Design, Synthesis, Potency and Cytoselectivity Of Anticancer Agents Derived Combinatorially From α-Aminosuberic Acid.

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Supporting Information

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Scheme S1: Synthesis of Some Antitumour Agents Based On HDAC Inhibition. Reagents: (a) 1. Na, EtOH; 2. methyl 6-iodohexanoate; (b) 10M HCl, reflux; (c) acetic anhydride, $NaHCO_3$, water; (d) Acylase I from aspergillus melleus, $CoCl_2$, phosphate buffer pH 7.2; (e) $SOCl_2$, MeOH, -20 °C; (f) R^1 (4-(dimethylamino)benzoic acid), HBTU, DIPEA, DMF; (g) R^2 (benzylamine), HBTU, DIPEA, DMF; (h) NaOH, THF (aq); (i) 1. 2-chlorotritylhydroxylamine resin, HATU, DIPEA, DMF; 2. TFA.

Synthesis of compounds 15-23.
The synthesis of compounds **15-23** was performed using similar methodology to that described in the main text with modifications due to differing side chain carboxylic acid methyl ester protection.

6-Iodohexanoic acid methyl ester: 6-Bromohexanoic acid methyl ester (10.6 g, 51.0 mmol), and sodium iodide (23 g, 150 mmol) were refluxed overnight in THF (100 mL). The solvent was removed under reduced pressure, and the residue dissolved in EtOAc (300 mL). After washing the organic layer with water (3 x 100 mL), and drying over magnesium sulfate, the solvent was removed under reduced pressure to afford the title ester as a dark oil (9.9 g, 82%), which was used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.75 (s, 3H); 3.18 (t (6.9 Hz), 2H); 2.32 (t (6.8 Hz), 2H); 1.84 (m, 2H); 1.62 (m, 2H), 1.41 (m, 2H).

(2*SR*)-Aminosuberic acid 58: Sodium metal (190 mg, 8.3 mmol) was added carefully to vigorously stirred dry ethanol (50 mL) under a stream of argon, and stirring continued until all the sodium had dissolved. Diethyl acetamidomalonate (870 mg, 4.0 mmol) was added in one portion, and stirring continued for a further 30 minutes. 6-Iodohexanoic acid methyl ethyl (1.1 g, 4.3 mmol) was then added, and the resulting solution refluxed over night. After removal of the solvent under reduced pressure, the resulting residue was dissolved in EtOAc (100 mL), and washed with 1M HCl (2 x 50 mL). The organic layer was dried over magnesium sulfate, and the solvent was removed under reduced pressure to afford a yellow oil of the di-substituted malonate (1.25 g, 3.6 mmol), which was refluxed overnight in 10M HCl (15 mL). The acid was removed under reduced pressure, and the resulting brown solid dissolved in water (30 mL) and washed with EtOAc (4 x 50 mL). The aqueous solution was desalted by rpHPLC to afford the title acid as a white solid after lyophilisation (540 mg, 71%). ^{1}H NMR (D_2O, 500 MHz): δ 4.01 (t (6.5 Hz), 1H); 2.34 (t (7.5 Hz), 2H); 1.91 (m, 2H); 1.56 (m, 2H); 1.34 (m, 4H). ^{13}C NMR (D_2O, 75 MHz): δ 176.3, 174.7, 60.1, 52.4, 40.6, 38.5, 32.6, 30.6.

(2*SR*)-Acetylaminosuberic acid 59: Aminosuberic acid (4.9 g, 25.9 mmol) was dissolved in water, and the pH was adjusted to 8 with $NaHCO_3$. Acetic anhydride (2.6 mL, 26.4 mmol) was added with stirring, and after ten minutes the reaction was purified by rpHPLC to provide the title compound as a white solid (4.7 g, 78%). ^{1}H NMR (D_2O, 300 MHz): δ 4.31 (m, 1H); 2.37 (t (6.8 Hz), 2H); 2.05 (s, 3H); 1.95 (m, 1H); 1.85 (m, 1H); 1.57 (m, 2H); 1.38 (m, 4H). ^{13}C NMR (D_2O, 75 MHz): δ 177.4, 174.3, 171.5, 59.7, 52.2, 40.5, 39.4, 32.5, 30.4, 20.2.

(2*S*)-2-Aminosuberic Acid 60: (2SR)-Acetylaminosuberic acid (2.0 g, 8.6 mmol) was dissolved in phosphate buffer (0.1 M, pH 7.2, 100 mL), and the pH adjusted to 7.2 by addition of 2M NaOH. The resulting solution was warmed to 39ºC, and $CoCl_2.6H_2O$ (20 mg) was added with gentle shaking. Acylase I (from apspergillus melleus, 100mg) was added to the solution, and the reaction was left to sit overnight at 39ºC. Analysis of an aliquot of the solution by ^{1}H NMR indicated a 1:1 mixture of the amine and the acetamide. Removal of solvent and purification by rpHPLC afforded (2S)-aminosuberic acid (0.7 g, 43%) and (2R)-acetylaminosuberic acid (0.9

g, 45%). For the derivative, Z-(2*S*)-Asu-OH, $[\alpha]_D$ –9.1 deg (DMF, 22°C).[42]

(2*R*)-Aminosuberic Acid 62: (2R)-Acetylaminosuberic acid **61** (0.9 g, 3.8 mmol) was dissolved in HCl (10 M, 10 mL) and the solution refluxed gently overnight. The solvent was removed under reduced pressure and residue dissolved in water (20 mL), and washed with EtOAc (2 x 20 mL). The organic layer was discarded, and the solvent removed from the aqueous layer to afford the title acid (0.6 g, 84%) as a yellow oil. For the derivative, Z-(2*R*)-Asu-OH, $[\alpha]_D$ +9.1 deg (DMF, 22°C).[42]

Methyl Ester formation (General Proceedure) 63: (2*S*) **60** or 2(*R*) **62** or (2*RS*)-Aminosuberic acid **58** (4.5 g, 23.8 mmol) was dissolved in dry methanol (60 mL), and the resulting solution cooled to -20ºC. Thionyl chloride (1.7 mL, 23.8 mmol) was added dropwise with stirring, while maintaining the reaction temperature at -20ºC. The reaction was followed by mass spectroscopy, and additional thionyl chloride (0.3 mL) was added in small aliquots until all the staring material had been consumed. Removal of the solvent under reduced pressure afforded the title ester in quantitative yield. ^{1}H NMR (D_2O, 300 MHz): δ 4.05 (t (6.0 Hz), 1H); 3.67 (s, 3H); 2.41 (t (7.4 Hz), 2H); 1.95 (m, 2H); 1.66 (m, 2H); 1.40 (m, 4H). ^{13}C NMR (D_2O, 75 MHz): δ 177.8, 176.4, 60.1, 59.1, 47.2, 40.5, 36.6, 34.7, 30.9.

Amide Formation (General Procedure) 64 and 65. To a stirred solution of the acid (1eq) in THF (2mL/mmol) at room temperature was added HBTU (1eq) and DIPEA (2eq). After five minutes a solution of the amine **63** (1eq) and DIPEA (2eq) in THF (1mL/mmol) was added, and stirring was continued for a further thirty minutes. After this time the THF was removed under reduced pressure, and the residue was taken up into ethyl acetate (10mL/mmol), and washed with equal portions of 1M HCl, $NaHCO_3$ and brine. The organic layer was dried over magnesium sulfate, and the solvent was removed under reduced pressure to yield the amide

Ester Hydrolysis (General Procedure). 2M NaOH (2.5 eq) was added to a solution of the ester (1eq) in methanol (5mL/mmol) at 0°C, and the solution was stirred for one hour. The solution was neutralized with citric acid, and the methanol removed under reduced pressure. Water (5mL/mmol) was added, and the acid extracted into ethyl acetate. The organic phase was dried over magnesium sulfate, and solvent was removed under reduced pressure to yield the crude acid which could be purified by RPHPLC.

Conversion to Hydroxamic Acid (General Procedure) 66. Commercially available N-Fmoc hydroxylamine 2-chlorotrityl resin (0.77 mmol/g, 1 eq) was shaken gently with 1:1 piperidine:DMF (5 mL/mmol) over night, and then flow washed with DMF for 1 minute. In a separate flask HATU (1 eq) was added to a solution of the acid (1 eq) and DIPEA (5 eq) dissolved in DMF (2 mL/mmol), and the resulting solution stirred gently for 5 minutes. The HATU activated acid was then added in one portion to the deprotected resin, and the resin was shaken gently for 1 hour. The resin was washed well with DCM, and then drained. TFA:water (99:1, 1 mL/mmol) was added, and the resin shaken for 20 minutes. The TFA was collected, and the resin washed with a further 1 mL of TFA. The TFA was removed by distillation, and the resulting oil purified by rpHPLC to provide the desired hydroxamic acid generally as a white solid. All Hydroxamic acids displayed ^{1}H NMR and HRMS consistent with their structures Table S1.

Table S1: Characterization data for compounds **6**, **15**-**57** showing retention times under two sets of rpHPLC conditions, high resolution mass spectral data for molecular ions, and ^{1}H-NMR spectral data.

Compound No.	rp-HPLC RT-Isocratic (min)	rp-HPLC RT-Gradient (min)	HRMS (g/mol)	MS-theoretical	^{1}H NMR
6	7.84^b	22.57	441.2597	441.2496	^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.05 (s, 1H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 7.3 Hz, 1H), 7.23 (m, 5H), 6.66 (d, , *J* = 8.5 Hz, 2H), 4.72 (m, 1H), 4.47 (dd, *J* = 14.6, 5.8 Hz, 1H), 4.29 (dd, *J* = 14.8, 5.8 Hz, 1H), 2.99 (s, 6H), 2.00 (m, 2H), 1.75 (m, 2H), 1.45-1.25 (m, 6H)
15	7.84^a	22.57	441.2597	441.2496	^{1}H NMR (d_6-DMSO, 500 MHz) δ 10.22, (s, 1H), 8.31 (t, *J* = 5.8 Hz, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 8.9 Hz, 2H), 7.23-7.11 (m, 5H), 6.61 (d, *J* = 8.9 Hz, 2H), 4.34 (m, 1H), 4.19 (d, *J* = 5.9 Hz, 2H), 2.88 (s, 6H), 1.83 (t, *J* = 7.3 Hz, 2H), 1.63 (m,2H) 1.37 (m, 2H), 1.25-1.15 (m, 4H)
16	7.64^c	22.53	441.2597	441.2496	^{1}H NMR (d_6-DMSO, 500 MHz) δ 10.22, (s, 1H), 8.32 (t, *J* = 5.9 Hz, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 8.9 Hz, 2H), 7.23-7.11 (m, 5H), 6.61 (d, *J* = 8.9 Hz, 2H), 4.34 (m, 1H), 4.19 (d, *J* = 5.9 Hz, 2H), 2.88 (s, 6H), 1.83 (t, *J* = 7.3 Hz, 2H), 1.63 (m,2H) 1.37 (m, 2H), 1.25-1.15 (m, 4H)
17	7.08^c	21.89	481.2821	481.2809	^{1}H NMR (d_6-DMSO, 600 MHz) δ 10.31 (s, 1H), 10.09 (s, 1H), 8.21 (ddd, *J* = 4.6, 8.6, 13.7 Hz, 1H), 7.95 (dd, *J* = 7.9, 24.4 Hz, 1H), 7.76 (t, *J* = 8.7 Hz, 2H), 7.10 (m, 4H), 6.70 (dd, *J* = 3.3, 8.8 Hz, 2H), 4.95 (m, 1H), 4.40 (m, 1H), 2.96 (s, 6H), 2.73 (m, 2H), 2.18 (t, *J* = 7.2 Hz, 1H), 1.92 (t, *J* = 7.2 Hz, 1H), 1.85 (m, 2H), 1.71 (m, 2H), 1.49 (m, 2H), 1.36 (m,2H), 1.27-1.15 (m, 4H)

18	4.71[c]	19.96	388.1872	388.1867	^{1}H NMR (d$_4$-Methanol, 500 MHz) δ 7.63 (s, 1H), 7.27-7.21 (m, 5H), 7.14 (s, 1H), 6.57 (s, 1H), 4.45 (m, 1H), 4.51, (m, 1H), 4.37 (m, 2H), 2.05 (t, *J* = 7.3 Hz, 2H), 1.92, (m, 1H), 1.78 (m, 1H), 1.59 (m, 2H), 1.36 (m, 4H)
19	5.33[c]	20.63	416.2246	416.2180	^{1}H NMR (d$_4$-Methanol, 500 MHz) δ 7.78 (s, 1H), 7.14 (s, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.77, (d, *J* = 8.0 Hz, 2H), 6.58 (s, 1H), 4.42 (m, 1H), 3.44 (m, 2H), 3.33 (m, 2H), 3.29 (s, 3H), 2.71 (t, *J* = 6.9 Hz, 2H), 1.77 (m, 1H), 1.66 (m, 1H), 1.55 (m, 2H), 1.28 (m, 4H)
20	5.19[c]	20.54	368.2192	368.2180	^{1}H NMR (d$_4$-Methanol, 500 MHz) δ 7.65 (d, *J* = 9.8 Hz, 1H), 7.13 (t, *J* = 1.5 Hz, 1H), 6.56 (s, 1H), 4.45 (m, 1H), 3.21 (m, 2H), 2.06 (t, *J* = 7.3 Hz, 2H), 1.91 (m, 1H), 1.77 (m, 1H), 1.6 (m, 2H), 1.39 (m, 7H), 0.90 (s, 6H)
21	ND	ND	399.2035	399.2027	^{1}H NMR (d$_6$-DMSO, 600 MHz) δ 10.30 (s, 1H), 9.04 (s, 1H), 8.69 (d, *J* = 4.4 Hz, 1H), 8.61 (s, 1H), 8.48 (m, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.92 (m, 1H), 7.49 (m, 1H), 7.31-7.21 (m, 5H), 4.44 (m, 1H), 4.27 (d, *J* = 6.0 Hz, 2H), 1.90 (t, *J* = 7.4 Hz, 2H), 1.71 (m, 2H), 1.47 (m, 2H), 1.30-1.18 (m, 4H)
22	ND	ND	379.2328	379.2340	^{1}H NMR (d$_6$-DMSO, 600 MHz) δ 10.30 (s, 1H), 9.03 (s, 1H), 8.69 (d, *J* = 4.4 Hz, 1H), 8.60 (d, *J* = 7.6 Hz, 1H), 8.54 (s, 1H), 8.21 (d, *J* = 7.8 Hz, 1H), 7.92 (m, 1H), 7.49 (dd, *J* = 4.8, 7.4 Hz, 1H), 4.36 (m, 1H), 3.10 (m, 2H), 1.92 (t, *J* = 7.5 Hz, 2H), 1.81 (m, 1H), 1.57 (m, 2H), 1.46 (m, 4H), 1.31-1.23 (m, 4H), 0.87 (d, *J* = 6.6 Hz, 6H)
23	ND	ND	ND	443.1925	ND
24	5.78[c]	20.96	437.2206	437.2183	^{1}H NMR (d$_6$-Acetone, 500 MHz) δ 10.76 (s, 2H), 9.93 (s, 1H), 7.87 (t, *J* = 6.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0Hz, 1H), 7.3-7.1 (m, 5H), 7.06 (t, *J* = 8 Hz, 1H), 4.64 (m, 1H), 4.42 (d, *J* = 6 Hz, 2H),4.39 (s, 1H), 1.96 (m, 2H), 1.80 (m, 2H), 1.60 (m, 2H), 1.4-1.3 (m, 4H)
25	6.33[c]	21.33	476.1200	476.1179	^{1}H NMR (d$_6$-Acetone, 500 MHz) δ 9.92 (s, 2H), 7.88

					(d, J = 8.5 Hz, 2H), 7.84 (d, J = 6.5, Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H), 7.28 (m, 3H), 7.21 (m, 1H), 4.62 (m, 1H), 4.42 (d, J = 6 Hz, 2H), 2.72 (s, 1H), 1.94 (m, 2H), 1.79 (m, 2H), 1.58 (m, 2H), 1.4-1.3 (m, 4H)
26	5.44[c]	15.05[d]	424.2242	424.2231	^{1}H NMR (d_6-DMSO, 600 MHz) δ 10.32 (s, 1H), 8.64 (s, 1H), 8.54 (t, J = 6.0 Hz 1H), 8.24 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 7.2 Hz, 2H), 7.44-7.36 (m, 3H), 7.31-7.22 (m, 5H), 6.78 (d, J = 15.8 Hz, 1H), 4.40 (m, 1H), 4.28 (d, J =5.5 Hz, 2H), 1.91 (t, J = 7.5 Hz, 2H), 1.69 (m, 1H), 1.56 (m, 1H), 1.45 (m, 2H), 1.31-1.23 (m, 4H)
27	6.43[a]	23.54	456.2842	456.2857	^{1}H NMR (d_6-Acetone, 500 MHz) δ 9.95 (s, 1H), 7.93 (s, 1H), 7.67 (br s, 1H), 7.28-7.20 (m, 5H), 6.69 (d, J = 8.0 Hz, 1H), 4.44 (m, 1H), 4.39 (d, J = 6.0 Hz, 2H), 1.99 (br s, 3H), 1.87 (m, 6H), 1.82 (m, 2H), 1.72 (m, 6H), 1.65-1.51 (m, 4H), 1.32 (m, 4H).
28	10.99[c]	23.33	488.2527	488.2544	^{1}H NMR (d_6-Acetone, 500 MHz) δ 9.91 (s, 1H), 7.80 (s, 1H), 7.68 (m, 2H), 7.64 (d, J = 7.5 Hz, 2H), 7.57 (d, J = 8.2 Hz, 2H), 7.46-7.38 (m, 5H), 7.35-7.20 (5H), 4.44 (m, 1H), 4.37 (d, J = 6.0 Hz, 2H), 3.62 (d, J = 4.2 Hz, 2H), 1.81 (m, 2H), 1.62 (m, 2H), 1.53 (m, 2H), 1.30 (m, 4H)
29	3.96[c]	18.73	404.1641	404.1639	^{1}H NMR (d_6-Acetone, 500 MHz) δ 9.90 (s, 1H), 7.85 (br s, 1H), 7.81 (dd, J = 3.7, 1.1 Hz, 1H), 7.74 (br s, 1H), 7.67 (dd, J = 5.0, 1.1 Hz, 1H), 7.29 (m, 5H), 7.21 (br s, 1H), 7.12 (dd, J = 5.0 Hz, 1H), 4.58 (m, 1H), 4.41 (d, J = 6.0 Hz, 2H), 1.76 (m, 2H), 1.57 (m, 2H), 1.46-1.30 (m, 6H)
30	6.70[a]	24.62	516.2501	516.2493	^{1}H NMR (d_6-Acetone, 500 MHz) δ 9.91 (s, 1H), 7.85 (d, J = 7.8Hz, 2H), 7.77 (br s, 1H), 7.70 (m, 4H), 7.40 (t, J = 7.5 Hz, 2H), 7.29 (m, 5H), 7.21 (br s, 1H), 6.61 (d, J = 7.6 Hz, 1H), 4.41 (d, J = 5.9 Hz, 2H), 4.33 (m, 1H), 4.22 (d, J = 6.9 Hz, 2H), 4.17 (m, 1H), 1.84 (m, 2H), 1.68 (m, 2H), 1.59 (m, 2H), 1.46-1.31 (m, 6H)
31	20.30[b]	23.74	428.2209	428.2180	^{1}H NMR (d_6-DMSO, 600 MHz) δ 10.31 (s, 1H), 8.40 (s, 1H), 7.41 (d, J = 8.1 Hz, 2H), 7.36-7.29 (m, 6H), 7.23 (d, J = 7.5 Hz, 2H), 5.02 (d, J = 3.5 Hz, 2H), 4.27 (dd, J = 5.6, 3.7 Hz, 2H), 3.97 (m 1H), 3.44 (br s,

					1H), 1.91 (t, J = 7.4 Hz, 2H), 1.69 (m, 1H), 1.56 (m, 1H), 1.45 (m, 2H), 1.31-1.23 (m, 4H)
32	14.70[a]	24.94	466.1968	466.1948	^{1}H NMR (d_6-DMSO, 600 MHz) δ 10.31 (s, 1H), 8.52 (t, J = 7.2 Hz, 1H), 8.1 (d, J = 8.1 Hz, 2H), 7.85 (d, J = 8.2 Hz, 2H), 7.64 (br s, 1H), 7.32-7.22 (m, 5H), 4.40 (m, 1H), 4.28 (d, J = 7.2 Hz, 2H), 1.91 (t, J = 7.5 Hz, 2H), 1.77 (m, 2H), 1.47 (m, 2H), 1.37-1.26 (m, 4H)
33	8.71[a]	20.37	451.2330	451.2340	^{1}H NMR (d_6-DMSO, 600 MHz) δ 10.82 (s, 1H), 10.32 (s, 1H), 8.42 (t, J = 6.0 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.29-7.18 (m, 5H), 7.05 (dd, , J = 7.0, 1.1 Hz, 1H), 6.94 (dd, , J = 7.0, 1.1 Hz, 1H), 4.24 (m, 1H), 3.56 (t, J = 7.5 Hz, 2H), 1.66 (m, 1H), 1.61 (m, 1H), 1.44 (m, 2H), 1.31-1.18 (m, 4H)
34	9.44 [a]	21.18	479.2641	479.2653	^{1}H NMR (d_6-DMSO, 600 MHz) δ 10.75 (s, 1H), 10.33 (s, 1H), 10.11 (s, 1H), 8.39 (t, J = 6.0 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.29-7.18 (m, 5H), 7.09 (d, J = 2.4 Hz, 1H), 7.05 (dd, , J = 7.0, 1.1 Hz, 1H), 6.94 (dd, , J = 7.0, 1.1 Hz, 1H), 4.27 (m, 1H), 2.66 (t, J = 7.5 Hz, 2H), 2.66 (t, J = 7.5 Hz, 2H), 2.21 (t, J = 7.7 Hz, 2H), 1.91 (t, J = 7.5 Hz, 2H), 1.85 (m, 2H), 1.62 (m, 1H), 1.53 (m, 1H), 1.45 (m, 2H), 1.30-1.18 (m, 4H)
35	9.23[b]	24.22	598.3010	598.3024	^{1}H NMR (d_6-DMSO, 600 MHz) δ 10.79 (s, 1H), 10.33 (s, 1H), 8.31 (t, J = 6.3 Hz, 1H), 8.09 (d, J = 6.3 Hz, 1H), 8.07 (d, J = 6.0 Hz, 1H), 7.33 (d, J =7.80 Hz, 1H), 7.29-7.16 (m, 10H), 7.03 (m, 1H), 6.89 (ddd, , J = 7.8, 7.0, 1.0 Hz, 1H), 4.57 (m, 1H), 4,27 (d, J = 6.0 Hz, 2H), 4.23 (m, 1H), 3.47 (d, J = 6.0 Hz, 2H), 2.99 (dd, d, J = 13.8, 4.3 Hz, 2H), 2.78 (dd, d, J = 13.7, 9.6 Hz, 2H), 1.90 (t, J = 7.5 Hz, 2H), 1.62 (m, 2H), 1.62 (m, 1H), 1.53 (m, 1H), 1.43 (m, 2H), 1.30-1.18 (m, 4H)
36	10.85[a]	23.12	515.1272	515.1289	^{1}H NMR (d_6-DMSO, 600 MHz) δ 11.80 (s, 1H), 10.31 (s, 1H), 8.55 (m, 2H), 7.85 (d, J = 1.8 Hz, 1H), 7.38 (d, J = 9.0 Hz, 1H), 7.29-7.24 (m, 5H), 7.21 (m, 1H), 4.46 (m, 1H), 4.30 (m, 2H), 1.90 (t, J = 7.5 Hz, 2H), 1.71 (m, 2H), 1.47 (m, 2H), 1.30-1.18 (m, 4H)

37	4.16[b]	20.63	453.2126	453.2133	^{1}H NMR (d_6-DMSO, 600 MHz) δ 11.27 (s, 1H), 10.31 (s, 1H), 8.77 (s, 1H), 8.51 (t, *J* = 6.0 Hz, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 7.29-7.22 (m, 5H), 7.05 (m, 1H), 6.87 (d, *J* = 2.4 Hz, 1H), 6.71 (dd, *J* = 8.7, 2.3 Hz, 1H), 4.46 (m, 1H), 4.30 (m, 2H), 1.90 (t, *J* = 7.5 Hz, 2H), 1.71 (m, 2H), 1.47 (m, 2H), 1.30-1.18 (m, 4H)
38	ND	ND	463.2360	463.2340	ND
39	7.91 [a]	17.41	453.2496	453.2497	^{1}H NMR (d_6-DMSO, 600 MHz) δ 10.33 (s, 1H), 10.08 (s, 1H), 8.36 (d, *J* = 7.8 Hz, 2H), 7.56 (m, 3H), 7.35 (m, 5H), 7.06 (br s, 1H), 6.80 (d, *J* = 15.8 Hz, 1H), 4.51 (m, 1H), 4.04 (br s, 1H), 1.93 (t, *J* = 7.5 Hz, 2H), 1.72-1.58 (m, 2H), 1.46 (m, 2H), 1.36-1,27 (m, 4H)
40	7.83[a]	17.23	457.2425	457.2446	^{1}H NMR (d_6-DMSO, 600 MHz) δ 10.32 (s, 1H), 9.94 (s, 1H), 7.55 (d, *J* = 7.8 Hz, 2H), 7.35 (m, 5H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.06 (br s, 1H), 5.02 (s, 2H), 4.10 (m, 1H), 4.04 (br s, 1H), 1.93 (t, *J* = 7.5 Hz, 2H), 1.64-1.58 (m, 2H), 1.46 (m, 2H), 1.34-1,27 (m, 4H)
41	8.34[a]	18.74	495.2226	495.2214	^{1}H NMR (d_6-DMSO, 600 MHz) δ 10.32 (s, 1H), 10.06 (s, 1H), 8.8 (d, *J* = 7.6 Hz, 2H), 8.15 (d, *J* = 8.2 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.05 (br s, 1H), 4.55 (m, 1H), 4.04 (br s, 1H), 1.93 (t, *J* = 7.5 Hz, 2H), 1.49 (m, 2H), 1.42 (m, 1H), 1.34-1,27 (m, 3H)
42	ND	ND	442.2434	442.2449	ND
43	7.77[a]	16.83	477.1145	477.1132	^{1}H NMR (d_6-DMSO, 600 MHz) δ 10.32 (s, 1H), 8.68 (t, *J* = 5.6 Hz, 1H), 8.64 (d, *J* = 7.6 Hz, 1H), 8.60 (d, *J* = 4.8 Hz, 1H), 8.02 (t, *J* = 7.4 Hz, 1H), 7.85 (d, *J* = 6.7 Hz, 2H), 7.69 (d, *J* = 11.0 Hz, 2H), 7.47 (m, 2H), 4.44 (d, *J* = 5.9 Hz, 2H), 4.42 (m, 1H), 1.92 (t, *J* = 7.5 Hz, 2H), 1.77-1.73 (m, 2H), 1.47 (m, 2H), 1.36-1.26 (m, 4H)
44	7.71[a]	16.57	477.1143	477.1132	^{1}H NMR (d_6-DMSO, 600 MHz) δ 10.32 (s, 1H), 8.73 (m, 3H), 8.66 (d, *J* = 7.3 Hz, 2H), 7.85 (d, *J* = 6.7 Hz, 2H), 7.69 (d, *J* = 11.0 Hz, 2H), 7.65 (d, *J* = 4.9 Hz, 2H), 4.46 (m, 2H), 4.40 (m, 1H), 1.92 (t, *J* = 7.5 Hz, 2H), 1.77-1.73 (m, 2H), 1.47 (m, 2H), 1.36-1.26 (m,

					4H)
45	3.16[b]	17.18	429.2146	429.2133	^{1}H NMR (d_6-DMSO, 600 MHz) δ 10.32 (s, 1H), 8.69 (m, 3H), 7.61 (m, 2H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.36-7.31 (m, 5H), 5.05 (m, 2H), 4.45 (m, 2H), 3.99 (m, 1H), 1.92 (t, *J* = 7.5 Hz, 2H), 1.64 (m, 1H), 1.56 (m, 1H), 1.46 (m, 2H), 1.36-1.26 (m, 4H)
46	13.63[a]	25.02	490.2324	490.2337	^{1}H NMR (d_6-DMSO, 600 MHz) δ 10.32 (s, 1H), 10.12 (s, 1H), 8.64 (m, 1H), 7.69 (m 2H), 7.63 (m, 3H), 7.58 (d, *J* = 7.8 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.36 (m, 3H), 7.32 (m, 2H), 5.03 (s, 2H), 4.14 (m, 1H), 1.92 (t, *J* = 7.5 Hz, 2H), 1.66 (m, 1H), 1.61 (m, 1H), 1.46 (m, 2H), 1.37-1.26 (m, 4H)
47	14.56[a]	25.38	538.1342	538.1336	^{1}H NMR (d_6-DMSO, 600 MHz) δ 10.32 (s, 1H), 10.22 (s, 1H), 8.71 (d, *J* = 7.5 Hz, 1H), 7.87 (d, *J* = 8.6 Hz, 2H), 7.70 (t, *J* = 9.0 Hz, 4H), 7.63 (m, 4H), 7.44 (t, *J* =7 .8 Hz, 2H), 7.32 (t, *J* = 7.9 Hz, 1H) 4.55 (m, 1H), 1.93 (t, *J* = 7.5 Hz, 2H), 1.80 (m, 2H), 1.49 (m, 2H), 1.43 (m, 1H), 1.37 (m, 1H), 1.26 (m, 2H)
48	ND	ND	ND	509.3122	ND
49	ND	ND	ND	505.2809	ND
50	7.47[b]	25.83	468.2483	468.2493	^{1}H NMR (d_6-DMSO, 600 MHz) δ 10.31 (s, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 7.2 Hz, 1H), 7.35 (m, 2H), 7.29 (m, 2H), 7.13 (m, 3H), 5.03 (m, 2H), 4.94 (m, 1H), 3.97 (m, 1H), 2.71 (m, 2H), 1.91 (t, *J* = 7.5 Hz, 2H), 1.84 (m, 2H), 1.69-1.54 (m, 4H), 1.45 (m, 2H), 1.31-1.23 (m, 4H). missing 2H
51	3.88[b]	20.23	478.2456	478.2449	^{1}H NMR (d_6-DMSO, 600 MHz) δ 10.54 (s, 1H), 10.32 (s, 1H), 8.78 (d, *J* = 4.3 Hz, 1H), 8.65 (m, 3H), 8.42 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.86 (d, *J* = 9.0 Hz, 1H), 7.66 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.60 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 6.7 (d, *J* = 9.0 Hz, 2H), 4.61 (m, 1H), 1.93 (t, *J* = 7.5 Hz, 2H), 1.49 (m, 2H), 1.48-1.45 (m, 2H), 1.31-1.23 (m, 4H)
52	6.81[b]	23.09	474.2148	474.2136	^{1}H NMR (d_6-DMSO, 600 MHz) δ 11.65 (s, 1H), 10.52 (s, 1H), 10.32 (s, 1H), 8.99 (d, *J* = 7.4 Hz, 1H), 8.78 (m, 1H), 8.65 (dd, *J* = 7.9, 1.1 Hz, 1H), 8.64 (s, 1H),

					8.39 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.69-7.66 (m, 2H), 7.60-7.57 (m, 2H), 7.43 (d, J = 8.3 Hz, 1H), 7.39 (s, 1H), 7.20 (t, *J* = 7.9 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 4.72 (m, 1H), 1.93 (t, *J* = 7.3 Hz, 2H), 1.50 (m, 4H), 1.48-1.30 (m, 4H)
53	10.37[a]	22.40	461.2174	461.2184	^{1}H NMR (d_6-DMSO, 600 MHz) δ 10.46 (s, 1H), 10.31 (s, 1H), 8.86 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.64 (dd, *J* = 7.7, 1.3 Hz, 1H), 8.41 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.31 (dd, *J* = 8.5, 3.6 Hz, 1H), 7.69 (dd, *J* = 8.3, 1.3 Hz, 1H),7.59-7.55 (m, 2H), 7.50 (d, *J* = 15.8 Hz, 1H), 7.65 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.44-7.7.39 (m, 3H), 6.84 (d, *J* = 15.8 Hz, 1H), 4.11 (m, 1H) 1.93 (t, *J* = 7.5 Hz, 2H), 1.64-1.58 (m, 2H), 1.46 (m, 2H), 1.34-1,27 (m, 4H)
54	12.23	25.20	503.1899	503.1901	^{1}H NMR (d_6-DMSO, 600 MHz) δ 10.56 (s, 1H), 10.31 (s, 1H), 9.28 (d, *J* = 7.4 Hz, 2H), 8.84 (dd, *J* = 4.1, 1.4 Hz, 1H), 8.63 (dd, *J* = 7.7, 1.3 Hz, 1H), 8.42 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.12 (d, *J* = 7.1 Hz, 1H), 7.83 (d, *J* 7.3 Hz, 2H), 7.69 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.63 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.59 (t, *J* = 7.9 Hz, 1H), 4.10 (m, 1H) 1.93 (t, *J* = 7.5 Hz, 2H), 1.64-1.58 (m, 2H), 1.46 (m, 2H), 1.34-1,27 (m, 4H)
55	8.61[b]	23.87	465.2137	465.2133	^{1}H NMR (d_6-DMSO, 600 MHz) δ 10.46 (s, 1H), 10.31 (s, 1H), 8.86 (dd, *J* = 4.1, 1.4 Hz, 1H), 8.64 (d, *J* = 7.1 Hz, 1H), 8.42 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.12 (d, *J* = 7.1 Hz, 1H), 7.69 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.66 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.37 (m, 3H), 7.30 (m, 2H), 5.01 (m, 2H), 4.10 (m, 1H), 1.93 (t, *J* = 7.5 Hz, 2H), 1.64-1.58 (m, 2H), 1.46 (m, 2H), 1.34-1,27 (m, 4H)
56	7.67[b]	23.43	432.2299	431.2289	^{1}H NMR (d_6-DMSO, 600 MHz) δ 10.46 (s, 1H), 10.31 (s, 1H), 8.86 (d, *J* = 3.8 Hz, 1H), 8.64 (d, *J* = 7.1 Hz, 1H), 8.42 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.94 (d, *J* = 7.1 Hz, 1H), 7.68 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.65 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 4.16 (m, 1H), 3.88 (m, 2H), 2,41 (m, 1H), 1.92 (t, *J* = 7.5 Hz, 2H), 1.83 (m, 2H), 1.46 (m, 2H), 1.35-1.28 (m, 4H), 0.91 (dd, *J* = 6.4, 3.8 Hz, 6H)

57	3.69[b]	19.86	479.2420	479.2401	^{1}H NMR (d$_6$-DMSO, 600 MHz) δ 10.54 (s, 1H), 8.78 (d, *J* = 4.3 Hz, 1H), 8.65 (m, 3H), 8.50 (m, 1H), 8.40 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.21 (s, 1H), 7.86 (d, *J* = 9.0 Hz, 1H), 7.66 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.60 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 9.0 Hz, 2H), 4.61 (m, 1H), 2.99 (s, 6H), 1.97 (m, 1H), 1.89 (m, 1H), 1.46-1.38 (m, 4H)

Analytical rpHPLC performed on Phenomenex Luna 5μ C18(2) 250 x 4.60 mm column run at 1 mL/minute using solvents (A) water/0.1% TFA and (B) water (10%)/acetonitrile (90%)/0.1% TFA. General gradient conditions 100% A to 100% B in 30 min. (a) Isocratic conditions 50% A / 50% B; (b) Isocratic conditions 55% A / 45% B; (c) Isocratic conditions 60% A / 40% B; (d) Gradient conditions 100% A to 100% B in 15 min.