Supporting Information

Amphiphilic α-helix mimetics based on a benzoylurea scaffold

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1. General Information

Reactions were carried out under a nitrogen or argon atmosphere in oven-dried glassware unless otherwise stated. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents.

1.1. Solvent & reagents

Anhydrous tetrahydrofuran and dichloromethane (from commercial sources) were obtained by filtration through activated alumina (powder ~150 mesh, pore size 58 Å, basic, Sigma-Aldrich) columns, or were dried on an MB-SPS-800 dry solvent system. Other solvents and reagents were used directly as received from commercial suppliers. Petrol refers to distilled light petroleum of fraction (30 ˚C - 40 ˚C).

1.2. Chromatography

Flash column chromatography was carried out using VWR Kieselgel 60 silica gel (60-63 µm). Thin-layer chromatography was carried out using Merck Kieselgel 60 F254 (230-400 mesh) fluorescent treated silica, visualized under UV light (250 nm) and by staining with aqueous potassium permanganate solution.

1.3. Spectroscopy

^{1}H and ^{13}C NMR spectra were recorded using a Bruker 500, 400, 300 or 250 MHz spectrometer running Topspin™ software and are quoted in ppm for measurement against a tetramethylsilane (TMS) or residual solvent peaks as internal standards. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (*J*) are given in Hertz (Hz). The ^{1}H NMR spectra are reported as follows: δ / ppm (number of protons, multiplicity, coupling constant *J* / Hz (where appropriate), assignment). Multiplicity is abbreviated as follows: s = singlet, br = broad, d = doublet, dd = doublet of doublets, t = triplet, dt = doublet of triplet, q = quartet, dq = doublet of quartet, quint. = quintet, sept. = septet, m = multiplet, v = very. Compound names are those generated by ChemBioDraw™ (CambridgeSoft) following IUPAC nomenclature. However, the NMR assignment numbering used is arbitrary and does not follow any particular convention. Numbering of compounds is illustrated on the spectra themselves; *vide infra*. The ^{13}C NMR spectra are reported in δ / ppm. Two-dimensional (COSY, HSQC, HMBC) NMR spectroscopy was used to assist the assignment of signals in the ^{1}H and ^{13}C NMR spectra. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer from a thin film deposited onto a sodium chloride plate or a diamond ATR module. Only selected maximum absorbances (ν_{max}) of the most intense peaks are reported (cm^{-1}). Low-resolution mass spectra were recorded on a Waters LCT premier XE Micromass spectrometer (ESI). High-resolution mass spectra were recorded on a Bruker MicroTof mass spectrometer (ESI) by the internal service at the Department of Organic Chemistry, University of Oxford. Melting points were recorded using a Leica Galen III hot-stage microscope apparatus and are reported uncorrected in degrees Celsius (˚C).

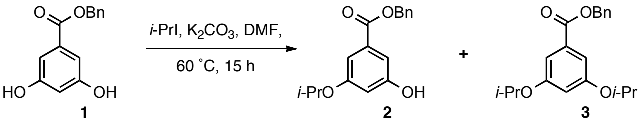
2. Practical experimental

Benzyl 3,5-dihydroxybenzoate: 1

According to a literature preparation[1] benzyl bromide (11.7 mL, 98.4 mmol) was added to a stirred solution of 3,5-dihydroxybenzoic acid (10.1 g, 65.6 mmol) and potassium hydrogen carbonate (7.87 g, 78.7 mmol) in *N*,*N*-dimethylformamide (110 mL). After overnight stirring at 40 ˚C the reaction was diluted with dichloromethane (700 mL), partitioned with ammonium chloride (700 mL) and extracted with dichloromethane (3 x 500 mL). The organic layers were combined, dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (2 : 1, petrol : diethyl ether) affording the title compound **1** (15.8 g, 64.8 mmol, 99 % yield) as a clear oil.

ν_{max} (neat) 3353, 1694, 1608, 1387, 1227, 1104, 1001, 969; δ_H (500 MHz, $(CD_3)_2SO$) 9.66 (2H, s, OH), 7.47 - 7.29 (5H, m, Ar-H), 6.88 (2H, d, *J* 2.2, H-1, H-5), 6.47 (1H, t, *J* 2.2, H-3), 5.30 (2H, s, CH$_2$); δ_C (125 MHz, $(CD_3)_2SO$) 166.5, 159.5, 137.1, 132.1, 129.4, 129.0, 128.9, 127.3, 108.4, 108.2, 108.0, 66.9; HRMS (ESI) found 267.0631; $C_{14}H_{12}NaO_4$ [M+Na]$^+$ requires 267.0628.

Benzyl 3-hydroxy-5-isopropoxybenzoate: 2

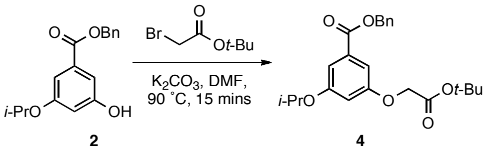


Isopropyl iodide (2.48 mL, 24.8 mmol) was added to a stirred solution of benzyl 3,5-dihydroxybenzoate **1** (5.05 g, 20.7 mmol) and potassium carbonate (4.57 g, 31.1 mmol) in *N*,*N*-dimethylformamide (25 mL). After overnight stirring at 60 ˚C the reaction was diluted with dichloromethane (500 mL), partitioned with ammonium chloride (500 mL) and extracted with dichloromethane (3 x 300 mL). The organic layers were combined, dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (20 : 1 → 1 : 2 petrol : diethyl ether) affording, in order of elution, 3,5-diisopropoxybenzoic acid **3** (1.64 g, 5.00 mmol, 24 % yield), the title compound **2** (2.69 g, 9.41 mmol, 45 % yield) and starting material **1** (1.54 g, 6.31 mmol, 30 % yield) as clear oils.

ν_{max} (neat) 3390, 2978, 1693, 1594, 1449, 1318, 1226, 1154, 1105, 1025, 766, 696; δ_H (500 MHz, $CDCl_3$) 7.50 - 7.35 (5H, m, Ar-H), 7.29 - 7.21 (2H, m, H-1, H-5), 6.70 (1H, t, *J* 2.2, H-3), 6.47 (1H, s, OH), 5.49 (2H, s, CH_2), 4.59 (1H, sept, *J* 6.1, $CH(CH_3)_2$), 1.37 (6H, d, *J* 6.1, $CH(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 167.2, 159.6, 157.5, 136.1, 132.3, 129.1, 128.9, 128.8, 128.6, 128.0, 110.1, 109.8, 109.7, 109.6, 108.8, 70.9, 70.7, 67.6, 22.4; HRMS (ESI) found 309.1084; $C_{17}H_{18}NaO_4$ $[M+Na]^+$ requires 309.1097.

3,5-Diisopropoxybenzoic acid **3**; ν_{max} (neat) 2977, 1719, 1592, 1448, 1376, 1296, 1156, 1113, 1003, 766; δ_H (500 MHz, $CDCl_3$) 7.48 - 7.31 (5H, m, Ar-H), 7.19 (2H, d, *J* 2.3, Ar-H), 6.62 (1H, t, *J* 2.3, Ar-H), 5.35 (2H, s, CH_2), 4.57 (2H, sept, *J* 6.1, $CH(CH_3)_2$), 1.34 (12H, d, *J* 6.1, $CH(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 166.8, 159.4, 136.5, 132.4, 129.0, 128.6, 128.6, 109.5, 109.3, 70.7, 67.2, 22.4; HRMS (ESI) found 351.1555; $C_{20}H_{24}NaO_4$ $[M+Na]^+$ requires 351.1567.

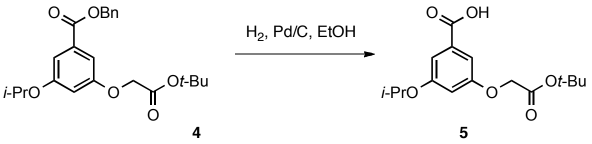
*Benzyl 3-(2-(*tert*-butoxy)-2-oxoethoxy)-5-isopropoxybenzoate: 4*



tert-Butyl bromoacetate (330 μL, 2.19 mmol) was added to a stirred solution of benzyl 3-hydroxy-5-isopropoxybenzoate **2** (521 mg, 1.82 mmol) and potassium carbonate (502 mg, 3.64 mmol) in *N*,*N*-dimethylformamide (3.0 mL). After 15 mins at 90 ˚C, t.l.c. (2 : 1, petrol : diethyl ether) indicated complete consumption of starting material (R_f 0.5) and the formation of a major product (R_f 0.8). The reaction was diluted with dichloromethane (50 mL), partitioned with ammonium chloride (50 mL) and extracted with dichloromethane (3 x 40 mL). The organic layers were combined, dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (8 : 1, petrol : diethyl ether) affording the title compound **4** (720 mg, 1.80 mmol, 99 % yield) as a clear oil.

ν_{max} (neat) 2978, 1752, 1719, 1594, 1452, 1370, 1299, 1223, 1147, 1107, 1012, 844, 765, 697; δ_H (500 MHz, $CDCl_3$) 7.50 - 7.36 (5H, m, Ar-H), 7.32 (1H, br, Ar-H), 7.20 (1H, br, Ar-H), 6.73 (1H, t, *J* 2.3, H-3), 5.39 (2H, s, CH_2), 4.61 (1H, sept, *J* 6.1, $CH(CH_3)_2$), 4.57 (2H, s, CH_2), 1.53 (9H, s, $C(CH_3)_3$), 1.38 (6H, d, *J* 6.1, $CH(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 168.1, 166.5, 159.4, 159.4, 136.4, 132.4, 129.0, 128.7, 128.6, 111.0, 108.4, 107.5, 82.9, 70.8, 67.3, 66.2, 28.5, 23.1, 22.4; HRMS (ESI) found 423.1765; $C_{23}H_{28}NaO_6$ $[M+Na]^+$ requires 423.1778.

*3-(2-(*tert*-Butoxy)-2-oxoethoxy)-5-isopropoxybenzoic acid: 5*

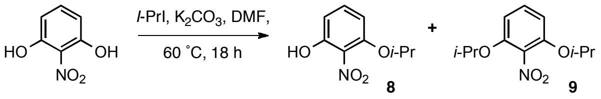


Palladium on carbon (28 mg, wet degussa type, 5 % palladium by weight) was added to a stirred solution of benzyl 3-(2-(*tert*-butoxy)-2-oxoethoxy)-5-isopropoxybenzoate **4** (137 mg, 0.34 mmol) in ethanol (2.0 mL). The solution was degassed three times with argon using a pump-flood procedure, and placed under hydrogen. After 3 h, t.l.c. (2 : 1, petrol : diethyl ether) indicated complete consumption of starting material (R_f 0.8) and the formation of a major product (R_f 0.1). The reaction was filtered (Celite™), washed with dichloromethane (80 mL) and concentrated *in vacuo*. Recrystallization (ethanol) afforded the title compound **5** (878 mg, 2.83 mmol, 91 % yield) as clear crystals.

ν_{max} (neat) 2982, 1745, 1685, 1595, 1144, 766, 729; δ_H (500 MHz, $CDCl_3$) 11.10

(1H, v br, CO_2H), 7.33 (1H, br, Ar-H), 7.22 (1H, br, Ar-H), 6.77 (1H, t, *J* 2.2, H-3), 4.62 (1H, sept, *J* 6.0, $CH(CH_3)_2$), 4.59 (2H, s, CH_2), 1.55 (9H, s, $C(CH_3)_3$), 1.38 (6H, d, *J* 6.0, $CH(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 172.2, 168.2, 159.5, 159.4, 131.7, 111.2, 109.4, 107.8, 83.1, 70.9, 66.2, 28.5, 22.3; HRMS (ESI) found 333.1307; $C_{16}H_{22}NaO_6$ $[M+Na]^+$ requires 333.1309.

3-Isopropoxy-2-nitrophenol: 8

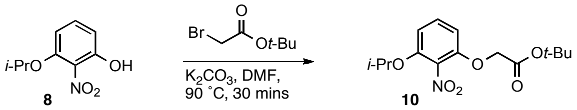


Isopropyl iodide (775 μL, 7.74 mmol) was added to a stirred solution of 2-nitroresorcinol (1.00 g, 6.45 mmol) and potassium carbonate (1.42 g, 10.32 mmol) in *N*,*N*-dimethylformamide (5.0 mL). After 18 h stirring at 60 ˚C the reaction was diluted with dichloromethane (70 mL), partitioned with ammonium chloride (70 mL) and extracted with dichloromethane (3 x 50 mL). The organic layers were combined, dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (4 : 1 → 2 : 1 petrol : diethyl ether) affording, in order of elution, 1,3-diisopropoxy-2-nitrobenzene **9** (501 mg, 2.10 mmol, 32 % yield) and the title compound **8** (684 mg, 3.47 mmol, 54 % yield) as clear oils.

ν_{max} (neat) 3390, 2982, 1588, 1531, 1462, 1353, 1182, 1104, 1053, 913, 857, 789; δ_H (400 MHz, $CDCl_3$) 9.93 (1H, br, OH), 7.35 (1H, t, *J* 8.4, Ar-H), 6.64 (1H, dd, *J* 8.4, 1.1, Ar-H), 6.53 (1H, d, *J* 8.4, Ar-H), 4.66 (1H, sept, *J* 6.1, $CH(CH_3)_2$), 1.40 (6H, d, *J* 6.1, $CH(CH_3)_2$); δ_C (63 MHz, $CDCl_3$) 155.8, 154.7, 135.7, 128.7, 110.4, 106.4, 73.2, 22.3; HRMS (ESI) found 196.0611; $C_9H_{10}NO_4$ $[M-H]^-$ requires 196.0615.

1,3-Diisopropoxy-2-nitrobenzene **9**; ν_{max} (neat) 2981, 1609, 1583, 1535, 1475, 1374, 1259, 1107, 1074; δ_H (500 MHz, $CDCl_3$) 7.25 (1H, t, *J* 8.6, Ar-H), 6.58 (2H, d, *J* 8.6, Ar-H), 4.59 (2H, sept, *J* 6.1, $CH(CH_3)_2$), 1.33 (12H, d, *J* 6.1, $CH(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 150.9, 135.1, 130.9, 107.0, 72.8, 22.3; HRMS (ESI) found 262.1046; $C_{12}H_{17}NNaO_4$ $[M+Na]^+$ requires 262.1050.

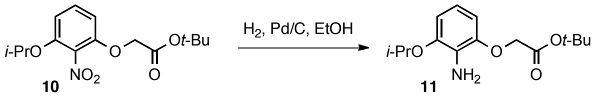
tert-*Butyl 2-(3-isopropoxy-2-nitrophenoxy)acetate: 10*



tert-Butyl bromoacetate (270 μL, 1.81 mmol) was added to a stirred solution of 3-isopropoxy-2-nitrophenol **8** (297 mg, 1.51 mmol) and potassium carbonate (417 mg, 3.02 mmol) in *N*,*N*-dimethylformamide (2.0 mL). After 30 mins at 90 ˚C, t.l.c. (2 : 1, petrol : diethyl ether) indicated complete consumption of starting material (R_f 0.3) and the formation of a major product (R_f 0.4). The reaction was diluted with dichloromethane (30 mL), partitioned with ammonium chloride (30 mL) and extracted with dichloromethane (3 x 30 mL). The organic layers were combined, dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (4 : 1, petrol : diethyl ether) affording the title compound **10** (459 mg, 1.48 mmol, 98 % yield) as a clear oil.

ν_{max} (neat) 2981, 1750, 1611, 1587, 1536, 1478, 1371, 1228, 1113, 734; δ_H (400 MHz, $CDCl_3$) 7.26 (1H, t, *J* 8.5, Ar-H), 6.66 (1H, d, *J* 8.5, Ar-H), 6.44 (1H, d, *J* 8.5, Ar-H), 4.60 (1H, sept, *J* 6.1, $CH(CH_3)_2$), 4.57 (2H, s, CH_2), 1.46 (9H, s, $C(CH_3)_3$), 1.33 (6H, d, *J* 6.1, $CH(CH_3)_2$); δ_C (63 MHz, $CDCl_3$) 167.2, 151.0, 150.8, 134.2, 131.0, 108.2, 105.3, 83.3, 73.0, 66.8, 28.4, 22.3; HRMS (ESI) found 334.1257; $C_{15}H_{21}NNaO_6$ $[M+Na]^+$ requires 334.1261.

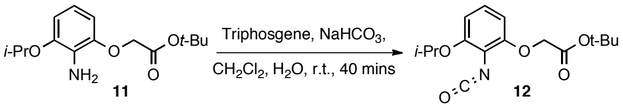
tert-*Butyl 2-(2-amino-3-isopropoxyphenoxy)acetate: 11*



Palladium on carbon (25 mg, wet degussa type, 5 % palladium by weight) was added to a stirred solution of *tert*-Butyl 2-(3-isopropoxy-2-nitrophenoxy)acetate **10** (126 mg, 0.405 mmol) in ethanol (3.0 mL). The solution was degassed three times with argon using a pump-flood procedure, and placed under hydrogen. After 12 h, t.l.c. (2 : 1, petrol : diethyl ether) indicated complete consumption of starting material (R_f 0.4) and the formation of a major product (R_f 0.3). The reaction was filtered (Celite™), washed with dichloromethane (80 mL) and concentrated *in vacuo*, affording the title compound **11** (112 mg, 0.40 mmol, 99 % yield) as a clear oil.

ν_{max} (neat) 3160, 2975, 1687, 1611, 1509, 1432, 1389, 1275, 1260, 1114, 1091, 1019, 770; δ_H (250 MHz, $CDCl_3$) 6.70 - 6.56 (2H, m, Ar-H), 6.45 (1H, dd, *J* 7.6, 1.6, Ar-H), 4.58 (2H, s, CH_2), 4.56 (1H, sept, *J* 6.1, $CH(CH_3)_2$), 3.96 (2H, v br, NH_2), 1.54 (9H, s, $C(CH_3)_3$), 1.39 (6H, d, *J* 6.1, $CH(CH_3)_2$); δ_C (63 MHz, $CDCl_3$) 168.9, 146.8, 146.3, 128.3, 116.9, 108.5, 106.4, 82.6, 71.4, 67.5, 28.5, 22.8; HRMS (ESI) found 282.1698; $C_{15}H_{24}NO_4$ $[M+H]^+$ requires 282.1700.

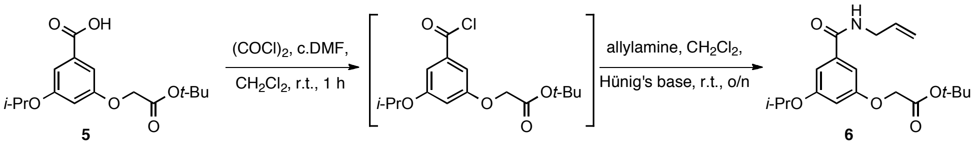
tert-*Butyl 2-(2-isocyanato-3-isopropoxyphenoxy)acetate: 12*



Triphosgene (58 mg, 0.19 mmol) was added to a vigorously stirred emulsion of *tert*-butyl 2-(2-amino-3-isopropoxyphenoxy)acetate **11** (109 mg, 0.39 mmol) and sodium hydrogen carbonate (65 mg, 0.776 mmol) in water (1.5 mL) and dichloromethane (1.5 mL). After 40 mins, t.l.c. (2 : 1, petrol : diethyl ether) indicated complete consumption of starting material (R_f 0.3) and the formation of a major product (R_f 0.9). The reaction was diluted with dichloromethane (30 mL), partitioned with water (30 mL) and extracted with dichloromethane (3 x 30 mL). The organic layers were combined, dried (sodium sulfate), filtered and concentrated *in vacuo*. The residue was carried forward without further purification.

δ_H (250 MHz, $CDCl_3$) 7.04 (1H, t, *J* 8.4, Ar-H), 6.62 (1H, d, *J* 8.4, Ar-H), 6.44 (1H, dd, *J* 8.4, 1.0, Ar-H), 4.63 (1H, sept, *J* 6.1, $CH(CH_3)_2$), 4.62 (2H, s, CH_2), 1.51 (9H, s, $C(CH_3)_3$), 1.42 (6H, d, *J* 6.1, $CH(CH_3)_2$); δ_C (63 MHz, $CDCl_3$) 167.9, 153.1, 152.3, 132.4, 125.5, 114.7, 107.8, 105.7, 82.9, 72.4, 66.9, 28.4, 22.5

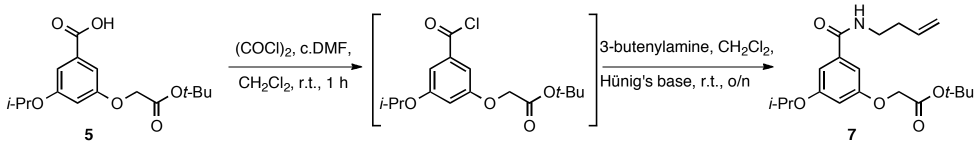
tert-*Butyl 2-(3-(allylcarbamoyl)-5-isopropoxyphenoxy)acetate: 6*



N,*N*-dimethylformamide (2 drops) was added to a stirred solution of 3-(2-(*tert*-butoxy)-2-oxoethoxy)-5-isopropoxybenzoic acid **5** (331 mg, 1.07 mmol) and oxalyl chloride (0.90 mL) in dichloromethane (10 mL). After 1 h, the reaction was concentrated, re-dissolved in dichloromethane (5.0 mL) and cooled to 0 ˚C. Hünig's Base (300 µL, 1.71 mmol) and allylamine (112 µL, 1.50 mmol) were added successively. After overnight stirring, the reaction was diluted with dichloromethane (30 mL), partitioned with ammonium chloride (30 mL) and extracted with dichloromethane (3 x 25 mL). The organic layers were combined, dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (1 : 1, petrol : diethyl ether) affording the title compound **6** (373 mg, 1.07 mmol, 100 % yield) as a clear oil.

ν_{max} (neat) 3322, 1978, 1752, 1640, 1590, 1534, 1442, 1304, 1229, 1147, 844; δ_H (500 MHz, $CDCl_3$) 6.96 (1H, br, Ar-H), 6.91 (1H, br, Ar-H), 6.63 (1H, t, *J* 2.2, H-3), 6.18 (1H, br, N-H), 5.97 (1H, ddt, *J* 17.2, 10.2, 5.7, H-10), 5.30 (1H, ddt, *J* 17.2, 1.6, 1.3, H-11), 5.23 (1H, ddt, *J* 10.2, 1.6, 1.3, H-11'), 4.61 (1H, sept, *J* 6.0, $CH(CH_3)_2$), 4.57 (2H, s, CH_2), 4.11 (2H, tt, *J* 5.7, 1.6, H-9), 1.54 (9H, s, $C(CH_3)_3$), 1.38 (6H, d, *J* 6.0, $CH(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 168.1, 167.4, 159.6, 159.6, 137.2, 134.4, 117.2, 108.2, 106.1, 105.4, 83.0, 70.8, 66.2, 42.9, 28.5, 22.4; HRMS (ESI) found 350.1956; $C_{19}H_{28}NO_5$ $[M+H]^+$ requires 350.1962.

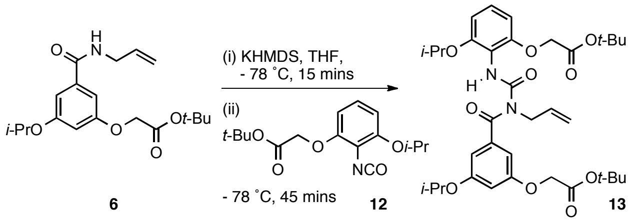
tert-*Butyl 2-(3-(but-3-en-1-ylcarbamoyl)-5-isopropoxyphenoxy)acetate: 7*



N,*N*-dimethylformamide (2 drops) was added to a stirred solution of 3-(2-(*tert*-butoxy)-2-oxoethoxy)-5-isopropoxybenzoic acid **5** (360 mg, 1.16 mmol) and oxalyl chloride (1.00 mL) in dichloromethane (15 mL). After 1 h, the reaction was concentrated, re-dissolved in dichloromethane (5.0 mL) and cooled to 0 ˚C. Hünig's Base (570 µL, 3.25 mmol) and 3-butenylamine hydrochloride (175 mg, 1.62 mmol) were added successively. After overnight stirring, the reaction was diluted with dichloromethane (30 mL), partitioned with ammonium chloride (30 mL) and extracted with dichloromethane (3 x 25 mL). The organic layers were combined, dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (1 : 1, petrol : diethyl ether) affording the title compound **7** (421 mg, 1.16 mmol, 100 % yield) as a clear oil.

ν_{max} (neat) 2991, 2978, 1753, 1640, 1590, 1538, 1441, 1147, 844; δ_H (500 MHz, CDCl$_3$) 6.92 (1H, br, Ar-H), 6.88 (1H, br, Ar-H), 6.62 (1H, t, *J* 2.2, H-3), 6.15 (1H, br, N-H), 5.86 (1H, ddt, *J* 16.9, 10.0, 6.8, H-11), 5.23 - 5.17 (1H, m, H-12), 5.19 - 5.15 (1H, m, H-12'), 4.61 (1H, sept, *J* 6.0, CH(CH$_3$)$_2$), 4.57 (2H, s, CH$_2$), 3.56 (2H, dt, *J* 6.6, 6.0, H-9), 2.41 (2H, dt, *J* 7.0, 6.6, H-10), 1.54 (9H, s, C(CH$_3$)$_3$), 1.38 (6H, d, *J* 6.0, CH(CH$_3$)$_2$); δ_C (125 MHz, CDCl$_3$) 168.1, 167.5, 159.6, 159.6, 137.4, 135.6, 118.0, 108.1, 106.0, 105.4, 83.0, 70.8, 66.1, 39.3, 34.1, 28.5, 22.4; HRMS (ESI) found 386.1938; $C_{20}H_{29}NNaO_5$ $[M+Na]^+$ requires 386.1932.

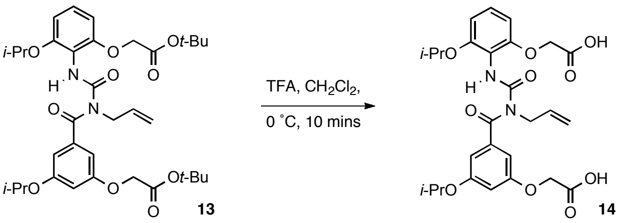
tert-*Butyl 2-(3-(allyl((2-(2-(*tert-*butoxy)-2-oxoethoxy)-6-isopropoxyphenyl)carbamoyl)carbamoyl)-5-isopropoxyphenoxy)acetate: 13*



Potassium hexamethyldisilazane (440 μL as a 0.5 molar solution in toluene, 0.22 mmol) was added dropwise to a stirred solution of *tert*-butyl 2-(3-(allylcarbamoyl)-5-isopropoxyphenoxy)acetate **6** (70 mg, 0.20 mmol) in tetrahydrofuran at – 78 ˚C. After 15 mins stirring, a solution of *tert*-butyl 2-(2-isocyanato-3-isopropoxyphenoxy)acetate **12** (68 mg, 0.22 mmol) was added dropwise over 15 mins. After a further 45 mins at – 78 ˚C acetic acid (5 drops) was added. The reaction mixture was diluted with dichloromethane (10 mL), partitioned with ammonium chloride (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic layers were combined, dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (2 : 1 → 1 : 1, petrol : diethyl ether) affording the title compound **13** (34 mg, 51.8 μmol, 25 % yield) and recovered *tert*-butyl 2-(3-(allylcarbamoyl)-5-isopropoxyphenoxy)acetate **6** (11 mg, 31.5 μmol, 16 % yield) as clear oils.

ν_{max} (neat) 3252, 2979, 1553, 1722, 1657, 1539, 1518, 1371, 1152; δ_H (400 MHz, CDCl$_3$) 10.23 (1H, s, N-H), 7.11 (1H, t, *J* 8.4, Ar-H), 6.66 (1H, t *J* 1.8, Ar-H), 6.63 (1H, d, *J* 8.2, Ar-H), 6.57 (1H, t, *J* 2.0, Ar-H), 6.55 (1H, t, *J* 2.2, Ar-H), 6.46 (1H, d, *J* 8.4, Ar-H), 5.88 (1H, ddt, *J* 17.4, 10.6, 5.5, H-20), 5.16 (1H, dd, *J* 10.6, 1.1, H-22), 5.12 (1H, dd, *J* 17.4, 1.1, H-22'), 4.57 - 4.46 (2H, m, CH(CH$_3$)$_2$), 4.57 (2H, s, CH$_2$), 4.50 (2H, s, CH_2), 4.37 (2H, d, *J* 4.8, H-20), 1.50 (9H, s, $C(CH_3)_3$), 1.47 (9H, s, $C(CH_3)_3$), 1.34 (6H, d, *J* 6.0, $CH(CH_3)_2$), 1.33 (6H, d, *J* 6.0, $CH(CH_3)_2$); δ_C (63 MHz, $CDCl_3$) 174.6, 168.6, 168.0, 159.5, 159.4, 154.7, 154.3, 152.9, 138.4, 134.6, 127.5, 117.1, 116.7, 108.5, 107.4, 106.2, 105.4, 104.7, 83.0, 82.5, 71.8, 70.8, 67.4, 66.2, 49.5, 28.5, 22.6, 22.4; HRMS (ESI) found 679.3199; $C_{35}H_{48}N_2NaO_8$ $[M+Na]^+$ requires 679.3201.

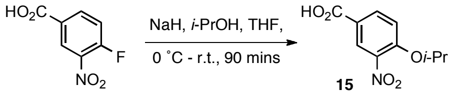
2-(3-(Allyl((2-(carboxymethoxy)-6-isopropoxyphenyl)carbamoyl)carbamoyl)-5-isopropoxyphenoxy)acetic acid: 14



Trifluoroacetic acid (0.5 mL) was added to a stirred solution of *tert*-butyl 2-(3-(allyl((2-(2-(*tert*-butoxy)-2-oxoethoxy)-6-isopropoxyphenyl)carbamoyl)carbamoyl)-5-isopropoxyphenoxy)acetate **13** (25 mg, 38.1 μmol) in dichloromethane (0.5 mL) at 0 ˚C. After 10 mins, t.l.c. (1 : 1, petrol : diethyl ether) indicated complete consumption of starting material (R_f 0.4) and the formation of a major product (R_f 0.0). Chloroform (2.0 mL) was added, the mixture concentrated *in vacuo* and this process repeated several times; affording the title compound **14** as a white amorphous solid.

ν_{max} (neat) 2980, 1762, 1737, 1692, 1594, 1376, 1116; δ_H (500 MHz, $CDCl_3$) 10.91 (1H, s, N-H), 7.38 (2H, v br, CO_2H), 7.23 (1H, t, *J* 8.5, Ar-H), 6.75 - 6.70 (2H, m, Ar-H), 6.66 - 6.63 (2H, m, Ar-H), 6.61 (1H, d, *J* 8.5, Ar-H), 5.91 (1H, ddt, *J* 17.3, 10.3, 4.8, H-21), 5.26 (1H, d, *J* 10.3, H-22), 5.17 (1H, d, *J* 17.3, H-22'), 4.84 (2H, s, CH_2), 4.72 (2H, s, CH_2), 4.62 (1H, sept, *J* 6.1, $CH(CH_3)_2$), 4.59 (1H, sept, *J* 6.1, $CH(CH_3)_2$), 4.45 (2H, d, *J* 4.6, H-20), 1.43 (6H, d, *J* 6.1, $CH(CH_3)_2$), 1.39 (6H, d, *J* 6.1 $CH(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 175.1, 172.8, 171.1, 159.8, 159.1, 153.8, 153.3, 151.9, 137.7, 134.0, 128.1, 117.0, 115.7, 108.4, 107.7, 105.8, 104.6, 104.2, 72.3, 71.0, 65.8, 65.3, 49.9, 22.6; HRMS (ESI) found 567.1949; $C_{27}H_{32}N_2NaO_{10}$ $[M+Na]^+$ requires 567.1949.

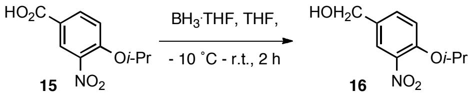
4-Isopropoxy-3-nitrobenzoic acid: 15



Isopropanol (81 μL, 1.06 mmol) was added dropwise to a stirred slurry of sodium hydride (74 mg, 1.84 mmol as a 60 % dispersion oil) in tetrahydrofuran (4.0 mL) at ˚C. After 15 mins, 4-fluoro-3-nitrobenzoic acid (131 mg, 0.71 mmol) was added and the cooling bath removed after a further 30 mins of stirring. After a further 3 h, t.l.c. (90 : 10 : 1, dichloromethane : methanol : acetic acid) indicated complete consumption of starting material (R_f 0.7) and the formation of a major product (R_f 0.65). The reaction was diluted with dichloromethane (15 mL), partitioned with 1.0 *N* hydrochloric acid (aqueous, 15 mL) and extracted with dichloromethane (15 mL). The organic layers were combined, dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (200 : 10 : 1, dichloromethane : methanol : acetic acid) affording the title compound **15** (157 mg, 0.70 mmol, 98 % yield) as an amorphous brown solid.

ν_{max} (neat) 2923, 1701, 1613, 1534, 1288, 1104, 759; δ_H (500 MHz, CD_3OD) 8.31 (1H, d, *J* 2.2, H-1), 8.15 (1H, dd, *J* 8.8, 2.2, H-5), 7.30 (1H, d, *J* 8.9, H-4), 4.9 (1H, sept, *J* 6.1, $CH(CH_3)_2$), 1.38 (6H, d, *J* 6.1, $CH(CH_3)_2$); δ_C (125 MHz, CD_3OD) 166.7, 154.6, 140.7, 135.0, 126.7, 123.0, 115.5, 73.2, 21.1; HRMS (ESI) found 248.0532; $C_{10}H_{11}NNaO_5$ $[M+Na]^+$ requires 248.0529.

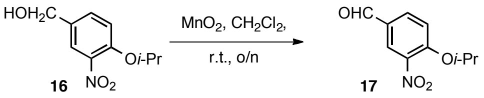
(4-Isopropoxy-3-nitrophenyl)methanol: 16



Borane·tetrahydrofuran complex (570 μL as a 1.0 molar solution) was added dropwise to a stirred solution of 4-isopropoxy-3-nitrobenzoic acid **15** (81 mg, 0.36 mmol) in tetrahydrofuran (1.0 mL) at – 10 ˚C. The reaction mixture was allowed to attain room temperature over 1 h, with t.l.c. (90 : 10 : 1, dichloromethane, methanol, acetic acid) indicating complete consumption of starting material (R_f 0.4) and the formation of a major product (R_f 0.6). The reaction mixture was diluted with dichloromethane (10 mL), cooled to 0 ˚C and quenched cautiously with acetic acid : water (50 : 50) until evolution of gas ceased. The resultant mixture was partitioned with sodium hydrogen carbonate (15 mL) and extracted with dichloromethane (15 mL). The organic layers were combined, dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (2 : 1, diethyl ether : petrol) affording the title compound **16** (70 mg, 0.33 mmol, 92 %) as a clear oil.

ν_{max} (neat) 3353, 2981, 1621, 1526, 1351, 1277, 1259, 1105, 948, 810; δ_H (500 MHz, $CDCl_3$) 7.80 (1H, br, Ar-H), 7.52 (1H, dd, *J* 8.5, 2.0, Ar-H), 7.10 (1H, d, *J* 8.5, Ar-H), 4.70 (1H, sept, *J* 6.1, $CH(CH_3)_2$), 4.69 (2H, br, CH_2), 2.36 (1H, br, OH), 1.42 (6H, d, *J* 6.1, $CH(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 151.0, 141.3, 133.6, 132.7, 124.8, 73.3, 64.1, 22.3; HRMS (ESI) found 234.0733; $C_{10}H_{13}NNaO_4$ $[M+Na]^+$ requires 234.0737.

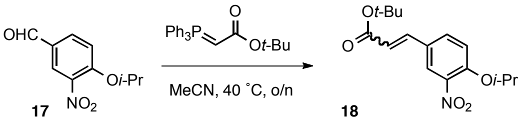
4-Isopropoxy-3-nitrobenzaldehyde: 17



Manganese dioxide (278 mg, 3.20 mmol) was added to a stirred solution of (4-isopropoxy-3-nitrophenyl)methanol **16** (45 mg, 0.21 mmol) in dichloromethane (3.0 mL). After overnight stirring t.l.c. (2 : 1, diethyl ether : petrol) indicated complete consumption of starting material (R_f 0.3) and the formation of a major product (R_f 0.6). The reaction mixture was filtered (Celite™), washed with dichloromethane (40 mL) and concentrated *in vacuo*. The residue was purified by flash column chromatography (1 : 1, petrol : diethyl ether) affording the title compound **17** (40 mg, 0.19 mmol, 89 % yield) as a clear oil.

δ_H (500 MHz, $CDCl_3$) 9.96 (1H, s, CHO), 8.33 (1H, d, *J* 2.0, H-1), 8.08 (1H, dd, *J* 8.6, 2.2, Ar-H), 7.26 (1H, d, *J* 8.7, Ar-H), 4.88 (1H, sept, *J* 6.1, $CH(CH_3)_2$), 1.50 (6H, d, *J* 6.1, $CH(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 189.2, 156.2, 141.3, 134.6, 128.9, 127.9, 115.8, 73.9, 22.2; HRMS (ESI) found 264.0843; $C_{11}H_{15}NNaO_5$ $[M+Na]^+$ requires 264.0842.

tert-*Butyl 3-(4-isopropoxy-3-nitrophenyl)acrylate: 18*

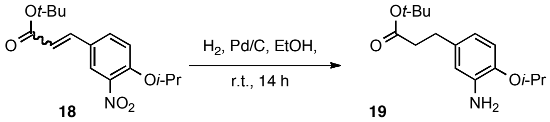


(*tert*-Butoxycarbonyl-methylene)triphenyl-phosphorane (66 mg, 0.17 mmol) was added to a stirred solution of 4-isopropoxy-3-nitrobenzaldehyde **17** (28 mg, 0.13 mmol) in acetonitrile (3.0 mL). After overnight stirring at 40 °C, t.l.c. (1 : 1, petrol :

diethyl ether) indicated complete consumption of starting material (R_f 0.3) and formation of a major product (R_f 0.8). The reaction mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (10 : 1, petrol : diethyl ether), affording the title compound **18** as an inseparable 15 : 1 mixture of (*E*) and (*Z*) isomers (39 mg, 0.13 mmol, 95 % yield) as a clear oil.

ν_{max} (neat) 3045, 2360, 1706, 1615, 1279, δ_H (250 MHz, $CDCl_3$) major isomer: 7.94 (1H, d, *J* 2.2, H-1), 7.63 (1H, dd, *J* 8.7, 2.2, Ar-H), 7.51 (1H, d, *J* 16.0, H-7), 7.10 (1H, d, *J* 8.8, Ar-H), 6.32 (1H, d, *J* 16.0, H-8), 4.74 (1H, sept, *J* 6.1, $CH(CH_3)_2$), 1.55 (9H, s, $C(CH_3)_3$), 1.43 (6H, d, *J* 6.1, $CH(CH_3)_2$); δ_C (63 MHz, $CDCl_3$) 168.2, 152.7, 141.4, 141.0, 133.2, 127.4, 125.1, 121.0, 116.3, 81.2, 73.3, 28.6, 22.2; HRMS (ESI) found 330.1300; $C_{16}H_{21}NNaO_5$ $[M+Na]^+$ requires 330.1312.

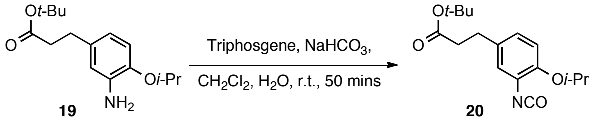
tert-*Butyl 3-(3-amino-4-isopropoxyphenyl)propanoate: 19*



Palladium on carbon (110 mg, wet degussa type, 5 % palladium by weight) was added to a stirred solution of *tert*-butyl 3-(4-isopropoxy-3-nitrophenyl)acrylate **18** (1.11 g, 3.61 mmol) in ethanol (10 mL). The solution was degassed three times with argon using a pump-flood procedure, and placed under hydrogen. After 14 h, t.l.c. (6 : 1, petrol : diethyl ether) indicated complete consumption of starting material (R_f 0.3) and the formation of a major product (R_f 0.2). The reaction was filtered (Celite™), washed with dichloromethane (220 mL) and concentrated *in vacuo.* The residue was purified by flash column chromatography (6 : 1, petrol : diethyl ether) affording the title compound **19** (944 mg, 3.38 mmol, 94 % yield) as a clear oil.

ν_{max} (neat) 3377, 2975, 1727, 1617, 1514, 1368, 1223, 1144; δ_H (500 MHz, $CDCl_3$) 6.76 (1H, d, *J* 8.1, Ar-H), 6.62 (1H, d, *J* 2.2, Ar-H), 6.57 (1H, dd, *J* 8.1, 2.2, Ar-H), 4.52 (1H, sept, *J* 6.1, $CH(CH_3)_2$), 2.82 (2H, t, *J* 7.6, H-7), 2.53 (2H, t, *J* 7.6, H-8), 1.48 (9H, s, $C(CH_3)_3$), 1.38 (6H, d, *J* 6.1, $CH(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 173.0, 144.2, 137.6, 134.1, 118.4, 115.9, 114.3, 80.6, 71.3, 37.8, 31.0, 28.5, 22.7; HRMS (ESI) found 280.1896; $C_{16}H_{26}NO_3$ $[M+H]^+$ requires 280.1907.

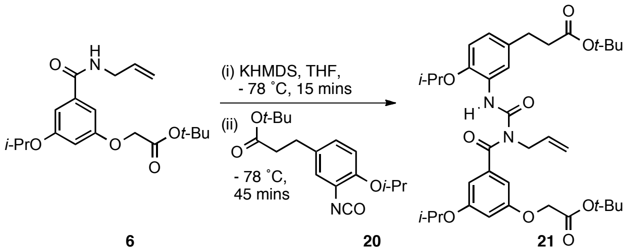
tert-*Butyl 3-(3-isocyanato-4-isopropoxyphenyl)propanoate: 20*



Triphosgene (428 mg, 1.44 mmol) was added to a vigorously stirred emulsion of *tert*-butyl 3-(3-amino-4-isopropoxyphenyl)propanoate **19** (944 mg, 3.38 mmol) and sodium hydrogen carbonate (606 mg, 7.22 mmol) in water (30 mL) and dichloromethane (30 mL). After 50 mins, t.l.c. (6 : 1, petrol : diethyl ether) indicated complete consumption of starting material (R_f 0.2) and the formation of a major product (R_f 0.5). The reaction was diluted with dichloromethane (70 mL), partitioned with water (70 mL) and extracted with dichloromethane (3 x 70 mL). The organic layers were combined, dried (sodium sulfate), filtered and concentrated *in vacuo*. The residue was carried forward without further purification.

δ_H (500 MHz, $CDCl_3$) 6.99 (1H, dd, *J* 6.4, 2.0, Ar-H), 6.88 (1H, d, *J* 2.0, Ar-H), 6.85 (1H, d, *J* 6.4, Ar-H), 4.64 (1H, sept, *J* 6.1, $CH(CH_3)_2$), 2.85 (2H, d, *J* 7.6, H-7), 2.53 (2H, d, *J* 7.6, H-8), 1.47 (9H, s, $C(CH_3)_3$), 1.43 (6H, d, *J* 6.1, $CH(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 172.6, 150.6, 133.7, 131.6, 126.1, 125.2, 124.1, 113.4, 80.9, 72.2, 37.5, 30.6, 28.5, 22.3

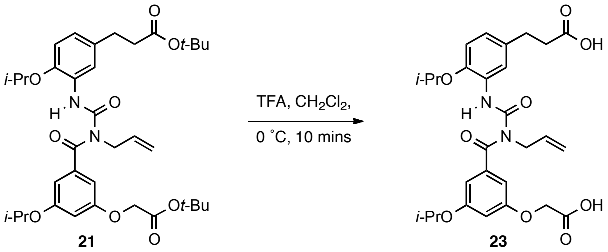
tert-*Butyl 3-(3-(3-allyl-3-(3-(2-(*tert*-butoxy)-2-oxoethoxy)-5-isopropoxybenzoyl)ureido)-4-isopropoxyphenyl)propanoate: 21*



Potassium hexamethyldisilazane (940 μL as a 0.5 molar solution in toluene, 0.47 mmol) was added dropwise to a stirred solution of *tert*-butyl 2-(3-(allylcarbamoyl)-5-isopropoxyphenoxy)acetate **6** (119 mg, 0.39 mmol) in tetrahydrofuran at – 78 ˚C. After 15 mins stirring, a solution of *tert*-butyl 3-(3-isocyanato-4-isopropoxyphenyl)propanoate **20** (136 mg, 0.39 mmol) was added dropwise over 15 mins. After a further 45 mins at – 78 ˚C acetic acid (10 drops) was added. The reaction mixture was diluted with dichloromethane (25 mL), partitioned with ammonium chloride (25 mL) and extracted with dichloromethane (3 x 25 mL). The organic layers were combined, dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (4 : 1, petrol : diethyl ether) affording the title compound **21** (157 mg, 0.24 mmol, 61 % yield) as a clear oil.

ν_{max} (neat) 2978, 1753, 1712, 1659, 1592, 1537, 1440, 1147, 877; δ_H (500 MHz, $CDCl_3$) 11.67 (1H, s, N-H), 8.28 (1H, d, *J* 1.9, Ar-H), 6.91 (1H, dd, *J* 8.3, 1.9, Ar-H), 6.88 (1H, d, *J* 8.3, Ar-H), 6.65 (1H, br, Ar-H), 6.60 (1H, t, *J* 2.2, Ar-H), 6.57 (1H, br, Ar-H), 5.92 (1H, ddt, *J* 17.3, 10.5, 4.9, H-21), 5.22 (1H, dd, *J* 10.5, 0.9, H-22), 5.13 (1H, dd, *J* 17.3, 0.9, H-22'), 4.62 (1H, sept, *J* 6.1, $CH(CH_3)_2$), 4.56 (1H, sept, *J* 6.1, $CH(CH_3)_2$), 4.55 (2H, s, CH_2), 4.43 (2H, d, *J* 4.9, H-20), 2.92 (2H, t, *J* 7.6, H-17), 2.59 (2H, t, *J* 7.6, H-18), 1.55 (9H, s, $C(CH_3)_3$), 1.48 (9H, s, $C(CH_3)_3$), 1.44, (6H, d, *J* 6.1, $CH(CH_3)_2$), 1.38 (6H, d, *J* 6.1, $CH(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 174.7, 172.9, 167.9, 159.6, 159.6, 151.9, 145.7, 138.3, 134.4, 133.9, 129.5, 123.7, 120.4, 116.9, 113.7, 107.2, 105.3, 104.5, 83.1, 80.6, 72.3, 70.9, 66.2, 49.4, 37.9, 31.3, 28.5, 28.5, 22.7, 22.5; HRMS (ESI) found 677.3409; $C_{36}H_{50}N_2NaO_9$ $[M+Na]^+$ requires 677.3409.

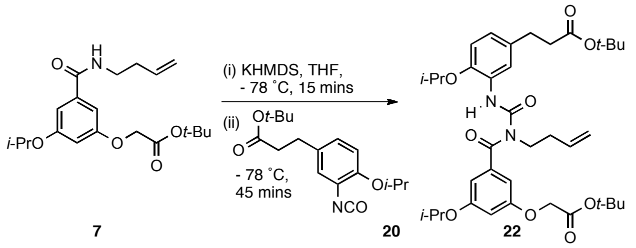
3-(3-(3-Allyl-3-(3-(carboxymethoxy)-5-isopropoxybenzoyl)ureido)-4-isopropoxyphenyl)propanoic acid: 23



Trifluoroacetic acid (0.5 mL) was added to a stirred solution of *tert*-butyl 3-(3-(3-allyl-3-(3-(2-(*tert*-butoxy)-2-oxoethoxy)-5-isopropoxybenzoyl)ureido)-4-isopropoxyphenyl)propanoate **21** (13 mg, 19.9 μmol) in dichloromethane (0.5 mL) at 0 °C. After 10 mins, t.l.c. (4 : 1, petrol : diethyl ether) indicated complete consumption of starting material (R_f 0.3) and the formation of a major product (R_f 0.0). Chloroform (2.0 mL) was added, the mixture concentrated *in vacuo* and this process repeated several times; affording the title compound **23** as a white amorphous solid.

ν_{max} (neat) 2979, 1711, 1593, 1540, 1441, 1378; δ_H (500 MHz, $CDCl_3$) 11.42 (1H, s, N-H), 8.54 (2H, br, CO_2H), 8.25 (1H, s, Ar-H), 6.92 (1H, dd, *J* 8.3, 1.6, Ar-H), 6.88 (1H, d, *J* 8.3, Ar-H), 6.71 (1H, br, Ar-H), 6.63 (1H, t, *J* 2.2, Ar-H), 6.57 (1H, br, Ar-H), 5.89 (1H, ddt, *J* 17.4, 10.4, 3.7, H-21), 5.20 (1H, d, *J* 10.4, H-22), 5.14 (1H, d, *J* 17.4, H-22'), 4.71 (2H, s, CH_2), 4.62 (1H, sept, *J* 6.1, $CH(CH_3)_2$), 4.58 (1H, sept, *J* 6.1, $CH(CH_3)_2$), 4.41 (2H, d, *J* 3.7, H-20), 2.96 (2H, t, *J* 7.5, H-17), 2.73 (2H, t, *J* 7.5, H-18), 1.44 (6H, d, *J* 6.1, $CH(CH_3)_2$), 1.38 (6H, d, *J* 6.1, $CH(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 179.0, 174.4, 173.8, 159.8, 159.1, 152.1, 146.0, 138.2, 134.3, 133.1, 129.2, 123.9, 120.5, 116.9, 113.6, 107.8, 105.7, 103.8, 72.2, 70.9, 65.2, 49.4, 36.3, 30.8, 22.5, 22.4; HRMS (ESI) found 565.2159; $C_{28}H_{34}N_2NaO_9$ $[M+Na]^+$ requires 565.2157.

tert-*Butyl 3-(3-(3-(but-3-en-1-yl)-3-(3-(2-(*tert*-butoxy)-2-oxoethoxy)-5-isopropoxybenzoyl)ureido)-4-isopropoxyphenyl)propanoate: 22*



Potassium hexamethyldisilazane (1.70 mL as a 0.5 molar solution in toluene, 0.71 mmol) was added dropwise to a stirred solution of *tert*-butyl 2-(3-(but-3-en-1-ylcarbamoyl)-5-isopropoxyphenoxy)acetate **7** (218 mg, 0.71 mmol) in tetrahydrofuran at – 78 ˚C. After 15 mins stirring, a solution of *tert*-butyl 3-(3-isocyanato-4-isopropoxyphenyl)propanoate **20** (259 mg, 0.71 mmol) was added dropwise over 15 mins. After a further 45 mins at – 78 ˚C acetic acid (10 drops) was added. The reaction mixture was diluted with dichloromethane (40 mL), partitioned with ammonium chloride (40 mL) and extracted with dichloromethane (3 x 40 mL). The organic layers were combined, dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (4 : 1, petrol : diethyl ether) affording the title compound **22** (305 mg, 0.46 mmol, 64 % yield) as a clear oil.

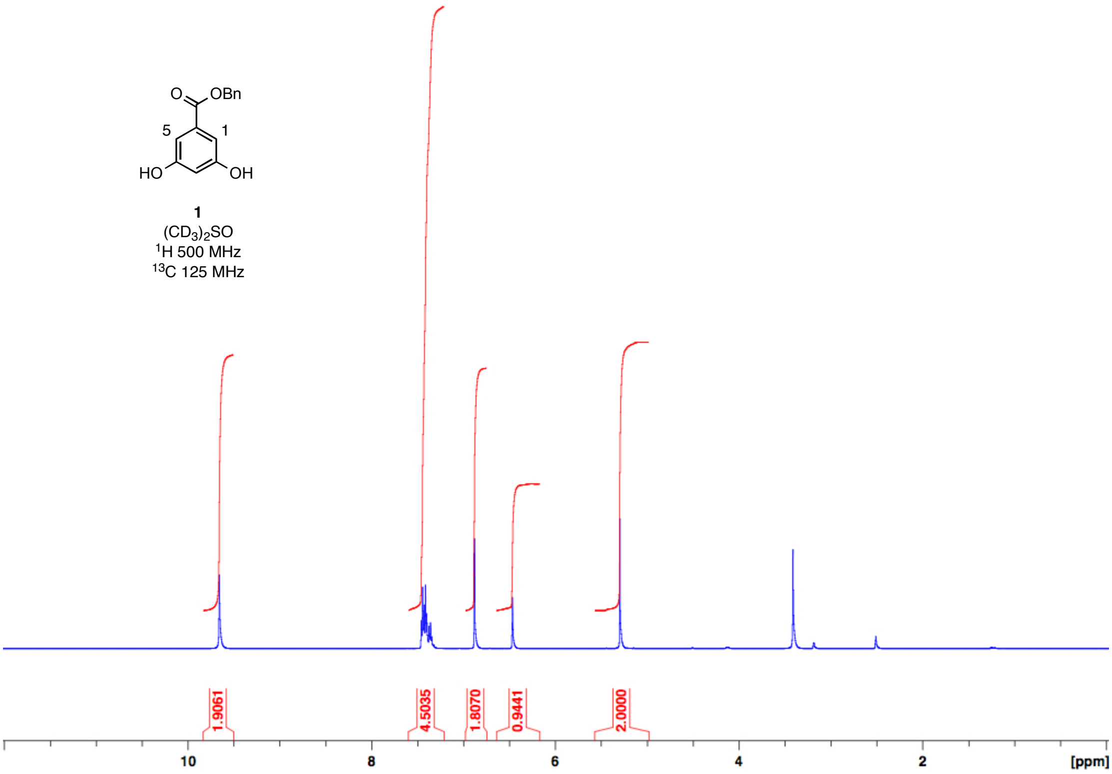
ν_{max} (neat) 2978, 1753, 1708, 1591, 1367, 1146, 1113, 845, 732; δ_H (250 MHz, $CDCl_3$) 11.55 (1H, br, N-H), 8.27 (1H, d, *J* 1.5, Ar-H), 6.95 - 6.83 (2H, m, Ar-H), 6.64 (1H, br, Ar-H), 6.60 (1H, t, *J* 2.2, Ar-H), 6.55 (1H, br, Ar-H), 5.76 - 5.54 (1H, m, H-22), 5.11 - 4.98 (2H, m, H-23, H-23'), 4.60 (1H, sept, *J* 6.1, $CH(CH_3)_2$), 4.58 (1H, sept, *J* 6.1, $CH(CH_3)_2$), 4.56 (2H, s, CH_2), 3.88 (2H, t, *J* 7.3, H-20), 2.92 (2H, t, *J* 7.9, H-17), 2.59 (2H, t, *J* 7.9, H-18), 2.39 (2H, dt, *J* 7.2, 7.1, H-21), 1.54 (9H, s, $C(CH_3)_3$), 1.48 (9H, s, $C(CH_3)_3$), 1.42 (6H, d, *J* 6.1, $CH(CH_3)_2$), 1.38 (6H, d, *J* 6.1, $CH(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 174.1, 172.4, 167.4, 159.3, 159.3, 151.6, 145.3, 138.1, 134.2, 133.5, 129.0, 123.2, 119.8, 117.6, 113.3, 107.0, 104.7, 104.2, 82.6, 80.1, 71.8, 70.4, 65.7, 46.3, 37.5, 34.0, 30.9, 28.1, 28.1, 22.1, 21.9; HRMS (ESI) found 691.3539; $C_{37}H_{52}N_2NaO_9$ $[M+Na]^+$ requires 691.3565.

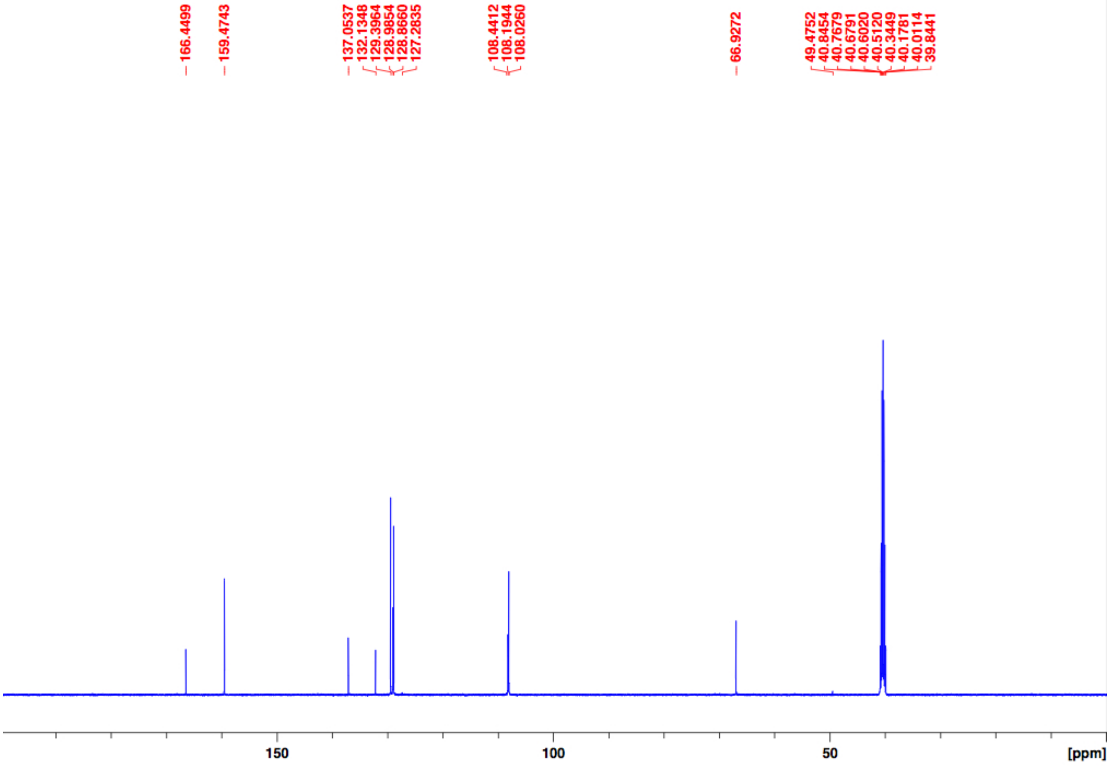
3. References

1 Guo, W.; Li, J. F.; Fan, N. J.; Wu, W. W.; Zhou, P. W.; Xia, C. Z. *Synth. Commun.* **2005**, *35,* 145.

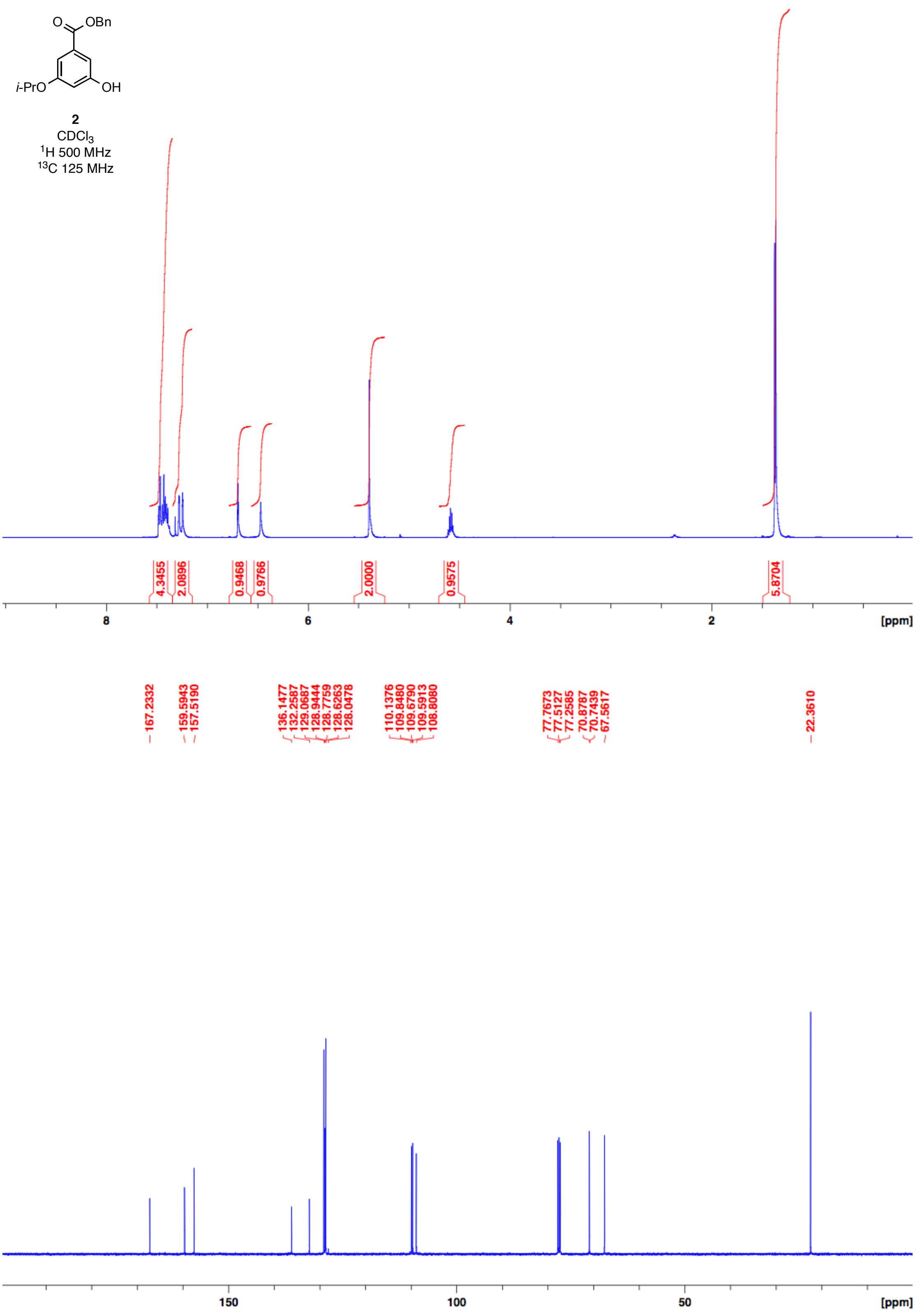
4. NMR Spectra

Benzyl 3,5-dihydroxybenzoate: 1





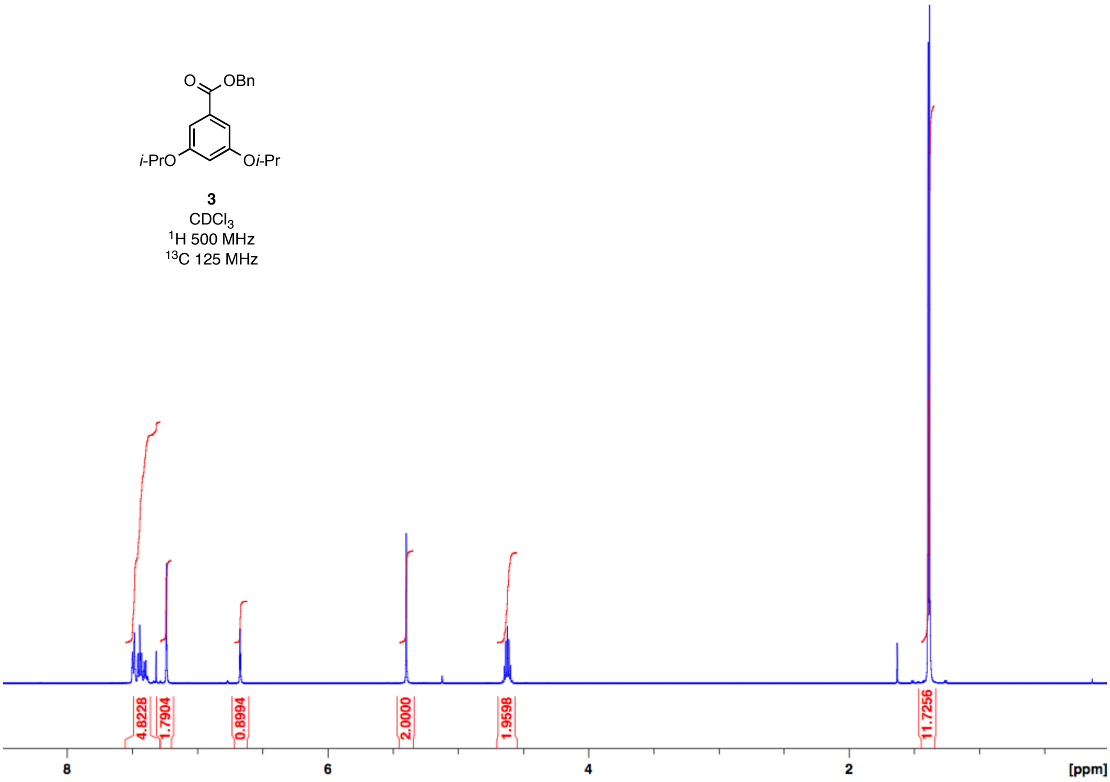
Benzyl 3-hydroxy-5-isopropoxybenzoate: 2

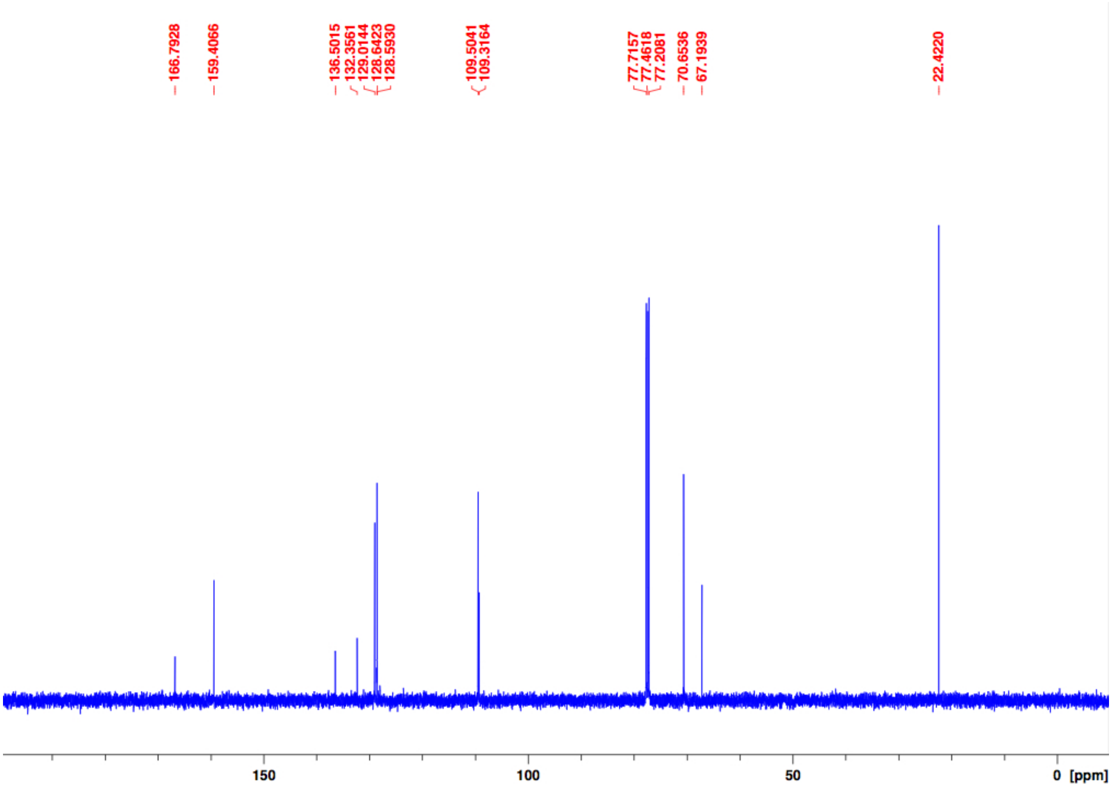


2
$CDCl_3$
^1H 500 MHz
^{13}C 125 MHz

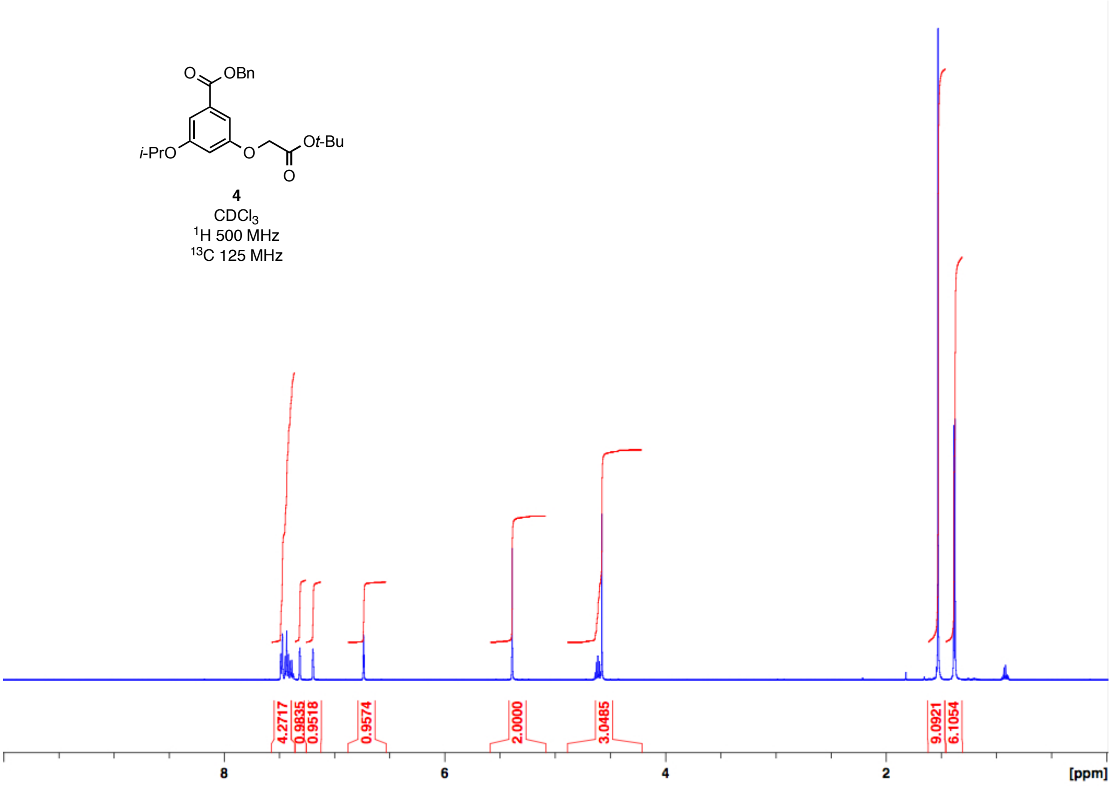
3,5-Diisopropoxybenzoic acid: 3

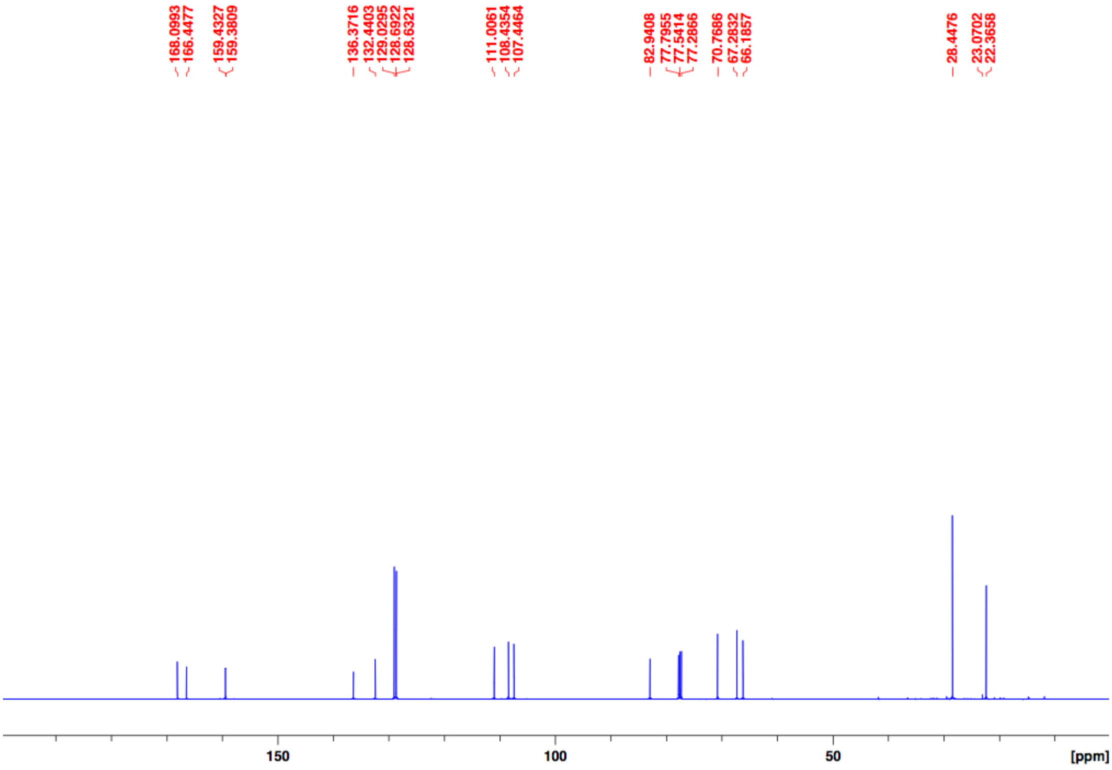
3
$CDCl_3$
^1H 500 MHz
^{13}C 125 MHz



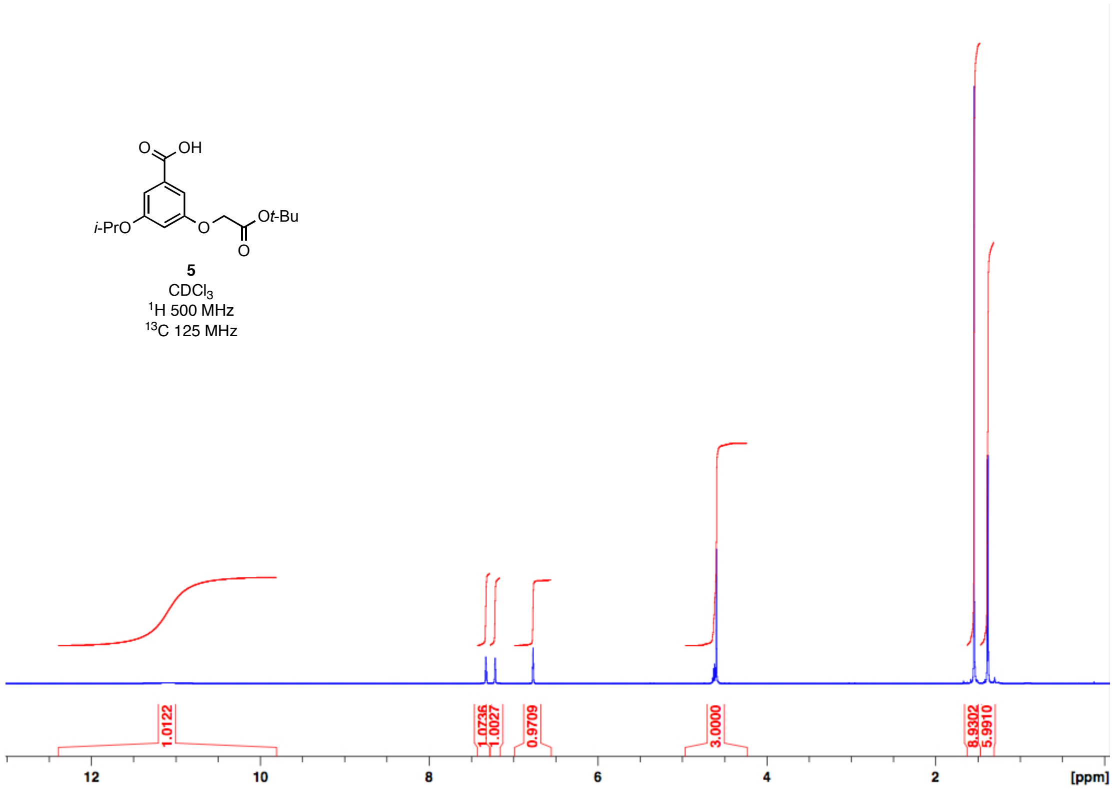


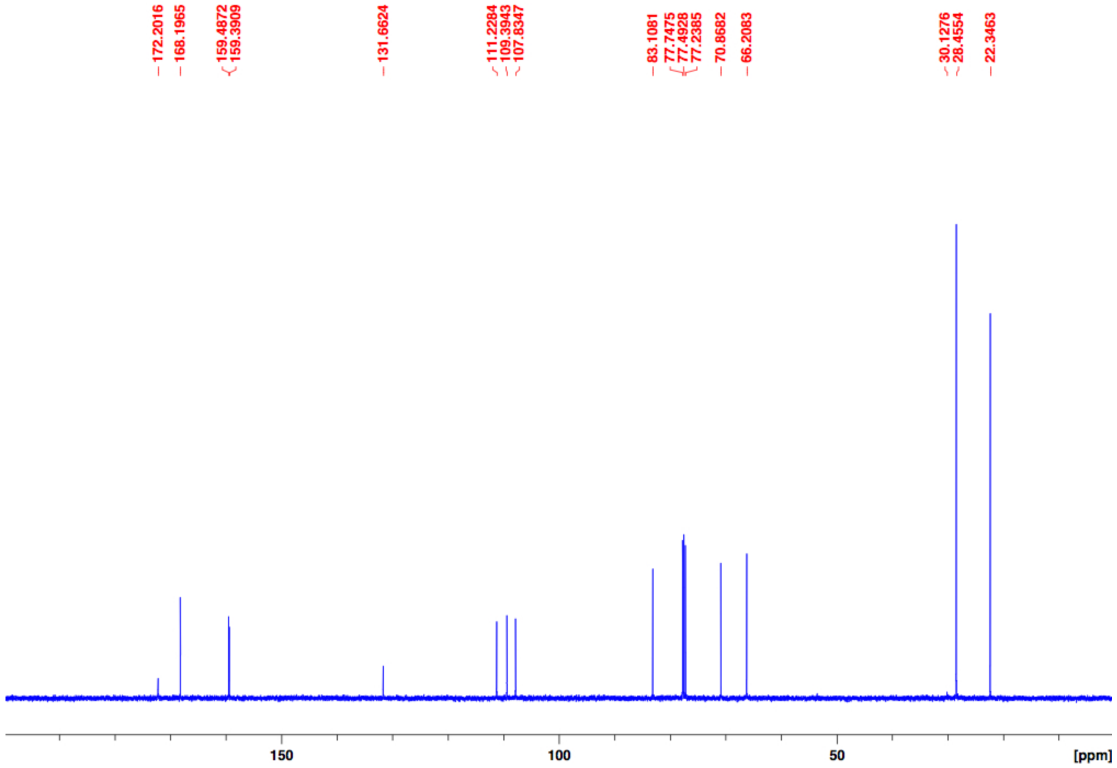
*Benzyl 3-(2-(*tert*-butoxy)-2-oxoethoxy)-5-isopropoxybenzoate: 4*



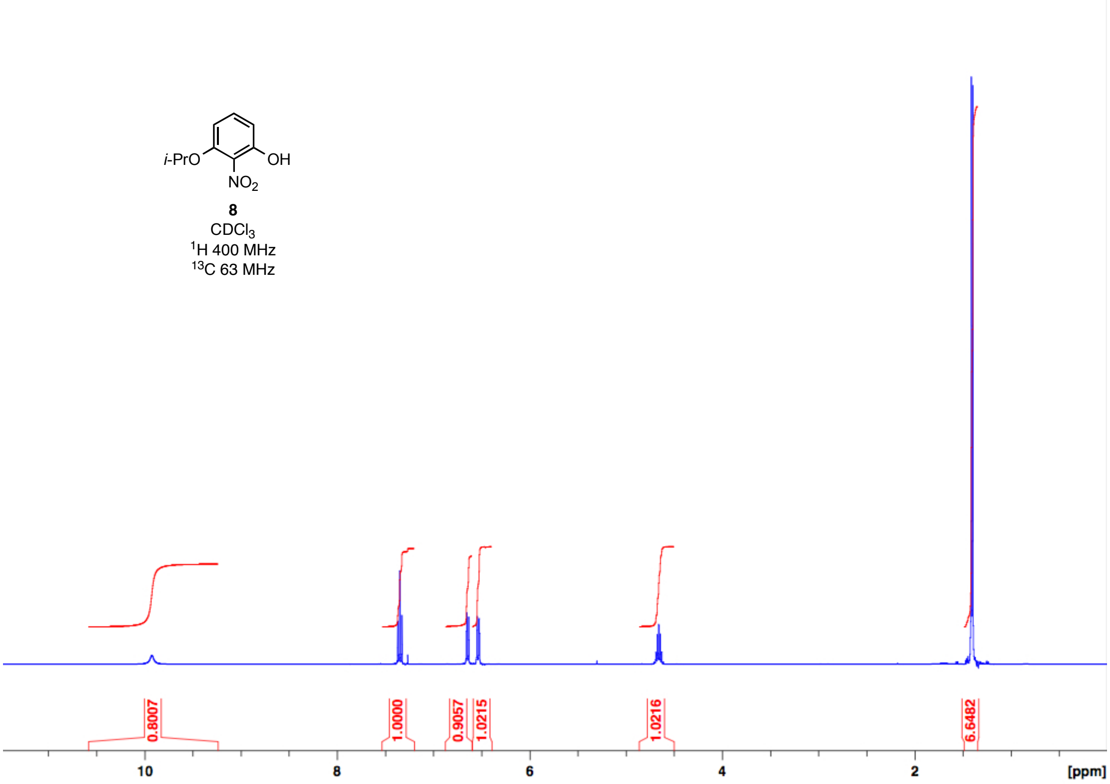


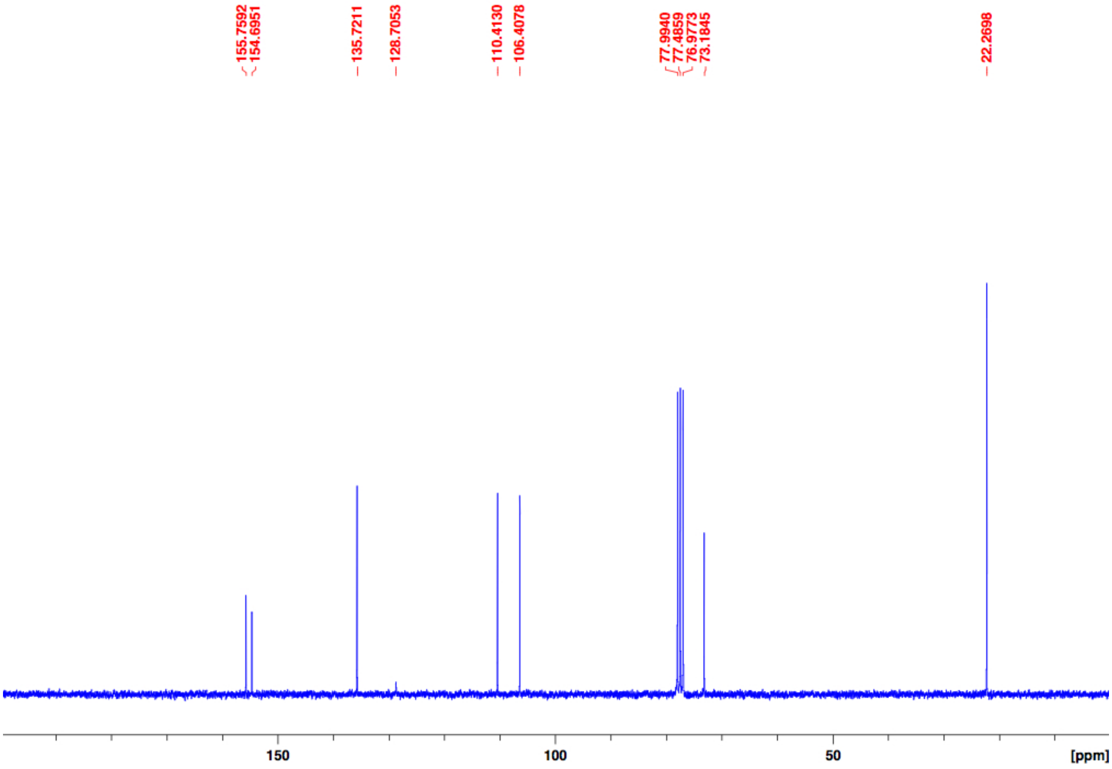
*3-(2-(*tert*-Butoxy)-2-oxoethoxy)-5-isopropoxybenzoic acid: 5*



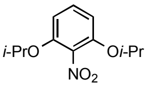


3-Isopropoxy-2-nitrophenol: 8

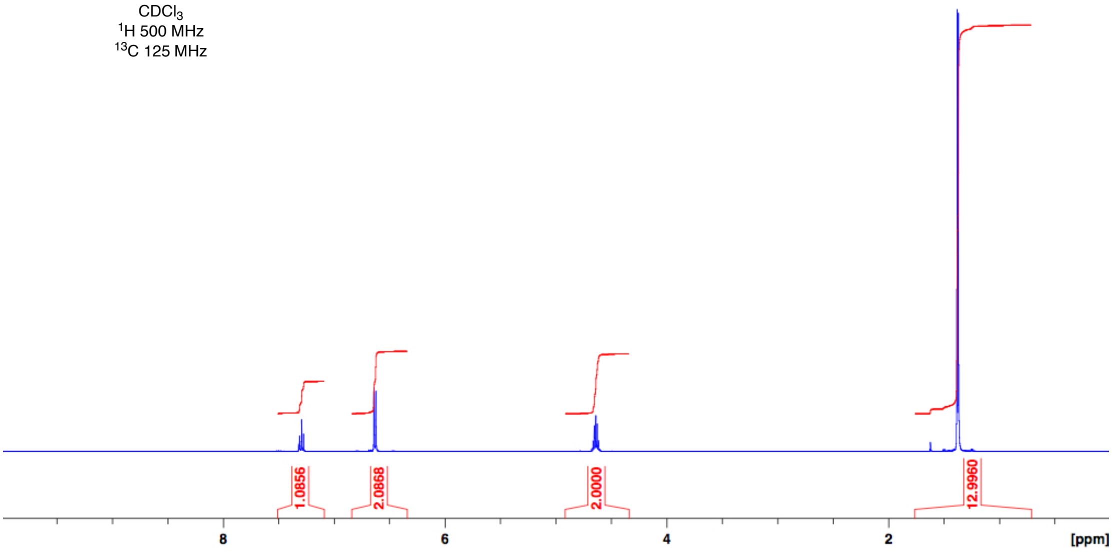


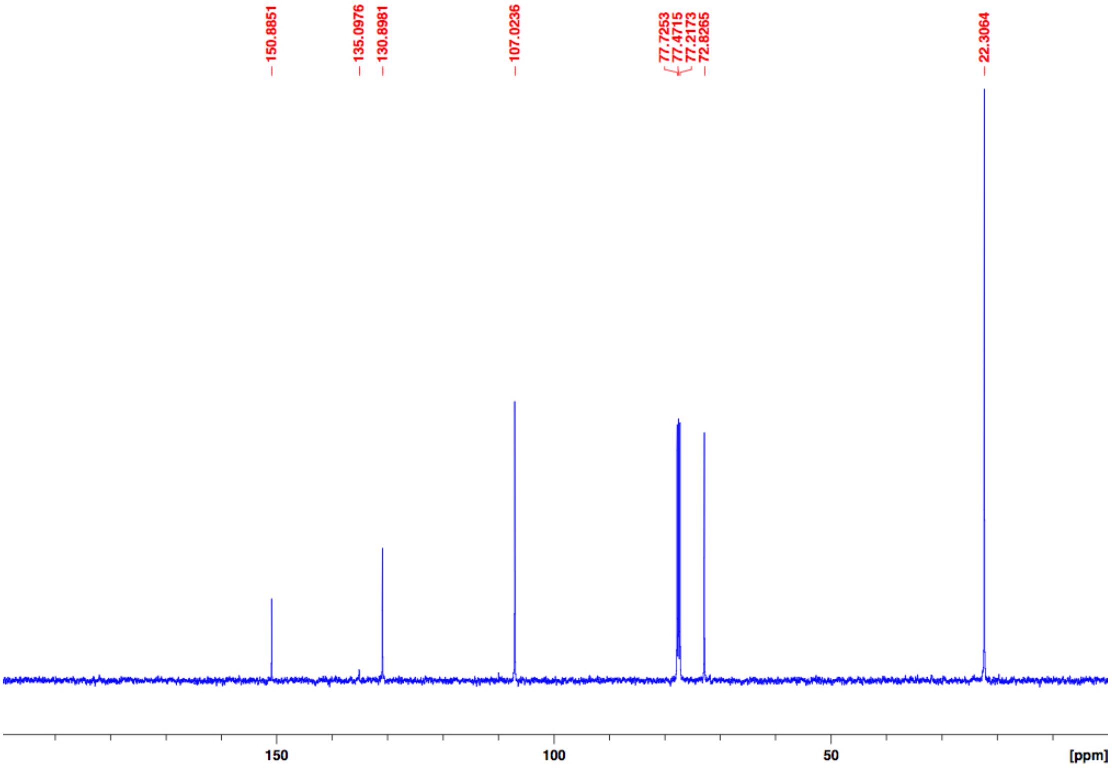


1,3-Diisopropoxy-2-nitrobenzene: 9



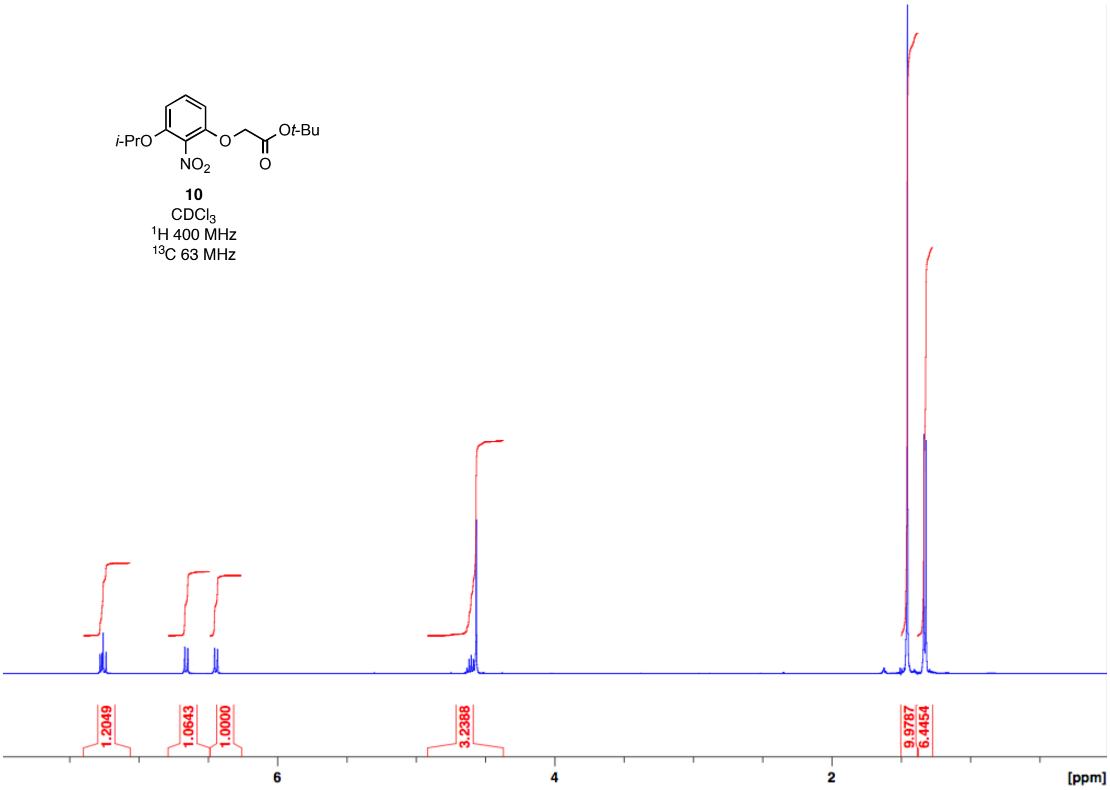
9
$CDCl_3$
^1H 500 MHz
^{13}C 125 MHz

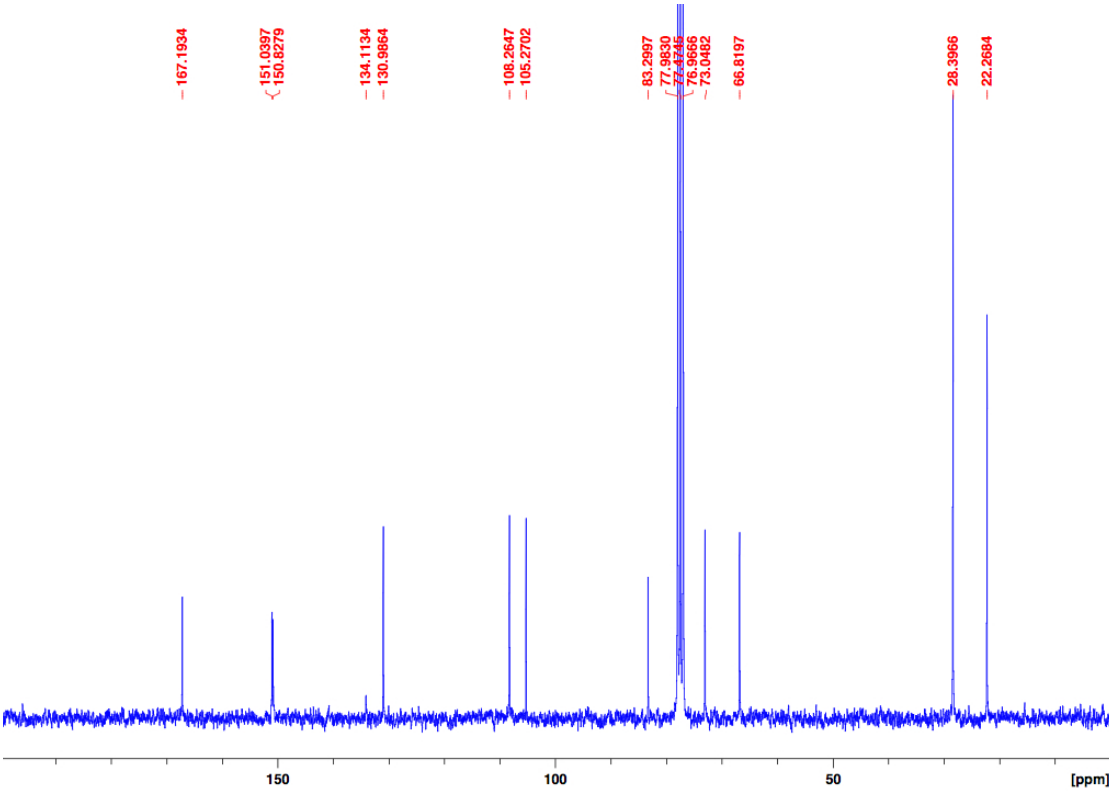




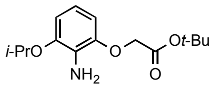
tert-*Butyl 2-(3-isopropoxy-2-nitrophenoxy)acetate: 10*

10
$CDCl_3$
^1H 400 MHz
^{13}C 63 MHz

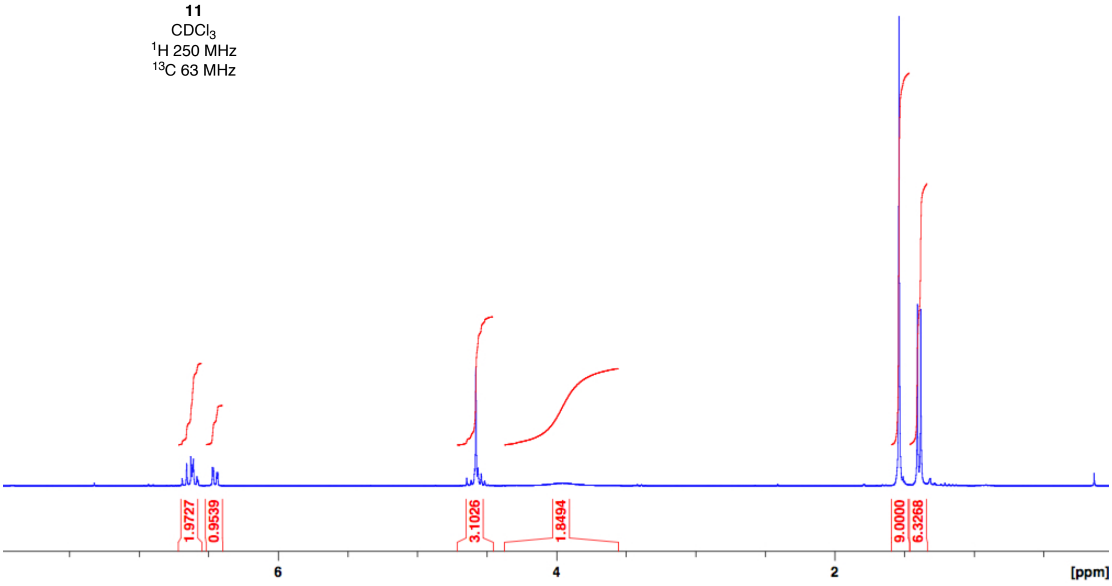


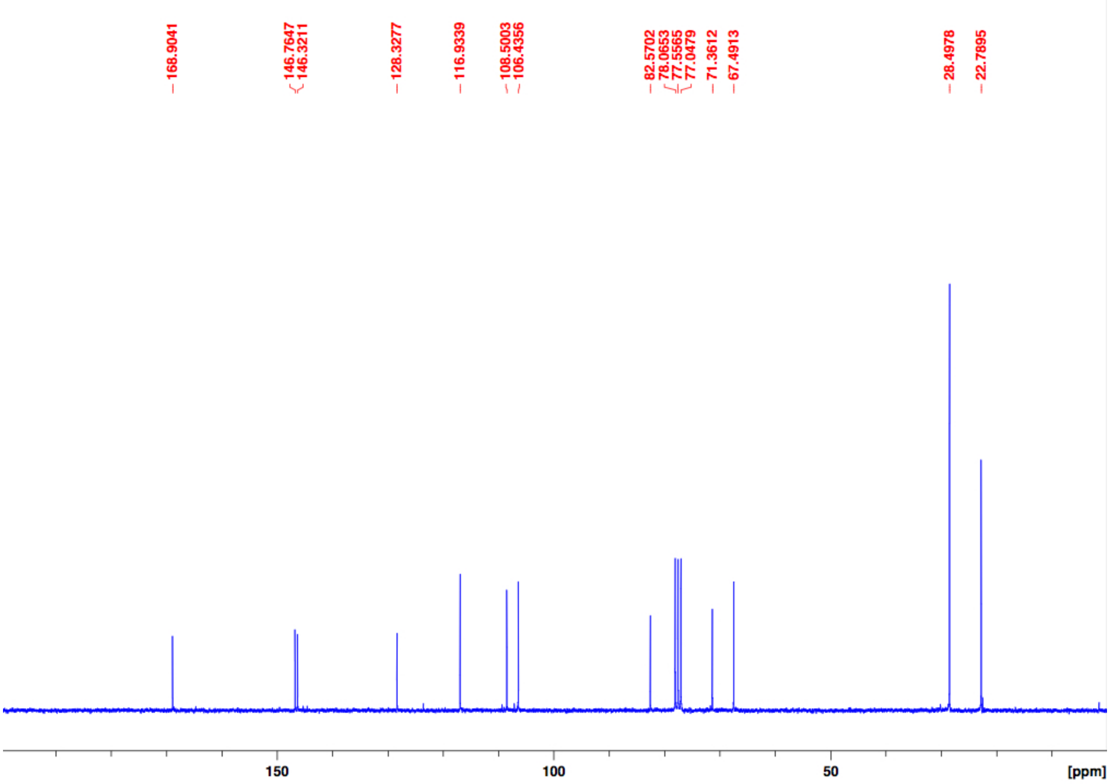


tert-*Butyl 2-(2-amino-3-isopropoxyphenoxy)acetate: 11*

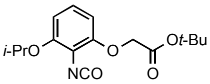


11
$CDCl_3$
^1H 250 MHz
^{13}C 63 MHz

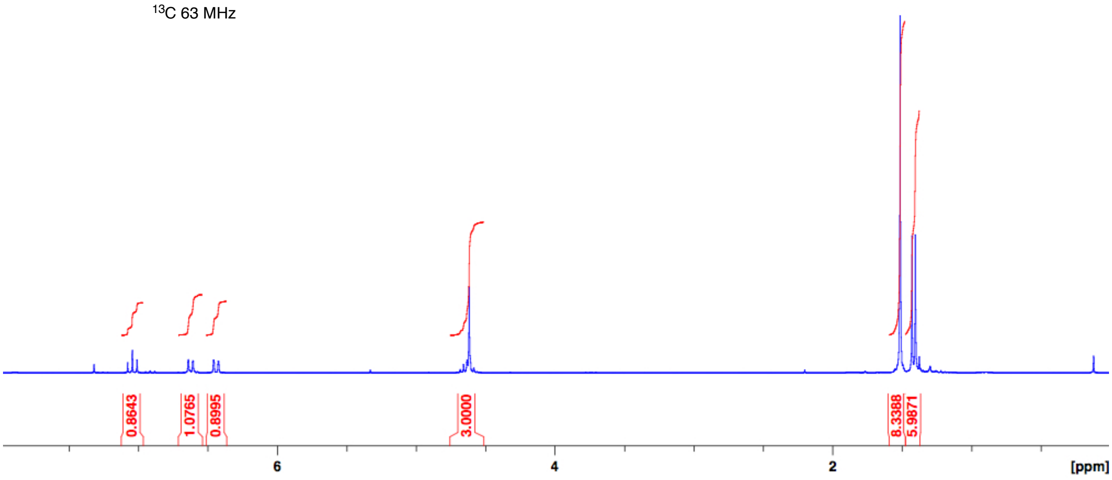


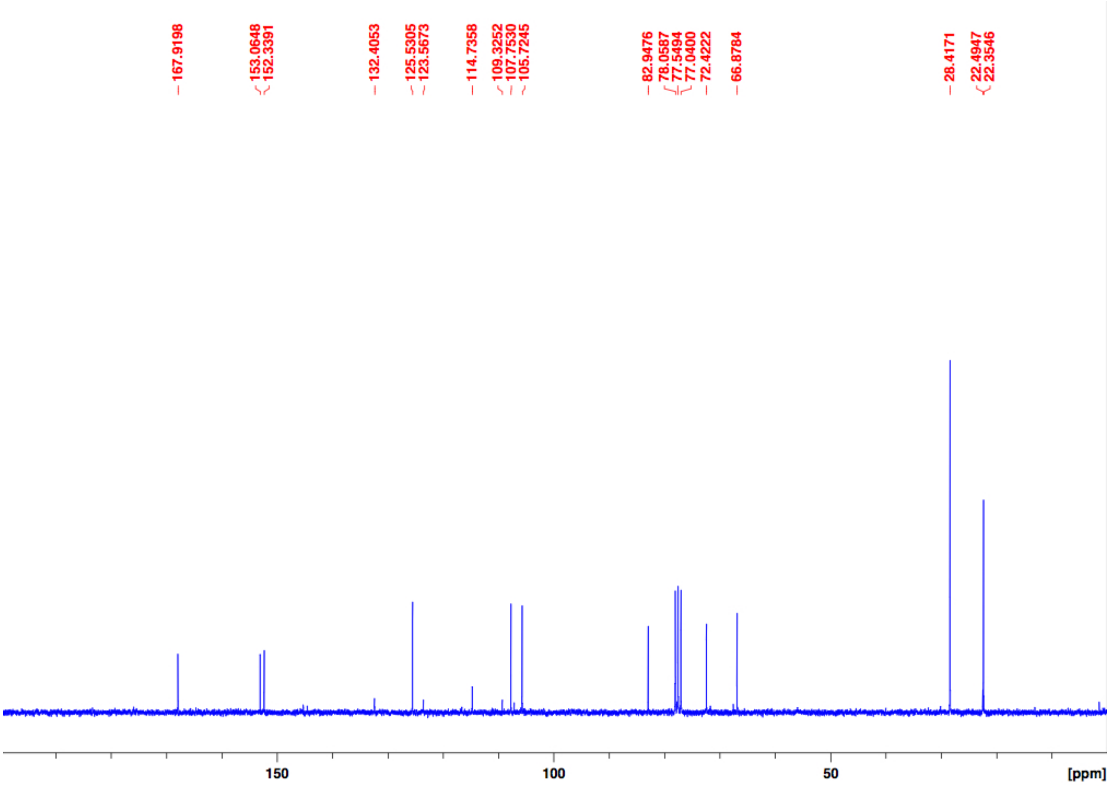


tert-*Butyl 2-(2-isocyanato-3-isopropoxyphenoxy)acetate: 12*



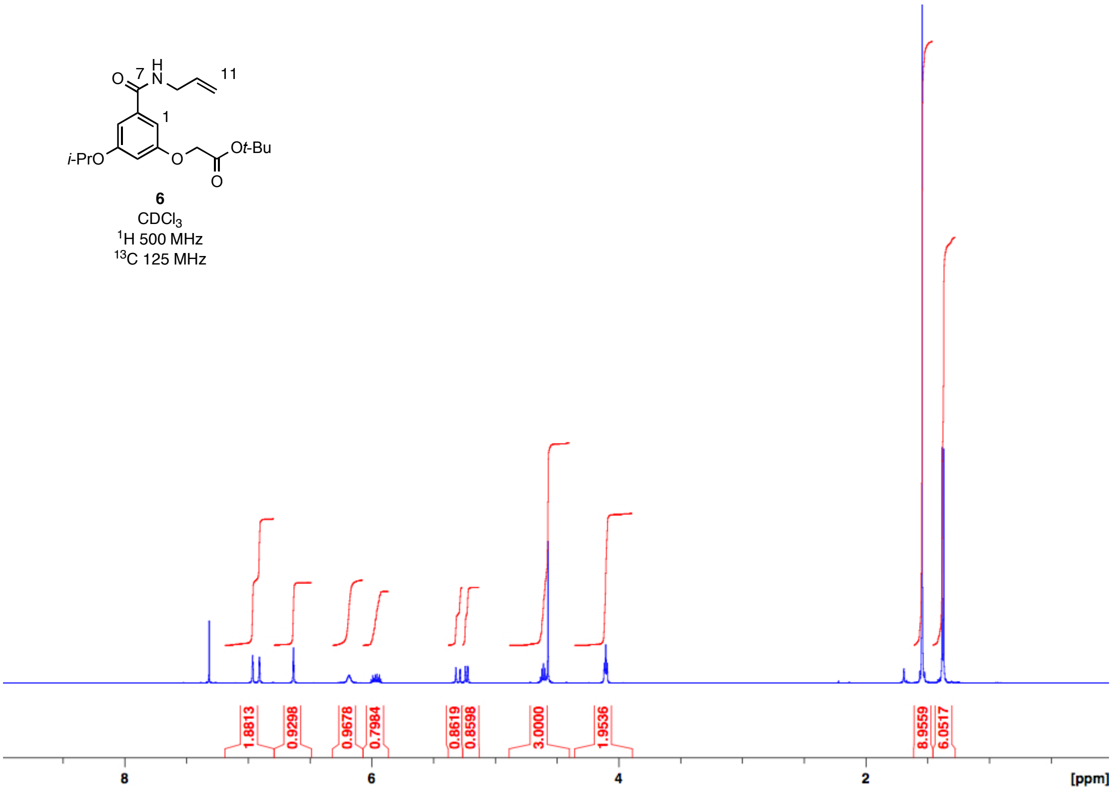
12
$CDCl_3$
^1H 250 MHz
^{13}C 63 MHz

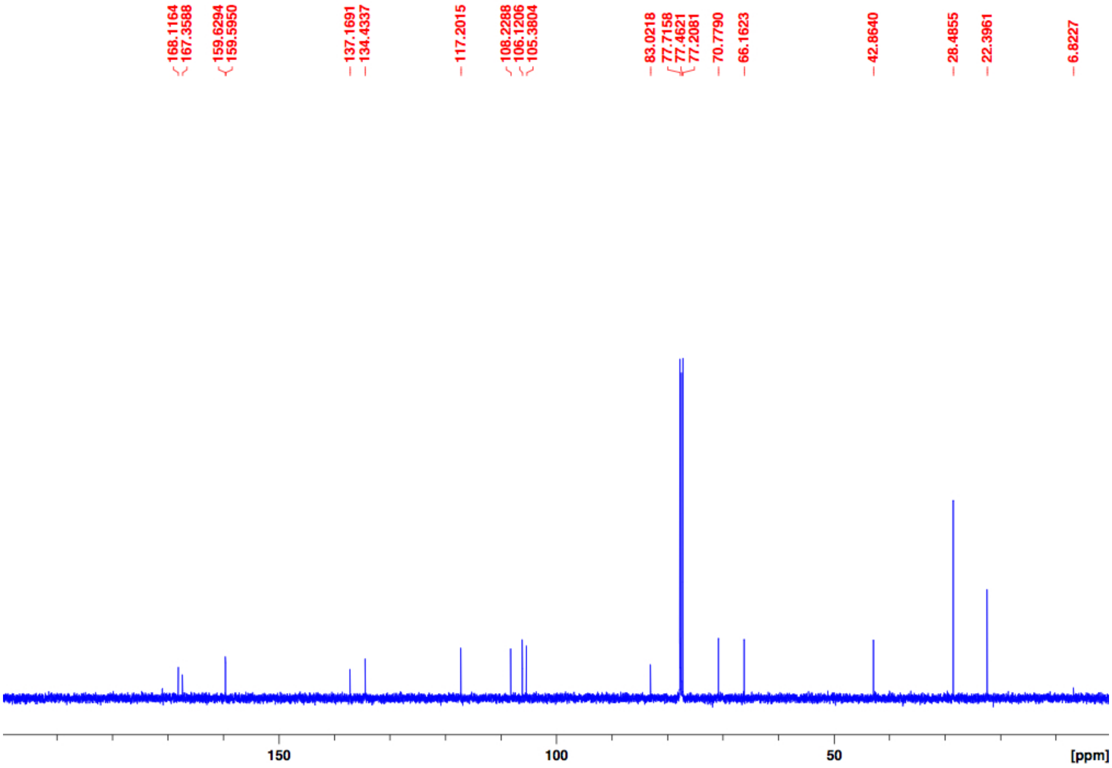




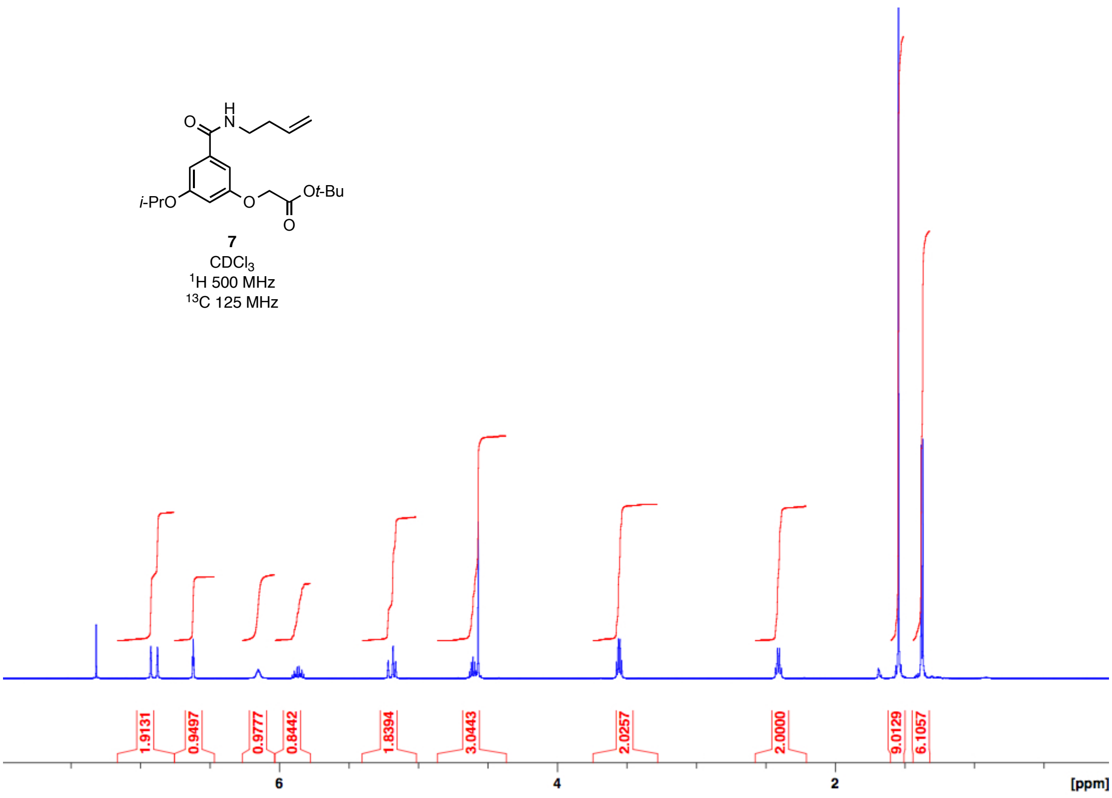
tert-*Butyl 2-(3-(allylcarbamoyl)-5-isopropoxyphenoxy)acetate: 6*

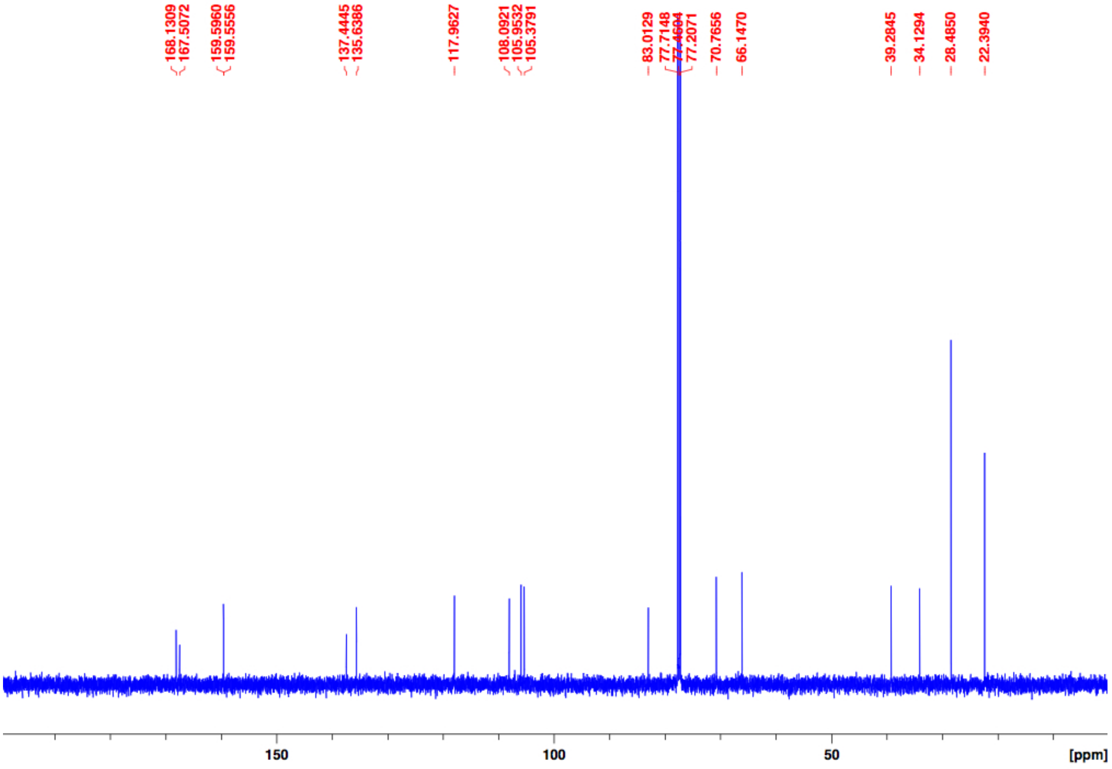
6
$CDCl_3$
^1H 500 MHz
^{13}C 125 MHz



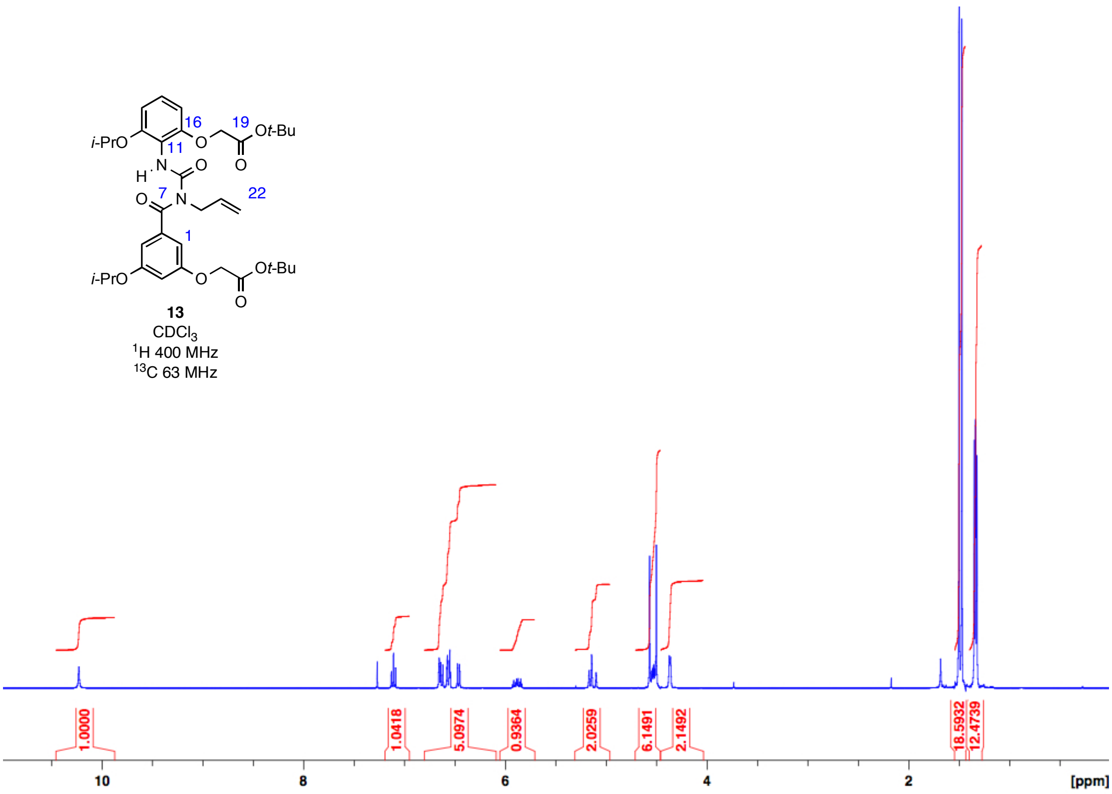


tert-*Butyl 2-(3-(but-3-en-1-ylcarbamoyl)-5-isopropoxyphenoxy)acetate: 7*

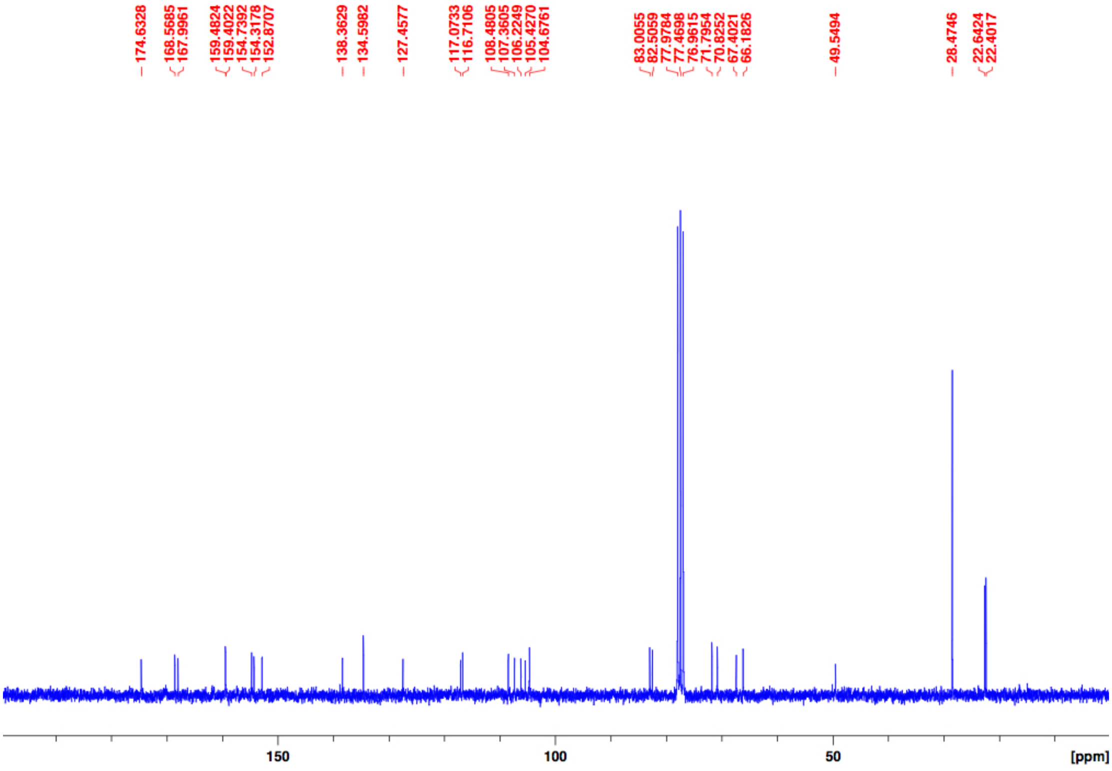




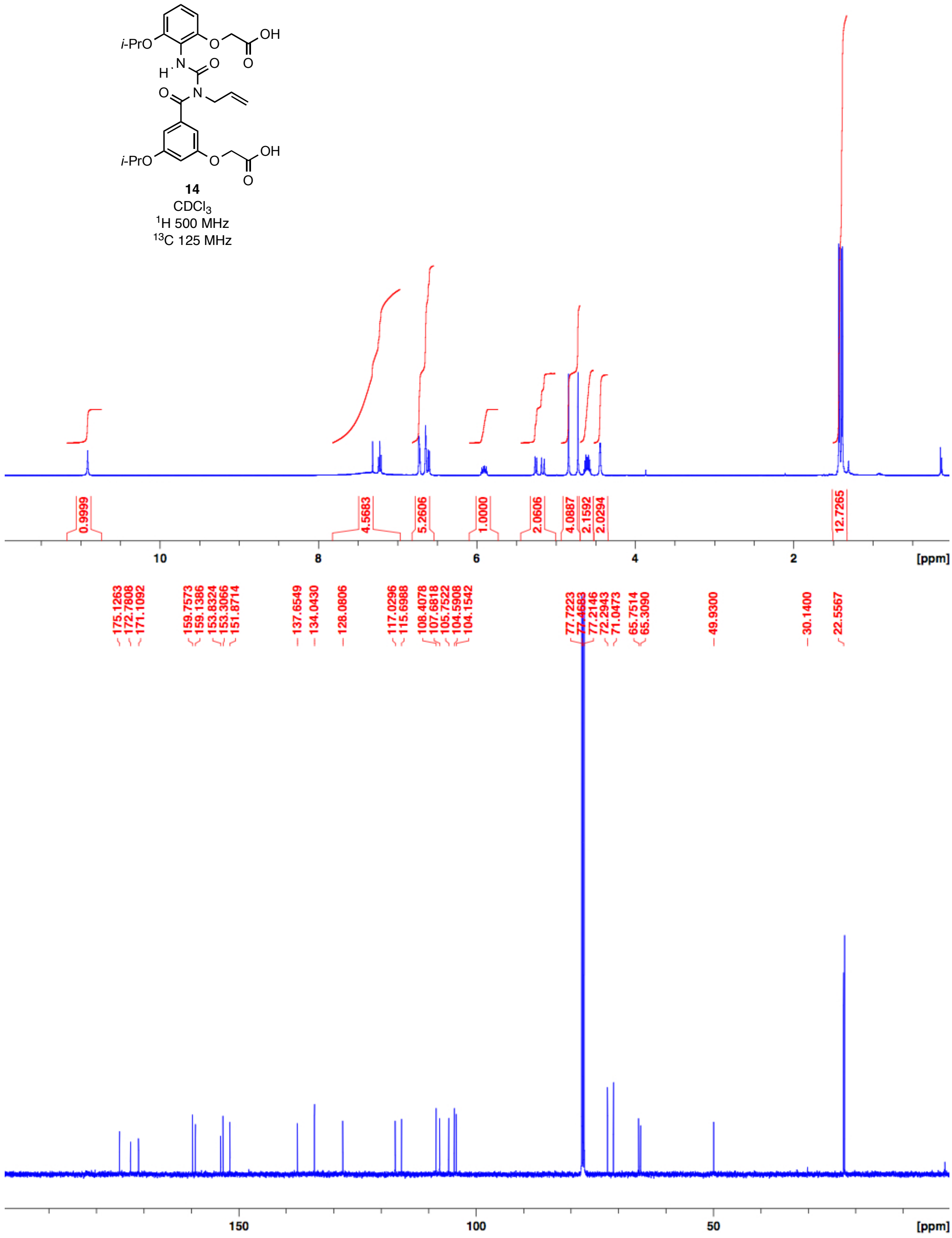
tert-*Butyl 2-(3-(allyl((2-(2-(*tert*-butoxy)-2-oxoethoxy)-6-isopropoxyphenyl)carbamoyl)carbamoyl)-5-isopropoxyphenoxy)acetate: 13*



13
$CDCl_3$
^{1}H 400 MHz
^{13}C 63 MHz

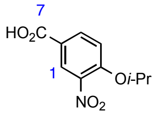


2-(3-(Allyl((2-(carboxymethoxy)-6-isopropoxyphenyl)carbamoyl)carbamoyl)-5-isopropoxyphenoxy)acetic acid: 14

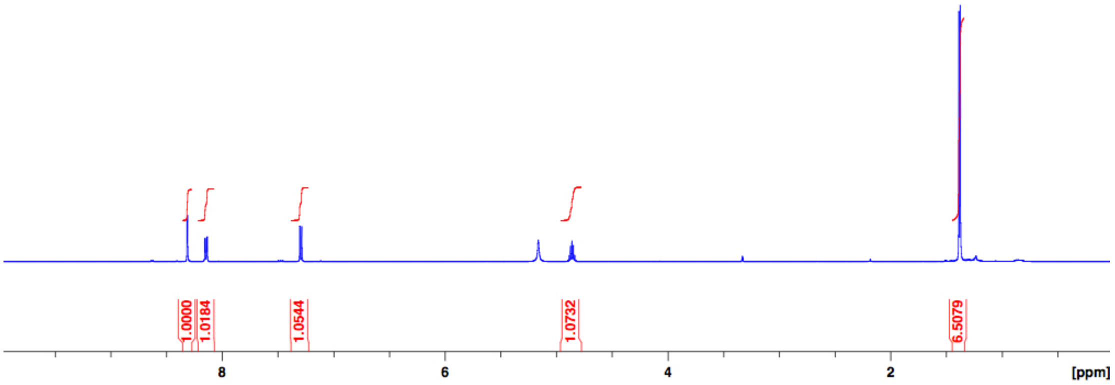


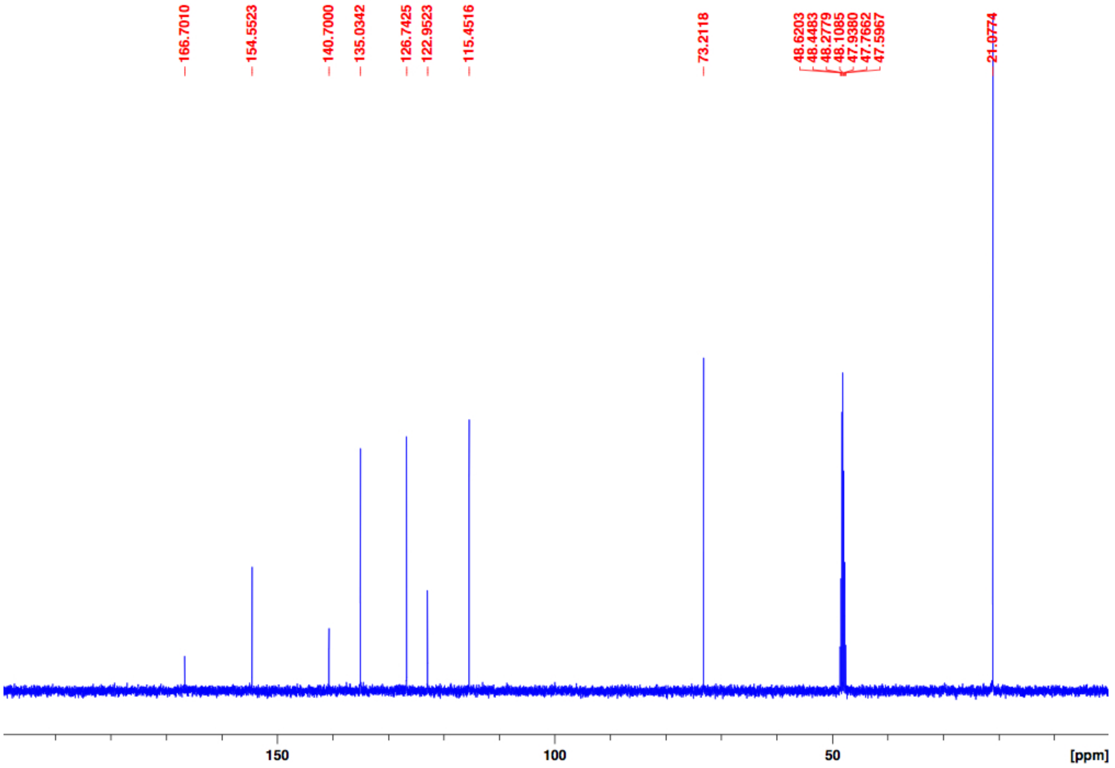
14
$CDCl_3$
^1H 500 MHz
^{13}C 125 MHz

4-Isopropoxy-3-nitrobenzoic acid: 15

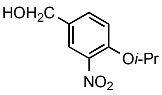


15
CD_3OD
^{1}H 500 MHz
^{13}C 125 MHz





(4-Isopropoxy-3-nitrophenyl)methanol: 16



16
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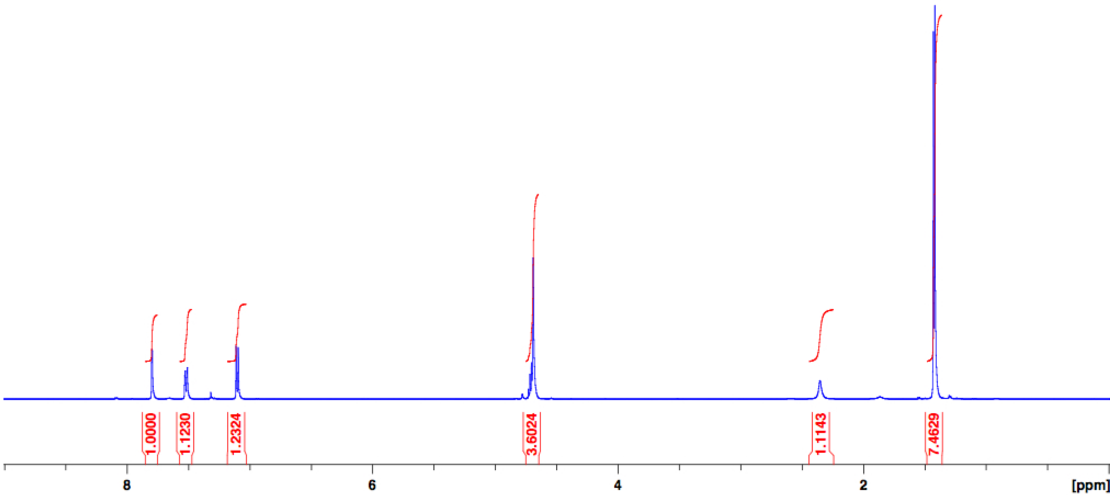
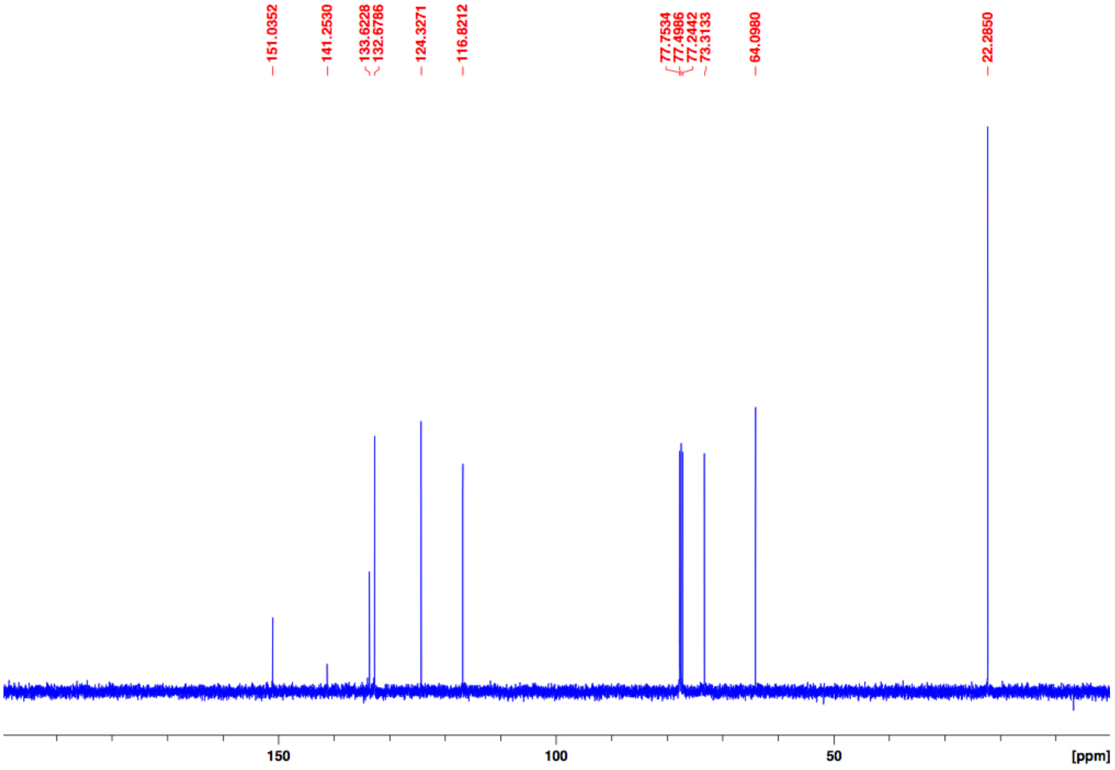
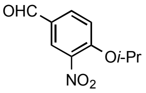
^{1}H 500 MHz
^{13}C 125 MHz

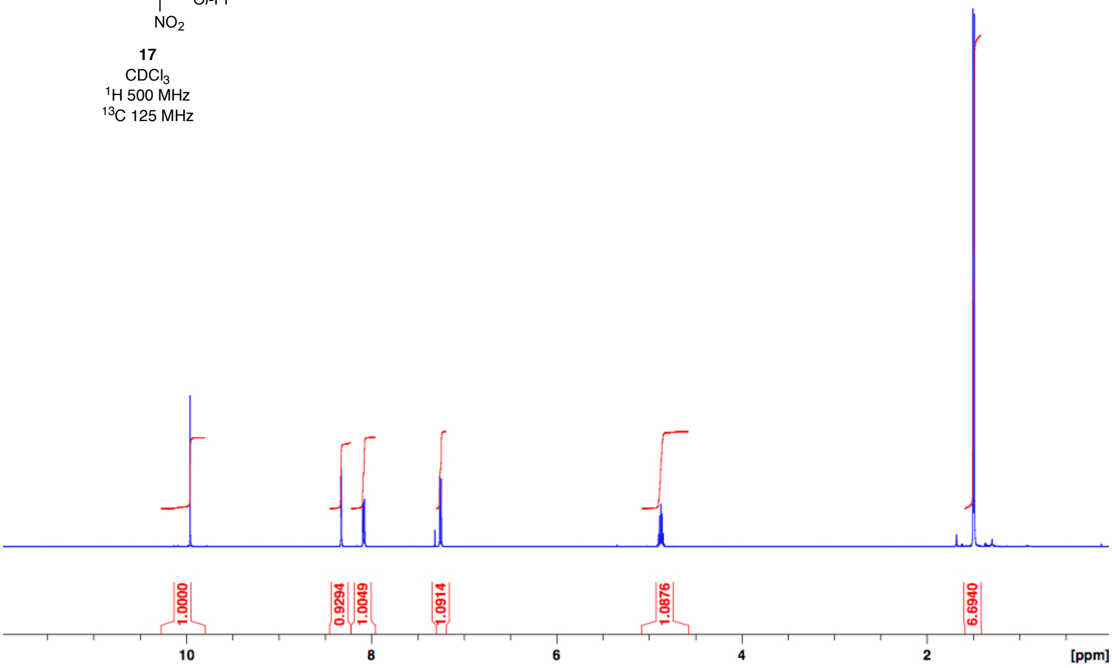


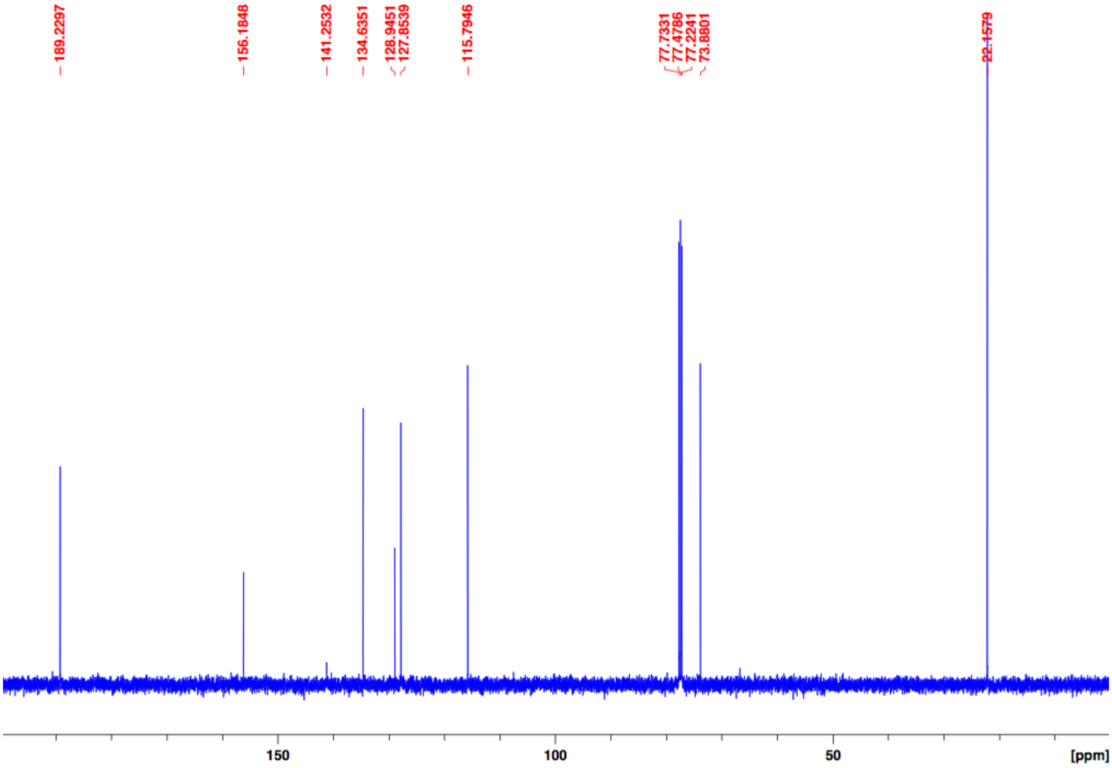


4-Isopropoxy-3-nitrobenzaldehyde: 17



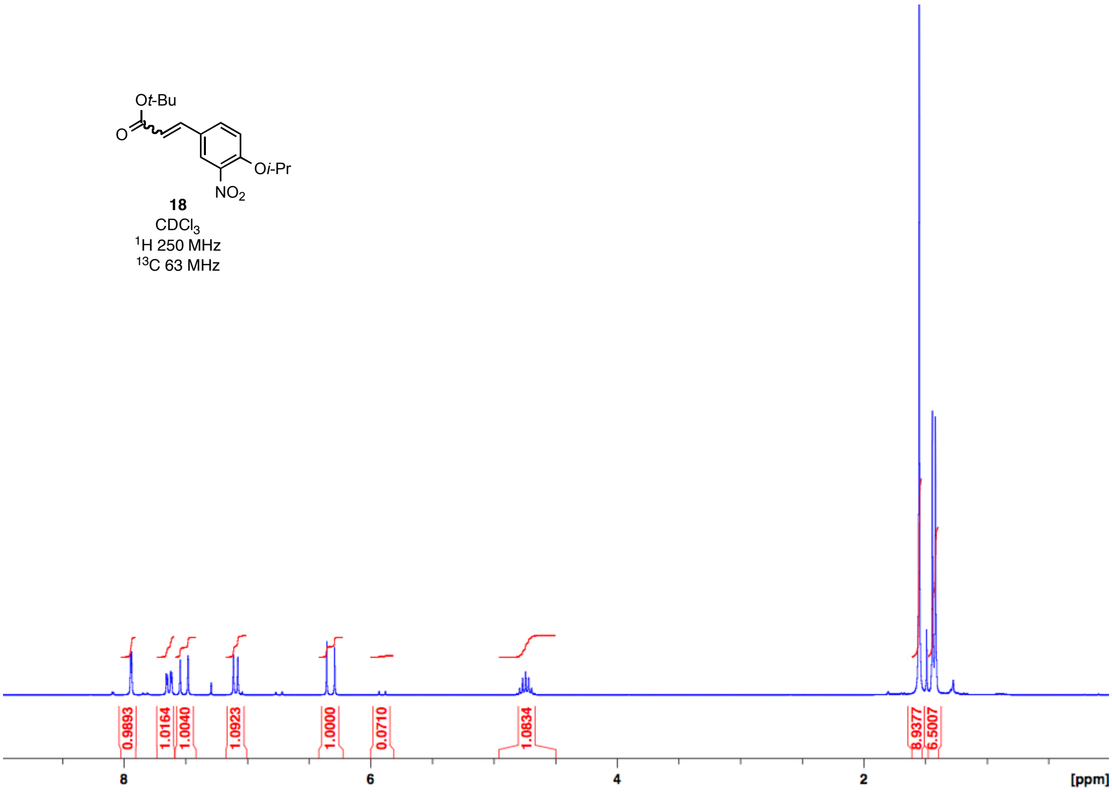
17
$CDCl_3$
^1H 500 MHz
^{13}C 125 MHz

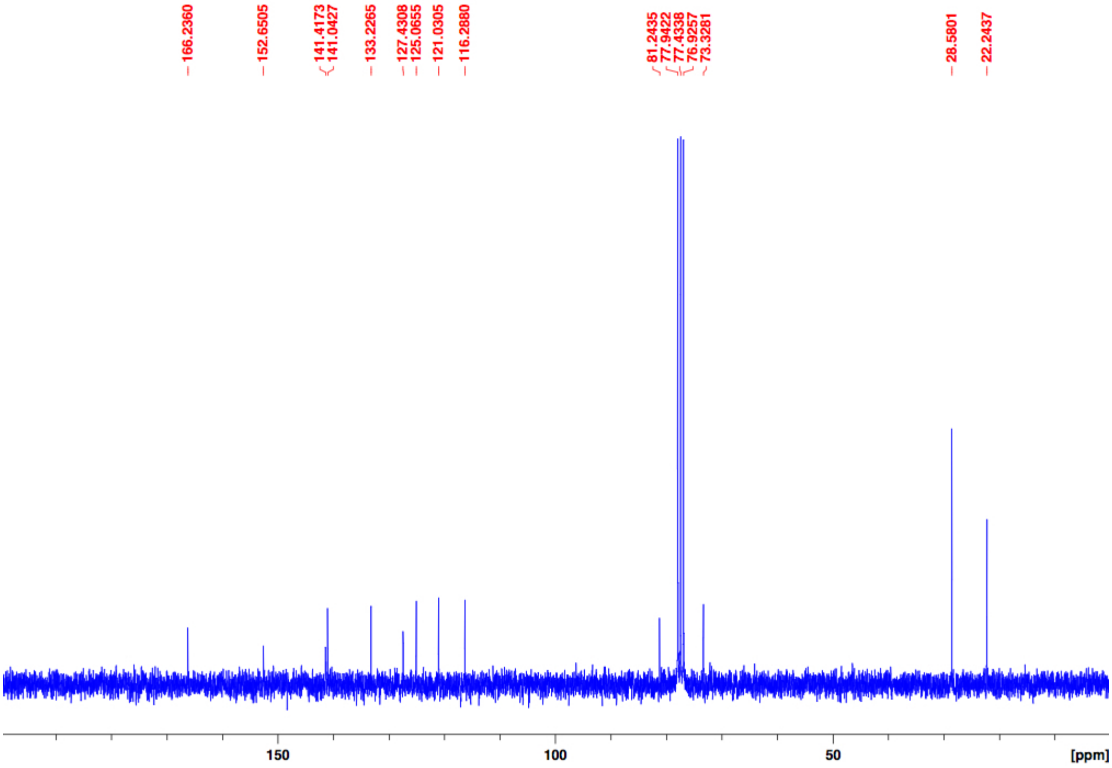




tert-*Butyl 3-(4-isopropoxy-3-nitrophenyl)acrylate: 18*

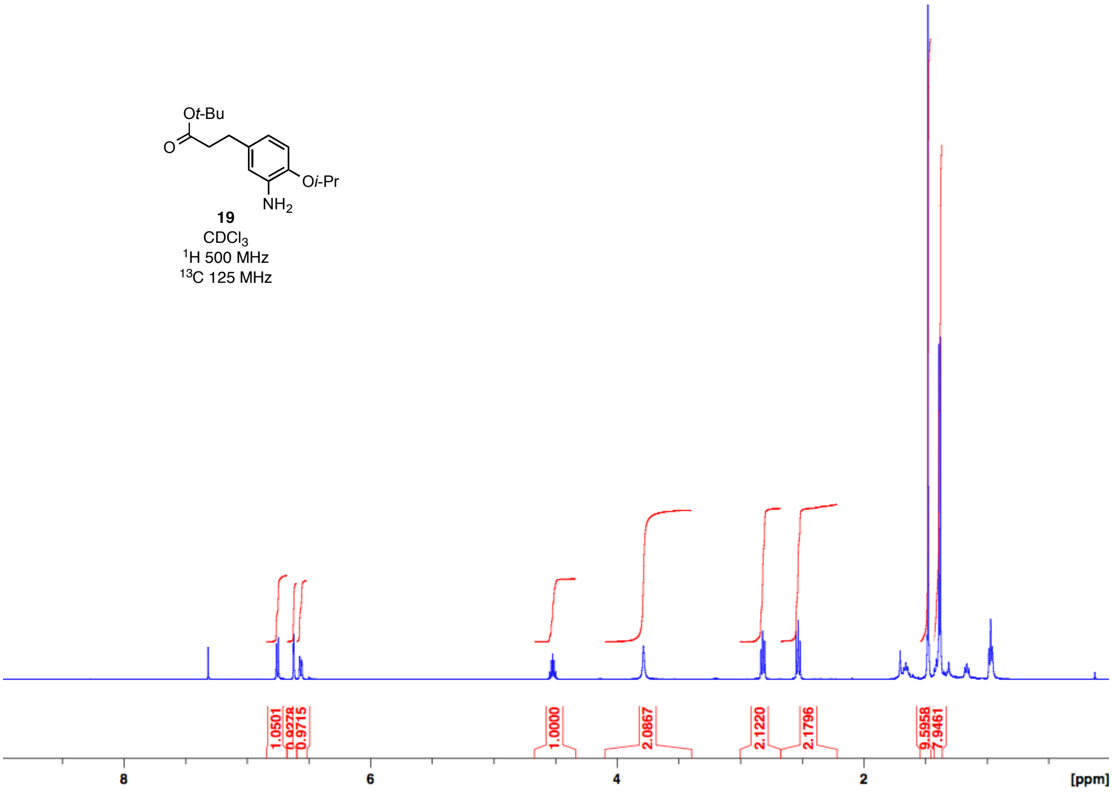
18
$CDCl_3$
^1H 250 MHz
^{13}C 63 MHz

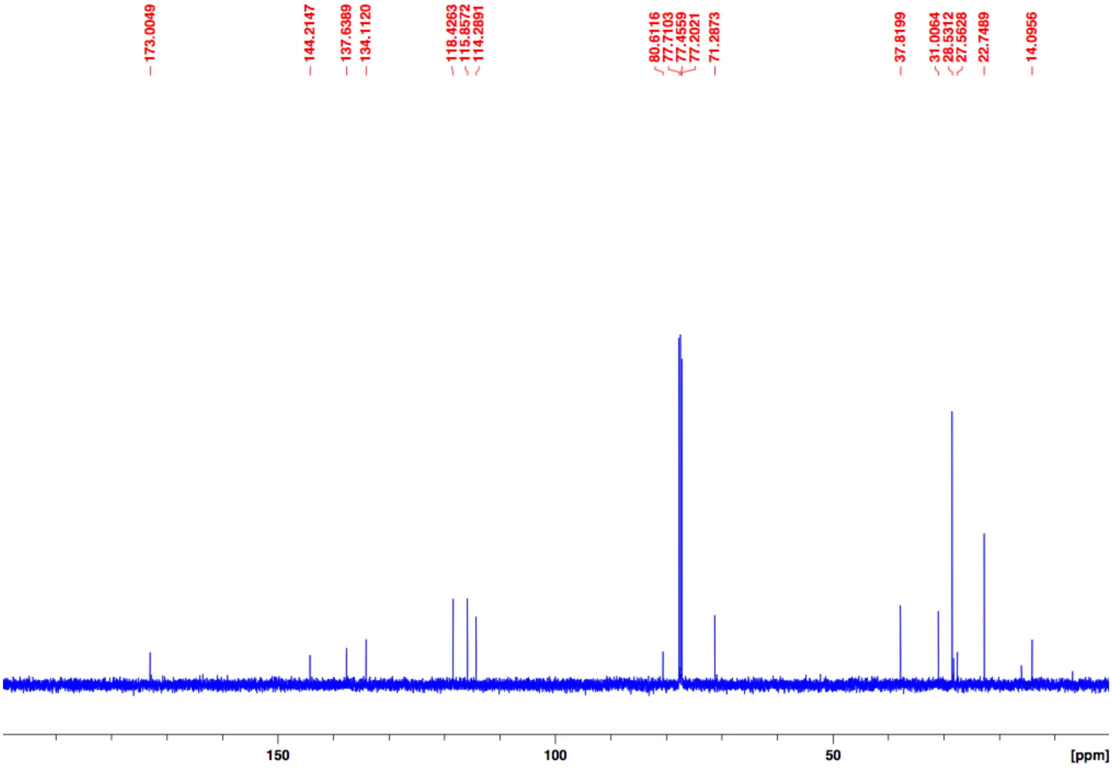




tert-*Butyl 3-(3-amino-4-isopropoxyphenyl)propanoate: 19*

19
CDCl$_3$
^{1}H 500 MHz
^{13}C 125 MHz





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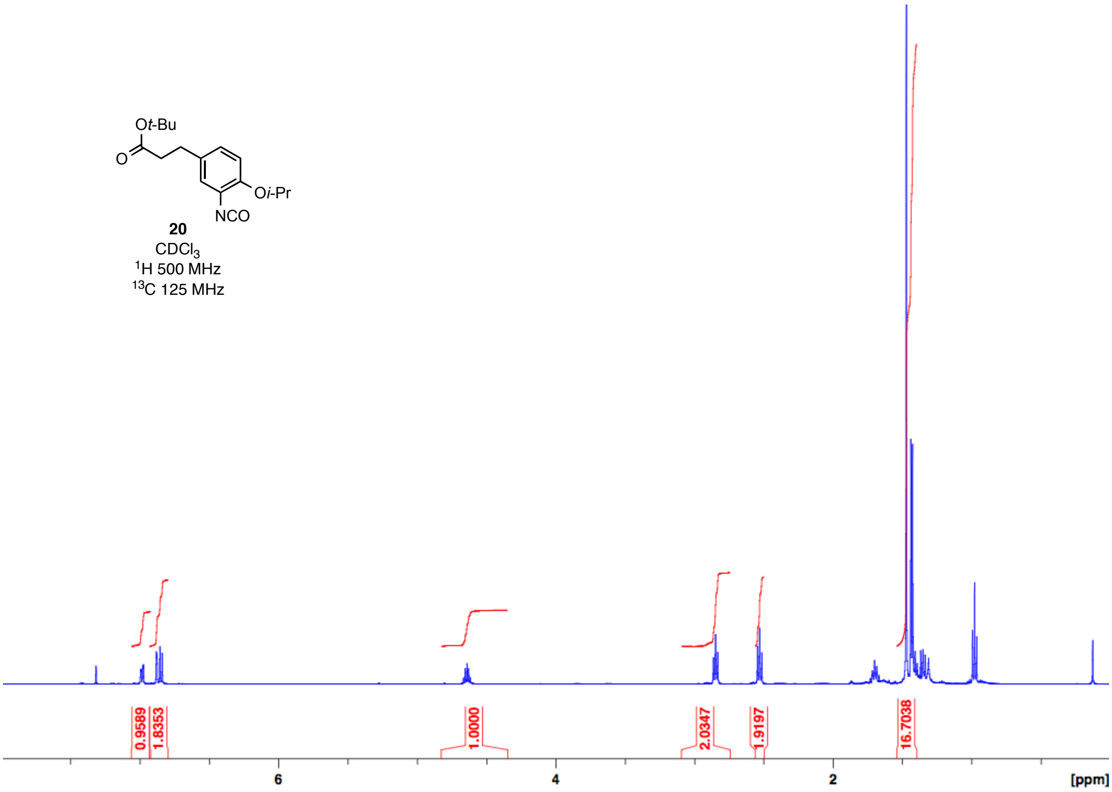

20
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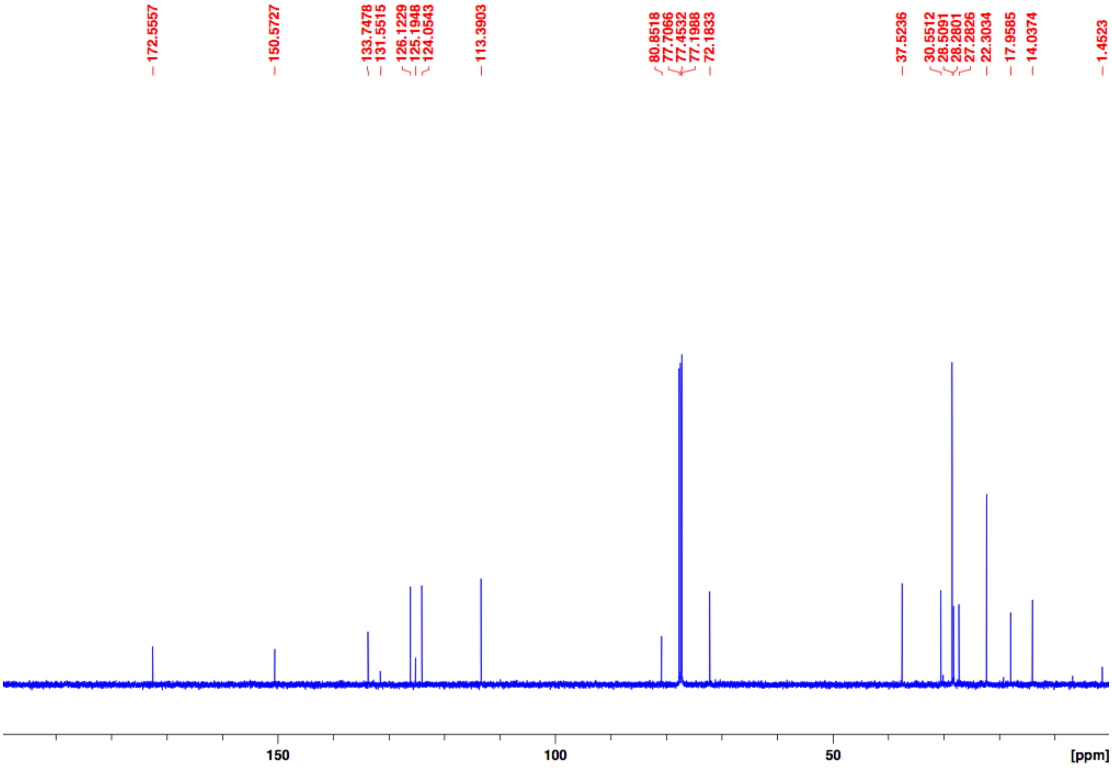
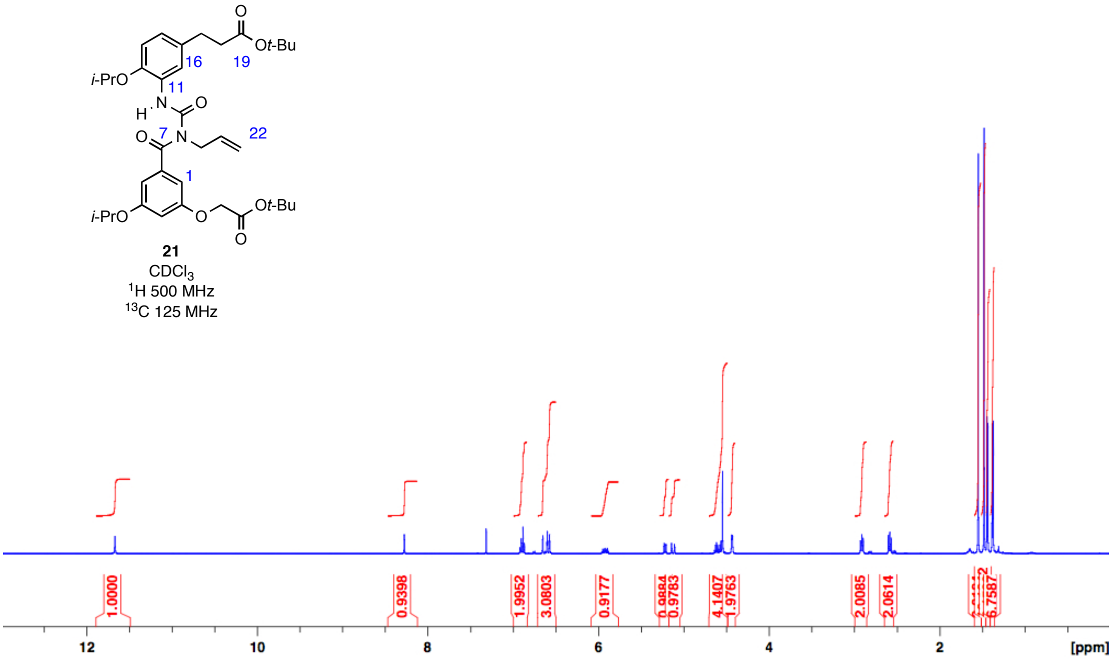
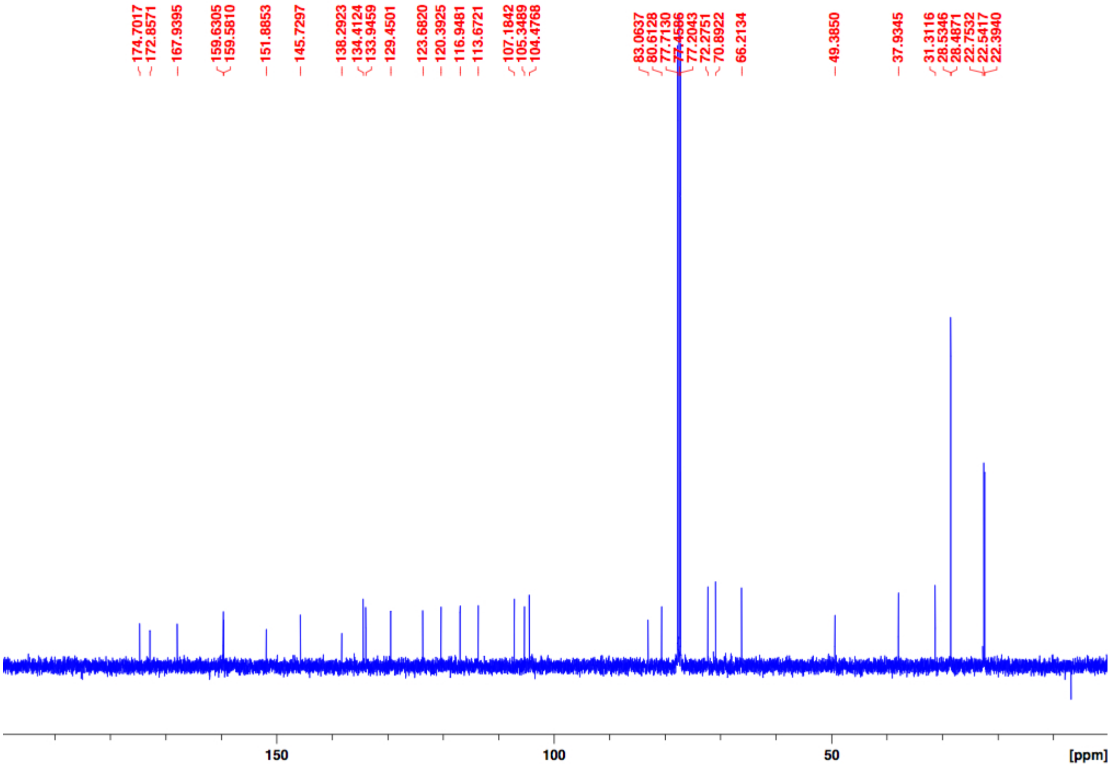
^1H 500 MHz
^{13}C 125 MHz



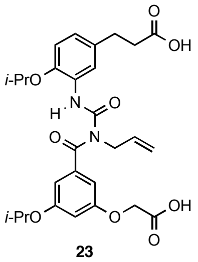
tert-Butyl 3-(3-(3-allyl-3-(3-(2-(tert-butoxy)-2-oxoethoxy)-5-isopropoxybenzoyl)ureido)-4-isopropoxyphenyl)propanoate: 21



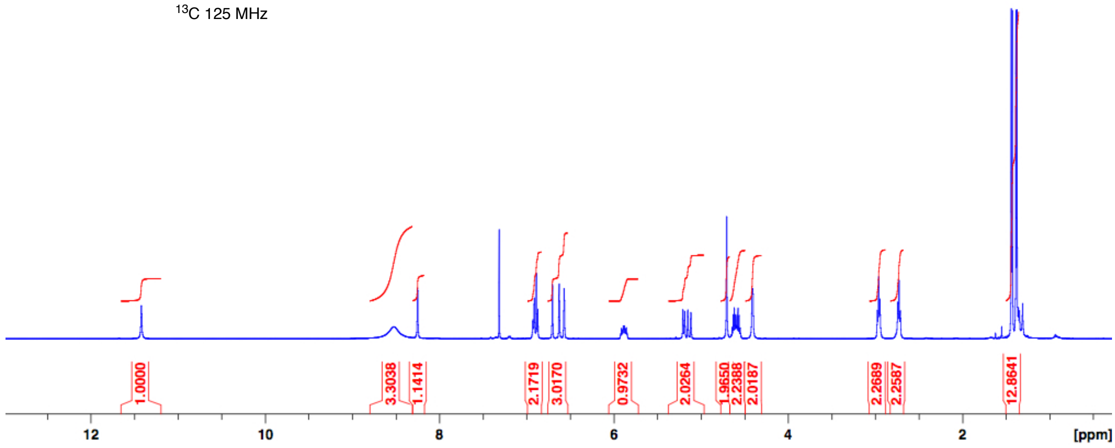
21
$CDCl_3$
^1H 500 MHz
^{13}C 125 MHz

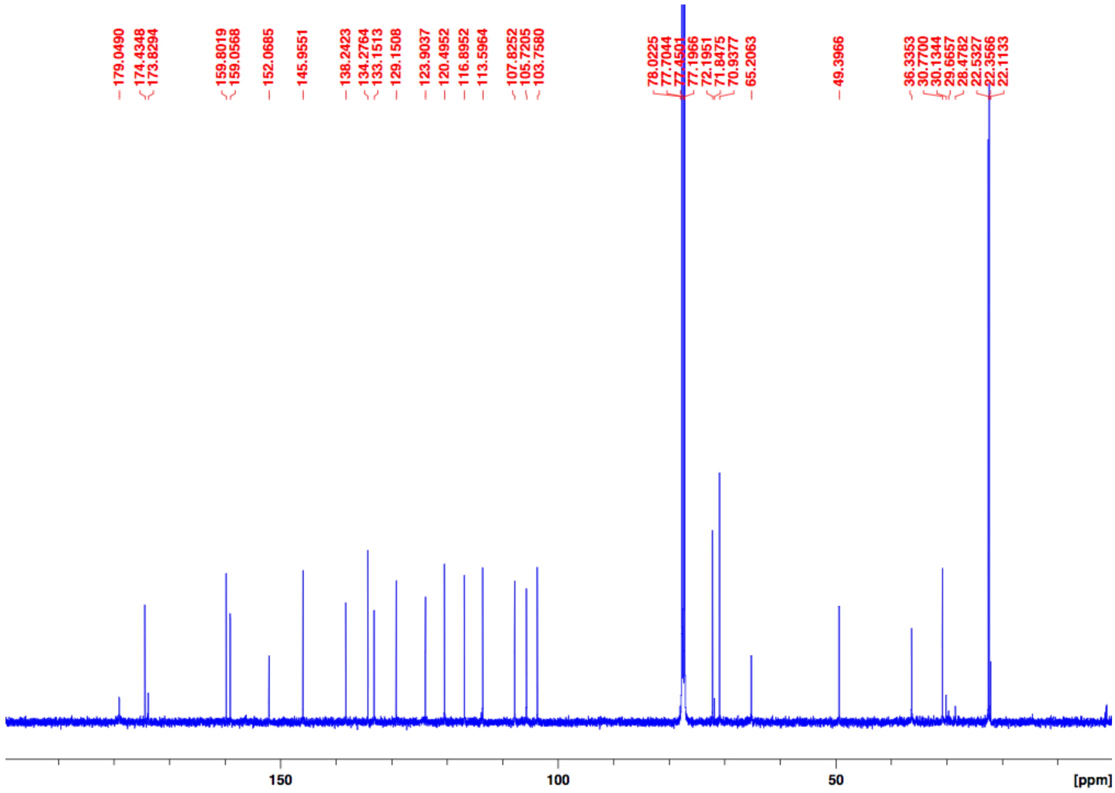


3-(3-(3-Allyl-3-(3-(carboxymethoxy)-5-isopropoxybenzoyl)ureido)-4-isopropoxyphenyl)propanoic acid: 23



23
$CDCl_3$
^1H 500 MHz
^{13}C 125 MHz





tert-Butyl 3-(3-(3-(but-3-en-1-yl)-3-(3-(2-(tert-butoxy)-2-oxoethoxy)-5-isopropoxybenzoyl)ureido)-4-isopropoxyphenyl)propanoate: 22