Supplementary material (ESI) for Organic & Biomolecular Chemistry

Supplementary Information for

Substituent Effects on Aromatic Stacking Interactions

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General Synthetic and Analysis Procedures: Chemicals were purchased and used without further purification. CH_2Cl_2 was dried by distillation from CaH_2. Thin layer chromatography was carried out using aluminium sheets coated with silica gel 60F (Merck), and the plates were inspected using UV light. Column chromatography was carried out using silica gel 40-60 μm (BDH). Preparative TLC was performed using 20 cm x 20 cm, 1500 μm silica gel plates containing UV 254 nm indicator (Analtech). Melting points were determined using a Reichter Kofler hot stage. Elemental analyses were carried out using a Perkin Elmer 2400 CHN analyzer working at 975 ^{o}C. FAB mass spectra were carried out on a Kratos MS 80 in positive ion mode with *m*-nitrobenzyl alcohol as a matrix. ES+ and ES- mass spectra were obtained on a Micromass Platform spectrometer. GC/MS traces and chemical ionization spectra were obtained using a Perkin Elmer TurboMass mass spectrometer and Autosystem XL gas chromatograph. ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on either a Bruker AC250 or AMX400 spectrometer with residual solvent as an internal standard. Fluorine chemical shifts were referenced to an external $CFCl_3$ reference. All chemical shifts are quoted in ppm on the δ scale and the coupling constants expressed in Hz. Signal splitting patterns are described as follows: s (singlet), br s (broad singlet), d (doublet), t (triplet), m (multiplet), * denotes signal due to nitropyrrole minor conformer as

detailed in reference[1]. † denotes signal due to ~30% *Z*-methylamide conformer of compounds **20d** and **20f** (or their precursors) as discussed in the main text.

Reactions were carried out according to the following general procedures unless otherwise stated:

Acid chloride preparation. Acid chlorides were formed by suspending the corresponding acid in dry CH_2Cl_2 under a nitrogen atmosphere. An excess of oxalyl chloride was added and 1-2 drops of catalytic *N,N*-dimethylformamide. The reaction mixture was stirred until all the acid had gone in to solution (typically 30-60 minutes), and the CH_2Cl_2 and excess oxalyl chloride were removed under reduced pressure. The acid chloride was used without further purification.

Amide coupling reactions. These reactions were carried out in CH_2Cl_2 under a nitrogen atmosphere. The acid chloride was prepared as above, redissolved in CH_2Cl_2 and added dropwise to a stirred solution of the amine and base (where applicable) in CH_2Cl_2 or $CHCl_3$. The reactions were stirred until the reaction was considered to be complete (typically for 16 h) and the solvent removed under reduced pressure. Products were isolated by column chromatography or preparative TLC.

Piperidine deprotection using Me_3SiI. The benzylchloroformate-protected or bis(benzylchloroformate)-protected compound was dissolved in CH_2Cl_2 or CH_3CN respectively. Me_3SiI was added, and the mixture stirred until the reaction was complete as determined by TLC (0.5 - 16 h). The solvent was removed under reduced pressure, and the resulting solid was washed repeatedly with diethyl ether and dried.

Piperidine and aniline deprotection using H_2/Pd black. The bis-(benzylchloroformate)-protected compound was dissolved in methanol, one small spatula of Pd black was added and the reaction was stirred under a H_2 atmosphere for 16 h. The reaction mixture was filtered through cotton wool and the solvent removed under reduced-pressure.

Solubilising group coupling. The solubilising group acid (Sol-OH), 1-hydroxybenzotriazole (HOBt) and 1,3-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) were dissolved in CH_2Cl_2 and stirred for 1 h, and then the free piperidine was added portion-wise with a few drops of triethylamine. The reaction mixture was stirred for 16 h. The reaction was quenched with a small amount of methanol, and the solvent was removed under reduced pressure. The reaction mixture was redissolved in CH_2Cl_2 washed with 1 M HCl, saturated Na_2CO_3 and dried over Na_2SO_4. The product was isolated by column chromatography or preparative TLC (CH_2Cl_2/Methanol 98:2).

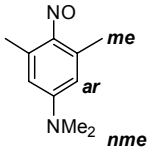
***Compound 1*: 4-nitroso-*N,N*,3,5-tetramethylaniline.** *N,N*-tetramethylaniline (10.26 g, 6.66 ml, 68.0 mmol) was dissolved in concentrated HCl (100 ml) at -10 ^oC in an ethylene glycol/dry ice bath. Sodium nitrite (4.69 g, 68 mmol) in water (8.4 ml) was added below the surface of the stirring HCl solution over 1h. After one further hour, the reaction mixture was allowed to return to room temperature before water (20 ml) was carefully added. Concentrated NaOH solution was added to basify the aqueous phase. The green product was extracted from the yellow aqueous phase with CH_2Cl_2 (100 ml). The organic phase was passed through a cotton wool plug to remove emulsified water and the solvent removed under reduced pressure to yield green crystals (3.27 g, 50%) which were used without further purification.

^1H NMR ($CDCl_3$) δ

6.30 (s, 2H, ***ar***)

3.14 (s, 6H, ***nme***)

2.65 (s, 6H, ***me***)



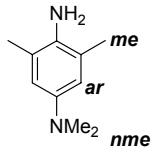
^{13}C NMR ($CDCl_3$) δ161.7, 154.4, 138.2, 110.8, 40.2, 21.2 ppm

***Compound 2: N,N*,2,6-tetramethylaniline.** A green solution of 4-nitro-*N,N*,3,5-tetramethylaniline (**1**) (0.3 g, 15.4 mmol) was refluxed with $SnCl_2$ (9.0g, 47.5 mmol) in ethanol

(100 ml) for 1.5 h until it changed to a brown/deep red colour. The reaction was allowed to cool to room temperature, concentrated NaOH was added to basify the solution. A pink precipitate formed leaving an orange solution. Water (200 ml) was added and the product extracted with CH_2Cl_2 (1000 ml). The product was identified as a purple spot by TLC. The solvent was removed under reduced pressure to yield a brown oil which was purified using column chromatography (silica, ethylacetate/hexane 50:50 v/v, pink/yellow band collected). The solvent was removed under reduced pressure to yield a pink/orange oil (2.6g, 90%), which was used without further purification.

^{1}H NMR of free base ($CDCl_3$) δ

6.55 (s, 2H, ***ar***)
3.25 (br s, 2H, ***nh2***)
2.85 (s, 6H, ***nme***)
2.18 (s, 6H, ***me***)



ESMS *m/z* 165.1398 (MH^+) (calculated for $C_{10}H_{17}N_2$ 165.1392)

Compound 3: **3,5-dimethyl-4-nitroanisole.** Concentrated nitric acid (69% v/v, 4 ml) in glacial acetic acid (6 ml) was added dropwise over 1h to a stirred solution of 3,5-dimethylanisole (3.0 g, 22 mmol) in glacial acid (40 ml) at 15 ^{o}C. The reaction was stirred for 30 minutes after which time a very dark blue colouration developed. The reaction mixture was neutralised with 1 M NaOH and extracted with CH_2Cl_2 (3 x 200 ml). The organic phase was passed through a cotton wool plug to remove suspended water and the solvent removed under reduced pressure. GC/MS(CI) and ^{1}H NMR identified the yellow crystals collected (3.7 g) to be a ~50:50 mixture of 3,5-dimethyl-4-nitroanisole and 3,5-dimethyl-2-nitroanisole. This isomer mixture was dissolved in ethanol (250 ml) and refluxed with $SnCl_2$ (30 g, 0.158 mol) for 70 h. The reaction mixture was allowed to cool and added to 1 M NaOH solution (1000 ml). The cream coloured precipitate and product were extracted with CH_2Cl_2 (1000 ml) and the organic phase was seen to turn a pink colour. The residual colouration in the aqueous phase was extracted with

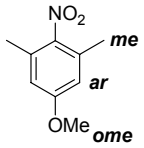
diethyl ether. The organic extracts were combined, solvents were removed under reduced pressure and products purified by column chromatography (silica, CH_2Cl_2). Unreacted 3,5-dimethyl-4-nitroanisole (**3**) was the first yellow band to elute (1.8 g, 50%). The unwanted 3,5-dimethyl-2-nitroanisole had been completely reduced to more highly retained 2,6-dimethyl-3-nitroaniline (brown/pink band).

^{1}H NMR ($CDCl_3$) δ

6.59 (s, 2H, ***ar***)

3.80 (s, 3H, ***ome***)

2.31 (s, 6H, ***me***)



^{13}C NMR ($CDCl_3$) δ160.0, 145.5, 132.4, 113.9, 55.5, 18.4 ppm

CI GC/MS *m/z* 182 (MH^+), (calculated for $C_9H_{12}NO_3$ 182)

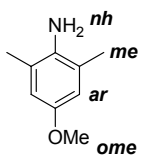
Compound 4: **2,6-dimethyl-4-methoxyaniline.** Glacial acetic acid (15 ml) was carefully added dropwise to 3,5-dimethyl-4-nitroanisole (**3**) (0.85 g 47.0 mmol) and zinc metal dust (1.30 g) refluxing in toluene (10 ml). After 2.5 h the colour of the solution changed from yellow to red/brown with a white precipitate. The reaction was allowed to cool and filtered. The solvent was removed from the filtrate to yield a dark oil, which was subsequently dissolved in CH_2Cl_2 (100 ml) and washed with 1 M NaOH (100 ml). The organic layer was removed and the aqueous layer was extracted with further CH_2Cl_2 until all colouration was removed. CH_2Cl_2 extracts were combined and passed through a cotton wool plug to remove suspended water. The solvent was removed under reduced pressure to yield a dark oil. The oil was dissolved in diethyl ether and acidified (HCl) diethyl ether added to precipitate the hydrochloride salt of the product from solution. The purple precipitate was filtered off and dried under vacuum (0.61 g, 69%).

^{1}H NMR free base ($CDCl_3$) δ

6.55 (s, 2H, ***ar***)

3.72 (s, 3H, ***ome***)

2.16 (s, 6H, ***me***)



Not seen (s, 2H, ***nh***)

^{1}H NMR HCl salt ($CDCl_3$) δ

10.21 (br s, 3H, ***nh***)

6.55 (s, 2H, ***ar***)

3.82 (s, 3H, ***ome***)

2.65 (s, 6H, ***me***)

ESMS *m/z* 152.1080 (MH^+), (calculated for $C_9H_{14}NO$ 152.1075)

***Compound 5: N*-tosyl-2,6-dimethylaniline.** 2,6-Dimethylaniline (34.0 g, 28.0 mmol) and toluenesulphonyl chloride (63.9 g 33.7 mmol) were dissolved/suspended in pyridine (75 ml) and refluxed for 4 h. The reaction mixture was poured whilst stirring into 2 M HCl solution (250 ml), and extracted with diethyl ether. The solvent was removed under reduced pressure. The resulting solid was recrystallised from hot ethanol to yield white crystals (47.2 g, 61%).

^{1}H NMR ($CDCl_3$) δ

7.57 (d, J = 7.1 Hz, 2H, ***tar1***)

7.24 (d, J = 7.1 Hz, 2H, ***tar2***)

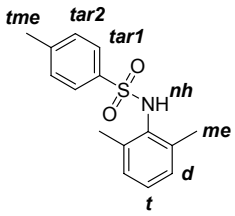
7.08 (t, 1H, ***t***)

6.99 (d, 2H **ar**)

6.08 (br s, 1H, ***nh***)

2.41 (s, 3H, ***tme***)

2.03 (s, 6H, ***me***)



^{13}C NMR ($CDCl_3$) δ 143.6, 137.7, 132.6, 129.6, 128.7, 127.7, 127.2, 21.5, 18.7 ppm

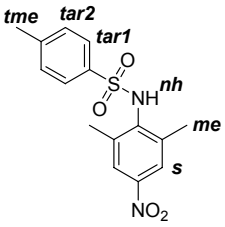
FAB MS *m/z* 276 (MH^+), (calculated for $C_{15}H_{18}NO_2S$ 276).

CHN Found C 65.55 H 6.25 N 5.00 S 11.59 (calculated for $C_{15}H_{17}NO_2S$ C 65.43 H 6.22 N 5.09 S 11.64)

mp 124-126 °C

***Compound 6: N*-tosyl-2,6-dimethyl-4-nitroaniline.** *N*-tosyl-2-6-dimethylaniline (**5**) (7.05 g, 25.6 mmol) was suspended in glacial acetic acid (145 ml), conc. nitric acid (30 ml) and water (145 ml). To this was added sodium nitrite (3.53 g, 51.3mmol) and the reaction was heated at 140 ^{o}C for 4 h. The reaction mixture was cooled to room temperature and then cooled in a refrigerator overnight. The resulting colourless crystals were filtered off and washed repeatedly with water until the washings were neutral (6.1 g, 74%).

^{1}H NMR ($CDCl_3$) δ



7.90 (s, 2H, ***s***)

7.60 (d, J = 7.1Hz, 2H, ***tar1***)

7.30 (d, J = 7.1 Hz, 2H, ***tar2***)

6.20 (br s, 1H, ***nh***)

2.45 (s, 3H, ***tme***)

2.15 (s, 6H, ***me***)

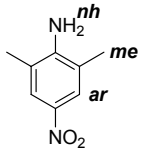
^{13}C ($CDCl_3$) δ 146.3, 144.6, 139.4, 138.8, 137.3, 130.1, 127.2, 123.7, 21.8, 19.2 ppm

HRMS-CI *m/z* 320.0843 (M+), (calculated for $C_{15}H_{16}N_2O_4S$ 320.0831)

mp 165-167 °C

***Compound 7:* 2,6-dimethyl-4-nitroaniline.** *N*-Tosyl-2,6-dimethyl-4-nitroaniline (**6**) (3.0 g, 9.4 mmol) was dissolved in H_2SO_4 (15 ml) and water (1 ml) and warmed at 40^{o}C for 16 h. The reaction mixture was poured slowly into an ice/water/NaOH mixture. This was extracted with ethyl acetate. The solvent was removed under reduced pressure to yield yellow crystals (1.0 g, 64%).

^{1}H NMR ($CDCl_3$) δ



7.90 (s, 2H, ***ar***)

4.30 (br s, 2H, ***nh***)

2.20 (s, 6H, ***me***)

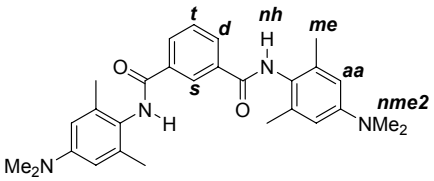
^{13}C ($CDCl_3$) δ 149.3, 138.1, 124.5, 120.4, 17.4 ppm

HRMS-CI *m/z* 166.0734 (M^+), (calculated for $C_8H_{10}N_2O_2$ 166.0742)

mp 165-167ºC

***Compound 8a: N,N'*-bis[(2,6-dimethyl-4-dimethylamino)-phenyl]-isophthalamide. 8a** was prepared by the standard amide coupling procedure using 2,6-dimethyl-4-dimethylaminoaniline (**2**) (0.80 g, 0.48 mmol), isophthaloyl dichloride (0.48 g, 0.24 mmol) and triethylamine (0.60 g, 0.58 mmol) in CH_2Cl_2 (50 ml). Purification by column chromatography (ethyl acetate/hexane 60:30, first band) yielded a colourless solid (0.85 g, 76%).

^{1}H NMR ($CDCl_3$) δ



8.46 (s, 1H, ***s***)

8.10 (d, J = 7.6 Hz, 2H, ***d***)

7.62 (t, J = 7.6 Hz, 1H, ***t***)

7.39 (s, 2H, ***nh***)

6.49 (s, 4H, ***aa***)

2.93 (s, 12H, ***nme2***)

2.25 (s, 12H, ***me***)

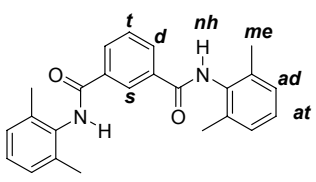
^{13}C NMR ($CDCl_3$) δ165.7, 149.9, 136.1, 135.2, 130.2, 125.9, 123.0, 112.2, 40.7, 18.9 ppm

HRMS-CI *m/z*: 459.2773 (MH^+), (calculated for $C_{28}H_{35}N_4O_2$: 459.2760)

mp >250°C

***Compound 8b: N,N'*-bis(2,6-dimethylphenyl)-isophthalamide**. **8b** was prepared by the standard amide coupling procedure using 2,6-dimethylaniline (2.0 g, 16.5 mmol), isophthaloyl dichloride (1.65 g, 8.1 mmol) and triethylamine (3.3 g, 32.8 mmol), with a catalytic amount of 4-dimethylaminopyridine in CH_3CN (120 ml). Purification by column chromatography (ethyl acetate/hexane 60:30) yielded a colourless solid (1.3 g, 43%).

^{1}H NMR ($CDCl_3$) δ



8.50 (s, 1H, ***s***)

8.13 (d, J = 7.6 Hz, 2H, ***d***)

7.66 (t, J = 7.6 Hz, 1H, ***t***)

7.50 (s, 2H, ***nh***)

7.14 (m, 6H, ***at, ad***)

2.29 (s, 12H, ***me***)

^{13}C NMR ($CDCl_3$) δ 164.9, 135.5, 135.0, 133.4, 130.4, 129.4, 128.4, 127.7, 126.1, 18.5 ppm

HRMS-ES *m/z*: 373.1898 (MH^+), (calculated for $C_{24}H_{25}N_2O_2$ 373.1916)

mp >250 °C

***Compound 8c: N,N'*-bis-(4-methoxy-2,6-dimethyl-phenyl)-isophthalamide. 8c** was prepared by the standard amide coupling procedure using 2,6-dimethyl-4-methoxyaniline (**4**) (1.0 g, 6.6 mmol), isophthaloyl dichloride (0.68 g, 3.3 mmol) and triethylamine (1.53 g, 8.0 mmol) in CH_2Cl_2 (80 ml). Purification by column chromatography (gradient of CH_2Cl_2/methanol 100:0 to 97:3) yielded a colourless solid (0.38 g, 27%).

^{1}H NMR ($CDCl_3$) δ

8.48 (s, 1H, ***s***)

8.11 (d, J = 7.6 Hz, 2H, ***d***)

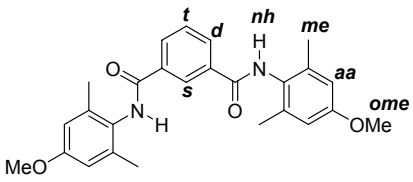
7.64 (t, J = 7.6 Hz, 1H, ***t***)

7.43 (s, 2H, ***nh***)

6.67 (s, 4H, ***aa***)

3.79 (s, 6H, ***ome***)

2.26 (s, 12H, ***me***)



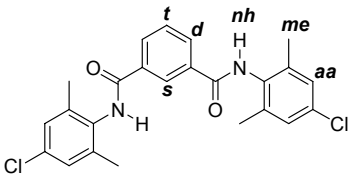
^{13}C NMR ($CDCl_3$) δ: 165.3, 158.5, 137.0, 135.0, 130.3, 129.3, 126.3, 126.0, 113.5, 55.3, 18.8 ppm

HRMS-ES *m/z*: 433.2118 (MH^+), (calculated for $C_{26}H_{29}N_2O_4$: 433.2127)

***Compound 8d: N,N'*-bis-(4-chloro-2,6-dimethyl-phenyl)-isophthalamide**. **8d** was prepared by the standard amide coupling procedure using 2,6-dimethyl-4-chloroaniline (0.64 g, 3.3 mmol),

isophthaloyl dichloride (0.12 g, 0.8 mmol) and triethylamine (0.51 g, 5.0 mmol) in CH_2Cl_2 (20 ml). Purification by preparative TLC (CH_2Cl_2 / methanol 95:5) yielded a colourless solid (0.32 g, 87%).

^{1}H NMR ($CDCl_3$) δ



8.48 (s, 1H, ***s***)

8.13 (d, J = 7.6 Hz, 2H, ***d***)

7.67 (t, J = 7.6 Hz, 1H, ***t***)

7.44 (s, 2H, ***nh***)

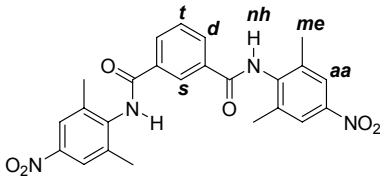
7.14 (s, 4H, ***aa***)

2.27 (s, 12H, ***me***)

^{13}C NMR ($CDCl_3$/ CD_3OD) δ 166.1, 137.5, 134.4, 132.7, 132.5, 130.8, 129.2, 128.0, 126.3 ppm

HRMS-ES *m/z*: 441.1153 (MH^+), (calculated for $C_{24}H_{23}N_2O_2Cl_2$: 441.1137)

***Compound 8e: N,N'*-bis-(2,6-dimethyl-4-nitro-phenyl)-isophthalamide**. **8e** was prepared by the standard amide coupling procedure using **2,6**-dimethyl-4-nitroaniline (**7**) (0.64 g, 3.8 mmol), isophthaloyl dichloride (0.39 g, 1.9 mmol) in refluxing pyridine (20 ml) for 3 days. Purification by column chromatography (CH_2Cl_2/Methanol 100:0 to 98:2) yielded a colourless solid (0.30 g, 33%).^{1}H NMR ($CDCl_3$) δ



8.52 (s, 1H, ***s***)

8.18 (d, J = 7.6 Hz, 2H, ***d***)

8.03 (s, 4H, ***aa***)

7.73 (t, J = 7.6 Hz, 1H, ***t***)

7.58 (s, 2H, ***nh***)

2.40 (s, 12H, ***me***)

^{13}C NMR (DMSO-d_6) δ: 165.0, 145.7, 134.2, 137.9, 134.8, 131.4, 129.2, 127.7, 122.9, 18.6 ppm

HRMS-CI *m/z*: 463.1619 (MH^+), (calculated for $C_{24}H_{23}N_4O_6$: 463.1617)

HRMS-ES *m/z*: 485.1427 (MNa^+), (calculated for $C_{24}H_{22}N_4O_6Na$: 485.1437)

mp >250 °C

***Compound 9: N,N'*-bis-(2,6-difluoro-phenyl)-isophthalamide. 9** was prepared by the standard amide coupling procedure using 2,6-difluoroaniline (0.60 g, 4.6 mmol), isophthaloyl dichloride (0.16 g, 0.8 mmol) and triethylamine (0.16 g, 1.6 mmol) in CH_2Cl_2 (10 ml). Purification by preparative TLC (Et_2O, first band) yielded a colourless solid (0.09 g, 31%).

^{1}H NMR ($CDCl_3$) δ

8.50 (s, 1H, ***s***)

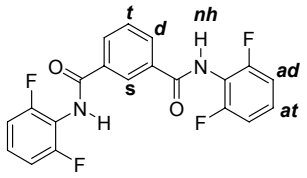
8.16 (d, J = 7.6 Hz, 2H, ***d***)

7.67 (t, J = 7.6 Hz, 1H, ***t***)

7.53 (s, 2H, ***nh***)

7.26 (under $CDCl_3$, 4H, ***ad***)

7.02 (t, J = 8.0 Hz, 2H, ***at***)



^{13}C NMR ($CDCl_3$/CD_3OD) δ166.0 (t), 159.3 (d), 156.8 9 (d), 133.7, 131.6, 129.1, 127.9 (t), 126.8, 111.7 (dd) ppm

^{19}F NMR ($CDCl_3$) δ-118 ppm

HRMS-ES *m/z*: 389.0913 (MH^+), (calculated for $C_{20}H_{13}N_2O_2F_4$: 389.0913)

***Compound 10: N,N'*-dihexyl-isophthalamide**. **10** was prepared as previously described.[2]

***Compound 11:* 4,4-bis-(4-amino-3,5-dimethyl-phenyl)-piperidine-1-carboxylic acid benzyl ester**. **11** was prepared as previously described.[1]

***Compound 12g:* 4-(4-Amino-3,5-dimethyl-phenyl)-4-3-piperidine-1-carboxylic acid benzyl ester**. **12g** was prepared as previously described.[1]

***Compound 13a:* 4-(4-amino-3,5-dimethyl-phenyl)-4-[4-(2,6-dimethyl-benzoylamino)-3,5-dimethyl-phenyl]-piperidine-1-carboxylic acid benzyl ester. 13a** was prepared by the standard amide coupling procedure using 2,6-dimethyl benzoic acid (0.75 g, 5.0 mmol), **11** (11.4 g, 24.9 mmol) and

triethylamine (0.61 g, 6.0 mmol) in CH_2Cl_2 (200 ml). The reaction mixture was washed with 1 M HCl to recover excess **11**. Purification by medium pressure column chromatography (CH_2Cl_2/methanol 98:2) yielded a colourless solid (1.50 g, 51%).

^{1}H NMR (DMSO-d_6) δ

9.66 (s, 1H, ***p1***)

7.40-7.30 (m, 6H, ***n2***, ***pr2***, ***pr3***, ***pr4***)

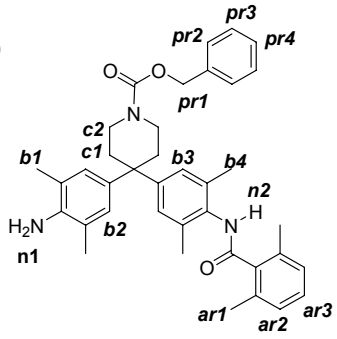
7.21 (t, 1H, ***ar2***)

7.10 (d, 2H, ***ar1***)

7.01 (s, 2H, ***b3***)

6.88 (s, 2H, ***b2***)

5.05 (s, 2H, ***pr1***)



3.60-3.20 (m, 6H, ***n1***, ***c2***)

2.38 (s, 6H, ***m1***)

2.30-2.10 (m, 4H, ***c1***)

2.24 (s, 6H, ***b4***)

2.11 (s, 6H, ***b1***)

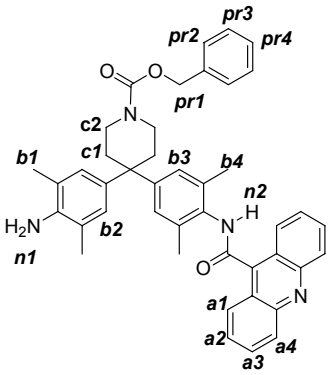
^{13}C NMR ($CDCl_3$) δ168.4, 161.5, 155.4, 134.8, 134.5, 128.9, 128.4, 127.8, 127.7, 127.1, 127.0, 105.5, 66.9, 43.5, 41.0, 20.0, 19.9, 18.3 ppm

HRMS-CI m/z 590.3339 (MH^+), (calculated for $C_{38}H_{44}N_3O_3$ 590.3382)

Compound 13b: **4-(4-amino-3,5-dimethyl-phenyl)-4--piperidine-1-carboxylic acid benzyl ester. 13b** was prepared as previously described.[1]

Compound 13c: **4-{4-[(acridine-9-carbonyl)-amino]-3,5-dimethyl-phenyl}-4-(4-amino-3,5-dimethyl-phenyl)-piperidine--carboxylic acid benzyl ester. 13c** was prepared by the standard amide coupling procedure using 9-acridine-carboxylic acid (2.0 g, 8.9 mmol), **11** (20 g, 44.7 mmol) and pyridine (5 ml) in CH_2Cl_2. Purification by column chromatography (CH_2Cl_2/methanol 98:2, second band was excess **8**, third band was product) yielded a yellow solid (3.3 g, 60%).

^{1}H NMR ($CDCl_3$) δ



8.19 (d, 2H, ***a1***)

8.10 (d, 2H, ***a4***)

7.87 (s, 1H, ***n2***)

7.70 (t, 2H, ***a3***)

7.50 (t, 2H, ***a2***)

7.40-7.30 (m, 5H, ***pr2***, ***pr3***, ***pr4***)

7.03 (s, 2H, ***b3***)

6.83 (s, 2H, ***b2***)

5.05 (s, 2H, ***pr1***)

3.80-3.30 (m, 6H, ***n1***, ***c2***)

2.47 (s, 6H, ***b4***)

2.40-2.20 (m, 4H, ***c1***)

2.16 (s, 6H, ***b1***)

^{13}C NMR ($CDCl_3$) δ 165.5, 155.3, 148.4, 147.4, 141.0, 140.8, 136.9, 134.6, 131.0, 130.3, 129.6, 128.4, 127.9, 127.7, 127.1, 126.9, 126.8, 125.1, 122.3, 121.7, 66.9, 45.5, 41.0, 35.8, 20.0, 18.0 ppm

HRMS-CI m/z 663.3363 (MH^+), (calculated for $C_{43}H_{43}N_4O_3$ 663.3378)

mp 163-165 ºC

Compound 13e: **4-(4-amino-3,5-dimethyl-phenyl)-4-[4-(2,6-dimethyl-4-nitro-benzoylamino)-3,5-dimethyl-phenyl]-piperidine-1-carboxylic acid benzyl ester. 13e** was prepared by the standard amide coupling procedure using 2,6-dimethyl-4-nitrobenzoic acid (0.75 g, 4.0 mmol, prepared according to the procedure described in reference[3] **11** (3.0 g, 6.5 mmol) and triethylamine (1.1 g, 10.9 mmol) in toluene (200 ml). The reaction mixture was refluxed overnight. The reaction mixture was washed with 1 M HCl to recover excess **11**. Purification by column chromatography (CH_2Cl_2/methanol 98:2) yielded a yellow solid (0.50 g, 20%)

^{1}H NMR ($CDCl_3$) δ

7.91 (s, 2H, ***ar2***)

7.40-7.30 (m, 5H, ***pr2***, ***pr3***, ***pr4***)

7.06 (s, 1H, ***n2***)

6.98 (s, 2H, ***b3***)

6.81 (s, 2H, ***b2***)

5.10 (s, 2H, ***pr1***)

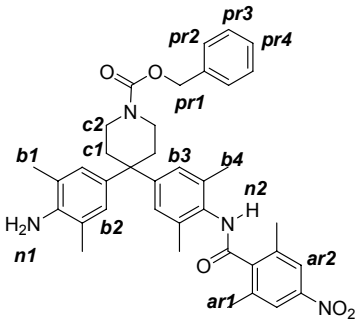
3.72-3.35 (m, 6H, ***n1***, ***c2***)

2.56 (s, 6H, ***ar1***)

2.42-2.19 (m, 4H, ***c1***)

2.32 (s, 6H, ***b4***)

2.15 (s, 6H, ***b1***)



^{13}C NMR ($CDCl_3$) δ 166.61, 155.40, 147.31, 147.28, 143.60, 140.83, 140.45,136.82, 136.43, 135.24, 134.42, 131.15, 130.65, 122.45, 121.82, 121.63, 66.90, 53.50, 43.40, 41.04, 35.87, 19.99, 19.85, 18.06 ppm

HRMS-CI m/z 635.323 (MH^+), (calculated for $C_{38}H_{43}N_4O_5$ 635.321)

mp 121-122°C

Compound 13f: **4-(4-amino-3,5-dimethyl-phenyl)-4-(3,5-dimethyl-4-pentafluorobenzoylamino-phenyl)-piperidine-1-carboxylic acid benzyl ester. 13f** was prepared as previously described.[1]

Compound 14a: **4-[4-(2,6-dimethyl-benzoylamino)-3,5-dimethyl-phenyl]-4-{3,5-dimethyl-4-[(4-nitro-1H-pyrrole-2-carbonyl)-amino]-phenyl}-piperidine-1-carboxylic acid benzyl ester. 14a** was prepared by the standard amide coupling procedure using 4-nitro-pyrrole-2-carboxylic acid (0.49 g, 0.32 mmol), **13a** (1.56 g, 0.26 mmol) and pyridine (1 ml) in CH_2Cl_2 (75 ml). Purification by column chromatography (CH_2Cl_2/methanol 98:2), yielded a pale yellow solid (0.80 g, 41%).

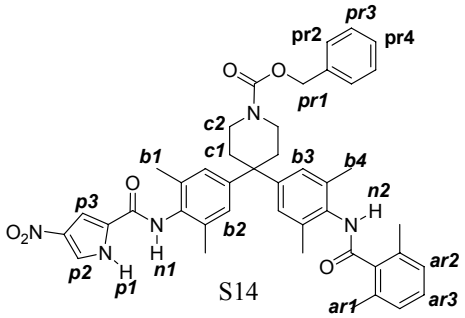
^{1}H NMR (DMSO-d_6) δ

12.91 (s, 1H, ***p1***)

9.69 (s, 1H, ***n2***)

9.62 (s, 1H, ***n1***)

7.97 (s, 1H, ***p2***)



7.64 (s, 1H, ***p3***)

7.50-6.90 (m, 8H, ***ar2***, ***ar3***, ***pr2***, ***pr3***, ***pr4***)

5.07 (s, 2H, ***pr1***)

3.60-3.40 (m, 4H, ***c2***)

2.39 (s, 6H, ***ar1***)

2.45-2.35 (m, 4H, ***c1***)

2.28 (s, 6H, ***b4***)

2.15 (s, 6H, ***b1***)

^{13}C NMR (DMSO-d_6) δ 167.9, 158.2, 155.0, 145.5, 145.0, 139.0, 137.5, 136.8, 135.9, 135.5, 134.3, 133.1, 132.5, 128.8, 128.6, 128.2, 127.9, 126.7, 126.5, 106.5, 66.5, 43.8, 35.2, 20.1, 20.0, 18.9 ppm

HRMS-CI m/z 728.3481 (MH^+), (calculated for $C_{43}H_{46}N_5O_6$ 728.3448).

mp 192-194 ºC

Compound 14b: **4-{4-[(anthracene-9-carbonyl)-amino]-3,5-dimethyl-phenyl}-4-{3,5-dimethyl-4-[(4-nitro-1H-pyrrole-2-carbonyl)-amino]-phenyl}-piperidine-1-carboxylic acid benzyl ester. 14b** was prepared as previously described.[1]

Compound 14c: **4-{4-[(acridine-9-carbonyl)-amino]-3,5-dimethyl-phenyl}-4-{3,5-dimethyl-4-[(4-nitro-1H-pyrrole-2-carbonyl)-amino]-phenyl}-piperidine-1-carboxylic acid benzyl ester. 14c** was prepared by the standard amide couplings procedure using 4-nitropyrrole-2-carboxylic acid (0.30 g, 2.0 mmol) in CH_2Cl_2 (50 ml), **13c** (1.05 g, 1.51 mmol) and pyridine (1 ml) in CH_2Cl_2 (100 ml). Purification by column chromatography (CH_2Cl_2/methanol 98:2) yielded a yellow solid (1.1 g, 85%).

^{1}H NMR (DMSO-d_6) δ

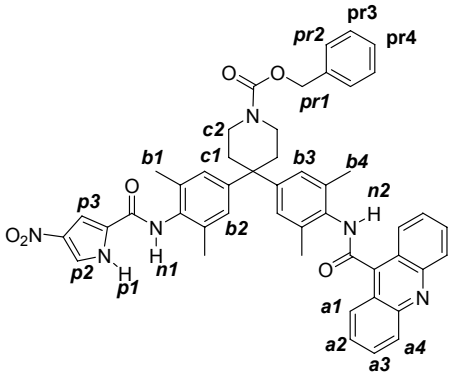
12.91 (s, 1H, ***p1***)

10.39 (s, 1H, ***n2***)

9.62 (s, 1H, ***n1***)

8.27-8.24 (m, 4H, ***a1***, ***a4***)

7.98-7.90 (m, 4H, ***p2***, ***a2***)



7.75 (t, 2H, ***a3***)

7.50-7.25 (m, 6H, ***p3***, ***pr2***, ***pr3***, ***pr4***)

7.22 (s, 2H, ***b3***)

7.18 (s, 2H, ***b2***)

5.08 (s, 2H, ***pr1***)

3.50-3.30 (m, 4H, ***c2***)

2.50-2.30 (m, 4H, ***c1***)

2.45 (s, 6H, ***b4***)

2.17 (m, 6H, ***b1***)

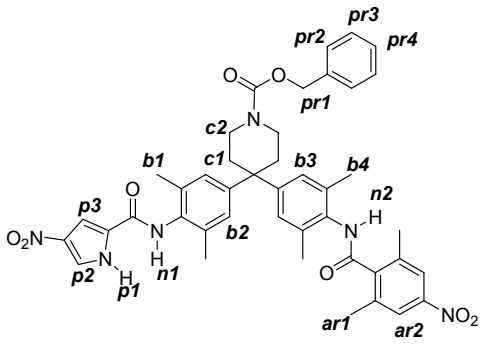
^{13}C NMR (DMSO-d_6) δ 164.7, 157.7, 154.5, 148.2, 145.1, 144.9, 142.1, 136.9, 136.3, 135.4, 132.1, 132.0, 1330.6, 129.4, 128.3, 127.7, 127.4, 126.9, 126.4, 126.0, 125.4, 121.9, 105.7, 66.0, 43.3, 40.8, 34.7, 19.4, 18.4 ppm

HRMS-CI m/z 801.3363 (MH^+), (calculated for $C_{48}H_{45}N_6O_6$ 801.3400).

mp 222-224 ºC

Compound 14e: **4-[4-(2,6-dimethyl-4-nitro-benzoylamino)-3,5-dimethyl-phenyl]-4-{3,5-dimethyl-4-[(4-nitro-1H-pyrrole-2-carbonyl)-amino]-phenyl}-piperidine-1-carboxylic acid benzyl ester. 14e** was prepared by the standard amide coupling procedure using 4-nitro-pyrrole-2-carboxylic acid (0.3 g, 1.9 mmol), **16a** (1.0 g, 1.6 mmol) and triethylamine (0.5 ml) in CH_2Cl_2 (100 ml). Purification by column chromatography (CH_2Cl_2/methanol 98:2) yielded a yellow solid (1.3 g, 88 %).

^{1}H NMR (DMSO-d_6) δ



12.24 (s, 1H, ***p1***)

9.35 (s, 1H, ***n1***)

9.17 (s, 1H, ***n2***)

7.85 (s, 2H, ***ar2***)

7.61 (s, 1H, ***p2***)

7.54 (s, 1H, ***p3***)

7.30-7.20(m, 5H, ***pr2***, ***pr3***, ***pr4***)

6.93 (s, 2H, ***b3***)

6.91 (s, 2H, ***b2***)

5.03 (s, 2H, ***pr1***)

3.48 (br s, 4H, ***c2***)

2.51 (s, 6H, ***ar1***)

2.40-2.30 (m, 4H, ***c1***)

2.27 (s, 6H, ***b4***)

2.14 (s, 6H, ***b1***)

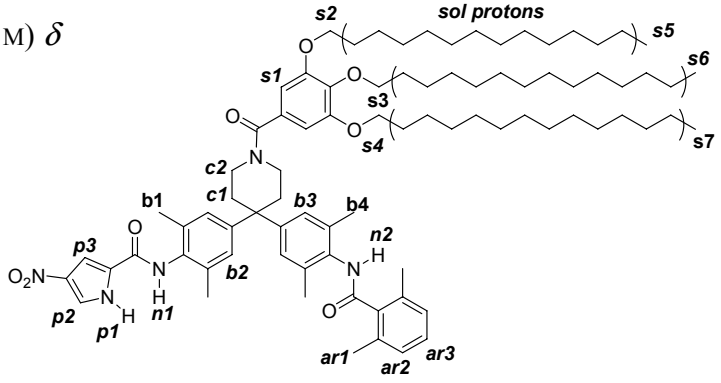
^{13}C (DMSO-d_6) δ 166.21, 157.96, 154.75, 146.81, 144.72, 144.39, 143.96, 135.43, 135.47, 134.83, 131.62, 128.00, 127.44, 127.17, 126.35, 125.89, 121.84, 66.32, 59.78, 43.18, 40.29, 20.58, 19.74, 19.49, 18.46, 13.75 ppm

HRMS-FAB *m/z* 773.330 (MH^+), (calculated for $C_{43}H_{45}N_6O_8$ 773.330)

Compound 14f: **4-{3,5-dimethyl-4-[(4-nitro-1H-pyrrole-2-carbonyl)-amino]-phenyl}-4-(3,5-dimethyl-4-pentafluorobenzoylamino-phenyl)-piperidine-1-carboxylic acid benzyl ester. 14f** was prepared as previously described.[1]

Compound 14g: **4-(4-acetylamino-3,5-dimethyl-phenyl)-4-{3,5-dimethyl-4-[(4-nitro-1H-pyrrole-2-carbonyl)-amino]-phenyl}-piperidine-1-carboxylic acid benzyl ester. 14g** was prepared as previously described.[1]

Compound 15a: **4-nitro-1H-pyrrole-2-carboxylic acid {4-[4-[4-(2,6-dimethyl-benzoylamino)-3,5-dimethyl-phenyl]-1-(3,4,5-tris-tetradecyloxy-benzoyl)-piperidin-4-yl]-2,6-dimethyl-phenyl}-amide. 15a** was prepared by the standard piperidine deprotection using Me_3SiI (~0.4 ml), **14a** (0.8 g, 1.1 mmol) in CH_2Cl_2 (100 ml), followed by the standard solubilising group coupling using a few drops of triethylamine, the solubilising group acid, Sol-OH (1.22 g, 1.6 mmol), 1,-3-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (0.42 g, 2.2 mmol) and 1-hydroxy-benzatriazole (HOBt) (0.29 g, 2.2 mmol) in CH_2Cl_2 (100 ml) to yield a pale yellow waxy solid (1.1 g, 75%).



^{1}H NMR ($CDCl_3$) (0.0068 M) δ

10.32 (br s, 1H, ***p1***)

10.05 (s, ***p1****)

7.65 (s, 1H, ***p2***)

7.46 (s, 1H, ***n1***)

7.27 (s, 1H, ***p3***)

7.19 (m, 1H, ***ar3***)

7.07 (m, 2H, ***ar2***)

6.99 (s, 2H, ***b3***)

6.98 (s, 2H, ***b2***)

6.94 (s, 1H, ***n2***)

6.54 (s, 2H, ***s1***)

5.37 (s, ***p3****)

3.93 (m, 6H, ***s2***, ***s3***, ***s4***)

3.85-3.50 (br m, 4H, ***c2***)

2.46 (s, 6H, ***ar1***)

2.34 (s, 6H, ***b4***)

2.19 (s, 6H, ***b1***)

2.50-2.10 (br m, 4H, ***c1***)

1.90-1.65, 1.55-1.0 (br m, 72H, ***sol protons***)

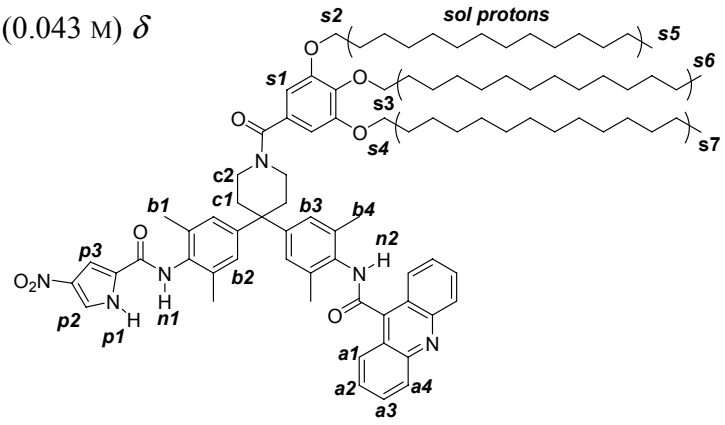
0.90-0.85 (m, 9H, ***s5***, ***s6***, ***s7***)

^{13}C NMR ($CDCl_3$) δ 170.5, 168.9, 158.5, 153.1, 145.3, 144.9, 139.1, 137.4, 137.1, 135.8, 135.3, 134.3, 131.5, 131.1, 130.6, 129.0, 127.8, 127.0, 126.5, 125.7, 105.3, 73.5, 69.2, 44.1, 31.9, 30.2, 29.7, 29.7, 29.6, 29.4, 29.3, 26.1, 22.6, 19.9, 18.7, 14.1 ppm

HRMS-CI *m/z*: 1334.9724 (MH^+), (calculated for $C_{84}H_{128}N_5O_8$ 1334.9762)

Compound 15b: **4-nitro-1H-pyrrole-2-carboxylic acid {4-[4-{4-[(anthracene-9-carbonyl)-amino]-3,5-dimethyl-phenyl}-1-(3,4,5-tris-tetradecyloxy-benzoyl)-piperidin-4-yl]-2,6-dimethyl-phenyl}-amide. 15b** was prepared as previously described.[1]

Compound 15c: **acridine-9-carboxylic acid {4-[4-{3,5-dimethyl-4-[(4-nitro-1H-pyrrole-2-carbonyl)-amino]-phenyl}-1-(3,4,5-tris-tetradecyloxy-benzoyl)-piperidin-4-yl]-2,6-dimethyl-phenyl}-amide. 15c** was prepared by the standard piperidine deprotection using Me_3SiI (~0.4 ml), **14c** (1.0 g, 1.25 mmol) in CH_2Cl_2 (50 ml), followed by the standard solubilising group coupling using a few drops of triethylamine, the solubilising group acid, Sol-OH (1.0 g, 1.4 mmol), 1,-3-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (0.37 g, 1.9 mmol) and 1-hydroxy-benzatriazole (HOBt) (0.25 g, 1.9 mmol) in CH_2Cl_2 (50 ml) to yield a pale yellow waxy solid (0.85 g, 50%).



^{1}H NMR ($CDCl_3$) (0.043 M) δ

11.11 (s, 1H, ***p1***)

10.75 (s, ***p1****)

8.15 (m, 2H, ***a1***)

8.11 (m, 2H, ***a4***)

8.07 (s, 1H, ***n1***)

7.90 (s, 1H, ***n2***)

7.53 (s, 1H, ***p2***)

7.47 (m, 2H, ***a2***)

7.69 (m, 2H, ***a3***)

7.29 (s, 1H, ***p3***)

7.07 (s, 2H, ***b3***)

6.97 (s, 2H, ***b2***)

6.54 (s, 2H, ***s1***)

5.37 (s, ***p3****)

3.97-3.95 (m, 6H, ***s2***, ***s3***, ***s4***)

3.90-3.50 (br m, 4H, ***c2***)

2.50-2.20 (br m, 4H, ***c1***)

2.46 (s, 6H, ***b4***)

2.13 (s, 6H, ***b1***)

1.90-1.70, 1.60-1.20 (m, 72H, ***sol protons***)

0.95-0.80 (m, 9H, ***s5***, ***s6***, ***s7***)

^{13}C NMR ($CDCl_3$) δ 170.5, 135.7, 158.3, 153.2, 148.5, 145.4, 140.6, 139.3, 137.6, 135.8, 135.4, 131.4, 131.0, 130.6, 130.3, 129.8, 127.2, 127.0, 126.6, 125.6, 124.9, 122.3, 105.5, 73.5, 69.3, 44.3, 31.9, 30.3, 29.7, 29.7, 29.6, 29.4, 29.3, 29.6, 26.1, 22.6, 20.0, 18.8, 14.0 ppm

HRMS-CI *m/z* 1407.9715 (MH^+), (calculated for $C_{89}H_{127}N_6O_8$ 1407.9715)

CHN Found C 74.54 H 8.97 N 5.83, (calculated for $C_{89}H_{126}N_6O_8 1.5H_2O$ C 74.49 H 9.06 N 5.86)

Compound 15e: **4-nitro-1H-pyrrole-2-carboxylic acid {4-[4-[4-(2,6-dimethyl-4-nitro-benzoylamino)-3,5-dimethyl-phenyl]-1-(3,4,5-tris-tetradecyloxy-benzoyl)-piperidin-4-yl]-2,6-dimethyl-phenyl}-amide. 15e** was prepared by the standard piperidine deprotection using Me_3SiI (~0.2 ml), **14e** (0.3 g, 0.4 mmol) in CH_2Cl_2 (50 ml), followed by the standard solubilising group coupling using a few drops of triethylamine, the solubilising group acid, Sol-OH (0.5 g, 0.4 mmol), 1,-3-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (0.8 g, 0.8 mmol) and 1-hydroxy-benzatriazole (HOBt) (0.1 g, 0.8 mmol) in CH_2Cl_2 (50 ml) to yield a pale yellow waxy solid (0.25 g, 45%).

^{1}H NMR (DMSO-d_6) δ

12.33 (s, 1H, ***p1***)

9.53 (s, 1H, ***n1***)

9.26 (s, 1H, ***n2***)

7.87 (s, 2H, ***ar2***)

7.62 (s, 1H, ***p2***)

7.56 (s, 1H, ***p3***)

6.95 (s, 2H, ***b3***)

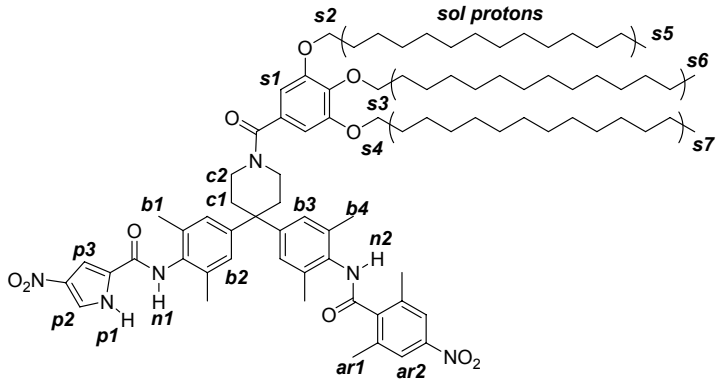
6.93 (s, 2H, ***b2***)

6.47 (s, 2H, ***s1***)

3.88 (m, 6H, ***s2***, ***s3***, ***s4***)

3.75-3.40 (m,4H,***c2***)

2.52 (s, 6H, ***ar1***)



2.40-2.30 (m, 4H, ***c1***)

2.28 (s, 6H, ***b4***)

2.14 (s, 6H, ***b1***)

1.80-1.20 (m, 72H, ***sol protons***)

0.90-0.85 (m, 9H, ***s5***, ***s6***, ***s7***)

^{13}C (DMSO-d_6) δ 169.82, 167.98, 166.46, 152.37, 147.09, 144.20, 141.70, 138.76, 137.32, 136.68, 135.79, 135.20, 135.16, 134.89, 130.83, 130.17, 126.57, 126.06, 125.38, 124.83, 124.36, 122.09, 107.08, 103.31, 73.12, 68.90, 24.19, 31.63, 30.69, 30.06, 29.95, 29.42, 29.40, 29.36, 29.06, 25.85, 22.39, 19.97, 19.74, 18.72, 10.98 ppm

HRMS-ES *m/z* 1379.957 (MH^+), (calculated for $C_{84}H_{127}N_6O_{10}$ 1379.961)

Compound 15f: **4-nitro-1H-pyrrole-2-carboxylic acid {4-[4-(3,5-dimethyl-4-pentafluorobenzoylamino-phenyl)-1-(3,4,5-tris-tetradecyloxy-benzoyl)-piperidin-4-yl]-2,6-dimethyl-phenyl}-amide. 15f** was prepared as previously described.[1]

Compound 15g: **4-nitro-1H-pyrrole-2-carboxylic acid {4-[4-(4-acetylamino-3,5-dimethyl-phenyl)-1-(3,4,5-tris-tetradecyloxy-benzoyl)-piperidin-4-yl]-2,6-dimethyl-phenyl}-amide. 15g** was prepared as previously described.[1]

Compound 16: **4-(4-amino-3,5-dimethyl-phenyl)-4-(4-benzyloxycarbonylamino-3,5-dimethyl-phenyl)-piperidine-1-carboxylic acid benzyl ester.** Benzyl chloroformate (0.53 g, 0.44 ml, 31.1 mmol) in CH_2Cl_2 (10 ml) was added to **11** (5.65 g, 12.4 mmol) in CH_2Cl_2 (125 ml) at 0 ^oC in the absence of additional base.[4] The reaction was allowed to return to room temperature and stirred for 16 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 1 M HCl to extract excess **11** (2 x 650 ml). The organic phase was collected and the solvent removed under reduced pressure before being washed with 1 M NaOH (200 ml). The solvent was removed under reduced pressure and the crude

product dissolved in diethyl ether by trituration. The diethyl ether solution was filtered through cotton wool and acidified (HCl) diethyl ether was added to precipitate the white HCl salt of the product. The precipitate was filtered, collected and neutralised to yield slightly yellow solid (1.29 g, 71%).

^{1}H NMR ($CDCl_3$) δ

7.38-7.07 (m, 10H, ***pr2, pr3, pr4, cb2, cb3, cb4***)

6.82 (s, 2H, ***b2***)

6.69 (s, 2H, ***b3***)

5.90 (s, 1H, ***n1***)

5.08 (s, 2H, ***cb1***)

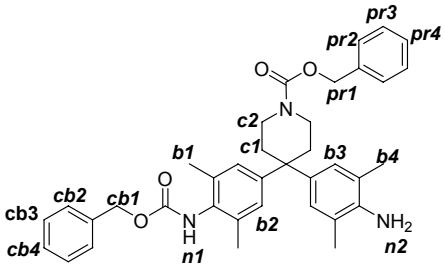
5.02 (s, 2H, ***pr1***)

3.60-3.27 (m, 8H, ***c1, c2***)

2.20 (br s, 2H, ***n2***)

2.10 (s, 6H, ***b1***)

2.05 (s, 6H, ***b4***)



^{13}C (CDCl3) δ 155.4, 154.4, 146.5, 140.7, 137.0, 136.5, 135.5, 135.0, 131.2, 128.6, 128.5, 128.2, 127.9, 127.8, 126.9, 126.7, 121.7, 67.1, 66.9, 43.5, 41.1, 36.1, 18.7, 18.1 ppm

HRMS-ES *m/z* 592.3190 (MH^+), (calculated for $C_{37}H_{42}N_3O_4$ 592.3175)

Compound 17: **4-(4-benzyloxycarbonylamino-3,5-dimethyl-phenyl)-4-(3,5-dimethyl-4-methylamino-phenyl)-piperidine-1-carboxylic acid benzyl ester. 16** (0.85 g, 14.3 mmol), 4 Å, 5 μm activated molecular sieves (8.45 g), glacial acetic acid (90 μl) and 37% formaldehyde in water (130 μl) in tetrahydrofuran (25 ml) were stirred for 16 h. The solvent was removed under reduced pressure and tetrahydrofuran (25 ml) was added, and this cycle repeated 3 times. 1 M sodium cyanoborohydride in tetrahydrofuran (1.43 ml) was added and the mixture stirred for 7 h. Glacial acetic acid (90 μl) was added and the reaction mixture stirred for 16 h. The reaction mixture was filtered through tightly packed cotton wool and the solvent was removed

under reduced pressure. The crude product was dissolved in CH_2Cl_2 (200 ml), washed with 1 M NaOH (200 ml), and suspended water removed by filtration through cotton wool. The solvent was removed under reduced pressure and the product was purified using column chromatography (CH_2Cl_2/methanol, 99.5:0.5, third band) to yield a slightly yellow solid (0.40 g, 46%).

^{1}H NMR ($CDCl_3$) δ

7.37-7.04 (m, 10H, ***pr2, pr3, pr4, cb2, cb3, cb4***)

6.84 (s, 2H, ***b2***)

6.75 (s, 2H, ***b3***)

6.26 (s, 1H, ***n1***)

5.08 (s, 2H, ***cb1***)

5.03 (s, 2H, ***pr1***)

3.63-3.31 (m, 8H, ***c2***)

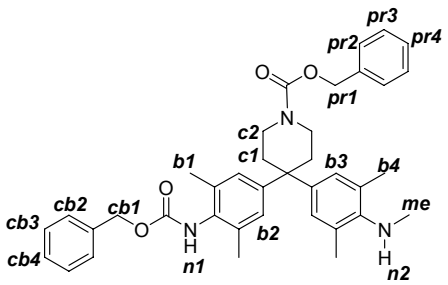
2.85 (s, 3H, ***me***)

2.66 (s, 2H, ***n2***)

2.22 (s, 2H, ***c1***)

2.15 (s, 6H, ***b1***)

2.11 (s, 6H, ***b4***)



^{13}C ($CDCl_3$) δ 155.5, 154.4, 146.0, 145.4, 138.9, 137.0, 136.5, 135.6, 131.5, 128.9, 128.5, 128.2, 127.9, 127.8, 127.4, 126.7, 67.0, 67.0, 43.6, 41.1, 36.0, 36.0, 35.4, 18.9, 18.8 ppm

HRMS-ES *m/z* 606.3318 (MH^+), (calculated for $C_{38}H_{44}N_3O_4$ 606.3332)

Compound 18d: 4-(4-benzyloxycarbonylamino-3,5-dimethyl-phenyl)-4-{4-[(2,6-difluoro-benzoyl)-methyl-amino]-3,5-dimethyl-phenyl}-piperidine-1-carboxylic acid benzyl ester. **18d** was prepared by the standard amide coupling procedure using 2,6-difluorobenzoyl chloride (0.060 g, 0.34 mmol), **17** (0.19 g, 0.31 mmol) and triethylamine (0.031 g, 0.31 mmol) in CH_2Cl_2 (10 ml). The solvent was removed under reduced pressure and the crude product dissolved in diethyl ether (10 ml) and acidified

(HCl) diethyl ether was added to precipitate any unreacted **17**, which was collected by filtration. The solvent was removed from the filtrate under reduced pressure to yield a colourless solid (0.24 g, 95%).

^{1}H NMR ($CDCl_3$) δ

7.47-7.13 (m, 10H + 70% 1H ***ar2, pr2, pr3, pr4, cb2, cb3, cb4***)

7.00-6.95 (m, 70% 2H, ***ar1***)

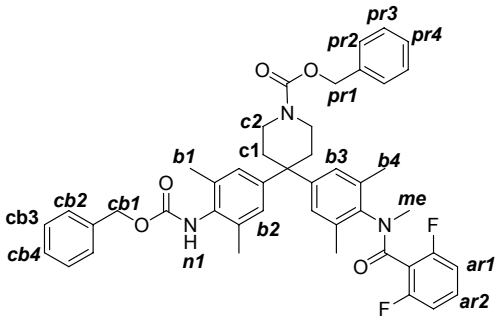
6.98 (s, 70% 2H, ***b3***)

6.96 (s, 70% 2H, ***b2***)

6.79 (s, 30% 2H, ***b2†***)

6.75 (s, 30% 2H, ***b3†)***

6.63 (m, 30% 3H, ***ar1†, ar2†***)



6.16 (s, 1H, ***n1***)

5.17 (s, 2H, ***cb1***)

5.11 (s, 70% 2H, ***pr1***)

5.10 (s, 30% 2H, ***pr1†***)

3.73-3.25 (m, 4H, ***c2***)

3.33 (s, 30% 3H, ***me†***)

3.06 (s, 70% 3H, ***me***)

2.33 (br s, 4H, ***c1***)

2.21 (s, 70% 6H, ***b4***)

2.21 (s, 70% 6H, ***b1***)

2.19 (s, 30% 6H, ***b4†***)

2.15 (s, 30% 6H, ***b1†***)

^{19}F ($CDCl_3$) δ -109***†***, -113 ppm

HRMS-ES *m/z* 746.3393 (MH^+), (calculated for $C_{45}H_{46}N_3O_5F_2$ 746.3406)

Compound 18e: **4-(4-benzyloxycarbonylamino-3,5-dimethyl-phenyl)-4-{4-[(2,6-dimethyl-4-nitro-benzoyl)-methyl-amino]-3,5-dimethyl-phenyl}-piperidine-1-carboxylic acid benzyl ester.** 2,6-dimethyl-4-nitrobenzoic acid chloride was generated according to the standard acid chloride preparation using 2,6-dimethyl-4-nitrobenzoic acid (0.43 g, 2.2 mmol) and oxalyl chloride (0.84 g, 6.6 mmol) in CH_2Cl_2 (12 ml). **18e** was then prepared by the standard amide coupling procedure using the

freshly prepared acid chloride, **17** (0.50 g, 0.83 mmol) and triethylamine (0.084 g, 0.83 mmol) in refluxing chloroform (15 ml) for 6 days. The solvent was removed under reduced pressure. The crude product dissolved in diethyl ether (10 ml) and acidified (HCl) diethyl ether was added to precipitate any unreacted **17**, which was collected by filtration. The product was purified by preparative TLC (CH_2Cl_2/methanol, 98:2) to yield a slightly yellow solid (0.58 g, 90%).

^{1}H NMR ($CDCl_3$) δ

7.95 (s, 2H, ***ar2***)

7.47-7.14 (m, 10H, ***pr2, pr3, pr4, cb2, cb3, cb4***)

6.95 (s, 4H, ***b3***, ***b2***)

6.01 (s, 1H, ***n1***)

5.17 (s, 2H, ***cb1***)

5.11 (s, 70% 2H, ***pr1***)

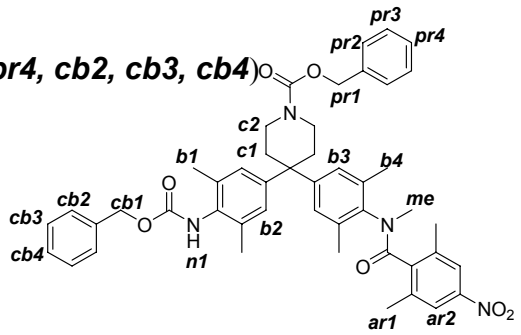
3.75-3.54 (m, 4H, ***c2***)

2.96 (s, 3H, ***me***)

2.56 (s, 6H, ***ar1***)

2.32 (br s, 10H, ***c1, b4***)

2.21 (s, 6H, ***b1***)



^{13}C ($CDCl_3$) δ 168.7, 155.4, 154.3, 147.5, 146.5, 144.3, 143.0, 137.3, 136.9, 136.4, 136.1, 135.8, 135.0, 131.6, 128.6, 128.5, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 126.9, 122.9, 67.0, 65.9, 43.8, 43.8, 40.9, 40.9, 37.0, 35.8, 35.5, 29.7, 20.4, 19.6, 18.8 ppm

HRMS-ES *m/z* 805.3602 (MNa^+), (calculated for $C_{47}H_{50}N_4O_7Na$ 805.3577)

Compound 18f: **4-(4-benzyloxycarbonylamino-3,5-dimethyl-phenyl)-4-[3,5-dimethyl-4-(methyl-pentafluorobenzoyl-amino)-phenyl]-piperidine-1-carboxylic acid benzyl ester. 18f** was prepared by the standard amide coupling procedure using pentafluorobenzoyl chloride (0.084 g, 0.36 mmol), **17** (0.20 g, 0.33 mmol) and triethylamine (0.033 g, 0.33 mmol) in CH_2Cl_2 (2 ml). The solvent was removed under reduced pressure and the crude product dissolved in diethyl ether (2 ml) and acidified

(HCl) diethyl ether was added to precipitate any unreacted **17**, which was collected by filtration. The solvent was removed from the filtrate under reduced pressure to yield a colourless solid (0.26 g, 99%).

^{1}H NMR ($CDCl_3$) δ

7.39-7.05 (m, 10H, ***pr2, pr3, pr4, cb2, cb3, cb4***)

6.91 (br s, 70% 2H, ***b3***)

6.88 (s, 70% 2H, ***b2***)

6.77 (s, 30% 2H, ***b2†***)

6.71 (s, 30% 2H, ***b3†)***

6.10 (s, 1H, ***n1***)

5.08 (s, 2H, ***cb1***)

5.03 (s, 70% 2H, ***pr1***)

5.02 (s, 30% 2H, ***pr1†***)

3.65-3.33 (m, 4H, ***c2***)

3.24 (s, 30% 3H, ***me†***)

3.02 (s, 70% 3H, ***me***)

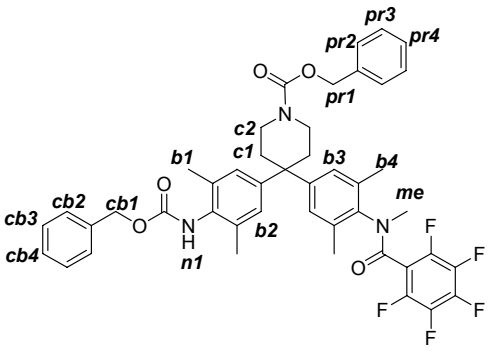
2.25 (br s, 4H, ***c1***)

2.16 (s, 70% 6H, ***b4***)

2.14 (s, 70% 6H, ***b1***)

2.11 (s, 30% 6H, ***b4†***)

2.09 (s, 30% 6H, ***b1†***)



^{19}F NMR ($CDCl_3$) δ-137***†***, -141, -152, -152***†***, -160, -162***†*** ppm

HRMS-ES *m/z* 800.3161 (MH^+), (calculated for $C_{45}H_{43}N_3O_5F_5$ 800.3123)

Compound 19d: ***N*-{4-[4-(4-amino-3,5-dimethyl-phenyl)-1-(3,4,5-tris-tetradecyloxy-benzoyl)-piperidin-4-yl]-2,6-dimethyl-phenyl}-2,6-difluoro-*N*-methyl-benzamide. 19d** was prepared by the standard piperidine deprotection using H_2/Pd black, **18d** (0.24 g, 0.32 mmol) in methanol (15 ml), followed by the standard solubilising group coupling using triethylamine (0.038 g, 0.38 mmol), the solubilising group acid, Sol-OH (0.22 g, 0.28 mmol), 1,-3-(dimethylaminopropyl)-3-ethylcarbodiimide

hydrochloride (EDC) (0.07 g, 0.34 mmol) and 1-hydroxy-benzatriazole (HOBt) (0.05 g, 0.37 mmol) in CH_2Cl_2 (7 ml) to yield a pale yellow waxy solid (0.30 g, 78%).

^{1}H NMR ($CDCl_3$) δ

7.45-7.29 (m, 70% 1H ***ar2***)

7.06-6.88 (m, 70% 2H, ***ar1***)

6.99 (s, 70% 2H, ***b3***)

6.83 (s, 70% 2H, ***b2***)

6.77 (s, 30% 2H, ***b2†***)

6.75 (s, 30% 2H, ***b3†)***

6.66 (m, 30% 3H, ***ar1†, ar2†***)

6.54 (s, 70% 2H, ***s1***)

6.52 (s, 30% 2H, ***s1†***)

3.94 (m, 6H, ***s2***, ***s3***, ***s4***)

3.73-3.27 (m, 4H, ***c2***)

3.32 (s, 30% 3H, ***me†***)

3.05 (s, 70% 3H, ***me***)

2.26-2.22 (br s, 6H, ***c1***, ***n1***)

2.25 (s, 70% 6H, ***b4***)

2.18 (s, 30% 6H, ***b4†***)

2.15 (s, 70% 6H, ***b1***)

2.10 (s, 30% 6H, ***b1†***)

1.84-1.64, 1.53-1.11 (m, 72H, ***sol protons***)

0.87 (m, 9H, ***s5***, ***s6***, ***s7***)

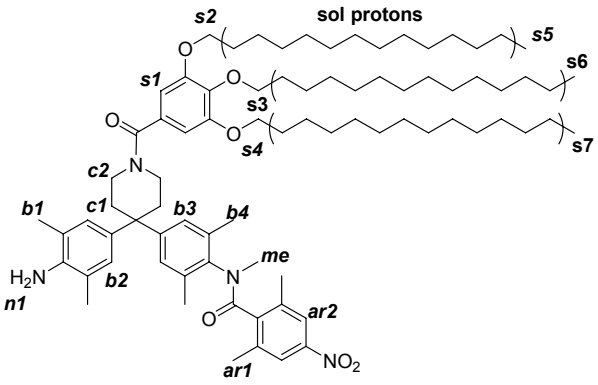
^{19}F ($CDCl_3$) δ-109***†***, -113 ppm

HRMS-ES *m/z* 1218.9409 (MH^+), (calculated for $C_{78}H_{122}N_3O_5F_2$ 1218.9353)

Compound 19e: ***N*-{4-[4-(4-amino-3,5-dimethyl-phenyl)-1-(3,4,5-tris-tetradecyloxy-benzoyl)-piperidin-4-yl]-2,6-dimethyl-phenyl}-2,6,*N*-trimethyl-4-nitro-benzamide. 19e** was prepared by the standard piperidine deprotection using Me_3SiI (0.4 ml), **18e** (0.36 g, 0.46 mmol) in CH_2Cl_2 (100 ml), followed by the standard solubilising group coupling using triethylamine (0.061 g, 0.60 mmol), the

solubilising group acid, Sol-OH (0.31 g, 0.41 mmol), 1,-3-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (0.10 g, 0.51 mmol) and 1-hydroxy-benzatriazole (HOBt) (0.075 g, 0.55 mmol) in CH_2Cl_2 (10 ml) to yield a pale yellow waxy solid (0.048 g, 8%).

^{1}H NMR ($CDCl_3$) δ



7.95 (m, 2H ***ar2***)

7.21 (s, 2H, ***b3***)

6.89 (br m, 2H, ***b2***)

6.55 (s, 2H, ***s1***)

3.94 (m, 6H, ***s2***, ***s3***, ***s4***)

3.63-3.29 (br m, 4H, ***c2***)

3.32 (br s, 2H, ***n1***)

2.96 (s, 3H, ***me***)

2.56 (s, 6H, ***ar1***)

2.31 (s, 6H, ***b4***)

2.26-2.22 (br s, 4H, ***c1***)

2.13 (s, 70% 6H, ***b1***)

1.84-1.64, 1.53-1.11 (m, 72H, ***sol protons***)

0.87 (m, 9H, ***s5***, ***s6***, ***s7***)

^{13}C ($CDCl_3$) δ 170.0, 168.8, 153.1, 152.8, 147.8, 147.5, 143.0, 140.9, 139.1, 137.0, 136.1, 134.8, 134.1, 131.0, 128.6, 127.6, 127.3, 126.9, 126.7, 122.9, 121.8, 108.3, 105.4, 73.5, 69.2, 69.1, 53.4, 45.06, 43.7, 39.3, 37.0, 36.9, 36.9, 35.7, 30.3, 29.7, 29.7, 29.7, 29.6, 29.6, 26.1, 22.7, 20.4, 19.6, 18.0, 14.1 ppm

HRMS-ES *m/z* 1277.9553 (MNa^+), (calculated for $C_{80}H_{126}N_4O_7Na$ 1277.9524)

Compound 19f: ***N*-{4-[4-(4-amino-3,5-dimethyl-phenyl)-1-(3,4,5-tris-tetradecyloxy-benzoyl)-piperidin-4-yl]-2,6-dimethyl-phenyl}-2,3,4,5,6-pentafluoro-*N*-methyl-benzamide.** **19f** was prepared by the standard piperidine deprotection using H_2/Pd black, **18f** (0.26 g, 0.33 mmol) in methanol (15 ml), followed by the standard solubilising group coupling using triethylamine (0.042 g, 0.42 mmol), the solubilising group acid, Sol-OH (0.25 g, 0.32 mmol), 1,-3-(dimethylaminopropyl)-3-

ethylcarbodiimide hydrochloride (EDC) (0.074 g, 0.38 mmol) and 1-hydroxy-benzatriazole (HOBt) (0.05 g, 0.36 mmol) in CH_2Cl_2 (7 ml) to yield a colourless waxy solid (0.23 g, 50%).

^{1}H NMR ($CDCl_3$) δ

6.96 (br d, 70% 2H ***b3***)

6.83 (s, 2H, ***b2***)

6.67 (s, 30% 2H, ***b3†)***

6.53 (s, 70% 2H, ***s1***)

6.53 (s, 30% 2H, ***s1†***)

3.93 (m, 6H, ***s2***, ***s3***, ***s4***)

3.50 (br s, 2H, ***n1***)

3.73-3.27 (m, 4H, ***c2***)

3.33 (s, 30% 3H, ***me†***)

3.08 (s, 70% 3H, ***me***)

2.50-2.00 (br m, 4H, ***c1***)

2.23 (s, 70% 6H, ***b4***)

2.17 (s, 30% 6H, ***b4†***)

2.15 (s, 70% 6H, ***b1***)

2.11 (s, 30% 6H, ***b1†***)

1.84-1.64, 1.53-1.11 (m, 72H, ***sol protons***)

0.87 (m, 9H, ***s5***, ***s6***, ***s7***)

^{19}F NMR ($CDCl_3$) δ: -137***†***, -141, -152, -153***†***, -160, -162***†*** ppm

HRMS-ES *m/z* 1272.9038 (MH^+), (calculated for $C_{78}H_{119}N_3O_5F_5$ 1272.9070)

Compound 20d: **4-nitro-1H-pyrrole-2-carboxylic acid {4-[4-{4-[(2,6-difluoro-benzoyl)-methyl-amino]-3,5-dimethyl-phenyl}-1-(3,4,5-tris-tetradecyloxy-benzoyl)-piperidin-4-yl]-2,6-dimethyl-phenyl}-amide. 20d** was prepared by the standard amide coupling procedure using 4-nitro-pyrrole-2-carboxylic acid (0.058 g, 0.37 mmol), **19d** (0.30 g, 0.25 mmol) and triethylamine (1 drop) in CH_2Cl_2 (10 ml). Purification by preparative TLC (CH_2Cl_2/methanol 97:3), yielded a pale yellow waxy solid (0.13 g, 38%).

^{1}H NMR ($CDCl_3$) (0.061 M) δ

11.07 (s, 95% 1H ***p1, p1†***)

10.74 (s, 5% 1H ***p1****)

8.39 (s, 30% 1H, ***n1†***)

8.30 (s, 70% 1H, ***n1***)

7.53 (s, 30% 2H ***p2†, p3†***)

7.41 (s, 70% 1H ***p2***)

7.35-7.25 (m, 70% 1H ***ar2***)

7.26 (s, 70% 1H ***p3***)

7.06-6.88 (m, 70% 2H, ***ar1***)

7.00 (s, 70% 2H, ***b3***)

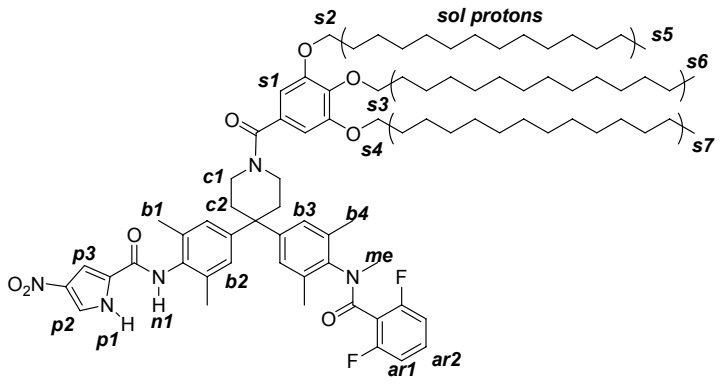
6.91 (s, 70% 2H, ***b2***)

6.88 (s, 30% 2H, ***b3†***)

6.76 (s, 30% 2H, ***b2†***)

6.55 (s, 70% 2H, ***s1***)

6.52 (s, 30% 2H, ***s1†***)



6.35-6.21 (m, 30% 3H, ***ar1†, ar2†***)

5.28 (s, ***p3****)

3.94 (m, 6H, ***s2***, ***s3***, ***s4***)

3.73-3.27 (m, 4H, ***c2***)

3.31 (s, 30% 3H ***me†***)

3.06 (s, 70% 3H ***me***)

2.40-2.22 (br s, 4H, ***c1***)

2.23 (s, 70% 6H, ***b4***)

2.19 (s, 30% 6H, ***b4†***)

2.11 (s, 30% 6H, ***b1†***)

2.07 (s, 70% 6H, ***b1***)

1.84-1.65, 1.56-1.11 (m, 72H, ***sol protons***)

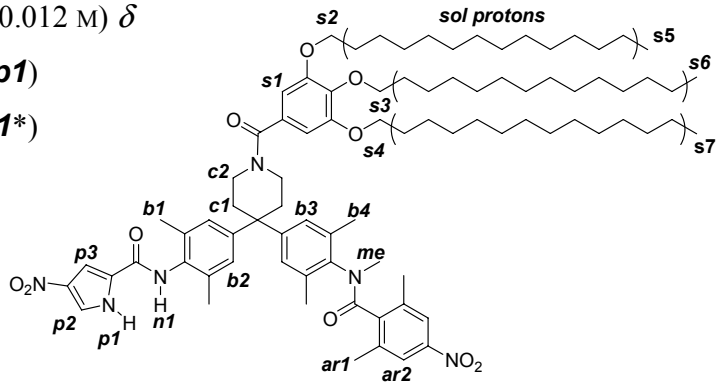
0.87 (m, 9H, ***s5***, ***s6***, ***s7***)

^{19}F ($CDCl_3$) δ-109***†***, -113 ppm

HRMS-ES *m/z* 1378.9252 (MNa^+), (calculated for $C_{83}H_{123}N_5O_8F_2Na$ 1378.9237)

Compound 20e: **4-nitro-1H-pyrrole-2-carboxylic acid {4-[4-{4-[(2,6-dimethyl-4-nitro-benzoyl)-methyl-amino]-3,5-dimethyl-phenyl}-1-(3,4,5-tris-tetradecyloxy-benzoyl)-piperidin-4-yl]-2,6-dimethyl-phenyl}-amide. 20e** was prepared by the standard amide coupling procedure using 4-nitro-pyrrole-2-carboxylic acid (0.018 g, 0.11 mmol), **19e** (0.049 g, 0.04 mmol) and pyridine (1 drop) in CH_2Cl_2 (10 ml). Purification by preparative TLC (CH_2Cl_2/methanol 98:2), yielded a pale yellow waxy solid (0.016 g, 28%).

^{1}H NMR ($CDCl_3$) (0.012 M) δ



10.52 (s, 95% 1H, ***p1***)

10.19 (s, 5% 1H, ***p1****)

7.92 (m, 1H, ***ar2***)

7.72 (s, 1H, ***n1***)

7.60 (s, 1H, ***p2***)

7.26 (s, 5% 1H ***p3***)

7.01 (br s, 2H, ***b3***)

6.97 (s, 2H, ***b2***)

6.55 (s, 2H, ***s1***)

5.37 (s, 5% 1H ***p3****)

3.94 (m, 6H, ***s2***, ***s3***, ***s4***)

3.85-3.38 (m, 4H, ***c2***)

2.97 (s, 3H, ***me***)

2.51 (s, 6H, ***ar1***)

2.43 (br s, 4H, ***c1***)

2.34 (s, 6H, ***b4***)

2.15 (s, 6H, ***b1***)

1.82-1.67, 1.56-1.11 (m, 72H, ***sol protons***)

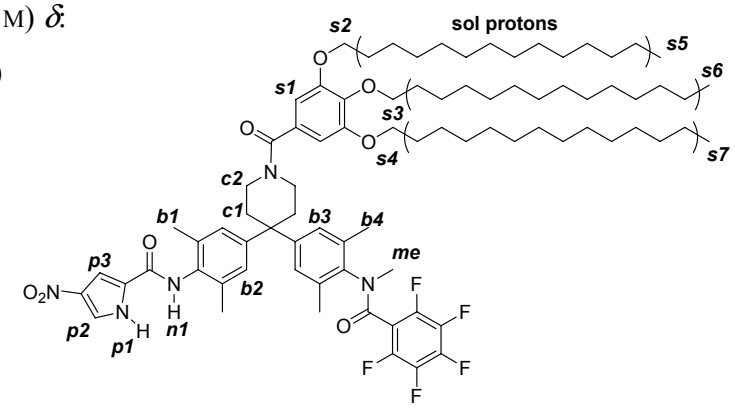
0.86 (m, 9H, ***s5***, ***s6***, ***s7***)

MS-ES *m/z* 1416 (MNa^+), (calculated for $C_{85}H_{129}N_6O_{10}Na$ 1416)

HRMS-ES *m/z* 1393.9728 (MH^+), (calculated for $C_{85}H_{129}N_6O_{10}$ 1392.97)

***Compound 20f*: 4-nitro-1H-pyrrole-2-carboxylic acid {4-[4-[3,5-dimethyl-4-(methyl-pentafluorobenzoyl-amino)-phenyl]-1-(3,4,5-tris-tetradecyloxy-benzoyl)-piperidin-4-yl]-2,6-dimethyl-phenyl}-amide. 20f** was prepared by the standard amide coupling procedure using 4-nitro-pyrrole-2-carboxylic acid (0.034 g, 0.21 mmol), **19f** (0.23 g, 0.18 mmol) and pyridine (1 drop) in CH_2Cl_2 (10 ml). Purification by preparative TLC (CH_2Cl_2/methanol 98:2), yielded a colourless waxy solid (0.25 g, 28%).

^{1}H NMR ($CDCl_3$) (0.0035 M) δ:



9.92 (s, 95% 1H, ***p1***, ***p1†***)
9.86 (s, 5% 1H, ***p1****)
7.77 (s, 70% 1H, ***p2***)
7.61 (s, 30% 1H, ***p2†***)
7.30 (s, 30% 1H, ***p3†***)
7.26 (s, 70% 1H, ***p3***)
7.20 (s, 70% 1H, ***n1***)
7.18 (s, 30% 1H, ***n1†***)
7.04 (s, 30% 2H, ***b3†***)
7.01 (s, 70% 2H, ***b3***)
6.87 (s, 30% 2H, ***b2†***)
6.86 (s, 70% 2H, ***b2***)
6.63 (s, 30% 2H, ***s1†***)
6.54 (s, 70% 2H, ***s1***)
5.34 (s, 5% ***p3****)
4.01-3.89 (m, 6H, ***s2***, ***s3***, ***s4***)
3.88-3.42 (br m, 4H, ***c2***)
3.33 (s, 30% 3H, ***nme†***)
3.11 (s, 70% 3H, ***nme***)
2.49-2.34 (br m, ***c1***)

2.25 (s, 70% 6H, ***b4***)

2.22 (s, 70% 6H, ***b1***)

2.19 (br s, 30% 2H, ***b1†, b4†***)

1.84-1.67, 1.64-1.15 (m, 72H, ***sol protons***)

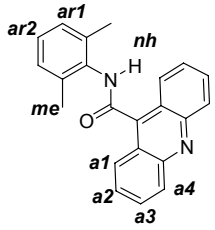
0.98-0.75 (m, 9H, ***s5***, ***s6***, ***s7***)

^{19}F NMR ($CDCl_3$) δ: -137***†***, -141, -152, -153***†***, -160, -162***†*** ppm

HRMS-ES *m/z*: 1410.9170 (MH^+), (calculated for $C_{83}H_{121}F_5N_5O_8$: 1410.9135)

***Compound 21c*: *N*-(2,6-dimethylphenyl)acridine-9-carboxamide. 21c** was prepared by the standard amide coupling procedure using acridine-9-carboxylic acid (0.10 g, 0.45 mmol), 2,6-dimethylaniline (0.10 g, 0.89mmol) and pyridine (2 drops) in CH_2Cl_2 (30 ml). Purification by column chromatography (CH_2Cl_2/methanol 100:0 to 99:1, second band) yielded a yellow solid (0.09 g, 62%). Crystals of suitable quality for X-ray crystal structure determination were grown by slow evaporation petroleum ether/CH_2Cl_2.

^{1}H NMR ($CDCl_3$) δ



8.29 (d, 2H, ***a1***)

8.22 (d, 2H, ***a4***)

7.79 (t, 2H, ***a3***)

7.59 (t, 2H, ***a2***)

7.52 (br s, 1H, ***nh***)

7.21 (br s, 3H, ***ar1***, ***ar2***)

2.53 (s, 6H, ***me***)

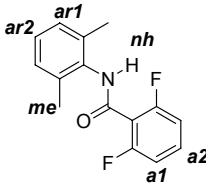
^{13}C NMR ($CDCl_3$) δ 165.5, 148.6, 135.2, 133.1, 130.3, 129.8, 128.8, 127.9, 126.9, 125.1, 122.4, 19.6

FAB-MS *m/z* 326 (M^+), (calculated for $C_{22}H_{18}N_2O$, 326)

mp > 230 °C (decomposes)

***Compound 21d*: *N*-(2,6-dimethylphenyl)-2,6-difluorobenzamide. 21d** was prepared by the standard amide coupling procedure using 2,6-difluorobenzoyl chloride (0.74g, 4.2 mmol), 2,6-dimethylaniline (0.56 g, 4.6 mmol) and triethylamine (0.23 g, 4.6 mmol) in CH_2Cl_2 (40 ml).

Recrystallisation from CH_2Cl_2/cyclohexane yielded 0.46 g (42%) of colourless solid. Crystals of suitable quality for X-ray crystal structure determination were grown by slow evaporation from ethanol.



^{1}H NMR ($CDCl_3$) δ

7.42 (m, 1H, ***ar2***)

7.13 (m, 4H, ***a1***, ***a2***, ***nh***)

7.00 (t, 2H, ***ar1***)

2.35 (s, 6H, ***me***)

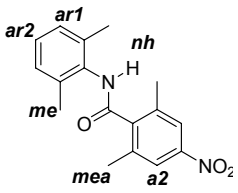
^{19}F ($CDCl_3$) δ -113 ppm

HRMS-ES *m/z*: 262.1044 (MH^+), (calculated for $C_{15}H_{14}NOF_2$ 262.1043)

CHN Found: C 68.88 H 4.95 N 5.31 (calculated for $C_{15}H_{13}NOF_2$, C 68.96, H 5.02 N 5.36)

mp 163-164 °C

***Compound 21e*: *N*-(2,6-dimethyl-4-nitrophenyl)-2,6-dimethylnitrobenzamide. 21e** was prepared by standard amide coupling procedure using 2,6-dimethyl-4-nitrobenzoic acid (0.3 g, 1.5 mmol), 2,6-dimethylaniline (0.2 g, 1.6 mmol), triethylamine (0.2 ml, 1.5 mmol) and a catalytic amount of 4-dimethylaminopyridine in CH_2Cl_2 (50 ml). Purification by column chromatography (CH_2Cl_2/methanol 100:0 to 99:1) yielded a yellow solid (0.06 g, 15%.) Crystals of suitable quality for X-ray crystal structure determination were grown from CH_2Cl_2 /petroleum ether.



^{1}H NMR ($CDCl_3$) δ

7.98 (s, 2H, ***a2***)

7.30 (s, 1H, ***nh***)

7.19 (t, 1H, ***ar2***)

7.05 (d, 2H, ***ar1***)

2.45 (s, 6H, ***mea***)

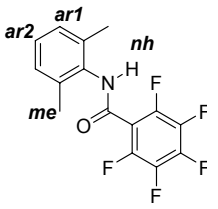
2.39 (s, 6H, ***me***)

FAB MS *m/z*: 299 (MH^+), (calculated for $C_{17}H_{19}N_2O_3$, 299)

mp > 230 °C (decomposes)

***Compound 21f*: *N*-(2,6-dimethylphenyl)-2,3,4,5,6-pentafluorobenzamide. 21f** was prepared by the standard amide coupling procedure using pentafluorobenzoyl chloride (1.00 g, 4.20 mmol), 2,6-dimethylaniline (0.56 g, 4.6 mmol) in CH_2Cl_2 (20 ml). The reaction mixture was washed with water and the solvent was removed under reduced pressure. Recrystallisation from CH_2Cl_2/cyclohexane yielded a colourless solid (1.21 g, 90%). Polymorph α was crystallised by slow evaporation from a mixture of CH_2Cl_2 and cyclohexane. Polymorph β was crystallised from CH_2Cl_2.

^{1}H NMR ($CDCl_3$) δ



7.22-7.11 (m, 4H, ***ar1***, ***ar2***, ***nh***)

2.31 (s, 6H, ***me***)

^{19}F ($CDCl_3$) δ: -141, -152, -160 ppm

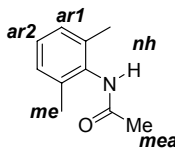
FAB-MS *m/z*: 316 (MH^+), (calculated for $C_{15}H_{11}F_5NO$ 316)

CHN Found: 57.06 H 2.98 N 4.21 (calculated for for $C_{15}H_{10}F_5NO$ C 57.15 H 3.20 N 4.44)

mp 188-189 °C (polymorph α)

***Compound 21g*: *N*-(2,6-dimethylphenyl)acetamide.** 3 ml acetic anhydride was poured over 2,6-dimethylaniline (2.0 g, 16.5 mmol) and stirred gently. After approximately 2 minutes a white precipitate formed which was filtered, washed repeatedly with water and dried (2.7 g, 78%). Crystals of suitable quality for X-ray crystal structure determination were grown by slow evaporation from CH_2Cl_2.

^{1}H NMR (DMSO-d_6) δ



9.24 (br s, 1H ***nh***)

7.05 (br s, 3H, ***ar1***, ***ar2***)

2.14 (s, 6H, ***me***)

2.04 (s, 3H, ***mea***)

^{13}C (DMSO-d_6) δ168.3, 135.9, 135.6, 128.0, 126.7, 23.0, 18.6 ppm

FAB-MS *m/z*: 164 (MH^+), (calculated for $C_{10}H_{14}NO$ 164)

mp 147 °C (decomposes)

***Compound 22a*: *N*-(4-(dimethylamino)-2,6-dimethylphenyl)-2,6-dimethylbenzamide. 22a** was prepared by the standard amide coupling procedure using 2,6-dimethyl benzoic acid (0.16 g, 1.04 mmol), 2,6-dimethyl-4-dimethylaminoaniline **2** (0.21 g, 1.25 mmol), triethylamine (0.126 g, 1.25 mmol) and a catalytic amount of 4-dimethylaminopyridine in CH_2Cl_2 (50 ml). Purification by column chromatography (CH_2Cl_2/methanol 100:0 to 99:1, first band) yielded a pale brown solid (0.12 g, 31%). Crystals of suitable quality for X-ray crystal structure determination were grown by slow evaporation petroleum ether/CH_2Cl_2.

^{1}H NMR ($CDCl_3$) δ

7.20 (t, 1H ***a2***)

7.05 (d, 2H, ***a1***)

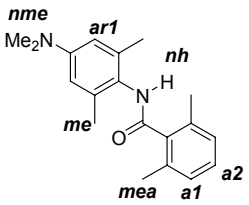
6.80 (br s, 1H, ***nh***)

6.50 (s, 2H, ***ar1***)

2.95 (s, 6H, ***nme***)

2.50 (s, 6H, ***mea***)

2.35 (s, 6H, ***me***)



^{13}C NMR ($CDCl_3$) δ169.0, 149.8, 137.9, 135.9, 134.6, 128.7, 127.7, 122.8, 112.6

FAB-MS *m/z*: 296 (M^+), (calculated for $C_{19}H_{24}N_2O$ 296)

mp 216-218 °C

***Compound 22b*: *N*-(4-(dimethylamino)-2,6-dimethylphenyl)-2,6-difluorobenzamide. 22b** was prepared by the standard amide coupling procedure using 2,6-difluorobenzoyl chloride (0.74 g, 4.2 mmol), *N,N*,2,6-tetramethylaniline dihydrochloride salt, **2** (0.996 g, 4.2 mmol) and triethylamine 1.30 g (12.6 mmol) in CH_2Cl_2 (40 ml). Purification by silica column chromatography CH2Cl2/methanol

(100:0 to 99:1) yielded a colourless solid 0.6 g (46%) of colourless solid. Crystals of suitable quality for X-ray structure determination were grown by slow evaporation from CH_2Cl_2.

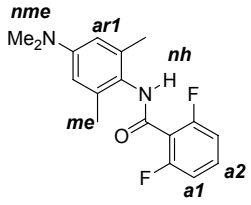
^{1}H NMR ($CDCl_3$) δ

7.13 (m, 4H, ***a1***, ***a2***, ***nh***)

7.00 (t, 2H, ***ar1***)

6.45 (s, 2H, ***ar1***)

2.95 (s, 6H, ***nme***)



^{19}F ($CDCl_3$) δ-113 ppm

HRMS-ES *m/z*: 304.1402 (MH^+), (calculated for $C_{17}H_{19}F_2N_2O$, 304.1387)

***Compound 22f*: *N*-(4-(dimethylamino)-2,6-dimethylphenyl)-2,3,4,5,6-pentafluorobenzamide. 22f** was prepared by the standard amide coupling procedure using pentafluorobenzoyl chloride (0.32 g, 1.42 mmol), 2,6-dimethyl-4-dimethylaminoaniline (0.21 g, 1.29 mmol) and triethylamine (0.14 g, 1.42 mmol) in CH_2Cl_2 (30 ml). Purification by column chromatography (CH_2Cl_2/methanol 100:0 to 99:1, first band) yielded a pale yellow solid 0.10 g, (22%). Crystals of suitable quality for X-ray structure determination were grown by slow evaporation from acetone/water.

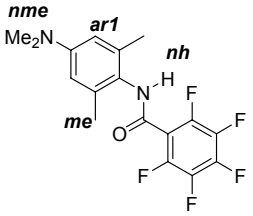
^{1}H NMR ($CDCl_3$) δ

7.00 (br s, 1H, ***nh***)

6.45 (s, 2H, ***a1***)

2.95 (s, 6H, ***nme***)

2.25 (s, 6H, ***me***)



^{13}C NMR ($CDCl_3$) δ156.6, 150.0, 135.9, 121.5, 111.9, 40.5, 18.6

^{19}F NMR ($CDCl_3$) δ-141, -151, -160

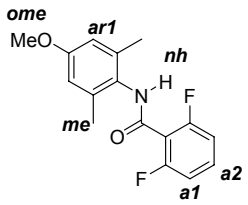
FAB-MS *m/z*: 358 (MH^+), (calculated for $C_{17}H_{16}F_5N_2O$, 358)

mp 205-207 °C

***Compound 23d*: 2,6-difluoro-*N*-(4-methoxy-2,6-dimethylphenyl)benzamide. 23d** was prepared by the standard amide coupling procedure using 2,6-difluorobenzoyl chloride (0.20 g, 1.15 mmol), 2,6-

dimethyl-4-methoxyaniline **4** (0.174 g, 1.15 mmol) and triethylamine 0.116 g (1.15 mmol) in CH_2Cl_2 (90 ml). Purification by silica column chromatography (CH_2Cl_2/methanol 100:0 to 97:3), yielded 0.6 g (46%) of colourless solid. Crystals of suitable quality for X-ray structure determination were grown by slow evaporation from CH_2Cl_2.

^{1}H NMR ($CDCl_3$) δ



7.40 (m, 1H, ***a2***)

7.02 (br s, 2H, ***nh***)

7.04-6.94 (m, 2H, ***a1***)

6.66 (s, 2H, ***ar1***)

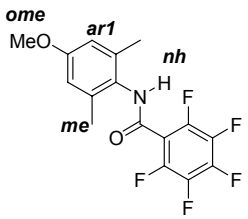
3.78 (s, 3H, ***ome***)

2.33 (s, 6H, ***me***)

HRMS-ES *m/z*: 292.1157 (MH^+), (calculated for $C_{16}H_{16}F_2NO_2$, 292.1149)

***Compound 23f*: 2,3,4,5,6-pentafluoro-*N*-(4-methoxy-2,6-dimethylphenyl)benzamide. 23f** was prepared by the standard amide coupling procedure using pentafluorobenzoyl chloride (0.33 g, 1.4 mmol), 2,6-dimethyl-4-methoxyaniline hydrochloride salt, 4 (0.25 g, 0.13 mmol), triethylamine 0.263 g (0.26 mmol) and a catalytic amount of 4-dimethylaminopyridine in CH_2Cl_2 (60 ml). Purification by silica column chromatography (CH_2Cl_2) yielded 0.38 g (85%) of colourless solid. Crystals of suitable quality for X-ray structure determination were grown by slow evaporation from CH_2Cl_2.

^{1}H NMR ($CDCl_3$) δ



7.11 (br s, 1H, ***nh***)

6.65 (s, 2H, ***ar1***)

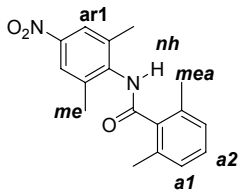
3.78 (s, 3H, ***ome***)

2.27 (s, 6H, ***me***)

HRMS-ES *m/z*: 346.0859 (MH^+), (calculated for $C_{16}H_{13}F_5NO_2$, 346.0866)

***Compound 24a*: *N*-(2,6-dimethyl-4-nitrophenyl)-2,6-dimethylbenzamide.** 2,6-dimethyl benzoic acid chloride (0.22 g, 1.51 mmol) and 2,6-dimethyl-4-nitroaniline **7** (0.25 g, 1.51 mmol) were refluxed in pyridine (10 ml) for 48 hours. The reaction mixture was washed repeatedly with 1 M HCl. The solvent was removed under reduced pressure and the product was purified by column chromatography (CH_2Cl_2/methanol 98:2) to yield a yellow solid 0.10 g (25%). Crystals of suitable quality for X-ray crystal structure determination were grown by slow evaporation petroleum ether/CH_2Cl_2.

^{1}H NMR ($CDCl_3$) δ



7.98 (s, 2H, ***ar1***)

7.30 (s, 1H, ***nh***)

7.19 (t, 1H, ***a2***)

7.05 (d, 2H, ***a1***)

2.45 (s, 6H, ***me***)

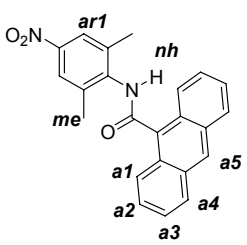
2.39 (s, 6H, ***mea***)

FAB MS *m/z*: 299 (MH^+), (calculated for $C_{17}H_{19}N_2O_3$, 299)

mp 230 °C (decomposes)

***Compound 24b*: *N*-(2,6-dimethyl-4-nitrophenyl)anthracene-9-carboxamide.** 9-anthracene-carboxylic acid chloride (0.40 g, 1.80 mmol) and 2,6-dimethyl-4-nitroaniline **7** (0.2 g, 1.2 mmol) in pyridine (10 ml) was refluxed for 24 hours. 2 M HCl was added to the cool reaction mixture and the organic products extracted with CH_2Cl_2. The combined organic extracts were washed with 1 M HCl and water. The organic phase was evaporated to dryness. The product was isolated by column chromatography (CH_2Cl_2/methanol 98:2) to yield a yellow solid 0.15 g (48%). Crystals of suitable quality for X-ray structure determination were grown by slow evaporation from CH_2Cl_2.

^{1}H NMR ($CDCl_3$) δ:



8.50 (s, 1H, ***a5***)

8.30 (d, 2H, ***a1***)

8.10 (d, 2H, ***a4***)

8.10 (s, 2H, ***ar1***)

7.65-7.45 (m, 4H, ***a2***,***a3***)

7.45 (br s, 1H, ***nh***)

2.60 (s, 6H, ***me***)

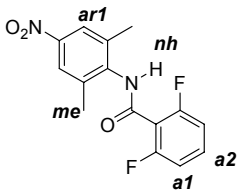
^{13}C NMR (DMSO-d_6) δ: 166.8, 145.4, 141.4, 137.2, 132.3, 130.7, 128.7, 128.0, 127.5, 127.0, 125.7, 124.9, 122.9, 19.3

FAB MS *m/z*: 370 (M^+) $C_{23}H_{18}N_2O_3$ requires 370.

mp >300 °C

***Compound 24d*: *N*-(2,6-dimethyl-4-nitrophenyl)-2,6-difluorobenzamide. 24d** was prepared by the standard amide coupling procedure using 2,6-difluorobenzoyl chloride (0.481 g, 2.2 mmol), 2,6-dimethyl-4-nitroaniline, **7** (0.46 g, 2.1 mmol) and triethylamine (0.21 g, 2.1 mmol) in CH_2Cl_2 (40 ml). After 16 hours, a further 100 µl of 2,6-difluorobenzoyl chloride was added and the reaction refluxed gently for 3 hours. Purification by silica column chromatography (CH_2Cl_2), yielded 0.2 g (32%) of colourless solid. Crystals of suitable quality for X-ray structure determination were grown by slow evaporation from ethanol.

^{1}H NMR ($CDCl_3$) δ



8.02 (s, 2H, ***ar1***)

7.46 (m, 1H, ***a2***)

7.25 (s, 1H, ***nh***)

7.04 (t, 2H, ***a1***)

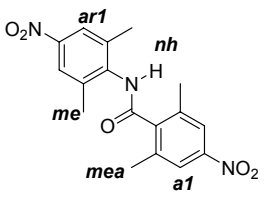
2.45 (s, 6H, ***me***)

HRMS-ES *m/z*: 307.0892 (MH^+), (calculated for $C_{15}H_{13}N_2O_3F_2$ 307.0894)

***Compound 24e*: *N*-(2,6-dimethyl-4-nitrophenyl)-2,6-dimethyl-4-nitrobenzamide. 24e** was prepared by standard amide coupling procedure using 2,6-dimethyl-4-nitrobenzoic acid (0.2 g, 1.0 mmol), 2,6-dimethyl-4-nitroaniline **7** (0.16 g, 1.0 mmol), triethylamine (0.2 ml, 1.5 mmol), and a catalytic amount of 4-dimethylaminopyridine in CH_2Cl_2 (50 ml). Purification by silica column chromatography (CH_2Cl_2)

yielded an orange solid 0.03 g (10%). Crystals of suitable quality for X-ray structure determination were grown by slow evaporation from ethanol.

^{1}H NMR (DMSO-d_6) δ



7.29 (s, 2H, ***ar1***)

6.63 (s, 2H, ***a1***)

2.45 (s, 6H, ***me***)

2.17 (s, 6H, ***a1***)

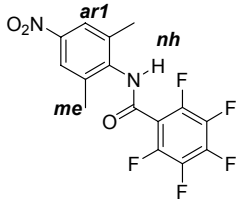
2.45 (s, 6H, ***mea***)

^{13}C NMR (DMSO-d_6) δ: 165.71, 147.10, 145.42, 140.61, 139.15, 137.14, 136.56, 122.91, 122.25, 19.47, 19.15

HRMS-CI *m/z*: 343.118 (M^+), (calculated for $C_{17}H_{17}N_3O_5$, 343.117)

***Compound 24f*: *N*-(2,6-dimethyl-4-nitrophenyl)-2,3,4,5,6-pentafluorobenzamide. 24f** was prepared by the standard amide coupling procedure using pentafluorobenzoyl chloride (0.16 g, 0.69 mmol), 2,6-dimethyl-4-nitroaniline **7** (0.102 g, 0.61 mmol), 0.062 g (0.61 mmol) triethylamine and a catalytic amount of 4-dimethylaminopyridine in CH_2Cl_2 (20 ml). Purification by silica column chromatography (CH_2Cl_2), yielded a colourless solid 0.06 g (27%). Crystals of suitable quality for X-ray structure determination were grown by slow evaporation from CH_2Cl_2.

^{1}H NMR ($CDCl_3$) δ



8.04 (s, 2H, ***ar1***)

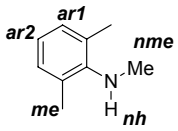
7.31 (br s, 1H, ***nh***)

2.43 (s, 6H, ***me***)

HRMS-ES *m/z*: 361.0596 (MH^+), (calculated for $C_{15}H_{10}N_2O_3F_5$, 361.0612)

***Compound 25*: *N*,2,6-trimethylbenzenamine.** 2,6-dimethylaniline (0.5 g, 4.1 mmol) was stirred with methyliodide (0.59 g, 4.1 mmol) until a solid mass had formed. The crude product was dissolved in CH_2Cl_2 (40 ml) and washed with 1 M NaOH solution (40 ml). The organic solvent was removed under vacuum to yield a pink oil 0.55 g (99 %). The product was used without further purification.

^{1}H NMR ($CDCl_3$) δ



7.12 (d, 2H, ***ar1***)

6.68 (t, 1H, ***ar2***)

3.16 (br s, 1H, ***nh***)

2.85 (s, 3H, ***nme***)

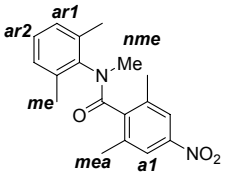
2.34 (s, 6H, ***me***)

^{13}C NMR ($CDCl_3$) δ: 147.6, 129.1, 128.9, 121.8, 35.4, 18.4

HRMS-EI *m/z*: 135.105435 (M^+), (calculated for $C_9H_{13}N$, 135.104800)

***Compound 26e*: *N*-(2,6-dimethylphenyl)-*N*,2,6-trimethyl-4-nitrobenzamide. 26e** was prepared by the standard amide coupling procedure using 2,6-dimethyl-4-nitrobenzoic acid (0.08 g, 0.4 mmol), *N*,2,6-trimethylbenzenamine **25** (0.05 g, 0.4 mmol), triethylamine (0.06 ml, 0.4 mmol), in CH_2Cl_2 (10 ml). Purification by preparative TLC (CH_2Cl_2) yielded a colourless solid 0.01 g (8%). Crystals of suitable quality for X-ray structure determination were grown by slow evaporation from ethanol.

^{1}H NMR ($CDCl_3$) δ



7.97 (s, 2H, ***a1***)

7.25-7.12 (m, 3H, ***ar1***, ***ar2***)

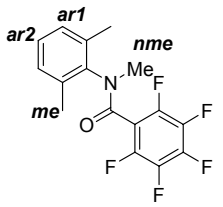
3.02 (s, 3H, ***nme***)

2.59 (s, 6H, ***mea***)

2.39 (s, 6H, ***me***)

***Compound 26f*: *N*-(2,6-dimethylphenyl)-2,3,4,5,6-pentafluoro-*N*-methylbenzamide. 26f** was prepared by the standard amide coupling procedure using pentafluorobenzoyl chloride (0.64 g, 2.8 mmol), *N*,2,6-trimethylbenzenamine **25** (0.34 g, 2.5 mmol), triethylamine (0.35 ml, 2.5 mmol), in CH_2Cl_2 (10 ml). Purification by silica column chromatography (CH_2Cl_2) yielded a colourless solid 0.56 g (68%). Crystals of suitable quality for X-ray structure determination were grown by slow evaporation from ethanol.

^{1}H NMR ($CDCl_3$) δ



7.25-7.05 (s, 70% 3H, ***ar1***, ***ar2***)

7.05-6.90 (s, 30% 3H, ***ar1†***, ***ar2†***)

3.30 (s, 30% 3H, ***nme†***)

3.08 (s, 70% 3H, ***nme***)

2.24 (s, 70% 6H, ***me***)

2.18 (s, 30% 6H, ***me†***)

^{19}F NMR ($CDCl_3$) δ: -137***†***, -141, -152, -153***†***, -160, -162***†*** ppm

HRMS-ES *m/z*: 329.0855 (M^+), (calculated for $C_{16}H_{12}F_5NO$, 329.0839)

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