ELECTRONIC, SUPPLEMENTARY INFORMATION (ESI)

Tetrahydro-pyrimido-indoles as selective LIMK inhibitors: synthesis, selectivity profiling and structure-activity studies

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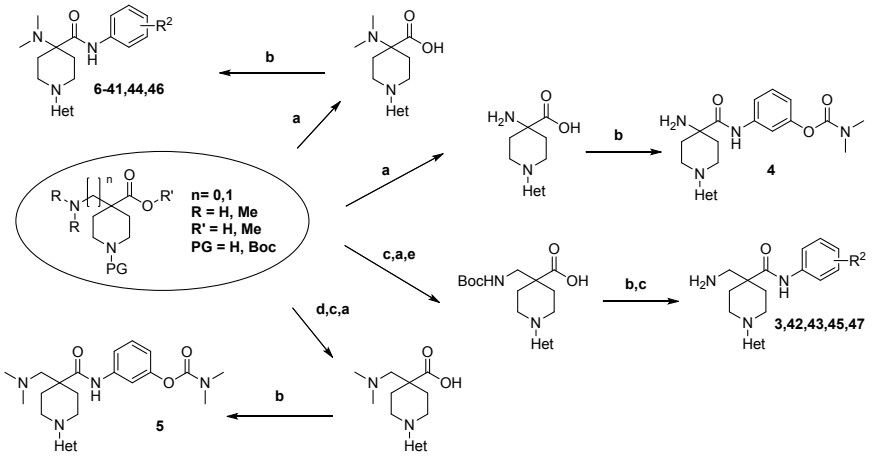
1. Chemistry



Scheme SI 1: Overview of compound synthesis. (a) Het-Cl, DIPEA, DMSO/water (1:1), 140°C, 16 h; (b) $ArNH_2$, T3P, DMAP, DCM, -15°C, 16 h; (c) DCM/TFA (10:1), rt, 48 h; (d) CH_2O, $NaBH_3CN$, MeOH, rt, 2 h; (e) Boc_2O, NaOH (1M)/Dioxane (1:2), 0°C to rt, 2 h.

1.1. General methods

All reagents and solvents were of commercial quality and were used without further purification. The purity of the final compounds and/or intermediates was characterised by high-performance liquid chromatography (HPLC) using a Waters Alliance system with a 2690 separation module, coupled to a 996 Waters photodiode array detector (PDA) and ZMD Micromass MS system simultaneously. The analytical column was a reversed-phase TSKgel Super-ODS C18 2 µm, 50 mm x 4.6 mm, from Tosoh Bioscience, used at a column temperature of 55 °C. Gradient elution was used (flow 2.75 mL/min), typically starting with 100% water and progressing to 100% acetonitrile over a period of 5 min, with both solvents containing 0.1% formic acid. All compounds have >95% purity as determined by HPLC (diode array detector, 200-400 nm). All masses were reported as those of the protonated parent ions (molecular weight range 100−800, cone voltage 25 V). ^{1}H and ^{13}C NMR spectra were taken on Varian Inova 300 or 400 MHz spectrometers from solutions in deuterated DMSO or MeOH.

1.2. Synthesis of Het-Cl

1.2.1. HetA-Cl

Synthesis described in:
M. Hammond, Y. Zhao, WO/2011/056739, 2011.

1.2.2. HetB-Cl

Synthesis described in:
U. Klar, G. Kettschau, D. Sülzle, F. Pühler, D. Kosemund, P. Lienau, U. Bömer, WO/2013/174743, 2013.

1.2.3. HetC-Cl

Synthesised described in:
U. Klar, G. Kettschau, D. Sülzle, F. Pühler, D. Kosemund, P. Lienau, U. Bömer, WO/2013/174743, 2013.

1.3. Synthesis of reference cpd 1

Synthesis described in:
B. A. Harrison, Z. Y. Almstead, H. Burgoon, M. Gardyan, N. C. Goodwin, J. Healy, Y. Liu, R. Mabon, B. Marinelli, L. Samala, Y. Zhang, T. R. Stouch, N. A. Whitlock, S. Gopinathan, B. McKnight, S. Wang, N. Patel, A. G. Wilson, B. D. Hamman, D. S. Rice, D. B. Rawlins, *ACS Med. Chem. Lett.*, 2015, **6**, 84-88.

1.4. General procedure a

To a mixture of Het-Cl (22.92 mmol) and piperidine derivative (27.5 mmol, 1.2 eq) in water/DMSO (35 mL/35 mL) was added DIPEA (32.0 mL, 183 mmol, 8.0 eq). The resulting mixture was refluxed overnight and cooled to room temperature. The suspension was diluted with H_2O (500 mL) and neutralized by drop wise addition of concentrated aqueous HCl to pH 6.3. The solid was collected by filtration and washed with H_2O. The solid was then dissolved in 1M aqueous NaOH (200 mL) and filtered. The filtrate was neutralized by drop wise addition of concentrated HCl to pH 6.7, resulting in a beige precipitation. The solid was collected by filtration and washed with H_2O, ACN (2x) and Et_2O. The obtained powder was suspended in ACN and freeze-dried to afford the desired intermediate, which was used for the next step without further purification.

1.5. General procedure b

To a suspension of carboxylic acid (100 mg) and DMAP (6 eq) in DCM (0.2 M) under nitrogen at -15°C was added T3P (3 eq) drop wise over a period of 20 min. The resulting mixture was stirred at -15°C until a solution was obtained (2 h) and the aniline (3 eq) was added drop wise. The reaction mixture was stirred at -15 °C for 1 h, slowly warmed to room temperature and stirred overnight. Saturated aq. $NaHCO_3$ was then added and the aqueous layer extracted with EtOAc. The organic phase was washed with saturated aq. NH_4Cl (x 2), $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was dissolved in DCM and purified by flash chromatography (DCM/MeOH 97/3 to 92/8).

1.6. General procedure c

To a solution of Boc-piperidine derivative (12 mmol) in DCM (100 mL) was added TFA (10 mL) at 0°C and the reaction mixture was stirred at rt for 48 h. Then saturated aq. K_2CO_3 solution (50 mL) was added and the resulting mixture was stirred for 30 min at 0°C. The water layer was extracted with DCM (3x 50 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to give the expected intermediate.

1.7. General procedure d

To a solution of piperidine derivative (100 mmol) in MeOH (500 mL) was added formaldehyde (6 g, 200 mmol, 2 eq). The mixture was stirred at room temperature for 10 min and $NaBH_3CN$ (18.8 g, 300 mmol) was added portion wise. The mixture was stirred for 2 h, basified by addition of saturated aq. $NaHCO_3$ until pH = 8, and then extracted with EtOAc (3x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated to give crude product, which was purified by column chromatography (hexane: EtOAc = 20:1) to give the desired intermediate.

1.8. General procedure e

To a solution of crude amine (33 mmol) in dioxane (100 ml) at 0°C were added NaOH (2.00 g, 50 mmol) in H_2O (50 mL) and $(Boc)_2O$ (7.22 g, 33 mmol, 1 eq). The mixture was stirred at rt for 16 h and concentrated under reduced pressure. H_2O (100 mL) was added and the aqueous layer was extracted with EtOAc (100 mL x 3). The aqueous layer was adjusted to pH = 5 by addition of 2N citric acid aqueous solution and extracted with EtOAc (200 mL x 4). The combined organic layer were dried over anhydrous Na_2SO4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (neutral conditions) to give the expected intermediate.

1.9. Characterisation

The purity of the compounds was assessed by LC-MS. All tested compounds showed a chromatographic purity above 95% and were obtained as white to off-white powders.

Cpd 2

Synthesis described in:
S. Boland, A. Bourin, J. Alen, J. Geraets, P. Schroeders, K. Castermans, N. Kindt, N. Boumans, L. Panitti, J. Vanormelingen, S. Fransen, S. Van de Velde, O. Defert, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 4005-4010.

Cpd 3

Cpd **3** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 12.02 (br s, 1H), 9.84 (s, 1H), 8.25 (s, 1H), 7.95 (br s, 2.5 H), 7.58-7.52 (m, 1H), 7.50-7.44 (m, 1H), 7.36-7.29 (m, 1H), 6.90-6.84 (m, 1H), 3.90-3.75 (m, 2H), 3.55-3.40 (m, 2H), 3.35-3.20 (m, 2H), 3.04 (s, 3H), 2.91 (s, 3H), 2.80-2.65 (m, 4H), 2.45-2.35 (m, 2H), 1.90-1.62 (m, 6H); MS m/z: 492.2 (MH^+), 182.2, 141.1.

Cpd 4

Cpd **4** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.93 (s, 1H), 10.25 (s, 1H), 8.63 (br s, 3H), 8.29 (s, 1H), 7.52-7.48 (m, 1H), 7.48 (t, 1H, *J* = 2 Hz), 7.37 (t, 1H, *J* = 8 Hz), 6.92 (ddd, 1H, *J* = 8 Hz, *J* = 2 Hz, *J* = 0.8 Hz), 4.27 (dt, 2H, *J* = 12 Hz, *J* = 0.4 Hz), 3.52 (t, 2H, *J* = 12 Hz), 3.04 (s, 3H), 2.90 (s, 3H), 2.84-2.78 (m, 2H), 2.80 (t, 2H, *J* = 6 Hz), 2.63-2.53 (m, 2H), 2.02 (d, 2H, *J* = 13.6 Hz), 1.88-1.80 (m, 2H), 1.79-1.71 (m, 2H); MS m/z: 478.3 (MH^+), 407.2, 189.2.

Cpd 5

Cpd **5** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 11.42 (s, 1H), 9.90 (br s, 1H), 8.13 (s, 1H), 7.52 (t, 1H, *J* = 2 Hz), 7.50-7.41 (m, 1H), 7.37-7.27 (m, 1H), 6.84 (br s, 1H), 3.90-3.45 (m, 4H), 3.35-3.20 (m, 2H), 3.04 (s, 3H), 2.91 (s, 3H), 2.82-2.62 (m, 7H), 2.4-2.1 (m, 5H), 1.90-1.6 (m, 6H); MS m/z: 520.4 (MH^+), 463.3, 283.2.

Cpd 6

Cpd **6** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 12.06 (s, 1H), 10.13 (s, 1H), 8.28 (s, 1H), 7.52-7.48 (m, 1H), 7.39 (t, 1H, *J* = 8 Hz), 7.01-6.94 (m, 1H), 4.17 (d, 2H, *J* = 12 Hz), 3.18 (t, 2H, *J* = 12 Hz), 3.04 (s, 3H), 2.91 (s, 3H), 2.85-2.65 (m, 12H), 2.15-2.01 (m, 2H), 1.90-1.80 (m, 2H), 1.78-1.68 (m, 2H); MS m/z: 506.4 (MH^+), 181.2, 149.8.

Cpd 7

Cpd **7** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.91 (s, 1H), 10.08 (s, 1H), 8.25 (s, 1H), 7.64 (dd, 2H, *J* = 9 Hz, *J* = 1 Hz), 7.40 (t, 2H, *J* = 8 Hz), 7.21 (t, 1H, *J* = 7 Hz), 4.16 (d, 2H, *J* = 14 Hz), 3.13 (t, 2H, *J* = 12 Hz), 2.90-2.65 (m, 12H), 2.08 (td, 2H, *J* = 12 Hz, *J* = 3 Hz), 1.89-1.79 (m, 2H), 1.77-1.69 (m, 2H); MS m/z: 419.2(MH^+), 170.3, 149.7.

Cpd 8

Cpd **8** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.86 (s, 1H), 10.13 (s, 1H), 8.24 (s, 1H), 7.67 (dd, 2H, *J* = 9 Hz, *J* = 5 Hz), 7.24 (t, 2H, *J* = 18 Hz), 4.15 (d, 2H, *J* = 13 Hz), 3.11 (t, 2H, *J* = 12 Hz), 2.85-2.62 (m, 12H), 2.06 (td, 2H, *J* = 12 Hz, *J* = 4 Hz), 1.89-1.79 (m, 2H), 1.78-1.68 (m, 2H); MS m/z: 437.3 (MH^+), 170.3, 149.8.

Cpd 9

Cpd **9** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 300 MHz): δ11.41 (s, 1H), 9.67 (s, 1H), 8.12 (s, 1H), 7.68 (dt, 1H, *J* = 12 Hz, *J* = 2 Hz), 7.52 (d, 1H, *J* = 8 Hz), 7.33 (q, 1H, *J* = 8 Hz), 6.89 (td, 1H, *J* = 8 Hz, *J* = 2 Hz), 3.89 (d, 2H, *J* = 13 Hz), 3.22 (t, 2H, *J* = 11 Hz), 2.80-2.61 (m, 4H), 2.24 (s, 6H), 2.13 (d, 2H, *J* = 14 Hz), 1.97-1.66 (m, 6H); MS m/z: 437.1 (MH^+), 170.2, 149.7.

Cpd 10

Cpd **10** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.77 (br s, 1H), 10.20 (br s, 1H), 8.23 (s, 1H), 7.53 (td, 1H, *J* = 8 Hz, *J* = 1 Hz), 7.42-7.30 (m, 2H), 7.27 (td, 1H, *J* = 7 Hz, *J* = 2 Hz), 4.16 (d, 2H, *J* = 13 Hz), 3.11 (br s, 2H), 2.92-2.62 (m, 12H), 2.07 (t, 2H, *J* = 11 Hz), 1.90-1.79 (m, 2H), 1.79-1.69 (m, 2H); MS m/z: 437.2 (MH^+), 170.3, 149.6.

Cpd 11

Cpd **11** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.83 (s, 1H), 10.05 (s, 1H), 8.25 (s, 1H), 7.34-7.28 (m, 2H), 7.28-7.21 (m, 2H), 4.19 (d, 2H, *J* = 13 Hz), 3.14 (t, 2H, *J* = 12 Hz), 2.85 (s, 5H), 2.77 (t, 4H, *J* = 5 Hz), 2.70 (t, 3H, *J* = 6 Hz), 2.24 (s, 3H), 2.11 (td, 2H, *J* = 12 Hz, *J* = 3 Hz), 1.89-1.79 (m, 2H), 1.79-1.69 (m, 2H); MS m/z: 433.2 (MH^+), 170.3, 149.7.

Cpd 12

Cpd **12** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.85 (s, 1H), 10.25 (s, 1H), 8.22 (s, 1H), 7.92 (d, 2H, *J* = 9 Hz), 7.86 (d, 2H, *J* = 9 Hz), 4.09 (d, 2H, *J* = 12 Hz), 3.18 (br s, 2H), 2.80-2.57 (m, 12H), 2.05 (t, 2H, *J* = 11 Hz), 1.88-1.78 (m, 2H), 1.78-1.68 (m, 2H); MS m/z: 444.2 (MH^+), 170.2, 149.7.

Cpd 13

Cpd **13** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.88 (s, 1H), 10.12 (s, 1H), 8.24 (s, 1H), 7.78 (d, 2H, *J* = 9 Hz), 7.22 (t, 1H, *J* = 148 Hz), 7.22 (d, 2H, *J* = 9 Hz), 4.15 (d, 2H, *J* = 13 Hz), 3.12 (br t, 2H, *J* = 11 Hz), 2.90-2.60 (m, 12H), 2.05 (td, 2H, *J* = 12 Hz, *J* = 2 Hz), 1.90-1.79 (m, 2H), 1.78-1.68 (m, 2H); MS m/z: 485.2 (MH^+), 170.2, 149.7.

Cpd 14

Cpd **14** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.41 (s, 1H), 9.94 (s, 1H), 9.36 (s, 1H), 8.11 (s, 1H), 7.53 (d, 4H, *J* = 16 Hz), 3.87 (d, 2H, *J* = 11 Hz), 3.22 (t, 2H, *J* = 11 Hz), 2.80-2.60 (m, 4H), 2.24 (s, 6H), 2.15 (d, 2H, *J* = 12 Hz), 2.02 (s, 3H), 1.94-1.66 (m, 6H); MS m/z: 476.2 (MH^+), 170.2, 151.1.

Cpd 15

Cpd **15** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 11.84 (s, 1H), 9.98 (s, 1H), 8.24 (s, 1H), 7.53 (d, 2H, *J* = 9 Hz), 6.96 (d, 2H, *J* = 9 Hz), 4.16 (d, 2H, *J* = 13 Hz), 3.75 (s, 3H), 3.09 (t, 2H, *J* = 13 Hz), 2.86-2.64 (m, 12H), 2.05 (t, 2H, *J* = 10 Hz), 1.90-1.79 (m, 2H), 1.79-1.67 (m, 2H); MS m/z: 449.2 (MH^+), 170.3, 149.7.

Cpd 16

Cpd **16** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.94 (s, 1H), 9.90 (s, 1H), 8.26 (s, 1H), 7.43 (d, 2H, *J* = 9 Hz), 6.79 (d, 2H, *J* = 9 Hz), 4.17 (d, 2H, *J* = 13 Hz), 3.10 (t, 2H, *J* = 13 Hz), 2.90 (s, 6H), 2.85-2.65 (m, 12H), 2.06 (td, 2H, *J* = 12 Hz, *J* = 3 Hz), 1.89-1.79 (m, 2H), 1.79-1.69 (m, 2H); MS m/z: 462.3 (MH^+), 229.8, 209.3.

Cpd 17

Cpd **17** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.88 (s, 1H), 10.00 (s, 1H), 8.25 (s, 1H), 7.48-7.42 (m, 2H), 7.28 (t, 1H, *J* = 8 Hz), 7.03 (d, 1H, *J* = 8 Hz), 4.16 (d, 2H, *J* = 13 Hz), 3.11 (t, 2H, *J* = 12 Hz), 2.86-2.65 (m, 12H), 2.32 (s, 3H), 2.06 (td, 2H, *J* = 12 Hz, *J* = 3 Hz), 1.89-1.79 (m, 2H), 1.77-1.69 (m, 2H); MS m/z: 433.2 (MH^+), 170.3, 149.7.

Cpd 18

Cpd **18** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 12.02 (s, 1H), 10.28 (s, 1H), 8.27 (s, 1H), 8.11 (s, 1H), 7.99 (d, 1H, *J* = 8 Hz), 7.65 (t, 1H, *J* = 8 Hz), 7.57 (d, 1H, *J* = 8 Hz), 4.15 (d, 2H, *J* = 13 Hz), 3.22 (t, 2H, *J* = 12 Hz), 2.92-2.62 (m, 12H), 2.07 (t, 2H, *J* = 12 Hz), 1.92-1.79 (m, 2H), 1.79-1.65 (m, 2H); MS m/z: 487.1 (MH^+), 170.2, 149.7.

Cpd 19

Cpd 1**9** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 11.67 (br s, 1H), 10.93 (s, 1H), 8.34 (d, 1H, *J* = 4 Hz), 8.26 (s, 1H), 8.05 (d, 1H, *J* = 8 Hz), 7.67 (t, 1H, *J* = 7 Hz), 7.61 (d, 1H, *J* = 8 Hz), 4.25 (d, 2H, *J* = 13 Hz), 3.32 (t, 2H, *J* = 12 Hz), 3.11-2.61 (m, 10H), 2.37-2.00 (m, 4H), 1.93-1.79 (m, 2H), 1.79-1.62 (m, 2H); MS m/z: 444.2 (MH^+), 170.2, 149.7.

Cpd 20

Cpd **20** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.92 (s, 1H), 10.01 (s, 1H), 8.25 (s, 1H), 7.35-7.21 (m, 3H), 6.79 (d, 1H, *J* = 7 Hz), 4.16 (d, 2H, *J* = 13 Hz), 3.76 (s, 3H), 3.13 (t, 2H, *J* = 12 Hz), 2.86-2.62 (m, 12H), 2.07 (t, 2H, *J* = 11 Hz), 1.90-1.79 (m, 2H), 1.79-1.67 (m, 2H); MS m/z: 449.2 (MH^+), 170.2, 149.7.

Cpd 21

Cpd **21** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.90 (s, 1H), 9.97 (s, 1H), 8.25 (s, 1H), 7.28 (t, 1H, *J* = 2 Hz), 7.26 (d, 1H, *J* = 8 Hz), 7.19 (d, 1H, *J* = 9 Hz), 6.77 (dd, 1H, *J* = 8 Hz, *J* = 2 Hz), 4.59 (septet, 1H, *J* = 6 Hz), 4.15 (d, 2H, *J* = 13 Hz), 3.12 (br s, 2H), 2.88-2.64 m, 12H), 2.06 (t, 2H, *J* = 11 Hz), 1.89-1.79 (m, 2H), 1.79-1.69 (m, 2H), 1.27 (d, 6H, *J* = 6 Hz); MS m/z: 477.2 (MH^+), 170.2, 149.7.

Cpd 22

Cpd **22** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.41 (s, 1H), 9.41 (s, 1H), 8.12 (s, 1H), 7.62-7.56 (m, 1H), 7.58 (s, 1H), 7.23 (t, 1H, *J* = 8 Hz), 6.98 (d, 1H, *J* = 8 Hz), 3.87 (d, 2H, *J* = 13 Hz), 3.36 (s, 2H), 3.23 (t, 2H, *J* = 11 Hz), 2.78-2.70 (m, 2H), 2.70-2.62 (m, 2H), 2.31 (br s, 4H), 2.25 (s, 6H), 2.16 (d, 2H, *J* = 14 Hz), 1.94-1.68 (m, 6H), 1.53-1.44 (m, 4H), 1.43-1.32 (m, 2H); MS m/z: 516.4 (MH^+), 259.0, 170.2.

Cpd 23

Cpd **23** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.85 (s, 1H), 10.24 (s, 2H), 8.24 (s, 1H), 7.86 (s, 1H), 7.68 (d, 1H, *J* = 8 Hz), 7.50 (t, 1H, *J* = 8 Hz), 7.35 (d, 1H, *J* = 8 Hz), 4.35 (s, 2H), 4.22-4.07 (m, 2H), 4.05-3.88 (m, 2H), 3.75-3.55 (m, 2H), 3.38-2.98 (m, 6H), 2.90-2.62 (m, 12H), 2.09 (t, 2H, *J* = 11 Hz), 1.89-1.79 (m, 2H), 1.79-1.69 (m, 2H); MS m/z: 518.3 (MH^+), 260.0, 170.2.

Cpd 24

Cpd **24** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 10.26 (s, 1H), 8.31-8.22 (m, 2H), 8.03-7.98 (m, 1H), 7.82-7.78 (m, 1H), 7.56 (t, 1H, *J* = 8 Hz), 4.27 (d, 2H, *J* = 12 Hz), 3.87 (s, 3H), 3.1 (t, 2H, *J* = 12 Hz), 2.90-2.65 (m, 12H), 2.15-2.02 (m, 2H), 1.92-1.83 (m, 2H), 1.78-1.70 (m, 2H); MS m/z: 507.3 (MH^+), 170.3, 149.7.

Cpd 25

Cpd **25** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 11.41 (s, 1H), 9.45 (s, 1H), 8.12 (s, 1H), 7.60 (s, 1H), 7.59 (d, 1H, *J* =7 Hz), 7.25 (t, 1H, *J* = 8 Hz), 6.96 (d, 1H, *J* = 8 Hz), 3.88 (d, 2H, *J* = 13 Hz), 3.65 (s, 2H), 3.61 (s, 3H), 3.22 (t, 2H, *J* = 11 Hz), 2.80-2.60 (m, 4H), 2.30-2.10 (m, 4H), 2.25 (s, 6H), 1.95-1.65 (m, 4H); MS m/z: 491.1 (MH^+), 201.1, 149.6.

Cpd 26

Cpd **26** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 300 MHz): 11.41 (s, 1H), 9.60 (s, 1H), 8.12 (s, 1H), 7.60 (t, 1H, *J* = 3 Hz), 7.53 (dd, 1H, *J* = 8 Hz, *J* = 1 Hz), 7.33 (t, 1H, *J* = 8 Hz), 6.82 (dd, 1H, *J* = 8 Hz, *J* = 2 Hz), 3.88 (d, 2H, *J* = 13 Hz), 3.22 (t, 2H, *J* = 11 Hz), 2.70 (br d, 4H, *J* = 24 Hz), 2.27 (s, 3H), 2.24 (s, 6H), 2.14 (br d, 2H, *J* = 13 Hz), 1.95-1.65 (m, 6H); MS m/z: 477.3 (MH^+), 170.3, 149.6.

Cpd 27

Cpd **27** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.81 (br s, 1H), 10.28 (br s, 1H), 8.28 (br s, 1H), 8.23 (s, 1H), 8.07 (ddd, 1H, *J* = 8 Hz, *J* = 2 Hz, *J* = 1 Hz), 7.75 (d, 1H, *J* = 8 Hz), 7.68 (t, 1H, *J* = 8 Hz), 4.12 (d, 2H, *J* = 13 Hz), 3.23 (s, 3H), 3.18 (br s, 2H), 2.90-2.60 (m, 12H), 2.06 (t, 2H, *J* = 11 Hz), 1.89-1.79 (m, 2H), 1.79-1.69 (m, 2H); MS m/z: 497.2 (MH^+), 170.3, 149.7.

Cpd 28

Cpd **28** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.41 (s, 1H), 9.71 (s, 1H), 9.52 (br s, 1H), 8.12 (s, 1H), 7.63 (s, 1H), 7.44 (d, 1H, *J* = 8 Hz), 7.24 (t, 1H, *J* = 8 Hz), 6.90 (d, 1H, *J* = 8 Hz), 3.95-3.80 (m, 2H), 3.23 (t, 2H, *J* = 10 Hz), 3.00 (s, 3H), 2.74 (s, 2H), 2.66 (s, 2H), 2.40-2.10 (m, 8H), 1.93-1.64 (m, 6H); MS m/z: 512.1 (MH^+), 256.4.

Cpd 29

Cpd **29** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.41 (s, 1H), 9.55 (br s, 1H), 8.12 (s, 1H), 8.09 (s, 1H), 7.74 (d, 1H, *J* = 8 Hz), 7.63 (d, 2H, *J* = 8 Hz), 7.47 (t, 1H, *J* = 8 Hz), 7.40-7.35 (m, 3H), 3.89 (d, 2H, *J* = 13 Hz), 3.25 (t, 2H, *J* = 12 Hz), 2.74 (s, 2H), 2.66 (s, 2H), 2.40-2.10 (m, 8H), 1.94-1.65 (m, 6H); MS m/z: 495.1 (MH^+), 247.9, 156.6, 119.7.

Cpd 30

Cpd **30** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual MeOH-*d4* signal (3.31 ppm); ^{1}H NMR (MeOH-*d4*, 400 MHz): δ 9.01 (br s, 1H), 8.71 (d, 1H, *J* = 5 Hz), 8.51 (d, 1H, *J* = 8 Hz), 8.28 (s, 1H), 8.12 (s, 1H), 7.90-7.80 (m, 2H), 7.65-7.57 (m, 2H), 4.40 (d, 2H, *J* = 13 Hz), 3.57 (t, 2H, *J* = 12 Hz), 2.95-2.77 (m, 12H), 2.28 (td, 2H, *J* = 12 Hz, *J* = 2 Hz), 1.96 (d, 2H, *J* = 6 Hz), 1.87 (d, 2H, *J* = 6 Hz); MS m/z: 496.1 (MH^+), 380.9, 248.4, 156.7, 119.7.

Cpd 31

Cpd **31** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.41 (s, 1H), 9.58 (s, 1H), 8.86 (s, 1H), 8.58 (d, 1H, *J* = 4 Hz), 8.12 (s, 1H), 8.05-7.95 (m, 2H), 7.80 (d, 1H, *J* = 8 Hz), 7.50 (dd, 1H, *J* = 8 Hz , *J* = 4 Hz), 7.45-7.35 (m, 2H), 3.90 (d, 2H, *J* = 13 Hz), 3.26 (t, 2H, *J* = 12 Hz), 2.74 (s, 2H), 2.66 (s, 2H), 2.27 (s, 6H), 2.16 (d, 2H, *J* = 13 Hz), 1.91 (t, 2H, *J* = 10 Hz), 1.82 (d, 2H, *J* = 6 Hz), 1.72 (d, 2H, *J* = 6 Hz); MS m/z: 496.1 (MH^+), 248.5, 156.7, 119.7.

Cpd 32

Cpd **32** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.41 (s, 1H), 9.58 (s, 1H), 8.12 (s, 1H), 7.95-7.88 (m, 1H), 7.64 (d, 1H, *J* = 8 Hz), 7.37 (t, 1H, *J* = 8 Hz), 7.15-7.10 (m, 3H), 6.15-6.10 (m, 2H), 3.90 (d, 2H, *J* = 13 Hz), 3.26 (t, 2H, *J* = 12 Hz), 2.74 (s, 2H), 2.66 (s, 2H), 2.26 (s, 6H), 2.14 (d, 2H, *J* = 13 Hz), 1.93 (t, 2H, *J* = 10 Hz), 1.85-1.75 (m, 2H), 1.75-1.65 (m, 2H); MS m/z: 484.1 (MH^+), 242.5, 119.7.

Cpd 33

Cpd **33** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.40 (s, 1H), 9.53 (s, 1H), 8.12 (s, 1H), 8.06 (s, 1H), 7.75 (s, 1H), 7.62 (d, 1H, *J* = 8 Hz), 7.41 (d, 1H, *J* = 8 Hz), 7.34 (t, 1H, *J* = 8 Hz), 6.89 (d, 1H, *J* = 4 Hz), 6.59 (dd, 1H, *J* = 3 Hz, *J* = 2 Hz), 3.89 (d, 2H, *J* = 13 Hz), 3.25 (t, 2H, *J* = 12 Hz), 2.74 (s, 2H), 2.70-2.60 (m, 2H), 2.26 (s, 6H), 2.17 (d, 2H, *J* = 13 Hz), 1.93 (t, 2H, *J* = 10 Hz), 1.85-1.75 (m, 2H), 1.75-1.65 (m, 2H); MS m/z: 485.1 (MH^+), 243.0, 119.7.

Cpd 34

Cpd **34** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual MeOH-*d4* signal (3.31 ppm); ^{1}H NMR (MeOH-*d4*, 400 MHz): δ 8.12 (s, 1H), 7.93 (s, 1H), 7.52 (d, 1H, *J* = 8 Hz), 7.45-7.35 (m, 4H), 7.09 (dd, 1H, *J* = 5 Hz, *J* = 4 Hz), 4.15-4.05 (m, 2H), 3.44 (t, 2H, *J* = 12 Hz), 2.90-2.80 (m, 2H), 2.80-2.70 (m, 2H), 2.47 (s, 6H), 2.36 (d, 2H, *J* = 12 Hz), 1.94 (t, 2H, *J* = 12 Hz), 1.95-1.85 (m, 2H), 1.85-1.75 (m, 2H); MS m/z: 501.2 (MH^+), 271.4, 251.1.

Cpd 35

Cpd **35** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.41 (s, 1H), 9.67 (s, 1H), 8.17 (s, 1H), 8.12 (s, 1H), 7.96 (s, 1H), 7.75 (d, 1H, *J* = 8 Hz), 7.65 (s, 1H), 7.45 (t, 1H, *J* = 8 Hz), 7.33 (d, 1H, *J* = 8 Hz), 7.12 (s, 1H), 3.90 (d, 2H, *J* = 13 Hz), 3.26 (t, 2H, *J* = 12 Hz), 2.80-2.70 (m, 2H), 2.70-2.60 (m, 2H), 2.26 (s, 6H), 2.14 (d, 2H, *J* = 13 Hz), 1.93 (t, 2H, *J* = 10 Hz), 1.85-1.75 (m, 2H), 1.75-1.65 (m, 2H); MS m/z: 485.1 (MH^+), 243.0, 119.6.

Cpd 36

Cpd **36** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 12.89 (br s, 1H), 11.41 (s, 1H), 9.49 (s, 1H), 8.12 (s, 1H), 7.80-7.75 (m, 1H), 7.65 (d, 1H, *J* = 8 Hz), 7.55-7.45 (m, 1H), 7.35-7.25 (m, 1H), 6.64 (s, 1H), 3.90 (d, 2H, *J* = 13 Hz), 3.26 (t, 2H, *J* = 12 Hz), 2.80-2.70 (m, 2H), 2.70-2.60 (m, 2H), 2.28 (s, 6H), 2.25-2.15 (m, 2H), 1.95-1.85 (m, 2H), 1.85-1.75 (m, 2H), 1.75-1.65 (m, 2H); MS m/z: 485.1 (MH^+), 243.0, 119.6.

Cpd 37

Cpd **37** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 11.94 (s, 1H), 10.22 (s, 1H), 8.49 (s, 1H), 8.26 (s, 1H), 8.05 (s, 1H), 7.74-7.66 (m, 2H), 7.58 (d, 1H, *J* = 8 Hz), 7.51 (t, 1H, *J* = 8 Hz), 4.17 (d, 2H, *J* = 13 Hz), 3.17 (t, 2H, *J* = 12 Hz), 2.92-2.62 (m, 12H), 2.10 (t, 2H, *J* = 11 Hz), 1.90-1.79 (m, 2H), 1.79-1.67 (m, 2H); MS m/z: 486.2 (MH^+), 170.2, 149.7.

Cpd 38

Cpd **38** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual MeOH-*d4* signal (3.31 ppm); ^{1}H NMR (MeOH-*d4*, 400 MHz): δ 9.08 (s, 1H), 8.22 (t, 1H, *J* = 2 Hz), 8.17 (s, 1H), 8.11 (s, 1H), 7.67 (d, 1H, *J* = 8 Hz), 7.57 (d, 1H, *J* = 8 Hz), 7.50 (t, 1H, *J* = 8 Hz), 4.06 (d, 2H, *J* = 13 Hz), 3.42 (t, 2H, *J* = 12 Hz), 2.83 (t, 2H, *J* = 5 Hz), 2.74 (t, 2H, *J* = 6 Hz), 2.39 (s, 6H), 2.27 (d, 2H, *J* = 13 Hz), 2.04 (td, 2H, *J* = 12 Hz, *J* = 2 Hz), 1.95-1.75 (m, 2H), 1.75-1.55 (m, 2H); MS m/z: 486.1 (MH^+), 243.5, 119.7.

Cpd 39

Cpd **39** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual MeOH-*d4* signal (3.31 ppm); ^{1}H NMR (MeOH-*d4*, 400 MHz): δ 9.06 (s, 1H), 8.51 (s, 1H), 8.27 (s, 1H), 7.93 (dd, 2H, *J* = 8 Hz, *J* = 2 Hz), 7.62 (t, 2H, *J* = 8 Hz), 4.39 (d, 2H, *J* = 13 Hz), 3.58 (t, 2H, *J* = 12 Hz), 2.95-2.75 (m, 6H), 2.87 (s, 6H), 2.27 (td, 2H, *J* = 12 Hz, *J* = 2 Hz), 2.00-1.90 (m, 2H), 1.90-1.80 (m, 2H); MS m/z: 487.0 (MH^+).

Cpd 40

Cpd **40** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.51 (s, 1H), 9.60 (s, 1H), 8.05 (s, 1H), 7.59 (s, 1H), 7.51 (d, 1H, *J* = 8 Hz), 7.29 (t, 1H, *J* = 8 Hz), 6.81 (t, 1H, *J* = 8 Hz), 4.27 (d, 2H, *J* = 12 Hz), 3.42-3.30 (m, 2H), 3.04 (s, 3H), 2.91 (s, 3H), 2.88 (t, 2H, *J* = 8 Hz), 2.80 (t, 2H, *J* = 8 Hz), 2.42-2.32 (m, 2H), 2.23 (s, 6H), 2.16-2.09 (m, 2H), 1.87-1.78 (m, 2H); MS m/z: 492.3 (MH^+), 421.3, 284.3, 181.1.

Cpd 41

Cpd **41** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 11.75 (s, 1H), 9.57 (s, 1H), 8.17 (s, 1H), 7.59 (t, 1H, *J* = 2 Hz), 7.51 (dd, 1H, *J* = 8 Hz, *J* = 1 H), 7.29 (t, 1H, *J* = 8 Hz), 6.82 (dd, 1H, *J* = 8 Hz, *J* = 2 Hz), 3.84 (d, 2H, *J* = 13 Hz), 3.39-3.17 (m, 4H), 3.04 (s, 3H), 2.92-2.85 (m, 2H), 2.91 (s, 3H), 2.40-2.27 (m, 2H), 2.25 (s, 6H), 2.15 (d, 2H, *J* = 13 Hz) 1.91 (td, 2H, *J* = 12 Hz, *J* = 3 Hz); MS m/z: 542.2 (MH^+), 471.2, 181.1.

Cpd 42

Cpd **42** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 12.1 (s, 1H), 10.00 (s, 1H), 8.35 (t, 1H, *J* = 2 Hz), 8.28 (s, 1H), 8.10-7.94 (m, 4H), 7.70 (dt, 1H, *J* = 8 Hz, *J* = 1 Hz), 7.50 (t, 1H, *J* = 8 Hz), 3.90-3.80 (m, 5H), 3.55-3.45 (m, 2H), 3.32-3.25 (m, 2H), 2.80-2.74 (m, 2H), 2.73-2.65 (m, 2H), 2.47-2.38 (m, 2H), 1.89-1.77 (m, 4H), 1.76-1.69 (m, 2H); MS m/z: 463.3 (MH^+), 152.1, 134.1.

Cpd 43

Cpd **43** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 12.55 (br s, 1H), 10.05 (s, 1H), 8.31 (s, 1H), 8.21 (br s, 3H), 7.70-7.65 (m, 2H), 7.28 (t, 1H, *J* = 8 Hz), 7.0 (d, 1H, *J* = 8 Hz), 4.00-3.85 (m, 2H), 3.70-3.5 (m, 4H), 3.65 (s, 2H), 3.61 (s, 3H), 3.32-3.28 (m, 2H), 2.80-2.65 (m, 4H), 1.87-1.78 (m, 4H), 1.75-1.65 (m, 2H); MS m/z: 477.1 (MH^+), 259.4.

Cpd 44

Cpd **44** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.51 (s, 1H), 9.49 (s, 1H), 8.05 (s, 1H), 7.63-7.57 (m, 2H), 7.25 (t, 1H, *J* = 8 Hz), 6.96 (d, 1H, *J* = 8 Hz), 4.26 (d, 2H, *J* = 12 Hz), 3.64 (s, 2H), 3.61 (s, 3H), 3.38 (t, 2H, *J* = 11 Hz), 2.88 (t, 2H, *J* = 6 Hz), 2.80 (t, 2H, *J* = 6 Hz), 2.42-2.32 (m, 2H), 2.23 (s, 6H), 2.16-2.09 (m, 2H), 1.87-1.78 (m, 2H); MS m/z: 477.4 (MH^+), 284.3, 163.2, 142.6.

Cpd 45

Cpd **45** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 12.65 (br s, 1H), 9.99 (s, 1H), 8.27 (s, 1H), 8.17 (br s, 3H), 7.65-7.60 (m, 2H), 7.28 (t, 1H, *J* = 8 Hz), 7.0 (d, 1H, *J* = 8 Hz), 4.20-4.05 (m, 2H), 3.75-3.65 (m, 2H), 3.65 (s, 2H), 3.61 (s, 3H), 3.32-3.28 (m, 2H), 2.95-2.80 (m, 4H), 2.50-2.35 (m, 2H), 1.90-1.80 (m, 2H); MS m/z: 463.1 (MH^+), 252.6.

Cpd 46

Cpd **46** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 11.69 (s, 1H), 9.46 (s, 1H), 8.17 (s, 1H), 7.60 (s, 1H), 7.59 (d, 1H, *J* = 8 Hz), 7.25 (t, 1H, *J* = 8 Hz), 6.97 (d, 1H, *J* = 8 Hz), 3.83 (d, 2H, *J* = 12 Hz), 3.65 (s, 2H), 3.62 (s, 3H), 3.29 (quintet, 4H, *J* = 12 Hz), 2.88 (t, 2H, *J* = 12 Hz), 2.41-2.27 (m, 2H), 2.25 (s, 6H), 2.16 (d, 2H, *J* = 12 Hz), 1.91 (td, 2H, *J* = 12, *J* = 4 Hz); MS m/z: 527.2 (MH^+), 284.8, 264.3.

Cpd 47

Cpd **47** was synthesised using the methods and protocols discussed above (see Scheme SI 1). The compound was characterised by LC-MS and ^{1}H NMR. NMR chemical shifts, (δ, ppm) were determined relative to the residual DMSO-*d6* signal (2.50 ppm); ^{1}H NMR (DMSO-*d6*, 400 MHz): δ 12.68 (br s, 1H), 10.01 (s, 1H), 8.33 (s, 1H), 8.19 (br s, 3H), 7.70-7.65 (m, 2H), 7.28 (t, 1H, *J* = 8 Hz), 7.0 (d, 1H, *J* = 8 Hz), 4.00-3.85 (m, 2H), 3.70-3.5 (m, 4H), 3.65 (s, 2H), 3.61 (s, 3H), 3.41 (t, 2H, *J* = 16 Hz), 3.32-3.28 (m, 2H), 2.94 (t, 2H, *J* = 4 Hz), 2.45-2.35 (m, 2H), 1.87-1.78 (m, 2H); MS m/z: 513.1 (MH^+), 277.6, 256.9.

2. Compound evaluation

2.1. Inhibitory activity against isolated kinases

On-target activities against LIMK1, LIMK2, ROCK2 and PKA were measured externally (Reaction Biology Corporation, Malvern, USA) in a radiometric assay, with an enzyme concentration of 1 nM and final ATP concentration of 1 μM.

Kinase selectivity data was also collected externally at Reaction Biology Corporation in a radiometric assay, against a panel of 342 kinases. The competing ATP concentration was 10 μM.

Further details regarding the assay technology can be found in literature (T. Anastassiadis, S. W. Deacon, K. Devarajan, H. Ma, J. R. Peterson, *Nat. Biotechnol.*, 2011, **29**, 1039-1045).

2.2. Caco-2 permeability

Caco-2 permeability was determined externally at Cerep SA (now Eurofins Cerep SA, Celle l'Evescault, France).

2.3. Compound stability in human plasma

Pooled, mixed gender, heparinised human plasma was purchased from Sera Laboratories International (Haywards Heath, UK). Plasma samples (195 μl) were spiked with 5 μl test compounds provided as 10 mM DMSO stock (final DMSO concentration 0.2%). The resulting mixtures were stirred (300 rpm) and incubated at 37°C for 60 min. Samples were taken at fixed time points and put into ice-cold acetonitrile containing the internal standard metoprolol (Sigma Aldrich, Steinheim, Germany) for protein precipitation. The remnant of compound was determined by LC-MS/MS (LC20AD, Shimadzu, Duisburg, Germany; 3200 Q TRAP LC-MS/MS system, AB Applied Biosystems, MSD Sciex, Nieuwerkerk aan den Ijssel, The Netherlands) using Analyst Software (AB Sciex). The $t_{1/2}$ values were then determined with GraphPad Prism 5.01 software, assuming one-phase decay.