Electronic Supplementary Material (ESI) for RSC Advances.

Supporting Information

Design Synthesis and Conformational Analyses of Bifacial Benzamide Based Foldamers

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Content

1. General experimental considerations

All commercial solvents were purchased and used without further purification unless stated otherwise. Commercially available starting materials and reagents were obtained from Sigma-Aldrich, Alfa Aesar or Fisher Scientific. Amino acid derivatives, coupling reagents and resins were purchased from Novabiochem. Purification by column chromatography was carried out using silica gel (40-63 µm mesh size). Analytical thin layer chromatography (TLC) was conducted using Merck 0.2 mm silica gel 60 F_{254} pre-coated aluminium sheets. ^{1}H and ^{13}C NMR spectra were measured using a Bruker DRX 500 series spectrometer. Chemical shifts are expressed as parts per million using solvent as internal standard and coupling constants (*J*) are reported to the nearest 0.1 Hz. The following abbreviations are used: s for singlet, d for doublet, t for triplet, q for quartet and m for multiplet. High resolution mass spectrometry (HRMS) was carried out by staff in the School of Chemistry using either a Waters GCT Premier mass spectrometer, using electron impact (EI), or a Bruker MicroTOF mass spectrometer, using electron spray ionisation (ESI). High resolution mass spectrometry (HRMS) was also performed using the open access Bruker Maxis impact mass spectrometer, with electro-spray ionisation (ESI). Infra-red spectra were recorded using a Perkin-Elmer Spectrum One FT-IR spectrophotometer. Elemental combustion analyses were performed by the School of Chemistry Microanalysis facility using a Carlo Erba Elemental Analyser MOD 1106 instrument and the found composition is reported to the nearest 0.05%. LC-MS experiments were run on a Bruker Daltonics HTCUltra^{TM} series spectrometer and were run through a C18 column on an methanol/water gradient (0-95% acetonitrile over 3 minutes). Analytical HPLC experiments were run on an Angilent 1290 Infinity LC series spectrometer. Mass-directed preparative HPLC experiments were run using an Angilent 1260 Infinity Preparative system spectrometer and analysed by a 6120 Quadrupole LC/MS detector.

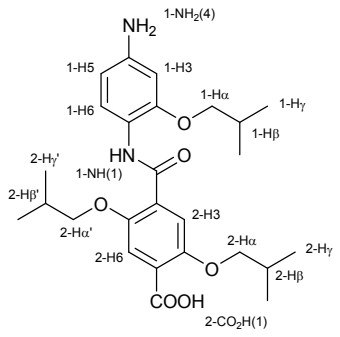
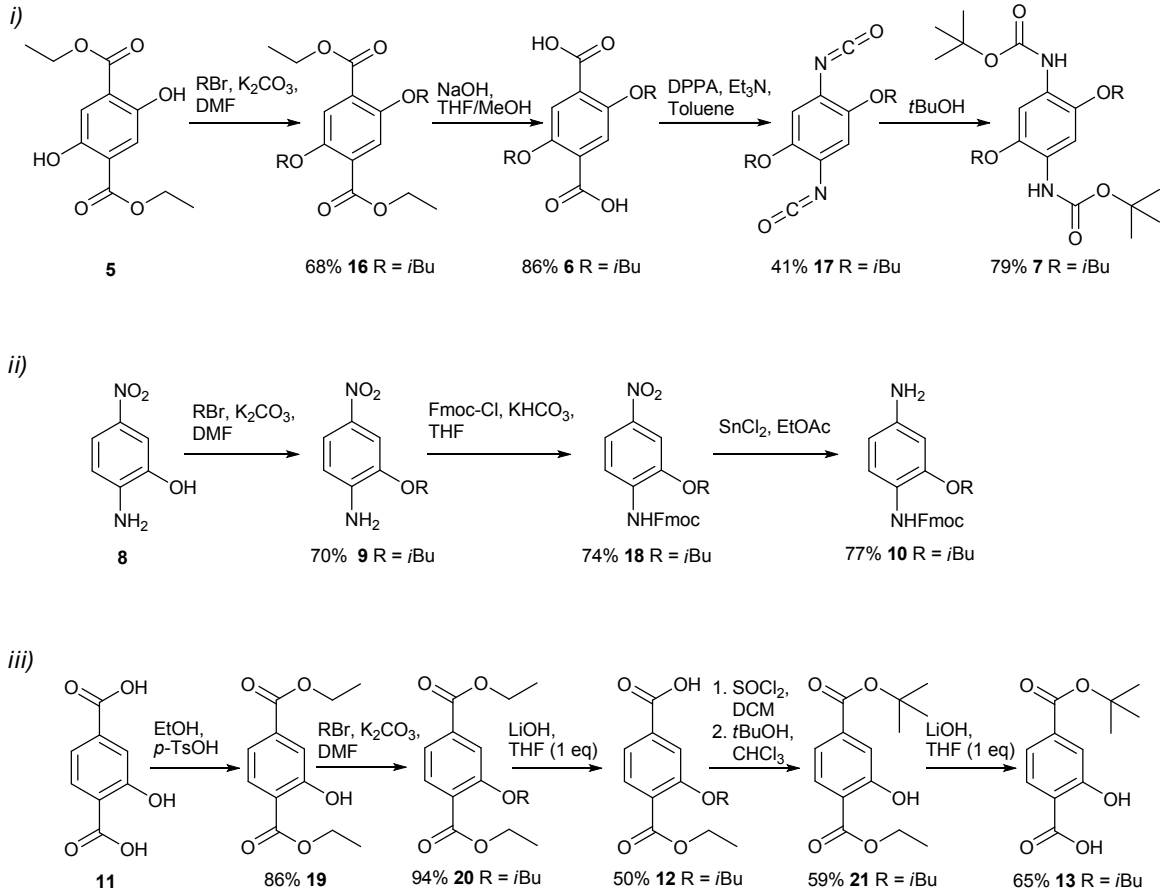


Figure S1. Example of compound assignment.

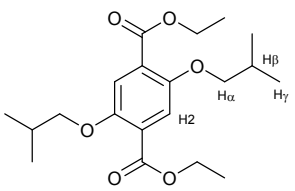
Assignment of the oligoamide compounds is as follows; naming proceeds from N to C terminus where each monomer residue is assigned a number with respect to its position on the chain. Aromatic rings are assigned to the lowest number for the substituent in the monomer intermediate. Side-chain assignment follows a peptide nomenclature pattern in which the carbon attached to the alkoxy oxygen is assigned as Cα. An example is given in **Figure S1**.

2. Monomer Syntheses and Characterization



Scheme S1. Synthetic route to the monomers (intermediate compounds are shown and numbered).

Diethyl 2,5-diisobutoxyterephthalate (16)

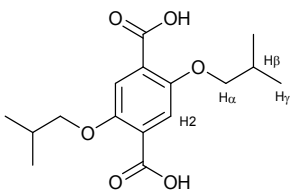


16

To a stirred solution of diethyl 2,5-dihydroxyterephthalate **5** (2.02 g, 7.95 mmol) and potassium carbonate (5.00 g, 36.2 mmol) in dimethylformamide (50 mL), isobutyl bromide (2.12 mL, 18.9 mmol) was added and the resulting suspension stirred at 90 °C under a nitrogen atmosphere. After 18 h the reaction was shown to be incomplete, so a further aliquot of isobutyl bromide (1 mL, 8.91 mmol) was added. After 40 h stirring, the resulting suspension was poured into water and extracted with ethyl acetate (3 × 60 mL). The combined organic fractions were washed with water (2 × 140 mL) and brine (4 × 140 mL), then dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting oil purified by column chromatography (*Stationary Phase*: Silica; *Mobile Phase*: dichloromethane) to afford the desired product **16** (1.98 g, 5.41 mmol, 68%) as a colourless solid; R_F: 0.47 (dichloromethane); δ_H (500 MHz, $CDCl_3$) 7.34 (s, 2 H, *H*2), 4.39 (q, *J* = 7.5 Hz, 4 H, CO_2CH_2), 3.78 (d, *J* = 6.5 Hz, 4 H, *H*α), 2.14-2.09 (m, 2

H, *H*β), 1.40 (t, *J* = 7.5 Hz, 6 H, $CO_2CH_2CH_3$), 1.05 (d, *J* = 6.5 Hz, 12 H, *H*γ); δ_C (125 MHz, $CDCl_3$) 166.3, 151.7, 124.6, 116.4, 76.0, 61.2, 28.4, 19.2, 14.3; (ν_{max}/cm^{-1} (solid state) = 3069, 2953, 2496, 1694, 1422, 1216, 1022, 781; ESI-HRMS: *m/z* $[M+Na]^+$ 389.1953. $C_{20}H_{30}NaO_6$ requires $[M+Na]^+$ 389.1935; Found: C, 65.55; H, 8.30; $C_{20}H_{30}O_6$ requires: C, 65.55; H, 8.25 %.

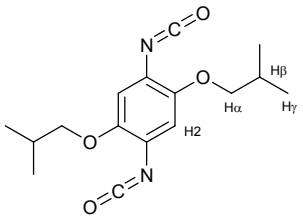
2,5-Diisobutoxyterephthalic acid (6)



6

Diethyl 2,5-diisobutoxyterephthalate **16** (501 mg, 1.37 mmol) was dissolved in a 1:1 mixture of methanol : tetrahydrofuran (30 mL) and a 10% sodium hydroxide solution (5 mL) was added, the resulting solution was stirred at room temperature overnight. The organic solvents were removed under reduced pressure and the remaining solution was poured into water (50 mL) and acidified *via* addition of hydrochloric acid (conc) to pH 1. The resulting suspension was extracted with dichloromethane (4 × 50 mL) and the organic fractions were combined and washed with water (2 × 150 mL), followed by brine (150 mL), and dried over $MgSO_4$. The organic solvents were evaporated to yield the target material **6** (365 mg, 1.18 mmol, 86%) as a colourless solid; δ_H (500 MHz, $CDCl_3$) 11.12 (s, broad, 2 H, CO_2H), 7.89 (s, 2 H, *H*2), 4.09 (d, *J* = 6.5 Hz, 4 H, *H*α), 2.27-2.22 (m, 2 H, *H*β), 1.11 (d, *J* = 6.5 Hz, 12 H, *H*γ); δ_C (125 MHz, $CDCl_3$) 164.1, 151.8, 122.7, 117.4, 77.4, 28.1, 19.1; ν_{max}/cm^{-1} (solid state) = 2970, 1737, 1366, 1443, 1227, 1032, 760; ESI-HRMS found *m/z* 309.1360 $[M-H]^-$ $C_{16}H_{21}O_6$ requires 309.1344; Found: C, 62.20; H, 7.10; $C_{16}H_{22}O_6$ requires: C, 61.92; H, 7.15 %.

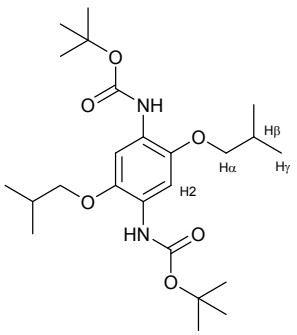
1,4-Diisobutoxy-2,5-diisocyanatobenzene (17)



17

To a stirred solution of 2,5-diisobutoxyterephthalic acid **6** (125 mg, 0.40 mmol) in anhydrous toluene (30 mL), triethylamine (125 µL, 0.90 mmol) followed by diphenylphosphoryl azide (163 µL, 0.76 mmol) were added and the resulting solution was stirred for 2 h at room temperature under a nitrogen atmosphere, then the reaction mixture was left overnight without stirring. Ethyl acetate was added and the resulting solution was washed with a saturated sodium bicarbonate solution and brine before being dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting dark purple oil purified by column chromatography (*Stationary Phase*: Silica; *Mobile Phase*: ethyl acetate/hexane, 3:1) to afford the desired product **17** (50 mg, 0.41 mmol, 41%) as a dark solid; δ_H (500 MHz, $CDCl_3$) 6.55 (s, 2 H, *H2*), 3.74 (d, *J* = 6.5 Hz, 4 H, *H*α), 2.18-2.12 (m, 2 H, *H*β), 1.05 (d, *J* = 7.0 Hz, 12 H, *H*γ); δ_C (125 MHz, $CDCl_3$) 147.0, 130.9, 120.8, 107.5, 75.8, 28.2, 19.2; ν_{max}/cm^{-1} (solid state) = 2957, 2254 (N=C=O stretch), 1540, 1450, 1220, 859.

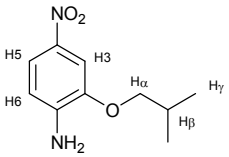
tert-Butyl 2,5-diisobutoxy-1,4-phenylenedicarbamate (7)



7

A solution of 1,4-diisobutoxy-2,5-diisocyanatobenzene **17** (45 mg, 0.15 mmol) was dissolved in anhydrous *tert*-butanol (10 mL) and heated to reflux overnight under a nitrogen atmosphere. The solvent was evaporated under reduced pressure and the resulting oil purified by column chromatography (*Stationary Phase*: Silica; *Mobile Phase*: ethyl acetate/hexane, 1:3) to afford the desired product **7** (53 mg, 0.12 mmol, 79%) as a brown solid; δ_H (500 MHz, $CDCl_3$) 7.75 (s, 2 H, *H*2), 6.98 (s, 2 H, N*H*), 3.78 (d, *J* = 6.5 Hz, 4 H, *H*α), 2.13-2.05 (m, 2 H, *H*β), 1.53 (s, 18 H, $NHCO_2C(CH_3)_3$), 1.04 (d, *J* = 6.5 Hz, 12 H, *H*γ); δ_C (125 MHz, $CDCl_3$) 152.9, 140.9, 122.6, 103.3, 80.1, 75.8, 28.4, 28.4 19.4; ν_{max}/cm^{-1} (solid state) = 3442, 2963, 1724, 1541, 1428, 1232, 1153, 1052, 861; ESI-HRMS found *m/z* 453.2970 $[M+H]^+$ $C_{24}H_{41}N_2O_6$ requires 453.2959.

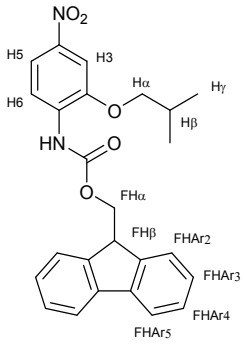
2-Isobutoxy-4-nitroaniline (9)



9

A solution of 2-amino-5-nitrophenol **8** (499 mg, 3.25 mmol) and potassium carbonate (1.12 g, 8.13 mmol) in dimethylformamide (15 mL) was stirred at 50 °C for 1 h. Isobutyl bromide (330 µL, 2.93 mmol) was added dropwise and the reaction was allowed to stir overnight, leading to complete conversion. The resulting suspension was poured in water and extracted with ethyl acetate (3 × 100 ml). The combined organic fractions were washed with water (3 × 100 ml), brine (5 × 100 ml), and then dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the resulting orange solid was dissolved in chloroform, filtered and purified by column chromatography (*Stationary Phase*: Silica; *Mobile Phase*: ethyl acetate) to afford the desired product **9** (430 mg, 2.05 mmol, 70%) as an orange solid; R_F: 0.71 (ethyl acetate); δ_H (500 MHz, $CDCl_3$) 7.81 (dd, *J* = 2.0, 8.8 Hz, 1 H, *H*5), 7.66 (d, *J* = 2.0 Hz, 1 H, *H*3), 6.65 (d, *J* = 8.8 Hz, 1 H, *H*6), 4.54 (s, broad, 2 H, NH_2), 3.86 (d, *J* = 6.5 Hz, 2 H, *H*α), 2.21-2.13 (m, 1 H, *H*β), 1.08 (d, *J* = 7.0 Hz, 6 H, *H*γ); δ_C (125 MHz, $CDCl_3$) 145.0, 143.3, 138.8, 119.0, 111.8, 106.7, 75.1, 28.2, 19.3; ν_{max}/cm^{-1} (solid state) = 3505, 3392, 2915, 1615, 1312, 1235, 745; ESI-HRMS found *m/z* 211.1078 $[M+H]^+$ $C_{10}H_{15}N_2O_3$ requires 211.1077; Found: C, 57.15; H, 6.55; N, 13.45; $C_{10}H_{14}N_2O_3$ requires: C, 57.13; H, 6.71; N, 13.33 %.

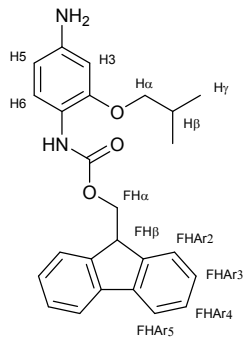
(9H-Fluoren-9-yl)methyl 2-isobutoxy-4-nitrophenylcarbamate (18)



18

A solution of 2-isobutoxy-4-nitroaniline **9** (505 mg, 2.40 mmol) and sodium bicarbonate (425 mg, 5.06 mmol) in tetrahydrofuran (50 mL) was stirred at reflux under a nitrogen atmosphere. A solution of 1-(9-fluorenyl)methylchloroformate (952 mg, 3.68 mmol) in tetrahydrofuran (10 mL) was added dropwise and the reaction allowed to stir at reflux overnight. The sodium bicarbonate was removed *via* hot filtration and the reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and the resulting precipitate collected *via* filtration to afford the desired product **18** (761 mg, 1.76 mmol, 74%) as a colourless solid; R_F: 0.86 (dichloromethane); δ_H (500 MHz, $CDCl_3$) 8.18 (s, broad, 1 H, N*H*), 7.89 (d, *J* = 8.0 Hz, 1 H, *H*6), 7.80 (d, *J* = 7.5 Hz, 2 H, F*H*Ar5), 7.74 (m, 1 H, *H*5), 7.62 (d, *J* = 7.5 Hz, 2 H, F*H*Ar2), 7.53 (s, 1 H, *H*3), 7.45-7.42 (m, 2 H, F*H*Ar4), 7.36-7.33 (m, 2 H, F*H*Ar3), 4.56 (d, *J* = 6.8 Hz, 2 H, F*H*α), 4.34 (t, *J* = 6.8 Hz, 1 H, F*H*β), 3.93 (d, *J* = 6.5 Hz, 2 H, *H*α), 2.28-2.20 (m, 1 H, *H*β), 1.12 (d, *J* = 7.0 Hz, 6 H, *H*γ); δ_C (125 MHz, $CDCl_3$) 152.7, 146.5, 143.5, 142.7, 141.4, 133.9, 128.0, 127.2, 125.0, 120.2, 117.6, 116.8, 106.2, 75.7, 67.7, 47.0, 28.1, 19.2; ν_{max}/cm^{-1} (solid state) = 3095, 2958, 1713, 1587, 1504, 1344, 1246, 734; ESI-HRMS found *m/z* 433.1767 $[M+H]^+$ $C_{25}H_{25}N_2O_5$ requires 433.1758; Found: C, 69.35; H, 5.50; N, 6.35; $C_{25}H_{24}N_2O_5$ requires: C, 69.43; H, 5.59; N, 6.48 %.

(9H-Fluoren-9-yl)methyl 4-amino-2-isobutoxyphenylcarbamate (10)

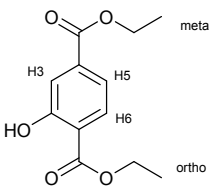


10

To a stirred solution of (9H-fluoren-9-yl)methyl 2-isobutoxy-4-nitrophenylcarbamate **18** (528 mg, 1.22 mmol) in ethyl acetate (15 mL) and tetrahydrofuran (3 mL), tin(II) chloride dihydrate (1.80 g, 7.04 mmol) was added and the resulting mixture stirred at 50 °C overnight under a nitrogen atmosphere. The reaction mixture was allowed to cool and poured over ice. The solution was basified to pH 8 by addition of a saturated sodium bicarbonate solution and the resulting basic mixture was allowed to stir for an hour. The aqueous mixture was extracted with ethyl acetate (3 × 100 mL) and the organic fractions were combined, washed with water (3 × 250 mL) and brine (2 × 250 mL) before being dried over $MgSO_4$. The organic solvents were evaporated and the resulting dark solid purified by column chromatography (*Stationary Phase*: Silica; *Mobile Phase*: dichloromethane to 1:1 dicholomethane / ethyl acetate) to afford the desired product **10** (378 mg, 0.94 mmol, 77%) as a purple solid; δ_H (500 MHz, $CDCl_3$) 7.80-7.78 (m, 3 H, F*H*Ar5 and *H*6), 7.64 (d, *J* = 5.5 Hz, 2 H, F*H*Ar2), 7.44-7.41 (m, 2 H, F*H*Ar4), 7.34-7.31 (m, 2 H, F*H*Ar3), 7.02 (s, broad, 1 H, N*H*), 6.32-6.29 (m, 2 H, *H*5 and *H*3), 4.46 (d, *J* = 6.8 Hz, 2 H, F*H*α), 4.33 (t, *J* = 6.8 Hz, 1 H, F*H*β), 3.76 (d, *J* = 6.5 Hz, 2 H, *H*α), 3.61 (s, broad, 2 H,

NH_2), 2.19-2.14 (m, 1 H, *H*β), 1.08 (d, *J* = 6.5 Hz, 6 H, *H*γ); δ_C (125 MHz, $CDCl_3$) 153.7, 148.9, 144.0, 142.8, 141.4, 127.7, 127.1, 125.2, 120.4, 120.0, 119.1, 107.1, 99.8, 74.9, 67.0, 47.2, 28.3, 19.3; ν_{max}/cm^{-1} (solid state) = 3312, 2960, 1705, 1534, 1448, 1224, 738; ESI-HRMS found *m/z* 403.2019 $[M+H]^+$ $C_{25}H_{27}N_2O_3$ requires 403.2016; Found: C, 74.20; H, 6.40; N, 6.80; $C_{25}H_{26}N_2O_3$ requires: C, 74.60; H, 6.51; N, 6.96 %.

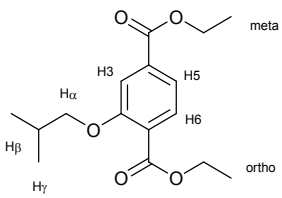
Diethyl 2-hydroxyterephthalate (19)



19

p-Toluenesulfonic acid (200 mg, 1.05 mmol) was added to a stirred solution of 2-hydroxyterephthalic acid **11** (2.00 g, 10.98 mmol) in anhydrous ethanol (125 mL) and the resulting solution refluxed at 90 °C under a nitrogen atmosphere. After 3 days the reaction was incomplete, so a further portion of *p*-toluenesulfonic acid (50 mg, 0.26 mmol) and anhydrous ethanol (50 mL) were added. After 3 more days, the organic solvent was evaporated under reduced pressure, the solid residue was redisolved in water and the resulting mixture basified with a saturated solution of $NaHCO_3$ to pH 8. The solution was extracted with ethyl acetate (3 × 60 mL); the combined organic fractions were washed with water (2 × 60 mL) and brine (1 × 60 mL) before being dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the desired product **19** (2.25 g, 9.45 mmol, 86%) as light brown oil; δ_H (500 MHz, $CDCl_3$) 10.85 (s, 1 H, O*H*), 7.91 (d, *J* = 8.5 Hz, 1 H, *H*6), 7.65 (d, *J* = 1.5 Hz, 1 H, *H*3), 7.53 dd, *J* = 1.5, 8.5 Hz , 1 H, *H*5), 4.45 (q, *J* = 7.0 Hz, 2 H, CO_2CH_2 *meta*), 4.39 (q, *J* = 7.0 Hz, 2 H, CO_2CH_2 *ortho*), 1.45 (t, *J* = 7.0 Hz, 3 H, $CO_2CH_2CH_3$ *meta*), 1.41 (t, *J* = 7.0 Hz, 3 H, $CO_2CH_2CH_3$ *ortho*); δ_C (125 MHz, $CDCl_3$) 169.6, 165.6, 161.4, 136.7, 130.0, 119.6, 118.8, 115.9, 61.9, 61.5, 14.2, 14.2; ν_{max}/cm^{-1} (solid state) = 3139, 2983, 1722, 1675, 1294, 1203, 1099, 754; ESI-HRMS: *m/z* $[M-H]^-$ 237.0727. $C_{12}H_{13}O_5$ requires $[M-H]^-$ 237.0768.

Diethyl 2-isobutoxyterephthalate (20)

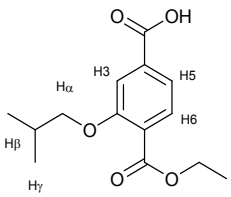


20

Isobutyl bromide (566 µL, 5.04 mmol) was added to a stirred solution of diethyl 2-hydroxyterephthalate **19** (1.00 g, 4.20 mmol) and potassium carbonate (1.28 g, 9.24 mmol) in dimethylformamide (20 mL), and the resulting suspension stirred at 50 °C overnight under a nitrogen atmosphere. The reaction was incomplete, so a further aliquot of isobutyl bromide (200 µL, 1.78 mmol) was added. After 15 h stirring, the resulting suspension was poured in water and extracted with ethyl acetate (3 × 60 mL); the combined organic fractions were washed with water (2 × 140 mL) and brine (4 × 140 mL) before being dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the desired product **20** (1.17 g, 3.98 mmol, 94%) as a yellow oil**;** δ_H (500 MHz, $CDCl_3$) 7.78 (d, *J* = 8.0 Hz, 1 H, *H*6), 7.62 (dd, *J* = 1.5, 8.0 Hz , 1 H, *H*5),

7.59 (d, *J* = 1.5 Hz, 1 H, *H*3), 4.40 (q, *J* = 7.0 Hz, 2 H, CO_2CH_2 *meta*), 4.39 (q, *J* = 7.0 Hz, 2 H, CO_2CH_2 *ortho*), 3.87 (d, *J* = 6.5 Hz, 2 H, *H*α), 2.20-2.12 (m, 1 H, *H*β), 1.42 (t, *J* = 7.0 Hz, 3 H, $CO_2CH_2CH_3$ *meta*), 1.40 (t, *J* = 7.0 Hz, 3 H, $CO_2CH_2CH_3$ *ortho*), 1.08 (d, *J* = 6.5 Hz, 6 H, *H*γ); δ_C (125 MHz, $CDCl_3$) 166.3, 165.9, 158.1, 134.5, 131.2, 124.9, 120.9, 113.6, 75.3, 61.4, 61.2, 28.4, 19.2, 14.3 (2 C); (ESI-HRMS: *m/z* $[M+H]^+$ 295.1538. $C_{16}H_{23}O_5$ requires $[M+H]^+$ 295.1540.

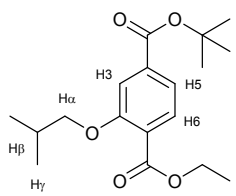
4-(Ethoxycarbonyl)-3-isobutoxybenzoic acid (12)



12

Lithium hydroxide monohydrate (286 mg, 6.82 mmol) was dissolved in the minimum quantity of water and added to a solution of diethyl 2-isobutoxyterephthalate **20** (2.23 g, 7.58 mmol) in tetrahydrofuran (50 mL). The reaction was stirred at room temperature for 18 h; further portions of lithium hydroxide monohydrate were added to achieve completion. The mixture was acidified with a 10% solution of potassium bisulphate to pH 4 and was extracted with ethyl acetate (3 × 60 mL); the combined organic fractions were washed with water (2 × 60 mL) and brine (1 × 60 mL) before being dried over $MgSO_4$. The solvent was removed under reduced pressure and the solid residue subjected to high pressure liquid chromatography [(50-95% MeCN:Water and 0.01% Formic acid) t = 8 min, XBridge Prep C18 column] to isolate the title compound **12** (1.00 g, 3.76 mmol, 50%) as a colourless solid; δ_H (500 MHz, $CDCl_3$) 7.81 (d, *J* = 8.0 Hz, 1 H, *H*6), 7.71 (dd, *J* = 1.0, 8.0 Hz , 1 H, *H*5), 7.59 (d, *J* = 1.0 Hz, 1 H, *H*3), 4.40 (q, *J* = 7.0 Hz, 2 H, CO_2CH_2), 3.87 (d, *J* = 6.5 Hz, 2 H, *H*α), 2.21-2.13 (m, 1 H, *H*β), 1.41 (t, *J* = 7.0 Hz, 3 H, $CO_2CH_2CH_3$), 1.08 (d, *J* = 7.0 Hz, 6 H, *H*γ); δ_C (125 MHz, $CDCl_3$) 171.1, 166.3, 158.1, 133.1, 131.3, 125.9, 121.6, 114.0, 75.3, 61.3, 28.4, 19.2, 14.3; (ν_{max}/cm^{-1} (solid state) = 2979, 2952, 2872, 1718, 1687, 1243, 1080, 764; ESI-HRMS: *m/z* $[M-H]^-$ 265.1085. $C_{14}H_{17}O_5$ requires $[M-H]^-$ 265.1081.

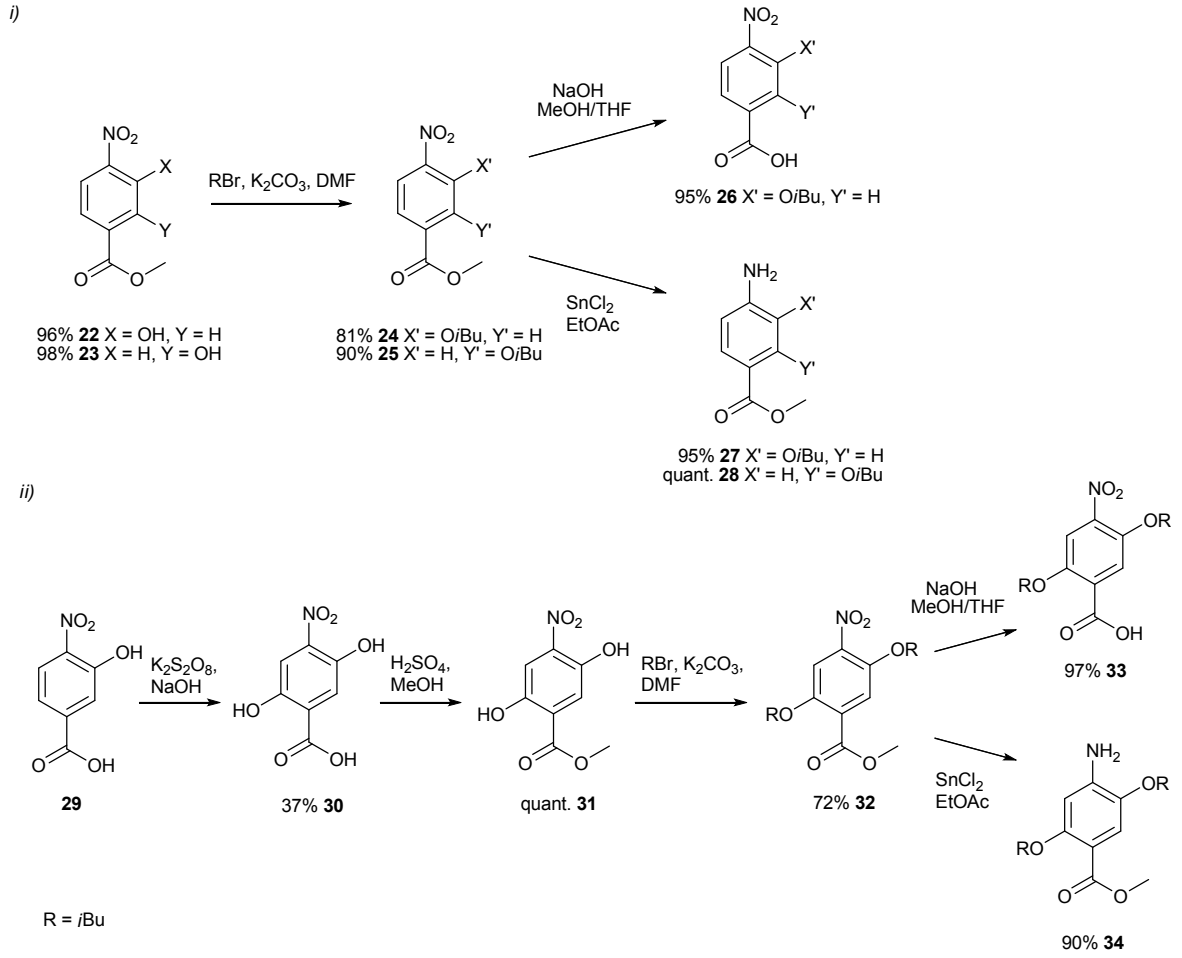
4-tert-butyl 1-ethyl 2-isobutoxyterephthalate (21)



21

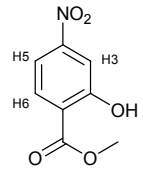
Under nitrogen atmosphere, a 20% solution of Ghosez's reagent in anhydrous chloroform (1.12 mL, 1.70 mmol) was added to a solution of 4-(ethoxycarbonyl)-3-isobutoxybenzoic acid **12** (300 mg, 1.13 mmol) in anhydrous chloroform (30 mL). The reaction was stirred at 50 °C for 3 h before *tert*-butanol (540 µL, 5.68 mmol) was added. The resulting mixture was stirred at 50 °C overnight. The organic solvents were evaporated and the resulting oil purified by column chromatography (*Stationary Phase*: Silica; *Mobile Phase*: hexane / chloroform / ethyl acetate, 75:25:5) to afford the desired product **21** (215 mg, 0.67 mmol, 59%) as a yellow oil; δ_H (500 MHz, $CDCl_3$) 7.76 (d, *J* = 7.5 Hz, 1 H, *H*6), 7.56 (d, *J* = 1.0 Hz, 1 H, *H*3), 7.55 (dd, *J* = 1.0, 7.5 Hz , 1 H, *H*5), 4.38 (q, *J* = 7.0 Hz, 2 H, CO_2CH_2), 3.85 (d, *J* = 6.5 Hz, 2 H, *H*α), 2.11-2.19 (m, 1 H, *H*β), 1.61 (s, 9

H, $CO_2C(CH_3)_3$), 1.39 (t, *J* = 7.0 Hz, 3 H, $CO_2CH_2CH_3$), 1.06 (d, *J* = 6.5 Hz, 6 H, *Hγ*); δ_C (125 MHz, $CDCl_3$) 166.4, 165.1, 158.2, 136.4, 131.1, 124.4, 120.7, 113.5, 81.7, 75.2, 61.1, 28.3, 28.1, 19.2, 14.3; (ν_{max}/cm^{-1} (solid state) = 2960, 2931, 2882, 1713, 1367, 1241, 1145, 962, 745; ESI-HRMS: *m/z* $[M+H]^+$ 323.1855. $C_{18}H_{27}O_5$ requires $[M+H]^+$ 323.1853.



Scheme S2. Synthetic route to the monomers (intermediate compounds are shown and numbered).

Methyl-2-hydroxy-4-nitrobenzoate (23)

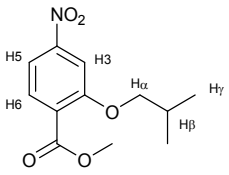


23

A stirred solution of 2-hydroxy-4-nitro benzoic acid (10.0 g, 54.6 mmol) and concentrated sulfuric acid (1.0 mL, 18.8 mmol) in anhydrous methanol (200 mL) under an argon atmosphere was heated at reflux. After 96 h stirring, the reaction mixture was concentrated to leave a pale yellow solid, which was poured into ethyl acetate, washed with water (2 × 100 mL) and the organic layer was dried over anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure to leave the pure product **23** (10.6 g, 53.8 mmol, 98%) as a pale yellow powder; R_F 0.51 (30% ethyl acetate in cyclohexane); δ_H (300 MHz, CD_3OD) 7.97 (d, *J* = 5.4 Hz, 1H, *H*6), 7.65 (s, 1H, *H*3), 7.62 (d, *J* = 5.4 Hz, 1H, *H*5), 3.91 (s, 3H, CO_2CH_3); δ_C (75 MHz, $CDCl_3$) 170.7, 163.2, 153.8, 133.09, 119.36, 114.9, 113.8, 53.9; ν_{max}/cm^{-1} (solid state) 3627, 2965, 1733,

1661, 1665, 1558, 1440, 1387, 1237; ESI-HRMS found *m/z* 196.0253 $[M-H]^-$ $C_8H_6NO_5$ requires 197.0324; Found: C, 49.05; H, 3.65; N, 7.00; $C_8H_7NO_5$ requires: C, 48.74; H, 3.58; N, 7.10 %.

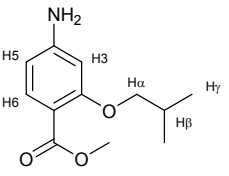
Methyl 2-isobutoxy-4-nitrobenzoate (25)



25

To a stirred solution of methyl-2-hydroxy-4-nitrobenzoate **23** (3.6 g, 18.3 mmol) and potassium carbonate (7.6 g, 54.8 mmol) in dimethylformamide (100 mL), isobutyl bromide (2.8 mL, 25.6 mmol) was added and the resulting mixture stirred at 50 °C during 20 h under a nitrogen atmosphere. The resultant suspension was allowed to cool, poured into water and extracted with ethyl acetate (3 × 150 mL). The combined organic fractions were washed with water (2 × 250 mL) and brine (4 × 300 mL) before being dried over $MgSO_4$. The organic solvent was evaporated resulting in an orange solid which was purified by column chromatography (*Stationary Phase*: Silica; *Mobile Phase*: ethyl acetate) to afford the product **25** (4.15 g, 16.4 mmol, 90%) as a bright yellow oil; R_F 0.86 (30% ethylacetate in dichloromethane); δ_H (500 MHz, CD_3OD) 7.77 (d, *J* = 8.5 Hz, 1 H, *H*6), 7.75 (s, 1 H, *H*3), 7.72 (d, *J* = 8.5 Hz 1 H, *H*5), 3.90 (s, 3 H, CO_2CH_3), 3.87 (d, *J* = 6 Hz, 2 H, *H*α), 2.14-2.09 (quin, *J* = 6 Hz, 1 H, *H*β), 1.07 (d, *J* = 6 Hz, 6H, *H*γ); δ_C (126 MHz, CD_3OD) 167.1 , 159.9, 152.1, 132.8, 127.5, 115.7, 108.8, 76.9, 53.0, 29.5, 19.6; ν_{max}/cm^{-1} (solid state) 3120, 2961, 1737, 1709, 1616, 1589, 1530 1489; HRMS: *m/z* $[M+Na]^+$ 276.0853. $C_{12}H_{15}NNaO_5$ requires $[M+Na]^+$ 276.0842; Found: C, 57.15; H, 6.05; N, 5.45; $C_{12}H_{15}NO_5$ requires C, 56.91; H, 5.97; N, 5.53 %

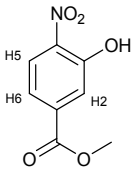
Methyl 4-amino-2-isobutoxybenzoate (28)



28

A solution containing methyl 2-isobutoxy-4-nitrobenzoate **25** (3.86 g, 15.2 mmol) in methanol (120 mL) and palladium on carbon (10 wt. %) was evacuated and flushed with nitrogen (3 times) and left under vacuum. Hydrogen was drawn into the flask and the reaction was left stirring at room temperature overnight. On completion, the reaction mixture was filtered through a celite pad and washed with methanol. The organic solvent was evaporated to dryness to yield the target product **28** (3.4 g, 15.2 mmol, quant.) as a grey gel; R_F 0.56 (30% ethylacetate in dichloromethane); δ_H (500 MHz, $CDCl_3$) 7.75 (d, *J* = 8.5 Hz, 1 H, *H*6), 6.21 (s, 1 H, *H*3), 6.18 (d, *J* = 8.5 Hz 1 H, *H*5), 4.10 (br, 2 H, NH_2), 3.84 (s, 3 H, OCH_3), 3.72 (d, *J* = 6.5 Hz, 2 H, *H*α), 2.19-2.11 (quin, *J* = 6.5 Hz, 1 H, *H*β), 1.04 (d, *J* = 6.5 Hz, 6H, *H*γ); δ_C (126 MHz, $CDCl_3$) 166.6, 161.3, 152.1, 134.2, 109.2, 106.3, 98.7, 75.0, 51.3, 28.3, 19.3; ν_{max}/cm^{-1} (solid state) 3635, 3445, 2977, 1732, 1433, 1395, 1221; HRMS: *m/z* $[M+Na]^+$ 246.1107. $C_{12}H_{15}NNaO_5$ requires $[M+Na]^+$ 246.1101.

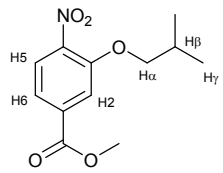
Methyl 3-hydroxy-4-nitrobenzoate (22)



22

Sulphuric acid (conc) (1.10 mL, 20.4 mmol) was added to a solution of 3-hydroxy-4-nitrobenzoic acid (10.0 g, 54.6 mmol) in MeOH (100 mL) and the resulting mixture heated at reflux overnight under a nitrogen atmosphere. The reaction mixture was allowed to cool to room temperature and the resulting precipitate collected *via* filtration to afford the desired product **22** (10.37 g, 52.6 mmol, 96%) as a yellow solid; R_F: 0.61 (dichloromethane); δ_H (500 MHz, $CDCl_3$) 10.51 (s, 1 H, O*H*), 8.19 (d, *J* = 9.0 Hz, 1 H, *H*5), 7.84 (d, *J* = 1.5 Hz, 1 H, *H*2), 7.63 (dd, *J* = 9.0, 1.5 Hz, 1 H, *H*6), 3.98 (s, 3 H, CO_2CH_3); δ_C (125 MHz, $CDCl_3$) 164.9, 154.7, 138.0, 135.8, 125.3, 121.7, 120.6, 52.9; ν_{max}/cm^{-1} (solid state) = 3317, 2962, 1722, 1587, 1436, 1223, 743; ESI-HRMS found *m/z* 196.0253 $[M-H]^-$ $C_8H_6NO_5$ requires 197.0324; Found: C, 48.80; H, 3.60; N, 6.90; $C_8H_7NO_5$ requires: C, 48.74; H, 3.58; N, 7.10 %.

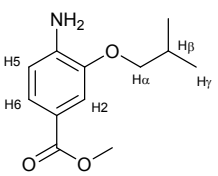
Methyl 3-isobutoxy-4-nitrobenzoate (24)



24

To a stirred solution of methyl-3-hydroxy-4-nitrobenzoate **22** (2.00 g, 10.2 mmol) and potassium carbonate (3.52 g, 25.5 mmol) in dimethylformamide (30 mL), isobutyl bromide (1.40 mL, 12.5 mmol) was added and the resulting mixture stirred at 50 °C overnight under a nitrogen atmosphere. The reaction was incomplete, so a further aliquot of isobutyl bromide (600 µL, 5.34 mmol) was added. After 20 h stirring, the resultant suspension was allowed to cool, poured into water and extracted with ethyl acetate (3 × 50 mL); the combined organic fractions were washed with water (2 × 150 mL) and brine (4 × 200 mL) before being dried over $MgSO_4$. The organic solvents were evaporated resulting in an orange solid **24** (2.09 g, 8.26 mmol, 81%); R_F: 0.65 (dichloromethane); δ_H (500 MHz, $CDCl_3$) 7.82 (d, *J* = 8.5 Hz, 1 H, *H*5), 7.73 (d, *J* = 1.5 Hz, 1 H, *H*2), 7.67 (dd, *J* = 8.5, 1.5 Hz, 1 H, *H*6), 3.97 (s, 3 H, CO_2CH_3), 3.93 (d, *J* = 6.5 Hz, 2 H, *H*α), 2.20-2.14 (m, 1 H, *H*β), 1.07 (d, *J* = 7.0 Hz, 6 H, *H*γ) ; δ_C (125 MHz, $CDCl_3$) 165.3, 152.1, 142.5, 134.7, 125.2, 121.1, 115.4, 76.0, 52.8, 28.2, 19.0; ν_{max}/cm^{-1} (solid state) = 3100, 2957, 1726, 1608, 1524, 1307, 1236, 750; ESI-HRMS found *m/z* 276.0841 $[M+Na]^+$ $C_{12}H_{15}NNaO_5$ requires 276.0842.

Methyl 4-amino-3-isobutoxybenzoate (27)

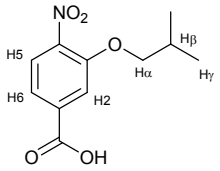


27

A solution containing methyl 3-isobutoxy-4-nitrobenzoate **24** (1.99 g, 7.86 mmol) in a 1:1 mixture of methanol : tetrahydrofuran (40 mL) and palladium on carbon (10 wt. %) was evacuated and flushed with nitrogen (3 times) and left under vacuum. Hydrogen was drawn into the flask and the reaction was left stirring at room temperature overnight. On completion, the reaction mixture was filtered through a celite pad and washed with methanol and tetrahydrofuran. The organic solvents were

evaporated to dryness to yield the target product **27** (1.66 mg, 7.44 mmol, 95%) as a beige solid; δ_H (500 MHz, $CDCl_3$) 7.54 (dd, *J* = 1.8, 8.0 Hz, 1 H, *H*6), 7.44 (d, *J* = 1.8 Hz, 1 H, *H*2), 6.67 (d, *J* = 8.0 Hz, 1 H, *H*5), 4.22 (s, broad, 2 H, NH_2), 3.87 (s, 3 H, CO_2CH_3), 3.83 (d, *J* = 6.5 Hz, 2 H, *H*α), 2.17-2.11 (m, 1 H, *H*β), 1.06 (d, *J* = 6.5 Hz, 6 H, *H*γ) ; δ_C (125 MHz, $CDCl_3$) 167.4, 145.6, 141.3, 123.9, 119.5, 113.1, 112.1, 74.7, 51.7, 28.3, 19.3; ν_{max}/cm^{-1} (solid state) = 3461, 3343, 3201, 2951, 1687, 1622, 1270, 766; ESI-HRMS found *m/z* 224.1281 $[M+H]^+$ $C_{12}H_{18}NO_3$ requires 224.1281.

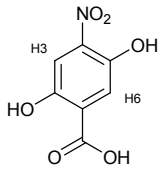
3-Isobutoxy-4-nitrobenzoic acid (26)



26

A solution of 10% aqueous sodium hydroxide (21 mL) was added to a solution of methyl 3-isobutoxy-4-nitrobenzoate **24** (3.50 g, 13.8 mmol) in a 1:1 mixture of methanol : tetrahydrofuran (90 mL). On completion, the organic solvents were removed under reduced pressure and the remaining solution was poured in water (100 mL) and acidified *via* addition of hydrochloric acid (conc) to pH 1. The resulting suspension was extracted with dichloromethane (4 × 100 mL), the organic fractions were combined and washed with water (2 × 200 mL) followed by brine (200 mL) and dried over $MgSO_4$. The organic solvents were evaporated to yield the target material **26** (3.15 g, 13.5 mmol, 95%) as a yellow solid; δ_H (300 MHz, DMSO-d_6) 7.96 (d, *J* = 8.3 Hz, 1H, *H*3), 7.74 (d, *J* = 1.3 Hz, 1H, *H*6), 7.63 (dd, *J* = 1.3, 8.3 Hz, 1H, *H*2), 4.01 (d, *J* = 6.4 Hz, 2H, *H*α), 2.03 (m, 1H, *H*β), 0.98 (d, *J* = 6.7 Hz, 6H, *H*γ); δ_C (75MHz, DMSO-d_6) 166.1, 151.4, 142.5, 136.0, 125.3, 121.5, 115.6, 75.5, 28.0, 19.0; ν_{max}/cm^{-1} (solid state) = 3088-2531, 2342-1817, 1693, 1310, 1015, 748; ESI-HRMS found *m/z* 238.0721 $[M-H]^-$, $C_{11}H_{12}NO_5$ requires 238.0721; Found C, 55.05; H, 5.45; N, 5.80%. $C_{11}H_{13}NO_5$ requires C, 55.23; H, 5.48; N, 5.86%

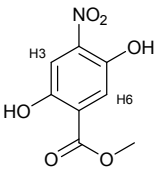
2,5-Dihydroxy-4-nitrobenzoic acid (30)



30

To a stirred solution of 3-hydroxy-4-nitrobenzoic acid **29** (40.00 g, 218.4 mmol) in 2 N aqueous sodium hydroxide solution (800 mL) was added dropwise a solution of potassium persulfate (59.00 g, 218.4 mmol) in water (1200 mL) The resulting solution was stirred at room temperature for 14 days. The reaction mixture was acidified *via* the addition of sulphuric acid (conc) to pH 1 and the resulting precipitate was removed by filtration. The aqueous solution was refluxed for 1 h. After cooling to room temperature the resulting precipitate was collected *via* filtration to yield the title compound **30** (16.11 g, 80.9 mmol, 37%) as gold microcrystals; δ_H (300 MHz, DMSO-d_6) 7.49 (1H, s, *H*6), 7.37 (1H, s, *H*3); δ_C (75MHz, DMSO-d_6) 170.1, 152.3, 143.1, 141.7, 119.7, 119.1, 112.5; ν_{max}/cm^{-1} (solid state) = 3533, 3400-2000, 169, 1598, 1442, 1244, 760, 627; ESI-HRMS found *m/z* 198.0049 $[M-H]^-$, $C_7H_4NO_6$ requires 198.0044; Found C, 42.05; H, 2.35; N, 6.80%. $C_7H_5NO_6$ requires C, 42.22; H, 2.53; N, 7.03%.

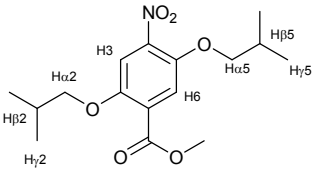
M**ethyl 2,5-dihydroxy-4-nitrobenzoate (31)**



31

To a stirred solution of 2,5-dihydroxy-4-nitrobenzoic acid **30** (5 g, 25.1 mmol) in methanol (200 mL) was added slowly concentrated sulphuric acid (2 mL) and the resulting solution was stirred at reflux overnight. The reaction mixture was allowed to cool to room temperature and sodium bicarbonate was added until carbon dioxide evolution ceased. The mixture was added to water (250 mL) and extracted with ethyl acetate (3 x 100 mL) and the combined organic fractions were washed with brine (100 mL). The organic solvent was removed by reduced pressure and the resulting orange solid was crystallised by chloroform to yield the title compound **31** (5.33 g, 25.0 mmol, quant.) as orange crystals; δ_H (300 MHz,$CDCl_3$) 10.19 (s, 1H, 5-O*H*), 9.75 (s, 1H, 2-O*H*), 7.71 (s, 1H, *H*3), 7.69 (s, 1H, *H*6), 4.02 (s, 3H, CO_2CH_3); δ_C (75MHz, $CDCl_3$) 168.9, 153.5, 146.7, 137.5, 121.4, 120.8, 112.8, 53.7; ν_{max}/cm^{-1} (solid state) = 3359,1695, 1440, 1220, 790; ESI-HRMS found *m/z* 212.0207 $[M-H]^-$, $C_8H_6NO_6$ requires 212.0273; Found C, 45.15; H, 3.25; N, 6.45%. $C_8H_7NO_6$ requires C, 45.08; H, 3.31; N, 6.57%

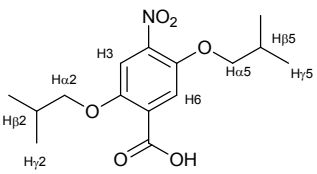
Methyl 2,5-diisobutoxy-4-nitrobenzoate (32)



32

To a stirred solution of methyl 2,5-dihydroxy-4-nitrobenzoate **31** (4.00 g, 18.8 mmol) and potassium carbonate (13.0 g, 93.8 mmol) in dimethylformamide (200 mL), isobutyl bromide (6.5 mL, 56.3 mmol) was added and the resulting mixture stirred at 50 °C overnight under a nitrogen atmosphere. On completion, the resulting suspension was allowed to cool to room temperature, poured into water and extracted with ethyl acetate (3 × 150 mL); the combined organic fractions were washed with water (2 × 250 mL) and brine (4 × 300 mL) before being dried over $MgSO_4$. The organic solvent was evaporated resulting in the title compound **32** (4.41 g, 13.6 mmol, 72%) was yielded as a yellow oil; δ_H (500 MHz, $CDCl_3$) 7.47 (s, 1H, *H*3), 7.39 (s, 1H, *H*6), 3.94 (s, 3H, CO_2CH_3), 3.85 (d, *J* = 6.4 Hz, 2H, *H*α2), 3.79 (d, *J* = 6.4 Hz, 2H, *H*α5), 2.11-2.17 (m, 2H, Hβ2, Hβ5), 1.04-1.07 (m, 24H, Hγ2, Hγ5); δ_C (75MHz, $CDCl_3$) 165.6, 151.6, 145.7, 141.7, 125.3, 118.0, 110.3, 76.6, 76.2, 52.5, 28.3, 28.3, 19.1, 19.0; ν_{max}/cm^{-1} (solid state) = 2960, 1739, 1529, 1392, 1217, 1024, 793; ESI-HRMS found *m/z* 348.1417 $[M+Na]^+$, $C_{16}H_{23}NNaO_6$ requires 348.1418.

2,5-Diisobutoxy-4-nitrobenzoic acid (33)

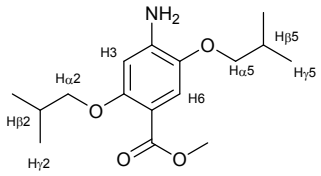


33

A solution of 10% aqueous sodium hydroxide (13 mL) was added to a solution of methyl 2,5-diisobutoxy-4-nitrobenzoate **32** (2.16 g, 8.0 mmol) in a 1:1 mixture of methanol : tetrahydrofuran (50 mL). On completion, the organic solvents were removed under reduced pressure and the remaining solution was poured in water (100 mL) and acidified *via* addition of hydrochloric acid (conc) to pH 1. The resulting suspension was extracted with

dichloromethane (4 × 100 mL), the organic fractions were combined and washed with water (2 × 200 mL) and brine (200 mL) before being dried over $MgSO_4$. The organic solvent was evaporated to yield the target material **33** (2.13 g, 6.84 mmol, 97%) as an amorphous yellow solid; δ_H (500 MHz, $CDCl_3$) 7.90 (s, 1H, *H*6), 7.50 (s, 1H, *H*3), 4.04 (d, *J* = 6.4 Hz, 2H, *H*α2), 3.91 (d, *J* = 6.4 Hz, 2H, *H*α5), 2.25 (m, 1H, Hβ2), 2.14 (m, 1H, Hβ5), 1.12 (m, 12H, Hγ2), 1.05 (m, 12H, Hγ5); δ_C (125MHz, $CDCl_3$) 163.7, 150.3, 146.9, 142.4, 121.9, 119.5, 110.1, 77.6, 76.6, 28.2, 28.1, 19.1, 19.0; ν_{max}/cm^{-1} (solid state) = 3229, 2961, 1747, 1525, 1203, 1003, 803; ESI-HRMS found *m/z* 334.1267 $[M+Na]_+$, $C_{15}H_{21}NNaO_6$ requires 334.1261.

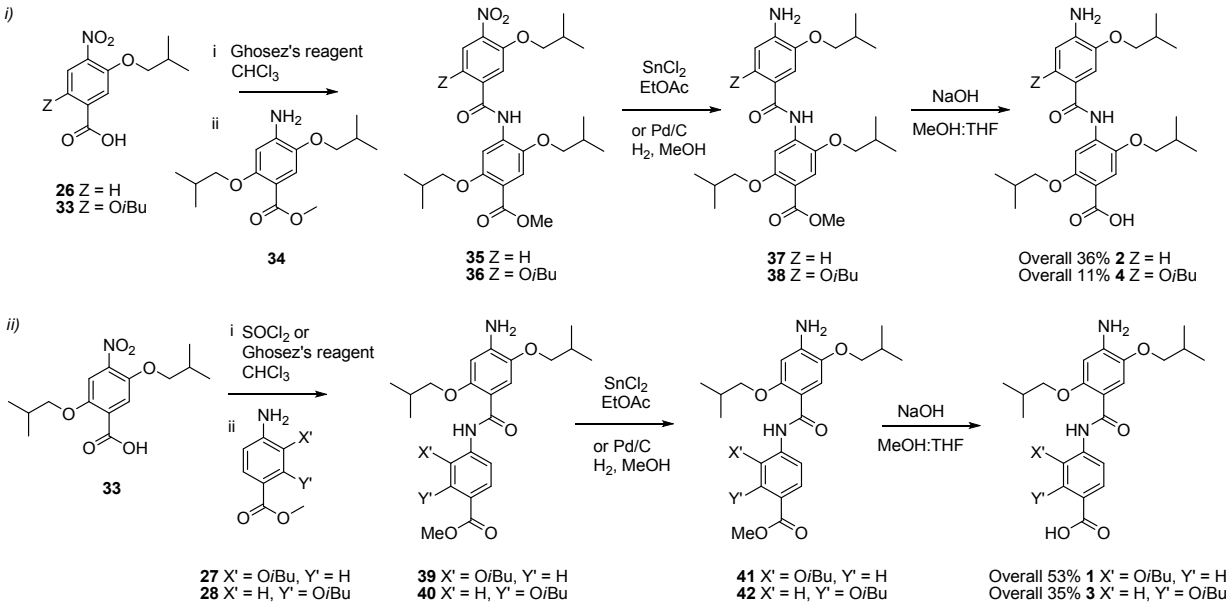
Methyl 4-amino-2,5-diisobutoxybenzoate (34)



34

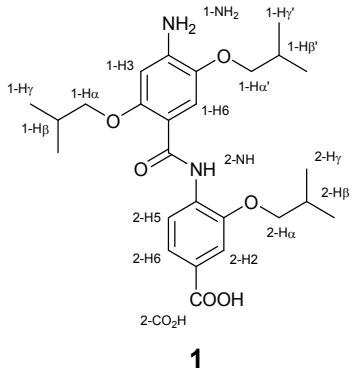
To a stirred solution of methyl 2,5-diisobutoxy-4-nitrobenzoate **32** (2.24 g, 6.89 mmol) in ethyl acetate (50 mL), tin(II) chloride dihydrate (9.32 g, 41.33 mmol) was added and the resulting mixture stirred at 50 °C overnight under a nitrogen atmosphere. On completion, the reaction mixture was allowed to cool and poured over ice. The solution was basified to pH 8 by addition of a saturated sodium bicarbonate solution and the resulting mixture was allowed to stir for an hour. The aqueous mixture was extracted with ethyl acetate (3 × 100 mL) and the organic fractions were combined, washed with water (3 × 250 mL) and brine (2 × 250 mL), dried over $MgSO_4$ and the organic solvents were evaporated to afford the desired product **34** (1.83 g, 6.2 mmol, 90%) as a light brown solid; δ_H (500 MHz, $CDCl_3$) 7.33 (s, 1H, *H*6), 6.29 (s, 1H, *H*3), 3.85 (3H, s, CO_2CH_3), 3.76 (d, *J* = 6.4 Hz, 2H, *H*α2), 3.71 (d, *J* = 6.4 Hz, 2H, *H*α5), 2.07-2.15 (m, 2H, Hβ2, Hβ5), 1.03-1.06 (m, 24H, Hγ2, Hγ5); δ_C (75MHz, $CDCl_3$) 166.8, 155.7, 142.2, 139.7, 114.8, 107.7, 100.0, 76.0, 75.2, 51.5, 28.5, 28.4, 19.4, 19.3; ν_{max}/cm^{-1} (solid state) = 3492, 3368, 2957, 1704, 1621,1523, 1445, 1252, 1210, 1035, 780; ESI-HRMS found *m/z* 318.1675 $[M+Na]^+$, $C_{16}H_{25}NNaO_4$ requires 318.1676.

3. Dimer Syntheses and Characterization



Scheme S3. Synthetic route to the dimers.

4-(4-amino-2,5-diisobutoxybenzamido)-3-isobutoxybenzoic acid (1)

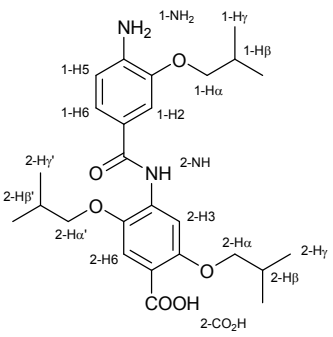


1

Under a nitrogen atmosphere, thionyl chloride (5 eq) was added to a stirred solution of 2,5-diisobutoxy-4-nitrobenzoic acid **14** (1 eq) in anhydrous dichloromethane (50 mL/g), and the resulting mixture was stirred at reflux overnight. The organic solvent and the excess thionyl chloride were co-evaporated under a nitrogen flow; this was repeated 3 times with further additions of dichloromethane to yield a yellowish solid. The resulting 2,5-diisobutoxy-4-nitrobenzoyl chloride was dissolved in anhydrous chloroform (50 mL/g) and methyl 4-amino-3-isobutoxybenzoate **26** (1 eq) was added. The resulting mixture was stirred at reflux under a nitrogen atmosphere. The organic solvent was evaporated under reduced pressure and the solid residue dissolved, without further isolation, in a 1:1 mixture of methanol : tetrahydrofuran (30 mL/g) and palladium on carbon (10 wt. %). The flask was evacuated and flushed with nitrogen (3 times) and left under vacuum, then hydrogen was drawn into the flask and the reaction was left stirring at room temperature overnight. On completion, the reaction mixture was filtered through a celite pad and washed with methanol and tetrahydrofuran. The resulting solid was reacted, without further purification, with a 10% sodium hydroxide solution (10 mL/g) in tetrahydrofuran (100 mL/g) at room temperature. On completion, the organic solvent was evaporated under reduced pressure and the solid residue subjected to high pressure liquid chromatography [(50-95% MeCN:Water and 0.1%

Formic acid) t = 8 min, 20 ml/min, XBridge Prep C18 column] to yield the target dimer **30** (53% overall yield) as a beige amorphous solid; δ_H (500 MHz, $CDCl_3$) 10.4 (s, broad, 1 H, 2-N*H*), 8.72 (d, 1 H, *J* = 7.5 Hz, 2-*H*5), 7.80 (dd, *J* = 1.5, 7.5 Hz, 1 H, 2-*H*6), 7.66 (s, 1 H, 1-*H*6), 7.62 (d, *J* = 1.5 Hz, 1 H, 2-*H*2), 6.40 (s, 1 H, 1-*H*3), 3.93 (d, *J* = 6.5 Hz, 2 H, 2-*H*α), 3.92 (d, *J* = 7.0 Hz, 2 H, 1-*H*α'), 3.84 (d, *J* = 6.5 Hz, 2 H, 1-*H*α), 2.23-2.09 (m, 3 H, 1-*H*β, 1-*H*β', 2-*H*β), 1.04 (d, *J* = 6.5 Hz, 6 H, 2-*H*γ), 1.03 (d, *J* = 7.0 Hz, 6 H, 1-*H*γ), 0.98 (d, *J* = 6.5 Hz, 6 H, 1-*H*γ'); δ_C (125 MHz, $CDCl_3$) 164.3, 152.7, 147.5, 146.1, 141.1, 139.4, 134.3, 131.2, 124.2, 123.1, 120.0, 119.2, 114.1, 112.6, 75.6, 75.6, 75.2, 28.3, 28.0, 27.8, 19.3, 19.3, 19.2; ν_{max}/cm^{-1} (solid state) = 3490, 3328, 2957, 2872, 1587, 1519, 1261, 1206, 1030, 768; ESI-HRMS found *m/z* 473.2663 $[M-H]^-$ $C_{26}H_{35}N_2O_6$ requires 473.2646.

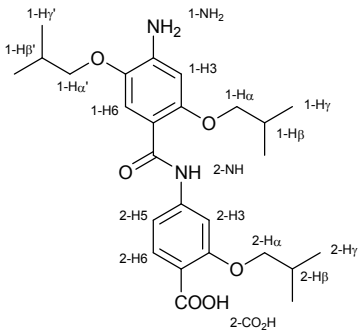
4-(4-amino-3-isobutoxybenzamido)-2,5-diisobutoxybenzoic acid (2)



2

Under a nitrogen atmosphere, Ghosez's reagent (1 eq) was added to a solution containing 3-isobutoxy-4-nitrobenzoic acid **26** (1 eq) in chloroform (40 mL/g) and the resulting mixture was refluxed for 3 hours. Methyl 4-amino-2,5-diisobutoxybenzoate **34** (1 eq) was subsequently added and heated at reflux overnight. The solvents were removed under reduced pressure and the resulting mixture dissolved, without further isolation of compound **35**, in a 1:1 mixture of methanol : tetrahydrofuran (30 mL/g) and palladium on carbon (10 wt. %). The flask was evacuated and flushed with nitrogen (3 times) and left under vacuum, then hydrogen was drawn into the flask and the reaction was left stirring at room temperature overnight. On completion, the reaction mixture was filtered through a celite pad and washed with methanol and tetrahydrofuran. The resulting solid was reacted, without further purification of compound **37**, with a 10% sodium hydroxide solution (10 mL/g) in tetrahydrofuran (100 mL/g) at room temperature. On completion, the organic solvent was evaporated under reduced pressure and the solid residue subjected to high pressure liquid chromatography [(50-95% MeCN:Water and 0.1% Formic acid) t = 8 min, 20 ml/min, XBridge Prep C18 column] to isolate the title compound **2** (36 % overall yield) as a beige amorphous solid; δ_H (500 MHz, $CDCl_3$) 8.84 (s, broad, 1 H, 2-N*H*), 8.55 (s, 1 H, 2-*H*3), 7.66 (s, 1 H, 2-*H*6), 7.43 (d, *J* = 2.0 Hz, 1 H, 1-*H*2), 7.32 (dd, *J* = 2.0, 8.0 Hz, 1 H, 1-*H*6), 6.88 (d, *J* = 8.0 Hz, 1 H, 1-*H*5), 4.09 (d, *J* = 6.5 Hz, 2 H, 2-*H*α), 3.92 (d, *J* = 6.5 Hz, 2 H, 2-*H*α'), 3.87 (d, *J* = 6.5 Hz, 2 H, 1-*H*α), 2.27-2.16 (m, 3 H, 1-*H*β, 2-*H*β, 2-*H*β'), 1.11 (d, *J* = 6.5 Hz, 6 H, 2-*H*γ'), 1.10 (d, *J* = 7.0 Hz, 6 H, 2-*H*γ), 1.07 (d, *J* = 7.0 Hz, 6 H, 1-*H*γ); δ_C (125 MHz, $CDCl_3$) 165.5, 165.1, 152.9, 141.9, 139.5, 134.1, 132.6, 120.1, 119.7, 114.0, 110.9, 110.8, 110.5, 103.7, 75.5, 75.1, 75.0, 28.4, 28.3, 28.2, 19.4, 19.3, 19.2; ν_{max}/cm^{-1} (solid state) = 3494, 3354, 2960, 2873, 1717, 1513, 1433, 1257, 1192, 1022, 751; ESI-HRMS found *m/z* 473.2664 $[M-H]^-$ $C_{26}H_{35}N_2O_6$ requires 473.2646.

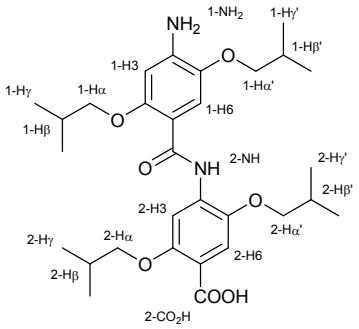
4-(4-amino-2,5-diisobutoxybenzamido)-2-isobutoxybenzoic acid (3)



3

Under nitrogen atmosphere, Ghosez's reagent (1 eq) was added to a solution containing 2,5-diisobutoxy-4-nitrobenzoic acid **33** (1 eq) in chloroform (40 mL/g) and the resulting mixture was refluxed for 3 hours. Methyl 4-amino-2-isobutoxybenzoate **28** (1 eq) was subsequently added and heated at reflux overnight. The solvents were removed under reduced pressure and the resulting mixture dissolved, without further isolation of compound **40**, in a 1:1 mixture of methanol : tetrahydrofuran (30 mL/g) and palladium on carbon (10 wt. %). The flask was evacuated and flushed with nitrogen (3 times) and left under vacuum, then hydrogen was drawn into the flask and the reaction was left stirring at room temperature overnight. On completion, the reaction mixture was filtered through a celite pad and washed with methanol and tetrahydrofuran. The resulting solid was reacted, without further purification of compound **42**, with a 10% sodium hydroxide solution (10 mL/g) in tetrahydrofuran (100 mL/g) at room temperature. On completion, the organic solvent was evaporated under reduced pressure and the solid residue subjected to high pressure liquid chromatography [(50-95% MeCN:Water and 0.1% Formic acid) t = 8 min, 20 ml/min, XBridge Prep C18 column] to isolate the title compound **3** (35 % overall yield) as a light brown amorphous solid; δ_H (500 MHz, $CDCl_3$) 10.34 (s, broad, 1 H, 2-N*H*), 8.31 (d, *J* = 1.5 Hz, 1 H, 2-*H*3), 8.11 (d, *J* = 8.5, 1 H, 2-*H*6), 7.66 (s, 1 H, 1-*H*6), 6.71 (dd, *J* = 1.5, 8.5 Hz, 1 H, 2-*H*5), 6.45 (s, 1 H, 1-*H*3), 4.10 (d, *J* = 7.5 Hz, 2 H, 2-*H*α), 3.91 (d, *J* = 6.5 Hz, 2 H, 1-*H*α), 3.84 (d, *J* = 7.0 Hz, 2 H, 1-*H*α'), 2.32-2.21 (m, 2 H, 2-*H*β, 1-*H*β), 2.17-2.09 (m, 1 H, 1-*H*β'),1.15 (d, *J* = 7.0 Hz, 6 H, 1-*H*γ), 1.11 (d, *J* = 7.0 Hz, 6 H, 2-*H*γ), 1.04 (d, *J* = 6.5 Hz, 6 H, 1-*H*γ'); δ_C (125 MHz, $CDCl_3$) 165.3, 164.4, 158.9, 153.0, 145.3, 142.1, 140.9, 134.1, 113.8, 112.1, 111.9, 109.4, 103.6, 98.5, 76.4, 76.4, 75.3, 28.6, 28.3, 28.2, 19.5, 19.3, 19.3; ν_{max}/cm^{-1} (solid state) = 3466, 3341, 2959, 2874, 1722, 1581, 1514, 1223, 1015, 760; ESI-HRMS found *m/z* 473.2659 $[M+H]^+$ $C_{26}H_{37}N_2O_6$ requires 473.2646.

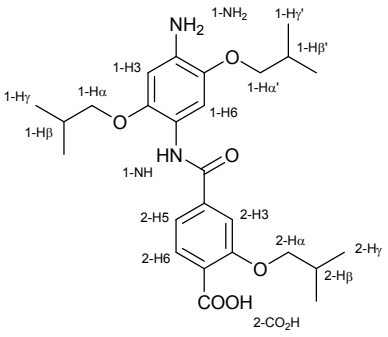
4-(4-amino-2,5-diisobutoxybenzamido)-2,5-diisobutoxybenzoic acid (4)



4

Under nitrogen atmosphere, Ghosez's reagent (1 eq) was added to a solution containing 2,5-diisobutoxy-4-nitrobenzoic acid **33** (1 eq) in chloroform (40 mL/g) and the resulting mixture was refluxed for 3 hours. Methyl 4-amino-2,5-diisobutoxybenzoate **34** (1 eq) was subsequently added and heated at reflux overnight. The solvents were removed under reduced pressure and the resulting mixture dissolved, without further isolation of compound **36**, in a 1:1 mixture of methanol : tetrahydrofuran (30 mL/g) and palladium on carbon (10 wt. %). The flask was evacuated and flushed with nitrogen (3 times) and left under vacuum, then hydrogen was drawn into the flask and the reaction was left stirring at room temperature overnight. On completion, the reaction mixture was filtered through a celite pad and washed with methanol and tetrahydrofuran. The resulting solid was reacted, without further purification of compound **38**, with a 10% sodium hydroxide solution (10 mL/g) in tetrahydrofuran (100 mL/g) at room temperature. On completion, the organic solvent was evaporated under reduced pressure and the solid residue subjected to high pressure liquid chromatography [(50-95% MeCN:Water and 0.1% Formic acid) t = 8 min, 20 ml/min, XBridge Prep C18 column] to isolate the title compound **4** (11% overall yield) as a brownish amorphous solid; δ_H (500 MHz, $CDCl_3$) 10.52 (s, broad, 1 H, 2-N*H*), 8.62 (s, 1 H, 2-*H*3), 7.66 (s, 1 H, 2-*H*6), 7.61 (s, 1 H, 1-*H*6), 6.43 (s, 1 H, 1-*H*3), 4.09 (d, *J* = 7.0 Hz, 2 H, 2-*H*α), 3.97 (d, *J* = 7.0 Hz, 2 H, 1-*H*α), 3.89 (d, *J* = 7.0 Hz, 2 H, 2-*H*α'), 3.83 (d, *J* = 6.5 Hz, 2 H, 1-*H*α'), 2.27-2.09 (m, 4 H, 1-*H*β, 1-*H*β', 2-*H*β, 2-*H*β'), 1.09 (d, *J* = 6.5 Hz, 6 H, 2-*H*γ), 1.04 (d, *J* = 6.5 Hz, 6 H, 1-*H*γ'), 1.02 (d, *J* = 6.5 Hz, 6 H, 2-*H*γ'), 0.97 (d, *J* = 7.0 Hz, 6 H, 1-*H*γ); δ_C (125 MHz, $CDCl_3$) 166.7, 164.6, 152.8, 152.7, 142.5, 141.4, 135.1, 114.6, 113.8, 110.5, 105.0, 100.6, 77.2, 76.9, 76.0, 75.3, 28.3, 28.3, 28.0, 27.7, 19.3, 19.3, 19.2, 19.2 (two quaternary carbons were not observed); ν_{max}/cm^{-1} (solid state) = 3489, 3329, 2958, 2872, 1587, 1582, 1259, 1199, 1025, 765; ESI-HRMS found *m/z* 545.3237 $[M-H]^-$ $C_{30}H_{44}N_2O_7$ requires 545.3221.

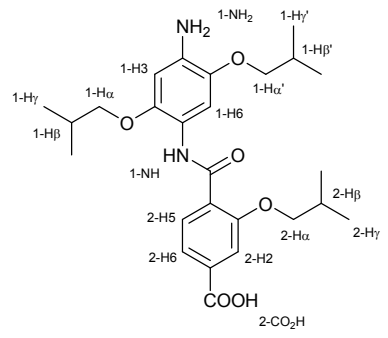
4-(4-amino-2,5-diisobutoxyphenylcarbamoyl)-2-isobutoxybenzoic acid (14aa)



14aa

tert-Butyl 2,5-diisobutoxy-1,4-phenylenedicarbamate **7** (1 eq) was dissolved in ahhydrous hydrogen chloride (4M) solution in 1,4-dioxane (30 mL/g) and stirred for 3h at room temperature. The solvent was evaporated under reduced pressure and the solid residue redissolved in anhydrous chloroform (150 mL/g) before the addition of triethylamine (115 µL, 0.83 mmol). The resulting mixture was heated to reflux and a solution of 4-(ethoxycarbonyl)-3-isobutoxybenzoic acid **12** (0.5 eq) and Ghosez's reagent (0.5 eq) in anhydrous chloroform (100 mL/g), previously stirred at 50 °C for 3 h, was added dropwise *via* a cannula. The reaction was stirred at reflux overnight. Up to this point, air free conditions were required. The organic solvent was evaporated under reduced pressure and the resulting solid was reacted, without further purification, with a 10% sodium hydroxide solution (10 mL/g) in tetrahydrofuran (100 mL/g) at room temperature. On completion, the organic solvent was evaporated under reduced pressure and the solid residue subjected to high pressure liquid chromatography [(50-95% MeCN:Water and 0.1% Formic acid) t = 8 min, 20 ml/min, XBridge Prep C18 column] to yield the target dimer **14aa** (14% overall yield) as a brown solid; δ_H (500 MHz, $CDCl_3$) 8.56 (s, broad, 1 H, 1-N*H*), 8.30 (d, *J* = 8.0 Hz, 1 H, 2-*H*6), 8.15 (s, 1 H, 1-*H*6), 7.72 (d, *J* = 1.0 Hz, 1 H, 2-*H*3), 7.45 (dd, *J* = 1.0, 8.0 Hz, 1 H, 2-*H*5), 6.40 (s, 1 H, 1-*H*3), 4.13 (d, *J* = 6.5 Hz, 2 H, 2-*H*α), 3.82 (d, *J* = 6.5 Hz, 2 H, 1-*H*α'), 3.78 (d, *J* = 6.5 Hz, 2 H, 1-*H*α), 2.31-2.23 (m, 1 H, 2-*H*β), 2.18-2.08 (m, 2 H, 1-*H*β, 1-*H*β'), 1.12 (d, *J* = 7.0 Hz, 6 H, 2-*H*γ), 1.07 (d, *J* = 7.0 Hz, 6 H, 1-*H*γ), 1.05 (d, *J* = 7.0 Hz, 6 H, 1-*H*γ'); δ_C (125 MHz, $CDCl_3$) 164.6, 162.3, 158.1, 142.4, 141.4, 140.2, 134.3, 133.1, 120.0, 118.5, 118.4, 112.3, 105.4, 100.1, 75.6, 75.6, 75.5, 28.5, 28.4, 28.1, 19.4, 19.3, 19.1; ν_{max}/cm^{-1} (solid state) = 3364, 2958, 2872, 1660, 1530, 1431, 1217, 1196, 1026, 743; ESI-HRMS found *m/z* 473.2659 $[M-H]^-$ $C_{26}H_{35}N_2O_6$ requires 473.2646.

4-(4-amino-2,5-diisobutoxyphenylcarbamoyl)-3-isobutoxybenzoic acid (14ab)

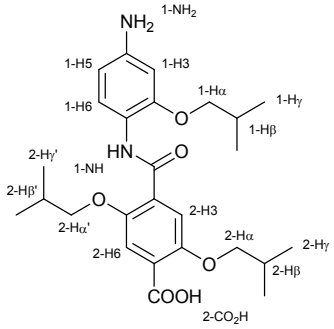


14ab

tert-Butyl 2,5-diisobutoxy-1,4-phenylenedicarbamate **7** (1 eq) was dissolved in ahhydrous hydrogen chloride (4M) solution in 1,4-dioxane (30 mL/g) and stirred for 3h at room temperature. The solvent was evaporated under reduced pressure and the solid residue redissolved in anhydrous chloroform (150 mL/g) before the addition of triethylamine (115 µL, 0.83 mmol). The resulting mixture was heated to reflux and a solution 4-(tert-butoxycarbonyl)-2-isobutoxybenzoic acid **13** (0.5 eq) and Ghosez's reagent (0.5 eq) in anhydrous chloroform (100 mL/g), previously stirred at 50 °C for 3 h, was added dropwise *via* a cannula. The reaction was stirred at reflux overnight. Up to this point, air free conditions were

required. The organic solvent was evaporated under reduced pressure and the resulting solid was reacted, without further purification, with a 10% TFA solution in tetrahydrofuran (100 mL/g) at room temperature. On completion, the organic solvent was evaporated under reduced pressure and the solid residue subjected to high pressure liquid chromatography [(50-95% MeCN:Water and 0.1% Formic acid) t = 8 min, 20 ml/min, XBridge Prep C18 column] to yield the target dimer **14ab** (23% overall yield) as a brown solid; δ_H (500 MHz, $CDCl_3$) 9.89 (s, broad, 1 H, 1-N*H*), 8.32 (d, *J* = 8.0 Hz, 1 H, 2-*H*5), 8.15 (s, 1 H, 1-*H*6), 7.82 (dd, *J* = 1.0, 8.0 Hz, 1 H, 2-*H*6), 7.73 (d, *J* = 1.0 Hz, 1 H, 2-*H*2), 6.41 (s, 1 H, 1-*H*3), 4.04 (d, *J* = 7.0 Hz, 2 H, 2-*H*α), 3.83 (d, *J* = 6.5 Hz, 2 H, 1-*H*α'), 3.74 (d, *J* = 7.0 Hz, 2 H, 1-*H*α), 2.30-2.22 (m, 1 H, 2-*H*β), 2.17-2.03 (m, 2 H, 1-*H*β, 1-*H*β'), 1.05 (d, *J* = 6.5 Hz, 6 H, 1-*H*γ'), 1.03 (d, *J* = 6.5 Hz, 6 H, 2-*H*γ), 0.98 (d, *J* = 7.0 Hz, 6 H, 1-*H*γ); δ_C (125 MHz, $CDCl_3$) 165.1, 162.0, 156.6, 143.1, 140.5, 132.6, 132.4, 127.7, 122.6, 119.3, 114.4, 110.1, 107.1, 101.1, 76.1, 76.3, 75.4, 28.5, 28.2, 27.9, 19.4, 19.3, 19.2; ν_{max}/cm^{-1} (solid state) = 3421, 3345, 2964, 1535, 1230, 1177, 1029, 824, 514; ESI-HRMS found *m/z* 473.2647 $[M+H]^+$ $C_{26}H_{37}N_2O_6$ requires 473.2646.

4-(4-amino-2-isobutoxyphenylcarbamoyl)-2,5-diisobutoxybenzoic acid (14ba)

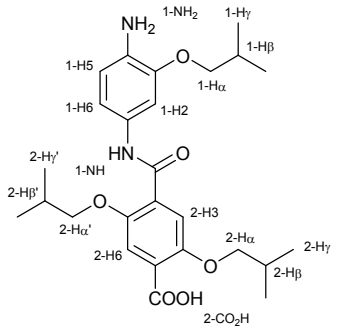


14ba

Under a nitrogen atmosphere, thionyl chloride (5 eq) was added to a stirred solution of 2,5-diisobutoxyterephthalic acid **14** (1 eq) in anhydrous dichloromethane (50 mL/g), and the resulting mixture was stirred at reflux overnight. The organic solvent and the excess thionyl chloride were co-evaporated under a nitrogen flow; this was repeated 3 times with further additions of dichloromethane to yield a yellow solid. The resulting 2,5-diisobutoxyterephthaloyl dichloride was dissolved in anhydrous chloroform (100 mL/g) and a solution of 2-isobutoxy-4-nitroaniline **26** (0.5 eq) in anhydrous chloroform (30 mL/g) was added dropwise. The resulting mixture was stirred at reflux under a nitrogen atmosphere. The organic solvent was evaporated under reduced pressure and the solid residue subjected to column chromatography (*Stationary Phase*: Silica; *Mobile Phase*: dichloromethane) to afford the desired product **29** as an orange solid. A solution containing 2,5-diisobutoxy-4-(2-isobutoxy-4-nitrophenylcarbamoyl)benzoic acid **29** in a 1:1 mixture of methanol : tetrahydrofuran (30 mL/g) and palladium on carbon (10 wt. %) was evacuated and flushed with nitrogen (3 times) and left under vacuum. Hydrogen was drawn into the flask and the reaction was left stirring at room temperature overnight. On completion, the reaction mixture was filtered through a celite pad and washed with methanol and tetrahydrofuran. The organic solvents were evaporated to dryness to yield the target dimer **15ba** (42% overall yield) as a orange solid; δ_H (500 MHz, $CDCl_3$) 9.97 (s, broad, 1 H, 1-N*H*), 8.20 (d, *J* = 8.5 Hz, 1 H, 1-*H*6), 7.98 (s, 1 H, 2-*H*3), 7.83 (s, 1 H, 2-*H*6), 6.33 (dd, *J* = 2.0, 8.5 Hz, 1 H, 1-*H*5), 6.31 (d, *J* = 2.0 Hz, 1 H, 1-*H*3), 4.09 (d, *J* = 6.5

Hz, 2 H, 2-*H*α), 4.01 (d, *J* = 7.0 Hz, 2 H, 2-*H*α'), 3.78 (d, *J* = 7.0 Hz, 2 H, 1-*H*α), 2.26-2.09 (m, 3 H, 1-*H*β, 2-*H*β, 2-*H*β'), 1.09 (d, *J* = 7.0 Hz, 6 H, 2-*H*γ), 1.02 (d, *J* = 6.5 Hz, 6 H, 1-*H*γ), 0.99 (d, *J* = 6.5 Hz, 6 H, 2-*H*γ'); δ_C (125 MHz, $CDCl_3$) 164.8, 161.2, 151.6, 151.1, 150.0, 144.0, 128.7, 123.1, 120.2, 119.3, 117.8, 116.4, 107.0, 99.8, 77.1, 77.0, 75.2, 28.1 (2 C), 27.9, 19.2, 19.2, 19.1; ν_{max}/cm^{-1} (solid state) = 3355, 2959, 2875, 1738, 1652, 1532, 1417, 1196, 1015, 741; ESI-HRMS found *m/z* 471.2493 $[M-H]^-$ $C_{26}H_{35}N_2O_6$ requires 471.2493; Found: C, 66.15; H, 7.40; N, 5.90; $C_{26}H_{36}N_2O_6$ requires: C, 66.08; H, 7.68; N, 5.93%.

4-(4-amino-3-isobutoxyphenylcarbamoyl)-2,5-diisobutoxybenzoic acid (14bb)

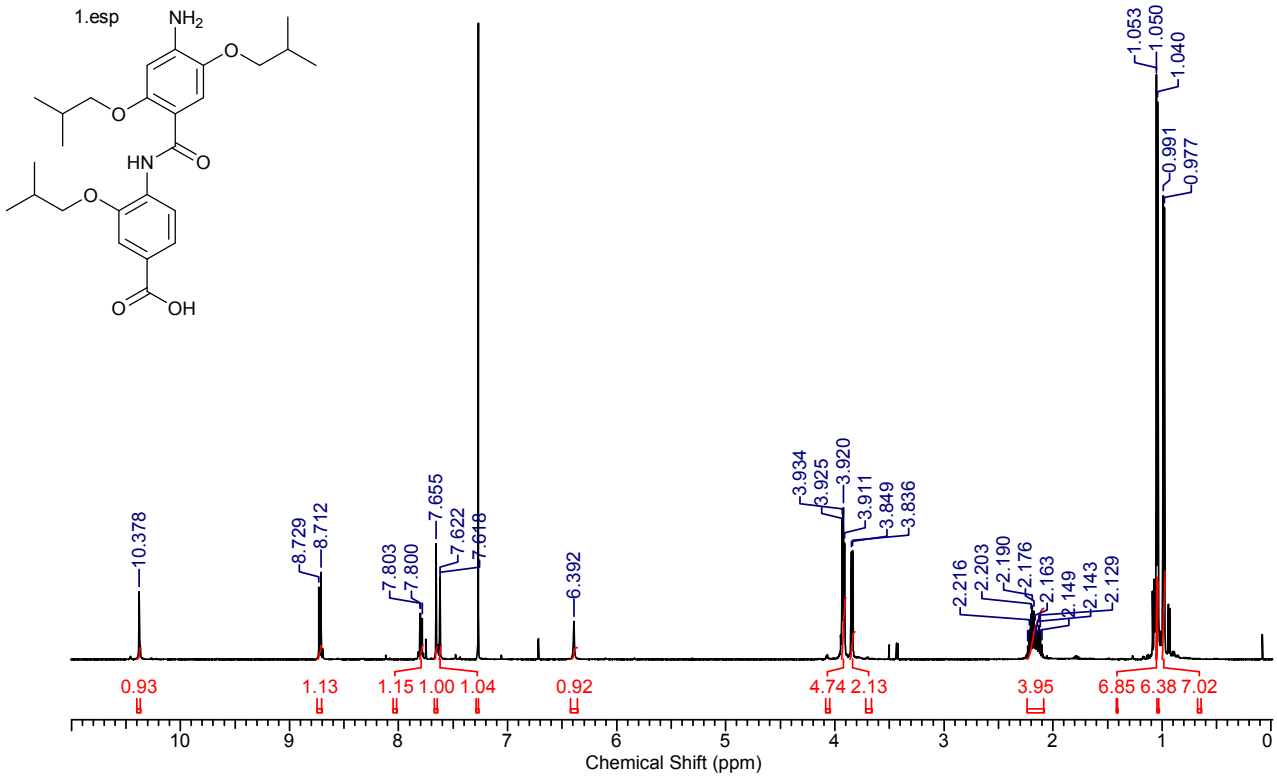


14bb

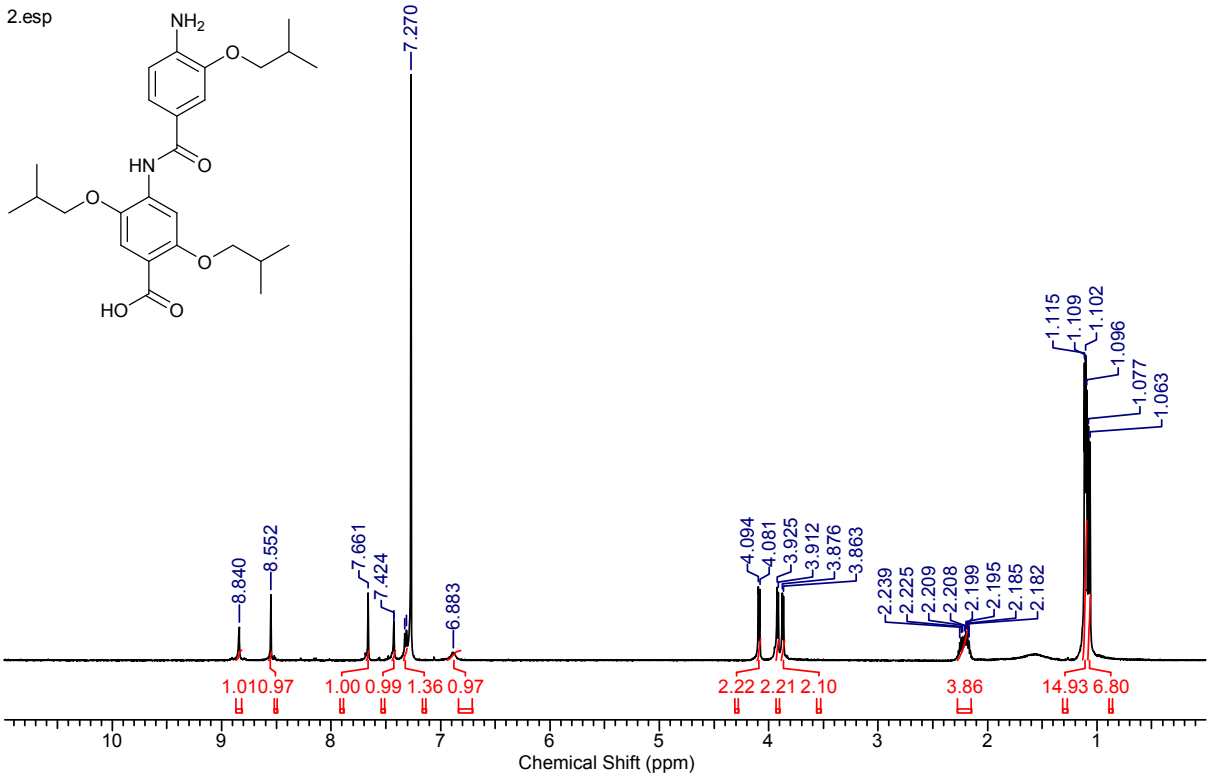
Under a nitrogen atmosphere, thionyl chloride (5 eq) was added to a stirred solution of 2,5-diisobutoxyterephthalic acid **6** (1 eq) in anhydrous dichloromethane (50 mL/g), and the resulting mixture was stirred at reflux overnight. The organic solvent and the excess thionyl chloride were co-evaporated under a nitrogen flow; this was repeated 3 times with further additions of dichloromethane to yield a yellow solid. The resulting 2,5-diisobutoxyterephthaloyl dichloride was dissolved in anhydrous chloroform (100 mL/g) and a solution of (9H-Fluoren-9-yl)methyl 4-amino-2-isobutoxyphenylcarbamate **10** (0.3 eq) in anhydrous chloroform (30 mL/g) was added dropwise. The resulting mixture was stirred at reflux under a nitrogen atmosphere. The organic solvent was evaporated under reduced pressure and the solid residue reacted, without further purification, with a 10% sodium hydroxide solution (10 mL/g) in tetrahydrofuran (100 mL/g) at room temperature. On completion, the organic solvent was evaporated under reduced pressure and the solid residue subjected to high pressure liquid chromatography [(50-95% MeCN:Water and 0.1% Formic acid) t = 8 min, 20 ml/min, XBridge Prep C18 column] to afford the desired product **14bb** (10% overall yield) as a yellow solid; δ_H (500 MHz, $CDCl_3$) 10.04 (s, broad, 1 H, 1-N*H*), 8.04 (s, 1 H, 2-*H*3), 7.83 (s, 1 H, 2-*H*6), 7.61 (d, *J* = 2.0 Hz, 1 H, 1-*H*5), 6.78 (dd, *J* = 2.0, 8.0 Hz, 1 H, 1-*H*6), 6.75 (d, *J* = 8.0 Hz, 1 H, 1-*H*2), 4.11 (d, *J* = 7.5 Hz, 2 H, 2-*H*α), 4.04 (d, *J* = 6.5 Hz, 2 H, 2-*H*α'), 3.83 (d, *J* = 6.5 Hz, 2 H, 1-*H*α), 2.33-2.12 (m, 3 H, 1-*H*β, 2-*H*β, 2-*H*β'), 1.16 (d, *J* = 7.0 Hz, 6 H, 2-*H*γ'), 1.10 (d, *J* = 7.0 Hz, 6 H, 2-*H*γ), 1.06 (d, *J* = 7.0 Hz, 6 H, 1-*H*γ); δ_C (125 MHz, $CDCl_3$) 164.6, 161.0, 151.6, 151.1, 147.0, 132.8, 130.0, 127.3, 120.5, 117.0, 116.5, 115.0, 112.4, 105.2, 77.2, 76.7, 74.7, 28.5, 28.4, 28.1, 19.4, 19.4, 19.2; ν_{max}/cm^{-1} (solid state) = 3355, 2959, 2875, 1738, 1652, 1532, 1417, 1196, 1015, 741; ESI-HRMS found *m/z* 473.2664 $[M-H]^-$ $C_{26}H_{35}N_2O_6$ requires 473.2646.

4. ^{1}H-NMR Spectra of dimers

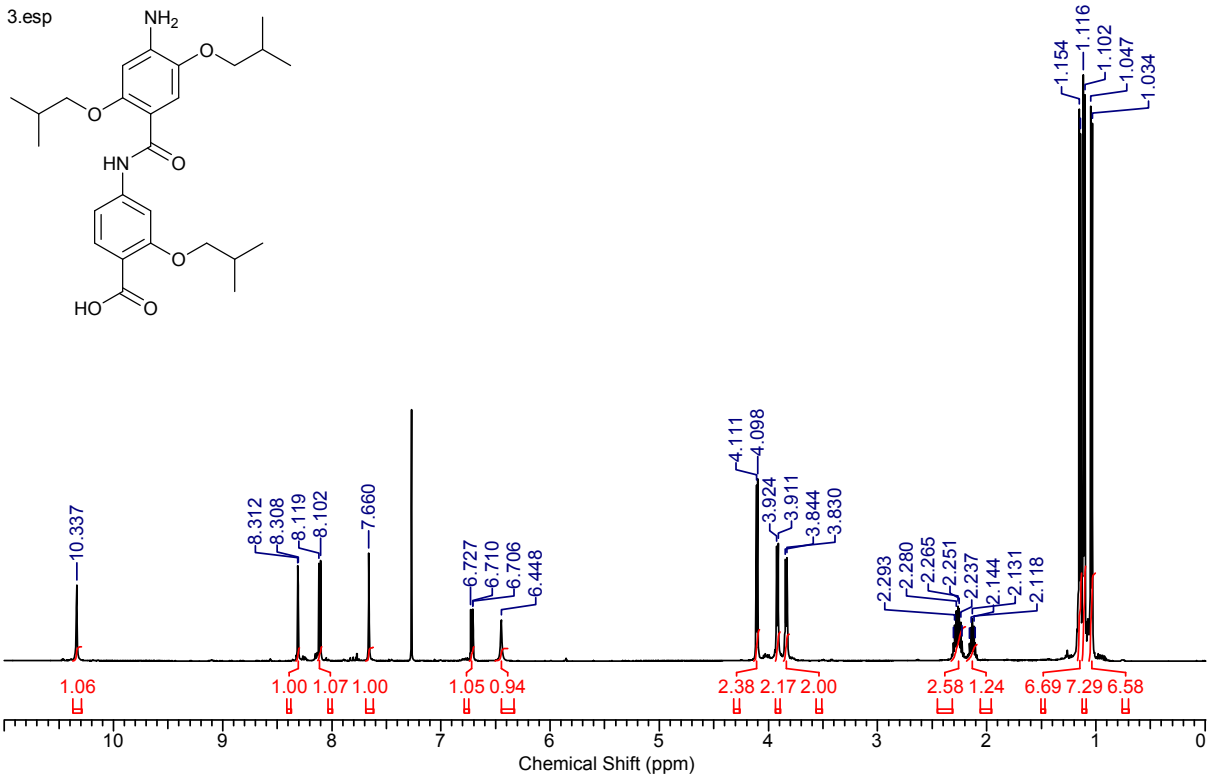
^{1}H-NMR Spectra of compound 1 ($CDCl_3$, 500 MHz)



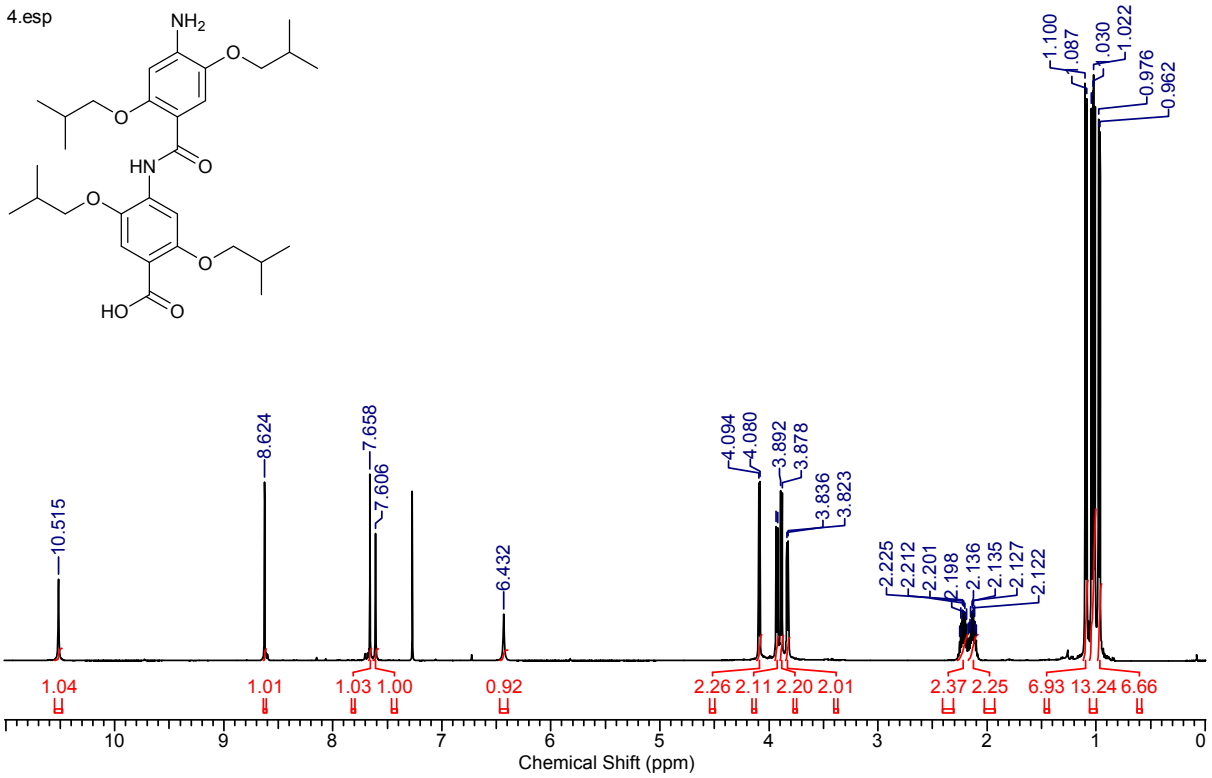
^{1}H-NMR Spectra of compound 2 ($CDCl_3$, 500 MHz)



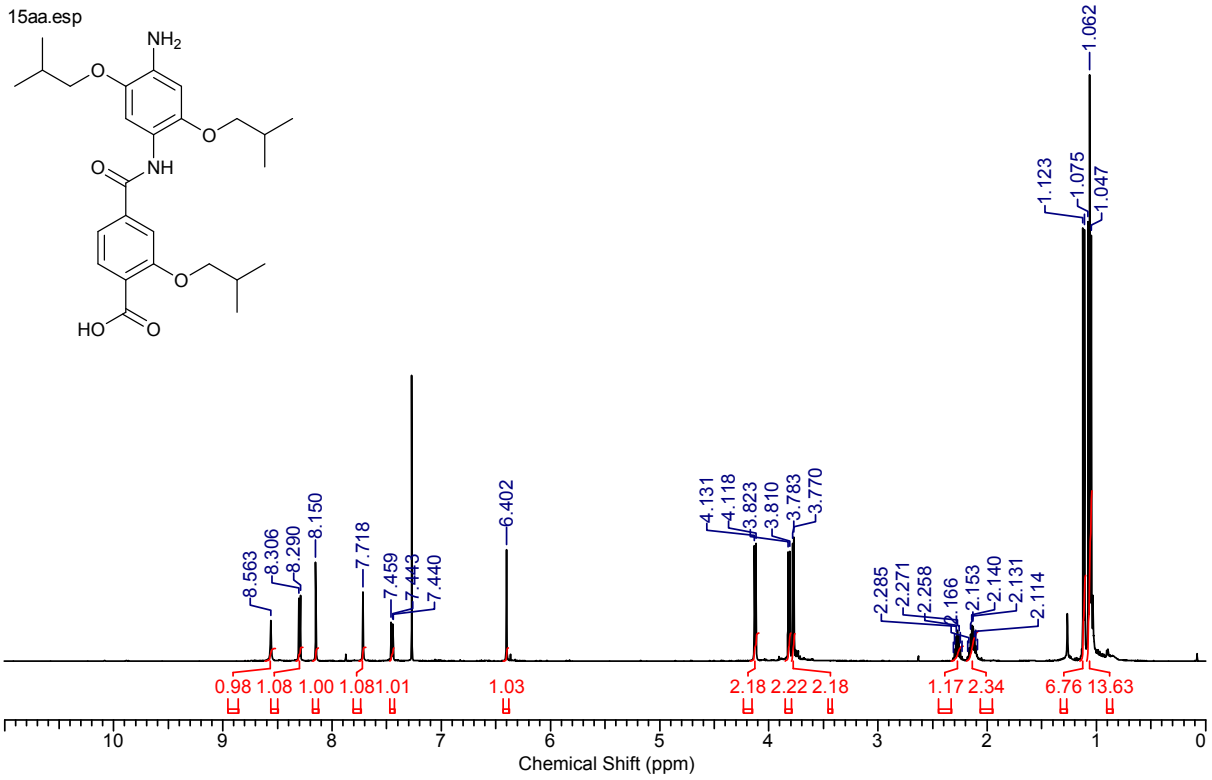
^{1}H-NMR Spectra of compound 3 ($CDCl_3$, 500 MHz)



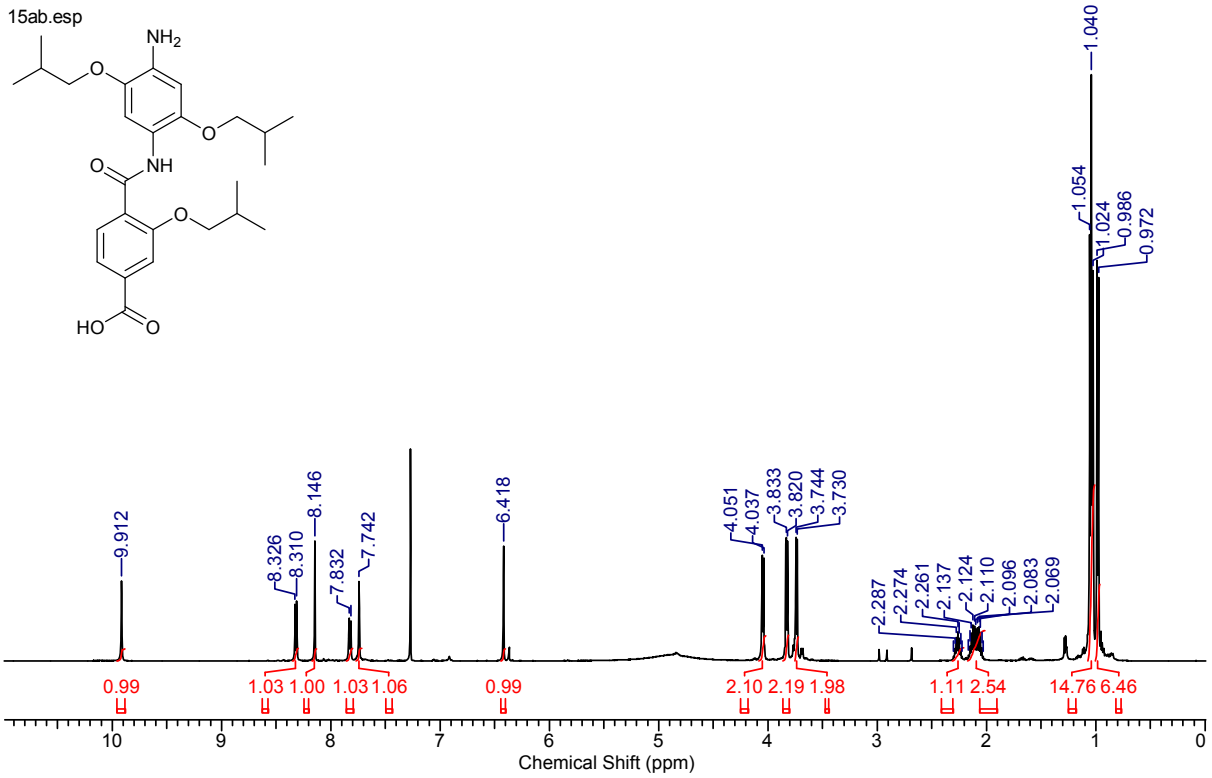
^{1}H-NMR Spectra of compound 4 ($CDCl_3$, 500 MHz)



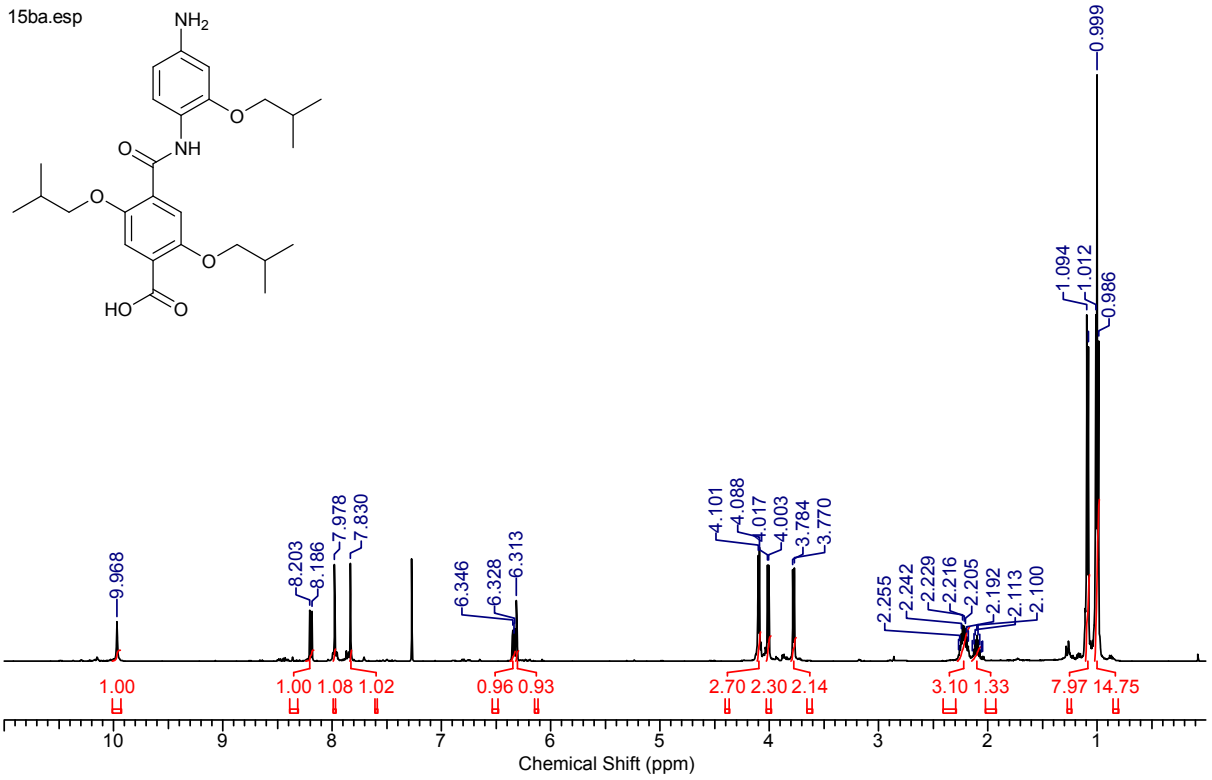
^{1}H-NMR Spectra of compound 14aa ($CDCl_3$, 500 MHz)



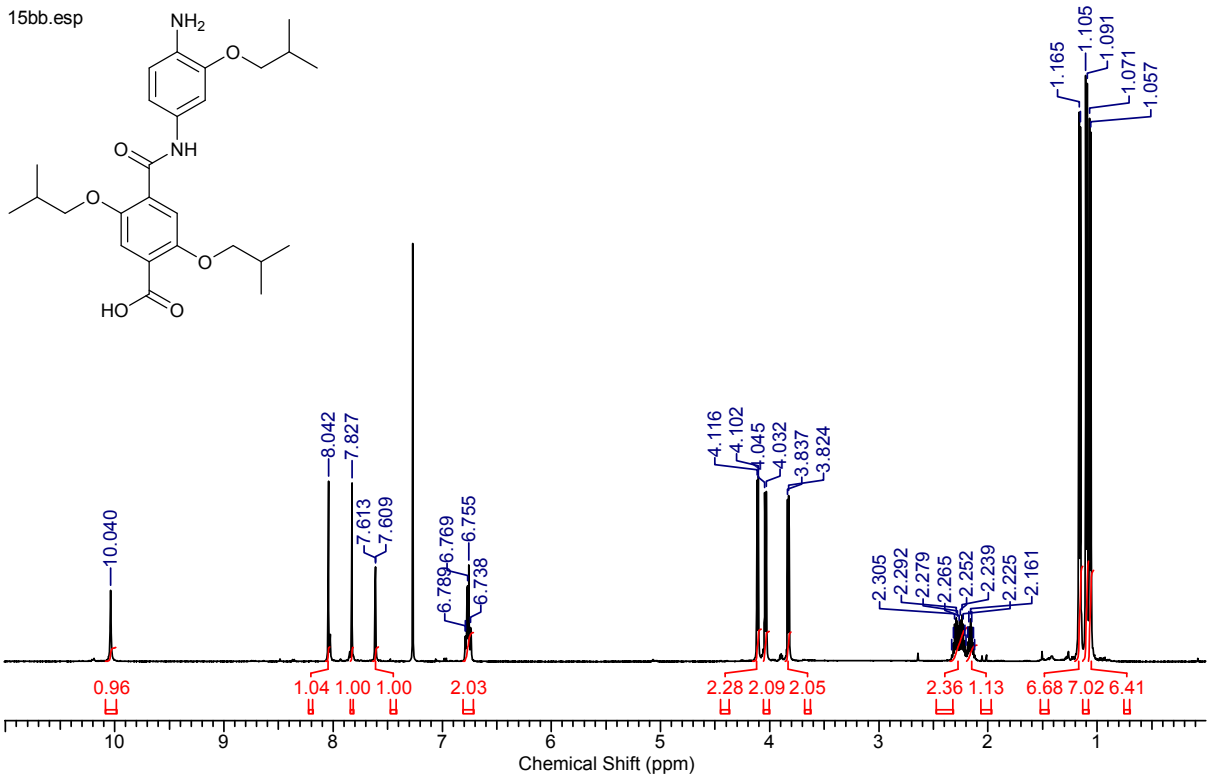
^{1}H-NMR Spectra of compound 14ab ($CDCl_3$, 500 MHz)



^{1}H-NMR Spectra of compound 14ba ($CDCl_3$, 500 MHz)

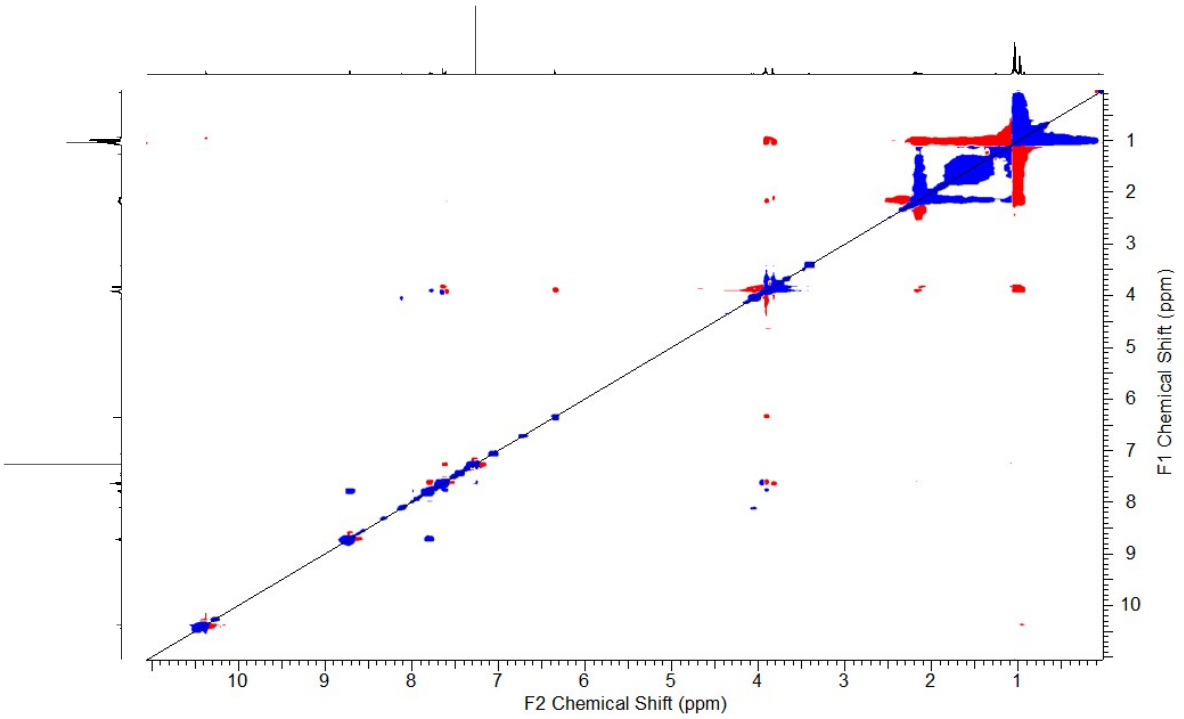


^{1}H-NMR Spectra of compound 14bb ($CDCl_3$, 500 MHz)

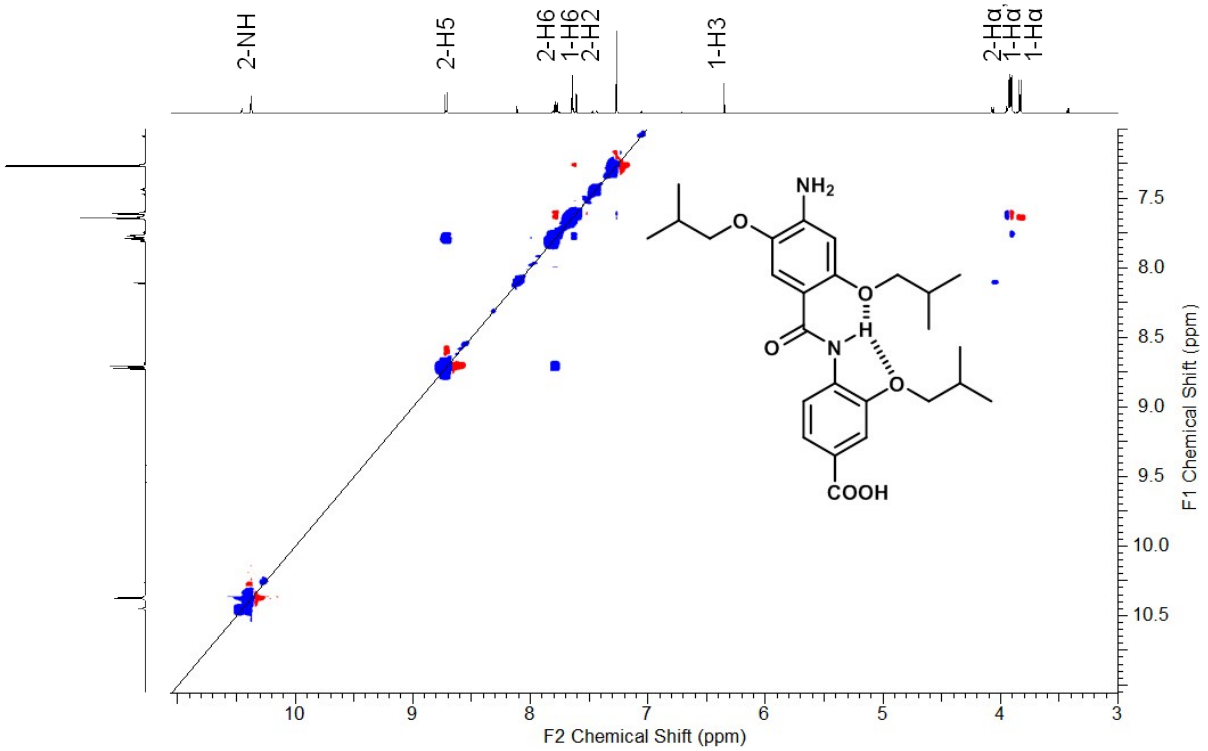


5. Conformational studies: 2D NMR SPECTRA (NOESY)

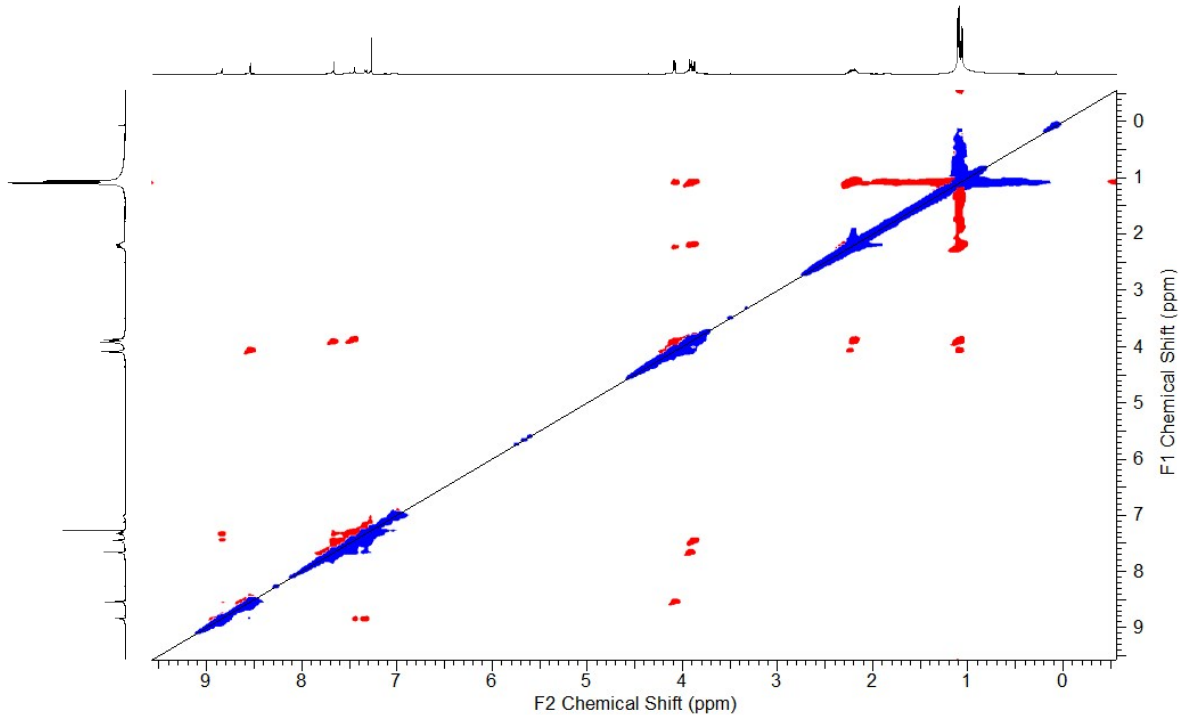
^{1}H-^{1}H NOESY Spectra of 1 (5 mM, $CDCl_3$, 500 MHz)



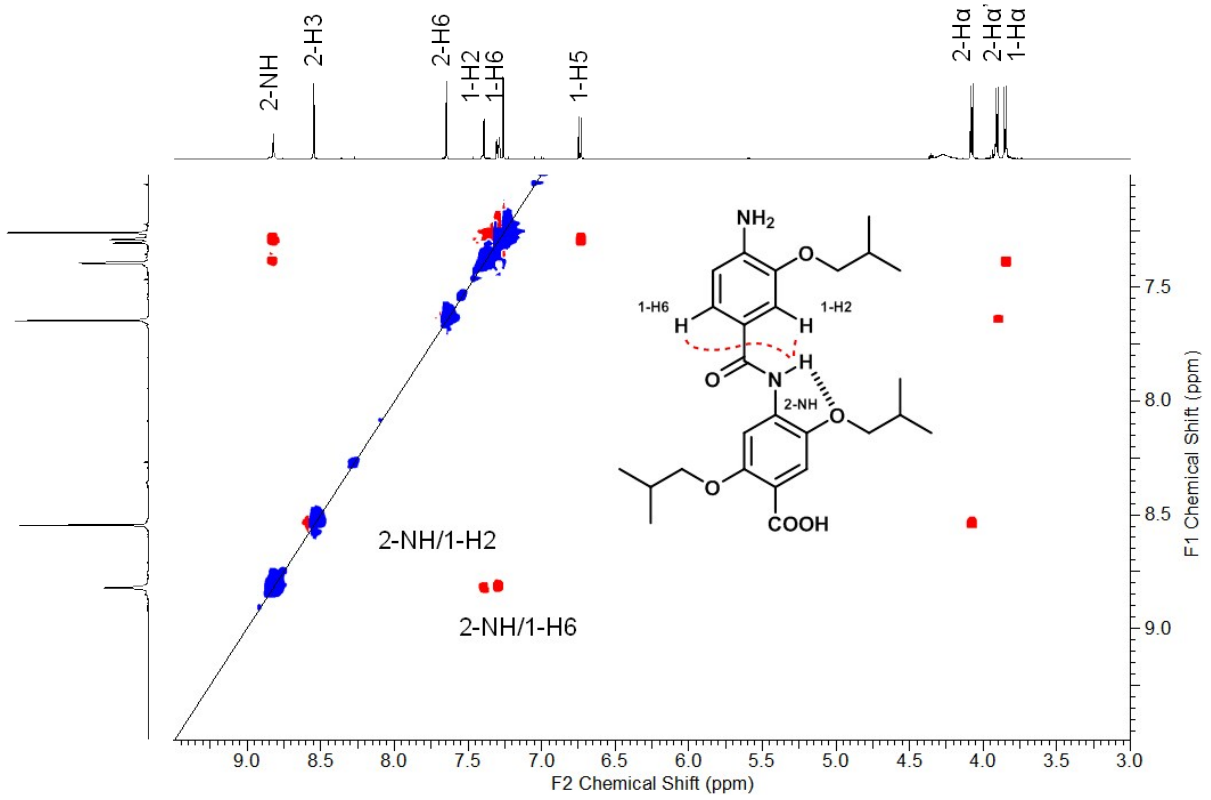
^{1}H–^{1}H NOESY spectra of 1 (aromatic region, $CDCl_3$, 500 MHz) illustrating key NOEs



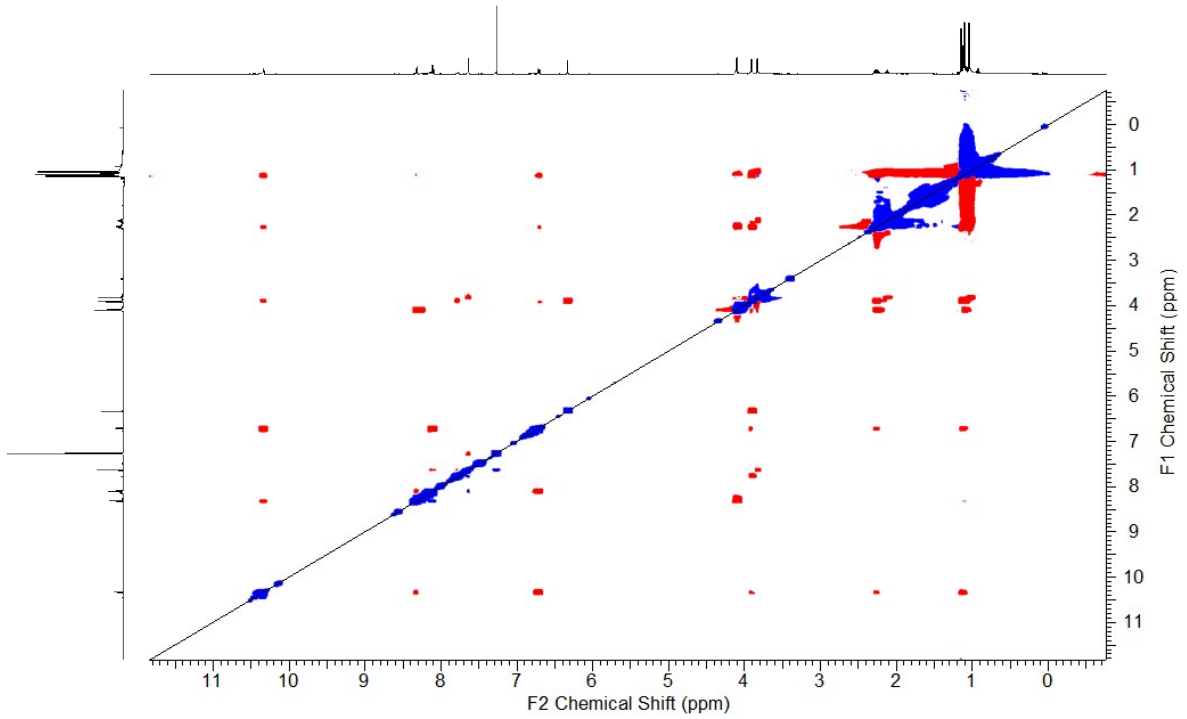
^{1}H-^{1}H NOESY Spectra of 2 (10 mM, $CDCl_3$, 500 MHz)



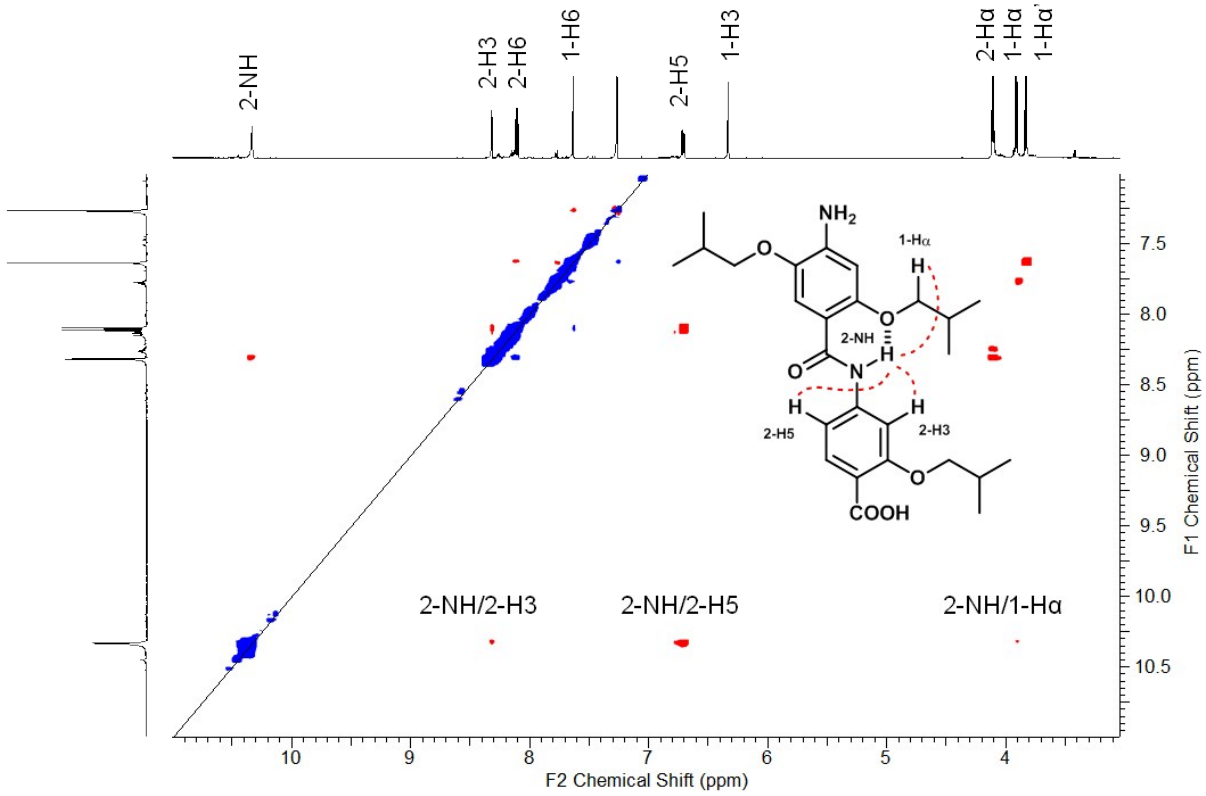
^{1}H–^{1}H NOESY spectra of 2 (aromatic region, $CDCl_3$, 500 MHz) illustrating key NOEs



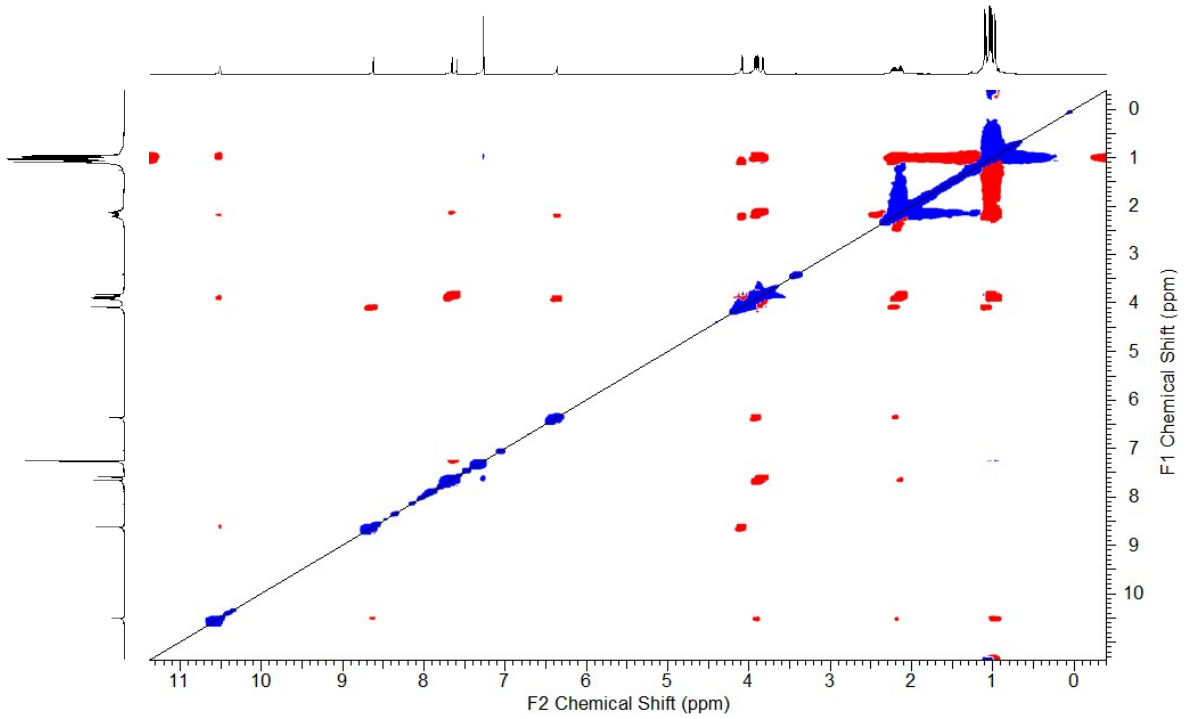
^{1}H-^{1}H NOESY Spectra of 3 (10 mM, $CDCl_3$, 500 MHz)



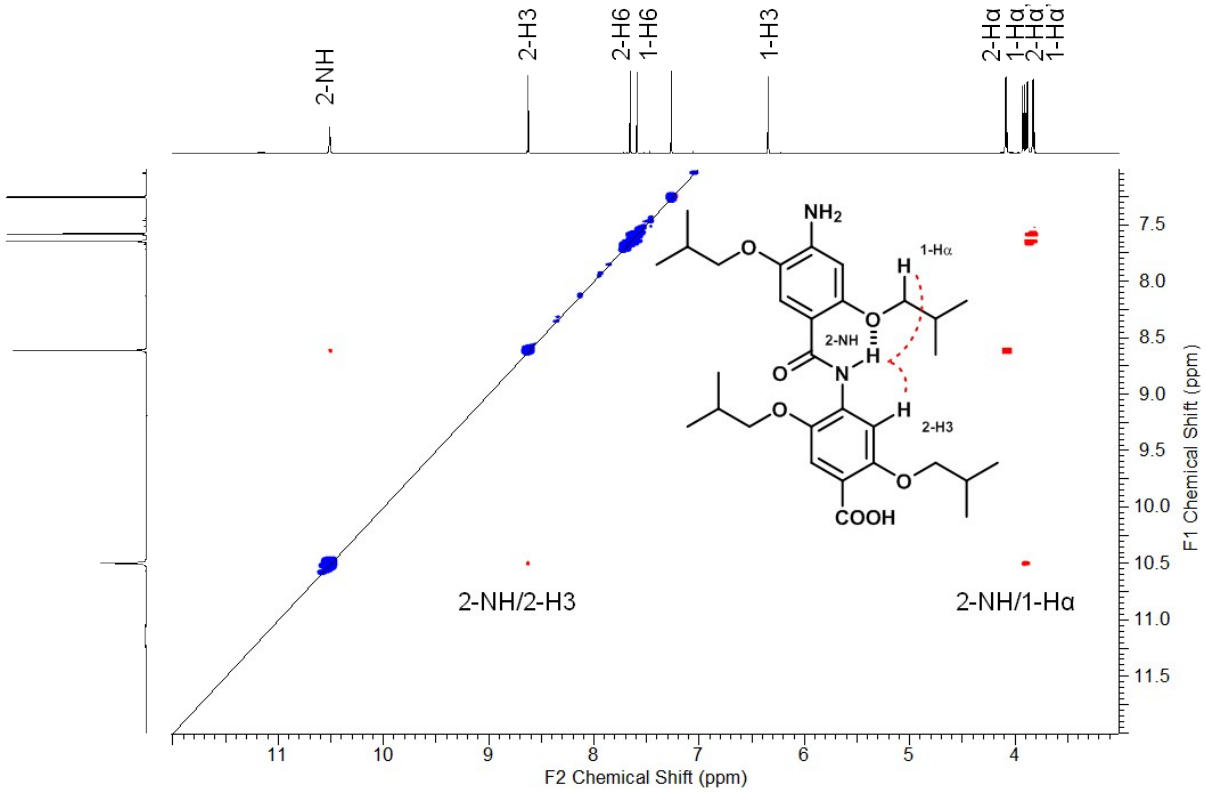
^{1}H–^{1}H NOESY spectra of 3 (aromatic region, $CDCl_3$, 500 MHz) illustrating key NOEs



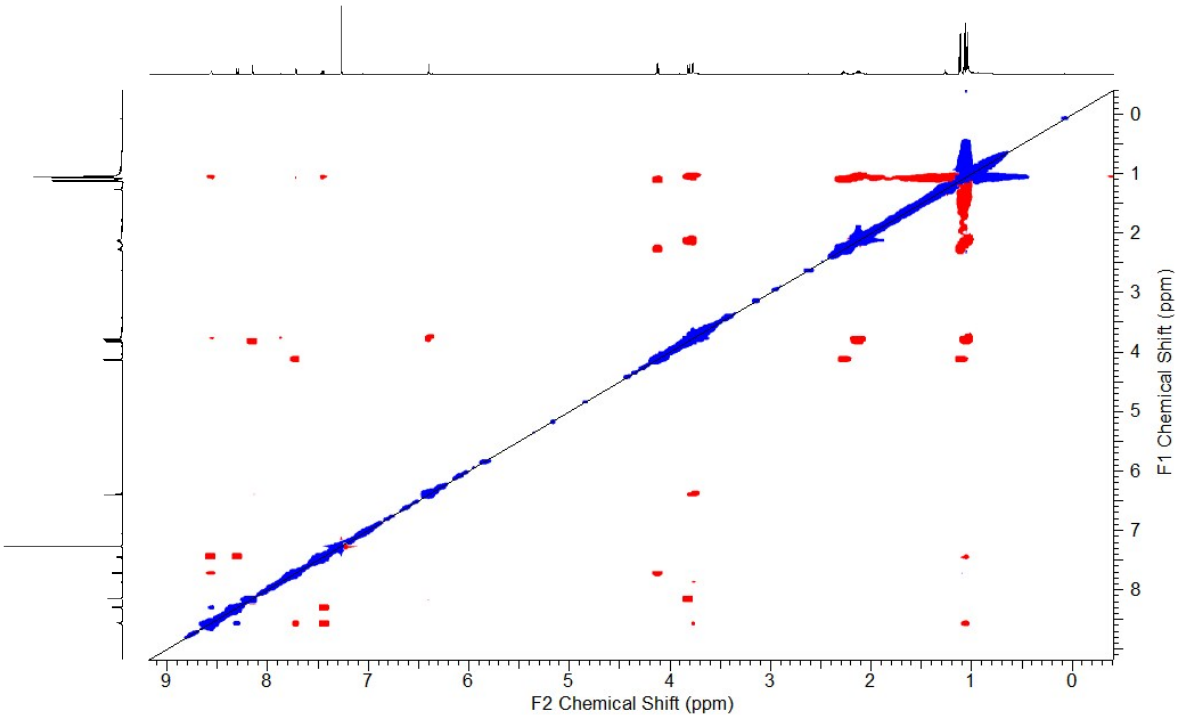
^{1}H-^{1}H NOESY Spectra of 4 (10 mM, $CDCl_3$, 500 MHz)



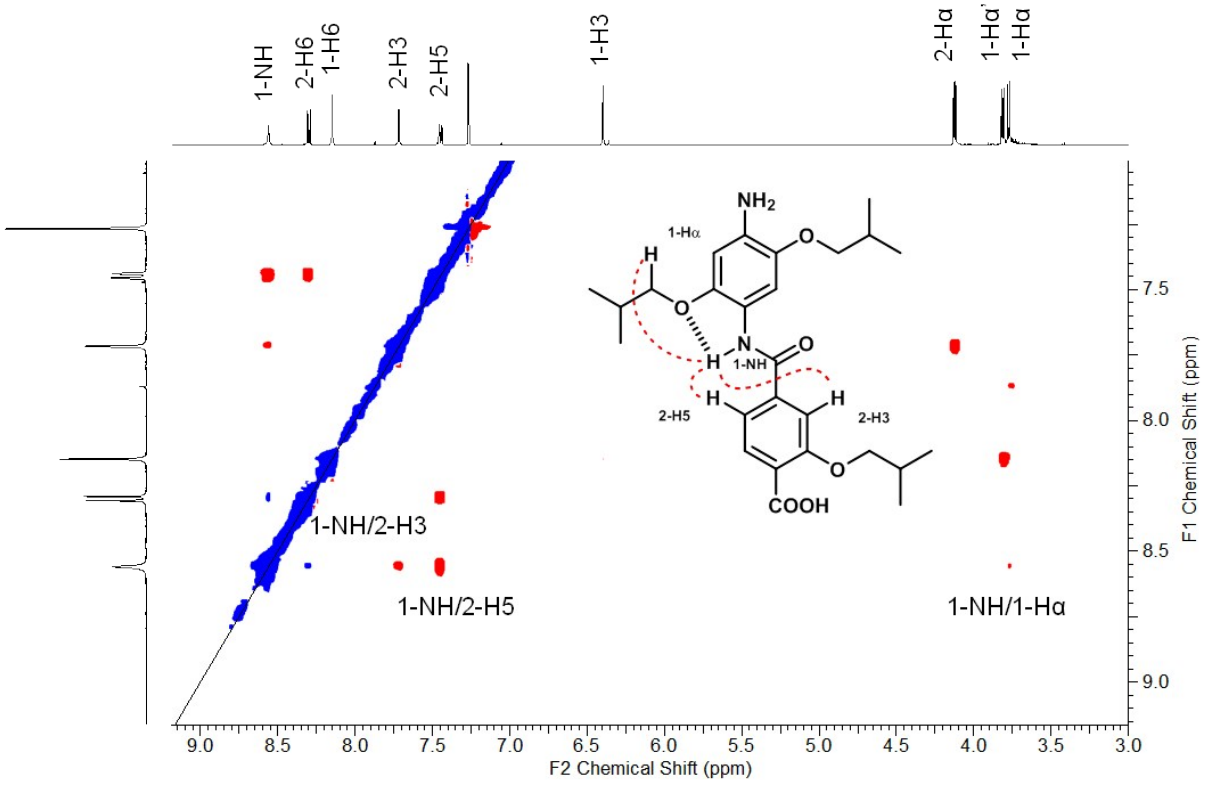
^{1}H–^{1}H NOESY spectra of 4 (aromatic region, $CDCl_3$, 500 MHz) illustrating key NOEs



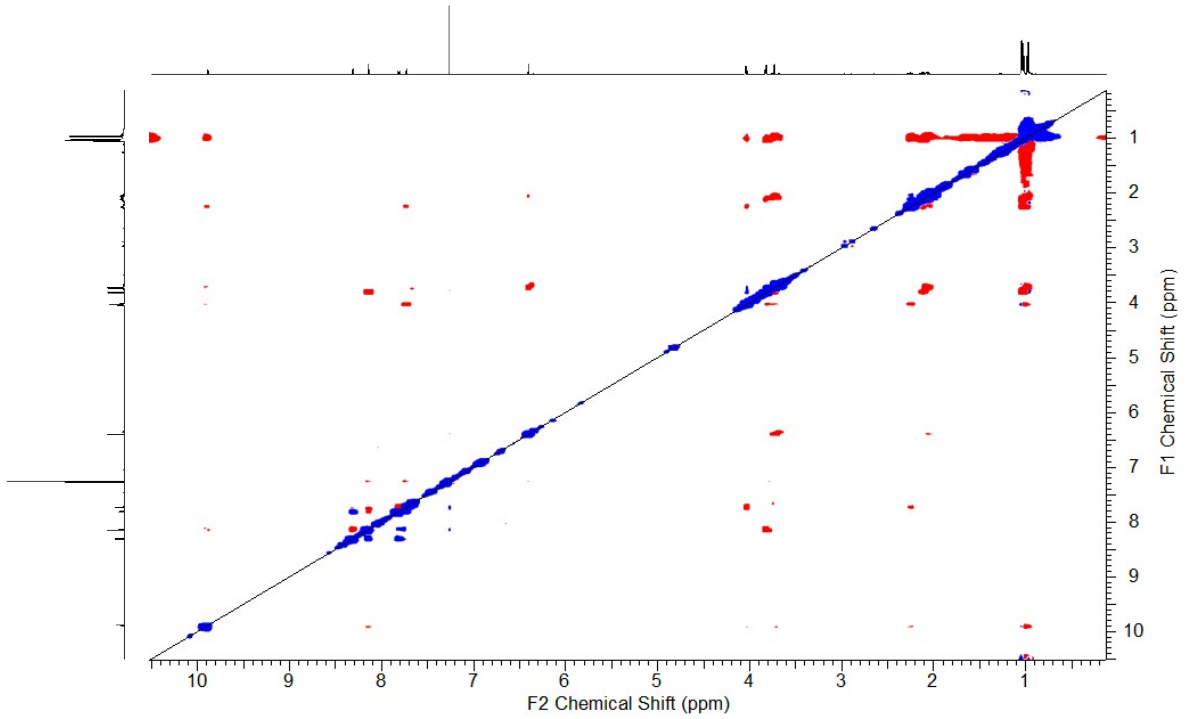
^{1}H-^{1}H NOESY Spectra of 14aa (5 mM, $CDCl_3$, 500 MHz)



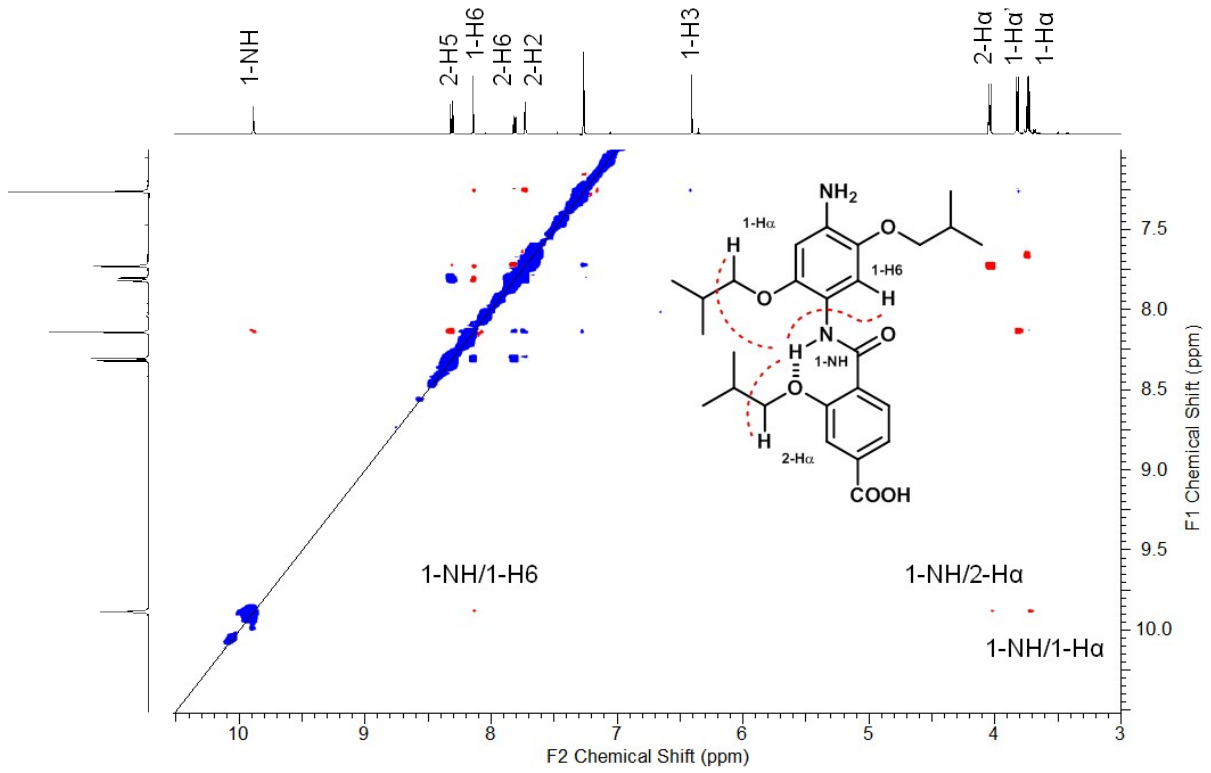
^{1}H–^{1}H NOESY spectra of 14aa (aromatic region, $CDCl_3$, 500 MHz) illustrating key NOEs



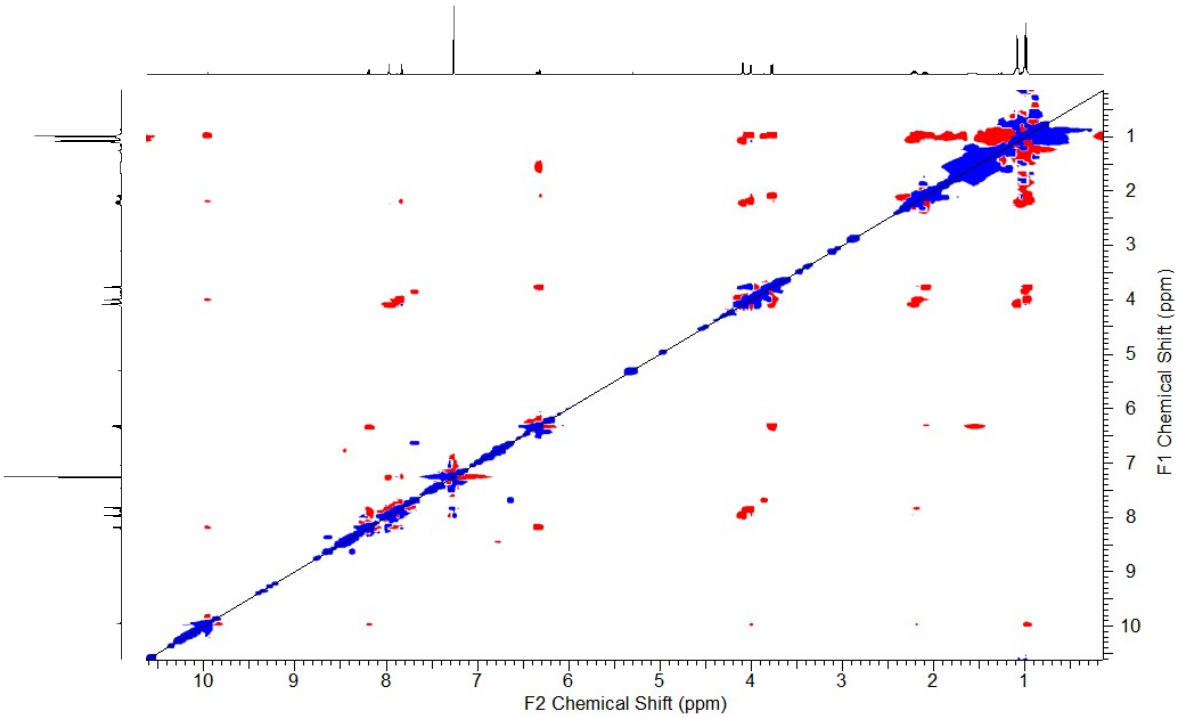
^{1}H-^{1}H NOESY Spectra of 14ab (10 mM, $CDCl_3$, 500 MHz)



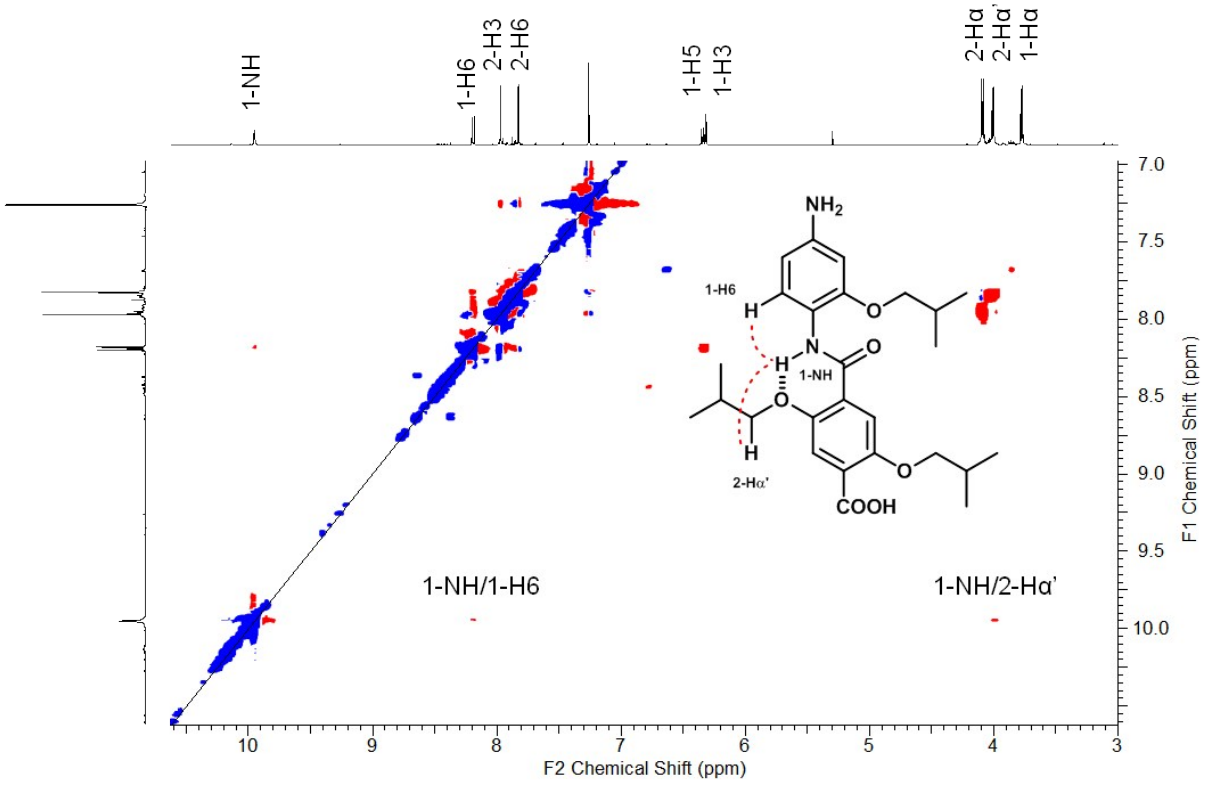
^{1}H–^{1}H NOESY spectra of 14ab (aromatic region, $CDCl_3$, 500 MHz) illustrating key NOEs



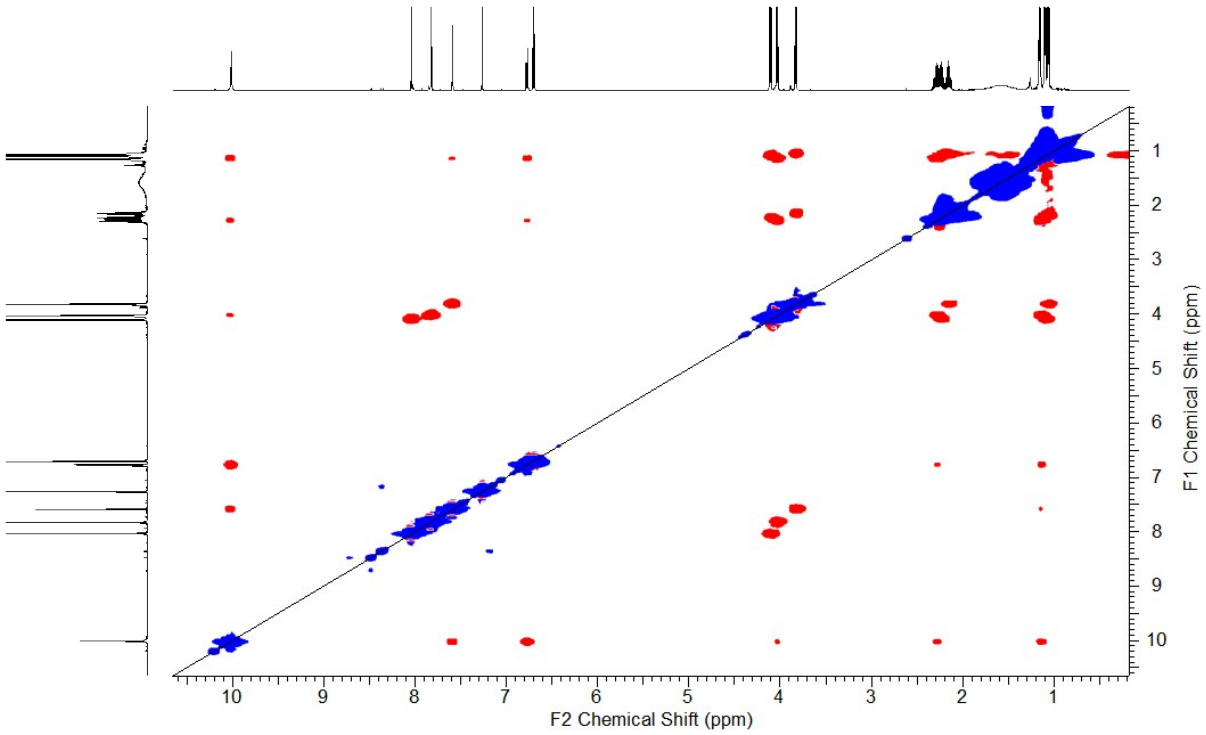
^{1}H-^{1}H NOESY Spectra of 14ba (10 mM, $CDCl_3$, 500 MHz)



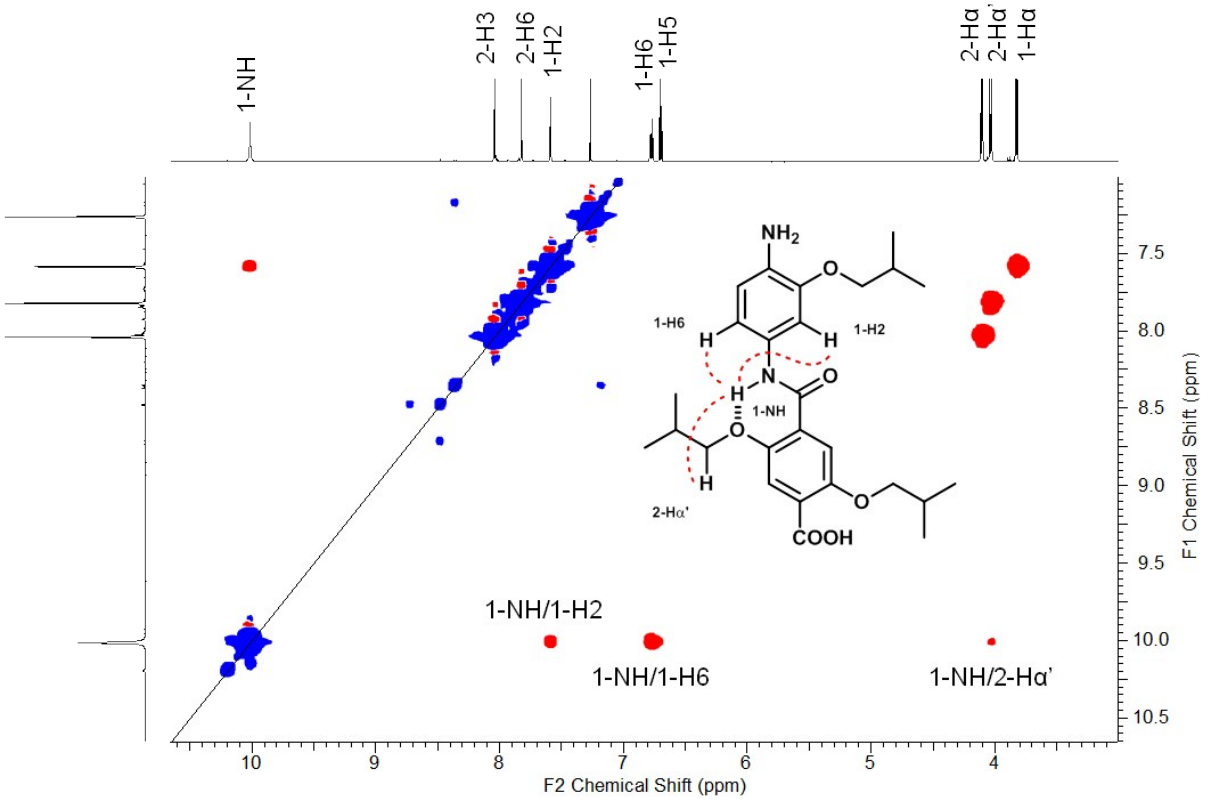
^{1}H–^{1}H NOESY spectra of 14ba (aromatic region, $CDCl_3$, 500 MHz) illustrating key NOEs



^{1}H-^{1}H NOESY Spectra of 14bb (10 mM, $CDCl_3$, 500 MHz)



^{1}H–^{1}H NOESY spectra of 14bb (aromatic region, $CDCl_3$, 500 MHz) illustrating key NOEs



6. H/D exchange studies

The relative rates of hydrogen/deuterium exchange in the conditions of a ^{1}H NMR study depend on different factors, such as the acidity of the NH proton, which will be affected by its electronic environment; the steric accessibility of the NH group and the strength of hydrogen bonding. The H atoms are anticipated to exchange more rapidly as more acidic they are, less sterical hindrance they present and weaker hydrogen bonds they perform.[1] Nevertheless, the correlation of the rate of exchange with the strength of the hydrogen bonding can be used to obtain additional information about these interactions.

The H/D exchange experiments were performed on compounds **1**, **2** and **14ba**, as models of the three different types of hydrogen bonding interactions. A 10% $CD_3OD/CDCl_3$ system was used with a substrate concentration of 10 mM to ensure pseudo first order kinetics. A distinct non-exchanging signal was used as an internal integration reference in order to minimize variability. The rate constant was determined from the slope of a non-linear least squares fit to the graph following **Equation 1** and the half-life of the H/D exchange determined using **Equation 2**.

Equation 1 $A_t = A_o e^{-kt}$

A_t *:* Integral of amide proton at time t

A_o *:* Integral of amide proton at time zero (fixed at 1)

k : reaction rate coeficient

Equation 2 $$t_{½} = \frac{ln\,2}{k}$$

The resulting graph is shown in **Figure S2**. The extracted $k_{H/D}$ and $t_{½}$ values for compounds **1**, **2** and **14ba** are listed in **Table S1**, together with the values for two other reported compounds **43** and **44**

from our group (**Figure S3**).[2-3] The order of magnitude for the amide proton exchange rate constants suggest the presence of a S(5), S(6) and bifurcated S(5)/S(6) H-bonding for compounds **2**, **14ba** and **1** respectively. These results are consistent with the proposed conformations from the ^{1}H-^{1}H NOESY analyses.

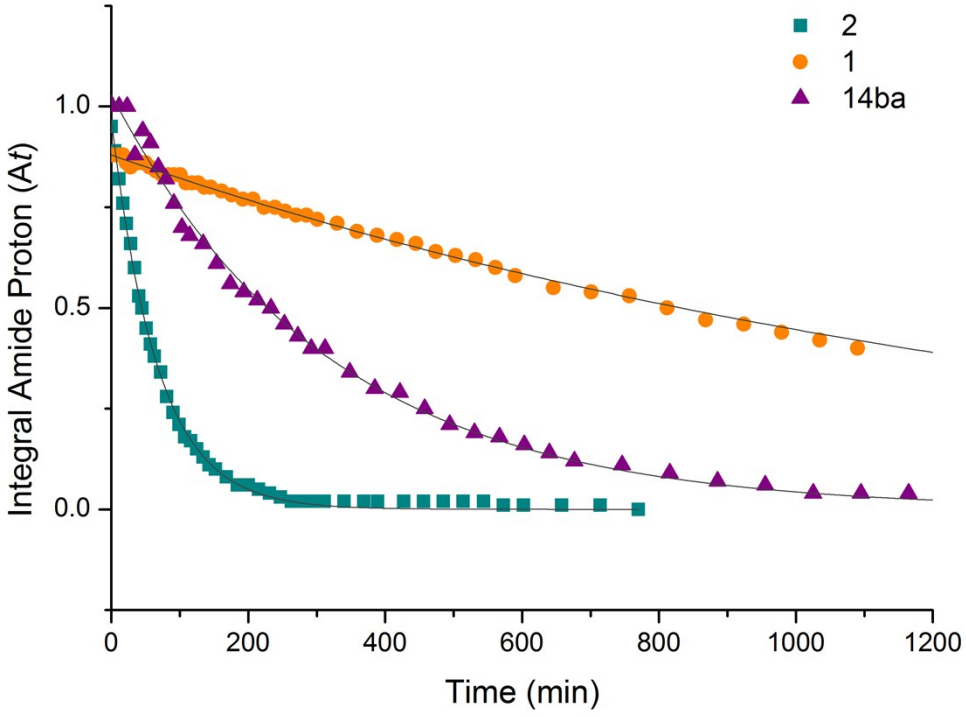


Figure S2. H/D exchange kinetics of compounds **1**, **2** and **14ba** in 10% $CD_3OD/CDCl_3$.

Table S1. Kinetic constants and $t_{1/2}$ based on H/D exchange in 10% $CD_3OD/CDCl_3$.

	$k_{H/D}$ (min^{-1})	$t_{½}$ (min)	H bonding
14ba	0.00305 ± 0.00005	228 ± 3	S(6)
1	6.7857×10^{-4} ± 0.0000093	1021.5 ± 14	S(5)/S(6)
2	0.01485 ± 0.00017	46.7 ± 0.5	S(5)
44 (1-NH)	0.00176 ± 0.00005	394 ± 12	S(6)
44 (2-NH)	0.00230 ± 0.00005	301 ± 6	S(6)
45 (1-NH)	0.0212 ± 0.0004	32.7 ± 0.6	S(5)
45 (2-NH)	0.0225 ± 0.0005	30.8 ± 0.7	S(5)

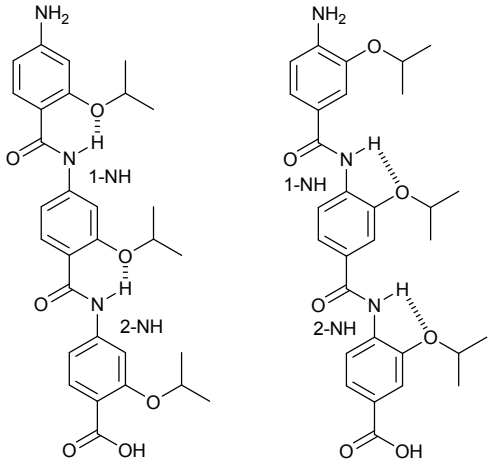


Figure S3. Reported reference compounds **44** and **45**, intramolecular hydrogen bonding interactions are shown.[2-3]

6. Additional Crystallographic Figures

Prismatic crystals were obtained by the slow evaporation of a solution of the compound in chloroform. A crystal of size 0.4 x 0.4 x 0.3 mm was used for data collection; θ range = 2.37≤θ≤ 26.13°, Crystals belong to the monoclinic space group *C2/c*, with one molecule in the asymmetric unit; Formula = $C_{26}H_{36}N_2O_6$; Formula weight = 472.57; a = 22.224(3) Å, b = 16.806(2) Å; c = 15.8146(19) Å, β = 113.877(6)°, Volume = 5401.2(12), Z = 8, D (calculated): 1. 162 g/cm^3, μ = 0.082 mm^{-1}, Reflections collected 19204; Independent reflections 5305; Observed reflections 4102 [I >2σ(I)]; R value = 0.0445, wR_2 = 0.1195. Measurements were carried out at 120 K on a Bruker-Nonius Apex X8 diffractometer equipped with an Apex II CCD detector and using graphite monochromated Mo-Kα radiation from a FR591 rotating anode generator. The structure was solved by direct methods using SHELXLS-97 and refined using SHELXL-97. . All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions and refined using a riding model. All Uiso(H) values were constrained to be 1.2 times (1.5 for methyl) Ueq of the parent atom. CCDC 1426299 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. There is minor disorder of one isobutyl group, with the orientation represented by C26 modelled with an occupancy of 0.75 and that of C26a of 0.25.

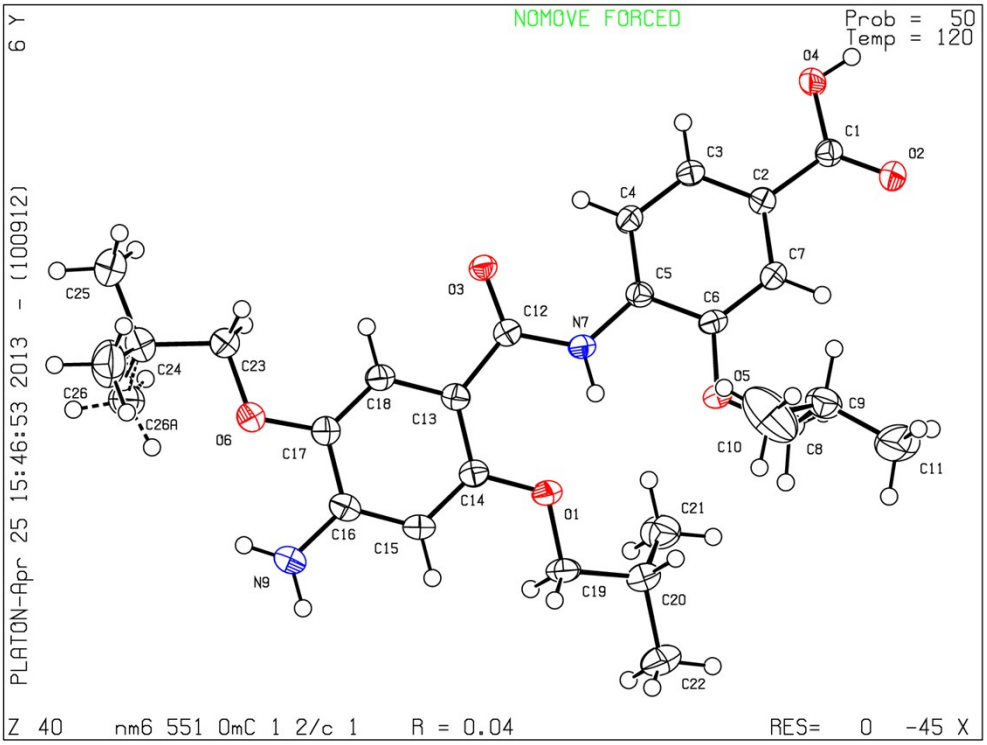


Figure S4. (a) Single X-ray crystal structure data for dimer **1**. (b) Solid State Packing Diagram for compound **1**.

7. Molecular Modelling

A conformational search was performed on the complete set of dimers. The structures were minimised by employing a full Monte Carlo search in the software Macromodel® using the Merk Molecular Force Fields (MMFs) method and sampling a total of 50,000 structures. Water was chosen as implicit solvent and free rotation around the amide bonds was allowed in order to increase the accuracy of the conformational search.

All the conformations within 1.5 kJ/mol from the lowest energy conformation were superimposed with the ER co-activator helix (PDB: 2QZO). A mean value of the Root Mean Square Deviation (RMSD) was calculated from the superimposition of the oxygen of the alkoxy group and the alpha carbon of the key aminoacids of the co-activator helix. The alignment was also investigated in the reverse dipole sequence (Fig S5-S11 – with RMSD values and the best alignment shown in a box). The RMSD values are summarized in each figure.

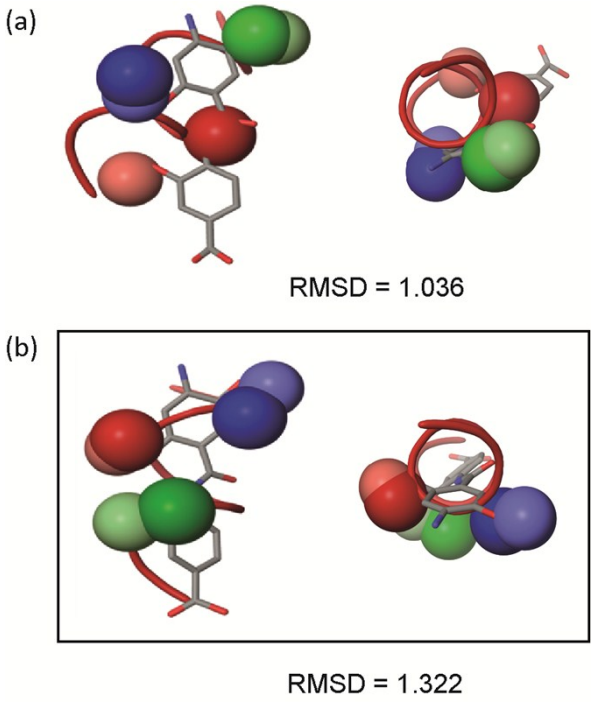


Figure S5. Overlay of the compound **1** with the native co-activator peptide. Co-activator residues are in dark colours and helix mimetics residues are in light colours: (a) Parallel alignment with the peptide dipole moment; (b) Antiparallel alignment with the peptide dipole moment (RMSD values are given for both alignments and the best alignment shown in a box).

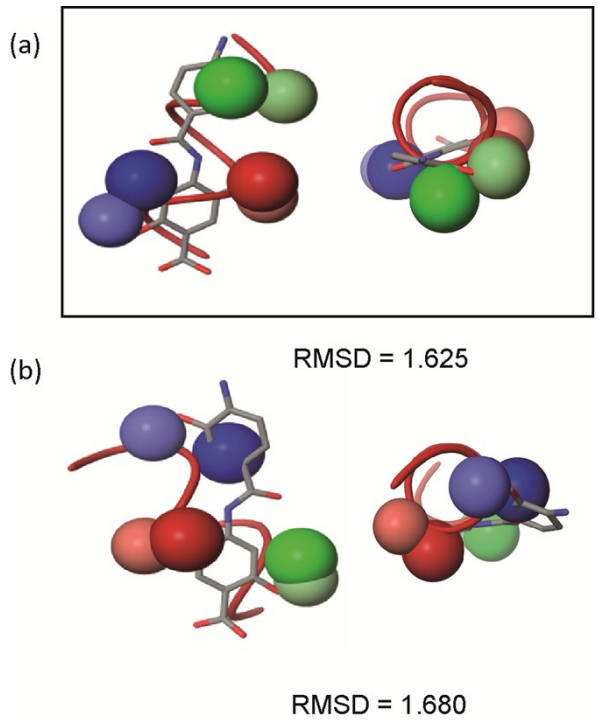


Figure S6. Overlay of the compound **2** with the native co-activator peptide. Co-activator residues are in dark colours and helix mimetics residues are in light colours: (a) Parallel alignment with the peptide dipole moment; (b) Antiparallel alignment with the peptide dipole moment (RMSD values are given for both alignments and the best alignment shown in a box).

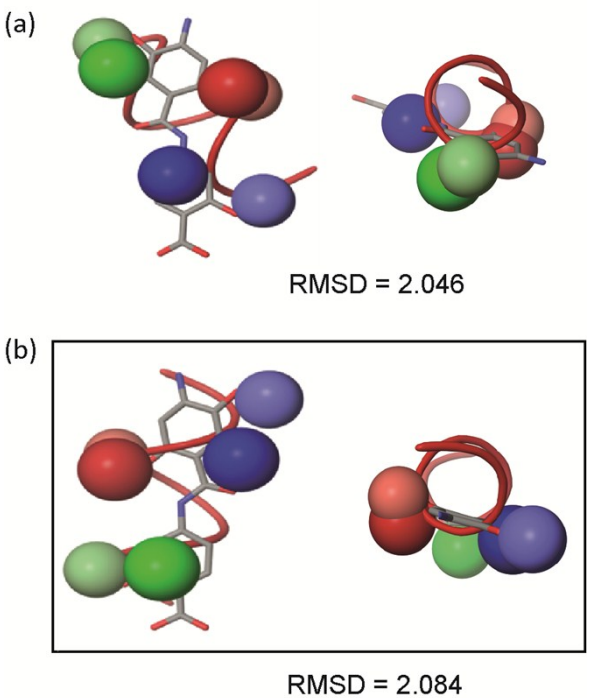


Figure S7. Overlay of the compound 3 with the native co-activator peptide. Co-activator residues are in dark colours and helix mimetics residues are in light colours: (a) Parallel alignment with the peptide dipole moment; (b) Antiparallel alignment with the peptide dipole moment (RMSD values are given for both alignments and the best alignment shown in a box).

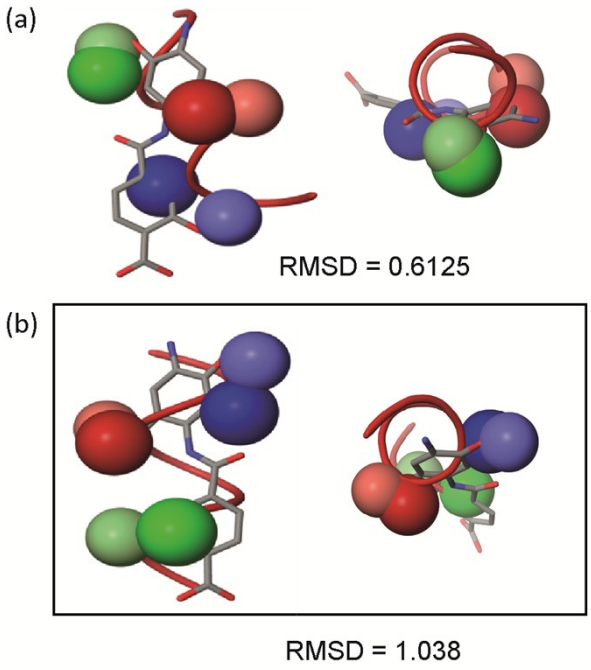


Figure S8. Overlay of the compound **14aa** with the native co-activator peptide. Co-activator residues are in dark colours and helix mimetics residues are in light colours: (a) Parallel alignment with the peptide dipole moment; (b) Antiparallel alignment with the peptide dipole moment (RMSD values are given for both alignments and the best alignment shown in a box).

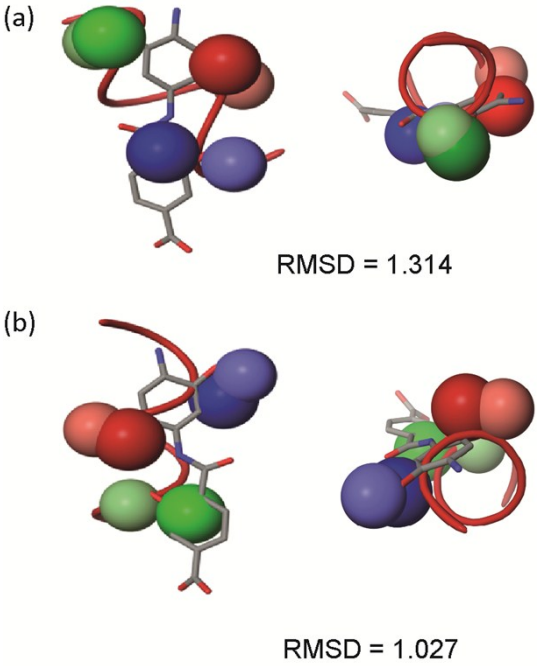


Figure S9. Overlay of the compound **14ab** with the native co-activator peptide. Co-activator residues are in dark colours and helix mimetics residues are in light colours: (a) Parallel alignment with the peptide dipole moment; (b) Antiparallel alignment with the peptide dipole moment (RMSD values are given for both alignments and the best alignment shown in a box).

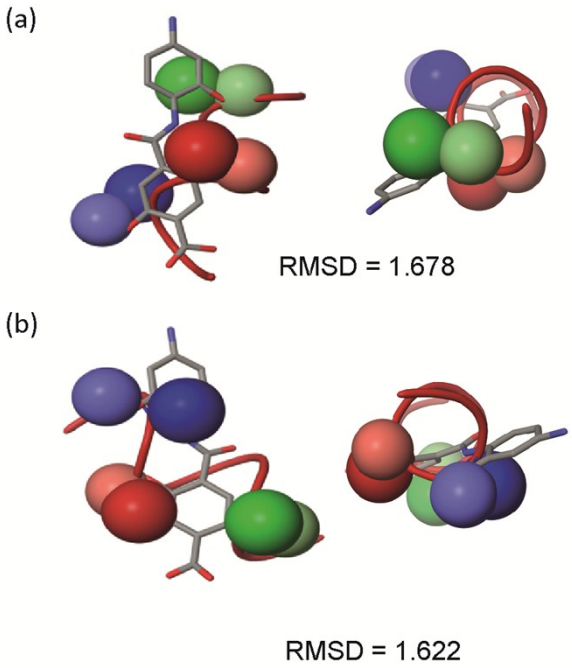


Figure S10. Overlay of the compound **14ba** with the native co-activator peptide. Co-activator residues are in dark colours and helix mimetics residues are in light colours: (a) Parallel alignment with the peptide dipole moment; (b) Antiparallel alignment with the peptide dipole moment (RMSD values are given for both alignments and the best alignment shown in a box).

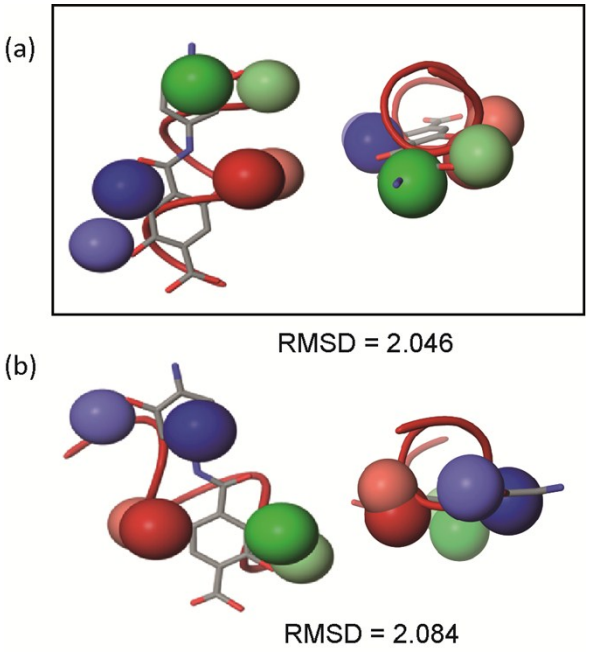


Figure S11. Overlay of the compound **14bb** with the native co-activator peptide. Co-activator residues are in dark colours and helix mimetics residues are in light colours: (a) Parallel alignment with the peptide dipole moment; (b) Antiparallel alignment with the peptide dipole moment (RMSD values are given for both alignments and the best alignment shown in a box).

8. Docking

The LBD of ERα (PDB ID: 2QZO) and AR (PDB: 1T7F) were prepared for docking using the Protein Preparation Wizard (Schrödinger) function in Maestro. Once the protein was refined, Glide (Schrödinger) was then used to create a grid box for docking. The structures of the ER and AR are dimeric; therefore only one monomer was used within the docking grid. The dimensions and position of the grid box were adjusted according to the coactivator binding pose, which must be centered and lie fully within the grid. The LigPrep (Schrödinger) function was then used to prepare the set of compounds for docking. Once arranged, the resulting compounds were docked into the LBD of the prepared protein using Glide XP (extra precision) mode.

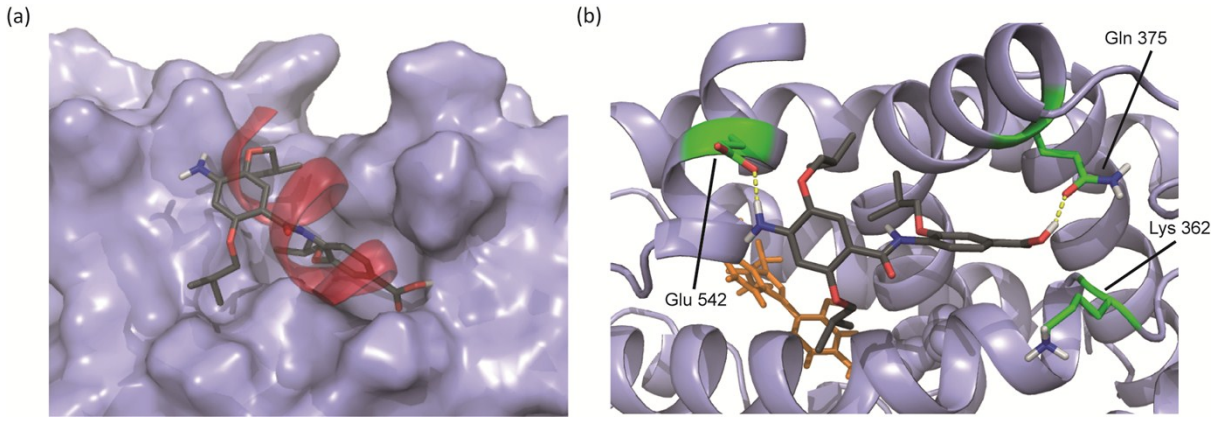


Figure S12. (a) Proposed binding mode of compound **1** in the ER co-activator-binding groove with the native helix in transparent red. (b) Proposed hydrogen bonding interactions between compound **1** and ER "charge clamp" residues.

9. References

[1] L. R. Steffel, T. J. Cashman, M. H. Reutershan, B. R. Linton, *J. Am. Chem. Soc.* **2007**, *129*, 12956-12957.

[2] V. Azzarito, P. Prabhakaran, A. I. Bartlett, N. S. Murphy, M. J. Hardie, C. A. Kilner, T. A. Edwards, S. L. Warriner, A. J. Wilson, *Org. Biomol. Chem.* **2012**, *10*, 6469-6472.

[3] P. Prabhakaran, V. Azzarito, T. Jacobs, M. J. Hardie, C. A. Kilner, T. A. Edwards, S. L. Warriner, A. J. Wilson, *Tetrahedron* **2012**, *68*, 4485-4491.