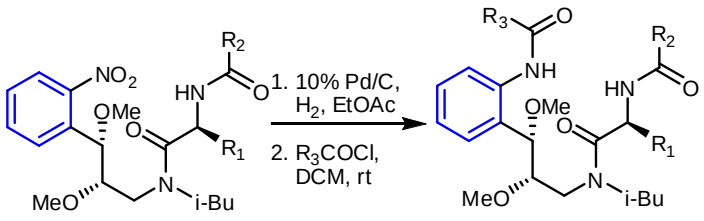


2.4(c-d) **S9**

Compound S_9:

To a suspension of compound **11(c-d)** (1 mmol) in THF (10 mL), DBU (1.5 mmol) was added and stirred the reaction mixture for 5 min. After completion of the reaction, reaction mixture concentrated and which was subjected to the next reaction without any purification.

To a suspension of above compound (0.3 mmol) in DCM (10 mL), acid chloride (0.45 mmol) was added at 0 °C and allowed to stir for 10 min. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution (5 mL), and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give pure compound **S_9**.



S9 **2.5(e-h)**

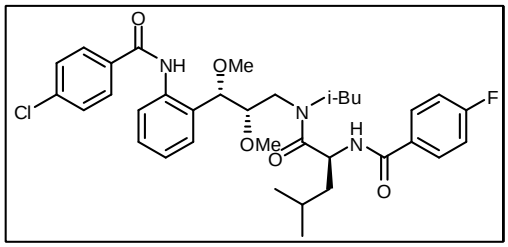
Compound 2.5(e-h):

To a suspension of compound **S_9** (1 mmol) in ethyl acetate (10 mL), 10% Pd/C (0.2 mmol) was added and stirred the reaction mixture for 12 h under hydrogen atmosphere. After completion of the reaction, reaction mixture was passed through celite and concentrated to leave 200 mg crude oil, which was subjected to the next reaction without any purification.

To a suspension of above compound (0.5 mmol) in DCM (10 mL), acid chloride (1 mmol) was added at 0 °C and allowed to stir for 10 min. After completion of the reaction, reaction mixture

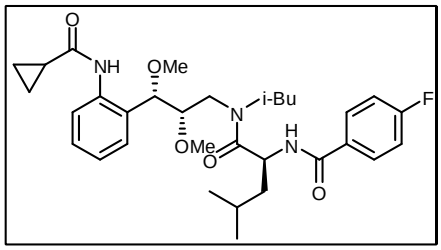
was quenched with sodium bicarbonate solution (5 mL), concentrated, and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give pure compound **13(e-h).**

4-chloro-N-(2-((1S,2S)-3-((S)-2-(4-fluorobenzamido)-N-isobutyl-4-methylpentanamido)-1,2-dimethoxypropyl)phenyl)benzamide (13e):



Molecular Formula: $C_{35}H_{43}ClFN_3O_5$; R_f : 0.5 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-86.3% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.04 (s 1H), 8.42 (m, 1H), 8.04-7.69 (m, 4H), 7.53-6.88 (m, 9H), 5.29-5.11 (m, 1H), 4.57-4.25 (m, 1H), 4.02-3.09 (m, 11H), 2.15-1.92 (m, 1H), 1.84-1.65 (m, 1H), 1.41 (m, 1H), 1.11-0.81 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.5, 173.4, 165.8, 163.8, 137.5, 133.7, 129.5, 129.4, 129.4, 129.4, 129.3, 129.0, 128.8, 128.8, 128.6, 128.5, 126.1, 123.9, 121.8, 115.6, 115.5, 115.4, 115.3, 85.6, 84.5, 83.4, 60.7, 60.4, 57.3, 57.1, 57.0, 49.5, 49.4, 48.3, 47.9, 42.6, 28.6, 26.7, 24.9, 24.7, 23.5, 21.5, 21.5, 20.3, 19.9, 19.8 ; LRMS: (ES+) m/z = 640.1 (M+1)

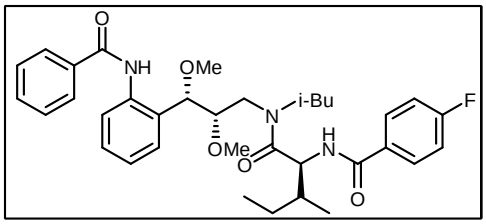
N-((S)-1-(((2S,3S)-3-(2-(cyclopropanecarboxamido)phenyl)-2,3-dimethoxypropyl) (isobutyl)amino)-4-methyl-1-oxopentan-2-yl)-4-fluorobenzamide (13f):



Molecular Formula: $C_{32}H_{44}FN_3O_5$; R_f (solvent system): 0.5 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-60.0% (white solid); ^{1}H

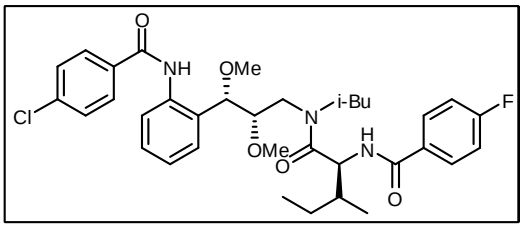
NMR ($CDCl_3$, 400 MHz): δ ppm 9.29 (s, 1H), 8.09 (m, 1H), 7.82 (m, 2H), 7.50 (d, *J* = 8.43 Hz, 1H), 7.39-7.23 (m, 2H), 7.22-6.93 (m, 4H), 5.29-5.14 (m, 1H), 4.41 (m, 1H), 4.08-3.77 (m, 1H), 3.69 (m, 1H), 3.59-3.40 (m, 2H), 3.37-3.18 (m, 6H), 2.00 (m, 1H), 1.88-1.66 (m, 2H), 1.64-1.35 (m, 3H), 0.95 (m, 17H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 178.2, 173.6, 173.5, 166.3, 166.0, 165.8, 163.5, 136.6, 130.0, 129.9, 129.7, 129.7, 129.6, 129.5, 129.4, 129.3, 128.7, 128.6, 128.4, 124.7, 115.5, 115.4, 115.3, 115.2, 84.4, 83.2, 60.8, 60.4, 57.4, 57.1, 57.0, 54.3, 49.9, 49.7, 48.4, 47.9, 42.6, 41.8, 29.56, 28.5, 26.7, 24.9, 24.7, 23.5, 23.4, 21.5, 21.5, 20.2, 20.1, 19.8, 19.7, 12.5, 8.6, 7.6, 7.5 ; LRMS: (ES+) m/z = 570.1 (M+1)

N-((2S,3R)-1-(((2S,3S)-3-(2-benzamidophenyl)-2,3-dimethoxypropyl)(isobutyl)amino)-3-methyl-1-oxopentan-2-yl)-4-fluorobenzamide (13g):

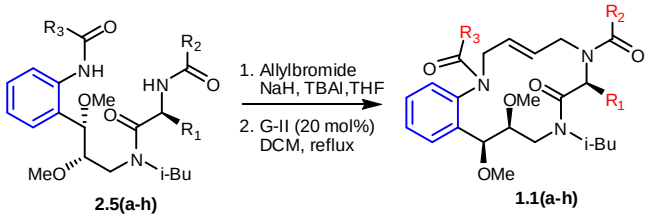


Molecular Formula: $C_{35}H_{44}FN_3O_5$; R_f : 0.5 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-86.3% (white solid); ^1H NMR ($CDCl_3$, 400 MHz): δ ppm 10.06 (s, 1H), 8.42 (m, 1H), 8.06-6.76 (m, 14H), 5.13-4.93 (m, 1H), 4.40 (m, 1H), 3.93-3.08 (m, 11H), 2.12-1.96 (m, 1H), 1.95-1.78 (m, 1H), 1.69-1.49 (m, 1H), 1.23-1.09 (m, 1H), 1.04-0.80 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.4, 172.3, 166.0, 165.9, 165.6, 164.8, 163.5, 137.6, 135.1, 134.9, 131.4, 131.4, 129.4, 129.3, 129.2, 129.2, 129.0, 128.9, 128.5, 128.5, 127.2, 127.0, 126.0, 123.8, 122.0, 115.6, 115.4, 86.0, 84.8, 83.9, 60.6, 60.2, 57.2, 57.0, 56.9, 54.8, 53.7, 53.5, 49.8, 49.1, 38.4, 38.2, 28.1, 26.6, 24.2, 23.9, 20.2, 20.0, 19.5, 16.0, 11.2, 11.1; LRMS: (ES+) m/z = 606.1 (M+1)

4-chloro-N-(2-((1S,2S)-3-((2S,3R)-2-(4-fluorobenzamido)-N-isobutyl-3-methylpentanamido)-1,2-dimethoxypropyl)phenyl)benzamide (13h):



Molecular Formula: $C_{35}H_{43}ClFN_3O_5$; R_f : 0.5 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-86.3% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.05 (s, 1H), 8.50 (d, *J* = 8.19 Hz, 1H), 8.04-7.90 (m, 2H), 7.88-7.67 (m, 2H), 7.51-7.30 (m, 3H), 7.22-6.78 (m, 4H), 5.12-4.90 (m, 1H), 4.37 (m, 1H), 3.89-3.05 (m, 10H), 2.11-1.96 (m, 1H), 1.93-1.81 (m, 1H), 1.64-1.51 (m, 1H), 1.25 (m, 1H), 1.05-0.82 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.6, 172.5, 166.0, 165.7, 163.8, 137.8, 137.7, 137.5, 1133.7, 133.4, 130.2, 129.5, 129.4, 129.3, 129.3, 129.3, 129.1, 129.0, 128.8, 128.8, 128.7, 128.7, 128.6, 126.1, 124.0, 122.0, 115.7, 115.5, 86.0, 84.9, 839, 60.7, 60.3, 57.3, 57.1, 57.0, 54.9, 53.8, 53.5, 49.2, 38.4, 38.3, 28.3, 26.7, 24.4, 24.0, 20.3, 20.1, 19.6, 16.1, 15.8, 11.3, 11.2; LRMS: (ES+) m/z = 640.1 (M+1)



2.5(a-h) **1.1(a-h)**

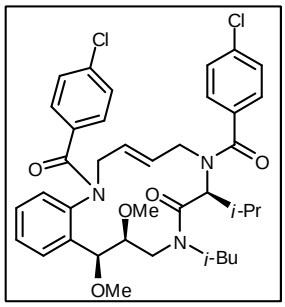
Macrocycle 1.1(a-h):

To a suspension of compound **2.5(a-h)** (0.2 mmol) in dry THF (10 mL), allyl bromide (2 mmol), NaH (1 mmol) and TBAI (0.02 mmol) were added at 0 °C and allowed to stirred at room temperature for 10 h. After completion of the reaction, reaction mixture was quenched with ammonium chloride solution (2 mL), concentrated, and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography (3:7 ethyl acetate/hexanes) to give the pure bisallyl product.

To above bisallyl compound (0.1 mmol) was taken in dry dichloromethane (50 mL) under nitrogen atmosphere and Grubb's 2nd generation catalyst (0.02 mmol) was added and reaction

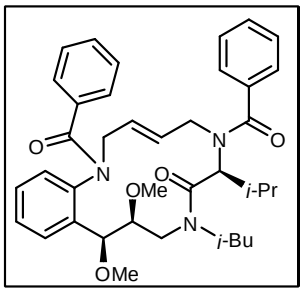
mixture was heated to 40 °C for 24 h. After completion of the reaction, reaction mixture was concentrated and subjected to column chromatography to give pure product **1.1(a-h)**.

((7S,11S,12S,E)-9-isobutyl-7-isopropyl-11,12-dimethoxy-8-oxo-7,8,9,10,11,12-hexahydro benzo[j][1,4,9]triazacyclotetradecine-1,6(2H,5H)-diyl)bis((4-chlorophenyl)methanone) (1.1a):



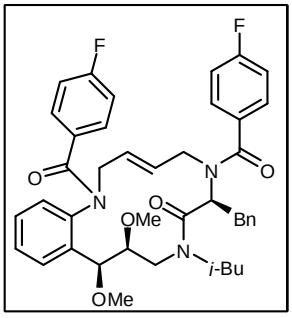
Molecular Formula: $C_{38}H_{45}Cl_2N_3O_5$; R_f : 0.3 (2:5 ethyl acetate/hexanes); Solvent system for column purification (2:5 to 1:2 ethyl acetate/hexanes); Yield-60% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.57 (d, *J* = 7.64 Hz, 1H), 7.51 (d, *J* = 8.30 Hz, 2H), 7.40-7.24 (m, 7H), 7.14 (d, *J* = 8.46 Hz, 2H), 7.06 (d, *J* = 7.59 Hz, 1H), 5.68 (bd, *J* = 16.0, 1H), 5.46 (d, *J* = 10.8, 1H), 5.33 (bd, *J* = 16.0, 1H), 4.94 (m, 1H), 4.39 (s, 1H), 4.20-4.01 (m, 3H), 3.86 (d, *J* = 18.25 Hz, 1H), 3.61-3.51 (m, 1H), 3.40 (dd, *J* = 13.24, 9.46 Hz, 1H), 3.23 (d, *J* = 9.13 Hz, 1H), 3.13 (s, 3H), 2.84 (dd, *J* = 14.58, 7.98 Hz, 1H), 2.78 (s, 3H), 2.50 (dd, *J* = 6.55, 3.92 Hz, 1H), 2.23-2.11 (m, 1H), 1.08 (dd, *J* = 6.21, 5.01 Hz, 6H), 1.00 (dd, *J* = 13.27, 6.59 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.1, 170.3, 168.8, 142.8, 136.5, 135.2, 134.8, 134.6, 133.5, 130.7, 130.2, 128.9, 128.6, 128.3, 127.9, 127.8, 126.9, 126.5, 77.3, 59.0, 57.0, 55.9, 55.0, 54.6, 46.0, 44.8, 29.6, 29.1, 28.2, 20.2, 20.0, 19.8, 17.9; LRMS: (ES+) m/z = 694.0 (M+1)

((7S,11S,12S,E)-9-isobutyl-7-isopropyl-11,12-dimethoxy-8-oxo-7,8,9,10,11,12-hexahydro benzo[j][1,4,9]triazacyclotetradecine-1,6(2H,5H)-diyl)bis((4-chlorophenyl)methanone) (1.1b):



Molecular Formula:$C_{38}H_{47}N_3O_5$; R_f: 0.3 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-68.5% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.52 (m, 3H), 7.39-7.22 (m, 9H), 7.15 (t, *J* = 7.53 Hz, 2H), 7.06 (d, *J* = 7.44 Hz, 1H), 5.75 (d, *J* = 16.66 Hz, 1H), 5.48 (d, *J* = 10.63 Hz, 1H), 5.35 (d, *J* = 15.34 Hz, 1H), 4.94 (d, *J* = 15.05 Hz, 1H), 4.47 (s, 1H), 4.19-4.10 (m, 1H), 4.08-3.96 (m, 2H), 3.93 (s, 1H), 3.52 (dd, *J* = 16.14, 3.89 Hz, 1H), 3.39 (dd, *J* = 12.82, 9.63 Hz, 1H), 3.33-3.26 (m, 1H), 3.12 (s, 3H), 2.91 (dd, *J* = 14.51, 7.53 Hz, 1H), 2.75 (s, 3H), 2.58-2.47 (m, 1H), 2.17 (m, 1H), 1.09 (dd, *J* = 6.31, 4.03 Hz, 6H), 1.03 (d, *J* = 6.82 Hz, 3H), 0.99 (d, *J* = 6.41 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.0, 170.4, 143.3, 136.3, 135.5, 134.9, 130.6, 130.3, 129.2, 128.8, 128.7, 128.7, 128.1, 127.7, 127.5, 126.8, 126.6, 126.2, 79.4, 59.1, 57.0, 55.8, 54.9, 54.2, 46.0, 45.0, 29.6, 29.0, 28.1, 20.3, 20.0, 17.9; LRMS: (ES+) m/z = 626.4 (M+1)

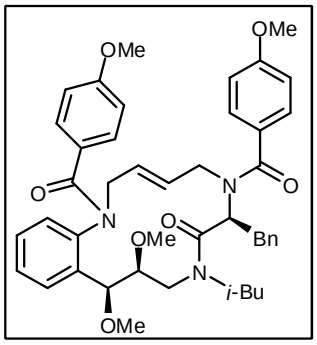
((7S,11S,12S,E)-7-benzyl-9-isobutyl-11,12-dimethoxy-8-oxo-7,8,9,10,11,12-hexahydro benzo[j][1,4,9]triazacyclotetradecine-1,6(2H,5H)-diyl)bis((4-fluorophenyl)methanone) (1.1c):



Molecular Formula: $C_{42}H_{45}F_2N_3O_5$; R_f : 0.25 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-80% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.56 (d, *J* = 7.67 Hz, 1H), 7.37-7.23 (m, 10H), 7.08 (m, 3H), 6.94 (t, *J* = 8.61 Hz, 2H), 6.82 (t, *J* = 8.49 Hz, 1H), 6.18 (t, *J* = 7.82 Hz, 1H), 5.70 (d, *J* = 16.0

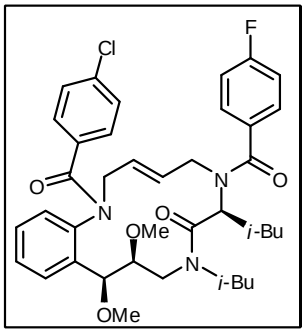
Hz, 1H), 5.34 (d, *J* = 15.93 Hz, 1H), 4.94 (d, *J* = 16.32 Hz, 1H), 4.39 (d, *J* = 1.08 Hz, 1H), 4.22 (dd, *J* = 18.28, 1.91 Hz, 1H), 4.14 (dd, *J* = 14.64, 7.77 Hz, 1H), 4.02 (d, *J* = 12.17 Hz, 1H), 3.76 (d, *J* = 18.32 Hz, 1H), 3.54 (d, *J* = 3.74 Hz, 1H), 3.34 (dd, *J* = 13.17, 9.58 Hz, 1H), 3.28-3.10 (m, 7H), 2.85 (dd, *J* = 14.69, 6.86 Hz, 1H), 2.74 (s, 3H), 1.92 (dd, *J* = 9.78, 3.80 Hz, 1H), 0.97 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.1, 170.0, 168.8, 164.8, 164.2, 162.3, 161.8, 143.0, 136.5, 134.8, 131.9, 131.9, 131.4, 131.3, 131.3, 131.2, 130.8, 129.7, 129.6, 128.9, 128.7, 128.5, 128.4, 128.3, 128.3, 127.8, 126.9, 126.8, 126.6, 115.1, 114.9, 114.9, 114.7, 79.6, 77.2, 59.0, 55.9, 55.2, 54.7, 51.9, 45.8, 44.8, 36.4, 29.6, 28.8, 20.3, 19.6; LRMS: (ES+) m/z = 710.1 (M+1)

((7S,11S,12S,E)-7-benzyl-9-isobutyl-11,12-dimethoxy-8-oxo-7,8,9,10,11,12-hexahydro benzo[j][1,4,9]triazacyclotetradecine-1,6-(2H,5H)-diyl)bis((4-methoxyphenyl)methanone) (1.1d):



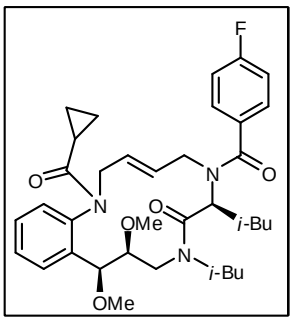
Molecular Formula: $C_{44}H_{51}N_3O_7$; R_f: 0.2 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-78.9% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.57 (d, *J* = 7.31 Hz, 1H), 7.43-7.20 (m, 12H), 7.08 (m, 3H), 6.75 (d, *J* = 8.18 Hz, 2H), 6.64 (d, *J* = 8.08 Hz, 2H), 6.14 (t, *J* = 7.6 Hz , 1H), 5.75 (d, *J* = 15.93 Hz, 1H), 5.38 (d, *J* = 15.2 Hz, 1H), 4.90 (d, *J* = 16.0 Hz, 1H), 4.45 (s, 1H), 4.07 (m, 4H), 3.94-3.82 (m, 2H), 3.73 (m, 7H), 3.60-3.46 (m, 1H), 3.39-3.08 (m, 8H), 2.79 (s, 4H), 1.98-1.82 (m, 2H), 0.94 (d, *J* = 6.58 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.6, 170.1, 161.1, 160.2, 136.8, 130.9, 130.9, 130.7, 129.7, 128.8, 128.7, 128.3, 128.2, 128.1, 127.5, 127.4, 126.9, 126.6, 113.2, 112.9, 79.5, 77.2, 59.1, 55.2, 55.1, 55.0, 54.8, 52.2, 45.5, 45.1, 36.4, 29.6, 29.6, 28.6, 20.2, 19.5; LRMS: (ES+) m/z = 734.3 (M+1)

(7S,11S,12S,Z)-1-(4-chlorobenzoyl)-6-(4-fluorobenzoyl)-7,9-diisobutyl-11,12-dimethoxy-1,2,6,7,9,10,11,12-octahydrobenzo[j][1,4,9]triazacyclotetradecin-8(5H)-one (1.1e):



Molecular Formula:$C_{39}H_{47}ClFN_3O_5$; R_f : 0.35 (3:7 ethyl acetate/hexane); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-63.5%(colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.55 (m, 3H), 7.30 (m, 5H), 7.14 (d, *J* = 8.49 Hz, 2H), 7.05 (dd, *J* = 11.83, 5.28 Hz, 3H), 5.90 (m, 1H), 5.70 (d, *J* = 15.6 Hz, 1H), 5.35 (d, *J* = 16.0 Hz, 1H), 4.90 (d, *J* = 15.6 Hz, 1H), 4.40 (s, 1H), 4.23-4.06 (m, 2H), 4.02 (d, *J* = 12.33 Hz, 1H), 3.90 (s, 1H), 3.60-3.49 (m, 1H), 3.37 (d, *J* = 13.19 Hz, 1H), 3.23 (d, *J* = 9.18 Hz, 1H), 3.13 (s, 3H), 2.91 (m, 1H), 2.78 (s, 3H), 2.18-2.01 (m, 1H), 1.90 (s, 1H), 1.65-1.48 (m, 2H), 1.13-0.97 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.0, 170.8, 168.9, 164.4, 161.9, 142.9, 136.6, 134.9, 130.8, 130.3, 128.9, 128.8, 128.7, 128.0, 127.8, 127.0, 126.5, 115.3, 115.1, 79.5, 59.0, 56.0, 55.1, 54.7, 49.1, 45.7, 44.6, 39.4, 31.8, 29.6, 28.8, 24.6, 23.5, 22.5, 20.5, 19.7, 14.0; LRMS: (ES+) m/z = 692.3 (M+1)

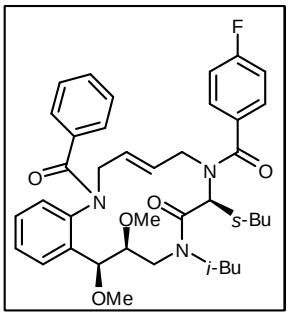
(7S,11S,12S,E)-1-(4-chlorobenzoyl)-6-(4-fluorobenzoyl)-7,9-diisobutyl -11,12-dimethoxy-1,2,6,7,9,10,11,12-octahydro benzo[j][1,4,9]triazacyclotetradecin-8(5H)-one (1.1f):



Molecular Formula:$C_{36}H_{48}FN_3O_5$; R_f: 0.4 (1:3 ethyl acetate/hexanes); Solvent system for column purification (1:3 to 3:7 ethyl acetate/hexanes);Yield-58.5% (colourless semi solid); ^{1}H NMR

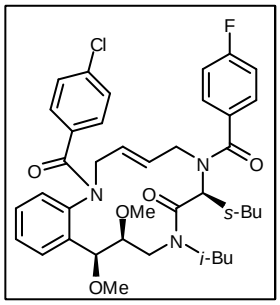
($CDCl_3$, 400 MHz): δ ppm 7.72 (d, *J* = 7.87 Hz, 1H), 7.51 (dd, *J* = 8.17, 5.54 Hz, 2H), 7.40 (m, 3H), 7.11 (dd, *J* = 10.31, 6.24 Hz, 3H), 5.95-5.86 (m, 1H), 5.50 (d, *J* = 16.4 Hz, 1H), 5.25 (d, *J* = 16.0 Hz, 1H), 4.70 (d, *J* = 14.8 Hz, 1H), 4.60 (s, 1H), 4.06 (m, 3H), 3.89-3.79 (m, 1H), 3.42 (s, 1H), 3.39-3.04 (m, 11H), 2.97-2.88 (m, 1H), 2.17-2.06 (m, 1H), 1.93-1.80 (m, 1H), 1.64-1.47 (m, 2H), 1.13-0.90 (m, 14H), 0.63 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 174.4, 172.1, 170.9, 143.1, 135.9, 130.9, 129.1, 128.9, 128.2, 128.2, 127.9, 127.1, 126.6, 115.3, 115.6, 79.1, 59.1, 56.8, 54.9, 52.9, 49.1, 45.4, 44.6, 39.3, 29.6, 28.7, 24.6, 23.5, 22.6, 20.5, 19.7, 12.8, 9.1, 8.7; LRMS: (ES+) m/z = 622.2 (M+1)

(7S,11S,12S,E)-1-benzoyl-7-sec-butyl-6-(4-fluorobenzoyl)-9-isobutyl-11,12-dimethoxy-1,2,6,7,9,10,11,12-octahydrobenzo[j][1,4,9] triazacyclotetradecin-8(5H)-one (1.1g):



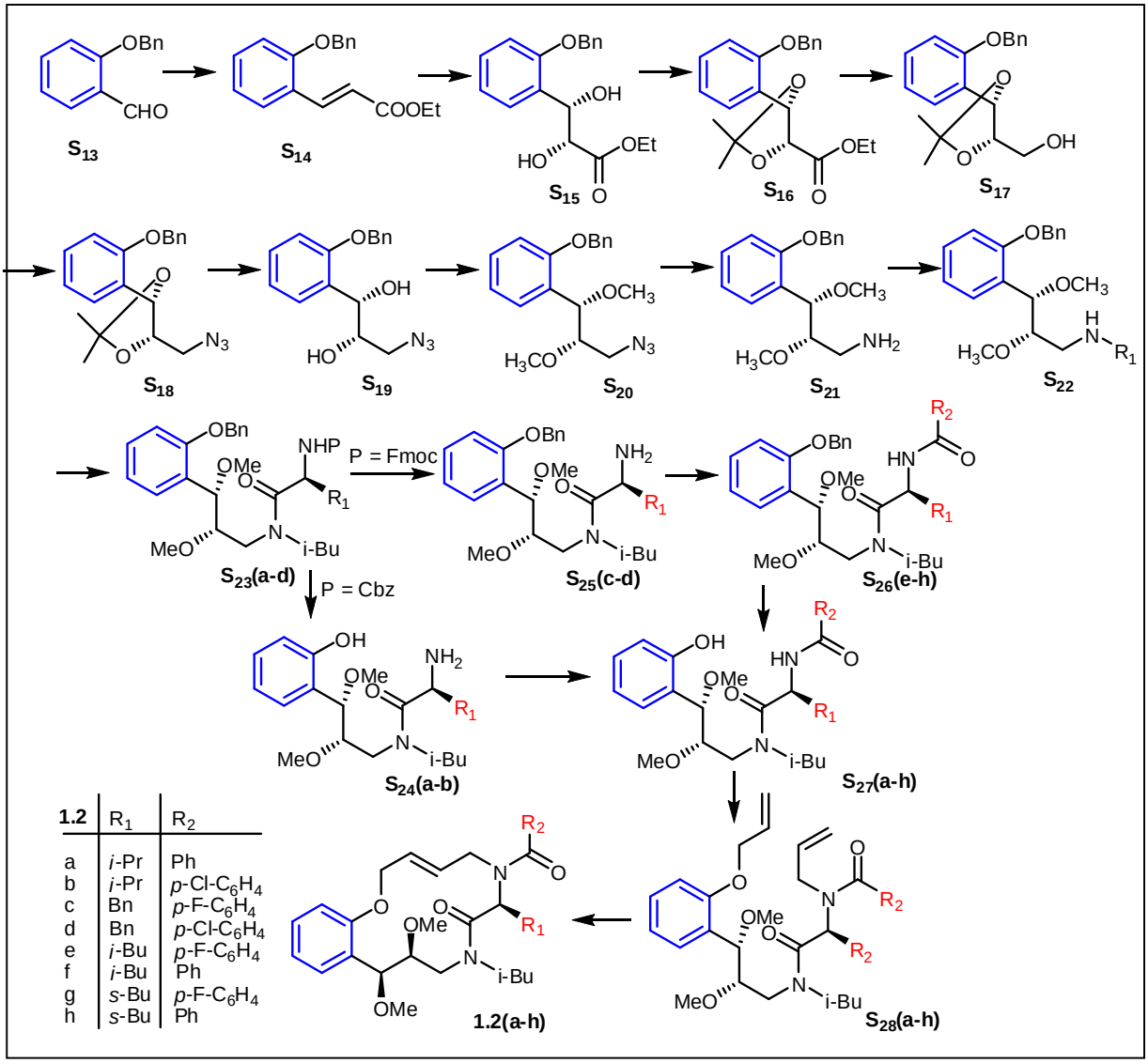
Molecular Formula: $C_{39}H_{48}FN_3O_5$; R_f :0.4 (1:3 ethyl acetate/hexanes); Solvent system for column purification (1:3 to 3:7 ethyl acetate/hexanes); Yield-65.6% (colourless semi solid); ^1H NMR ($CDCl_3$, 400 MHz): δ ppm 7.57 (m, 4H), 7.36-7.23 (m, 7H), 7.16 (d, *J* = 7.38 Hz, 3H), 7.10 (s, 2H), 7.04 (s, 2H), 5.75 (d, *J* = 15.6 Hz, 1H), 5.50 (d, *J* = 10.8 Hz, 1H), 5.35 (d, *J* = 15.6 Hz, 1H), 5.95 (d, *J* = 16.0 Hz, 1H), 4.42 (s, 1H), 4.25-4.14 (m, 1H), 4.05 (s, 2H), 3.94-3.82 (m, 1H), 3.61-3.50 (m, 1H), 3.45-3.35 (m, 1H), 3.29-3.21 (m, 1H), 3.13 (s, 3H), 2.93-2.81 (m, 1H), 2.69 (s, 3H), 2.37-2.24 (m, 2H), 1.81-1.63 (m, 1H), 1.59-1.46 (m, 1H), 1.13-1.05 (m, 6H), 1.01-0.91 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.3, 170.5, 170.0, 143.1, 135.3, 135.0, 132.4, 132.4, 130.6, 130.3, 128.9, 128.8, 128.7, 128.7, 128.6, 127.7, 127.6, 126.8, 126.7, 115.3, 115.1, 79.6, 59.0, 55.9, 55.8, 55.1, 54.5, 46.2, 44.9, 34.2, 31.8, 31., 29.6, 29.6, 29.3, 29.1, 23.9, 22.6, 20.3, 20.1, 16.0, 14.0, 11.0; LRMS: (ES+) m/z = 658.1 (M+1)

(7S,11S,12S,E)-7-sec-butyl-1-(4-chlorobenzoyl)-6-(4-fluorobenzoyl)-9-isobutyl-11,12-dimethoxy-1,2,6,7,9,10,11,12-octahydrobenzo[j][1,4,9]triazacyclotetradecin-8(5H)-one (1.3h):

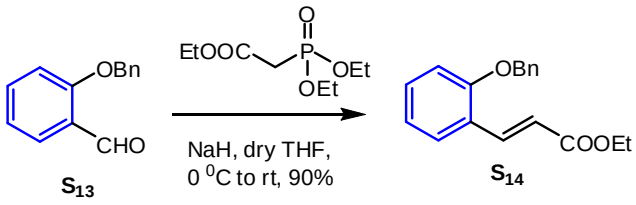


Molecular Formula:$C_{39}H_{47}ClFN_3O_5$; R_f : 0.25 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-71.2% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.56 (dd, *J* = 8.14, 5.18 Hz, 3H), 7.39-7.23 (m, 5H), 7.14 (d, *J* = 8.46 Hz, 2H), 7.05 (t, *J* = 8.27 Hz, 3H), 5.70 (d, *J* = 16.0 Hz, 1H), 5.53 (d, *J* = 10.75 Hz, 1H), 5.35(d, *J* = 16.0 Hz, 1H), 4.95(d, *J* = 16.0 Hz, 1H), 4.40 (s, 1H), 4.25-4.15 (m, 1H), 4.06 (s, 2H), 3.93-3.82 (m, 1H), 3.61-3.51 (m, 1H), 3.45-3.35 (m, 1H), 3.26 (s, 1H), 3.14 (s, 3H), 2.89-2.80 (m, 1H), 2.78 (s, 3H), 2.37-2.24 (m, 1H), 2.24-2.11 (m, 1H), 1.58-1.47 (m, 1H), 1.26 (s, 3H), 1.13-1.05 (m, 7H), 1.01-0.91 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.2, 170.5, 168.8, 164.3, 161.8, 142.9, 136.6, 134.9, 133.6, 132.4, 132.4, 130.8, 130.3, 128.9, 128.6, 128.6, 128.0, 127.8, 126.9, 126.5, 115.3, 115.1, 79.5, 59.0, 56.0, 55.8, 55.1, 54.7, 46.2, 44.9, 34.2, 29.2, 23.9, 20.3, 20.1, 16.0, 15.9, 11.0; LRMS: (ES+) m/z = 692.3 (M+1)

iv) General Experimental procedures of Macrocycle 1.2



1.2	R_1	R_2
a	*i*-Pr	Ph
b	*i*-Pr	*p*-Cl-C_6H_4
c	Bn	*p*-F-C_6H_4
d	Bn	*p*-Cl-C_6H_4
e	*i*-Bu	*p*-F-C_6H_4
f	*i*-Bu	Ph
g	*s*-Bu	*p*-F-C_6H_4
h	*s*-Bu	Ph

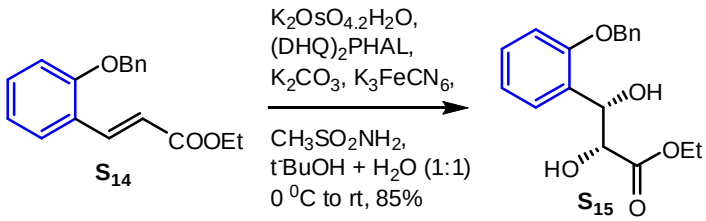


S_{13} S_{14}

(E)-ethyl 3-(2-(benzyloxy)phenyl)acrylate (S_{13}):

Experimental procedure as per Ref. compound **S_1**

Molecular Formula: $C_{18}H_{18}O_3$; R_f (solvent system): 0.25 (1:19 ethyl acetate/hexanes); Yield-92.4% (colourless liquid); Solvent system for column purification(1:19 to 1:9 ethyl acetate/hexanes);^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.09 (d, *J* = 16.17 Hz, 1H), 7.54 (d, *J* = 7.49 Hz, 1H), 7.46-7.36 (m, 4H), 7.31 (dd, *J* = 16.27, 7.80 Hz, 2H), 7.00-6.92 (m, 2H), 6.53 (d, *J* = 16.17 Hz, 1H), 5.17 (s, 2H), 4.25 (q, *J* = 7.11 Hz, 2H), 1.33 (t, *J* = 7.13 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 167.4, 157.2, 139.8, 136.6, 131.3, 128.6, 128.6, 127.9, 127.0, 123.9, 121.0, 118.8, 112.7, 70.3, 60.2, 14.3; LRMS: (ES+) m/z = 283.4 (M+1)

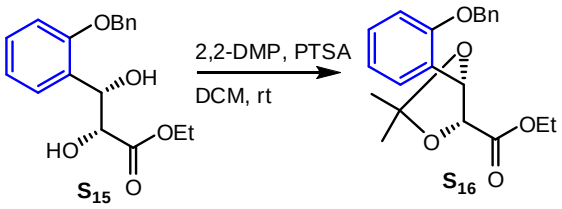


S_{14} S_{15}

(2R,3S)-ethyl 3-(2-(benzyloxy)phenyl)-2,3-dihydroxypropanoate (S_{15}):

Experimental procedure as per Ref. compound **S_2**

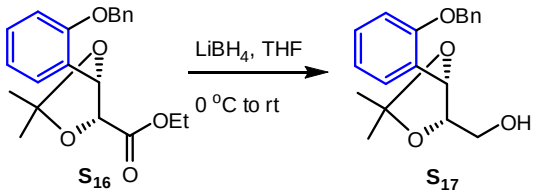
Molecular Formula: $C_{18}H_{20}O_5$; R_f (solvent system): 0.25 (3:7 ethyl acetate/hexanes); Yield-89.3% (colourless liquid); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.25-7.50 (m,, 7H), 7.03 (t, *J* = 7.50 Hz, 1H), 6.96 (d, *J* = 8.24 Hz, 1H), 5.44 (dd, *J* = 8.0, 2.0 Hz 1H), 5.18-5.06 (m, 2H), 4.51 (dd, *J* = 5.59, 2.32 Hz, 1H), 4.24 (m, 2H), 3.09 (d, *J* = 5.81 Hz, 1H), 2.94 (d, *J* = 8.12 Hz, 1H), 1.28-1.18 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.0, 155.0, 136.7, 128.8, 128.5, 128.5, 127.9, 127.2, 127.0, 121.0, 111.4, 73.2, 70.3, 69.9, 61.9, 14.0 ; LRMS: (ES+) m/z = 317.3 (M+1)



(4R,5S)-ethyl 5-(2-(benzyloxy)phenyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (S_{16}):

Experimental procedure as per Ref. compound **S_3**

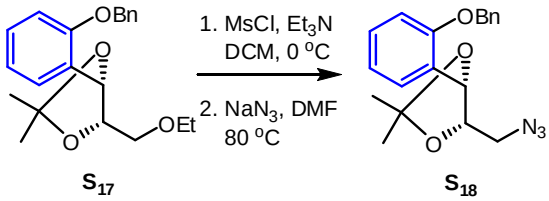
Molecular Formula: $C_{21}H_{24}O_5$; R_f : 0.25 (1:9 ethyl acetate/hexane); Solvent system for column purification (1:9 ethyl acetate/hexanes); Yield-88.7%.



((4S,5S)-5-(2-(benzyloxy)phenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (S_{17}):

Experimental procedure as per Ref. compound **2.2**

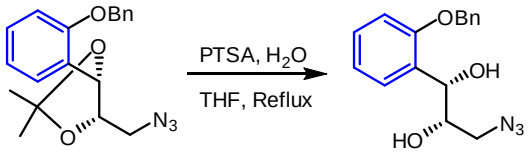
Molecular Formula: $C_{19}H_{22}O_4$; R_f : 0.3 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-90.8% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.58 (d, *J* = 7.60 Hz, 1H), 7.47-7.30 (m, 5H), 7.29-7.22 (m, 1H), 7.03 (t, *J* = 7.50 Hz, 1H), 6.95 (d, *J* = 8.23 Hz, 1H), 5.31 (d, *J* = 8.34 Hz, 1H), 5.12 (d, *J* = 11.52 Hz, 1H), 5.05 (d, *J* = 11.52 Hz, 1H), 3.88 (m, 1H), 3.78 (m, 1H), 3.67 (m, 1H), 1.56 (s, 3H), 1.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 155.7, 136.3, 128.9, 128.7, 128.2, 127.5, 127.0, m126.7, 121.4, 111.8, 108.9, 83.6, 73.7, 70.5, 61.8, 27.2, 27.0; LRMS: (ES+) m/z = 315.4 (M+1)



(4S,5S)-4-(azidomethyl)-5-(2-(benzyloxy)phenyl)-2,2-dimethyl-1,3-dioxolane (S_{18}):

Experimental procedure as per Ref. compound **S_4**

Molecular Formula: $C_{19}H_{21}N_3O_3$; R_f: 0.3 (1:9 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-86.5%

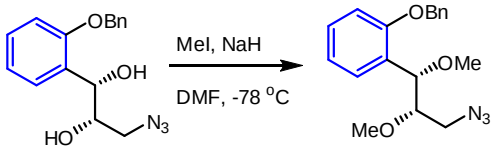


S18 **S19**

(1S,2S)-3-azido-1-(2-(benzyloxy)phenyl)propane-1,2-diol (S_{19}):

Experimental procedure as per Ref. compound **S_5**

Molecular Formula: $C_{16}H_{17}N_3O_3$; R_f : 0.25 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-99.26% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.39 (m, 6H), 7.27 (m, 1H), 6.99 (m, 2H), 5.14-5.04 (m, 2H), 4.89 (d, *J* = 5.03 Hz, 1H), 4.00 (d, *J* = 3.74 Hz, 1H), 3.25 (m, 2H), 3.11 (bs, 1H), 2.90 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 155.5, 136.6, 129.2, 128.7, 128.3, 128.1, 127.4, 121.3, 111.9, 73.7, 71.5, 70.3, 53.2; LRMS: (ES+) m/z = 300.4 (M+1)

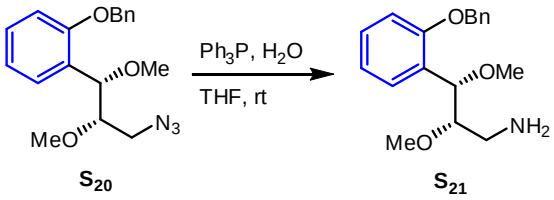


S19 **S20**

1-((1S,2S)-3-azido-1,2-dimethoxypropyl)-2-(benzyloxy)benzene (S_{20}):

Experimental procedure as per Ref. compound **S_6**

Molecular Formula: $C_{18}H_{21}N_3O_3$; R_f : 0.35 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-99.8% (brown liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.35 (m, 7H), 7.02 (t, *J* = 7.42 Hz, 1H), 6.97 (d, *J* = 8.21 Hz, 1H), 5.11 (q, *J* = 11.86 Hz, 2H), 4.77 (d, *J* = 4.64 Hz, 1H), 3.57 (m, 1H), 3.37 (dd, *J* = 12.74, 7.77 Hz, 1H), 3.30 (s, 3H), 3.25 (d, *J* = 6.20 Hz, 3H), 3.16 (dd, *J* = 12.73, 4.23 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 156.2, 136.8, 128.8, 128.6, 127.9, 127.9, 127.1, 126.6, 121.1, 111.8, 83.1, 77.7, 70.1, 60.0, 57.3, 51.7; LRMS: (ES+) m/z = 328.4 (M+1)

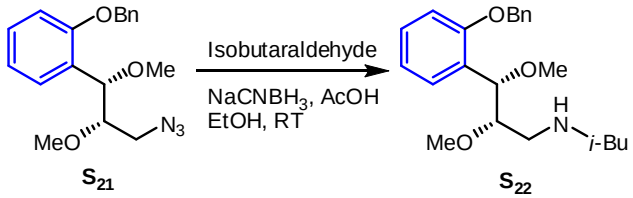


S20 **S21**

(2S,3S)-3-(2-(benzyloxy)phenyl)-2,3-dimethoxypropan-1-amine (S_{21}):

Experimental procedure as per Ref. compound **2.3**

Molecular Formula: $C_{18}H_{23}NO_3$; R_f: 0.3 (ethyl acetate); Solvent system for column purification (ethyl acetate); Yield-87.8% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.37 (m, 6H), 7.29-7.22 (m, 1H), 7.01 (t, *J* = 7.44 Hz, 1H), 6.96 (d, *J* = 8.24 Hz, 1H), 5.09 (q, *J* = 11.69 Hz, 2H), 4.80 (d, *J* = 6.44 Hz, 1H), 3.40 (s, 3H), 3.33 (dd, *J* = 9.21, 4.91 Hz, 1H), 3.22 (s, 3H), 2.66 (dd, *J* = 13.79, 3.94 Hz, 1H), 2.56 (dd, *J* = 13.80, 6.02 Hz, 1H), 1.56 (bs, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 156.5, 136.7, 128.6, 128.6, 128.0, 127.9, 127.6, 127.3, 121.2, 111.8, 85.9, 78.1, 70.2, 59.4, 57.0, 42.0; LRMS: (ES+) m/z = 302.4 (M+1)

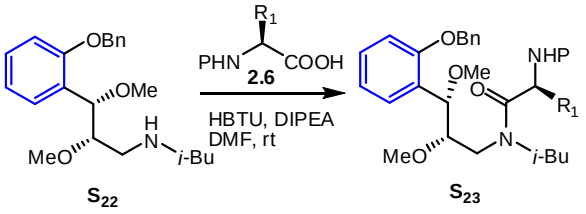


S21 **S22**

(2S,3S)-3-(2-(benzyloxy)phenyl)-N-isobutyl-2,3-dimethoxypropan-1-amine (S_{22}):

Experimental procedure as per Ref. compound **S_7**

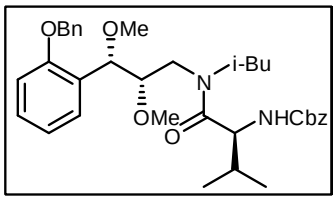
Molecular Formula: $C_{22}H_{31}NO_3$; R_f: 0.3 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-71.7% (brown liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.36 (m, 6H), 7.24 (t, *J* = 8.32 Hz, 1H), 7.00 (t, *J* = 7.46 Hz, 1H), 6.94 (d, *J* = 8.22 Hz, 1H), 5.14-5.03 (m, 2H), 4.79 (d, *J* = 5.45 Hz, 1H), 3.64-3.55 (m, 1H), 3.37 (s, 3H), 3.25 (d, *J* = 11.63 Hz, 3H), 2.69 (dd, *J* = 12.33, 8.37 Hz, 1H), 2.50 (dd, *J* = 12.39, 3.99 Hz, 1H), 2.30 (m, 2H), 1.65 (m, 1H), 0.85 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 156.2, 136.7, 128.2, 128.2, 127.8, 127.6, 127.4, 126.9, 120.7, 11.4, 83.1, 78.5, 69.8, 59.7, 57.7, 56.8, 50.2, 27.9, 20.3, 20.3; LRMS: (ES+) m/z = 358.5 (M+1)



Compound S_{23}:

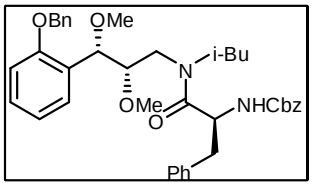
Experimental procedure as per Ref. compound **2.4**

Benzyl (S)-1-(((2S,3S)-3-(2-(benzyloxy)phenyl)-2,3-dimethoxypropyl)(isobutyl)amino)-3-methyl-1-oxobutan-2-ylcarbamate (S_{23}a):



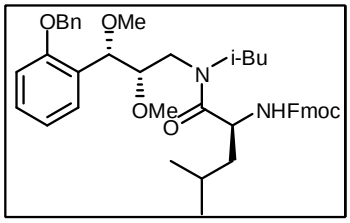
MolecularFormula: $C_{35}H_{46}N_2O_6$; R_f : 0.75 (3:7 ethyl acetate/ hexanes); Solvent system for column purification (1:4 to 1:3 ethyl acetate/hexanes); Yield: 95.6% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.60-7.19 (m, 12H), 7.15-6.92 (m, 2H), 5.15-5.03 (m, 4H), 4.70 (m, 4H), 4.55-4.35 (m, 1H), 3.80-3.60 (m, 1H), 3.45-3.05 (m, 7H), 1.85-1.70 (m, 2H), 1.02-0.75 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.0, 171.6, 156.3, 156.2, 156.1, 136.9, 136.5, 128.8, 128.7, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.9, 129, 127.8, 127.7, 127.7, 127.4, 127.3, 127.3, 126.9, 126.7, 121.3, 121.1, 121.0, 111.8, 111.8, 111.5, 83.9, 83.2, 82.4, 78.3, 70.2, 69.9, 66.6, 66.5, 60.5, 57.6, 57.3, 57.1, 57.0, 56.5, 55.7, 55.4, 53.9, 48.5, 48.3, 31.6, 31.4, 27.8, 26.4, 20.2, 20.1, 19.9, 19.8, 19.7, 19.4, 18.0, 16.8; LRMS: (ES+) m/z = 591.4 (M+1)

Benzyl (S)-1-(((2S,3S)-3-(2-(benzyloxy)phenyl)-2,3-dimethoxypropyl)(isobutyl)amino)-1-oxo-3-phenylpropan-2-ylcarbamate (S_{23}b):



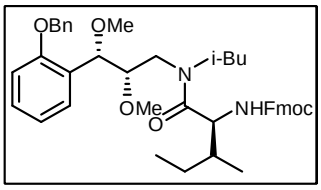
Molecular Formula: $C_{39}H_{46}N_2O_6$; R_f : 0.35 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield: 88.9% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.29 (m, 16H), 7.06-6.90 (m, 3H), 5.54-5.36 (m, 1H), 5.21-4.63 (m, 6H), 3.84-3.67 (m, 1H), 3.33-2.73 (m, 11H), 1.90-1.71 (m, 1H), 0.87-0.60 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.1, 171.6, 156.4, 156.1, 155.5, 155.4, 136.9, 136.8, 136.5, 136.4, 129.3, 128.8, 128.6, 128.6, 128.5, 128.4, 128.4, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7, 127.4, 127.3, 126.9, 126.6, 121.3, 121.0, 111.8, 111.6, 83.7, 82.1, 78.1, 77.7, 70.2, 70.0, 66.5, 66.5, 60.6, 60.4, 57.2, 57.0, 56.3, 54.7, 52.1, 51.9, 49.0, 39.8, 39.6, 28.0, 26.6, 20.2, 20.1, 20.0, 19.6 ; LRMS: (ES+) m/z = 638.7 (M+1)

(9H-fluoren-9-yl)methyl(S)-1-(((2S,3S)-3-(2-(benzyloxy)phenyl)-2,3-dimethoxypropyl) (isobutyl)amino)-4-methyl-1-oxopentan-2-ylcarbamate (12c):

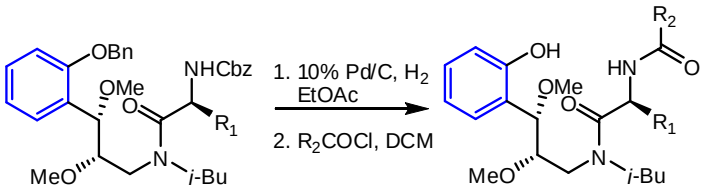


Molecular Formula: $C_{43}H_{52}N_2O_6$; R_f : 0.75 (3:7 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield: 91.5% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.75 (d, *J* = 7.50 Hz, 2H), 7.58 (d, *J* = 7.37 Hz, 2H), 7.51-7.19 (m, 11H), 7.09-6.90 (m, 2H), 5.54 (m, 1H), 5.19-5.02 (m, 2H), 4.74 (m, 2H), 4.42-4.14 (m, 3H), 3.88-3.71 (m, 1H), 3.38 (m, 1H), 3.29-3.01 (m, 7H), 2.01-1.75 (m, 1H), 1.50 (m, 1H), 1.37-1.23 (m, 1H), 1.04-0.73 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.3, 172.6, 156.1, 156.0, 143.9, 143.8, 143.8, 141.2, 141.2, 136.9, 136.9, 128.6, 128.5, 128.5, 127.9, 127.9, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 126.9, 125.2, 125.1, 125.1, 121.1, 121.1, 119.9, 119.8, 111.9, 111.6, 83.4, 82.1, 78.2, 70.2, 69.9, 66.7, 60.8, 57.3, 57.1, 56.5, 49.3, 49.1, 47.2, 47.1, 43.2, 42.8, 28.2, 26.5, 24.6, 24.4, 23.5, 21.4, 20.1, 19.8, 19.6; LRMS: (ES+) m/z = 693.5 (M+1)

(9H-fluoren-9-yl)methyl(2S,3R)-1-(((2S,3S)-3-(2-(benzyloxy) phenyl)-2,3-dimethoxypropyl) (isobutyl)amino)-3-methyl-1-oxo pentan-2-ylCarbamate (S_{23}d):



Molecular Formula: $C_{43}H_{52}N_2O_6$; R_f : 0.30 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield: 85.3% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.75 (d, *J* = 7.49 Hz, 2H), 7.58 (d, *J* = 7.30 Hz, 2H), 7.54-7.20 (m, 11H), 7.04 (t, *J* = 7.34 Hz, 1H), 6.94 (d, *J* = 8.20 Hz, 1H), 5.50 (d, *J* = 9.00 Hz, 1H), 5.09 (dd, *J* = 11.61, 8.19 Hz, 2H), 4.77-4.68 (m, 1H), 4.60-4.14 (m, 4H), 3.84 (t, *J* = 10.30 Hz, 2H), 3.47-2.99 (m, 8H), 1.90 (d, *J* = 7.22 Hz, 1H), 1.78-1.64 (m, 1H), 1.55-1.42 (m, 1H), 0.98-0.73 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.2, 171.7, 156.3, 156.2, 156.1, 144.0, 143.9, 143.9, 143.8, 141.2, 136.9, 128.7, 128.6, 128.5, 128.1, 127.9, 127.9, 127.7, 127.6, 127.6, 127.4, 127.3, 127.0, 126.9, 125.2, 125.1, 125.1, 121.3, 121.1, 119.9, 119.9, 111.8, 111.6, 83.9, 82.4, 78.3, 75.4, 70.2, 70.0, 66.7, 60.5, 57.2, 56.6, 55.5, 55.1, 48.6, 47.2, 47.1, 38.5, 38.3, 27.8, 26.4, 23.5, 23.4, 20.2, 20.1, 19.9, 19.5, 15.8, 11.4 ; LRMS: (ES+) m/z = 693.5 (M+1)



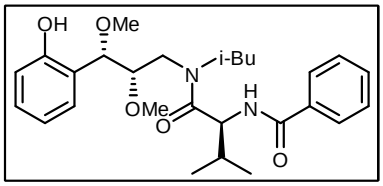
S_{23}(a-b) **S_{27}(a-d)**

Compound S_{27}(a-d):

To a suspension of compound **S_{23}(a-d)** (1 mmol) in ethyl acetate (10 mL), 10% Pd/C (0.2 mmol) was added and stirred the reaction mixture for 12 h under hydrogen atmosphere. After completion of the reaction, reaction mixture was passed through celite and concentrated to leave 200 mg crude oil, which was subjected to the next reaction without any purification.

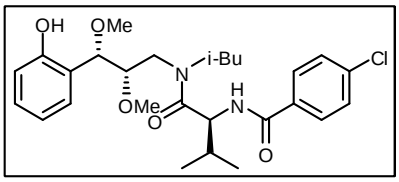
To a suspension of above compound (0.3 mmol) in DCM (10 mL), acid chloride (0.4 mmol) was added at 0 °C and allowed to stir for 10 min. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution (5 mL), concentrated, and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give pure compound **S_{28}(a-d)**.

N-((S)-1-(((2S,3S)-3-(2-hydroxyphenyl)-2,3-dimethoxypropyl)(isobutyl)amino)-3-methyl-1-oxobutan-2-yl)benzamide (S_{27}a):



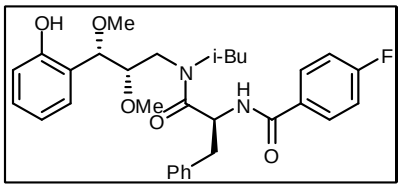
Molecular Formula: $C_{27}H_{38}N_2O_5$; R_f : 0.35 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield: 82.3% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.93 (m, 3H), 7.62-6.74 (m, 9H), 5.07 (m, 1H), 4.47-4.25 (m, 1H), 3.98-3.15 (m, 11H), 2.18-1.93 (m, 2H), 1.15-0.78 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.4, 172.1, 167.4, 166.8, 155.8, 155.3, 134.0, 134.0, 131.7, 131.6, 129.9, 129.5, 129.5, 129.4, 129.1, 128.5, 128.5, 128.2, 127.0, 122.9, 122.0, 120.1, 119.7, 117.5, 116.9, 85.1, 84.7, 83.6, 60.7, 60.4, 57.5, 57.5, 56.8, 54.6, 54.2, 53.8, 49.6, 49.0, 32.1, 32.0, 28.1, 26.7, 20.2, 20.1, 20.0, 20.0, 19.8, 19.4, 17.4, 17.3; LRMS: (ES+) m/z = 471.3 (M+1)

4-chloro-N-((S)-1-(((2S,3S)-3-(2-hydroxyphenyl)-2,3-dimethoxypropyl)(isobutyl)amino)-3-methyl-1-oxobutan-2-yl)benzamide (S_{27}b):



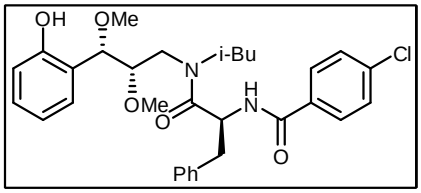
Molecular Formula: $C_{28}H_{40}N_2O_5$; R_f : 0.2 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:3 ethyl acetate/hexanes); Yield: 62.9% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.76 (m, 3H), 7.49-6.77 (m, 8H), 5.13-4.95 (m, 1H), 4.35 (m, 1H), 3.93-3.12 (m, 11H), 2.18-1.91 (m, 2H), 1.10-0.80 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.2, 172.0, 166.3, 165.8, 155.7, 155.2, 137.8, 132.4, 129.5, 129.5, 129.3, 129.1, 129.0, 128.8, 128.7, 128.7, 128.6, 128.6, 128.5, 128.4, 122.7, 122.0, 120.1, 119.8, 117.4, 117.0, 116.9, 85.0, 84.8, 83.7, 60.6, 60.4, 57.5, 56.8, 54.5, 54.3, 53.9, 49.5, 49.0, 32.0, 32.0, 28.0, 26.6, 20.2, 20.1, 20.0, 19.8, 19.4, 17.3, 17.2 ; LRMS: (ES+) m/z = 505.3 (M+1)

4-fluoro-N-((S)-1-(((2S,3S)-3-(2-hydroxyphenyl)-2,3-dimethoxypropyl)(isobutyl)amino)-1-oxo-3-phenylpropan-2-yl)benzamide (S_{27}c):

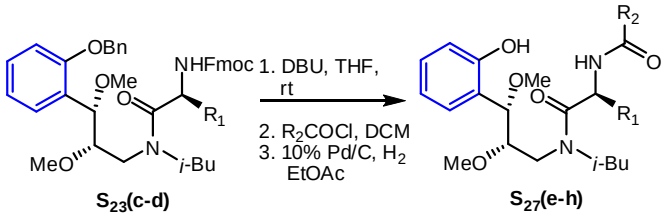


Molecular Formula: $C_{31}H_{37}FN_2O_5$; R_f : 0.3 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield: 85.7% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.74 (m, 2H), 7.34-6.75 (m, 14H), 5.35 (d, *J* = 7.67 Hz, 1H), 4.29 (dd, *J* = 13.53, 3.08 Hz, 1H), 3.95-3.68 (m, 2H), 3.58-2.95 (m, 13H), 1.84 (m, 2H), 0.92-0.70 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.3, 172.1, 165.9, 165.4, 155.8, 155.2, 136.2, 136.2, 129.6, 129.5, 129.4, 129.3, 129.3, 128.6, 128.5, 127.0, 126.9, 122.1, 120.1, 119.7, 117.4, 117.0, 115.6, 115.6, 115.4, 115.4, 84.6, 84.4, 83.3, 60.7, 60.1, 57.5, 57.4, 56.7, 54.9, 50.9, 50.6, 49.7, 49.2, 39.4, 39.3, 28.4, 26.8, 20.2, 20.1, 20.0, 19.6; LRMS: (ES+) m/z = 537.3 (M+1)

4-chloro-N-((S)-1-(((2S,3S)-3-(2-hydroxyphenyl)-2,3-dimethoxypropyl)(isobutyl)amino)-1-oxo-3-phenylpropan-2-yl)benzamide (S_{27}d):



Molecular Formula: $C_{31}H_{37}ClN_2O_5$; R_f : 0.4 (3:7 ethyl acetate/hexanes); Solvent system for column purification (1:3 ethyl acetate/hexanes); Yield: 83.6% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.67 (m, 3H), 7.50-6.74 (m, 14H), 5.35 (d, *J* = 7.34 Hz, 1H), 4.29 (m, 1H), 3.97-3.65 (m, 2H), 3.58-2.95 (m, 13H), 1.95-1.72 (m, 1H), 0.93-0.68 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.3, 172.2, 172.1, 165.9, 165.5, 155.8, 155.2, 137.9, 137.9, 136.1, 132.1, 132.1, 131.3, 129.6, 129.9, 129.5, 129.3, 129.3, 129.2, 128.7, 128.7, 128.6, 128.6, 128.5, 128.5, 128.5, 128.4, 127.1, 126.9, 122.5, 122.0, 120.2, 119.7, 117.4, 117.0, 84.6, 84.3, 83.3, 60.7, 60.1, 57.5, 57.4, 56.7, 54.9, 51.0, 50.6, 49.7, 49.2, 39.2, 28.4, 26.8, 20.2, 20.1, 20.0, 19.6; LRMS: (ES+) m/z = 553.3 (M+1)



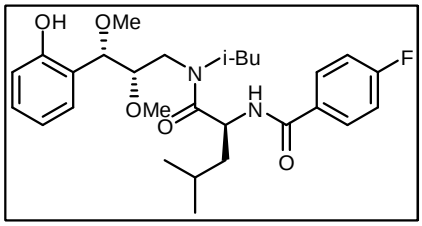
Compound S_{27}(e-h):

To a suspension of compound **S_{23}(c-d)** (1 mmol) in THF (10 mL), DBU (1.5 mmol) was added and stirred the reaction mixture for 5 min. After completion of the reaction, reaction mixture concentrated and which was subjected to the next reaction without any purification.

To a suspension of above compound (0.3 mmol) in DCM (10 mL), acid chloride (0.45 mmol) was added at 0 °C and allowed to stir for 10 min. After completion of the reaction mixture was quenched with sodium bicarbonate solution (5 mL), concentrated, and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give pure compound.

To a suspension of above compound (1 mmol) in ethyl acetate (10 mL), 10% Pd/C (0.2 mol) was added and stirred the reaction mixture for 12 h under hydrogen atmosphere. After completion of the reaction, reaction mixture was passed through celite and concentrated to leave 200 mg crude oil, which was purified by the column chromatography to give **S_{27}(e-h)**.

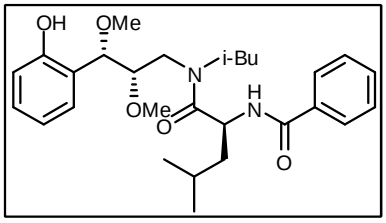
4-fluoro-N-((S)-1-(((2S,3S)-3-(2-hydroxyphenyl)-2,3-dimethoxypropyl)(isobutyl)amino)-4-methyl-1-oxopentan-2-yl)benzamide (S_{27}e):



Molecular Formula: $C_{28}H_{39}FN_2O_5$; R_f : 0.3 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:3 ethyl acetate/hexanes); Yield: 65.7% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.92 (m, 3H), 7.48-6.74 (m, 10H), 5.22 (m, 1H), 4.37 (m, 1H), 3.79 (m, 2H), 3.64-3.19 (m, 11H), 2.05 (m, 1H), 1.84-1.69 (m, 2H), 1.53-1.36 (m, 1H), 1.20-1.10 (m, 1H), 0.93 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.8, 173.6, 166.4, 165.9, 155.8, 155.3, 132.6,

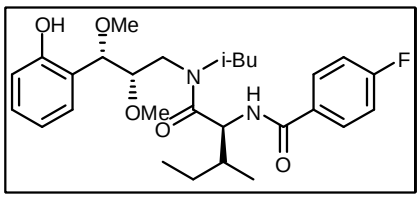
132.5, 129.7, 129.6, 129.5, 129.5, 129.5, 129.2, 128.8, 122.4, 122.0, 120.1, 119.7, 117.3, 116.9, 1156.6, 115.5, 115.5, 115.3, 115.3, 115.3, 84.6, 84.3, 83.1, 60.6, 60.6, 57.4, 57.0, 54.2, 49.5, 47.9, 42.6, 42.2, 29.6, 29.6, 28.5, 26.7, 24.9, 24.7, 23.5, 23.5, 21.5, 21.5, 20.1, 20.1, 19.8, 19.7 ; LRMS: (ES+) m/z = 501.1 (M-1)

N-((S)-1-(((2S,3S)-3-(2-hydroxyphenyl)-2,3-dimethoxypropyl)(isobutyl)amino)-4-methyl-1-oxopentan-2-yl)benzamide (S_{27}f):



Molecular Formula: $C_{28}H_{40}N_2O_5$; R_f : 0.25 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:3 ethyl acetate/hexanes); Yield: 75.6% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.81 (m, 2H), 7.44 (m4H), 7.18 (m 1H), 7.04-6.75 (m, 4H), 5.29-5.18 (m, 1H), 4.37 (m, 1H), 3.97-3.20 (m, 11H), 2.13-1.87 (m, 2H), 1.83-1.66 (m, 2H), 1.43 (m, 1H), 0.94 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.4, 173.3, 167.2, 166.8, 155.8, 155.3, 134.0, 133.8, 131.6, 131.6, 129.5, 129.4, 129.2, 128.8, 128.5, 127.0, 127.0, 122.5, 122.1, 120.1, 119.7, 117.3, 116.9, 84.7, 84.6, 83.2, 60.6, 57.4, 56.9, 49.4, 47.7, 42.9, 42.7, 29.6, 28.5, 26.7, 24.8, 24.7, 23.5, 23.5, 21.6, 21.6, 20.1, 20.1, 19.9, 19.7; LRMS: (ES+) m/z = 485.3 (M+1)

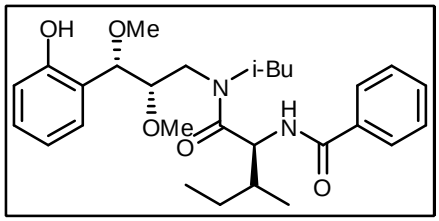
4-fluoro-N-((2S,3R)-1-(((2S,3S)-3-(2-hydroxyphenyl)-2,3-dimethoxypropyl)(isobutyl)amino)-3-methyl-1-oxopentan-2-yl)benzamide (S_{27}g):



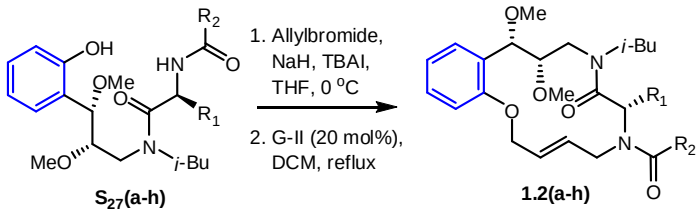
Molecular Formula: $C_{28}H_{39}FN_2O_5$; R_f : 0.2 (1:4 ethyl acetate/hexanes); Yield: 77.1% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.83 (m, 2H), 7.31-6.74 (m, 7H), 5.06 (m, 1H), 4.33 (m, 1H), 3.93-3.56 (m, 2H), 3.51-3.17 (m, 8H), 2.10-1.79 (m, 2H), 1.58 (m, 1H), 1.18 (m, 1H), 1.06-0.79 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.6, 172.2, 167.2, 166.7, 155.8, 155.3, 132.6, 132.5, 129.7, 129.6, 129.5, 129.5, 129.5, 129.2, 128.8, 122.4, 122.0, 120.1, 119.7, 117.3, 116.9, 1156.6, 115.5, 115.5, 115.3, 115.3, 115.3, 85.0, 83.6, 60.3, 56.9, 54.7, 53.4, 49.1,

38.6, 38.6, 29.6, 28.2, 26.7, 24.0, 20.2, 20.1, 20.0, n19.5, 16.0, 15.9, 11.3, 11.2; LRMS: (ES+) m/z = 503.3 (M+1)

N-((2S,3R)-1-(((2S,3S)-3-(2-hydroxyphenyl)-2,3-dimethoxypropyl)(isobutyl)amino)-3-methyl-1-oxopentan-2-yl)benzamide (S_{27}h):



Molecular Formula: $C_{28}H_{40}N_2O_5$; R_f: 0.2 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:3 ethyl acetate/hexanes); Yield: 62.9% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.81 (m, 3H), 7.56-7.36 (m, 3H), 7.25-6.73 (m, 6H), 5.10 (m, 1H), 4.33 (m, 1H), 3.93-3.58 (m, 2H), 3.51-3.19 (m, 8H), 2.10-1.78 (m, 2H), 1.70-1.53 (m, 2H), 1.23-1.12 (m, 1H), 1.07-0.79 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.6, 172.2, 167.2, 166.7, 158.8, 155.3, 134.0, 134.0, 131.7, 131.6, 129.5, 129.5, 129.4, 129.2, 128.5, 128.5, 127.1, 127.0, 122.8, 121.9, 120.1, 119.7, 117.6, 117.0, 109.9, 85.0, 83.6, 60.3, 56.9, 54.7, 53.4, 49.1, 38.6, 38.6, 29.6, 28.2, 26.7, 24.0, 20.2, 20.1, 20.0, 19.5, 16.0, 15.9, 11.3, 11.2; LRMS: (ES+) m/z = 485.3 (M+1)



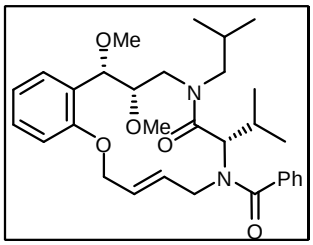
S_{27}(a-h) 1.2(a-h)

Macrocycle 1.2(a-h):

To a suspension of compound **S_{27}(e-h)** (0.2 mmol) in dry THF, allybromide (1 mmol), NaH (2 mmol) and TBAI (0.02 mmol) were added at 0 °C and allowed to stirred at room temperature for 10 h. After completion of the reaction, reaction mixture was quenched with ammonium chloride solution, concentrated, and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give the compound pure bis allyl product **S_{28}**.

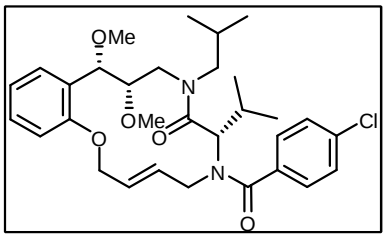
To suspension of above compound **S_{28}** (0.069 mmol) was taken in dry dichloromethane (50 mL) under nitrogen atmosphere and Grubb's 2nd generation catalyst (0.0138 mmol) was added and reaction mixture was heated to 40 °C for 24 h. After completion of the reaction, reaction mixture was concentrated and subjected to column chromatography using to give pure compound **1.2(a-h)**.

(7S,11S,12S,E)-6-benzoyl-9-isobutyl-7-isopropyl-11,12-dimethoxy-6,7,9,10,11,12-hexahydro -2H-benzo[m][1,6,9]oxadiazacyclotetradecin -8(5H)-one (1.2a):



Molecular Formula: $C_{31}H_{42}N_2O_5$; R_f : 0.35 (3:7 ethyl acetate/hexanes); Solvent system for column purification (1:3 ethyl acetate/hexanes); Yield: 60.5% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.46 (d, *J* = 6.73 Hz, 1H), 7.43-7.30 (m, 5H), 7.29-7.21 (m, 1H), 7.04 (t, *J* = 7.47 Hz, 1H), 6.79 (d, *J* = 8.08 Hz, 1H), 5.85 (ddd, *J* = 15.6 Hz, *J* = 8.8 Hz, *J* = 2.4 Hz, 1H), 5.46 (d, *J* = 10.61 Hz, 1H), 5.19 (dd, *J* = 15.65, 0.69 Hz, 1H), 4.71 (s, 1H), 4.37 (d, *J* = 0.71 Hz, 2H), 4.11 (dd, *J* = 13.01, 2.77 Hz, 1H), 4.04-3.76 (m, 4H), 3.48-3.34 (m, 4H), 3.12 (s, 3H), 2.94 (dd, *J* = 14.62, 7.43 Hz, 1H), 2.67-2.52 (m, 1H), 2.28-2.15 (m, 1H), 1.10-0.97 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): 172.2, 171.1, 155.2, 136.5, 129.2, 128.3, 128.1, 128.0, 127.8, 126.4, 124.9, 120.8, 110.7, 77.5, 65.0, 59.5, 57.2, 57.1, 54.7, 45.9, 45.7, 28.8, 27.3, 20.3, 20.0, 19.9, 17.7; LRMS: (ES+) m/z = 523.3 (M+1)

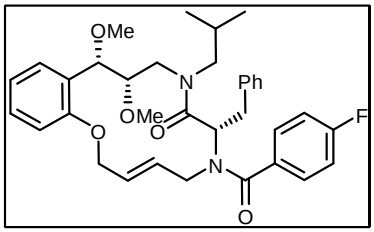
(7S,11S,12S,E)-6-(4-chlorobenzoyl)-9-isobutyl-7-isopropyl-11,12-dimethoxy-6,7,9,10,11,12-hexahydro-2H-benzo[m][1,6,9]oxadiazacyclotetradecin-8(5H)-one (1.2b):



Molecular Formula: $C_{31}H_{41}ClN_2O_5$; R_f : 0.4 (3:7 ethyl acetate/hexanes); Solvent system for column purification (1:3 ethyl acetate/hexanes); Yield: 65.0% (colourless semi solid); ^{1}H NMR

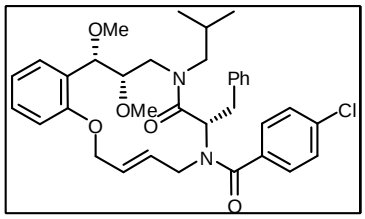
($CDCl_3$, 400 MHz): δ ppm 7.46 (d, *J* = 7.38 Hz, 1H), 7.37 (d, *J* = 8.28 Hz, 2H), 7.33-7.22 (m, 3H), 7.04 (t, *J* = 7.47 Hz, 1H), 6.80 (d, *J* = 8.07 Hz, 1H), 5.80 (ddd, *J* = 16.0 Hz, *J* = 9.6 Hz, *J* = 2.4 Hz, 1H), 5.43 (d, *J* = 10.60 Hz, 1H), 5.26 (d, *J* = 15.85 Hz, 1H), 4.70 (s, 1H), 4.38 (s, 2H), 4.10 (dd, *J* = 12.97, 2.87 Hz, 1H), 4.02 (d, *J* = 16.36 Hz, 1H), 3.88 (dd, *J* = 14.60, 7.58 Hz, 1H), 3.79 (dd, *J* = 16.39, 9.00 Hz, 2H), 3.43 (dd, *J* = 12.79, 10.68 Hz, 1H), 3.37 (s, 3H), 3.12 (s, 3H), 2.93 (dd, *J* = 14.58, 7.48 Hz, 1H), 2.64-2.51 (m, 1H), 2.19 (dd, *J* = 13.59, 6.75 Hz, 1H), 1.10-0.94 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 171.2, 170.8, 155.2, 135.3, 134.9, 128.3, 128.3, 128.1, 128.0, 127.7, 126.3, 125.0, 120.8, 110.7, 64.9, 59.5, 57.3, 57.1, 54.7, 46.0, 45.7, 28.8, 27.3, 20.3, 20.0, 19.9, 17.7; LRMS: (ES+) m/z = 557.2 (M+1)

(7S,11S,12S,E)-7-benzyl-6-(4-fluorobenzoyl)-9-isobutyl-11,12-dimethoxy-6,7,9,10,11,12-hexahydro-2H-benzo[m][1,6,9]oxadiazacyclotetradecin-8(5H)-one (1.2c):



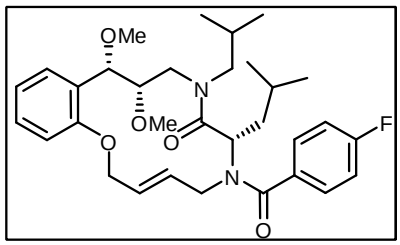
]Molecular Formula: $C_{35}H_{41}FN_2O_5$; R_f : 0.4 (3:7 ethyl acetate/hexanes); Solvent system for column purification (1:3 ethyl acetate/hexanes); Yield: 79.6% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.45 (t, *J* = 6.64 Hz, 1H), 7.36-7.22 (m, 7H), 7.08-6.94 (m, 5H), 6.80 (d, *J* = 8.00 Hz, 1H), 6.10 (t, *J* = 7.68 Hz, 1H), 5.85 (ddd, *J* = 15.6 Hz, *J* = 8.8 Hz, *J* = 2.4 Hz, 1H), 5.38-5.27 (m, 1H), 4.70 (s, 1H), 4.40 (d, *J* = 1.67 Hz, 2H), 4.21 (d, *J* = 16.41 Hz, 1H), 4.06 (dd, *J* = 12.90, 2.81 Hz, 1H), 3.91-3.71 (m, 3H), 3.43-3.32 (m, 4H), 3.27 (dd, *J* = 13.60, 7.21 Hz, 2H), 3.22-3.05 (m, 5H), 2.94 (dd, *J* = 14.62, 6.70 Hz, 1H), 2.09-1.93 (m, 1H), 0.99-0.91 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 170.9, 170.5, 155.1, 136.7, 132.1, 132.0, 129.7, 128.6, 128.6, 128.2, 128.2, 128.1, 127.7, 126.6, 126.3, 125.0, 120.8, 115.1, 114.8, 110.7, 77.6, 65.0, 56.4, 57.0, 54.8, 52.5, 45.8, 45.6, 35.7, 29.6, 28.3, 20.2, 19.4; LRMS: (ES+) m/z = 589.3 (M+1)

(7S,11S,12S,E)-7-benzyl-6-(4-chlorobenzoyl)-9-isobutyl-11,12-dimethoxy-6,7,9,10,11,12-hexahydro-2H-benzo[m][1,6,9]oxadiazacyclotetradecin-8(5H)-one (1.2d):



Molecular Formula: $C_{35}H_{41}ClN_2O_5$; R_f : 0.4 (1:3 ethyl acetate/hexanes); Solvent system for column purification (1:3 ethyl acetate/hexanes); Yield: 75.8% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.46 (d, *J* = 6.64 Hz, 1H), 7.36-7.22 (m, 10H), 7.04 (t, *J* = 7.42 Hz, 1H), 6.94 (d, *J* = 8.36 Hz, 2H), 6.80 (d, *J* = 7.96 Hz, 1H), 6.10 (t, *J* = 7.71 Hz, 1H), 5.85 (ddd, *J* = 15.2 Hz, *J* = 9.2 Hz, *J* = 2.4 Hz, 1H), 5.33 (d, *J* = 15.38 Hz, 1H), 4.70 (s, 1H), 4.40 (s, 2H), 4.21 (d, *J* = 16.44 Hz, 1H), 4.06 (dd, *J* = 12.98, 2.57 Hz, 1H), 3.80 (m, 3H), 3.42-3.33 (m, 4H), 3.31-3.06 (m, 7H), 2.95 (dd, *J* = 14.55, 6.62 Hz, 1H), 2.08-1.93 (m, 1H), 0.95 (dd, *J* = 6.50, 3.81 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 170.8, 170.5, 155.2, 136.7, 135.3, 134.4, 129.8, 128.3, 128.2, 128.2, 127.9, 127.69, 126.7, 126.3, 125.2, 120.9, 110.8, 77.6, 65.0, 59.5, 57.1, 54.9, 52.5, 45.8, 45.6, 35.7, 28.4, 20.2, 19.4; LRMS: (ES+) m/z = 605.3 (M+1)

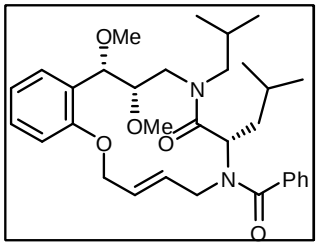
(7S,11S,12S,E)-6-(4-fluorobenzoyl)-7,9-diisobutyl-11,12-dimethoxy-6,7,9,10,11,12-hexahydro-2H-benzo[m][1,6,9]oxadiazacyclotetradecin-8(5H)-one (1.2e):



Molecular Formula: $C_{32}H_{43}FN_2O_5$; R_f : 0.3 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield: 82.1% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.46 (d, *J* = 7.26 Hz, 1H), 7.38 (dd, *J* = 8.30, 5.41 Hz, 2H), 7.26 (s, 1H), 7.07 (m, 4H), 6.80 (d, *J* = 8.08 Hz, 1H), 5.86 (d, *J* = 7.28 Hz, 1H), 5.80(ddd, *J* = 15.6 Hz, *J* = 9.2 Hz, *J* = 2.8 Hz, 1H), 5.33-5.24 (m, 1H), 4.71 (s, 1H), 4.38 (s, 2H), 4.07 (d, *J* = 9.24 Hz, 2H), 3.95-3.73 (m, 3H), 3.37 (s, 4H), 3.12 (s, 3H), 3.02-2.94 (m, 1H), 2.17 (s, 1H), 1.75 (d, *J* = 6.81 Hz, 3H), 1.62-1.50 (m, 1H), 1.10-0.99 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 171.4, 171.0, 155.2, 132.4, 132.4, 128.9, 128.8, 128.3, 128.1, 127.7, 126.4, 125.1, 120.8, 115.3,

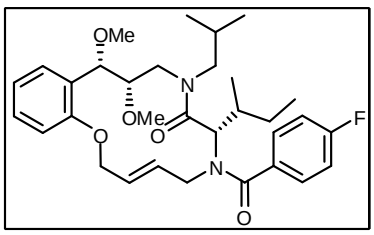
115.0, 110.8, 77.6, 65.0, 59.4, 57.2, 54.8, 49.7, 45.7, 45.5, 38.7, 29.6, 28.4, 24.7, 23.3, 22.8, 20.4, 19.6; LRMS: (ES+) m/z = 555.3 (M+1)

(7S,11S,12S,E)-6-benzoyl-7,9-diisobutyl-11,12-dimethoxy-6,7,9,10,11,12-hexahydro-2H benzo[m][1,6,9]oxadiazacyclotetradecin-8(5H)-one (1.2f):



Molecular Formula: $C_{32}H_{44}N_2O_5$; R_f : 0.4 (1:3 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield: 67.2% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.40 (m, 7H), 7.26-7.22 (m, 1H), 7.04 (t, *J* = 7.44 Hz, 1H), 6.79 (d, *J* = 8.01 Hz, 1H), 5.94-5.78 (m, 2H), 5.23 (d, *J* = 15.70 Hz, 1H), 4.72 (s, 1H), 4.37 (s, 2H), 4.11-4.01 (m, 2H), 3.95 (dd, *J* = 14.52, 7.92 Hz, 1H), 3.86 (dd, *J* = 16.49, 8.92 Hz, 1H), 3.77 (dd, *J* = 10.28, 1.73 Hz, 1H), 3.43 (dd, *J* = 12.90, 10.50 Hz, 1H), 3.38 (s, 3H), 3.13 (s, 3H), 2.99 (dd, *J* = 14.59, 6.59 Hz, 1H), 2.22-2.09 (m, 1H), 1.84 (dd, *J* = 8.38, 5.47 Hz, 1H), 1.78-1.69 (m, 2H), 1.59 (dd, *J* = 13.09, 6.61 Hz, 2H), 1.12-0.99 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 171.9, 171.5, 155.3, 136.4, 129.3, 128.3, 128.1, 128.0, 127.6, 126.6, 126.5, 125.0, 120.8, 110.8, 77.6, 65.1, 59.4, 57.2, 49.6, 45.6, 45.4, 38.7, 28.3, 24.6, 23.4, 22.8, 20.5, 19.6; LRMS: (ES+) m/z = 537.4 (M+1)

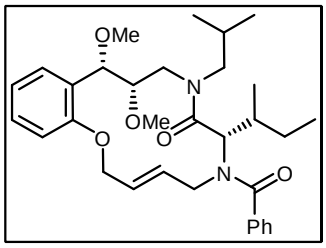
(7S,11S,12S,E)-7-sec-butyl-6-(4-fluorobenzoyl)-9-isobutyl-11,12-dimethoxy-6,7,9,10,11,12-hexahydro-2H-benzo[m][1,6,9]oxadiazacyclotetradecin-8(5H)-one (1.2g):



Molecular Formula: $C_{32}H_{43}FN_2O_5$; R_f : 0.3 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield: 67.5% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.46 (d, *J* = 7.43 Hz, 1H), 7.35 (dd, *J* = 8.25, 5.44 Hz, 2H), 7.26 (dd,

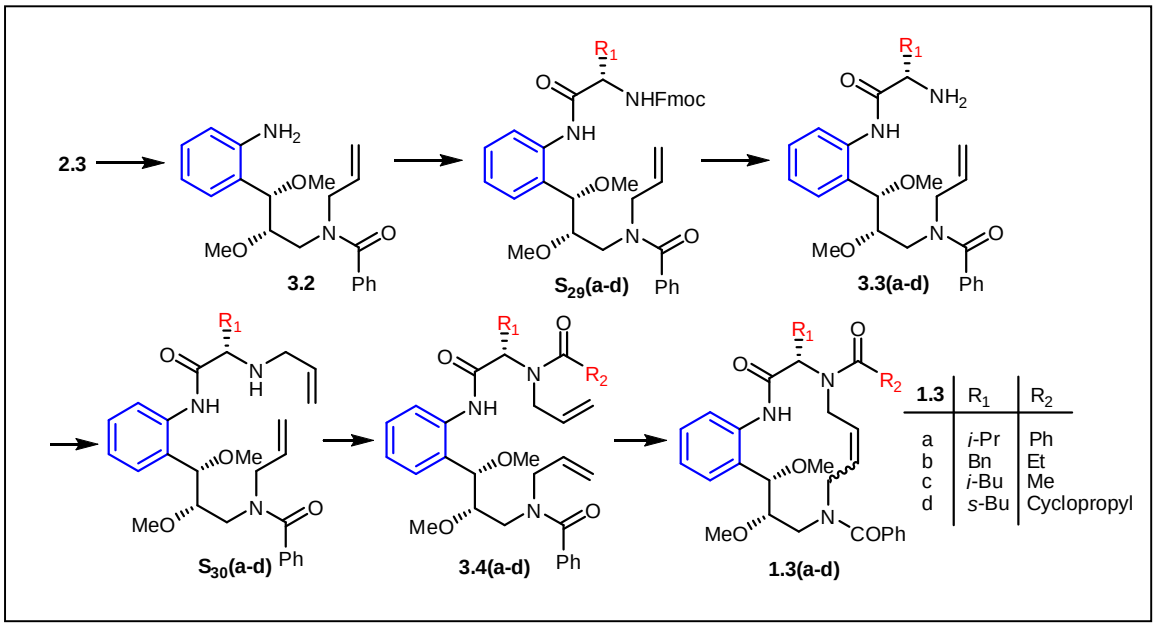
J = 9.00, 5.47 Hz, 1H), 7.13-7.00 (m, 3H), 6.79 (d, *J* = 8.08 Hz, 1H), 5.85 (ddd, *J* = 15.6 Hz, *J* = 9.2 Hz, *J* = 2.4 Hz, 1H), 5.48 (d, *J* = 10.71 Hz, 1H), 5.21 (d, *J* = 15.81 Hz, 1H), 4.69 (s, 1H), 4.37 (s, 2H), 4.10 (dd, *J* = 12.98, 2.82 Hz, 1H), 4.02 (d, *J* = 16.17 Hz, 1H), 3.93 (dd, *J* = 14.61, 7.44 Hz, 1H), 3.86-3.75 (m, 2H), 3.43 (dd, *J* = 12.75, 10.64 Hz, 1H), 3.37 (s, 3H), 3.12 (s, 3H), 2.92 (dd, *J* = 14.64, 7.54 Hz, 1H), 2.43-2.30 (m, 1H), 2.19 (m, 1H), 1.51-1.40 (m, 1H), 1.24-1.18 (m, 1H), 1.06 (t, *J* = 7.01 Hz, 6H), 1.00-0.92 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 171.3, 171.0, 155.2, 132.6, 132.6, 128.7, 128.6, 128.3, 128.1, 127.8, 126.3, 124.9, 120.8, 115.2, 115.0, 110.7, 77.6, 64.9, 59.5, 56.4, 56.3, 54.7, 46.1, 45.8, 33.3, 28.8, 23.8, 20.3, 19.9, 16.1, 11.1; LRMS: (ES+) m/z = 555.3 (M+1)

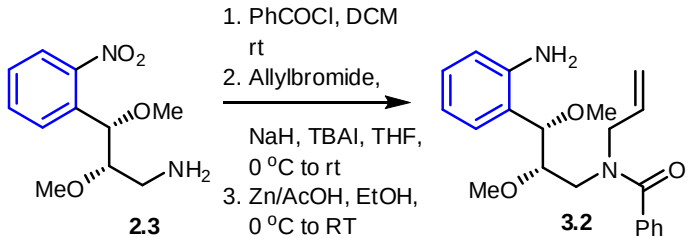
(7S,11S,12S,E)-7-sec-butyl-6-benzoyl-9-isobutyl-11,12-dimethoxy-6,7,9,10,11,12-hexahydro-2H-benzo[m][1,6,9]oxadiazacyclotetradecin-8(5H)-one (1.2h):



Molecular Formula: $C_{32}H_{44}N_2O_5$; R_f: 0.3 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield: 68.3% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.46 (d, *J* = 7.27 Hz, 1H), 7.43-7.30 (m, 5H), 7.25 (dd, *J* = 10.14, 2.65 Hz, 1H), 7.04 (t, *J* = 7.45 Hz, 1H), 6.79 (d, *J* = 8.03 Hz, 1H), 5.85 (ddd, *J* = 15.2 Hz, *J* = 8.8 Hz, *J* = 2.8 Hz, 1H), 5.50 (d, *J* = 10.74 Hz, 1H), 5.16 (d, *J* = 15.95 Hz, 1H), 4.70 (s, 1H), 4.35 (s, 2H), 4.11 (dd, *J* = 12.95, 2.83 Hz, 1H), 3.98 (dd, *J* = 14.41, 7.57 Hz, 2H), 3.88-3.77 (m, 2H), 3.43 (dd, *J* = 12.78, 10.53 Hz, 1H), 3.37 (s, 3H), 3.12 (s, 3H), 2.93 (dd, *J* = 14.61, 7.53 Hz, 1H), 2.44-2.32 (m, 1H), 2.27-2.13 (m, 1H), 1.55-1.44 (m, 1H), 1.25-1.18 (m, 1H), 1.07 (t, *J* = 6.49 Hz, 6H), 0.97 (dd, *J* = 6.57, 5.23 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.2, 171.1, 155.2, 136.5, 129.1, 128.3, 128.0, 128.0, 127.7, 126.4, 124.8, 120.7, 110.7, 77.5, 64.9, 59.4, 56.2, 56.2, 54.7, 46.1, 45.7, 33.3, 28.8, 23.7, 20.3, 19.9, 16.1, 11.1; LRMS: (ES+) m/z = 537.3 (M+1)

v) General Experimental procedures of Macrocycle 1.3





N-allyl-N-((2S,3S)-3-(2-aminophenyl)-2,3-dimethoxypropyl)benzamide (3.2):

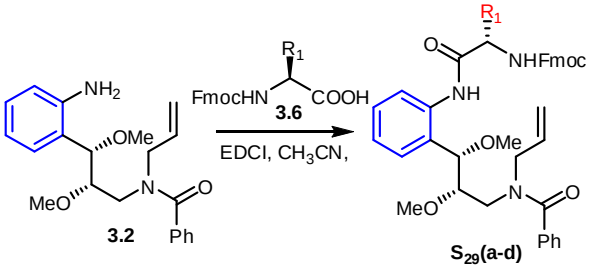
To a suspension of **2.3** (2.0 g, 8.32 mmol) in DCM (20 mL), benzoyl chloride (1.75 g, 12.48 mmol) was added at 0 °C and allowed to stir for 5 min. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution (15 mL), concentrated, and extracted with DCM (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give pure compound.

To suspension of above compound (1.0 g, 2.9 mmol) in dry THF, 60%NaH (348 mg, 14.5 mmol), allylbromide (1.25 mL, 14.5 mmol) and TBAI (10.7 mg, 0.029 mmol) were added at 0 °C, allowed to stir for 12 h. After completion the reaction mixture was quenched by using ammonium chloride solution (5 mL) and extracted with EtOAc (3 X 25 mL). Combined organic

layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was subjected next reaction without further purification.

To a suspension of above compound (1.5 g, 3.91 mmol) in EtOH (10 mL), Zn (5.07g, 78.03 mmol), AcOH (1.0 mL, 19.55 mmol) was added at 0 °C and allowed to stir the reaction mixture for 0.5 h. After completion of the reaction mixture was passed through celite and concentrated, to leave a crude oil, which was purified by column chromatography (2:3 ethyl acetate/hexane) to give the pure compound **3.2**.

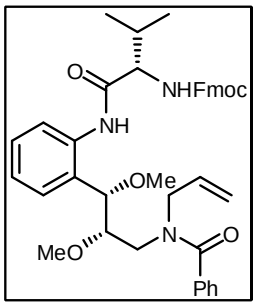
Molecular Formula: $C_{21}H_{26}N_2O_3$; R_f : 0.25 (2:3 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.28 (m, 5H), 7.13 (m, 2H), 6.83-6.47 (m, 2H), 5.93-5.56 (m, 1H), 5.11 (m, 2H), 4.42-3.75 (m, 6H), 3.66-3.13 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.2, 145.6, 136.5, 133.3, 129.5, 129.0, 128.7, 128.3, 128.1, 126.3, 125.2, 117.8, 117.2, 116.5, 85.0, 81.3, 60.2, 57.0, 57.0, 53.2, 47.7; LRMS: (ES+) m/z = 355.2 (M+1)



Compound S_{29}(a-d):

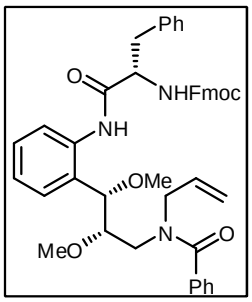
To a suspension of **3.2** (0.1 mmol) in Acetonitrile (10 mL), **3.6** (0.15 mmol), EDC·HCl (0.15 mmol) were added at room temperature and allowed to stirred for 3 h. After completion of the reaction mixture was quenched with sodium bicarbonate solution (5 mL), concentrated, and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give the pure compound **S_{29}(a-d).**

(9H-fluoren-9-yl)methyl(S)-1-(2-((1S,2S)-3-(N-allylbenzamido)-1,2-dimethoxypropyl) phenylamino)-3-methyl-1-oxobutan-2-ylcarbamate (S_{29}a):



Molecular Formula: $C_{41}H_{45}N_3O_6$; R_f : 0.25 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield- 89% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.75 (s, 1H), 8.30 (d, *J* = 6.40 Hz, 1H), 7.76 (d, *J* = 7.42 Hz, 2H), 7.62 (d, *J* = 7.17 Hz, 2H), 7.47-7.24 (m, 10H), 7.14 (m, 2H), 5.87-5.50 (m, 2H), 5.25-5.03 (m, 2H),4.37 (m, 5H), 3.98 (m, 4H), 3.52-3.01 (m, 8H), 2.47-2.19 (m, 1H), 1.11-0.93 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.3, 169.4, 156.4, 143.8, 141.2, 136.1, 133.2, 129.6, 128.9, 127.7, 127.0, 127.0, 126.3, 125.2, 125.0, 124.1, 121.9, 119.9, 117.4, 85.5, 83.6, 67.0, 61.1, 60.3, 57.3, 53.5, 47.2, 30.9, 19.4, 17.4, 14.1; LRMS: (ES+) m/z = 676.4 (M+1)

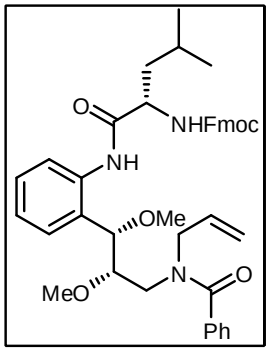
(9H-fluoren-9-yl)methyl(S)-1-(2-((1S,2S)-3-(N-allylbenzamido)-1,2-dimethoxypropyl) phenylamino)-1-oxo-3-phenylpropan-2-ylcarbamate (S_{29}b):



Molecular Formula: $C_{45}H_{45}N_3O_6$; R_f : 0.26 (3:7 ethyl acetate/hexane); Solvent system for column purification (3:7ethyl acetate/hexanes); Yield- 80.9%(colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 9.72 (s, 1H), 8.31 (d, *J* =7.49 Hz, 1H), 7.75 (d, *J* = 7.32 Hz, 2H), 7.53 (m, 2H), 7.43-7.07 (m, 17H), 5.98-5.78 (m, 1H), 5.69-5.47 (m, 1H), 5.06 (d, *J* = 11.30 Hz, 2H), 4.79-4.62 (m, 1H), 4.49 (s, 1H), 4.31 (s, 1H), 4.13 (m, 3H), 3.96 (m, 3H), 3.77-3.62 (m, 1H), 3.41-3.25 (m, 2H), 3.15 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.3, 171.1, 169.1, 169.0, 155.9, 143.7, 141.2, 136.7, 136.7, 136.1, 133.2, 129.7, 129.5, 129.0, 128.6, 128.5, 128.3, 127.7, 127.0, 126.9,

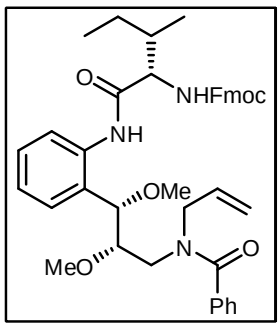
126.8, 126.3, 125.2, 125.0, 124.2, 122.0, 119.9, 117.3, 117.3, 85.8, 85.8, 83.4, 67.1, 60.3, 57.2, 56.9, 53.5, 53.5, 47.7, 47.1, 38.1; LRMS: (ES+) m/z = 724.4 (M+1)

(9H-fluoren-9-yl)methyl (S)-1-(2-((1S,2S)-3-(N-allylbenzamido)-1,2-dimethoxypropyl) phenylamino)-4-methyl-1-oxopentan-2-ylcarbamate (S_{29}c):

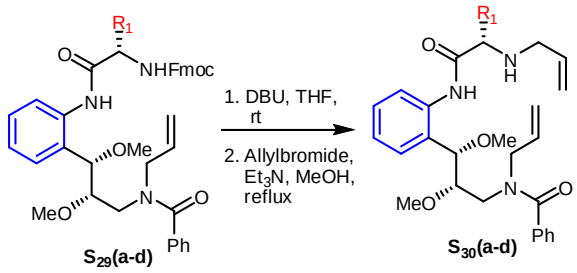


Molecular Formula: $C_{42}H_{47}N_3O_6$; R_f: 0.3 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield-85.4% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.75 (s, 1H), 8.29 (d, *J* =7.86 Hz, 1H), 7.77 (d, *J* = 7.35 Hz, 2H), 7.62 (d, *J* = 7.27 Hz, 2H), 7.47-7.26 (m, 10H), 7.19 (d, *J* = 6.91 Hz, 1H), 7.11 (d, *J* = 7.34 Hz, 1H), 5.86-5.73 (m, 1H), 5.73-5.57 (m, 1H), 5.26-5.03 (m, 2H), 4.58-4.47 (m, 1H), 4.47-4.18 (m, 4H), 4.03 (m, 3H), 3.75 (s, 1H), 3.49-3.37 (m, 1H), 3.26 (m, 6H), 1.94-1.69 (m, 4H), 1.65-1.50 (m, 1H), 0.99 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.3, 170.5, 156.2, 143.8, 141.2, 136.8, 136.1, 132.2, 129.7, 129.6, 129.0, 127.1, 127.0, 127.0, 1256.3, 125.2, 125.1, 124.2, 122.1, 119.1, 117.4, 85.6, 83.5, 66.9, 60.4, 57.2, 54.6, 53.6, 47.5, 47.1, 41.9, 24.8, 23.1, 21.8; LRMS: (ES+) m/z = 690.4 (M+1)

(9H-fluoren-9-yl)methyl(2S,3R)-1-(2-((1S,2S)-3-(N-allylbenzamido)-1,2-dimethoxypropyl) phenylamino)-3-methyl-1-oxopentan-2-ylcarbamate (S_{29}d):



Molecular Formula: $C_{42}H_{47}N_3O_6$; R_f: 0.3 (3:7 ethyl acetate/hexanes);Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield- 83.1% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.78 (s, 1H), 8.35 (d, *J* = 7.42 Hz, 1H), 7.77 (d, *J* = 7.42 Hz, 2H), 7.63 (d, *J* = 7.20 Hz, 2H), 7.47-7.27 (m, 11H), 7.18 (s, 1H), 7.11 (s, 1H), 5.85-5.56 (m, 2H), 5.25-5.02 (m, 2H), 4.60-4.44 (m, 1H), 4.30 (m, 4H), 3.98 (m, 3H), 3.87-3.72 (m, 1H), 3.55-3.36 (m, 1H), 3.27 (m, 7H), 2.19-2.06 (m, 1H), 1.91-1.73 (m, 1H), 1.67-1.47 (m, 1H), 1.26 (s, 1H), 1.10-0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.3, 169.4, 156.3, 143.8, 143.8, 141.2, 136.8, 136.1, 133.2, 129.7, 129.0, 128.4, 127.7, 127.0, 127.0, 126.3, 125.2, 125.1, 124.1, 121.7, 119.9, 117.3, 85.4, 83.5, 67.0, 60.7, 60.4, 57.3, 53.5, 47.4, 47.1, 37.5, 24.5, 15.7, 11.7; LRMS: (ES+) m/z = 690.4 (M+1)



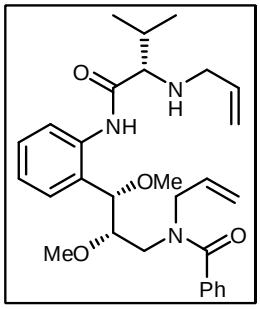
S29(a-d) **S30(a-d)**

Compound S_{30}(a-d):

To a suspension of compound **S_{29}(a-d)** (0.1 mmol) in THF (10 mL), DBU (0.15 mmol) was added and stirred the reaction mixture for 5 min. After completion of the reaction, reaction mixture concentrated and which was purified by column chromatography.

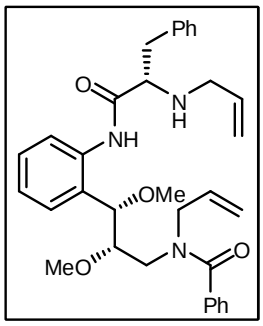
To a suspension of above compound (0.1 mmol) in MeOH (10 mL), allylbromide (0.5 mmol) and triethylamine (0.5 mmol) were added and allowed to reflux for 12 h. Concentrated the reaction mixture and purified by the column chromatography to give the pure compound **S_{30}(a-d).**

N-allyl-N-((2S,3S)-3-(2-((S)-2-(allylamino)-3-methylbutanamido)phenyl)-2,3-dimethoxypropyl) benzamide (S_{30}a):



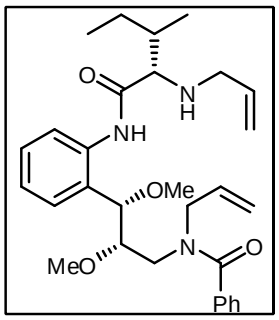
Molecular Formula: $C_{29}H_{39}N_3O_4$; R_f : 0.25 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield- 65.8% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.25 (s, 1H), 8.39 (d, *J* = 8.18 Hz, 1H), 7.36 (m, 7H), 7.25-7.05 (m, 1H), 6.03-5.60 (m, 1H), 5.13 (m, 4H), 4.44-4.32 (m, 1H), 4.12-3.82 (m, 2H), 3.76-3.52 (m, 1H), 3.51-2.99 (m, 11H), 2.21 (s, 1H), 1.11-0.85 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.7, 172.1, 136.3, 133.3, 129.4, 128.8, 128.3, 126.3, 123.7, 122.0, 117.3, 116.2, 85.4, 82.6, 68.6, 62.0, 60.4, 57.1, 53.2, 59.1, 31.6, 29.6, 19.8, 18.1; LRMS: (ES+) m/z = 494.3 (M+1)

N-allyl-N-((2S,3S)-3-(2-((S)-2-(allylamino)-3-phenylpropanamido)phenyl)-2,3-dimethoxypropyl)benzamide (S_{30}b):

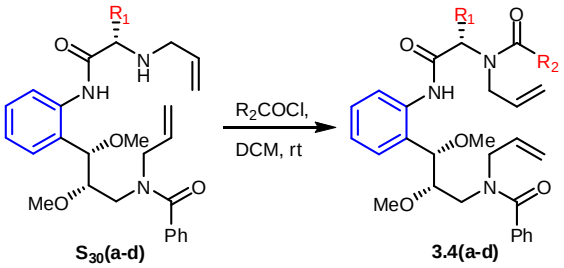


Molecular Formula: $C_{33}H_{39}N_3O_4$; R_f : 0.25 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield- 70.1% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.35 (s, 1H), 8.47-8.31 (m, 1H), 7.29 (m, 14H), 5.95-5.57 (m, 2H), 5.33-4.93 (m, 4H), 4.41-4.26 (m, 1H), 4.16-3.77 (m, 3H), 3.76-3.60 (m, 1H), 3.22 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.5, 172.2, 136.3, 133.3, 130.2, 129.5, 129.1, 128.3, 128.2, 126.7, 126.3, 123.8, 122.1, 117.2, 116.1, 85.8, 82.5, 64.2, 60.4, 57.0, 53.3, 51.0, 47.3, 39.2; LRMS: (ES+) m/z = 542.3 (M+1)

N-allyl-N-((2S,3S)-3-(2-((2S,3R)-2-(allylamino)-3-methylpentanamido)phenyl)-2,3-dimethoxypropyl)benzamide (S_{30}d):



Molecular Formula: $C_{30}H_{41}N_3O_4$; R_f (solvent system): 0.20 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield- 68.3% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.25 (s, 1H), 8.40 (d, *J* = 8.20 Hz, 1H), 7.37 (s, 6H), 7.24-7.17 (m, 1H), 7.15-6.87 (m, 1H), 6.04-5.59 (m, 2H), 5.14 (m, 4H), 4.48-4.30 (m, 1H), 4.11-3.80 (m, 3H), 3.77-3.56 (m, 1H), 3.24 (m, 10H), 2.00-1.86 (m, 1H), 1.31-1.15 (m, 1H), 1.03 (d, *J* = 6.92 Hz, 3H), 0.92 (d, *J* = 6.84 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.6, 172.1, 136.3, 133.3, 129.5, 129.4, 129.4, 128.8, 128.3, 126.3, 123.4, 122.0, 117.3, 116.3, 85.4, 82.6, 77.4, 67.8, 60.4, 57.1, 53.3, 51.9, 47.1, 38.5, 25.2, 16.1; LRMS: (ES+) m/z = 508.3 (M+1)

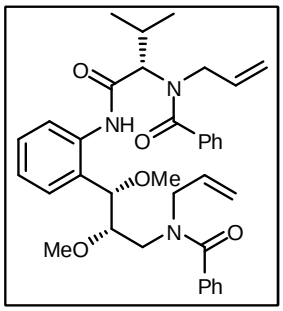


S30(a-d) **3.4(a-d)**

Compound 3.4(a-d):

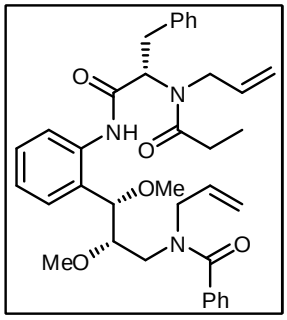
To a suspension of **S30(a-d)** (0.1 mmol) in DCM (10 mL), acid chloride (0.15 mmol) was added at 0 °C and allowed to stir for 5 min. After completion of the reaction mixture was quenched with sodium bicarbonate solution (5 mL), concentrated, and extracted with DCM (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give pure compound **3.4(a-d)**.

N-allyl-N-((S)-1-(2-((1S,2S)-3-(N-allylbenzamido)-1,2-dimethoxypropyl)phenylamino)-3-methyl-1-oxobutan-2-yl)benzamide (3.4a):



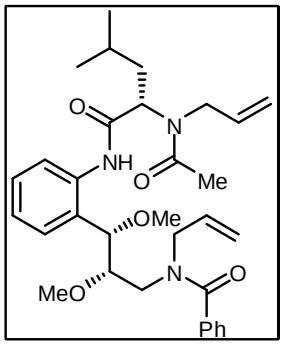
Molecular Formula: $C_{36}H_{43}N_3O_5$, R_f : 0.40 (2:3 ethyl acetate/hexanes), Solvent system for column purification (2;3 ethyl acetate/hexanes); Yield-82.6% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.70 (s, 1H), 8.17-7.95 (m, 1H), 7.38 (m, 12H), 7.20-6.96 (m, 2H), 5.85-5.56 (m, 2H), 5.26-5.03 (m, 2H), 5.00-4.65 (m, 2H), 4.55-4.34 (m, 1H), 3.97 (m, 6H), 3.36 (m, 9H), 2.62-2.44 (m, 1H), 1.08-0.80 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.2, 172.2, 168.4, 136.3, 133.9, 133.2, 129.9, 129.4, 129.1, 128.3, 128.3, 126.7, 126.3, 124.4, 123.1, 117.3, 83.7, 82.6, 65.2, 62.1, 60.5, 57.1, 53.4, 47.2, 33.4, 30.1, 26.8, 19.9, 18.6, 15.8, 13.3; LRMS: (ES+) m/z = 598.4 (M+1)

N-allyl-N-((2S,3S)-3-(2-((S)-2-(N-allylpropionamido)-3-phenylpropanamido)phenyl)-2,3-dimethoxypropyl)benzamide (3.4b):



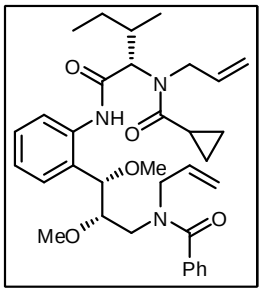
Molecular Formula: $C_{36}H_{43}N_3O_5$, R_f : 0.45 (2:3 ethyl acetate/hexanes), Solvent system for column purification (2:3 ethyl acetate/hexanes); Yield-83.8% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.50 (s, 1H), 8.36-8.04 (m, 1H), 7.57-6.96 (m, 14H), 5.90-5.51 (m, 2H), 5.44-4.97 (m, 5H), 4.45-4.22 (m, 1H), 3.96 (s, 5H), 3.74-3.37 (m, 3H), 3.16 (m, 8H), 2.50-2.20 (m, 2H), 1.09 (t, J = 7.27 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 174.8, 172.2, 168.6, 137.9, 136.3, 134.4, 133.2, 129.1, 128.6, 128.4, 128.3, 128.2, 126.3, 126.3, 124.0, 122.2, 117.4, 117.0, 85.0, 83.0, 77.4, 60.3, 60.3, 57.0, 48.7, 47.1, 34.6, 26.7, 9.2; LRMS: (ES+) m/z = 598.4 (M+1)

N-allyl-N-((2S,3S)-3-(2-((S)-2-(N-allylacetamido)-4-methylpentanamido)phenyl)-2,3-dimethoxypropyl)benzamide (3.4c):



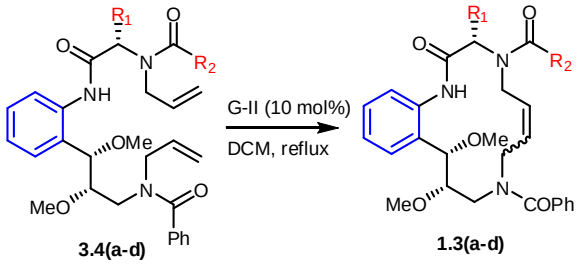
Molecular Formula: $C_{32}H_{43}N_3O_5$, R_f (solvent system): 0.35 (3:7 ethyl acetate/hexanes), Solvent system for column purification (2:3 ethyl acetate/hexanes); Yield-79.4% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.60 (s, 1H), 8.43-8.28 (m, 1H), 7.38 (s, 7H), 7.23-7.00 (m, 2H), 5.96-5.61 (m, 2H), 5.47-5.32 (m, 1H), 5.20 (m, 5H), 4.44-4.29 (m, 1H), 4.27-3.84 (m, 5H), 3.80-3.65 (m, 1H), 3.62-3.43 (m, 1H), 3.28 (m, 7H), 2.18 (s, 3H), 2.10-1.87 (m, 2H), 1.77-1.50 (m, 4H), 0.97 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.2, 172.0, 169.5, 136.2, 134.8, 133.2, 129.6, 128.7, 128.4, 126.3, 123.8, 121.6, 117.4, 116.9, 85.5, 83.3, 60.4, 57.3, 56.4, 53.3, 53.3, 48.5, 47.2, 37.3, 24.9, 24.3, 22.7, 22.0; LRMS: (ES+) m/z = 550.3 (M+1)

N-allyl-N-((2S,3S)-3-(2-((2S,3R)-2-(N-allylcyclopropanecarboxamido)-3-methylpentan amido)phenyl)-2,3-dimethoxypropyl)benzamide(3.4d):



Molecular Formula: $C_{34}H_{45}N_3O_5$, R_f : 0.40 (2:3 ethyl acetate/hexanes), Solvent system for column purification (2:3ethyl acetate/hexanes); Yield-75.2% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.50 (s, 1H), 8.15-7.96 (m, 1H), 7.53-7.19 (m, 7H), 7.17-6.87 (m, 1H), 6.02-5.61 (m, 2H), 5.35-5.05 (m, 4H), 4.97-4.73 (m, 1H), 4.39 (s, 3H), 3.97 (s, 3H), 3.84-3.60 (m, 1H),

3.30 (m, 7H), 2.25-2.08 (m, 1H), 1.77 (m, 1H), 1.53-1.37 (m, 1H), 0.94 (m, 9H), 0.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 174.9, 172.2, 168.6, 136.3, 135.1, 133.3, 128.3, 126.3, 124.2, 122.9, 122.9, 117.3, 116.2, 83.6, 82.5, 62.7, 60.2, 57.0, 53.3, 47.0, 46.6, 32.9, 24.6, 15.7, 12.0, 10.7, 8.8, 8.5, 8.2; LRMS: (ES+) m/z = 576.4 (M+1)

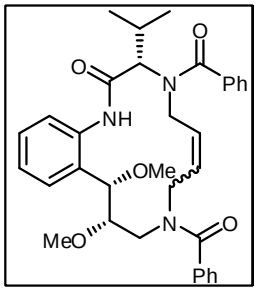


3.4(a-d) **1.3(a-d)**

Macrocycle 1.3(a-d):

To above bisallyl compound **3.4(a-d)** (0.1 mmol) in dry dichloromethane (50 mL) under nitrogen atmosphere and Grubbs' 2nd generation catalyst (0.01 mmol) was added and reaction mixture was heated to 40 °C for 24 h. After completion of the reaction, reaction mixture was concentrated and subjected to column chromatography to give pure product **1.3(a-d)**.

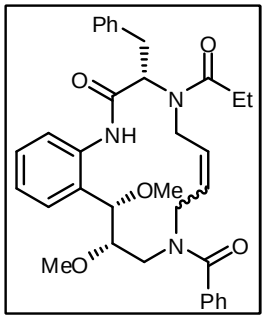
((3S,11S,12S,Z/E)-3-isopropyl-11,12-dimethoxy-2-oxo-2,3,11,12-tetrahydrobenzo[m][1,4,9] triazacyclotetradecine-4,9(1H,5H,8H,10H)-diyl)bis(phenylmethanone) (1.3a):



Molecular Formula: $C_{34}H_{39}N_3O_5$; R_f: 0.3 (2:3 ethyl acetate/hexane); Solvent system for column purification (2:3ethyl acetate/hexanes); Yield-78%(white semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.16-8.54 (m, 1H), 8.26-6.82 (m, 18H), 6.24-5.74 (m, 1H), 5.71-4.62 (m, 2H), 4.60-3.72 (m, 7H), 3.68-2.80 (m, 11H), 2.78-2.37 (m, 2H), 1.19 (dd, *J* = 31.69, 25.73 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.6, 172.3, 167.5, 136.4, 135.4, 130.2, 129.5, 129.3,

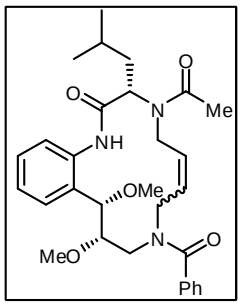
128.7, 128.3, 127.2, 126.6, 125.0, 90.1, 80.5, 67.6, 60.3, 59.3, 57., 54.8, 48.7, 41.3, 29.6, 27.1, 20.0, 18.5; LRMS: (ES+) m/z = 570.3 (M+1)

(3S,11S,12S,Z/E)-9-benzoyl-3-benzyl-11,12-dimethoxy-4-propionyl-3,4,5,8,9,10,11,12-octahydrobenzo[m][1,4,9]triazacyclotetradecin-2(1H)-one (1.3b):



Molecular Formula: $C_{34}H_{39}N_3O_5$; R_f: 0.3 (2:3 ethyl acetate/hexane); Solvent system for column purification (2:3ethyl acetate/hexanes); Yield-81%(white semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.57-8.88 (m, 1H), 8.54-7.93 (m, 1H), 7.69-6.87 (m, 14H), 6.21-5.52 (m, 2H), 4.40-3.66 (m, 4H), 3.33 (m, 11H), 2.63-2.10 (m, 3H), 0.92 (d, *J* = 6.49 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.9, 173.0, 172.4, 137.0, 136.9, 136.4, 135.9, 133.5, 129.5, 129.3, 129.1, 128.8, 128.4, 127.0, 126.6, 124.4, 121.5, 90.6, 81.7, 77.2, 62.7, 60.0, 56.8, 33.9, 31.8, 29.6, 25.7, 22.6, 14.0, 9.2; LRMS: (ES+) m/z = 570.3 (M+1)

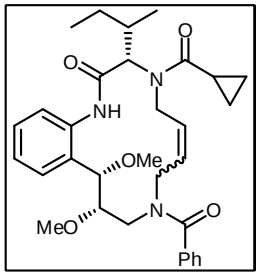
(3S,11S,12S,Z/E)-4-acetyl-9-benzoyl-3-isobutyl-11,12-dimethoxy-3,4,5,8,9,10,11,12-octahydrobenzo[m][1,4,9]triazacyclotetradecin-2(1H)-one (1.3c):



Molecular Formula: $C_{30}H_{39}N_3O_5$; R_f: 0.3 (2:3 ethyl acetate/hexanes); Solvent system for column purification (2:3ethyl acetate/hexanes); Yield-76% (white semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.60-8.98 (m, 1H), 8.66-7.97 (m, 1H), 7.64-6.73 (m, 8H), 6.32-5.33 (m, 3H), 4.39-4.17 (m, 1H), 4.15-3.77 (m, 3H), 3.72-2.98 (m, 8H), 2.33 (s, 4H), 1.99-1.84 (m, 1H), 1.84-1.67

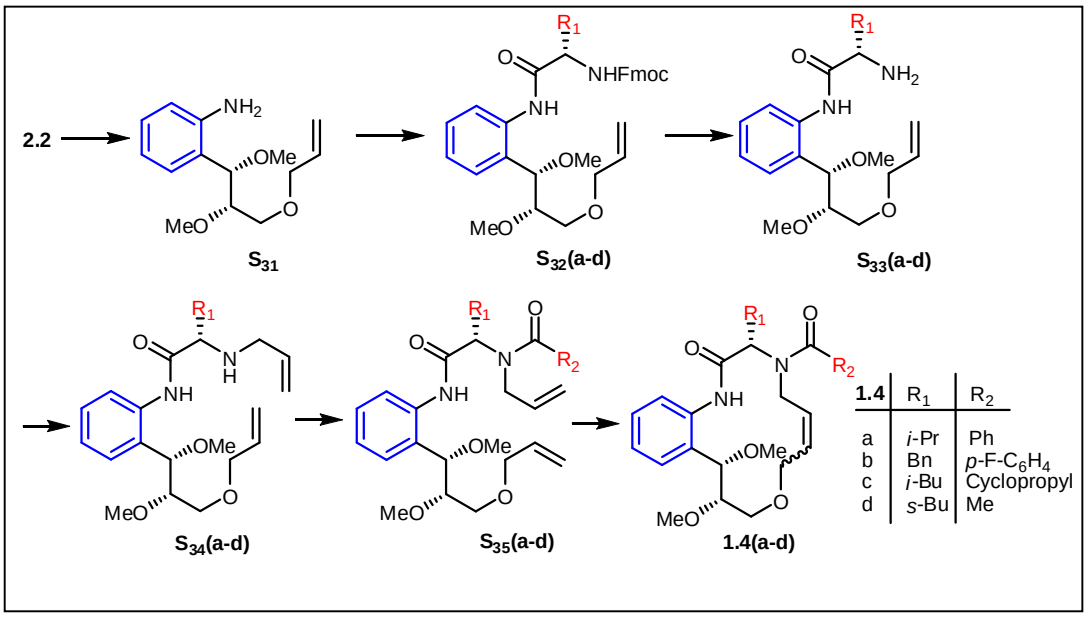
(m, 1H), 1.69-1.46 (m, 2H), 1.11-0.90 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.2, 172.4, 170.8, 170.3, 169.5, 167.8, 136.5, 135.9, 133.7, 130.7, 129.8, 129.5, 129.1, 128.3, 128.0, 127.3, 126.6, 124.4, 121.7, 90.8, 81.7, 81.0, 69.4, 60.3, 60.2, 60.1, 59.0, 57.7, 56.8, 55.0, 53.7, 53.5, 49.2, 44.8, 40.5, 37.3, 36.1, 31.8, 31.7, 29.6, 29.3, 29.2, 24.6, 24.6, 23.1, 22.7, 22.1, 21.7, 14.0; LRMS: (ES+) m/z = 522.3 (M+1)

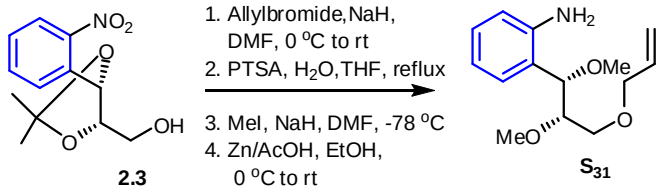
(3S,11S,12S,Z/E)-9-benzoyl-3-sec-butyl-4-(cyclopropanecarbonyl)-11,12-dimethoxy-3,4,5,8,9,10,11,12-octahydrobenzo[m][1,4,9]triazacyclotetra decin-2(1H)-one (1.3d):



Molecular Formula: $C_{32}H_{41}N_3O_5$; R_f: 0.2 (1:1 ethyl acetate/hexanes); Solvent system for column purification (2:3ethyl acetate/hexanes); Yield-77% (white semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.43-8.84 (m, 1H), 8.27-7.91 (m, 1H), 7.51-7.24 (m, 7H), 7.23-6.75 (m, 2H), 6.20-5.62 (m, 2H), 5.17-4.50 (m, 2H), 4.47-3.73 (m, 6H), 3.50 (d, *J* = 76.44 Hz, 9H), 2.52-2.14 (m, 2H), 2.02-1.77 (m, 1H), 1.27 (d, *J* = 7.18 Hz, 4H), 1.13-0.79 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.6, 173.1, 172.5, 136.6, 135.8, 133.2, 130.1, 129.6, 128.3, 127.2, 126.6, 124.5, 122.8, 90.6, 81.6, 77.2, 66.4, 61.0, 42.6, 29.6, 24.5, 20.5, 16.0, 14.1, 11.7, 11.5, 8.4; LRMS: (ES+) m/z = 548.3 (M+1)

vi) General Experimental procedures of Macrocycle 1.4





(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)aniline (S_{31}):

To a suspension of **7m** (500 mg, 1.97 mmol) in dry DMF (10 mL), 60% NaH (94.8 mg, 3.95 mmol) was added at 0 °C and allowed to stir for 30 min then added allylbromide (0.35 mL, 3.95 mmol). After completion of the reaction, reaction mixture was quenched with ammonium chloride solution (5 mL), and extracted with Ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was subjected to next reaction without further purification.

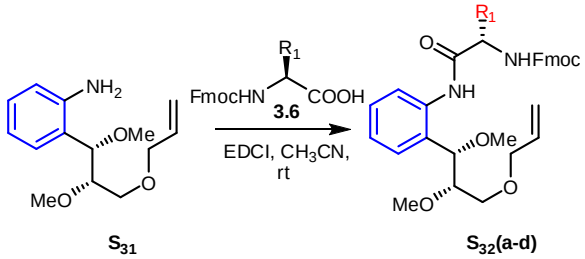
To suspension of above compound (500 mg, 1.71 mmol) in THF, PTSA (880 mg, 5.12 mmol) and water 1 mL were added, allowed to reflux for 6 h. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution (10 mL), and extracted with Ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous

sodium sulfate, filtered and concentrated to leave a crude oil, which was subjected to next reaction without further purification.

To a suspension of nitro compound (400 mg, 1.58 mmol) in DMF (10 mL), MeI (0.9 mL, 15.8 mmol) and 60% NaH (227.5 mg, 9.48 mmol) were added at 0 °C and allowed to stir the reaction mixture for 0.5 h. After completion of the reaction, reaction mixture was quenched with ammonium chloride solution (5 mL), and extracted with Ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was subjected to next reaction without further purification.

To a suspension of above compound (500 mg, 1.78 mmol) in EtOH (10 mL), Zn (2.3 g, 35.58 mmol), AcOH (0.5 mL, 8.9 mmol) was added at 0 °C and allowed to stir the reaction mixture for 0.5 h. After completion of the reaction, reaction mixture was passed through celite and concentrated, to leave a crude oil, which was purified by column chromatography to give the pure compound **S_{31}**.

Molecular Formula: $C_{14}H_{21}NO_3$; R_f (solvent system): 0.2 (1:4 ethyl acetate/hexane); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield- 65% for 4 steps LRMS: (ES+) m/z = 252.1 (M+1)

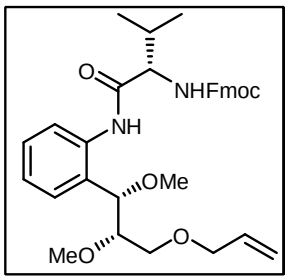


S_{31} **S_{32}(a-d)**

Compound S_{32}(a-d):

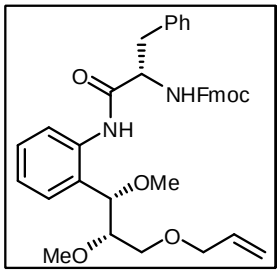
Experimental procedure as per ref. compound **S_{29}(a-d)**

(9H-fluoren-9-yl)methyl (S)-1-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenylamino)-3-methyl-1-oxobutan-2-ylcarbamate (S_{32}a):



Molecular Formula: $C_{34}H_{40}N_2O_6$; R_f : 0.4 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-99.5% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.22 (d, *J* = 8.05 Hz, 1H), 7.76 (d, *J* = 7.42 Hz, 2H), 7.62 (d, *J* = 7.32 Hz, 2H), 7.44-7.27 (m, 5H), 7.20 (d, *J* = 7.42 Hz, 1H), 7.09 (t, *J* = 7.47 Hz, 1H), 5.91-5.78 (m, 1H), 5.53 (d, *J* = 8.66 Hz, 1H), 5.22 (d, *J* = 17.31 Hz, 1H), 5.14 (d, *J* = 10.34 Hz, 1H), 4.47 (q, *J* = 9.25 Hz, 2H), 4.38-4.29 (m, 1H), 4.24 (t, *J* = 7.03 Hz, 1H), 4.16 (dd, *J* = 8.14, 6.09 Hz, 1H), 3.91 (d, *J* = 4.77 Hz, 2H), 3.65-3.52 (m, 2H), 3.43 (s, 3H), 3.28-3.17 (m, 4H), 2.28 (m, 1H), 1.02 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 169.2, 156.1, 143.6, 143.6, 141.0, 136.3, 134.2, 129.0, 128.4, 127.4, 127.0, 126.8, 124.9, 124.8, 123.9, 121.9, 119.7, 119.7, 116.9, 83.4, 72.1, 68.7, 66.8, 61.1, 59.1, 57.2, 30.9, 19.1, 17.5; LRMS: (ES+) m/z = 541.3 (M+1)

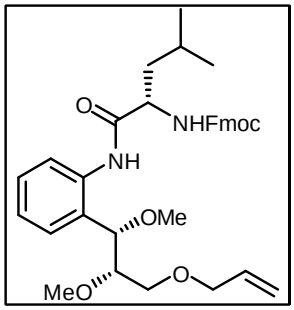
(9H-fluoren-9-yl)methyl (S)-1-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenylamino)-1-oxo-3-phenylpropan-2-ylcarbamate (S_{32}b):



Molecular Formula: $C_{38}H_{40}N_2O_6$; R_f : 0.25 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-98.5% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.62 (s, 1H), 8.22 (d, *J* = 7.71 Hz, 1H), 7.77 (d, *J* = 7.46 Hz, 2H), 7.57 (t, *J* = 7.26 Hz, 2H), 7.46-7.13 (m, 13H), 7.09 (t, *J* = 7.40 Hz, 1H), 5.81 (m, 1H), 5.44 (d, *J* = 7.08 Hz, 1H), 5.16 (m, 2H), 4.61 (d, *J* = 5.94 Hz, 1H), 4.55-4.44 (m, 1H), 4.39 (d, *J* = 4.53 Hz, 1H), 4.25 (m, 6.90 Hz, 2H), 3.85 (s, 2H), 3.55-3.38 (m, 2H), 3.24 (m, 5H), 3.17-3.05 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 168.9, 155.7, 143.7, 414.2, 136.5, 136.2, 134.4, 129.5, 129.3, 128.7,

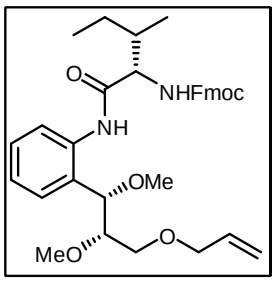
128.7, 127.7, 127.0, 125.1, 125.0, 124.2, 122.1, 119.9, 11.9, 117.1, 84.3, 83.3, 72.3, 68.3, 67.1, 59.2, 57.4, 56.8, 47.1, 38.4; LRMS: (ES+) m/z = 621.3 (M+1)

(9H-fluoren-9-yl)methyl (S)-1-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenylamino)-4-methyl-1-oxopentan-2-ylcarbamate (S_{32}c):

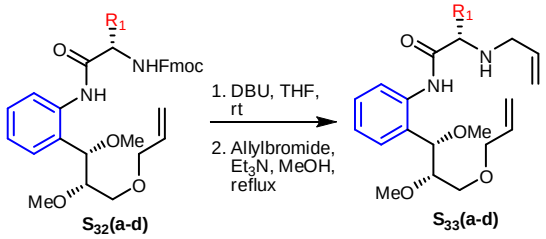


Molecular Formula: $C_{35}H_{42}N_2O_6$; R_f : 0.25 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-97.8% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.66 (s, 1H), 8.21 (d, *J* = 7.90 Hz, 1H), 7.76 (d, *J* = 7.44 Hz, 2H), 7.62 (d, *J* = 7.34 Hz, 2H), 7.45-7.27 (m, 5H), 7.19 (d, *J* = 7.41 Hz, 1H), 7.09 (t, *J* = 7.45 Hz, 1H), 5.92-5.78 (m, 1H), 5.41 (d, *J* = 7.83 Hz, 1H), 5.22 (d, *J* = 17.26 Hz, 1H), 5.15 (d, *J* = 10.36 Hz, 1H), 4.55-4.41 (m, 2H), 4.34 (m, 2H), 4.23 (t, *J* = 6.90 Hz, 1H), 3.91 (s, 2H), 3.68-3.55 (m, 2H), 3.41 (d, *J* = 14.20 Hz, 3H), 3.23 (d, *J* = 11.34 Hz, 4H), 1.79 (m, 3H), 1.67-1.53 (m, 1H), 1.00 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 170.4, 156.0, 143.8, 143.8, 141.2, 136.7, 134.4, 129.2, 128.7, 127.7, 127.6, 127.1, 127.0, 125.1, 125.0, 124.1, 122.2, 119.9, 119.9, 117.1, 84.1, 84.1, 83.6, 72.3, 69.0, 66.9, 59.4, 57.4, 54.7, 47.2, 42.1, 24.8, 23.0, 22.0; LRMS: (ES+) m/z = 587.3 (M+1)

(9H-fluoren-9-yl)methyl(2S,3R)-1-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenyl amino)-3-methyl-1-oxopentan-2-ylcarbamate (S_{32}d):



Molecular Formula: $C_{35}H_{42}N_2O_6$; R_f : 0.3 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-96.9% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.60 (s, 1H), 8.24 (d, *J* = 7.96 Hz, 1H), 7.76 (d, *J* = 7.46 Hz, 2H), 7.61 (d, *J* = 7.44 Hz, 2H), 7.35 (m, 5H), 7.19 (d, *J* = 7.34 Hz, 1H), 7.09 (t, *J* = 7.47 Hz, 1H), 5.91-5.78 (m, 1H), 5.51 (d, *J* = 8.60 Hz, 1H), 5.21 (d, *J* = 17.13 Hz, 1H), 5.14 (d, *J* = 10.44 Hz, 1H), 4.47 (dd, *J* = 10.46, 6.82 Hz, 2H), 4.39-4.28 (m, 1H), 4.27-4.15 (m, 2H), 3.97-3.82 (m, 2H), 3.58 (m, 2H), 3.44 (s, 3H), 3.28-3.15 (m, 4H), 2.09-1.96 (m, 1H), 1.63-1.50 (m, 1H), 1.21 (m, 1H), 1.08-0.89 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 169.4, 156.2, 143.8, 143.8, 141.2, 136.6, 134.4, 129.2, 128.7, 127.7, 127.6, 127.1, 127.0, 125.1, 125.0, 124.1, 122.1, 119.9, 119.9, 117.1, 83.5, 72.3, 68.9, 67.0, 60.7, 59.4, 57.5, 47.2, 37.8, 24.7, 15.6, 11.6; LRMS: (ES+) m/z = 587.3 (M+1)

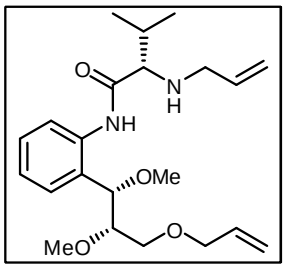


S32(a-d) **S33(a-d)**

Compound S_{33}(a-d):

Experimental procedure as per ref. compound **S_{30}(a-d)**

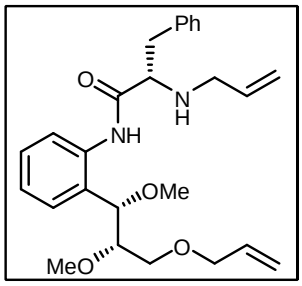
(S)-2-(allylamino)-N-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenyl)-3-methylbutanamide (S_{33}a):



Molecular Formula: $C_{22}H_{34}N_2O_4$; R_f : 0.25(1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-65.5% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.23 (s, 1H), 8.32 (d, *J* = 8.20 Hz, 1H), 7.32 (t, *J* = 7.73 Hz, 1H), 7.21 (d, *J* = 7.54 Hz, 1H), 7.07 (t, *J* = 7.48 Hz, 1H), 5.98-5.76 (m, 2H), 5.21 (dd, *J* = 17.21, 8.43 Hz, 2H), 5.12 (dd, *J* = 10.01, 1.62 Hz, 2H), 4.47 (d, *J* = 6.77 Hz, 1H), 3.91-3.79 (m, 2H), 3.73-

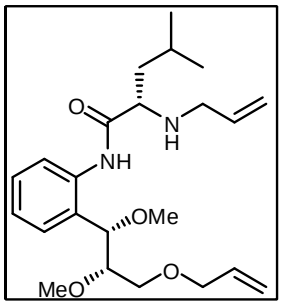
3.66 (m, 1H), 3.54-3.46 (m, 4H), 3.35 (dd, *J* = 14.02, 5.01 Hz, 1H), 3.31-3.25 (m, 3H), 3.18 (dd, *J* = 14.05, 6.83 Hz, 1H), 3.11-3.02 (m, 2H), 2.22 (m, 1H), 1.06 (d, *J* = 6.92 Hz, 3H), 0.98 (d, *J* = 6.85 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.5, 136.8, 136.1, 134.4, 129.6, 128.7, 126.8, 123.7, 122.0, 117.0, 116.5, 84.7, 82.6, 72.3, 68.9, 68.5, 59.2, 57.3, 51.9, 31.6, 19.7, 18.2; LRMS: (ES+) m/z = 391.3 (M+1)

(S)-2-(allylamino)-N-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenyl)-3-phenylpropanamide (S_{33}b):



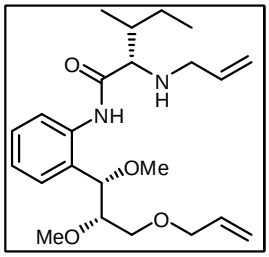
Molecular Formula: $C_{26}H_{34}N_2O_4$; R_f : 0.25(3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield-66.5% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.36 (s, 1H), 8.32 (d, *J* = 8.17 Hz, 1H), 7.39-7.15 (m, 7H), 7.07 (t, *J* = 7.37 Hz, 1H), 5.78 (m, 2H), 5.26-4.99 (m, 4H), 4.41 (d, *J* = 6.79 Hz, 1H), 3.91-3.76 (m, 2H), 3.54-3.38 (m, 6H), 3.33-3.08 (m, 6H), 3.03-2.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.4, 137.3, 136.7, 135.7, 134.5, 129.7, 129.2, 128.8, 128.7, 126.9, 126.9, 123.8, 122.1, 117.0, 116.3, 85.0, 82.3, 72.3, 68.9, 63.7, 59.4, 57.2, 51.1, 39.1; LRMS: (ES+) m/z = 439.2 (M+1)

(S)-2-(allylamino)-N-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenyl)-4-methylpentanamide (S_{33}c):

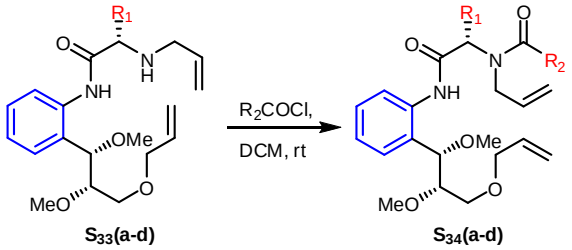


Molecular Formula: $C_{23}H_{36}N_2O_4$; R_f: 0.3(1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-72.3% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.23 (s, 1H), 8.27 (d, *J* = 8.17 Hz, 1H), 7.32 (t, *J* = 7.73 Hz, 1H), 7.20 (d, *J* = 7.42 Hz, 1H), 7.07 (t, *J* = 7.43 Hz, 1H), 5.98-5.77 (m, 2H), 5.26-5.17 (m, 2H), 5.16-5.09 (m, 2H), 4.46 (d, *J* = 6.66 Hz, 1H), 3.94-3.81 (m, 2H), 3.71-3.62 (m, 1H), 3.56-3.46 (m, 4H), 3.39-3.15 (m, 6H), 3.09 (dd, *J* = 10.41, 4.63 Hz, 1H), 1.83-1.63 (m, 2H), 1.53-1.43 (m, 1H), 0.97 (t, *J* = 6.12 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.7, 136.9, 136.0, 134.4, 129.6, 128.7, 126.9, 123.7, 122.2, 117.1, 116.4, 84.8, 82.7, 72.3, 68.9, 61.6, 59.3, 57.3, 51.4, 43.3, 25.1, 23.1, 22.0; LRMS: (ES+) m/z = 405.3 (M+1)

(2S,3R)-2-(allylamino)-N-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenyl)-3-methylpentanamide (S_{33}d):



Molecular Formula: $C_{23}H_{36}N_2O_4$; R_f : 0.35 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-68.5% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.23 (s, 1H), 8.33 (d, *J* = 8.20 Hz, 1H), 7.32 (t, *J* = 7.75 Hz,1H), 7.21 (d, *J* = 7.50 Hz, 1H), 7.07 (t, *J* = 7.75 Hz, 1H), 5.97-5.76 (m, 2H), 5.25-5.16 (m, 2H), 5.12 (dd, *J* = 10.17, 4.60 Hz, 2H), 4.47 (d, *J* = 6.82 Hz, 1H), 3.91-3.80 (m, 2H), 3.73-3.67 (m, 1H), 3.54-3.45 (m, 4H), 3.35 (dd, *J* = 14.09, 5.17 Hz, 1H), 3.29 (d, *J* = 7.66 Hz, 3H), 3.17 (dd, *J* = 14.11, 6.91 Hz, 1H), 3.13-3.04 (m, 2H), 1.98-1.87 (m, 1H), 1.64-1.50 (m, 3H), 1.25 (m, 2H), 1.02 (d, *J* = 6.92 Hz, 3H), 0.92 (t, *J* = 7.38 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.6, 136.8, 136.1, 134.4, 129.6, 128.7, 126.8, 123.7, 122.0, 117.0, 116.5, 84.7, 82.6, 72.3, 68.9, 67.9, 59.3, 57.3, 52.0, 38.5, 25.3, 16.1, 11.8; LRMS: (ES+) m/z = 405.3 (M+1)

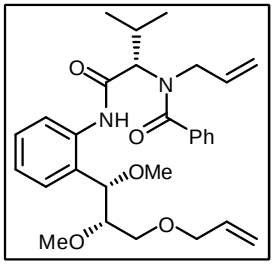


S33(a-d) **S34(a-d)**

Compound S_{34}(a-d):

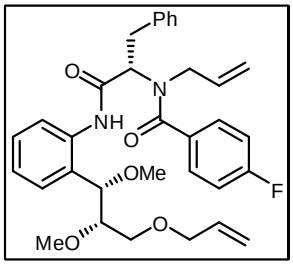
Experimental procedure as per ref. compound **3.4(a-d)**

N-allyl-N-((S)-1-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenylamino)-3-methyl-1-oxobutan-2-yl)benzamide (S_{34}a):



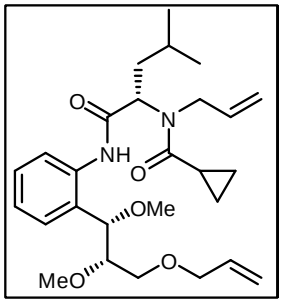
Molecular Formula: $C_{29}H_{38}N_2O_5$; R_f : 0.25 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-90.5% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.65 (s, 1H), 8.07 (s, 1H), 7.52-7.22 (m, 8H), 7.13 (t, *J* = 7.46 Hz, 1H), 5.95-5.60 (m, 2H), 5.23 (m, 1H), 5.15 (d, *J* = 10.35 Hz, 1H), 4.98-4.87 (m, 1H), 4.86-4.72 (m, 1H), 4.56 (s, 2H), 3.85-4.20 (m, 5H), 3.80-3.69 (m, 1H), 3.68-3.46 (m, 4H), 3.36-3.18 (m, 6H), 2.71-2.55 (m, 1H), 1.96-1.69 (m, 1H), 1.09 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.3, 168.6, 136.6, 136.3, 134.5, 133.9, 129.6, 128.8, 128.4, 126.8, 124.5, 123.2, 117.7, 117.0, 83.1, 82.7, 72.3, 69.3, 65.5, 59.4, 57.4, 49.6, 26.9, 20.0, 19.0; LRMS: (ES+) m/z = 495.3 (M+1)

N-allyl-N-((S)-1-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenylamino)-1-oxo-3-phenylpropan-2-yl)-4-fluorobenzamide (S_{34}b):



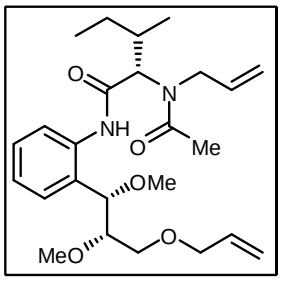
Molecular Formula: $C_{33}H_{37}FN_2O_5$; R_f : 0.4 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-85.6% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.57 (s, 1H), 8.19 (s, 1H), 7.39-7.05 (m, 11H), 5.85 (m, 1H), 5.45 (m, 1H), 5.20-4.80 (m, 3H), 4.72 (s, 1H), 4.50 (s, 1H), 3.87-3.35 (m, 6H), 3.28-3.07 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 171.7, 168.3, 162.1, 137.8, 136.6, 134.4, 133.4, 132.2, 129.5, 129.4, 129.3, 129.2, 128.6,128.5, 126.7, 124.1, 122.7, 118.9, 117.1, 115.4, 115.1, 84.6, 82.6, 72.3, 68.2, 62.2, 58.5, 57.4, 53.0, 29.6; LRMS: (ES+) m/z = 561.3 (M+1)

N-allyl-N-((S)-1-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenylamino)-4-methyl-1-oxopentan-2-yl)cyclopropanecarboxamide (S_{34}c):

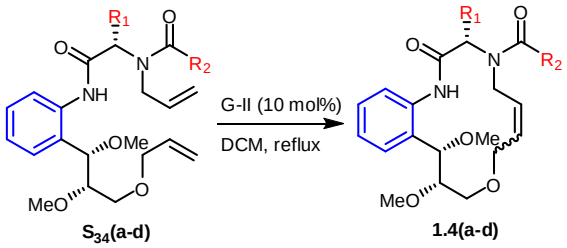


Molecular Formula: $C_{27}H_{40}N_2O_5$; R_f: 0.3 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-92.3% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.45 (s, 1H), 8.18 (d, *J* = 8.17 Hz, 1H), 7.40-7.24 (m, 2H), 7.19 (d, *J* = 7.52 Hz, 1H), 7.07 (t, *J* = 7.45 Hz, 1H), 6.02-5.79 (m, 2H), 5.36-5.09 (m, 5H), 4.45 (d, *J* = 5.14 Hz, 1H), 4.40-4.28 (m, 1H), 4.10 (dd, *J* = 18.10, 5.16 Hz, 1H), 3.91 (dd, *J* = 11.34, 6.12 Hz, 2H), 3.66 (dd, *J* = 9.20, 4.65 Hz, 1H), 3.57 (dd, *J* = 10.21, 3.91 Hz, 1H), 3.45 (s, 3H), 3.26 (s, 3H), 3.17 (dd, *J* = 10.14, 5.10 Hz, 1H), 2.01-1.88 (m, 1H), 1.82-1.73 (m, 1H), 1.66-1.52 (m, 2H), 1.12-0.91 (m, 8H), 0.84-0.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 174.9, 169.6, 136.9, 135.3, 134.5, 128.9, 128.4, 127.1, 123.9, 122.2, 116.9, 116.4, 83.7, 83.2, 72.3, 69.1, 59.3, 57.3, 56.5, 47.2, 37.4, 24.9, 22.5, 22.5, 12.0, 8.5, 8.3; LRMS: (ES+) m/z = 473.3 (M+1)

N-allyl-N-((2S,3R)-1-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenylamino)-3-methyl-1-oxopentan-2-yl)cyclopropanecarboxamide (S_{34}d):



Molecular Formula: $C_{25}H_{38}N_2O_5$; R_f : 0.35 (1:4 ethyl acetate/ hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-83.5% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.41 (d, *J* = 12.94 Hz, 1H), 8.06 (d, *J* = 8.13 Hz, 1H), 7.30 (m, 1H), 7.23 (d, *J* = 7.37 Hz, 1H), 7.09 (t, *J* = 7.47 Hz, 1H), 5.83 (m, 2H), 5.17 (m, 4H), 4.83 (d, *J* = 11.01 Hz, 1H), 4.47 (d, *J* = 5.33 Hz, 1H), 4.11 (t, *J* = 6.45 Hz, 2H), 3.92 (m, 3H), 3.69-3.62 (m, 1H), 3.59-3.51 (m, 4H), 3.28 (d, *J* = 10.68 Hz, 4H), 3.17 (dd, *J* = 10.29, 5.18 Hz, 1H), 2.30-2.25 (m, 1H), 2.21-2.08 (m, 4H), 1.42 (m, 1H), 1.13-0.98 (m, 5H), 0.93-0.87 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 171.9, 169.5, 137.0, 134.7, 134.4, 128.9, 128.4, 126.8, 123.8, 121.9, 17.0, 116.9, 83.9, 83.5, 72.2, 69.0, 59.2, 57.4, 56.3, 48.4, 37.3, 24.9, 22.7, 22.2, 22.0; LRMS: (ES+) m/z = 445.2 (M+1)

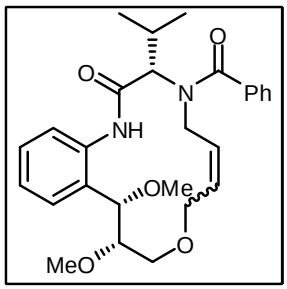


S$_{34}$(a-d) **1.4(a-d)**

Macrocycle 1.4(a-d):

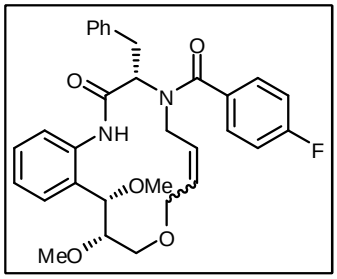
Experimental procedure as per ref. compound **1.1(a-d)**

3S,11S,12S,Z/E)-4-benzoyl-3-isopropyl-11,12-dimethoxy-4,5,8,10,11,12-hexahydro-1H-benzo[j][1,6,9]oxadiazacyclotetradecin-2(3H)-one (1.4a):



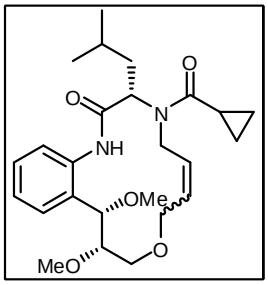
Molecular Formula: $C_{27}H_{34}N_2O_5$; R_f: 0.25 (3:7 ethyl acetate/hexane); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield-88%(white semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.49-9.23 (m, 1H), 8.99-8.71 (m, 1H), 8.14-7.95 (m, 1H), 7.70 (d, *J* = 6.49 Hz, 1H), 7.46 (s, 6H), 7.33 (d, *J* = 5.96 Hz, 2H), 7.19-6.94 (m, 2H), 5.95-5.53 (m, 1H), 5.50-4.91 (m, 1H), 4.34-3.89 (m, 5H), 3.65 (s, 4H), 3.43 (s, 7H), 2.76-2.51 (m, 1H), 1.22-0.97 (m, 6H), 0.85 (t, *J* = 6.56 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.2, 167.4, 136.3, 135.9, 135.6, 133.6, 130.3, 130.0, 129.4, 129.2, 128.7, 127.2, 124.7, 124.0, 82.5, 72.5, 67.6, 60.1, 57.6, 57.2, 41.5, 29.6, 27.3, 19.9, 18.5; LRMS: (ES+) m/z = 467.2 (M+1).

(3S,11S,12S,Z/E)-3-benzyl-4-(4-fluorobenzoyl)-11,12-dimethoxy-4,5,8,10,11,12-hexahydro-1H-benzo[j][1,6,9]oxadiazacyclotetradecin-2(3H)-one (1.4b):



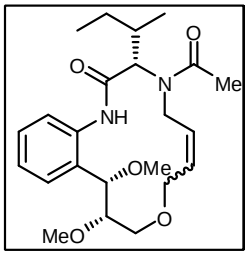
Molecular Formula: $C_{31}H_{33}FN_2O_5$; R_f : 0.25 (2:3 ethyl acetate/hexane); Solvent system for column purification (2:3 ethyl acetate/hexanes);Yield-86%(white semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.69-8.78 (m, 1H), 8.43-7.96 (m, 1H), 7.54-7.18 (m, 7H), 7.03 (d, *J* = 5.17 Hz, 6H), 6.18-5.29 (m, 2H), 5.02-4.33 (m, 1H), 4.30-3.70 (m, 4H), 3.50 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 171.2, 167.0, 136.9, 136.5, 135.8, 134.5, 131.3, 130.2, 129.8, 129.4, 128.7, 126.9, 124.5, 122.6, 115.8, 115.6, 82.2, 73.9, 72.9, 63.7, 60.4, 59.8, 57.1, 29.7; LRMS: (ES+) m/z = 533.2 (M+1).

(3S,11S,12S,Z/E)-4-(cyclopropanecarbonyl)-3-isobutyl-11,12-dimethoxy-4,5,8,10,11,12-hexahydro-1H-benzo[j][1,6,9]oxadiazacyclotetradecin-2(3H)-one (1.4c):



Molecular Formula: $C_{25}H_{36}N_2O_5$; R_f: 0.3 (2:3 ethyl acetate/hexane); Solvent system for column purification (2:3 ethyl acetate/hexanes); Yield-85%(white semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.29 (d, *J* = 11.56 Hz, 4H), 5.87 (d, *J* = 5.25 Hz, 1H), 4.16 (s, 5H), 3.58 (s, 5H), 3.30 (s, 6H), 1.91 (dd, *J* = 13.50, 6.51 Hz, 3H), 1.66-1.47 (m, 1H), 1.26 (s, 2H), 1.08-0.86 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 174.0, 169.7, 136.0, 131.9, 129.8, 128.8, 128.8, 124.2, 123.2, 88.8, 83.5, 71.4, 59.2, 57.0, 54.5, 37.0, 29.6, 24.7, 22.9, 22.8, 22.3, 11.7, 8.7, 8.3; LRMS: (ES+) m/z = 445.3 (M+1)

(3S,11S,12S,Z/E)-4-(cyclopropanecarbonyl)-3-(seco-butyl)-11,12-dimethoxy-4,5,8,10,11,12-hexahydro-1H-benzo[j][1,6,9]oxadiazacyclotetradecin-2(3H)-one (1.4d):



Molecular Formula: $C_{25}H_{36}N_2O_5$; R_f: 0.3 (1:1 ethyl acetate/hexane); Solvent system for column purification (2:3 ethyl acetate/hexanes); Yield-85%(white semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.36-8.97 (m, 1H), 8.36-7.91 (m, 1H), 7.50-7.26 (m, 2H), 7.21-6.89 (m, 2H), 5.81 (s, 2H), 5.17-4.49 (m, 1H), 4.32-3.74 (m, 5H), 3.65 (s, 3H), 3.36 (d, *J* = 19.65 Hz, 6H), 2.87-2.53 (m, 1H), 2.31 (s, 4H), 1.47-1.21 (m, 4H), 1.12-0.87 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.4, 171.1, 168.8, 167.5, 135.9, 134.8, 132.2, 129.9, 129.3, 128.8, 124.4, 124.1, 122.5, 114.0, 83.0, 82.7, 73.5, 72.3, 72.0, 67.9, 60.2, 59.4, 57.6, 57.2, 53.3, 44.3, 40.6, 32.7, 32.3, 29.6, 29.6, 24.5, 24.2, 22.1, 21.9, 16.7, 16.0, 11.5, 10.7; LRMS: (ES+) m/z = 419.2 (M+1)

vii) Zebrafish Screening Assay

Small molecule tool box from this study (total 85 compounds) was subjected to search for compounds affecting epiboly during early embryonic development,[1-3,4,5,6] angiogenesis,[7-10] neurogenesis[11] in zebrafish embryo-based assays.[12-14] These assays are well-documented in the literature.[6,9,15-17] Embryos were obtained by natural mating and staged according to the literature procedure.[18] Zebrafish embryos of stages older than 24 hours post fertilization (hpf) were treated with 0.03% PTU (*N*-phenylthiourea) when needed to inhibit pigment formation. Wild type AB line, and transgenic lines Tg (fli:EGFP, islet1:GFP) were used to assess the effects on epiboly, angiogenesis and neurogenesis respectively. Zebrafish embryos for small molecule screening experiments were collected via pair-wise matings, cleaned and incubated in PTU treated E3 water at 28.3 ^{o}C. One to four cell stage embryos were then distributed into 96 well clear bottom plate (Corning). The compound exposure was done in 96 well plate (Corning) and three embryos were taken in each well containing 200 µl of (0.5 to 15µM) compound in PTU treated egg water. The 96 well plates were incubated at 28.3 ^{o}C and the embryos were allowed to grow until 10 hpf or 30 hpf to assess the effect on epiboly, angiogenesis/neurogenesis respectively. Phenotypes were scored using a Zeiss Axiovert 200 inverted microscope equipped with a cooled CCD camera. Photographs were processed and assembled using Photoshop software (see **Figure 1**).

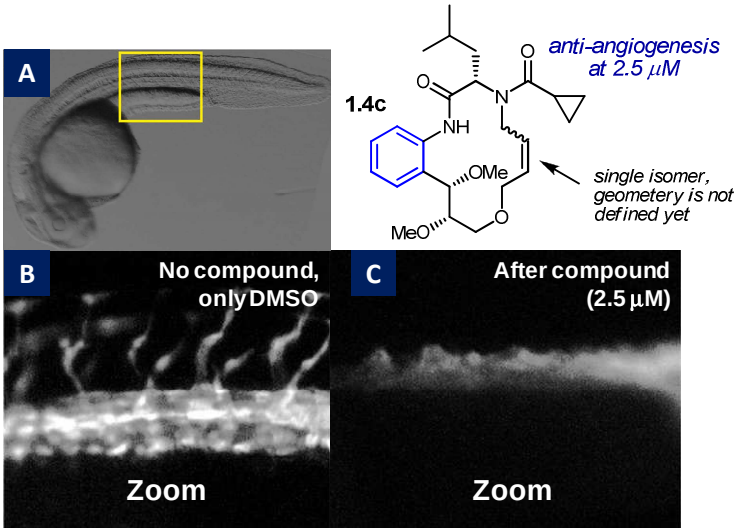
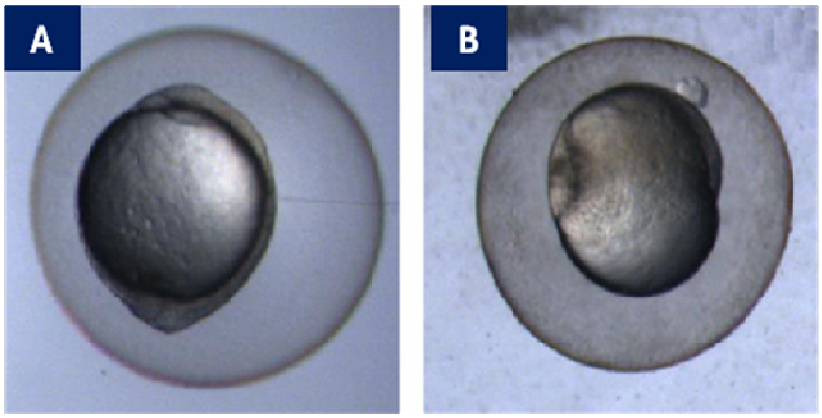


Figure 1: (**A**) Wild-type zebrafish embryo at 30 hpf of development, region zoomed in panels **B** and **C** is shown by a yellow box, (**B**) zoom section of wild-type or vehicle treated embryo, and (**C**) zoom section after treatment with compound **1.4c**.



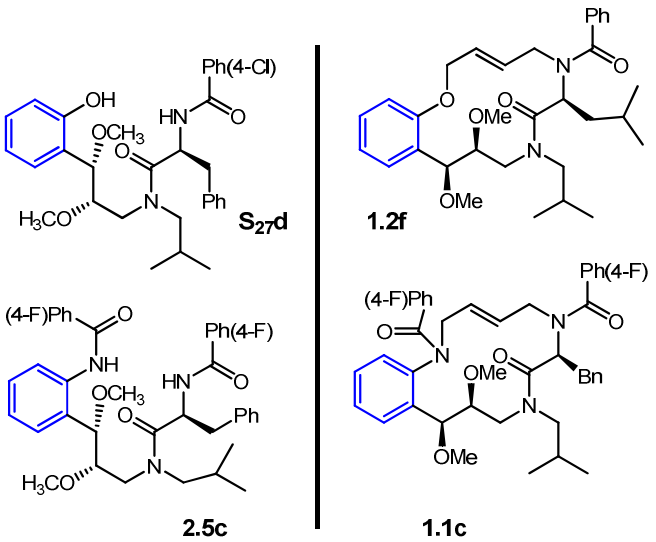


Figure 2: Zebrafish early embryonic development Assay. (A) DMSO exposed embryos at 10 hpf of development, (B) small molecule exposed embryos causing a delay in epiboly.

viii) References

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