Supporting information for

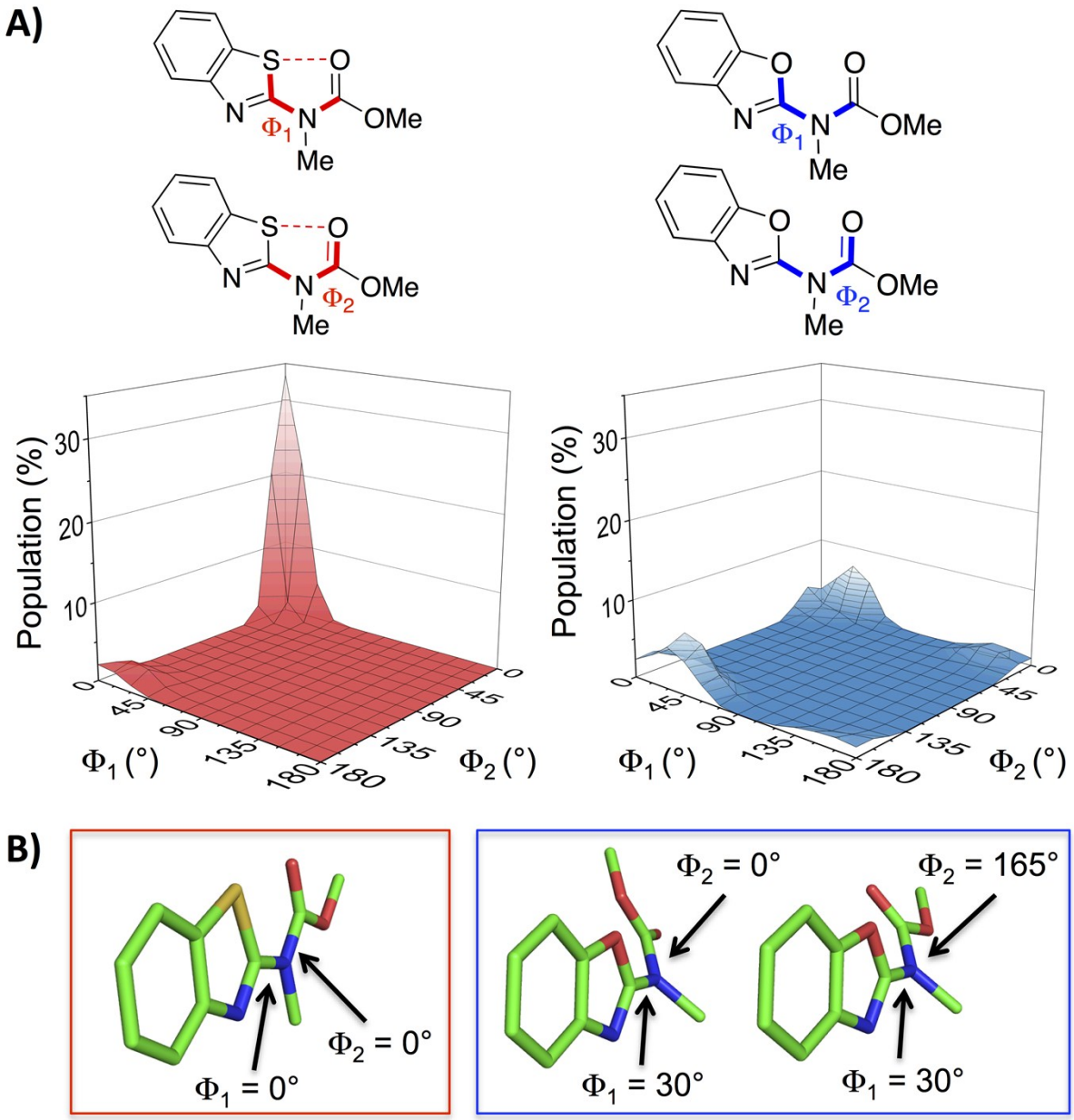
Non-Covalent S···O Interactions Control Conformation in a Scaffold that Disrupts Islet Amyloid Polypeptide Fibrillation

Hayden Peacock, Jinghui Luo, Tohru Yamashita, James Luccarelli, Sam Thompson* and Andrew D. Hamilton*

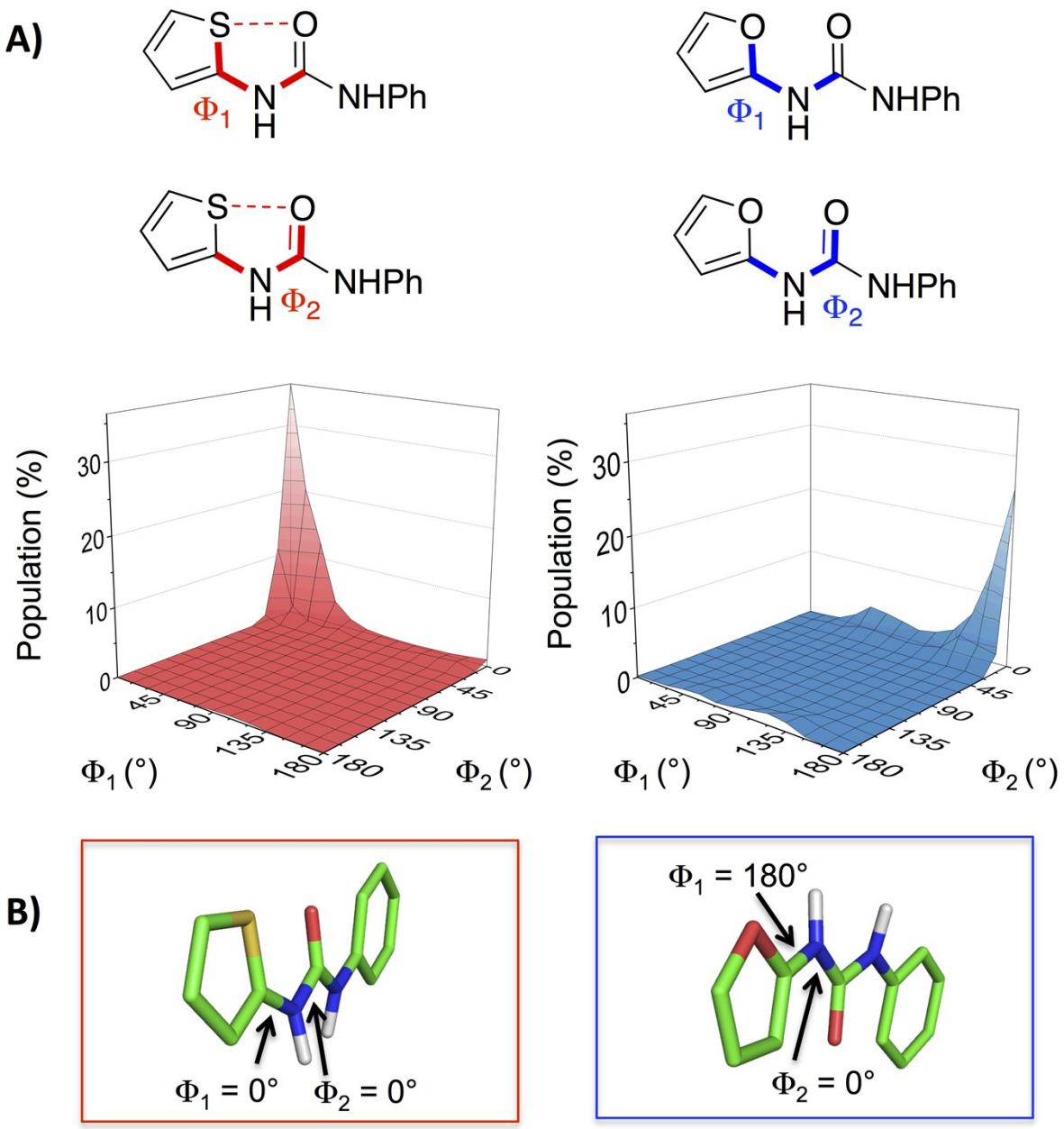
Chemistry Research Laboratory, University of Oxford
12 Mansfield Road, Oxford, OX1 3TA, U.K.
andrew.hamilton@chem.ox.ac.uk, sam.thompson@chem.ox.ac.uk

Table of contents

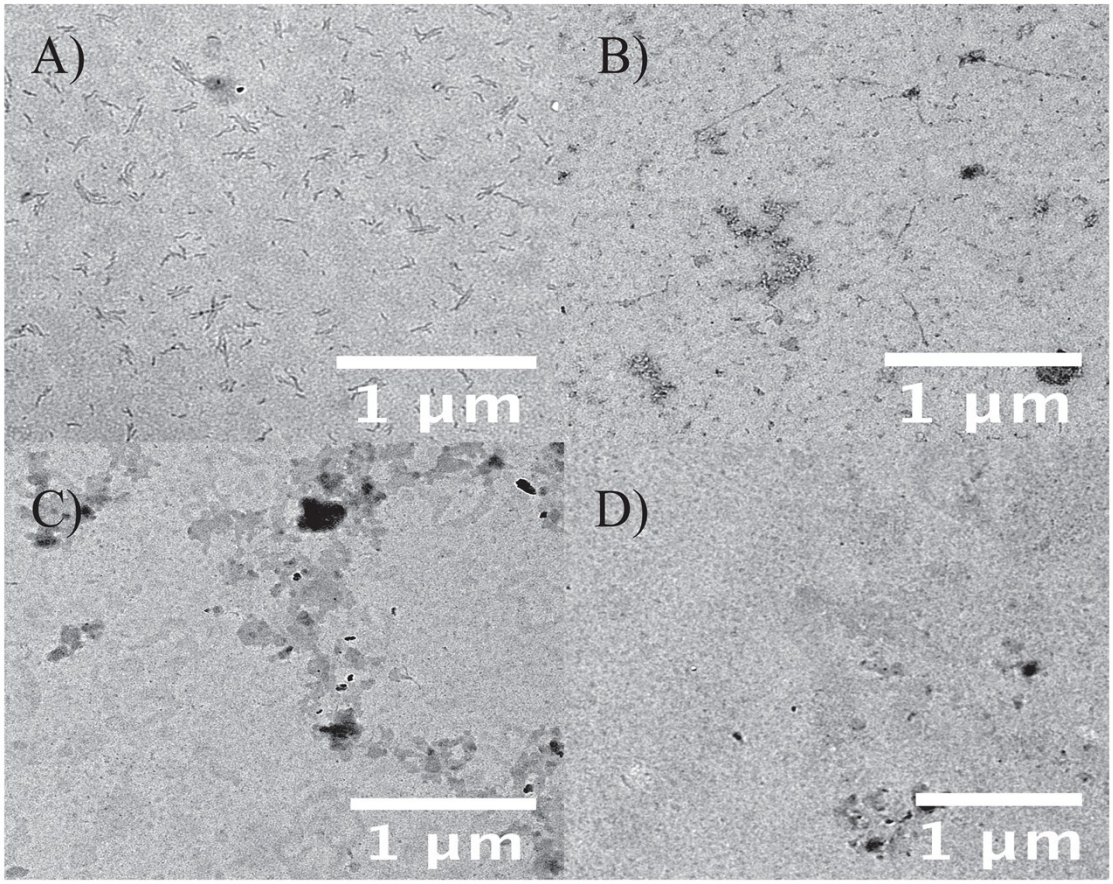
1. Supplementary figures



Supplementary Figure 1 *[Enlarged version of **Figure 1** from the main manuscript]* **A)** Dihedral contour plots of a model system depicting the difference in conformational preference between benzothiazole and benzoxazole rings. The relevant dihedral angles are depicted in bold and the plots show the Boltzmann population of conformers at 298 K. **B)** The model systems displayed in their most highly populated conformations (benzothiazole system in the red box and benzoxazole system in the blue box). The calculations were performed at the M06-2X/6-31G(d,p) level of theory with implicit aqueous solvent (see section 5).



Supplementary Figure 2. Dihedral contour plots of an alternative model system depicting the difference in conformational preference between thiophene and furan rings. The relevant dihedral angles are depicted in bold and the plots show the Boltzmann population of conformers at 298 K. B) The model systems displayed in their most highly populated conformations. The calculations were performed at the M06-2X/6-31G(d,p) level of theory with implicit aqueous solvent (see section 5).



Supplementary Figure 3. Electron microscope images of IAPP aggregates in the absence **(A)**; and presence of: **21 (B)**; **19 (C)**; and **22 (D)**. The samples were taken from the wells after ThT assays.

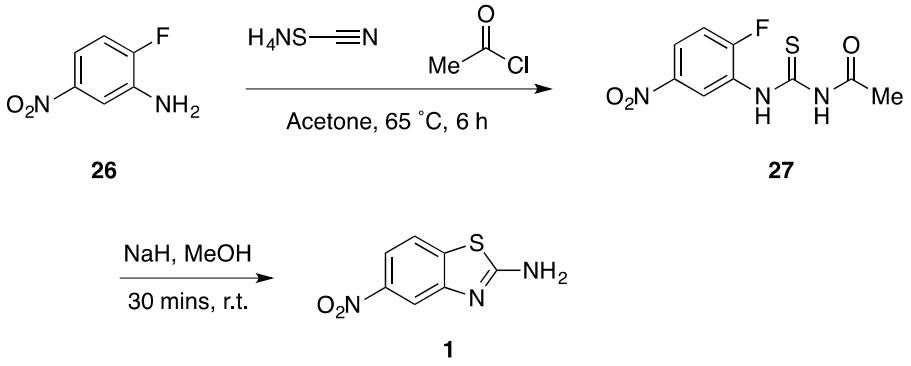
2. Details of Synthesis

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. Tetrahydrofuran (THF), dichloromethane (DCM), *N*,*N*'-dimethylformamide (DMF) and methanol (MeOH) were anhydrous (dried on an MB-SPS-800 solvent purification system). Other solvents and reagents were used directly as received from commercial suppliers. All aqueous solutions were saturated unless specified otherwise.

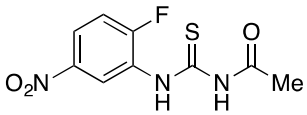
Flash column chromatography was carried out using Merck 60 silica gel. Thin-layer chromatography was carried out using Merck Kieselgel 60 F254 (230-400 mesh) fluorescent treated silica, visualized under UV light (254 nm) or by staining with aqueous potassium permanganate solution.

^{1}H and ^{13}C NMR spectra were recorded using a Bruker spectrometer (400, 500 or 600 MHz) running TopSpin™ software and are quoted in ppm for measurement against residual solvent peaks. 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 (number of protons, multiplicity, coupling constant). Multiplicity is abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, m = multiplet, br = broad. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer from a thin film deposited onto a diamond ATR module. Only selected maximum absorbances (ν_{max}) of the most intense peaks are reported (cm^{-1}). High-resolution mass spectra were recorded by the internal service at the Department of Chemistry, University of Oxford, using a Bruker MicroTof (ESI) or an Agilent 7200 Accurate Mass Q-TOF GC/MS with an MSD Direct Inlet Probe (ammonia CI). Compound names are those generated by ChemBioDraw™ (CambridgeSoft) following IUPAC nomenclature.

5-Nitrobenzo[d]thiazol-2-amine (1)

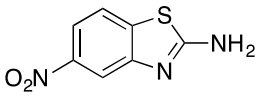


***N*-((2-Fluoro-5-nitrophenyl)carbamothioyl)acetamide (27)**



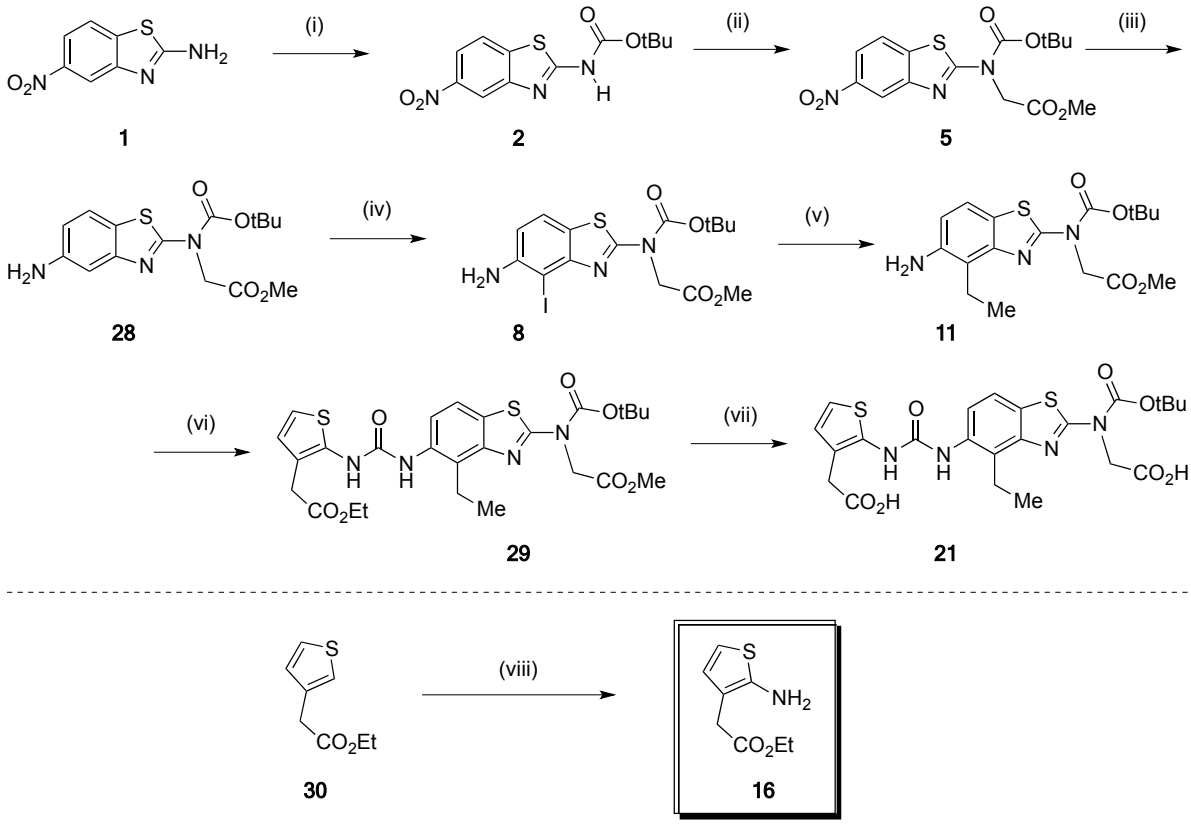
Acetyl chloride (8.0 mL, 11 mmol) was added to a solution of ammonium thiocyanate (8.60 g, 11.3 mmol) in acetone (125 mL) and the mixture was stirred for 1 h. The solids were removed by filtration. 2-Fluoro-5-nitroaniline **26** (15.9 g, 10.2 mmol) was added to the filtrate, and this solution was heated at 65 ˚C for 6 h. The solids were isolated by filtration, washed with diethyl ether, hexane and acetone to give *the title compound* **27** (16.1 g, 62.6 mmol, 61 % yield); δ_H (400 MHz, DMSO-d_6) 12.74 (1H, s), 11.84 (1H, s), 9.25 (1H, dd, *J*=6.6, 2.69), 8.15 - 8.28 (1H, m), 7.62 (1H, t, *J*=9.5), 2.19 (3H, s); δ_C (101 MHz, DMSO-d_6) 180.2, 173.6, 158.8 (d, *J*=257) 143.6, 127.7, 123.6, 121.4, 117.1, 24.2; $\delta_F\{^1H\}$ (377 MHz, DMSO-d_6) -113.7; IR 3201, 2981, 1696, 1347, 1236, 742; HRMS (ESI) calculated for $C_9H_7FN_3O_3S$ [$(M-H)^-$]: 256.0198 found 256.0195.

5-Nitrobenzo[*d*]thiazol-2-amine (1)



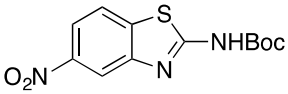
Sodium hydride (3.37 g, 84.3 mmol, 60 % w/w dispersion in mineral oil) was cautiously added portion-wise to methanol (84 mL) and the resultant mixture stirred for 30 mins. *N*-((2-Fluoro-5-nitrophenyl)carbamothioyl)acetamide **27** (16.1 g, 62.6 mmol) was added as a solution in methanol (690 mL). The mixture was allowed to stand for 16 h, the solids were isolated by filtration and washed with diethyl ether-methanol to yield *the title compound* **1** (12.0 g, 61.5 mmol, 98% yield); δ_H (400 MHz, DMSO-d_6) 8.04 (1 H, d, *J*=2.2) 7.97 (2 H, brs) 7.90 - 7.94 (1 H, m) 7.83 - 7.89 (1 H, m); δ_C (101 MHz, DMSO-d_6) 169.1, 153.2, 146.1, 139.1, 121.6, 115.4, 111.4; IR 3421, 2918, 2850, 1653, 1338, ; HRMS (ESI) calculated for $C_7H_6N_3O_2S$ [$(M+H)^+$]: 196.0175 found 196.0176.

2-((*tert*-Butoxycarbonyl)(5-(3-(3-(carboxymethyl)thiophen-2-yl)ureido)-4-ethylbenzo[d]thiazol-2-yl)amino)acetic acid (21)



(i) NaH, DMF, Boc_2O, 60 ˚C, 4 h; (ii) NaH, DMF; methyl bromoacetate, 0 ˚C to r.t.; (iii) H_2, Pd/C, THF-MeOH, r.t.; (vi) NIS, MeCN, 0 ˚C; (v) *(1)* potassium vinyltrifluoroborate, $PdCl_2$(dppf), Et_3N, EtOH, reflux; *(2)* H_2, Pd/C, THF-MeOH, r.t.; (vi) ethyl 2-(2-aminothiophen-3-yl)acetate **16**, phosgene, Et_3N, CH_2Cl_2, 0 ˚C; (vii) aq. NaOH, THF-MeOH, 60 ˚C; (viii) *(1)* NH_4NO_3, TFAA $CHCl_3$, 10−20 ˚C; *(2)* Fe, aq. HCl, EtOH, reflux; Boc = t-BuOCO, Me = methyl, Et = ethyl, t-Bu = tert-butyl, DMF = N,N-dimethylformaldehyde, dppf = 1,1'-bis(diphenylphosphino)ferrocene, THF = tetrahydrofuran, NIS = N-iodosuccinimide, TFAA = trifluoroacetic anhydride r.t. = room temperature, Ac = CH_3CO.

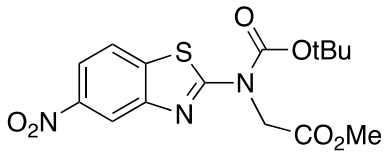
tert-Butyl (5-nitrobenzo[*d*]thiazol-2-yl)carbamate (2)



4-(Dimethylamino)pyridine (48 mg, 0.4 mmol) and di-*tert*-butyl dicarbonate (13.1 g, 60.0 mmol) were added to a solution of 5-nitrobenzo[*d*]thiazol-2-amine **1** (7.80 g, 40.0 mmol) in *N*,*N*-dimethylformamide (300 mL) and heated at 60 ˚C for 4 h. Water (80 mL) and methanol (60 mL) were added and the mixture stirred for 5 mins. Water (200 mL) was added and the resulting precipitate was isolated by filtration, washed with water and petroleum ether to yield *the title compound* **2** as a pale yellow solid. (5.60 g, 19.0 mmol, 47 % yield); δ_H (400 MHz, DMSO-d_6) 12.21 (1 H, brs), 8.42 (1 H, d, *J*=2.2), 8.23 (1 H, d, *J*=8.8), 8.11 (1 H, dd, *J*=8.80, 2.2), 1.52 (9 H, s); δ_C (101 MHz, DMSO-d_6) 162.9, 152.9, 149.4, 146.3, 139.0, 122.7, 117.5,

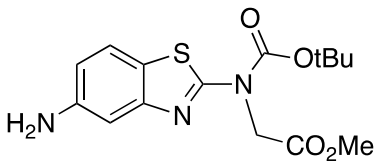
114.7, 82.4, 27.8; IR 3055, 1712, 1517; HRMS (ESI) calculated for $C_{12}H_{14}N_3O_4S$ [$(M+H)^+$]: 296.0700 found 296.0700.

Methyl 2-((*tert*-butoxycarbonyl)(5-nitrobenzo[d]thiazol-2-yl)amino)acetate (5)



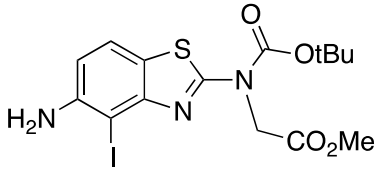
Sodium hydride (488 mg, 12.2 mmol, 60 % w/w dispersion in mineral oil) was added to a solution of *tert*-butyl (5-nitrobenzo[d]thiazol-2-yl)carbamate[1] **2** (3.00 g, 10.2 mmol) in *N*,*N*-dimethylformamide (30 mL) at 0 ˚C and the mixture was stirred for 15 min. Then methyl bromoacetate (1.45 mL, 15.3 mmol) was added and the mixture was warmed to room temperature and stirred for 1 h. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed twice with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude residue was purified by column chromatography (1:19 to 1:3 ethyl acetate: hexane) to give the *title compound* **5** as a pale yellow solid (2.58 g, 7.02 mmol, 69 % yield); δ_H (400 MHz, $CDCl_3$) 8.62 (1H, d, *J* 2.1), 8.17 (1H, dd, *J* 8.7, 2.1), 7.90 (1H, d, *J* 8.7), 5.02 (2H, s), 3.84 (3H, s), 1.62 (9H, br s); δ_C (101 MHz, $CDCl_3$) 168.7, 163.0, 157.4, 148.8, 146.6, 140.6, 121.2, 118.1, 116.5, 85.3, 52.5, 48.1, 28.0; IR 1747, 1720, 1504, 1211, 1142, 742; HRMS (ESI) calculated for $C_{15}H_{18}N_3O_6S$ [$(M+H)^+$]: 368.0910 found 368.0899.

Methyl 2-((5-aminobenzo[d]thiazol-2-yl)(*tert*-butoxycarbonyl)amino)acetate (28)



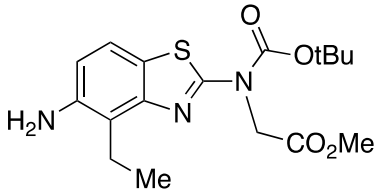
A mixture of nitro compound **5** (4.70 g, 12.8 mmol) and palladium on carbon (10 % w/w, 2.00 g, 1.89 mmol Pd) in tetrahydrofuran (20 mL) and methanol (20 mL) was stirred under a hydrogen atmosphere (balloon) for 2.5 h. Filtration and concentration *in vacuo* afforded a crude solid, which was washed with diethyl ether to yield the *title compound* **28** as a pale brown solid (3.21 g, 9.51 mmol, 74 % yield); δ_H (400 MHz, $CDCl_3$) 7.42 (1H, d, *J* 8.2), 6.99 (1H, d, *J* 1.8), 6.60 (1H, dd, *J* 8.4, 2.0), 4.89 (2H, s), 3.69 (3H, s), 3.65 (2H, br s), 1.50 (9H, br s); δ_C (101 MHz, $CDCl_3$) 169.2, 161.3, 152.4, 150.0, 144.8, 123.9, 121.2, 113.1, 106.9, 84.1, 52.3, 48.0, 28.0; IR 2979, 1740, 1410, 1243, 1192, 844; HRMS (ESI) calculated for $C_{15}H_{20}N_3O_4S$ [$(M+H)^+$]: 338.1169 found 338.1153.

Methyl 2-((5-amino-4-iodobenzo[d]thiazol-2-yl)(*tert*-butoxycarbonyl)amino)acetate (8)



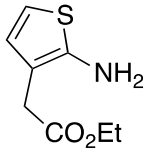
N-Iodosuccinimide (2.14 g, 9.52 mmol) was added to a solution of aniline **28** (3.21 g, 9.52 mmol) in acetonitrile (45 mL) at 0 ˚C. The mixture was warmed to room temperature and stirred for 10 min. Aqueous sodium thiosulfate was added and the mixture was extracted with ethyl acetate. The organic extract was concentrated *in vacuo* and the resultant residue was purified by column chromatography (1:19 to 1:9 ethyl acetate: hexane) to yield the *title compound* **8** as a pale brown solid (4.37 g, 9.43 mmol, 99 % yield); δ_H (400 MHz, $CDCl_3$) 7.46 (1H, d, *J* 8.2), 6.74 (1H, d, *J* 8.4), 5.02 (2H, s), 4.25 (2H, br s), 3.83 (3H, s), 1.60 (9H, s); δ_C (101 MHz, $CDCl_3$) 169.1, 160.4, 152.2, 150.7, 146.0, 121.5, 120.9, 112.0, 84.4, 77.2, 52.3, 48.2, 28.0; IR 1740, 1412, 1148, 1007, 764; HRMS (ESI) calculated for $C_{15}H_{19}IN_3O_4S$ [$(M+H)^+$]: 464.0135 found 464.0122.

Methyl 2-((5-amino-4-ethylbenzo[d]thiazol-2-yl)(*tert*-butoxycarbonyl)amino)acetate (11)



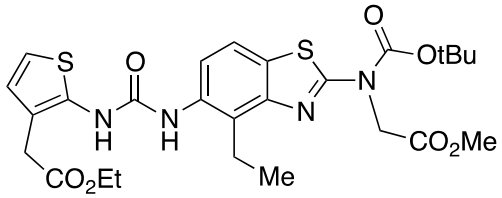
A mixture of iodide **8** (1.50 g, 3.24 mmol), potassium vinyltrifluoroborate (2.17 g, 16.2 mmol), $PdCl_2$(dppf) (237 mg, 0.324 mmol) and triethylamine (1.36 mL, 9.72 mmol) in ethanol (20 mL) was stirred at reflux under Ar for 3 h. The mixture was diluted with water and extracted twice with ethyl acetate. The combined organic layers were concentrated *in vacuo*. The crude product was purified by column chromatography (1:19 to 1:9 ethyl acetate: hexane). The product was dissolved in tetrahydrofuran (5 mL) and methanol (5 mL). To this mixture was added palladium on carbon (10 % w/w, 500 mg, 0.47 mmol Pd) and the mixture was stirred under hydrogen atmosphere (balloon pressure) for 0.5 h. The mixture was filtered, and concentration *in vacuo* afforded the crude product, which was purified by column chromatography (1:4 to 2:3 ethyl acetate : hexane) to yield *the title compound* **11** as a white solid (500 mg, 1.37 mmol, 42 % yield); δ_H (400 MHz, $CDCl_3$) 7.30 (1H, d, *J* 8.2), 6.62 (1H, d. *J* 8.4), 4.89 (2H, s), 3.69 (3H, s), 3.60 (2H, br s), 2.86 (2H, q, *J* 7.6), 1.51 (9H, br s), 1.12 (3H, t, *J* 7.6); δ_C (101 MHz, $CDCl_3$) 169.4, 159.8, 152.4, 148.5, 142.0, 123.6, 120.6, 118.2, 113.6, 83.9, 52.2, 48.2, 28.1, 19.9, 13.0; IR 3615, 2972, 1743, 1594, 1243, 1146, 770; HRMS (ESI) calculated for $C_{17}H_{24}N_3O_4S$ [$(M+H)^+$]: 366.1482 found 366.1473.

Ethyl 2-(2-aminothiophen-3-yl)acetate (16)



Ammonium nitrate (3.60 g, 45.0 mmol) and trifluoroacetic anhydride (2.5 mL, 18.0 mmol) were added to a solution of ethyl 3-thiophene acetate **30** (1.54 g, 9.00 mmol) in chloroform (30 mL). The mixture was stirred for 1 h while the temperature was maintained between 10 and 20 ˚C. Aqueous sodium bicarbonate solution was added and the mixture was extracted twice with dichloromethane. The organic extracts were dried (magnesium sulfate), concentrated *in vacuo* and re-dissolved in absolute ethanol (30 mL). Iron(0) powder (5.03 g, 90.0 mmol) and 3 *N* aqueous hydrochloric acid (2 mL) were added and the mixture was heated at reflux for 30 min. Aqueous sodium bicarbonate solution was added and the mixture was extracted with ethyl acetate three times. The combined organic layers were concentrated *in vacuo* and the residue was purified by column chromatography (1 : 4 diethyl ether : petroleum ether 30-40) to yield *the title compound* **16** as a brown oil (549 mg, 2.97 mmol, 33 %); R_f = 0.21 (1 : 4 diethyl ether : petroleum ether 30-40); δ_H (600 MHz, $CDCl_3$) 6.57 (1 H, d, *J*=5.7), 6.40 (1 H, d, *J*=5.5), 4.07 (2 H, q, *J*=7.2), 3.83 (2 H, brs), 3.39 (2 H, s), 1.19 (3 H, t, *J*=7.2); δ_C (151 MHz, $CDCl_3$) 171.6, 146.7, 128.3, 114.7, 111.2, 60.9, 33.4, 14.1; IR 3340, 2981, 1723, 1459, 1184, 1029, 680; HRMS (ESI) calculated for $C_8H_{12}NO_2S$ [$(M+H)^+$]: 186.0583 found 186.0584.

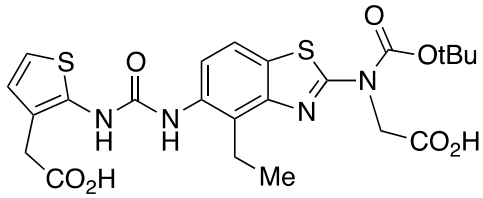
Ethyl 2-(2-(3-(2-((*tert*-butoxycarbonyl)(2-methoxy-2-oxoethyl)amino)-4-ethylbenzo[d]thiazol-5-yl)ureido)thiophen-3-yl)acetate (29)



A solution of ethyl 2-(2-aminothiophen-3-yl)acetate **16** (633 mg, 3.42 mmol) in dichloromethane (10 mL) was added to a solution of phosgene (20 % in toluene, 3.88 mL, 7.36 mmol) at 0 ˚C. Triethylamine (1.53 mL, 10.9 mmol) was added, the mixture was stirred 0 ˚C for 30 min and then concentrated *in vacuo*. The residue was dissolved in dichloromethane (10 mL), then triethylamine (1.53 mL, 10.9 mmol) and aniline **11** (500 mg, 1.37 mmol) were added. After stirring for 1 h, the mixture was diluted with water and extracted with dichloromethane. The organic layer was concentrated *in vacuo* and the residue was purified by column chromatography (1:4 to 1:1 ethyl acetate: hexane) to yield *the title compound* **29** as a pale brown amorphous solid (665 mg, 0.844 mmol, 62 % yield); δ_H

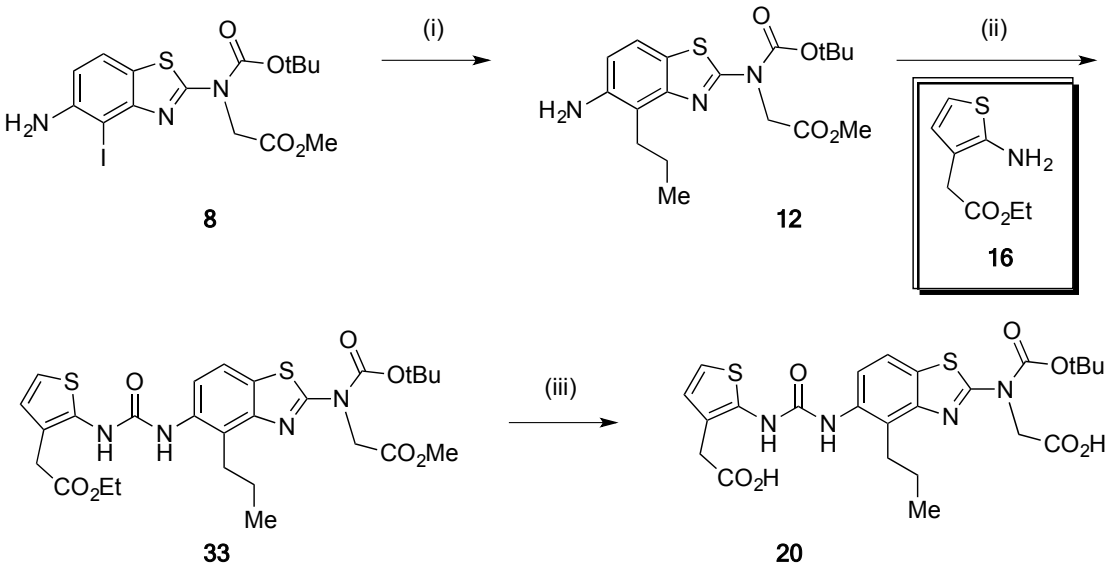
(400 MHz, $CDCl_3$) 7.94 (1H, brs), 7.37 (1H, d, J=7.2), 7.26 (1H, d, J=8.4), 6.79 (1H, brs), 6.66 (1H, brs), 4.85 (2H, brs), 3.89 (2H, q, J=6.7), 3.66 (3H, s), 3.39 (2H, brs), 2.69-2.92 (2H, m), 1.50 (9H, brs), 0.94-1.08 (6H, m); δ_C (101 MHz, $CDCl_3$) 171.3, 169.2, 159.8, 155.1, 152.3, 148.0, 136.5, 136.0, 132.2, 131.8, 131.0, 126.6, 122.1, 118.9, 118.1, 84.2, 61.1, 52.2, 48.1, 33.3, 28.0, 20.6, 14.0, 14.0; IR 3291, 2979, 2360, 1736, 1712, 1514, 1153, 1033; HRMS (ESI) calculated for $C_{26}H_{33}N_4O_7S_2$ [$(M+H)^+$]: 577.1785 found 577.1767.

2-((*tert*-Butoxycarbonyl)(5-(3-(3-(carboxymethyl)thiophen-2-yl)ureido)-4-ethylbenzo[d]thiazol-2-yl)amino)acetic acid (21)



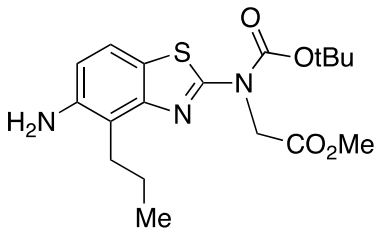
2 *N* aqueous NaOH (1.44 mL, 2.88 mmol) was added to a solution of diester **29** (330 mg, 0.572 mmol) in tetrahydrofuran (3 mL) and methanol (3 mL). The mixture stirred at room temperature for 1 h, then at 50 ˚C for 2 h. The mixture was acidified with 3 *N* aqueous HCl and extracted with ethyl acetate. The organic extract was washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The resulting solid was washed with ethyl acetate and diethyl ether to yield *the title compound* **21** as a brown solid (101 mg, 0.189 mmol, 33 % yield); δ_H (400 MHz, DMSO-d_6) 12.59 (2H, br s), 9.22 (1H, s), 8.34 (1H, s), 7.72 (1H, d, *J* 7.7), 7.68 (1H, d, *J* 7.7), 6.89 (1H, d, *J* 5.5), 6.78 (1H, d, *J* 5.5), 4.86 (2H, br s), 3.56 (2H, s), 2.95-3.07 (2H, m), 1.54 (9H, s), 1.14-1.23 (3H, m); δ_C (101 MHz, DMSO-d_6) 172.6, 170.2, 160.2, 153.0, 152.6, 147.9, 137.1, 134.3, 128.4, 127.8, 127.1, 120.4, 118.7, 116.9, 116.3, 84.2, 48.4, 33.2, 28.0, 20.4, 14.6; IR 2980, 2361, 1712, 1637, 1236, 1148, 632; HRMS (ESI) calculated for $C_{23}H_{26}N_4NaO_7S_2$ [$(M+Na)^+$]: 557.1135 found 557.1117.

2-((*tert*-Butoxycarbonyl)(5-(3-(3-(carboxymethyl)thiophen-2-yl)ureido)-4-propylbenzo[d]thiazol-2-yl)amino)acetic acid (20)



(i) *n*-propyl magnesium chloride, zinc chloride, $PdCl_2$(dppf), THF, reflux; (ii) ethyl 2-(2-aminothiophen-3-yl)acetate **16**, phosgene, Et_3N, CH_2Cl_2, 0 ˚C; (iii) aq. NaOH, THF-MeOH, 60 ˚C. Me = methyl, Et = ethyl, *t*-Bu = *tert*-butyl, dppf = 1,1'-bis(diphenylphosphino)ferrocene, DMF = *N,N*-dimethylformaldehyde, THF = tetrahydrofuran, NIS = *N*-iodosuccinimide.

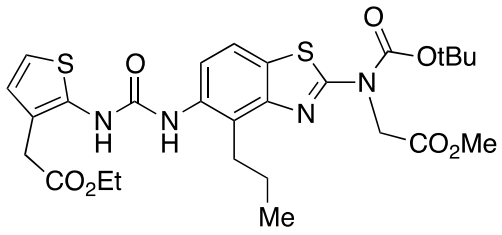
Methyl 2-((5-amino-4-propylbenzo[d]thiazol-2-yl)(*tert*-butoxycarbonyl)amino)acetate (12)



A solution of zinc(II) chloride (0.5 M in tetrahydrofuran, 35 mL, 17.5 mmol) was added to of a solution of *n*-propyl magnesium chloride (2 M in diethyl ether, 8.70 mL, 17.3 mmol) and stirred for 30 min at room temperature. Then iodide **8** (1.60 g, 3.46 mmol) in tetrahydrofuran (10 mL) and $PdCl_2$(dppf) (253 mg, 40.346 mmol) were added and the mixture was stirred at 65 ˚C for 2 h. The mixture was diluted with water and extracted twice with ethyl acetate. The combined organic layers were concentrated *in vacuo* and the residue was purified by column chromatography (1:4 to 2:3 ethyl acetate: hexane) to yield *the title compound* **12** as a pale brown solid (404 mg, 1.06 mmol, 31 % yield); δ_H (400 MHz, $CDCl_3$) 7.29 (1H, d, *J* 8.2), 6.61 (1H, d, *J* 8.4), 4.87 (2H, s), 3.68 (3H, s), 3.60 (2H, br s), 2.82 (2H, t, *J* 7.6), 1.41-1.61 (11H, m), 0.89 (3H, t, *J* 7.4); δ_C (101 MHz, $CDCl_3$) 169.3, 159.6, 152.4, 149.0, 142.3, 123.5, 119.1, 118.2, 113.6, 83.9, 52.1, 48.2, 28.6, 28.1, 21.8, 14.2; IR 3383, 2958, 2361,

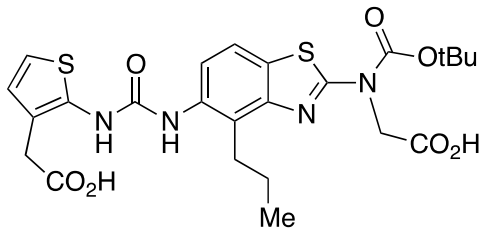
1746, 1714, 1514, 1236, 1145; HRMS (ESI) calculated for $C_{18}H_{25}N_3NaO_4S$ [$(M+Na)^+$]: 402.1458 found 402.1446.

Ethyl 2-(2-(3-(2-((*tert*-butoxycarbonyl)(2-methoxy-2-oxoethyl)amino)-4-propylbenzo[d]thiazol-5-yl)ureido)thiophen-3-yl)acetate (33)



A solution of ethyl 2-(2-aminothiophen-3-yl)acetate **16** (650 mg, 3.51 mmol) in dichloromethane (10 mL) was added a solution of phosgene (20 % in toluene, 2.88 mL, 5.62 mmol) at 0 ˚C. Triethylamine (1.57 mL, 11.3 mmol) was added and the mixture was stirred at 0 ˚C for 30 min. The solvent was removed *in vacuo* and the residue was re-dissolved in dichloromethane (10 mL). Triethylamine (1.57 mL, 11.3 mmol) and aniline **12** (476 mg, 1.25 mmol) were added and the mixture was stirred for 1 h, then diluted with water and extracted with dichloromethane. The organic extract was concentrated *in vacuo* and the residue purified by column chromatography (1:4 to 1:1 ethyl acetate : hexane) to yield *the title compound* **33** as a pale brown amorphous solid (576 mg, 0.975 mmol, 78 % yield); δ_H (400 MHz, $CDCl_3$) 7.52 (1H, d, *J* 8.4), 7.41 (1H, d, *J* 8.1), 6.65-6.78 (1H, m), 6.51 (1H, br s), 4.86 (2H, s), 3.89 (2H, q, *J* 7.0), 3.68 (3H, s), 3.44 (2H, s), 2.77-2.89 (2H, m), 1.38-1.67 (11H, m), 1.04 (3H, t, *J* 7.1), 0.81 (3H, t, *J* 7.3); δ_C (101 MHz, $CDCl_3$) 171.4, 171.2, 169.1, 159.8, 155.1, 153.6, 148.4, 136.4, 136.0, 132.5, 126.8, 126.7, 121.9, 119.1, 118.3, 84.1, 61.1, 52.1, 48.1, 33.3, 29.2, 28.0, 22.9, 14.1, 14.0; IR 3306, 2958, 1718, 1509, 1242, 1146, 1030; HRMS (ESI) calculated for $C_{27}H_{35}N_4O_7S_2$ [$(M+H)^+$]: 591.1941 found 591.1925.

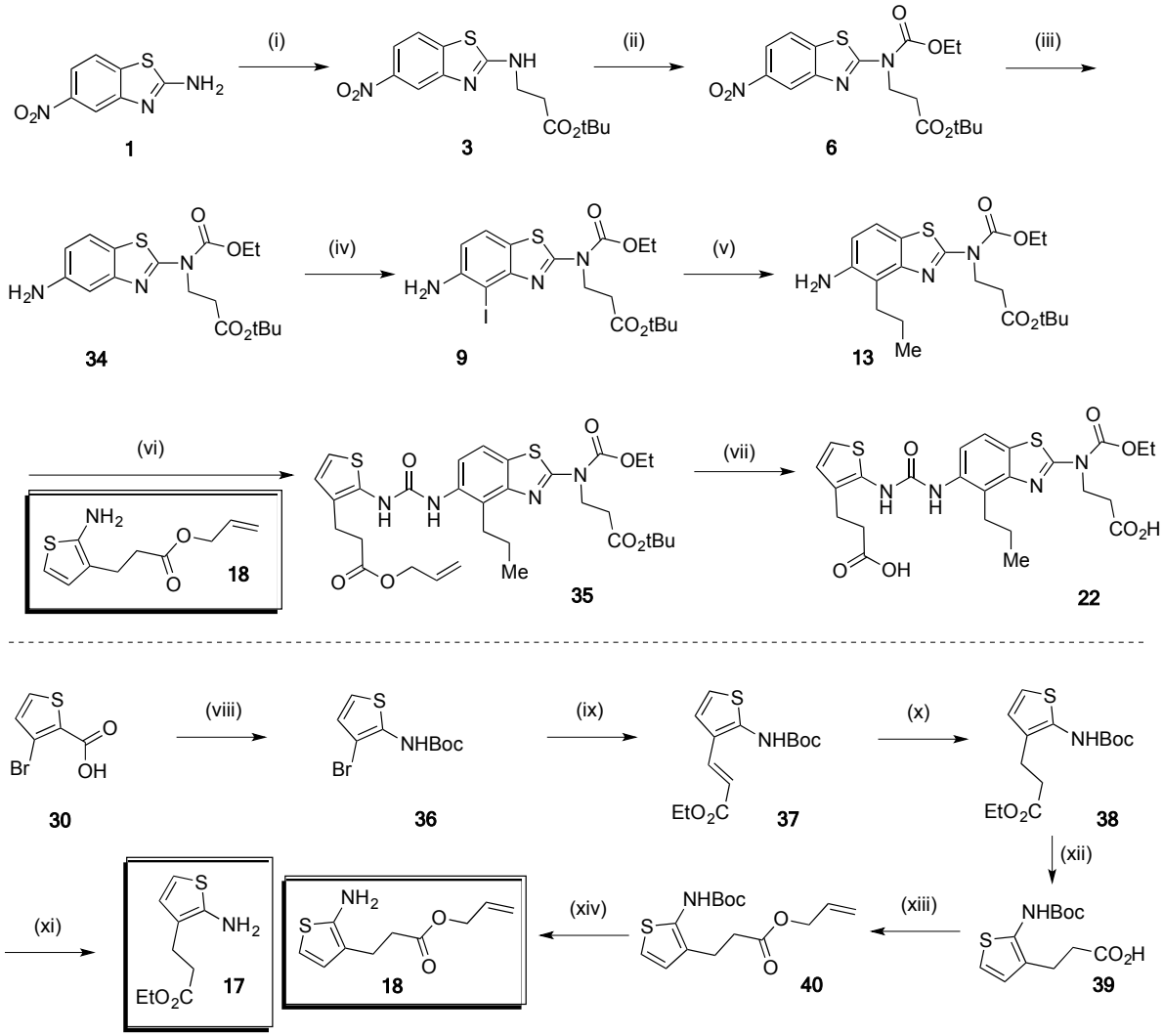
2-((*tert*-Butoxycarbonyl)(5-(3-(3-(carboxymethyl)thiophen-2-yl)ureido)-4-propylbenzo[d]thiazol-2-yl)amino)acetic acid (20)



2 *N* aqueous NaOH (0.78 mL, 1.56 mmol) was added to a solution of diester **33** (368 mg, 0.623 mmol) in tetrahydrofuran (3 mL) and methanol (3 mL). The mixture was stirred at 60 ˚C for 1 h, then acidified with 3 *N* aqueous HCl and extracted with ethyl acetate. The organic extract was washed with brine, dried (magnesium sulfate) and concentrated *in vacuo* to give

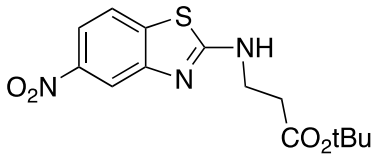
a crude solid. The solid was washed with ethyl acetate and diethyl ether to yield *the title compound* **20** as a pale brown solid (202 mg, 0.368 mmol, 59 % yield); δ_H (400 MHz, DMSO-d_6) 9.21 (1H, s), 8.30 (1H, s), 7.60-7.80 (2H, m), 6.87-6.94 (1H, m), 6.73-6.83 (1H, m), 3.56 (2H, s), 2.99 (2H, t, *J* 7.6), 1.47-1.71 (11H, m), 0.90 (3H, t, *J* 7.3); δ_C (101 MHz, DMSO-d_6) 172.6, 172.4, 170.1, 160.0, 153.1, 148.4, 137.1, 134.6, 128.4, 127.1, 126.5, 120.7, 118.7, 117.0, 116.4, 84.3, 48.4, 33.2, 28.5, 28.0, 22.8; IR 3245, 2962, 2358, 1711, 1638, 1511, 1235, 1150, 633; HRMS (ESI) calculated for $C_{24}H_{28}N_4NaO_7S_2$ [(M+Na)$^+$]: 571.1291 found 571.1275.

3-(2-(3-(2-((2-Carboxyethyl)(ethoxycarbonyl)amino)-4-propylbenzo[d]thiazol-5-yl)ureido)thiophen-3-yl)propanoic acid (22)



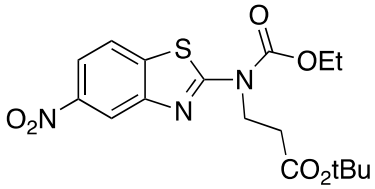
(i) (1) *i*-BuONO, $CuCl_2$·H_2O, MeCN, r.t. to 60 ˚C; (2) $H_2NCH_2CH_2CO_2t$-Bu, *i*-Pr_2NEt, DMF, r.t.; (ii) diethylpyrocarbonate, DMAP, MeCN; (iii) H_2, Pd/C, THF-MeOH, r.t.; (iv) NIS, MeCN, 0 ˚C; (v) *n*-Pr magnesium chloride, zinc chloride, $PdCl_2$(dppf), THF, reflux; (vi) allyl 3-(2-aminothiophen-3-yl)propanoate **18**, phosgene, Et_3N, CH_2Cl_2, 0 ˚C (vii) (1) piperidine, $Pd(PPh_3)_4$, THF, r.t.; (2) TFA, CH_2Cl_2; (viii) DPPA, Et_3N, *t*-BuOH, 90 ˚C, 16 h; (ix) ethyl acrylate, $PdCl_2$(dppf), Et_3N, DMF, 100 ˚C, 10 h; (x) nickel(II) chloride, NaBH4, MeOH, 0 ˚C - r.t., 1 h; (xi) TFA, CH_2Cl_2, 0 ˚C, 30 mins; (xii) aq. NaOH, THF-MeOH, r.t., 30 mins, (xiii) allyl bromide, potassium carbonate, DMF, r.t., 30 mins; (xiv) TFA, CH_2Cl_2, r.t., 30 mins. *i* = iso, *t*-Bu = *tert*-butyl, Me = methyl, r.t. = room termperature, Pr = propyl, Et = ethyl, DMAP = 4-dimethylaminopyridine, DMF = *N,N*-dimethylformaldehyde, THF = tetrahydrofuran, NIS = *N*-iodosuccinimide, dppf = 1,1'-bis(diphenylphosphino)ferrocene, TFA = trifluoroacetic acid.

***tert*-Butyl 3-((5-nitrobenzo[d]thiazol-2-yl)amino)propanoate (3)**



Isobutyl nitrile (6.20 mL, 46.2 mmol) was added to a mixture of $CuCl_2 \bullet 2H_2O$ (6.30 g, 36.9 mmol) in acetonitrile (80 mL) and stirred for 10 min at room temperature. Then 5-nitrobenzo[d]thiazol-2-amine **1** (6.00 g, 30.8 mmol) was added and the mixture was stirred at room temperature for 30 min, and at 60 ˚C for 1 h. The mixture was diluted with 3 *N* aqueous HCl and filtered. The filtrate was extracted with ethyl acetate and organic layer was dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was passed through a pad of silica gel (ethyl acetate), concentrated *in vacuo* and re-dissolved in *N*,*N*'-dimethylformamide (80 mL). *tert*-Butyl 3-aminopropanoate (6.74 g, 46.4 mmol) and diisopropylethylamine (10.7 mL, 61.6 mmol) were added to the solution. After stirring at room temperature for 16 h, the mixture was diluted with ethyl acetate and washed with brine three times. The solvent was removed *in vacuo* and the residue was purified by column chromatography (1:4 to 2:3 ethyl acetate : hexane) to yield *the title compound* **3** as a yellow solid (5.11 g, 15.8 mmol, 51 % yield); δ_H (400 MHz, $CDCl_3$) 8.38 (1H, d, *J* 2.3), 8.00 (1H, dd, *J* 8.6, 2.2), 7.69 (1H, d, *J* 8.5), 6.03 (1H, br s), 3.80 (2H, q, *J* 5.8), 2.65-2.72 (2H, m), 1.50 (9H, s); δ_C (101 MHz, $CDCl_3$) 171.7, 168.4, 152.9, 146.8, 138.0, 120.6, 116.4, 113.7, 81.6, 40.7, 34.6, 28.1; IR 3359, 2971, 1711, 1623, 1515, 1130, 950, 755; HRMS (ESI) calculated for $C_{14}H_{16}N_3O_4S$ [$(M-H)^+$]: 322.0856 found 322.0860.

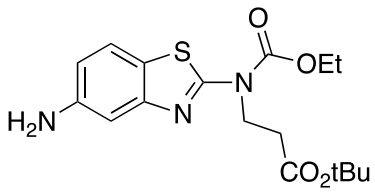
***tert*-Butyl 3-((ethoxycarbonyl)(5-nitrobenzo[d]thiazol-2-yl)amino)propanoate (6)**



Diethylpyrocabonate (3.33 mL, 22.6 mmol) and 4-(dimethylamino)pyridine (92.2 mg, 0.755 mmol) were added to a solution of amine **3** (4.87 g, 15.1 mmol) in tetrahydrofuran (30 mL). After stirring for 1 h at room temperature, the mixture was diluted with ethyl acetate and washed with brine. The organic layer was through a pad of silica gel (ethyl acetate) and the solvent was removed *in vacuo*. The residue was washed with diethyl ether and hexane to yield *the title compound* **6** as a white solid (5.50 g, 13.9 mmol, 92 % yield); δ_H (400 MHz, $CDCl_3$) 8.58 (1H, d, *J* 2.1), 8.09 (1H, dd, *J* 8.7, 2.3), 7.82 (1H, d, *J* 8.7), 4.42-4.49 (2H, m), 4.37 (2H, q, *J* 7.2), 2.63-2.73 (2H, m), 1.33-1.41 (12H, m); δ_C (101 MHz, $CDCl_3$) 170.2, 162.8, 154.1, 149.2, 146.6, 140.3, 121.2, 118.1, 116.5, 81.1, 64.1, 43.4, 33.7, 28.0, 14.4; IR 1705, 1511,

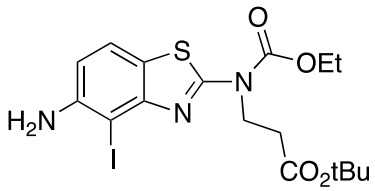
1285, 1161, 837, 742; HRMS (ESI) calculated for $C_{17}H_{22}N_3O_6S$ [$(M+H)^+$]: 396.1223 found 396.1211.

***tert*-Butyl 3-((5-aminobenzo[d]thiazol-2-yl)(ethoxycarbonyl)amino)propanoate (34)**



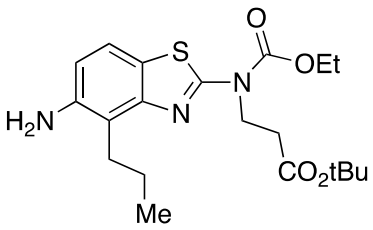
Nitro compound **6** (5.30 g, 13.4 mmol) and palladium on carbon (10 % w/w, 2.00 g, 1.89 mmol Pd) were combined in tetrahydrofuran (50 mL). The mixture was stirred under hydrogen atmosphere (balloon pressure) for 1.5 h. Filtration and concentration *in vacuo* afforded a crude solid, which was collected and washed with diethyl ether to give *the title compound* **34** as a white solid (4.18 g, 11.4 mmol, 85 % yield); δ_H (400 MHz, $CDCl_3$) 7.54 (1H, d, *J* 8.4), 7.15 (1H, d, *J* 2.1), 6.72 (1H, dd, *J* 8.4, 2.1), 4.48-4.54 (2H, m), 4.42 (2H, q, *J* 7.1), 3.78 (2H, br s), 2.71-2.80 (2H, m), 1.47 (9H, s), 1.44 (3H, t, *J* 7.2); δ_C (101 MHz, $CDCl_3$) 170.6, 161.0, 154.0, 150.5, 145.1, 123.4, 121.2, 113.1, 106.8, 80.8, 63.4, 43.0, 33.9, 28.0, 14.4; IR 1707, 1504, 1475, 1201, 1152, 764; HRMS (ESI) calculated for $C_{17}H_{24}N_3O_4S$ [$(M+H)^+$]: 366.1482 found 366.1471.

***tert*-Butyl 3-((5-amino-4-iodobenzo[d]thiazol-2-yl)(ethoxycarbonyl)amino)propanoate (9)**



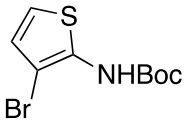
N-Iodosuccinimide (2.39 g, 10.6 mmol) was added to a solution of aniline **34** (3.88 g, 10.6 mmol) in acetonitrile (25 mL) and stirred for 30 min at room temperature. Aqueous sodium thiosulfate was added and the mixture was extracted with ethyl acetate. The solvent was removed *in vacuo* and the residue was purified by column chromatography (1:9 to 3:7 ethyl acetate : hexane) to yield *the title compound* **9** as a brown oil (4.84 g, 9.85 mmol, 93 % yield); δ_H (400 MHz, $CDCl_3$) 7.48 (1H, d, *J* 8.4), 6.71 (1H, d, *J* 8.4), 4.51-4.62 (2H, m), 4.42 (2H, q, *J* 7.1), 4.27 (2H, br s), 2.78-2.86 (2H, m), 1.47 (9H, s), 1.44 (3H, t, *J* 7.2); δ_C (101 MHz, $CDCl_3$) 170.6, 160.3, 153.9, 151.1, 146.0, 121.2, 120.9, 112.0, 80.8, 77.3, 63.6, 43.3, 33.8, 28.1, 14.4; IR 3365, 2977, 1709, 1504, 1404, 1193, 1146, 845; HRMS (ESI) calculated for $C_{17}H_{22}IN_3NaO_4S$ [$(M+Na)^+$]: 514.0267 found 514.0252.

***tert*-Butyl 3-((5-amino-4-propylbenzo[d]thiazol-2-yl)(ethoxycarbonyl)amino)propanoate (13)**



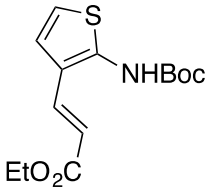
A solution of zinc(II) chloride (0.5 M in tetrahydrofuran, 39 mL, 19.6 mmol) was added to a solution of *n*-propyl magnesium chloride (2 M in diethyl ether, 9.80 mL, 19.6 mmol) and stirred for 30 min at room temperature. Then iodide **9** (1.93 g, 3.93 mmol) in tetrahydrofuran (10 mL) and $PdCl_2$(dppf) (288 mg, 0.393 mmol) were added and the mixture was stirred at 65 ˚C for 2.5 h. The mixture was diluted with water and extracted twice with ethyl acetate. The combined organic layers were concentrated *in vacuo* and the residue was purified by column chromatography (3:17 to 3:7 ethyl acetate : hexane) to yield *the title compound* **13** as a brown oil (558 mg, 1.37 mmol, 35 % yield); δ_H (400 MHz, $CDCl_3$) 7.32 (1H, d, *J* 8.4), 6.63 (1H, d, *J* 8.4), 4.46, (2H, m), 4.42 (2H, dd, *J* 8.5, 7.0), 3.62 (2H, br s), 2.84-2.92 (2H, m), 2.59-2.70 (2H, m), 1.56-1.68 (2H, m), 1.38 (9H, s), 1.33 (3H, t, *J* 7.1), 0.93 (3H, t, *J* 7.3); δ_C (101 MHz, $CDCl_3$) 170.7, 159.4, 153.9, 149.4, 142.3, 123.3, 119.2, 118.3, 113.6, 80.7, 63.3, 43.2, 33.8, 28.6, 28.0, 22.0, 14.4, 14.4; IR 2977, 1711, 1510, 1408, 1193, 1145, 1029, 764; HRMS (ESI) calculated for $C_{20}H_{30}N_3O_4S$ [$(M+H)^+$]: 408.1940 found 408.1951.

***tert*-Butyl (3-bromothiophen-2-yl)carbamate (36)**



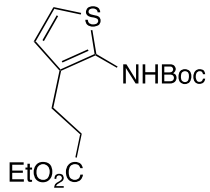
A solution of 3-bromothiophene-2-carboxylic acid **30** (5.00 g, 24.2 mmol), diphenylphosphoryl azide (6.3 mL, 29 mmol) and triethylamine (4.0 mL, 29 mmol) in *tert*-butanol (50 mL) was heated at 90 ˚C for 16 h. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (5 : 95 ethyl acetate : petroleum ether 30-40) to yield *the title compound* **36** as a yellow oil (4.55 g, 68 %). δ_H (500 MHz, $CDCl_3$) 7.08 (1 H, br), 6.86 (1 H, d, *J* 5.8), 6.80 (1 H, d, *J* 5.8), 1.55 (9 H, s); δ_C (126 MHz, $CDCl_3$) 151.9, 134.9, 126.3, 116.5, 93.3, 82.1, 28.2; IR 3391, 2978, 1720, 1564, 1478, 1152; HRMS (ESI) calculated for $C_9H_{12}NO_2{}^{79}BrNa$ [$(M+Na)^+$]: 299.9664 found 299.9665.

Ethyl (*E*)-3-(2-((*tert*-butoxycarbonyl)amino)thiophen-3-yl)acrylate (37)



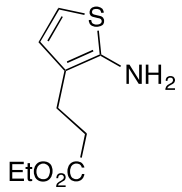
Ethyl acrylate (1.8 mL, 17 mmol), $PdCl_2$(dppf) (241 mg, 0.33 mmol) and triethylamine (1.4 mL, 10 mmol) were added to solution of bromide **9** (918 mg, 3.30 mmol) in *N*,*N*'-dimethylformamide (10 mL). The mixture was heated at 110 ˚C for 16 h, then diluted with ethyl acetate and brine. The organic layer was isolated, washed three times with brine and concentrated *in vacuo*. The residue was purified by column chromatography (1:9 to 2:8 ethyl acetate:hexane) to yield *the title compound* **37** as a dark orange oil (304 mg, 31 % yield); δ_H (500 MHz, $CDCl_3$) 7.61 (1 H, d, *J* 15.6), 7.36 (1 H, br), 7.02 (1 H, d, *J* 5.8), 6.85 (1 H, d, *J* 5.8), 6.18 (1 H, d, *J* 15.6), 4.26 (2 H, q, *J* 7.2), 1.54 (9 H, s), 1.33 (3 H, t, *J* 7.1); δ_C (126 MHz, $CDCl_3$) 167.6, 152.0, 141.8, 133.9, 129.1, 122.3, 118.1, 115.9, 82.3, 60.5, 28.2, 14.3; IR 3291, 2979, 1689, 1554, 1242, 1154; HRMS (ESI) calculated for $C_{14}H_{18}NO_4S$ [$(M\text{-}H^+)^-$]: 296.0951 found 296.0963.

Ethyl 3-(2-((*tert*-butoxycarbonyl)amino)thiophen-3-yl)propanoate (38)



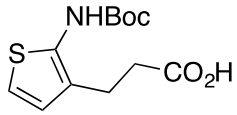
Nickel(II) chloride (18 mg, 14 mmol) and sodium borohydride (28 mg, 0.74 mmol) were added to a solution of alkene **37** (431 mg, 1.45 mmol) in methanol (10 mL) at 0 ˚C. The mixture was stirred at 0 ˚C for 30 min and then warmed to room temperature and stirred for 1.5 h, at which point the ^{1}H NMR spectrum of an aliquot of reaction mixture confirmed complete consumption of the starting material. Aqueous ammonium chloride was added and the mixture was extracted twice with dichloromethane. The organic extracts were concentrated *in vacuo* and the residue was purified by column chromatography (15:85 diethyl ether:petroleum ether 30-40) to yield *the title compound* **38** as a colorless oil (228 mg, 53 % yield); δ_H (400 MHz, $CDCl_3$) 7.71 (1 H, br), 6.83 (1 H, d, *J* 5.6), 6.65 (1 H, d, *J* 5.4), 4.11 (2 H, q, *J* 7.1), 2.77 (2 H, t, *J* 6.4), 2.58 (2 H, t, *J* 6.9), 1.52 (9 H, s), 1.22 (3 H, t, *J* 7.2); δ_C (101 MHz, $CDCl_3$) 174.0, 153.2, 135.1, 125.8, 125.0, 117.6, 80.8, 60.8, 34.5, 28.2, 22.0, 14.0; IR 3325, 2979, 2360, 1716, 1578, 1497, 1247, 1161; HRMS (ESI) calculated for $C_{14}H_{21}NNaO_4S$ [$(M+Na)^+$]: 322.1084 found 322.1081.

Ethyl 3-(2-aminothiophen-3-yl)propanoate (17)



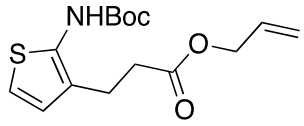
Trifluoroacetic acid (2 mL) was added to a solution of carbamate **38** (228 mg, 0.763 mmol) in dichloromethane (2 mL) and the mixture was stirred at room temperature for 30 min. Aqueous sodium bicarbonate solution was added and the mixture was extracted twice with dichloromethane. The organic extracts were dried (magnesium sulfate) and concentrated *in vacuo* to yield *the title compound* **17** as a colorless oil (149 mg, 98 % yield); δ_H (400 MHz, $CDCl_3$) 6.59 (1 H, d, *J* 5.6), 6.47 (1 H, d, *J* 5.6), 4.11 (2 H, q, *J* 7.1), 3.64 (2 H, br), 2.73 - 2.76 (2 H, m), 2.54 - 2.59 (2 H, m), 1.22 (3 H, t, *J* 7.1); δ_C (101 MHz, $CDCl_3$) 173.7, 144.9, 127.6, 121.3, 111.4, 60.5, 34.6, 21.8, 14.1; IR 3335, 2928, 1724, 1456, 1189; HRMS (ESI) calculated for $C_9H_{14}NO_2S$ [$(M+H)^+$]: 200.0740 found 200.0741.

3-(2-((*tert*-Butoxycarbonyl)amino)thiophen-3-yl)propanoic acid (39)



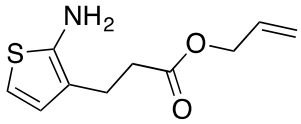
2 *N* Aqueous NaOH (3.4 mL, 6.8 mmol) was added to a solution of **38** (1.34 g, 4.48 mmol) in tetrahydrofuran (10 mL) and methanol (10 mL). The mixture was stirred for 30 min at room temperature. The reaction mixture was acidified to pH 2 by addition of 1 *N* aqueous HCl and extracted three times with ethyl acetate. The organic extracts were washed with brine, dried (magnesium sulfate) and concentrated *in vacuo* to yield *the title compound* **39** (1.19 g, 98 % yield); δ_H (600 MHz, $CDCl_3$) 7.51 (1 H, br), 6.84 (1 H, d, *J* 5.5), 6.68 (1 H, d, *J* 5.3), 2.79 (2 H, br), 2.66 (2 H, br), 1.51 (9 H, s); δ_C (151 MHz, $CDCl_3$) 179.3, 153.1, 135.0, 125.9, 124.7, 117.8, 81.1, 34.1, 28.2, 21.7; IR 3296, 2979, 1704, 1250, 1159; HRMS (ESI) calculated for $C_{12}H_{16}NO_4S$ [$(M-H)^-$]: 270.0806 found 270.0805.

Allyl 3-(2-((*tert*-butoxycarbonyl)amino)thiophen-3-yl)propanoate (40)



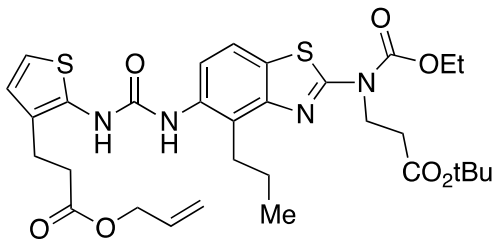
Allyl bromide (0.46 mL, 5.3 mmol) and potassium carbonate (909 mg, 6.59 mmol) were added to a solution of acid **39** (1.19 g, 4.39 mmol) in *N*,*N*'-dimethylformamide (15 mL). The mixture was stirred at room temperature for 30 min, then diluted with brine and extracted with ethyl acetate. The organic extract was washed four times with brine, dried (magnesium sulfate) and concentrated *in vacuo* to yield *the title compound* **40** (1.30 g, 95 % yield); δ_H (600 MHz, $CDCl_3$) 7.59 (1 H, br), 6.85 (1 H, d, *J* 5.5), 6.67 (1 H, d, *J* 5.5), 5.80 - 5.93 (1 H, m), 5.20 - 5.32 (2 H, m), 4.57 (2 H, d, *J* 5.9), 2.79 (2 H, t, *J* 6.8), 2.64 (2 H, t, *J* 6.6), 1.53 (9 H, s); δ_C (151 MHz, $CDCl_3$) 173.6, 153.2, 135.2, 131.8, 125.8, 125.0, 118.5, 117.8, 80.9, 65.5, 34.5, 28.3, 22.0; IR 3328, 2979, 1717, 1578, 1496, 1368, 1246, 1160; HRMS (ESI) calculated for $C_{15}H_{20}NO_4S$ [$(M-H)^-$]: 310.1119 found 310.1120.

Allyl 3-(2-aminothiophen-3-yl)propanoate (18)



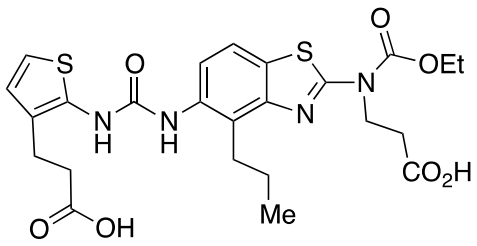
Trifluoroacetic acid (0.1 mL) was added to a solution of carbamate **40** (15 mg, 0.048 mmol) in dichloromethane (1 mL). The mixture was stirred at room temperature for 2 h. Aqueous sodium bicarbonate solution was added and the mixture was extracted three times with ethyl acetate, dried (magnesium sulfate), and concentrated *in vacuo* to yield *the title compound* **18** (10 mg, 98 % yield); δ_H (600 MHz, $CDCl_3$) 6.62 (1 H, d, *J* 5.5), 6.50 (1 H, d, *J* 5.5), 5.85 - 5.96 (1 H, m), 5.22 - 5.32 (2 H, m), 4.59 (2 H, d, *J* 5.7), 3.79 (2 H, br), 2.79 (2 H, t, *J* 7.2), 2.64 (2 H, t, *J* 7.1); HRMS (ESI) calculated for $C_{10}H_{14}NO_2S$ [$(M+H)^+$]: 212.0740 found 212.0740.

Allyl 3-(2-(3-(2-((3-(*tert*-butoxy)-3-oxopropyl)(ethoxycarbonyl)amino)-4-propylbenzo[d]thiazol-5-yl)ureido)thiophen-3-yl)propanoate (35)



A solution of allyl 3-(2-aminothiophen-3-yl)propanoate **18** (542 mg, 2.57 mmol) in dichloromethane (5 mL) was added to a solution of phosgene (20 % in toluene, 2.07 mL, 4.11 mmol) at 0 ˚C. Triethylamine (1.15 mL, 8.22 mmol) was added and the mixture was stirred at 0 ˚C for 30 min. The solvent was removed *in vacuo* and the residue was re-dissolved in dichloromethane (5 mL). Triethylamine (1.15 mL, 8.22 mmol) and aniline **13** (427 mg, 1.05 mmol) were added and the mixture was stirred for 1 h, then diluted with water and extracted with dichloromethane. The organic extract was concentrated *in vacuo* and dissolved in *tert*-butanol (5 mL). Potassium carbonate (2.60 g, 11.6 mmol) was added and the mixture was stirred at 60 ˚C for 1h, then diluted with water and extracted with ethyl acetate. The organic extract was concentrated *in vacuo* and purified by column chromatography (3:17 to 2:3 ethyl acetate : hexane) to yield *the title compound* **35** as a pale yellow solid (114 mg, 0.177 mmol, 17 % yield); δ_H (400 MHz, $CDCl_3$) 7.60-7.69 (2H, m), 7.00-7.08 (1H, m), 6.79 (1H, d, *J* 5.3), 6.57 (1H, br), 5.73-5.89 (1H, m), 5.18-5.29 (2H, m), 4.36-4.65 (4H, m), 3.01 (2H, d, *J* 7.3), 2.83 (2H, t, *J* 6.4), 2.73-2.79 (2H, m), 2.60-2.67 (2H, m), 1.57-1.69 (2H, m), 1.41-1.51 (12H, m), 0.95 (3H, t, *J* 7.3); δ_C (101 MHz, $CDCl_3$) 173.3, 170.5, 159.6, 154.8, 153.9, 148.8, 134.8, 132.7, 131.1, 130.5, 129.6, 126.2, 121.6, 118.4, 118.4, 118.4, 118.4, 80.8, 65.4, 63.5, 43.2, 34.2, 33.7, 29.3, 28.0, 23.0, 22.2, 14.4, 14.2; IR 1734, 1631, 1442, 1195, 766; HRMS (ESI) calculated for $C_{31}H_{41}N_4O_7S_2$ [$(M+H)^+$]: 645.2411 found 645.2383.

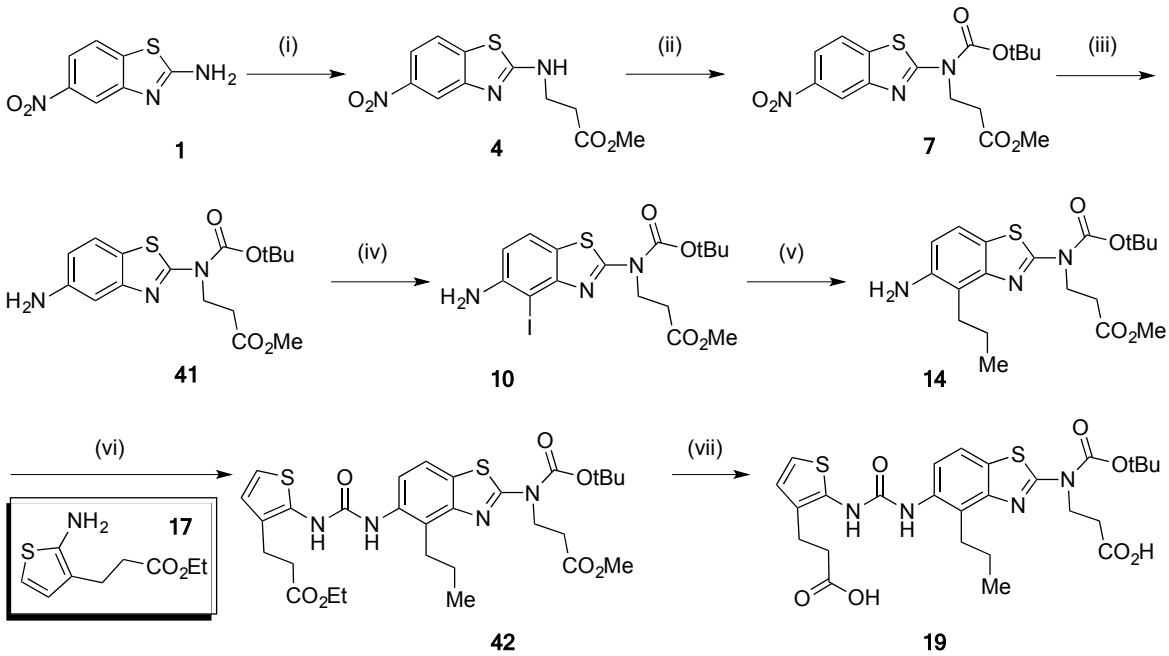
3-(2-(3-(2-((2-Carboxyethyl)(ethoxycarbonyl)amino)-4-propylbenzo[d]thiazol-5-yl)ureido)thiophen-3-yl)propanoic acid (22)



Piperidine (0.062 mL, 0.630 mmol) and tetrakis(triphenylphosphine)palladium(0) (14.6 mg, 0.0126 mmol) were added to a solution of diester **35** (81.3 mg, 0.126 mmol) in tetrahydrofuran (5 mL). The mixture was stirred at room temperature for 30 min, then

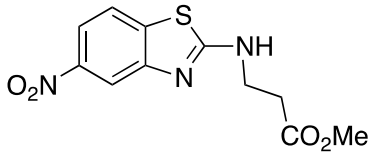
diluted with 3 *N* aqueous HCl and extracted with ethyl acetate. The organic extract was washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The residue was dissolved in dichloromethane (2 mL) and treated with trifluoroacetic acid (2 mL). After stirring for 4 h at room temperature, the mixture was concentrated *in vacuo.* Diethyl ether was added, causing the crude product to solidify. This was collected and washed with ethyl acetate to yield *the title compound* **22** as a brown solid (30.5 mg, 0.0556 mmol, 44 % yield); δ_H (400 MHz, DMSO-d_6) 12.33 (2H, br s), 9.12 (1H, s), 8.33 (1H, s), 7.70-7.77 (1H, m), 7.61-7.67 (1H, m), 6.89 (1H, d, *J* 5.5), 6.78 (1H, d, *J* 5.5), 4.42 (2H, t, *J* 7.3), 4.34 (2H, q, *J* 7.2), 3.03 (2H, t, *J* 7.3), 2.68-2.83 (4H, m), 2.57 (2H, t, *J* 7.3), 1.58-1.70 (2H, m), 0.94 (3H, t, *J* 7.3); δ_C (101 MHz, DMSO-d_6) 174.4, 172.8, 159.8, 153.9, 153.2, 148.7, 135.3, 134.6, 128.2, 126.6, 126.0, 123.1, 120.7, 118.6, 116.7, 63.8, 34.2, 32.6, 28.9, 28.0, 23.0, 22.7, 14.5, 14.4; IR 2981, 2359, 1712, 1632, 1231, 639; HRMS (ESI) calculated for $C_{24}H_{29}N_4O_7S_2$ [$(M+H)^+$]: 549.1472 found 549.1460.

3-(2-(3-(2-((*tert*-Butoxycarbonyl)(2-carboxyethyl)amino)-4-propylbenzo[d]thiazol-5-yl)ureido)thiophen-3-yl)propanoic acid (19)



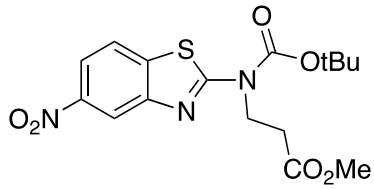
(i) (1) *i*-BuONO, $CuCl_2{\cdot}H_2O$; MeCN, r.t. to 60 ˚C; (2) $H_2NCH_2CH_2CO_2Me$, *i*-Pr_2NEt, DMF, r.t.; (ii) Boc_2O, DMAP, THF; (iii) H_2, Pd/C, THF-MeOH, r.t.; (iv) NIS, MeCN, 0 ˚C; (v) *n*-propyl magnesium chloride, zinc chloride, $PdCl_2$(dppf), THF, reflux; (vi) ethyl 3-(2-aminothiophen-3-yl)propanoate **17**, phosgene, Et_3N, CH_2Cl_2, 0 ˚C; (vii) aq. NaOH, THF-MeOH. *i* = iso, *n* = normal, *t*-Bu = *tert*-butyl, DMF = *N,N*-dimethylformaldehyde, Boc = *t*-BuOCO, THF = tetrahydrofuran, NIS = *N*-iodosuccinimide, Me = methyl, r.t. = room termperature, Pr = propyl, Et = ethyl, DMAP = 4-dimethylaminopyridine, dppf = 1,1'-bis(diphenylphosphino)ferrocene, TFA = trifluoroacetic acid.

Methyl 3-((5-nitrobenzo[d]thiazol-2-yl)amino)propanoate (4)



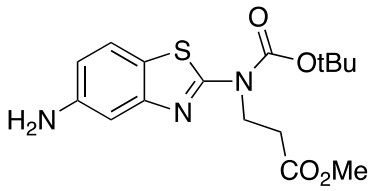
Isoamyl nitrite (3.1 mL, 23 mmol) was added to a mixture of $CuCl_2 \bullet 2H_2O$ (3.15 g, 18.5 mmol) in acetonitrile (40 mL) and stirred for 10 min at room temperature. Then 5-nitrobenzo[d]thiazol-2-amine **1** (3.00 g, 15.4 mmol) was added and the mixture was stirred at room temperature for 30 min, and at 60 ˚C for 1 h. The mixture was diluted with 1 *N* aqueous HCl, filtered and extracted with ethyl acetate. The organic extract was dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was passed through a pad of silica gel (ethyl acetate), concentrated *in vacuo* and then re-dissolved in *N*,*N*'-dimethylformamide (40 mL). Methyl 3-aminopropanoate hydrochloride (10.7 g, 77 mmol) and diisopropylethylamine (26.8 mL, 154 mmol) were added to the solution. After stirred at room temperature for 16 h, the mixture was diluted with ethyl acetate and washed with brine three times. The solvent was removed *in vacuo* and the residue was purified by column chromatography (1:3 to 2:3 ethyl acetate : hexane) to yield *the title compound* **4** as a yellow solid (1.79 g, 6.37 mmol, 41 % yield); δ_H (400 MHz, DMSO-d_6) 8.58 (1 H, t, *J* 5.4), 8.08 (1 H, d, *J* 2.2), 7.92 (1 H, d, *J* 8.6), 7.87 (1 H, dd, *J* 8.6, 2.2 Hz), 3.60 - 3.69 (5 H, m), 2.71 (2 H, t, *J* 6.6); δ_C (101 MHz, DMSO-d_6) 171.7, 168.1, 152.8, 146.1, 138.6, 121.5, 115.6, 111.8, 51.5, 33.1; IR 3367, 2362, 1734, 1547, 1512, 1340; HRMS (ESI) calculated for $C_{11}H_{12}N_3O_4S$ [$(M+H)^+$]: 282.0543 found 282.0543.

Methyl 3-((tert-butoxycarbonyl)(5-nitrobenzo[d]thiazol-2-yl)amino)propanoate (7)



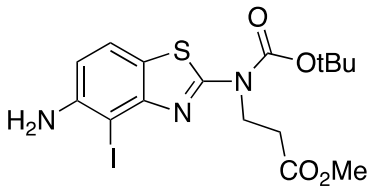
A mixture of amine **4** (2.37 g, 8.43 mmol), di-*tert*-butyldicarbonate (2.76 g, 12.7 mmol) and 4-(dimethylamino)pyridine (102 mg, 0.84 mmol) in tetrahydrofuran (20 mL) was stirred for 4 h at room temperature. The solvent was removed *in vacuo* and the residue was purified by column chromatography (1:9 – 3:7 diethyl ether:petroleum ether 30-40) to yield *the title compound* **7** as a pale yellow foam (2.87 g, 89 % yield). δ_H (400 MHz, $CDCl_3$) 8.47 (1 H, d, *J* 2.2) 8.02 (1 H, dd, *J* 8.6, 2.2) 7.77 (1 H, d, *J* 8.8) 4.44 (2 H, t, *J* 7.5) 3.65 (3 H, s) 2.77 (2 H, t, *J* 7.3) 1.57 (9 H, s); δ_C (101 MHz, $CDCl_3$) 171.3, 162.6, 152.3, 149.0, 146.3, 140.2, 120.9, 117.7, 116.0, 84.8, 51.6, 43.3, 32.2, 27.9; IR 2981, 1712, 1517, 1342, 1253, 1148; HRMS (CI+) calculated for $C_{16}H_{20}N_3O_6S$: 382.1073 found 382.1074.

Methyl 3-((5-aminobenzo[d]thiazol-2-yl)(*tert*-butoxycarbonyl)amino)propanoate (41)



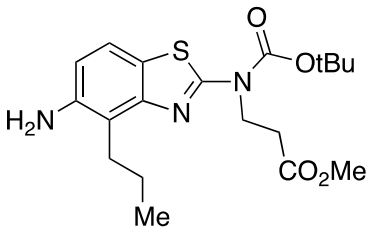
Nitro compound **7** (2.54g, 6.67 mmol) and palladium/carbon (10 % w/w, 707 mg, 0.67 mmol Pd) were combined in tetrahydrofuran (20 mL) and methanol (20 mL) and the mixture was stirred under hydrogen atmosphere (balloon pressure) for 2.5 h. The mixture was filtered and concentrated *in vacuo* to yield *the title compound* **41** (2.21 g, 94 % yield); δ_H (600 MHz, $CDCl_3$) 7.47 (1 H, d, *J* 8.4), 7.08 (1 H, d, *J* 2.0), 6.66 (1 H, dd, *J* 8.4, 2.0), 4.47 (2 H, t, *J* 7.5), 3.68 (5 H, br), 2.79 (2 H, t, *J* 7.5 Hz) 1.59 (9 H, s); δ_C (151 MHz, $CDCl_3$) 171.8, 161.0, 152.5, 150.5, 145.1, 123.4, 121.0, 112.9, 106.7, 84.0, 51.7, 43.2, 32.7, 28.1; IR 3371, 1712, 1504, 1439, 1394, 1150; HRMS (CI+) calculated for $C_{16}H_{22}N_3O_4S$ [$(M+H)^+$]: 352.1331 found 352.1331.

Methyl 3-((5-amino-4-iodobenzo[d]thiazol-2-yl)(*tert*-butoxycarbonyl)amino)propanoate (10)



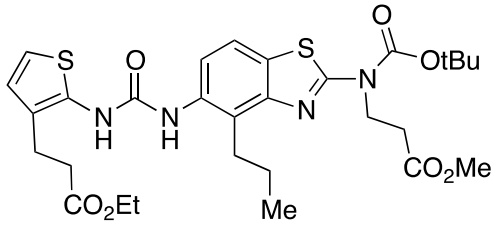
N-Iodosuccinimide (1.32 g, 5.86 mmol) was added to a solution of aniline **41** (2.06 g, 5.86 mmol) in acetonitrile (20 mL) and the mixture was stirred at room temperature for 15 min. Aqueous sodium thiosulfate was added and the mixture was extracted with ethyl acetate. The organic extract was concentrated *in vacuo* and the residue was purified by column chromatography (1: 19 to 2 : 3 ethyl acetate : hexane) to yield *the title compound* **10** as a light yellow solid (2.36 g, 4.95 mmol, 84 % yield); δ_H (500 MHz, $CDCl_3$) 7.42 (1 H, d, *J* 8.2), 6.71 (1 H, d, *J* 8.4), 4.52 (2 H, t, *J* 7.3), 4.22 (2 H, br), 3.69 (3 H, s), 2.87 (2 H, t, *J* 7.3), 1.60 (9 H, s); δ_C (126 MHz, $CDCl_3$) 171.9, 160.3, 152.5, 151.1, 145.9, 121.3, 120.8, 111.9, 84.2, 77.3, 51.8, 43.5, 32.5, 28.2; IR 3461, 3367, 2979, 2361, 1707, 1504, 1393, 1238, 1144; HRMS (CI+) calculated for $C_{16}H_{21}IN_3O_4S$: 478.0297 found 478.0303.

Methyl 3-((5-amino-4-propylbenzo[*d*]thiazol-2-yl)(*tert*-butoxycarbonyl)amino)propanoate (14)



A solution of zinc(II) chloride (0.5 M in tetrahydrofuran, 42 mL, 21.0 mmol) was added to a solution of *n*-propyl magnesium chloride (2 M in diethyl ether, 10.5 mL, 21.0 mmol) and stirred for 30 min at room temperature. Iodide **10** (2.00 g, 4.19 mmol) and $PdCl_2$(dppf) (307 mg, 0.419 mmol) were added and the mixture was heated at reflux for 1.5 h. Aqueous ammonium chloride was added and the mixture was extracted with ethyl acetate. The organic extract was concentrated *in vacuo* and purified by column chromatography (1:4 – 1:1 ethyl acetate:hexane) to yield *the title compound* **14** as a red oil (295 mg, 18 % yield); δ_H (400 MHz, $CDCl_3$) 7.36 (1 H, d, *J* 8.3), 6.68 (1 H, d, *J* 8.3), 4.49 (2 H, t, *J* 7.3), 3.69 (5 H, br), 2.94 (2 H, t, *J* 7.3), 2.81 (2 H, t, *J* 7.6), 1.62 - 1.73 (2 H, m), 1.60 (9 H, s), 0.98 (3 H, t, *J* 7.3); δ_C (101 MHz, $CDCl_3$) 171.9, 159.5, 152.6, 149.3, 142.1, 123.4, 119.2, 118.2, 113.4, 83.7, 51.6, 43.3, 32.6, 28.6, 28.1, 21.9, 14.3; IR 3378, 2957, 2360, 1710, 1395, 1146; HRMS (CI+) calculated for $C_{19}H_{28}N_3O_4S$ [$(M+H)^+$]: 394.1801 found 394.1796.

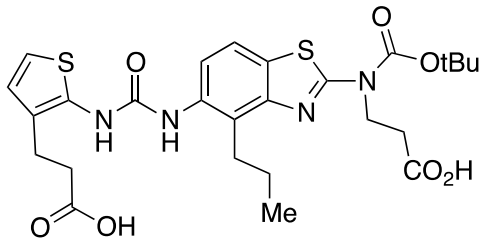
Ethyl 3-(2-(3-(2-((*tert*-butoxycarbonyl)(3-methoxy-3-oxopropyl)amino)-4-propylbenzo[d]thiazol-5-yl)ureido)thiophen-3-yl)propanoate (42)



A solution of ethyl 3-(2-aminothiophen-3-yl)propanoate **17** (152 mg, 0.762 mmol) in dichloromethane (5 mL) was added to a solution of phosgene (20 % in toluene, 0.62 mL, 1.22 mmol) at 0 ˚C. Triethylamine (0.34 mL, 2.4 mmol) was added and the mixture was stirred at 0 ˚C for 30 min, then concentrated *in vacuo*. The residue was dissolved in dichloromethane (5 mL). Triethylamine (0.34 mL, 2.4 mmol) and aniline **14** (295 mg, 0.749 mmol) were added and the mixture was stirred for 1 h, then diluted with water and extracted with dichloromethane. The organic extract was concentrated *in vacuo* and the residue was purified by column chromatography (1:9 to 1:2 ethyl acetate : hexane) to give *the title compound* **42** as a pale yellow solid (181 mg, 0.292 mmol, 14 % yield); δ_H (400 MHz, $CDCl_3$) 7.43-7.54 (2H, m), 6.88 (1H, br), 6.59-6.71 (2H, m), 4.36-4.45 (2H, m), 3.91 (2H, q, *J* 7.1), 3.61

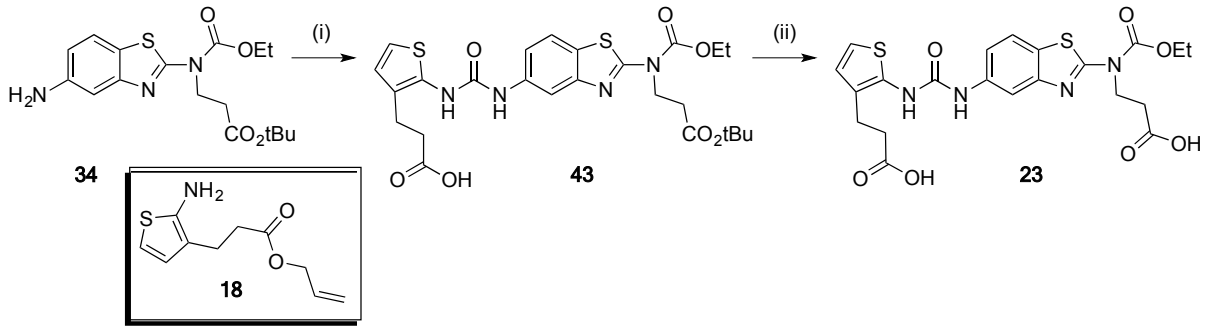
(3H, s), 2.88 (2H, t, *J* 7.5), 2.73 (4H, t, *J* 7.48), 2.44-2.53 (2H, m), 1.44-1.62 (12H, m), 1.05-1.11 (3H, m), 0.83 (3H, t, *J* 7.3); δ_C (126 MHz, $CDCl_3$) 173.8, 171.8, 159.7, 154.5, 152.5, 148.9, 135.7, 134.7, 132.7, 130.5, 126.4, 126.1, 125.5, 121.2, 118.4, 84.1, 60.8, 51.7, 43.4, 34.4, 32.5, 29.3, 28.2, 23.1, 22.2, 14.2, 14.1; IR 3301, 2960, 2360, 1709, 1510, 1396, 1245, 1153; HRMS (ESI) calculated for $C_{29}H_{39}N_4O_7S_2$ [$(M+H)^-$]: 619.2255 found 619.2253.

3-(2-(3-(2-((*tert*-Butoxycarbonyl)(2-carboxyethyl)amino)-4-propylbenzo[d]thiazol-5-yl)ureido)thiophen-3-yl)propanoic acid (19)



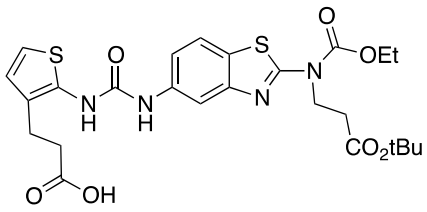
2 *N* Aqueous NaOH (0.366 mL, 0.732 mmol) was added to a solution of diester **42** (181 mg, 0.292 mmol) in tetrahydrofuran (3 mL) and methanol (3 mL). The mixture was stirred at room temperature for 3 h, then acidified with 3 *N* aqueous HCl and extracted with ethyl acetate. The organic extract was washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified by column chromatography (1:1 ethyl acetate : hexane, then 100 % ethyl acetate, then 1:5 methanol : ethyl acetate) to give *the title compound* **19** as a pale yellow solid (6.3 mg, 10.9 mmol, 4 % yield); δ_H (400 MHz, CD_3OD) 7.51 (1H, d, *J* 8.5), 7.37 (1H, d, *J* 8.5), 6.85 (1H, d, *J* 5.5), 6.70 (1H, d, *J* 5.7), 4.39 (2H, t, *J* 7.3), 2.94-2.98 (2H, m), 2.73-2.80 (2H, m), 2.67 (2H, t, *J* 7.3), 2.50 (2H, t, *J* 7.5), 1.55-1.63 (2H, m), 1.52 (9H, s), 0.89 (3H, t, *J* 7.3); δ_C (125 MHz, DMSO-d_6) 174, 172.4, 159.2, 152.8, 152.2, 148.3, 135.0, 134.2, 127.6, 126.1, 125.7, 122.6, 120.1, 118.1, 116.1, 83.6, 43.4, 33.9, 32.4, 28.4, 27.6, 22.6, 22.3, 14.0; IR 3346, 2960, 2930, 2871, 2360, 2341, 1710; HRMS (ESI) calculated for $C_{26}H_{33}O_7N_4S_2$ [$(M-H)^-$]: 577.1785 found 577.1785.

3-(2-(3-(2-((2-Carboxyethyl)(ethoxycarbonyl)amino)benzo[d]thiazol-5-yl)ureido)thiophen-3-yl)propanoic acid (23)



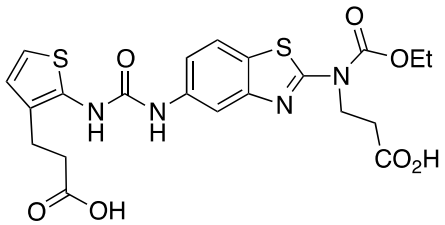
(i) (1) allyl 3-(2-aminothiophen-3-yl)propanoate **17**, phosgene, Et_3N, CH_2Cl_2, 0 °C; (2) piperidine, $Pd(PPh_3)_4$, THF, r.t.;
(ii) TFA, CH_2Cl_2. Et = ethyl, Ph = C_6H_5, *t*-Bu = *tert*-butyl, THF = tetrahydrofuran, TFA = trifluoroacetic acid.

3-(2-(3-(2-((3-(*tert*-Butoxy)-3-oxopropyl)(ethoxycarbonyl)amino)benzo[d]thiazol-5-yl)ureido)thiophen-3-yl)propanoic acid (43)



A solution of allyl 3-(2-aminothiophen-3-yl)propanoate **18** (542 mg, 2.57 mmol) in dichloromethane (5.0 mL) was added to a solution of phosgene (20 % in toluene, 2.07 mL, 4.11 mmol) at 0 ˚C. Triethylamine (1.15 mL, 8.22 mmol) was added and the mixture was stirred at 0 ˚C for 30 min. The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (5 mL). Triethylamine (1.15 mL, 8.22 mmol) and aniline **34** (940 mg, 2.57 mmol) were added, and the mixture was stirred for 1 h, then diluted with water and extracted with dichloromethane. The organic extract was concentrated *in vacuo* and the residue was purified by column chromatography (3:17 to 2:3 ethyl acetate : hexane). The purified product was dissolved in tetrahydrofuran (10 mL), then piperidine (0.980 mL, 9.88 mmol) and tetrakis(triphenylphosphine)palladium(0) (227 mg, 0.197 mmol) were added. The mixture was stirred at room temperature for 4 h, then diluted with 3 *N* aqueous HCl and extracted with ethyl acetate. The organic extract was concentrated *in vacuo* and purified by column chromatography (ethyl acetate) to yield *the title compound* **43** as a white solid (431 mg, 0.513 mmol, 30 % yield); δ_H (400 MHz, DMSO-d_6) 9.11 (1H, s), 8.97 (1H, br s), 8.06 (1H, d, *J* 2.0), 7.84 (1H, d, *J* 8.5), 7.27 (1H, dd, *J* 8.6, 2.1), 6.91 (1H, d, *J* 5.5), 6.78 (1H, d, *J* 5.5), 4.41 (2H, t, *J* 7.2), 4.34 (2H, q, *J* 7.0), 2.73-2.78 (2H, m), 2.70 (2H, t, *J* 7.3), 2.55 (3H, t, *J* 8.1), 1.31-1.39 (12H, m); δ_C (101 MHz, DMSO-d_6) 174.5, 170.4, 161.3, 153.8, 152.4, 149.7, 138.4, 135.0, 126.4, 126.2, 123.4, 121.8, 116.7, 115.6, 110.2, 80.6, 63.8, 43.3, 34.4, 33.9, 28.0, 22.7, 14.5; IR 3272, 2976, 1725, 1705, 1542, 1446, 1285, 664; HRMS (ESI) calculated for $C_{25}H_{31}N_4O_7S_2$ [$(M+H)^+$]: 563.1628 found 563.1607.

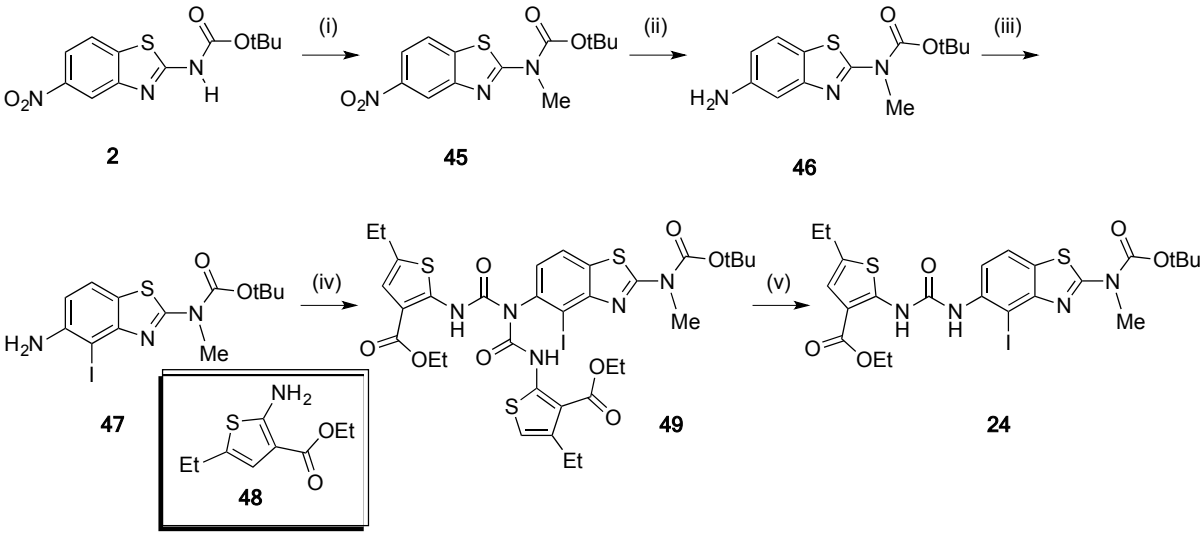
3-(2-(3-(2-((2-Carboxyethyl)(ethoxycarbonyl)amino)benzo[d]thiazol-5-yl)ureido)thiophen-3-yl)propanoic acid (23)



Trifluoroacetic acid (2 mL) was added to a solution of ester **43** (300 mg, 0.533 mmol) in dichloromethane (2 mL). The mixture was stirred for 6 h at room temperature, then

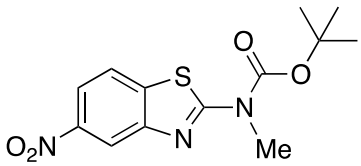
concentrated *in vacuo*. Toluene and dichloromethane were added, which caused the crude product to solidify. The solid was collected and washed with ethyl acetate to yield *the title compound* **23** as a brown solid (260 mg, 0.513 mmol, 96 % yield); δ_H (400 MHz, DMSO-d_6) 12.33 (1H, br s), 9.06 (1H, s), 8.92 (1H, s), 8.05 (1H, d, *J* 2.0), 7.85 (1H, d, *J* 8.5), 7.28 (1H, dd, *J* 8.6, 2.1), 6.91 (1H, d, *J* 5.7), 6.78 (1H, d, *J* 5.5), 4.40 (2H, t, *J* 7.5), 4.33 (2H, q, *J* 7.1), 2.67-2.81 (4H, m), 2.53-2.58 (2H, m), 1.34 (3H, t, *J* 7.1); δ_C (101 MHz, DMSO-d_6) 174.5, 172.8, 161.3, 153.9, 152.4, 149.8, 138.4, 135.0, 126.4, 126.2, 123.4, 121.8, 116.7, 115.6, 110.3, 63.8, 43.4, 34.3, 32.8, 22.6, 14.5; IR 3274, 2982, 1699, 1641, 1199, 1134, 630; HRMS (ESI) calculated for $C_{21}H_{23}N_4O_7S_2$ [$(M+H)^+$]: 507.0989 found 507.1002.

Ethyl 2-(3-(2-((*tert*-Butoxycarbonyl)(methyl)amino)-4-iodobenzo[d]thiazol-5-yl)ureido)-5-ethylthiophene-3-carboxylate (24)



(i) NaH, DMF; MeI, 0 ˚C to r.t.; (ii) H_2, Pd/C, THF-MeOH, r.t.; (iii) NIS, MeCN, 0 ˚C; (iv) methyl 2-amino-5-ethylthiophene-3-carboxylate **48**, phosgene, Et_3N, CH_2Cl_2, 0 ˚C; (v) K_2CO_3, THF-EtOH, 60 ˚C. Me = methyl, Et = ethyl, *t*-Bu = *tert*-butyl, DMF = *N,N*-dimethylformaldehyde, THF = tetrahydrofuran, NIS = *N*-iodosuccinimide.

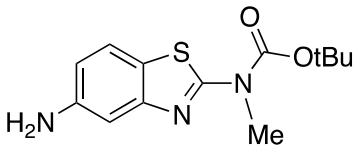
tert-Butyl (5-nitrobenzo[d]thiazol-2-yl)carbamate (45)



Sodium hydride (60% w/w dispersion in mineral oil, 813 mg, 20.3 mmol) was added to a solution of *tert*-butyl (5-nitrobenzo[d]thiazol-2-yl)carbamate[1] **2** (5.00 g, 16.9 mmol) in *N*,*N*'-dimethylformamide (50 mL) at 0 ˚C. The mixture was stirred at 0 ˚C for 15 min. Then, methyl iodide (1.58 mL, 25.4 mmol) was added and the mixture was warmed to room temperature and stirred for 15 min. Water was added, which caused a precipitate to appear. The precipitate was collected and washed with diethyl ether and hexane to give *the title*

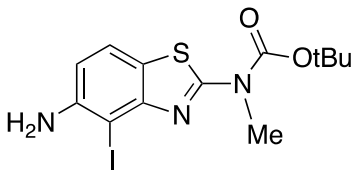
compound **45** as a pale brown solid (5.20 g, 16.8 mmol, 99 % yield); δ_H (400 MHz, $CDCl_3$) 8.66 (1H, d, *J* 2.1), 8.16 (1H, dd, *J* 8.7, 2.1), 7.89 (1H, d, *J* 8.7), 3.71 (3H, s), 1.66 (9H, s); δ_C (101 MHz, DMSO-d_6) 164.3, 149.2, 146.7, 140.7, 123.0, 118.3, 115.6, 106.1, 84.7, 35.1, 28.1; IR 2925, 1714, 1649, 1415, 1303, 738; HRMS (ESI) calculated for $C_{13}H_{16}N_3O_4S$ [$(M+H)^+$]: 310.0856 found 310.0843.

***tert*-Butyl (5-aminobenzo[d]thiazol-2-yl)(methyl)carbamate (46)**



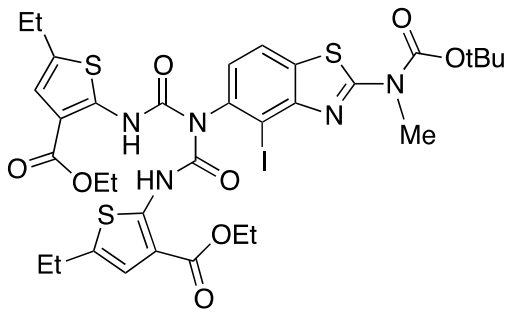
Nitro compound **45** (4.00 g, 12.9 mmol) and palladium on carbon (10 % w/w, 3.00 g, 2.83 mmol Pd) were combined in tetrahydrofuran (20 mL) and methanol (20 mL). The mixture was stirred under hydrogen atmosphere (balloon pressure) for 4 h, then filtered and concentrated *in vacuo.* The residue was purified by column chromatography (3:7 to 1:1 ethyl acetate : hexane) to yield *the title compound* **46** as a white solid (2.85 g, 10.2 mmol, 79 % yield); δ_H (400 MHz, $CDCl_3$) 7.52 (1H, d, *J* 8.4), 7.14 (1H, d, *J* 2.1), 6.70 (1H, dd, *J* 8.3, 2.2), 3.77 (2H, br), 3.66 (3H, s), 1.63 (9H, s); δ_C (101 MHz, $CDCl_3$) 162.3, 153,1, 150.4, 145.1, 123.1, 112.9, 106.6, 83.6, 34.6, 28.2; IR 3204, 1791, 1596, 1421, 1144, 847; HRMS (ESI) calculated for $C_{13}H_{18}N_3O_2S$ [$(M+H)^+$]: 280.1114 found 280.1103.

***tert*-Butyl (5-amino-4-iodobenzo[d]thiazol-2-yl)(methyl)carbamate (47)**



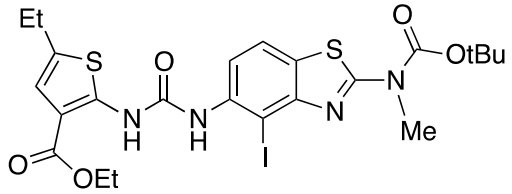
N-Iodosuccinimide (1.49 g, 6.62 mmol) was added to a solution of aniline **46** (1.85 g, 6.62 mmol) in acetonitrile (20 mL) at 0 ˚C. The mixture was warmed to room temperature and stirred for 10 min. Aqueous sodium thiosulfate was added and the mixture was extracted with ethyl acetate. The organic extract was concentrated *in vacuo* and the residue was purified by column chromatography (1:19 to 1:8 ethyl acetate : hexane) to yield *the title compound* **47** as a yellow solid (1.88 g, 4.64 mmol, 70 % yield); δ_H (400 MHz, $CDCl_3$) 7.40 (1H, d, *J* 8.3), 6.71 (1H, d, *J* 8.3), 4.23 (2H, br s), 3.68 (3H, s), 1.61 (9H, s); δ_C (101 MHz, $CDCl_3$) 161.1, 153.2, 151.1, 145.8, 121.4, 120.8, 111.8, 83.7, 77.2, 34.6, 28.2; IR 1700, 1372, 1219, 1148; HRMS (ESI) calculated for $C_{13}H_{17}IN_3O_2S$ [$(M+H)^+$]: 406.0080 found 406.0067.

Diethyl 2,2'-((((2-((*tert*-butoxycarbonyl)(methyl)amino)-4-iodobenzo[*d*]thiazol-5-yl)azanediyl)bis(carbonyl))bis(azanediyl))bis(5-ethylthiophene-3-carboxylate) (49)



A solution of methyl 2-amino-5-ethylthiophene-3-carboxylate **48** (917 mg, 4.60 mmol) in dichloromethane (20 mL) was added to a solution of phosgene (20 % in toluene, 3.88 mL, 7.36 mmol) at 0 ˚C. Triethylamine (2.06 mL, 14.7 mmol) was added and the mixture was stirred for 30 min at 0 ˚C, then concentrated *in vacuo*. The residue was dissolved in dichloromethane (20 mL). Triethylamine (2.06 mL, 14.7 mmol) and aniline **47** (746 mg, 1.84 mmol) were added and the mixture was stirred for 1 h at room temperature, then diluted with water and extracted with dichloromethane. The organic extract was concentrated *in vacuo* and purified by column chromatography (1:19 to 1:4 ethyl acetate : hexane) to yield *the title compound* **49** as a pale yellow solid (1.41 g, 1.64 mmol, 89 % yield); δ_H (400 MHz, $CDCl_3$) 7.94 (1H, d, *J* 8.2), 7.38 (1H, d, *J* 8.2), 6.90 (2H, s), 4.18-4.29 (4H, m), 3.73 (3H, s), 2.69-2.82 (4H, m), 1.67 (9H, s), 1.22-1.35 (12H, m); δ_C (101 MHz, $CDCl_3$) 164.4, 162.2, 153.3, 152.5, 151.1, 146.0, 137.1, 136.0, 133.5, 124.7, 122.2, 119.8, 113.4, 95.53, 84.4, 60.4, 34.7, 28.2, 22.8, 15.5, 14.4; IR 1700, 1441, 1192, 1149, 772; HRMS (ESI) calculated for $C_{33}H_{38}IN_5NaO_8S_3$ [$(M+Na)^+$]: 879.09217 found 879.08294.

Ethyl 2-(3-(2-((*tert*-butoxycarbonyl)(methyl)amino)-4-iodobenzo[d]thiazol-5-yl)ureido)-5-ethylthiophene-3-carboxylate (24)



Potassium carbonate (467 mg, 3.30 mmol) was added to a mixture of urea **49** (1.41 g, 1.65 mmol) in tetrahydrofuran (10 mL) and ethanol (10 mL). The mixture was stirred at 60 ˚C for 30 min, then filtered and concentrated *in vacuo*. The residue was purified by column chromatography (1:19 to 1:4 ethyl acetate : hexane) to yield *the title compound* **24** as a pale brown solid (973 mg, 1.53 mmol, 93 % yield); δ_H (400 MHz, $CDCl_3$) 10.58 (1H, s), 7.91 (1H, d, *J* 8.5), 7.68 (1H, d, *J* 1.1), 7.04 (1H, s), 6.85 (1H, t, *J* 1.1), 4.30 (2H, q, *J* 7.7), 3.70 (3H, s), 2.74 (2H, dd, *J* 7.5, 1.0), 1.62 (9H, s), 1.37 (3H, d, *J* 6.5), 1.30 (3H, t, *J* 6.9); δ_C (101 MHz, $CDCl_3$)

165.7, 161.7, 153.2, 151.1, 151.0, 149.1, 136.7, 128.2, 120.9, 118.9, 118.9, 110.6, 86.5, 84.1, 60.4, 34.6, 28.2, 22.8, 15.5, 14.4; IR 1703, 1666, 1559, 1246, 1187, 761; HRMS (ESI) calculated for $C_{23}H_{28}IN_4O_5S_2$ [$(M+H)^+$]: 631.0514 found 631.0540.

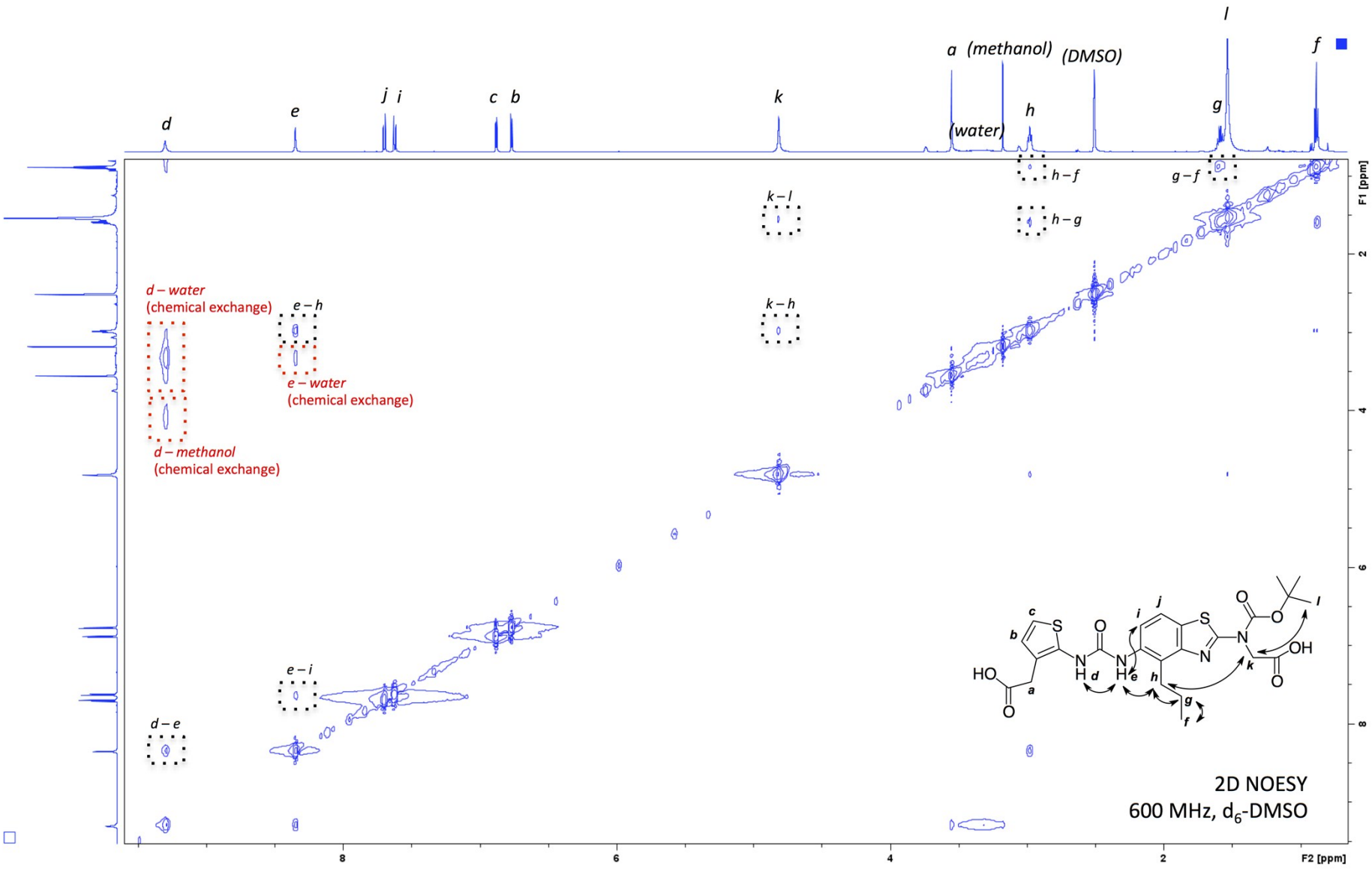
3. Conformational analysis

X-ray crystallography

Single crystals of **24** were obtained by vapour diffusion (chloroform/hexane). Low temperature (100 K) diffraction studies were carried out using Beamline I19(EH1) at Diamond Light Source.[2] Raw frame data were reduced using CrysAlisPRO (Oxford Diffraction/Agilent Technologies UK Ltd, Yarnton, England) and the structure was solved using SuperFlip.[3] Full-matrix least-squares refinement of the structures was carried out using CRYSTALS.[4,5] Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1453550) and copies of these data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.

NMR spectroscopy

The 2D NOESY spectrum of **20** (17 mg•mL^{-1} in d_6-DMSO) was recorded at 298 K on a Bruker AVIII HD 600 with BB-F/1H Prodigy nitrogen cryoprobe using 0.5 s mixing time and 10 s relaxation delay.

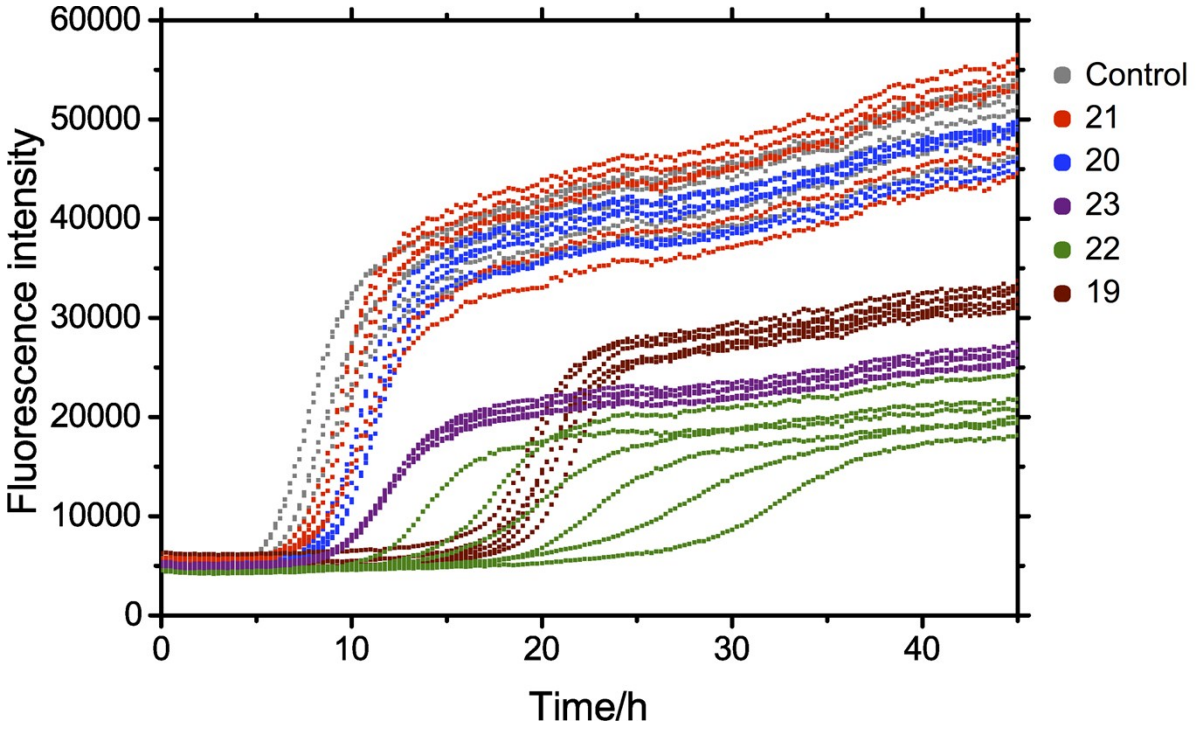

d
e
j i
c b
k
a (methanol)
(water)
(DMSO)
h
g
l
f
h – f
g – f
h – g
k – l
k – h
d – water
(chemical exchange)
e – h
e – water
(chemical exchange)
d – methanol
(chemical exchange)
e – i
d – e
2D NOESY
600 MHz, d6-DMSO
F1 [ppm]
F2 [ppm]
2
4
6
8

4. IAPP Experimental Procedures

Thioflavin T assay

Human IAPP peptide (AS-60804) was purchased from AnaSpec, Inc. The peptide was dissolved in hexafluoroisopropanol and left to stand for 1 h. It was then evaporated to dryness under a stream of nitrogen gas, dissolved in DMSO, divided into aliquots and stored at – 30 ˚C. 5 mg•mL^{-1} liposomes were prepared in 20 mM potassium phosphate buffer, 100 mM NaCl buffer, pH 7.2 and filtered through a 100 nM extrusion film. The DOPG and DOPC lipids were obtained from Avanti Polar Lipids. In fibrillation kinetics, 10 μM IAPP peptide, 500 μg•mL^{-1} liposome (DOPG and DOPC in a molar ratio of 1:1) and 50 μM ThT were mixed with/without 50 μM test compounds. 30 μL of each sample was transferred into a 384-well plate and sealed. All of the samples were prepared on ice. The assays were recorded with an Infinite M1000 PRO microplate reader every 15 min, using excitation and emission wavelengths of 446 and 490 nm, respectively. The assays were performed in six replicates in 20 mM potassium phosphate buffer, 100 mM NaCl, pH 7.2, at 25 ˚C, and average fluorescence signals were calculated. Every fluorescence curve was fitted with a sigmoid equation.[6] $T_{1/2}$ values are reported as the average ± standard deviation.

Full data (six replicates) for ThT assay



Imaging

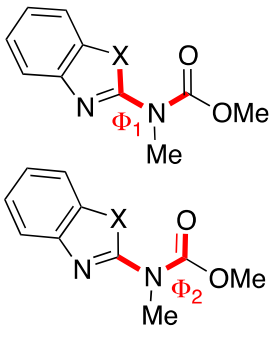
The samples for electron microscopy were taken from the wells after ThT assays. The samples were stained with 2 % uranyl acetate on carbon 400 mesh Cu grid. The images were taken at 120 kV on a transmission electron microscope (FEI Tecnai 12).

Circular dichroism

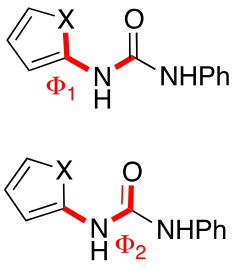
IAPP (6 μL of a 1.0 mM solution in hexafluoroisopropanol) was combined with 258 μL of 20 mM potassium phosphate buffer, 100 mM NaCl, pH 7.2. Then, either **19** (6 μL of a 1.0 mM solution in hexafluoroisopropanol) or an equivalent volume of hexafluoroisopropanol was added. LUVs were added (30 μL of a 10 mg/mL stock, DOPG/DOPC 1:1, 100 nm). The sample was pipette-mixed, transferred to a 1 mm path length quartz cuvette and CD spectra were recorded at 0.5 nm intervals from 200 nm to 260 nm (Applied Photophysics Chirascan instrument). Spectral acquisitions and incubations were performed at ambient temperature. Triplicate spectra were averaged, subtracted from a triplicate-averaged background scan (i.e. a sample containing an equivalent volume hexafluoroisopropanol in place of IAPP) and then smoothed using the Savitsky–Golay method[7] with a polynomial order of three and a smoothing window of 10 points (OriginPro 2015 software).

5. Computational modeling

Structures were built in *Maestro*[8] and optimized in *Jaguar*.[9] Calculations utilized the M06-2X[10] hybrid meta-GGA functional in combination with a Pople 6-31G(d,p) basis set for all elements.[11,12] Calculations were performed using the implicit Poisson Boltzmann Finite element method,[13] with water as solvent. Unless otherwise stated, all energies are quoted in kJ/mol and Boltzmann populations are at 298 K and a standard state of 1 mol/L. Dihedral scans fixed angles Φ_1 and Φ_2 to the stated dihedral angle; all other distances, angles, and dihedrals were relaxed. Default convergence criteria were used.



Model system 1
X = S, O



Model system 2
X = S, O

Table of relative energies from dihedral scans

Dihedral angles (°)		Relative energy (kJ/mol)			
Φ1	**Φ2**	**Model 1 (Sulfur)**	**Model 1 (Oxygen)**	**Model 2 (Sulfur)**	**Model 2 (Oxygen)**
0	0	0	2.419518	0	13.793014
0	15	1.219794	1.686034	2.914817	13.459237
0	30	6.90112	3.705253	8.825765	21.582155
0	45	18.243627	9.535715	24.251367	28.50795
0	60	32.74153	19.494403	41.809089	37.456702
0	75	47.368888	30.766374	51.94579	48.985837
0	90	62.298922	44.416749	46.068345	41.85827
0	105	45.790864	29.546568	37.88446	35.256327
0	120	32.108966	18.273778	29.139882	27.713107
0	135	19.820935	9.617453	24.985212	21.634947
0	150	11.659239	4.466087	25.08659	15.959936
0	165	7.596744	2.656999	29.394254	13.970996
0	180	6.901055	2.824885	38.890912	11.935262
15	0	1.051454	0.966056	1.409568	12.403673
15	15	6.379507	3.316347	6.755538	12.176303
15	30	13.605581	5.841559	15.429659	19.121685
15	45	25.086993	12.557685	27.376031	25.766749
15	60	39.756694	24.213453	37.734795	33.785659
15	75	54.173373	39.178071	52.099995	47.86273
15	90	52.714909	35.484334	44.75516	42.578702
15	105	40.473551	25.743423	37.317202	35.762659
15	120	27.677091	16.37088	31.075534	27.545132
15	135	16.576754	8.734874	28.388198	22.333896
15	150	9.16601	3.383452	29.529477	15.656097
15	165	6.480334	1.817152	34.402279	13.271758
15	180	7.181381	1.735923	29.490771	11.101617
30	0	4.685632	0	2.661527	10.403206
30	15	12.971583	4.324549	9.904958	9.853369
30	30	19.527725	10.443162	17.272544	16.771706
30	45	31.29938	17.522033	26.894799	22.981706
30	60	45.546916	30.476944	38.104683	33.042507
30	75	57.727037	39.486175	50.280395	45.201543
30	90	49.343356	33.523295	44.143074	40.69896
30	105	37.684291	25.362881	37.406384	33.261273
30	120	25.89589	17.019576	32.944158	26.090838
30	135	16.13293	9.264117	31.270279	20.084688
30	150	9.684946	3.837265	33.277703	14.988122
30	165	6.928758	0.326856	31.684762	11.71742
30	180	9.095624	0.763474	23.248833	10.309856

45	0	10.783887	0.703271	5.678765	6.947049
45	15	19.43732	8.353102	11.468328	10.114111
45	30	24.584888	12.173538	17.905328	13.567615
45	45	35.725574	22.342046	25.912851	22.14253
45	60	49.496989	35.708361	37.753879	33.052643
45	75	57.512029	41.118699	48.674517	44.39888
45	90	49.097122	35.500754	43.152431	39.464741
45	105	38.127504	27.712093	37.834512	33.010511
45	120	27.263844	18.917613	35.312968	25.000156
45	135	18.368126	10.795014	33.938826	17.987915
45	150	12.637662	4.565412	37.161202	12.011257
45	165	10.234235	0.637105	24.043871	9.710976
45	180	12.792116	1.351346	18.443168	8.870611
60	0	17.289915	4.38724	7.945323	4.945928
60	15	26.377679	13.288406	9.564679	7.709833
60	30	28.814571	15.90354	19.777035	12.956433
60	45	39.345834	25.986847	27.231835	18.810397
60	60	52.245401	38.262531	38.830845	32.083961
60	75	64.628147	50.493564	47.537536	41.264088
60	90	52.345314	40.111876	44.409249	37.885431
60	105	41.840017	31.850126	39.871947	31.1536
60	120	31.571065	22.215882	37.65912	22.668617
60	135	23.059977	13.376765	36.417604	15.149747
60	150	17.478536	6.828413	28.521896	10.842121
60	165	15.222429	2.753465	19.12109	8.617995
60	180	17.616012	3.243144	15.952489	8.408935
75	0	24.768109	9.840206	10.291681	5.22695
75	15	25.847768	13.431487	13.485429	7.520705
75	30	31.630903	18.222284	15.991511	12.380712
75	45	41.559216	27.304812	26.374708	20.73327
75	60	53.640051	38.832476	38.043342	31.0449
75	75	65.420019	51.350155	48.480982	42.370596
75	90	58.766903	46.647888	44.537794	37.582749
75	105	48.393684	36.954357	40.949601	29.173559
75	120	37.848038	26.364118	37.199549	20.775135
75	135	29.160066	16.747021	31.298109	14.497364
75	150	22.787992	9.411657	21.853054	10.107516
75	165	19.713382	5.943984	16.833623	9.767094
75	180	23.770283	8.398098	14.393674	9.745153
90	0	30.841245	18.532332	11.881583	5.746576
90	15	26.864127	13.780644	13.520117	8.060741
90	30	31.708904	17.896916	17.800217	13.661811
90	45	40.690051	26.140562	25.472653	21.383137
90	60	51.745318	37.560101	35.901186	32.590572
90	75	62.918216	49.65794	50.032004	43.730327

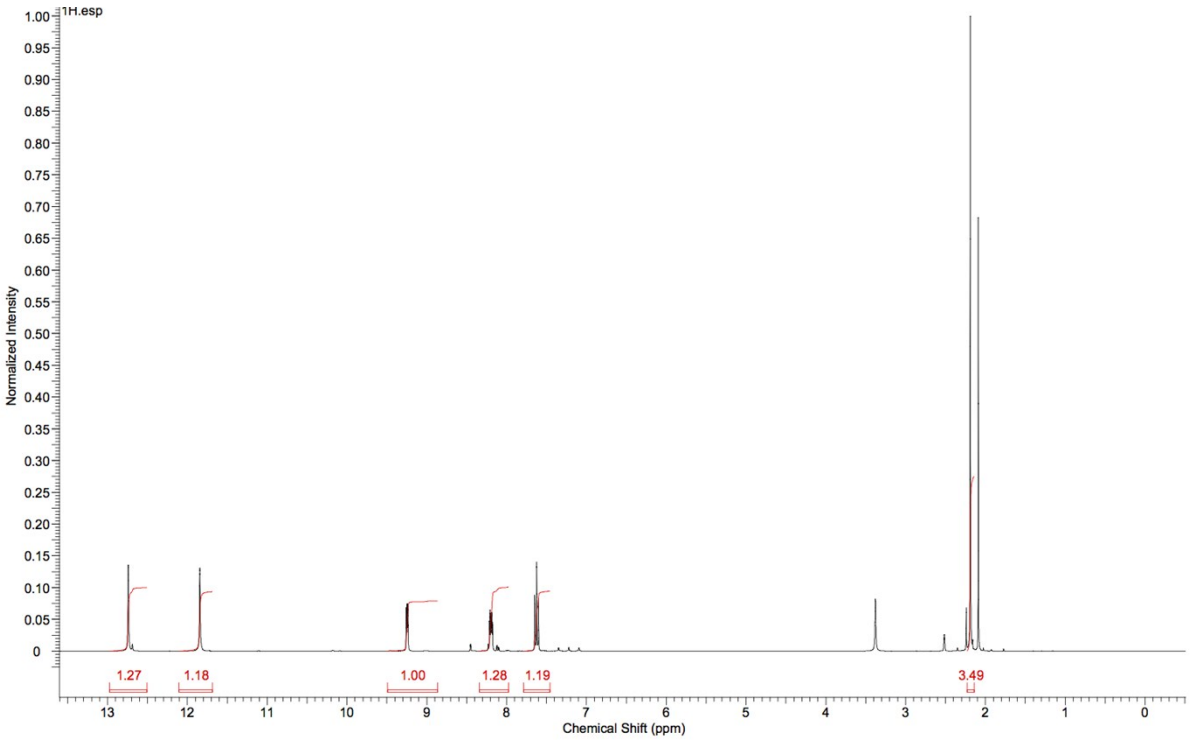
90	90	64.972929	59.26528	45.533255	37.916225
90	105	54.407717	42.241255	41.159935	29.626037
90	120	43.160883	30.742279	34.919577	21.010458
90	135	33.496443	20.450699	25.539656	14.738956
90	150	26.610676	12.970472	19.744596	11.657573
90	165	24.12315	10.517166	15.184993	11.143229
90	180	28.020649	15.053247	12.089775	8.734192
105	0	30.935422	12.817939	12.695511	6.542825
105	15	25.952102	11.503351	13.091648	8.5794
105	30	29.89319	15.35553	15.181855	13.612263
105	45	38.018129	23.450109	21.786918	21.165928
105	60	48.40479	34.431197	35.851623	32.280559
105	75	59.0296	45.888204	51.382237	44.202303
105	90	66.917008	55.037581	46.202464	38.362497
105	105	57.466119	45.764467	40.011288	30.58143
105	120	45.685873	33.17987	32.527786	22.200442
105	135	35.595924	23.151015	24.584411	16.984081
105	150	28.368313	15.877463	18.807686	13.386881
105	165	26.644749	12.620372	13.913635	10.504508
105	180	27.393979	12.893773	11.393303	7.645606
120	0	24.458289	8.967426	12.895617	6.008305
120	15	23.773466	7.832183	11.690726	8.137158
120	30	27.863606	11.948248	14.004788	13.611336
120	45	35.089679	19.508445	21.444467	19.012314
120	60	44.932624	30.030404	35.518838	32.128398
120	75	54.6517	41.166665	52.076385	44.877666
120	90	61.839304	49.389178	45.737088	38.285155
120	105	57.755843	45.972257	39.066016	30.762925
120	120	45.71538	33.863045	31.669453	23.485343
120	135	36.130931	23.47125	23.899047	18.040058
120	150	29.267542	15.709411	17.030993	13.021756
120	165	28.747705	13.788563	12.848869	8.959196
120	180	23.159517	7.6221	11.744012	6.896012
135	0	23.422068	5.520857	11.775034	5.062496
135	15	22.685474	4.789284	10.484649	7.001331
135	30	26.695959	8.838414	13.118802	11.851923
135	45	33.412182	16.298776	21.554826	20.958524
135	60	41.721751	26.106304	36.140834	36.908176
135	75	50.410322	36.017397	51.851693	44.475954
135	90	57.01177	43.80865	45.159432	37.950919
135	105	56.0337	43.115997	38.0691	30.634129
135	120	44.422681	30.726377	30.433907	23.200747
135	135	34.859002	20.558331	22.114481	16.83899
135	150	28.474768	12.396395	15.932637	11.09343
135	165	27.139213	10.706791	13.604146	7.859664

135	180	22.179244	5.046759	13.727427	7.479028
150	0	23.276435	3.790788	11.101909	3.441717
150	15	22.986129	3.260432	9.850201	4.569952
150	30	25.761952	7.063342	16.479067	10.941853
150	45	31.427771	14.075739	26.362346	21.402769
150	60	39.066932	22.786926	35.947013	29.440986
150	75	47.010849	32.070606	50.420249	43.220164
150	90	52.836149	39.24333	43.395574	37.43491
150	105	53.124575	37.816007	36.621192	29.735507
150	120	42.249368	26.198094	28.288072	22.554312
150	135	33.547516	16.148304	20.646573	15.219336
150	150	28.429733	9.27591	16.418137	10.806528
150	165	25.365185	7.139147	15.885065	9.660998
150	180	22.932204	4.222526	18.412268	10.92369
165	0	24.32889	4.129735	9.765296	1.550501
165	15	23.562625	3.377678	9.199462	5.066581
165	30	24.954772	6.171037	16.027896	10.821761
165	45	30.205852	12.540971	28.192616	21.749708
165	60	37.209758	20.937058	41.798521	28.680344
165	75	44.982363	30.051308	48.90116	41.620395
165	90	50.802114	36.808407	41.940007	36.628685
165	105	49.279269	32.23324	35.641461	29.448573
165	120	39.364965	22.02625	27.212562	21.418201
165	135	31.750682	13.057933	21.545319	14.719435
165	150	27.466897	7.84692	18.934097	11.895629
165	165	24.642602	5.375654	21.377151	12.304372
165	180	23.806413	3.922774	25.004146	15.239041
180	0	25.126911	4.999456	8.85689	0
180	15	24.6099	4.732836	13.193206	5.583257
180	30	25.69854	6.451884	20.131246	12.776026
180	45	30.034489	12.424933	23.098268	22.963565
180	60	37.142764	20.971137	40.161858	32.463059
180	75	45.426941	30.496213	49.38201	42.745588
180	90	59.13795	45.888729	42.726134	37.510818
180	105	45.670445	28.433675	36.690215	29.556667
180	120	37.226042	19.437831	28.776015	21.246135
180	135	30.115258	12.055987	24.3615	14.66209
180	150	26.25635	6.711094	24.092045	15.247116
180	165	24.75559	4.456475	26.587079	16.111827
180	180	25.5664	4.34306	33.284124	22.591121

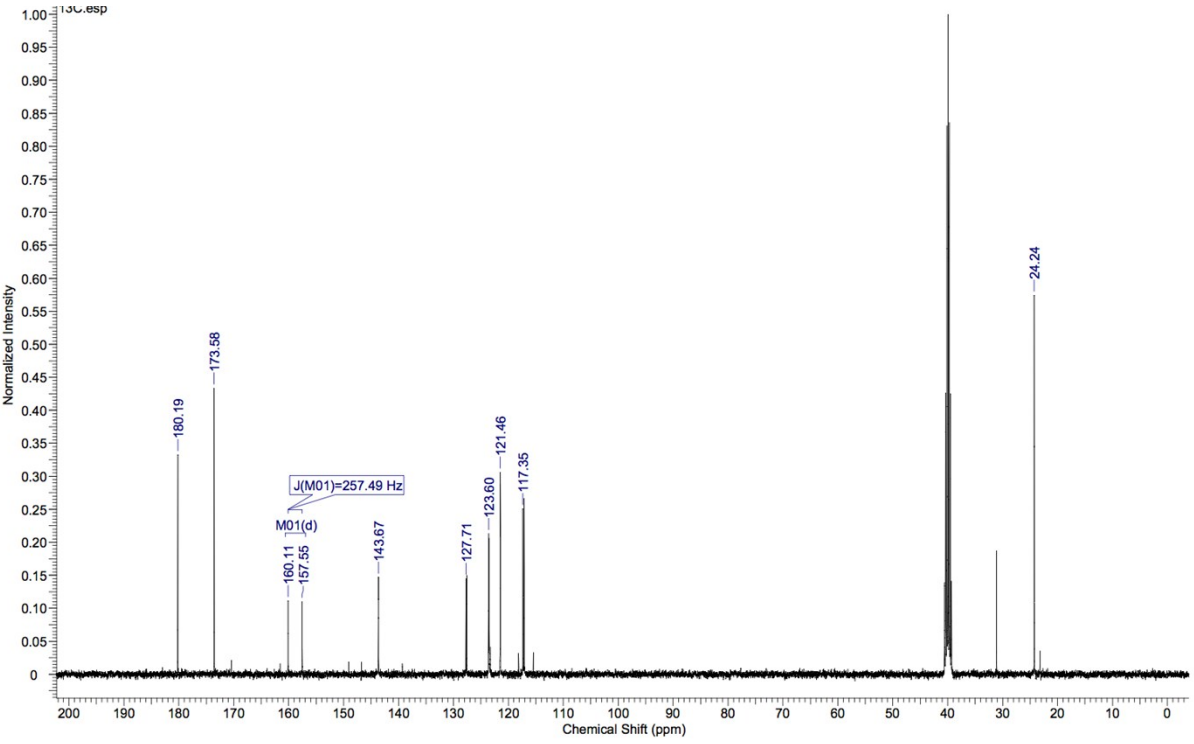
6. NMR Spectra

N-((2-Fluoro-5-nitrophenyl)carbamothioyl)acetamide (27)

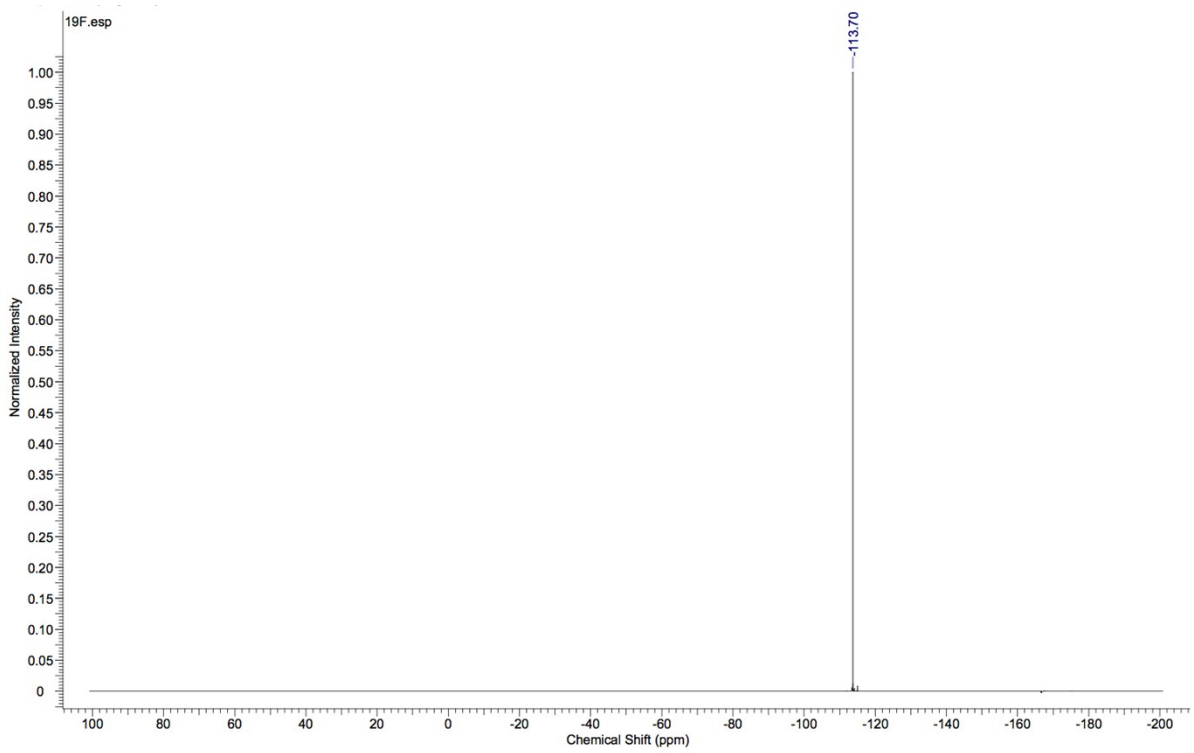
^{1}H, 400 MHz, d_6-DMSO



^{13}C, 101 MHz, d_6-DMSO

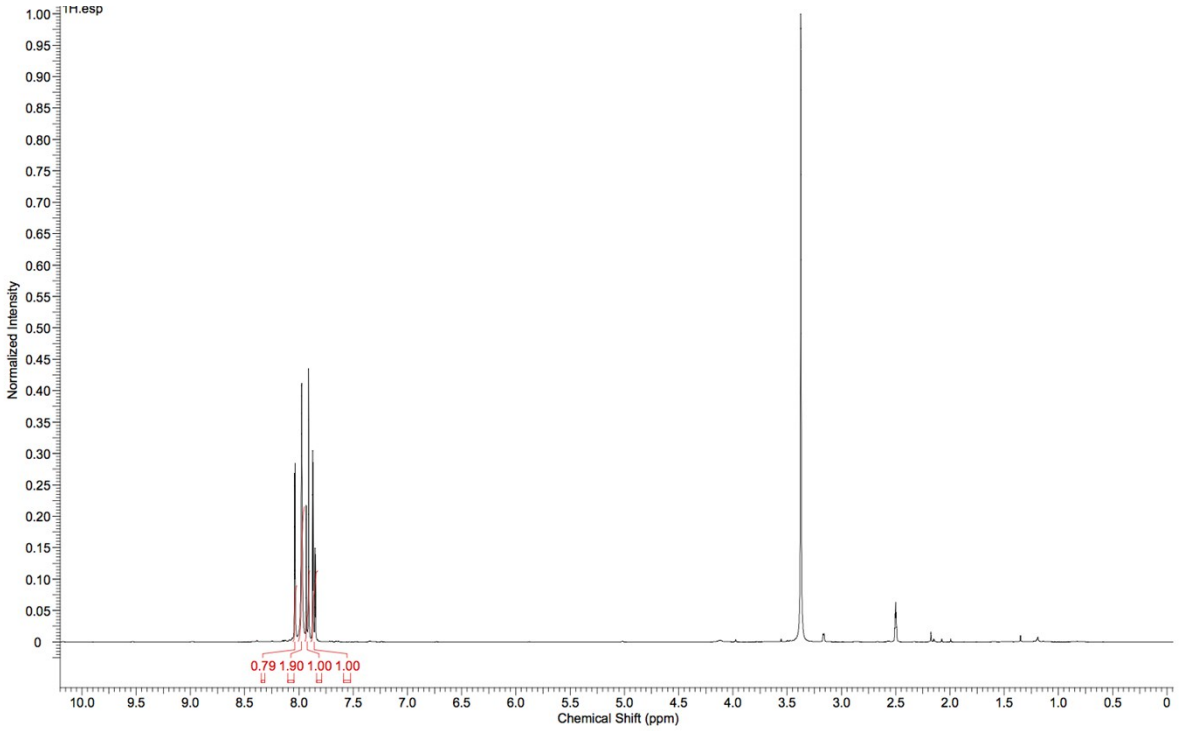


$^{19}F\{^{1}H\}$, 377 MHz, d_6-DMSO

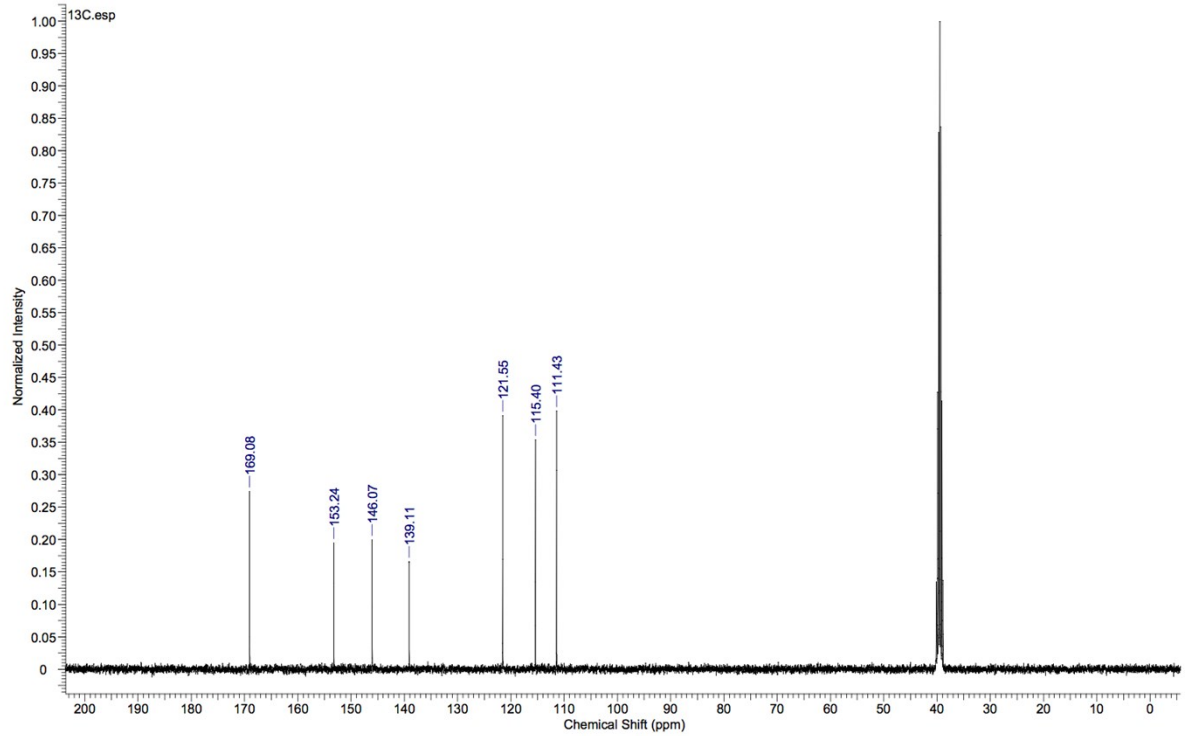


5-Nitrobenzo[*d*]thiazol-2-amine (1)

^{1}H, 400 MHz, d_6-DMSO

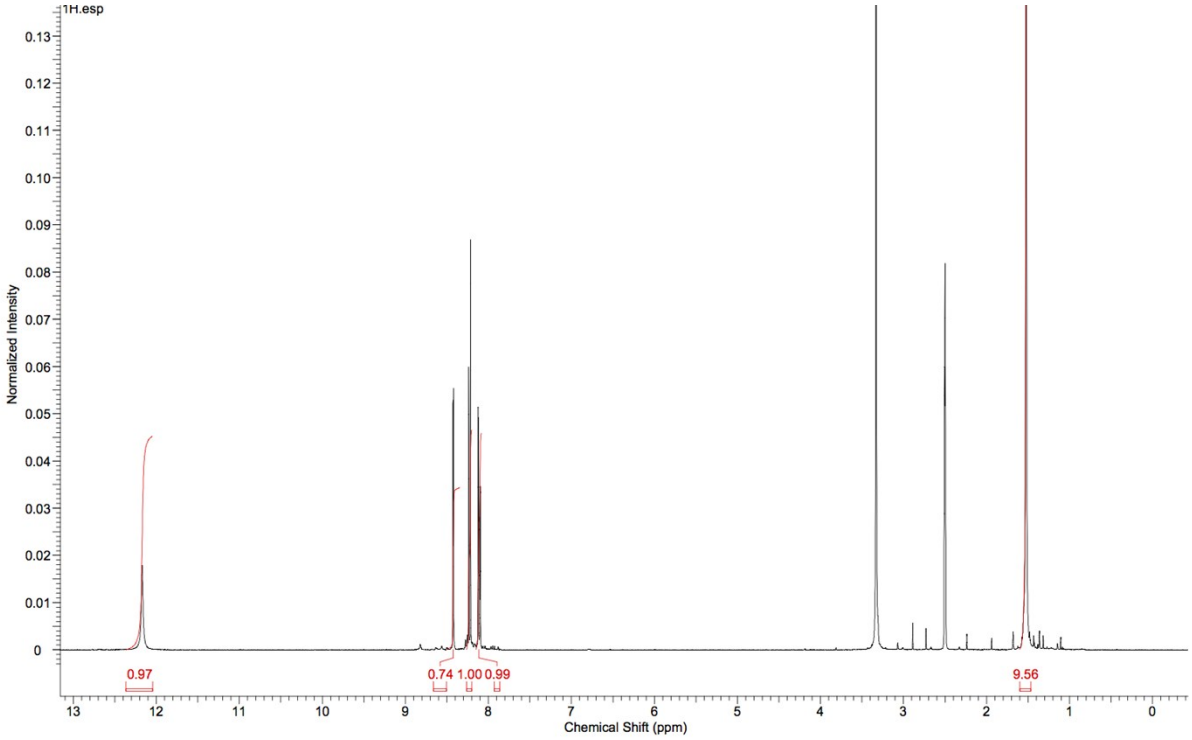


^{13}C, 101 MHz, d_6-DMSO

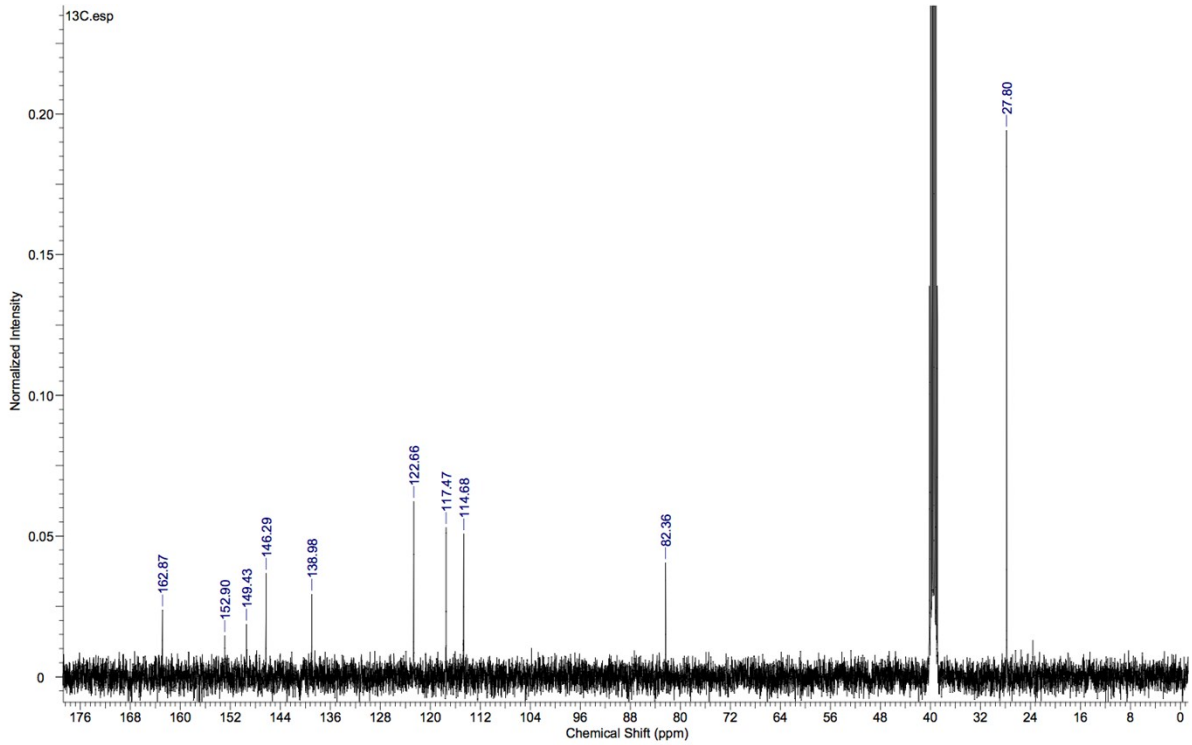


tert-Butyl (5-nitrobenzo[*d*]thiazol-2-yl)carbamate (2)

^{1}H, 400 MHz, d_6-DMSO

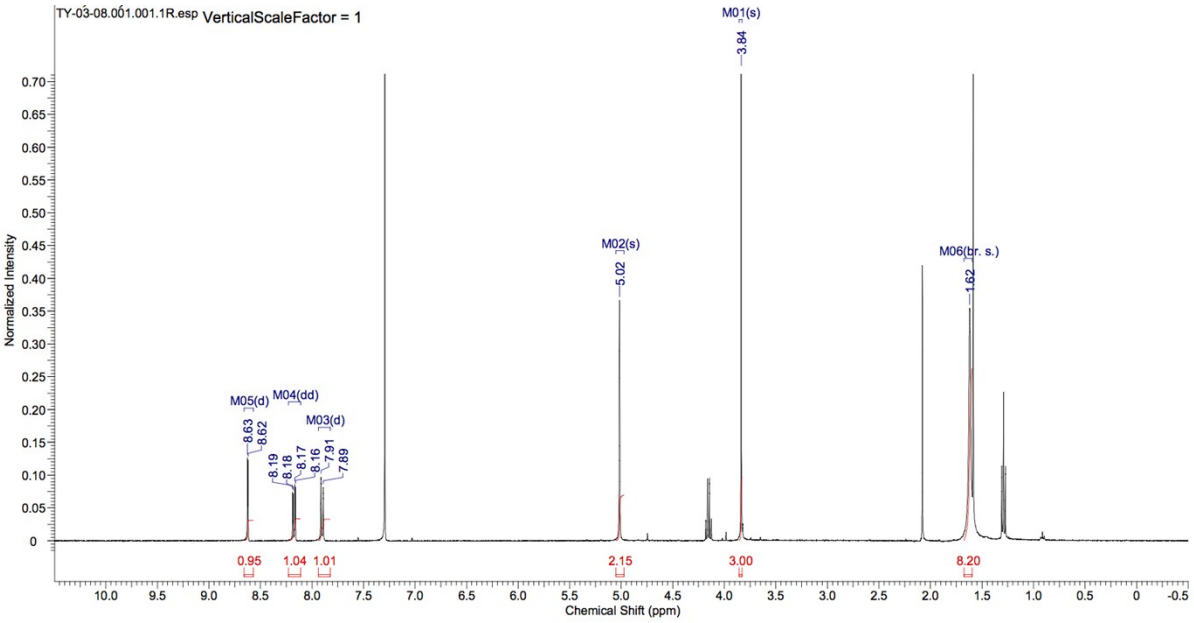


^{13}C, 101 MHz, d_6-DMSO

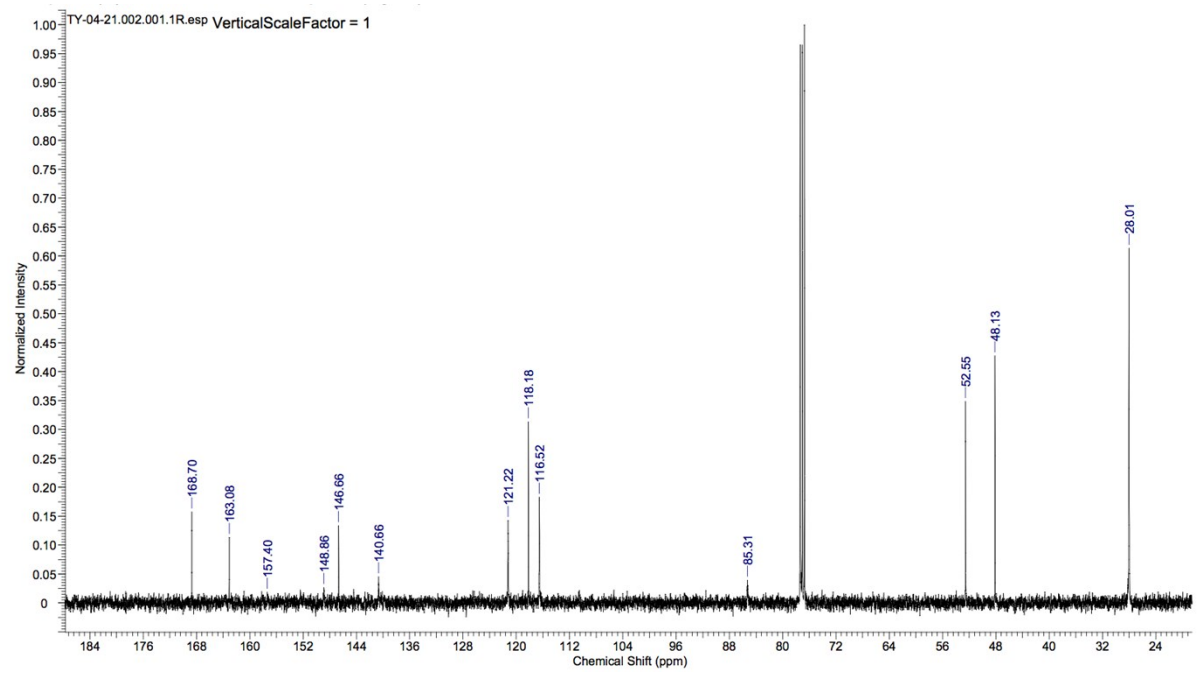


Methyl 2-((*tert*-butoxycarbonyl)(5-nitrobenzo[d]thiazol-2-yl)amino)acetate (5)

^{1}H, 400 MHz, $CDCl_3$

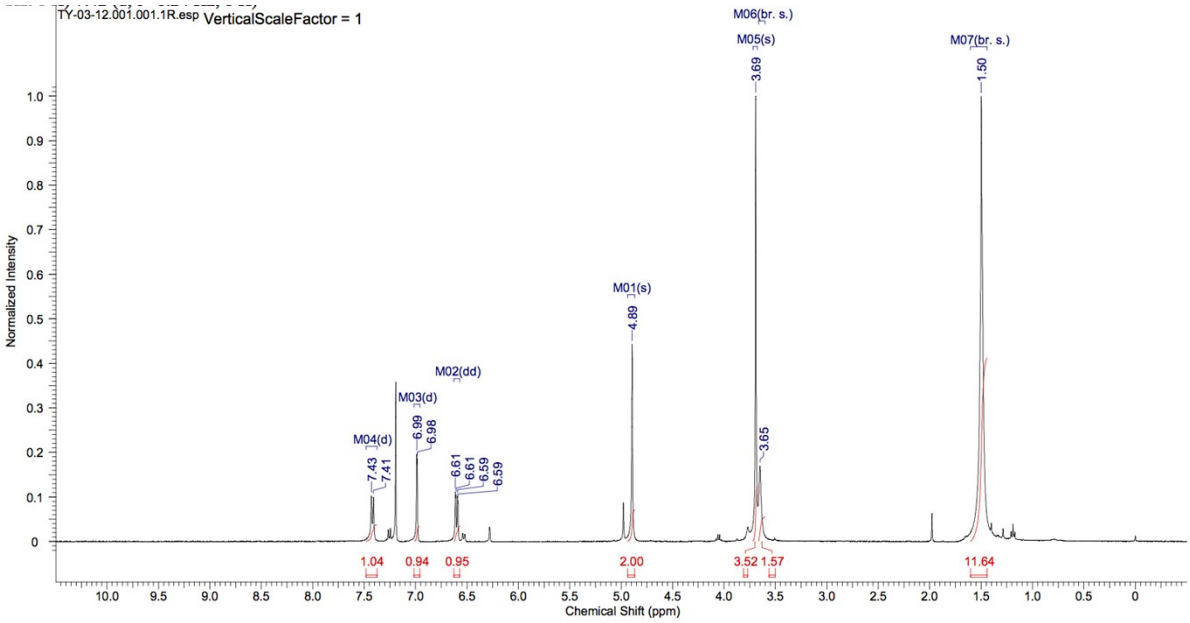


^{13}C, 101 MHz, $CDCl_3$

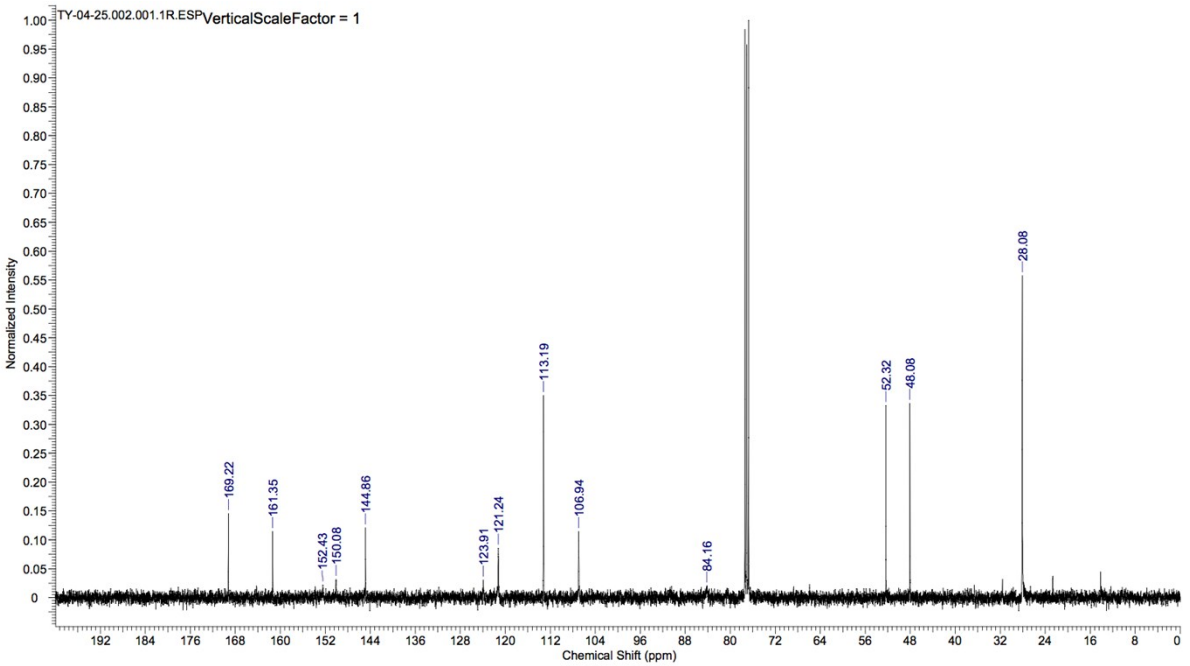


Methyl 2-((5-aminobenzo[d]thiazol-2-yl)(*tert*-butoxycarbonyl)amino)acetate (28)

^{1}H, 400 MHz, $CDCl_3$

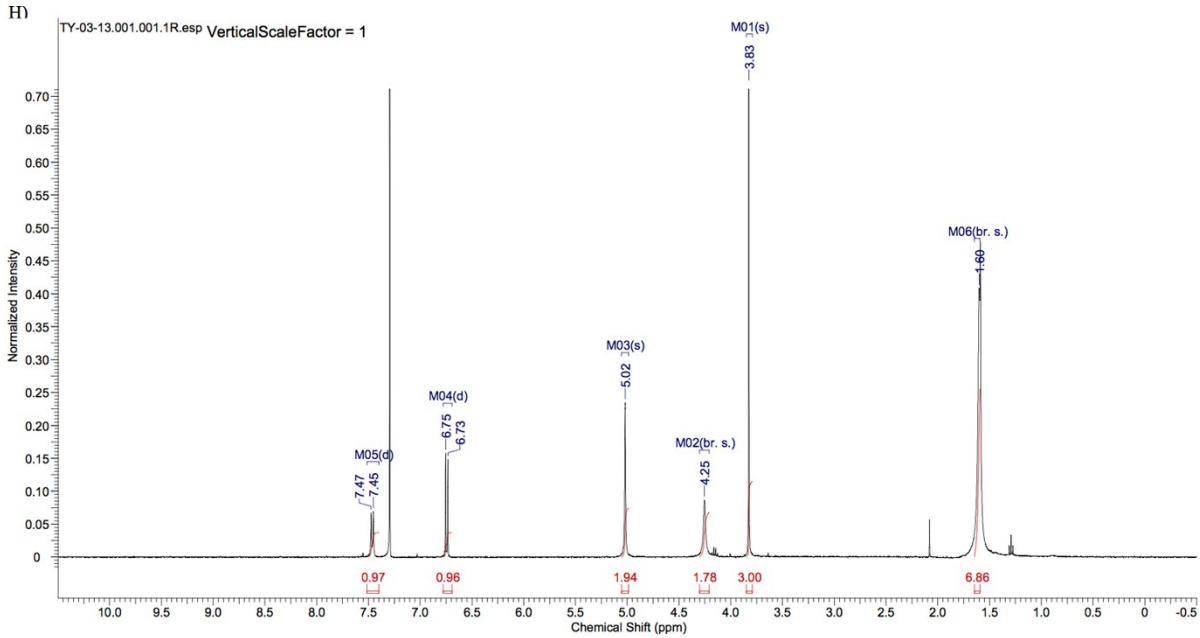


^{13}C, 101 MHz, $CDCl_3$

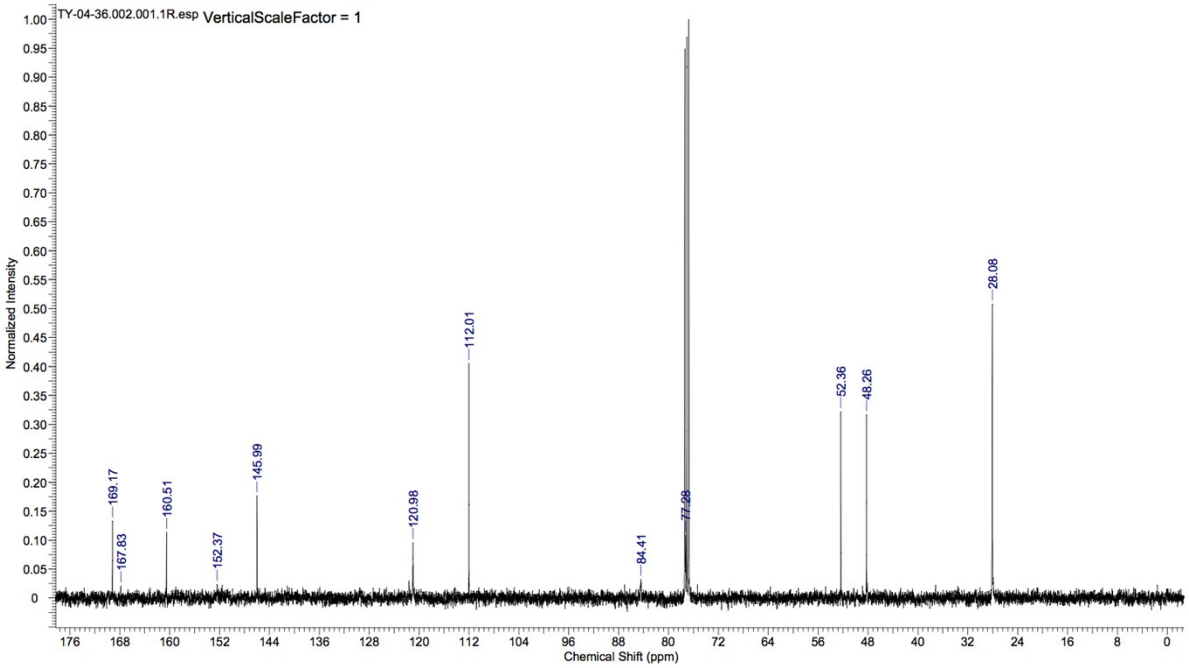


Methyl 2-((5-amino-4-iodobenzo[d]thiazol-2-yl)(*tert*-butoxycarbonyl)amino)acetate (8)

^{1}H, 400 MHz, $CDCl_3$

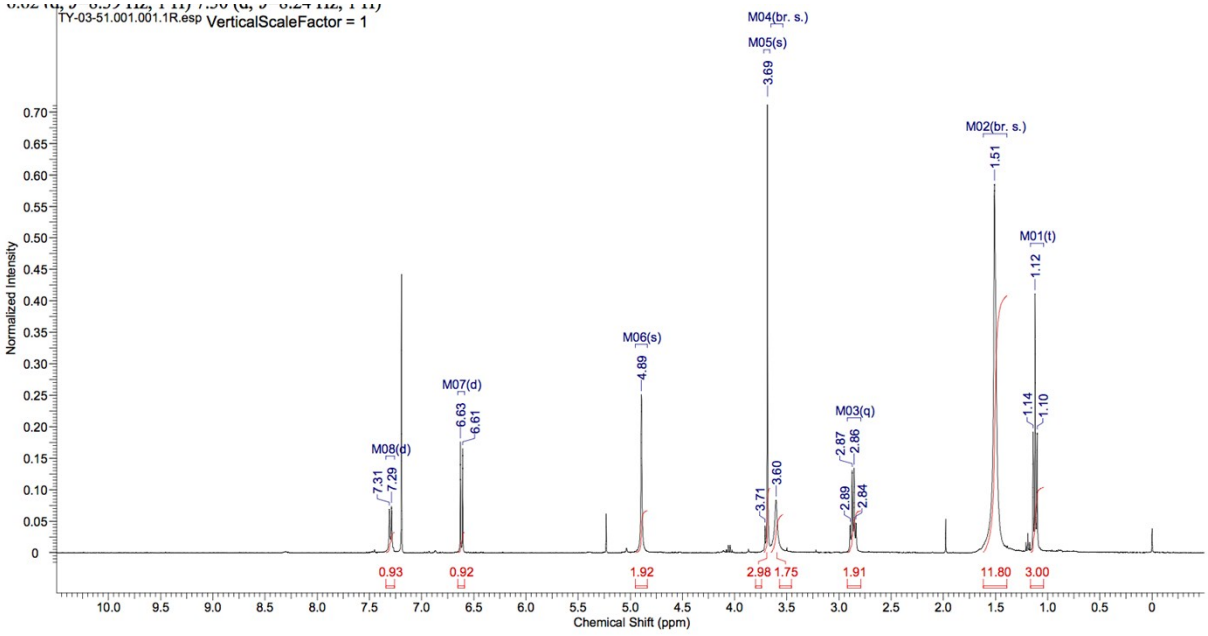


^{13}C, 101 MHz, $CDCl_3$

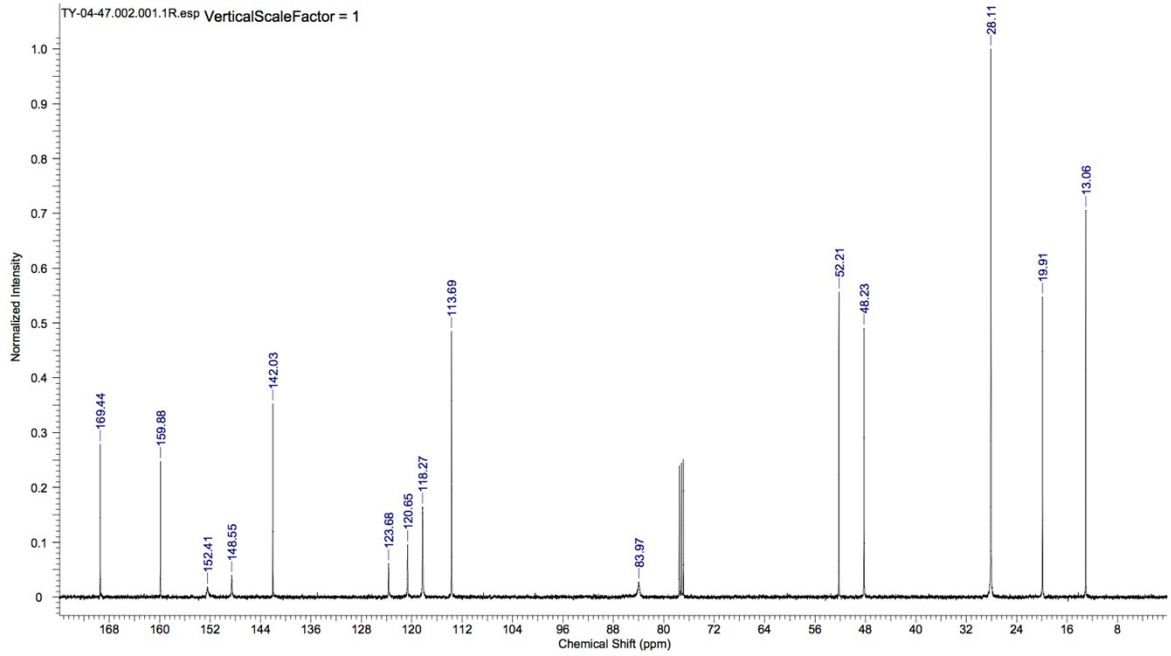


Methyl 2-((5-amino-4-ethylbenzo[d]thiazol-2-yl)(*tert*-butoxycarbonyl)amino)acetate (11)

^{1}H, 400 MHz, $CDCl_3$

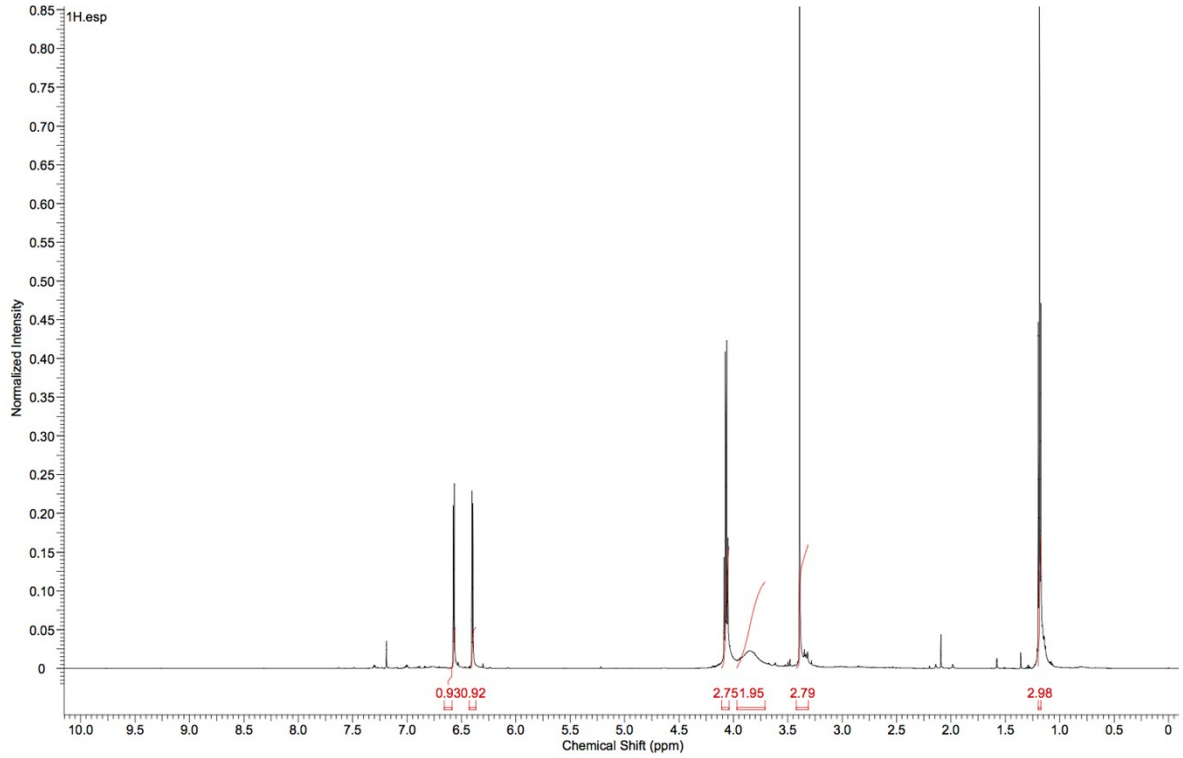


^{13}C, 101 MHz, $CDCl_3$

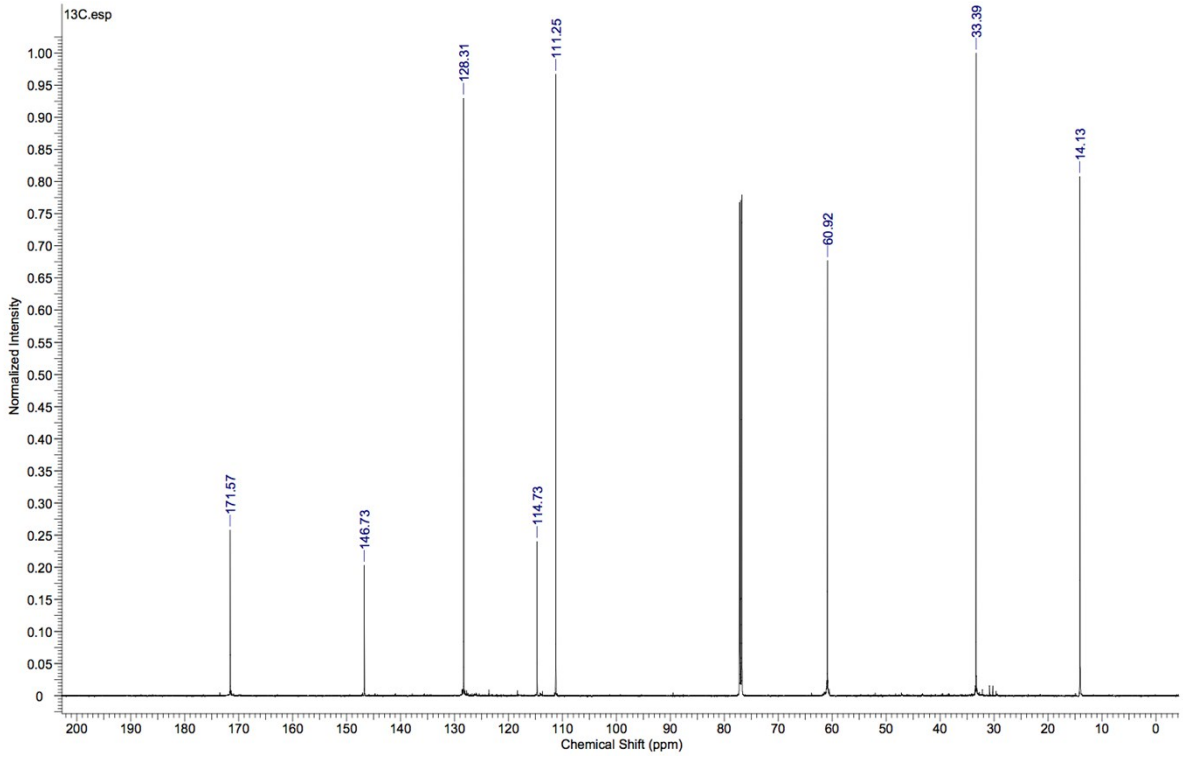


Ethyl 2-(2-aminothiophen-3-yl)acetate (16)

^{1}H, 600 MHz, $CDCl_3$

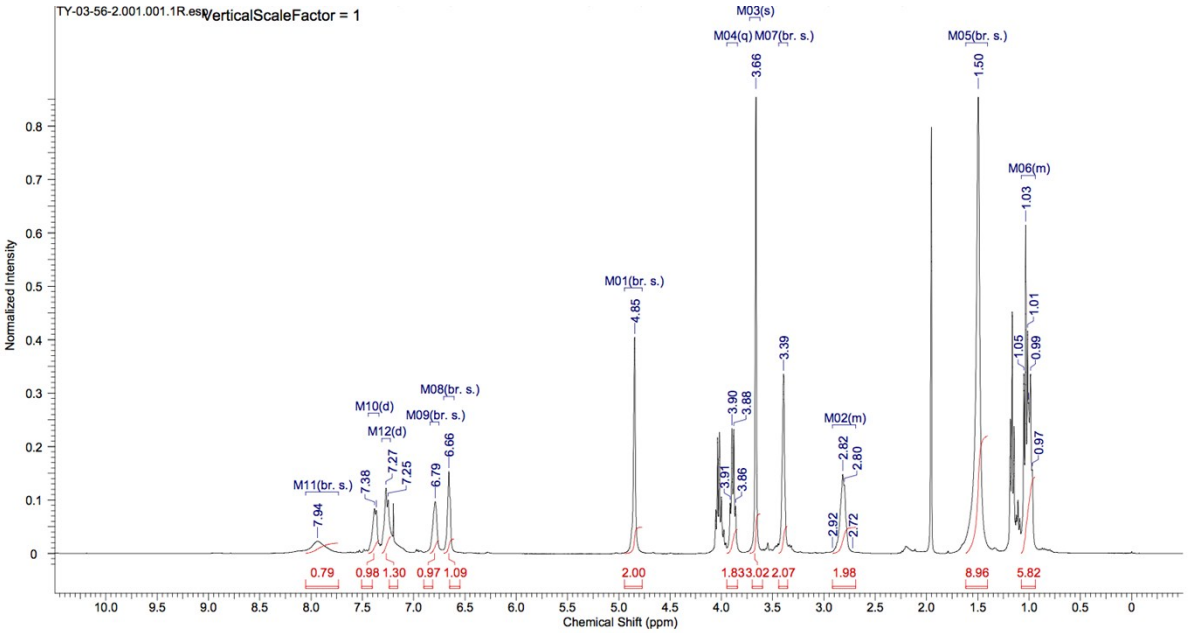


^{13}C, 151 MHz, $CDCl_3$

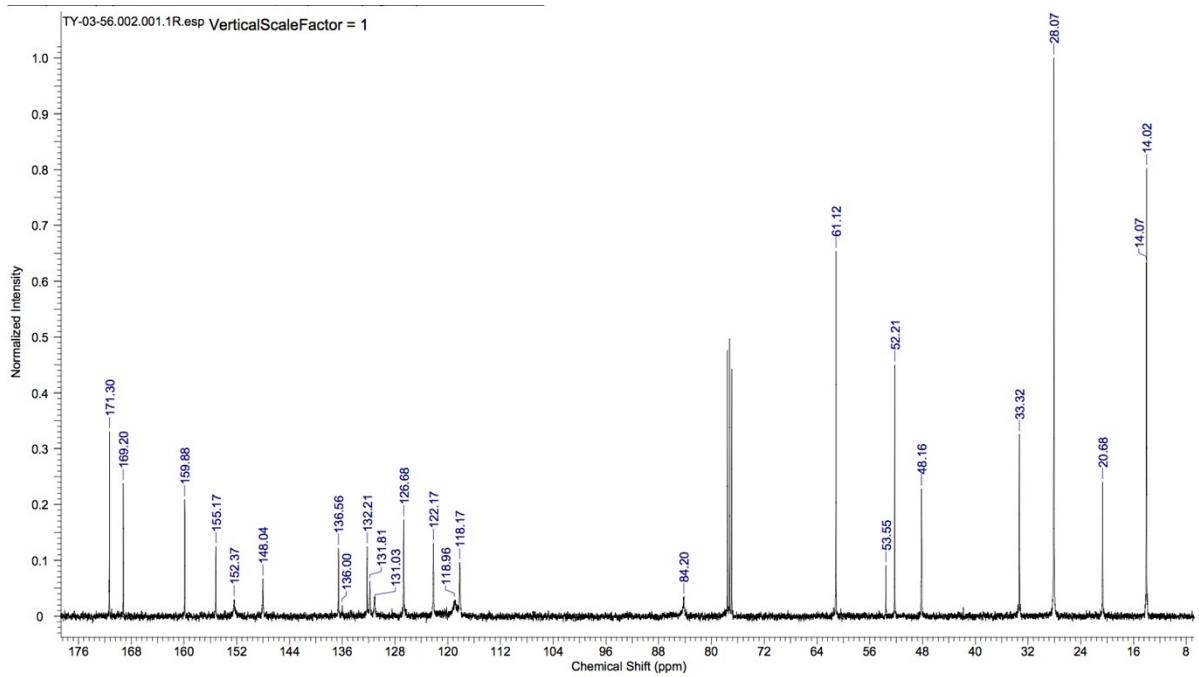


Ethyl 2-(2-(3-(2-((*tert*-butoxycarbonyl)(2-methoxy-2-oxoethyl)amino)-4-ethylbenzo[d]thiazol-5-yl)ureido)thiophen-3-yl)acetate (29)

^{1}H, 400 MHz, $CDCl_3$

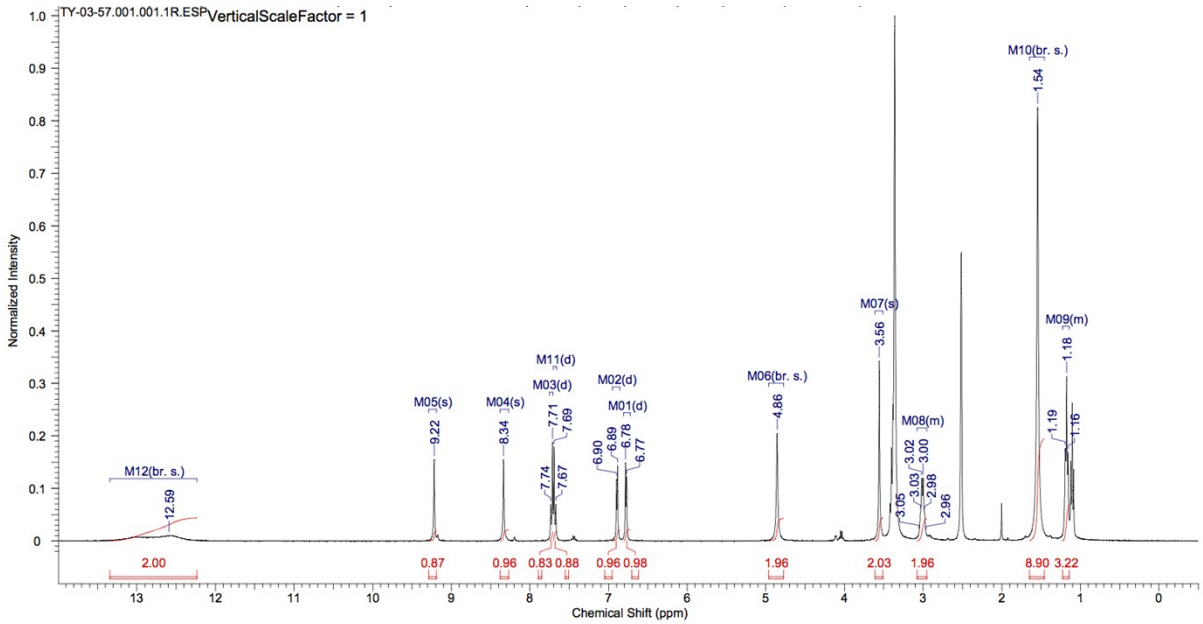


^{13}C, 101 MHz, $CDCl_3$

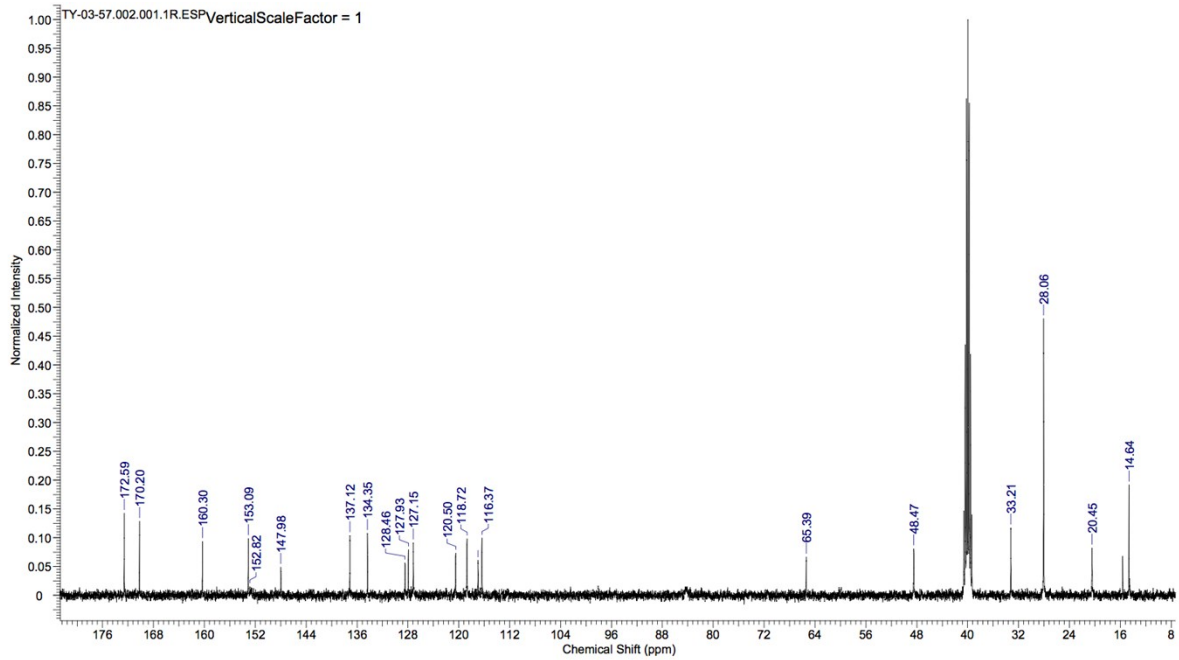


2-((*tert*-Butoxycarbonyl)(5-(3-(3-(carboxymethyl)thiophen-2-yl)ureido)-4-ethylbenzo[d]thiazol-2-yl)amino)acetic acid (21)

^{1}H, 400 MHz, d_6-DMSO

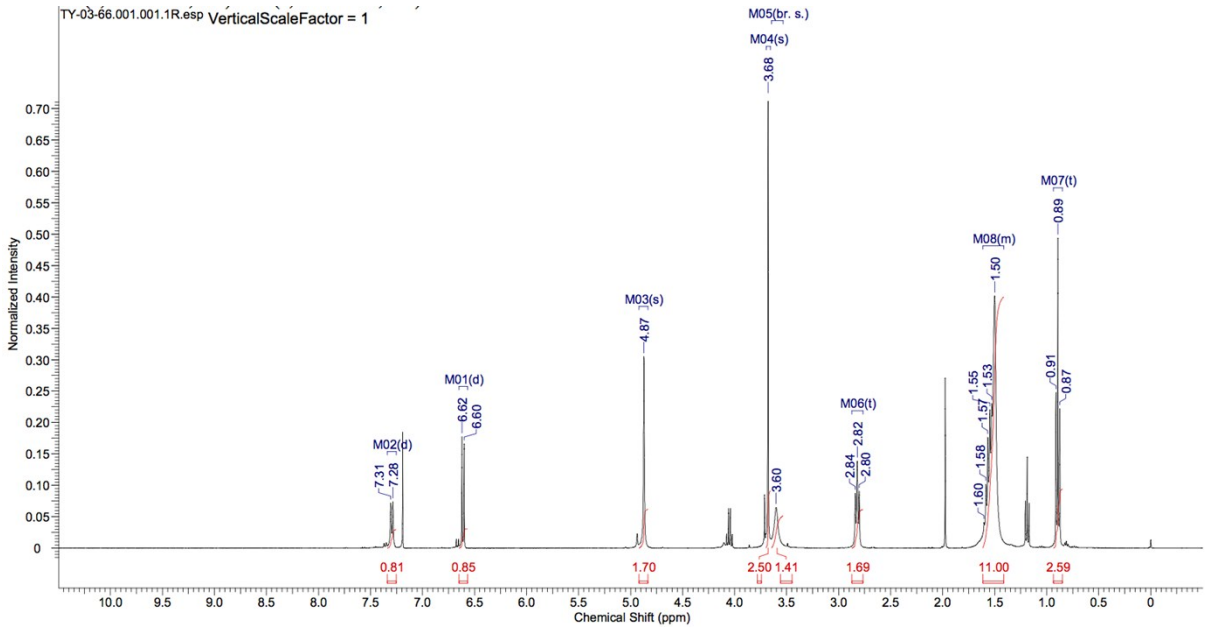


^{13}C, 101 MHz, d_6-DMSO

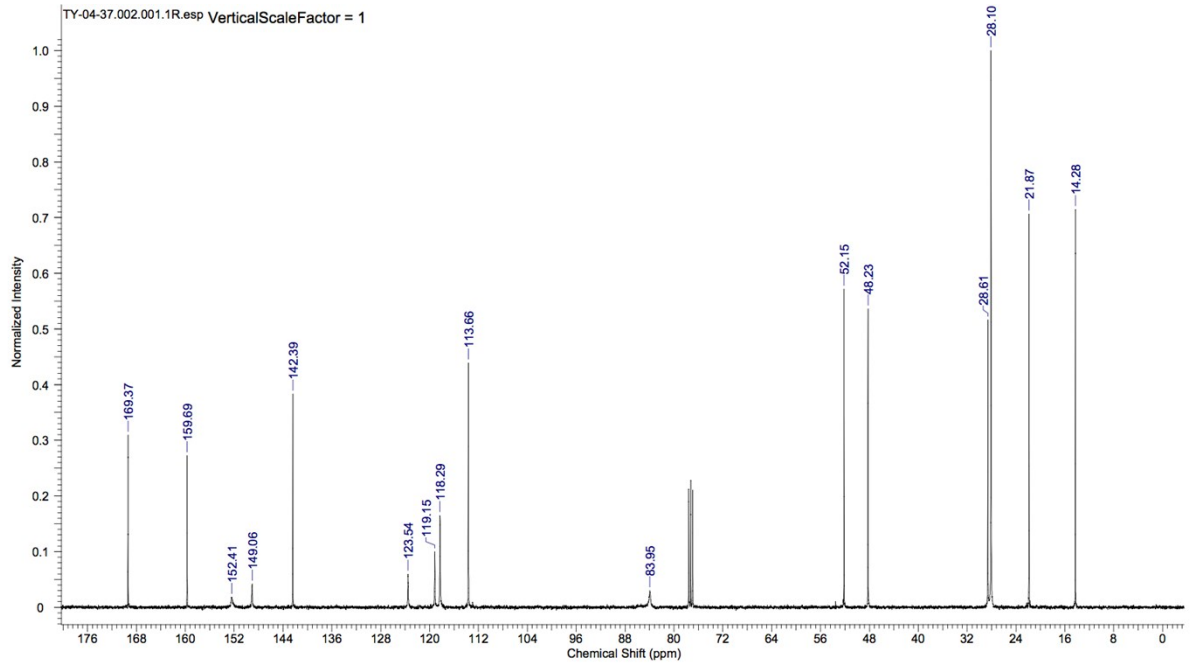


Methyl 2-((5-amino-4-propylbenzo[d]thiazol-2-yl)(*tert*-butoxycarbonyl)amino)acetate (12)

^{1}H, 400 MHz, $CDCl_3$

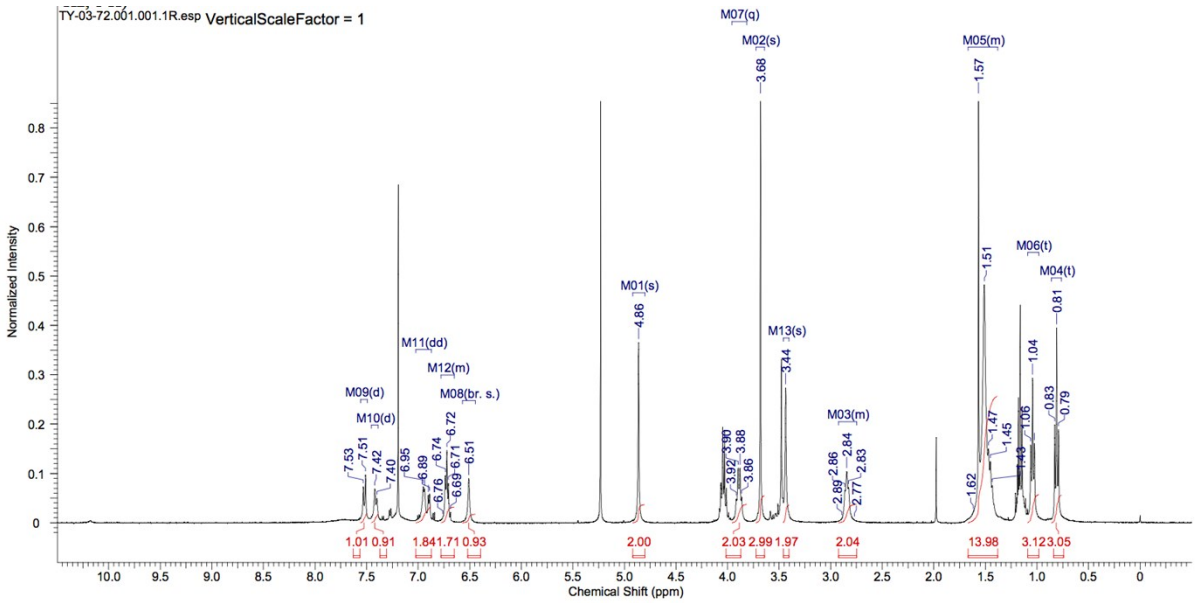


^{13}C, 101 MHz, $CDCl_3$

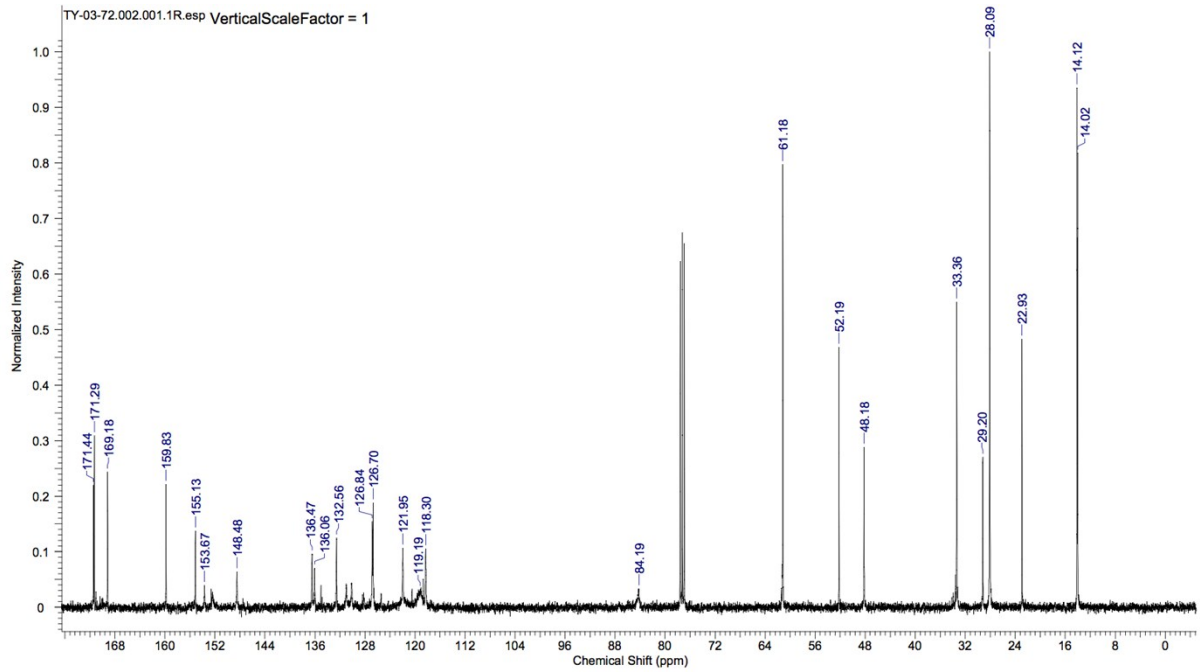


Ethyl 2-(2-(3-(2-((*tert*-butoxycarbonyl)(2-methoxy-2-oxoethyl)amino)-4-propylbenzo[d]thiazol-5-yl)ureido)thiophen-3-yl)acetate (33)

^{1}H, 400 MHz, $CDCl_3$

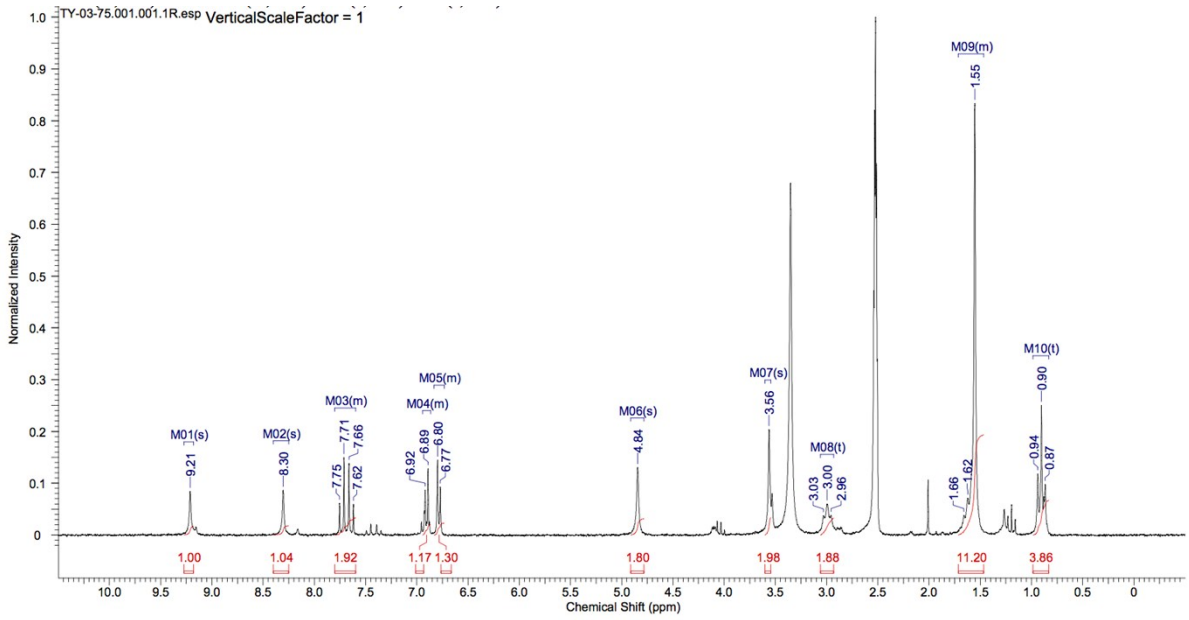


^{13}C, 101 MHz, $CDCl_3$

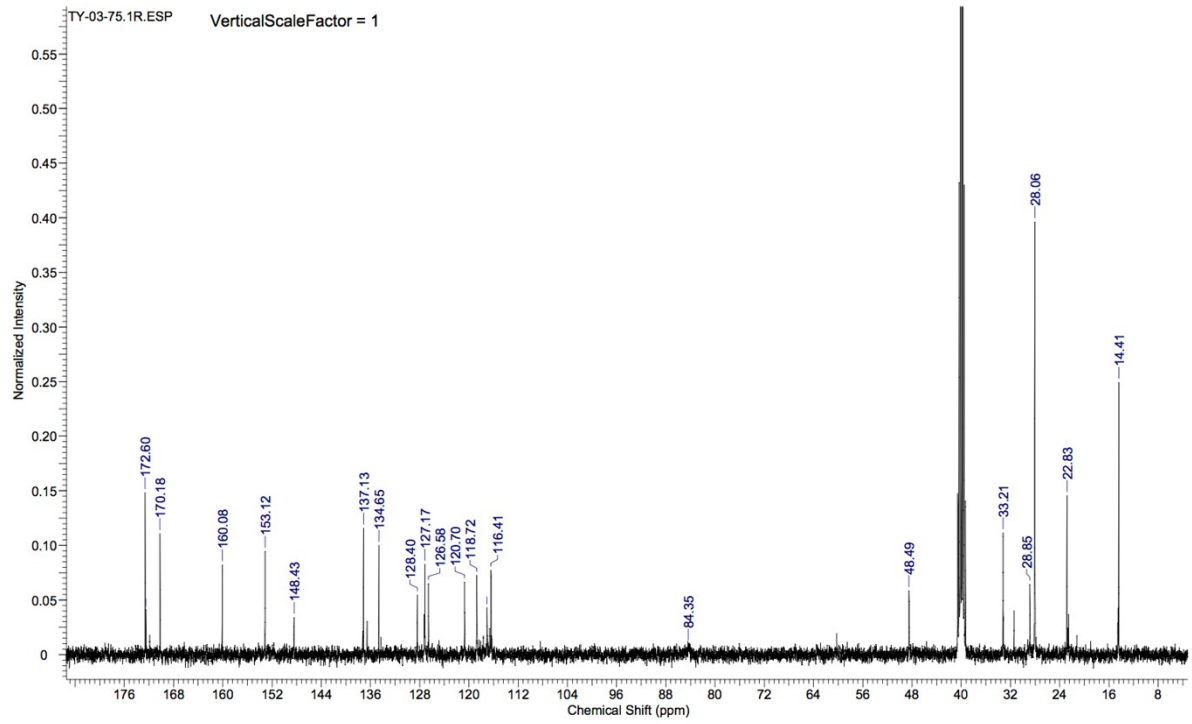


2-((*tert*-Butoxycarbonyl)(5-(3-(3-(carboxymethyl)thiophen-2-yl)ureido)-4-propylbenzo[d]thiazol-2-yl)amino)acetic acid (20)

^{1}H, 400 MHz, d_6-DMSO

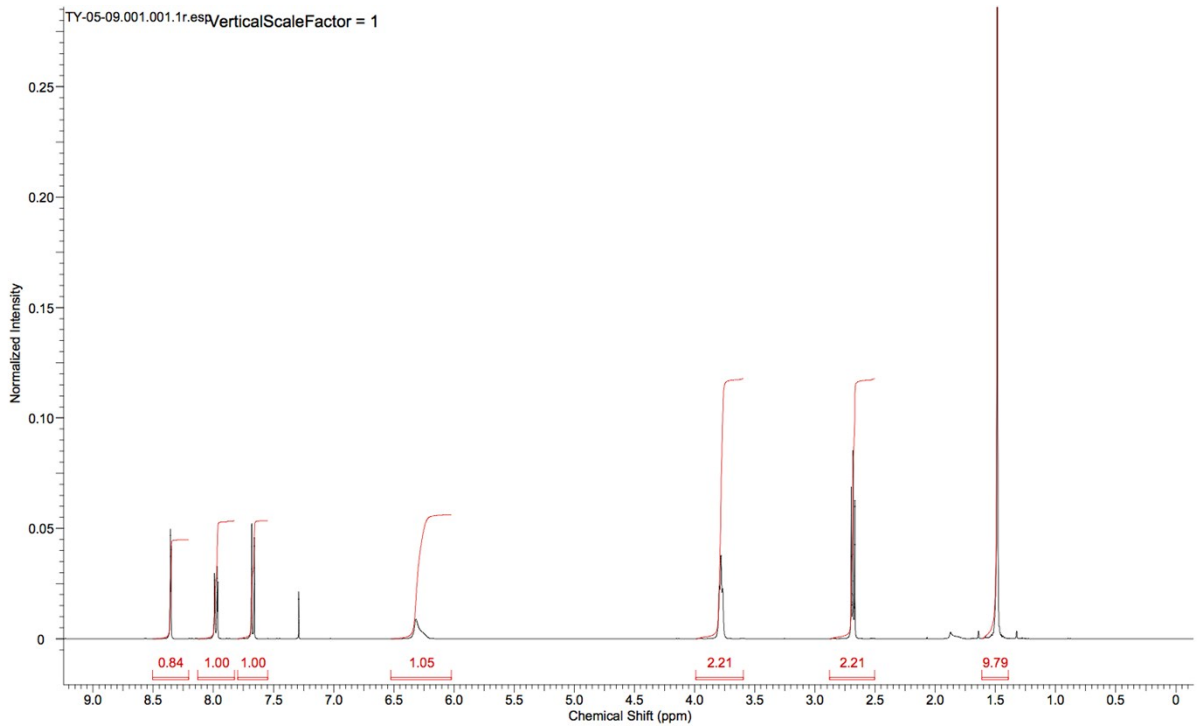


^{13}C, 101 MHz, d_6-DMSO

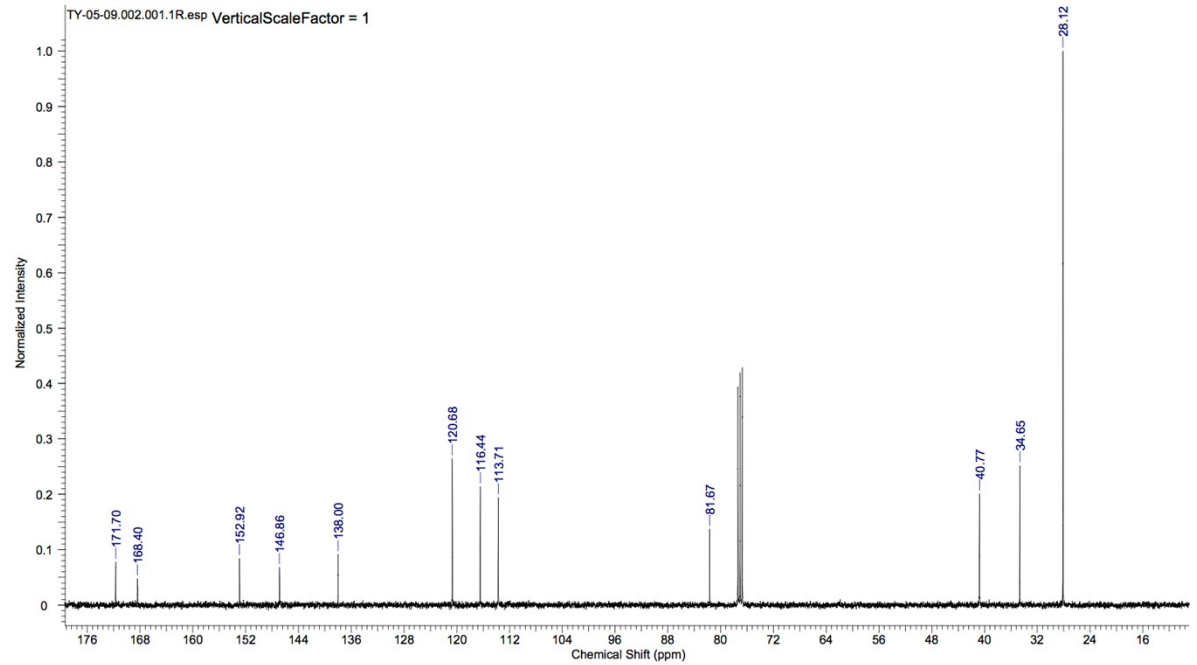


tert-Butyl 3-((5-nitrobenzo[d]thiazol-2-yl)amino)propanoate (3)

^{1}H, 400 MHz, $CDCl_3$

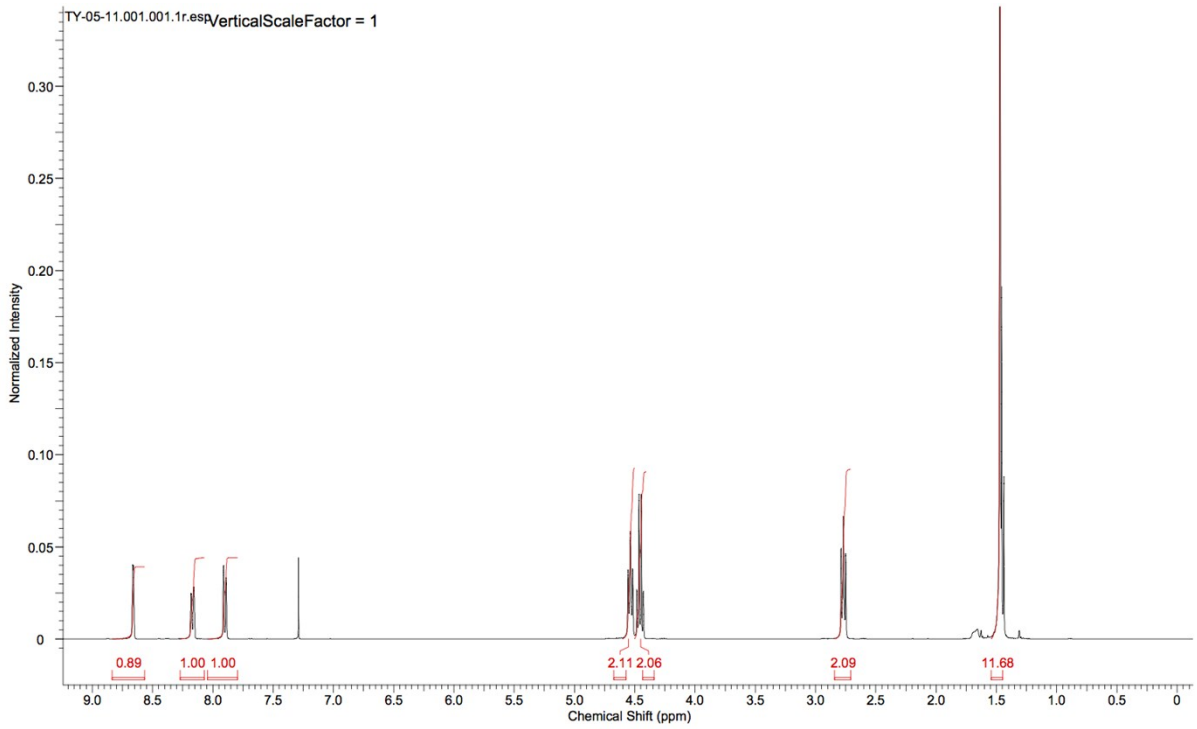


^{13}C, 101 MHz, $CDCl_3$

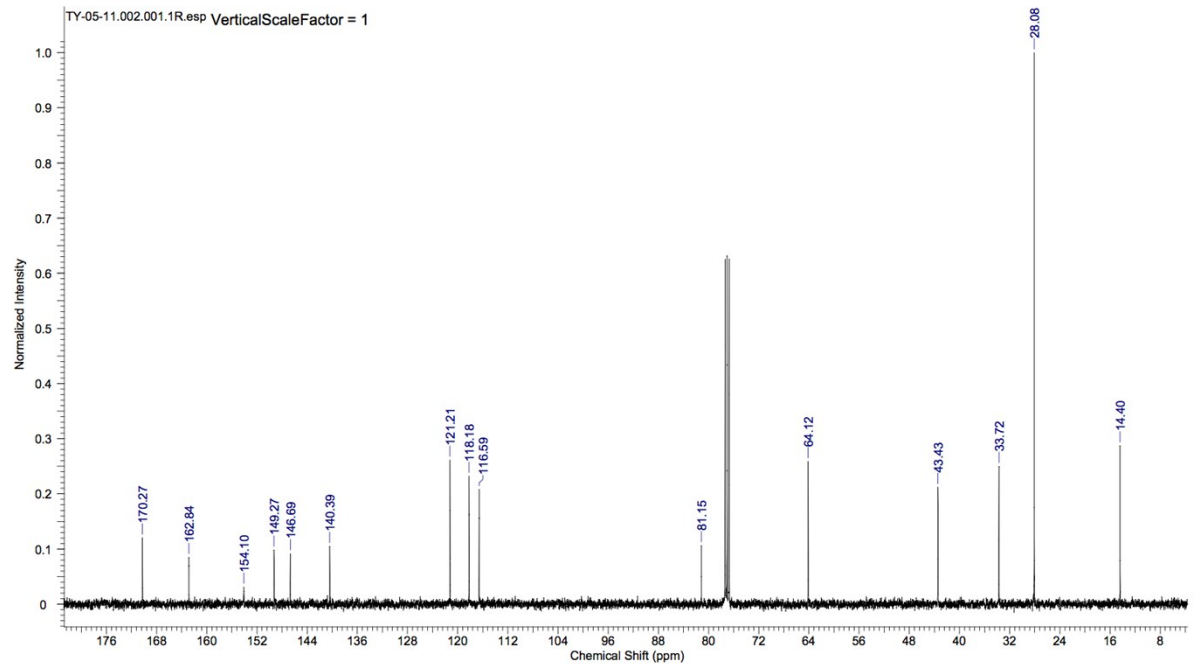


tert-Butyl 3-((ethoxycarbonyl)(5-nitrobenzo[d]thiazol-2-yl)amino)propanoate (6)

^{1}H, 400 MHz, $CDCl_3$

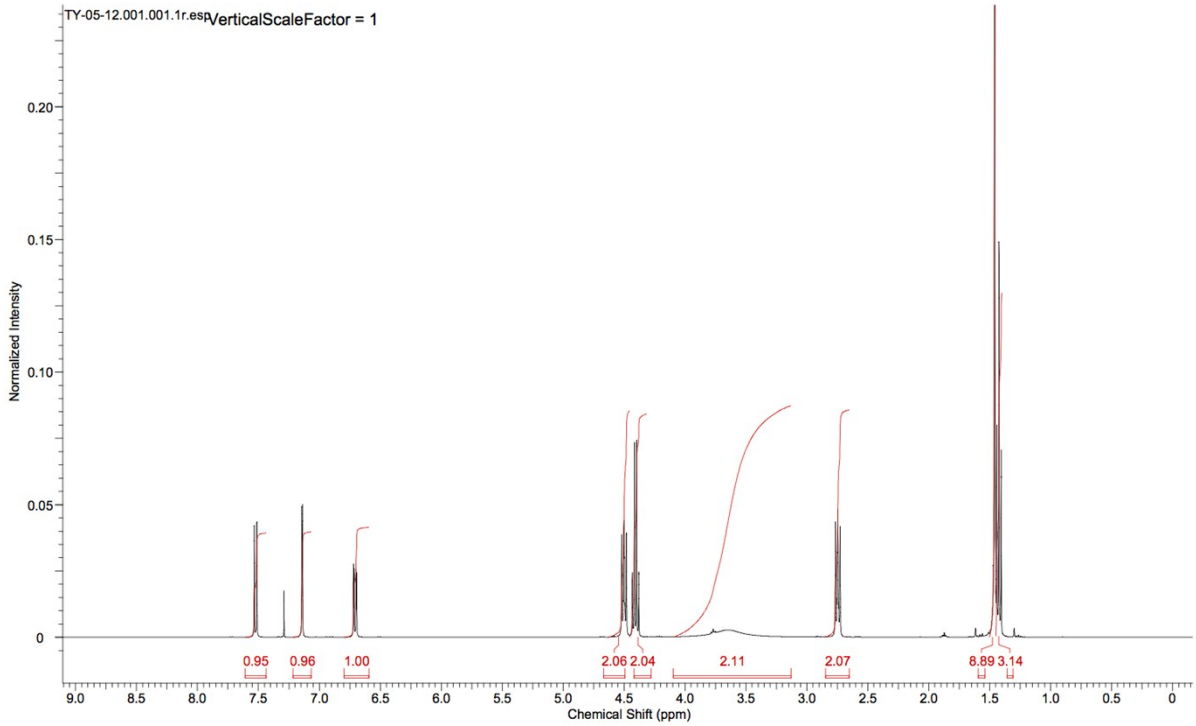


^{13}C, 101 MHz, $CDCl_3$

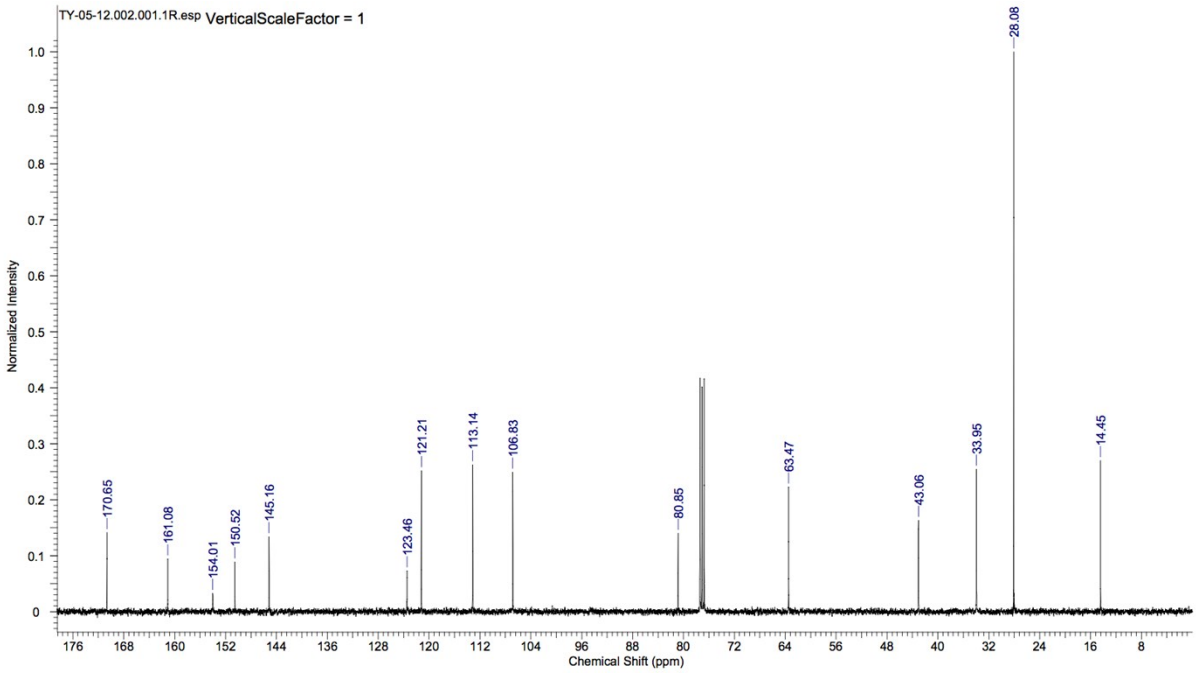


tert-Butyl 3-((5-aminobenzo[d]thiazol-2-yl)(ethoxycarbonyl)amino)propanoate (34)

^{1}H, 400 MHz, $CDCl_3$

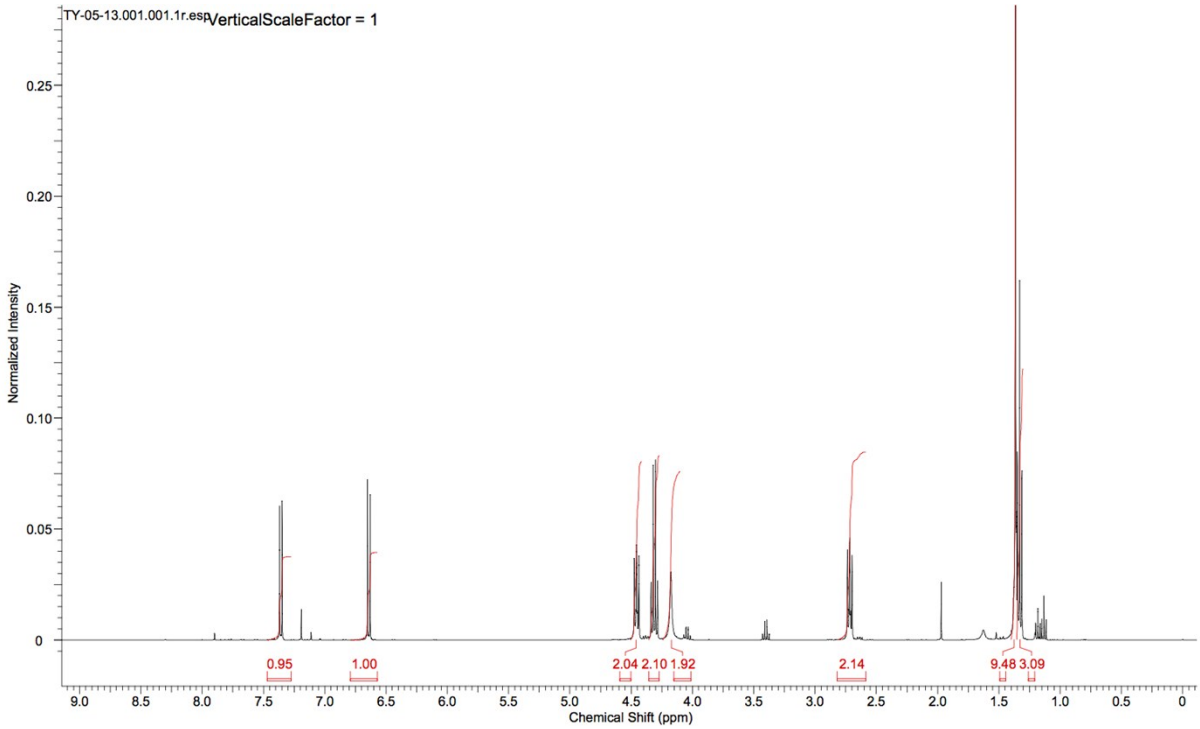


^{13}C, 101 MHz, $CDCl_3$

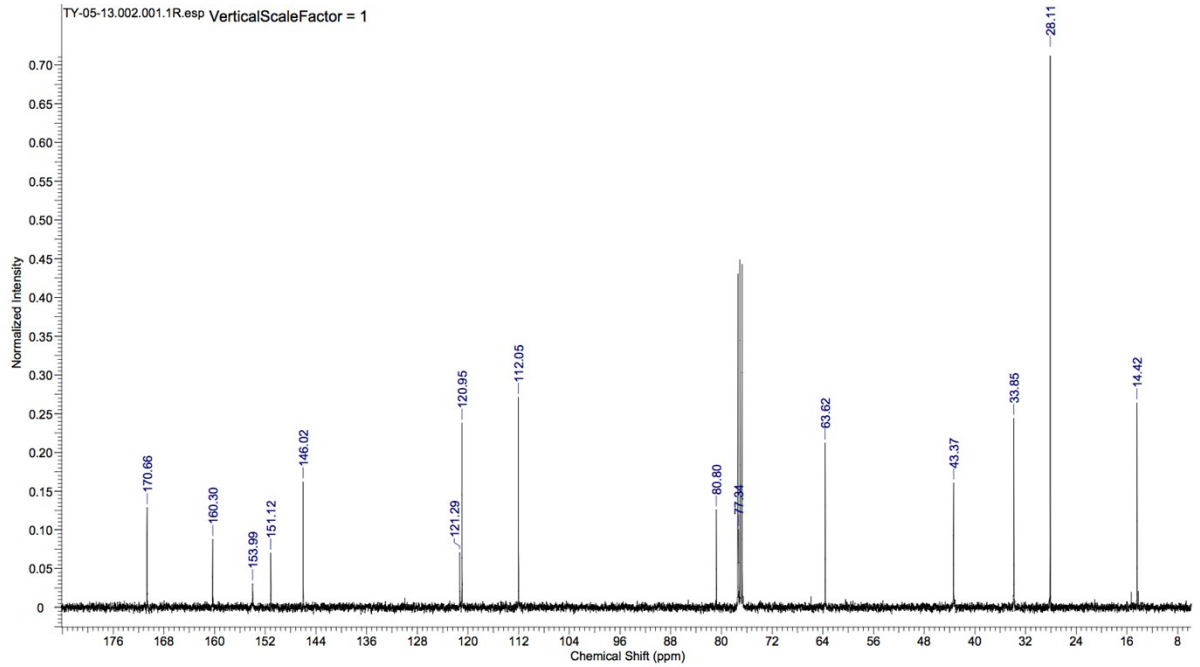


tert-Butyl 3-((5-amino-4-iodobenzo[d]thiazol-2-yl)(ethoxycarbonyl)amino)propanoate (9)

^{1}H, 400 MHz, $CDCl_3$

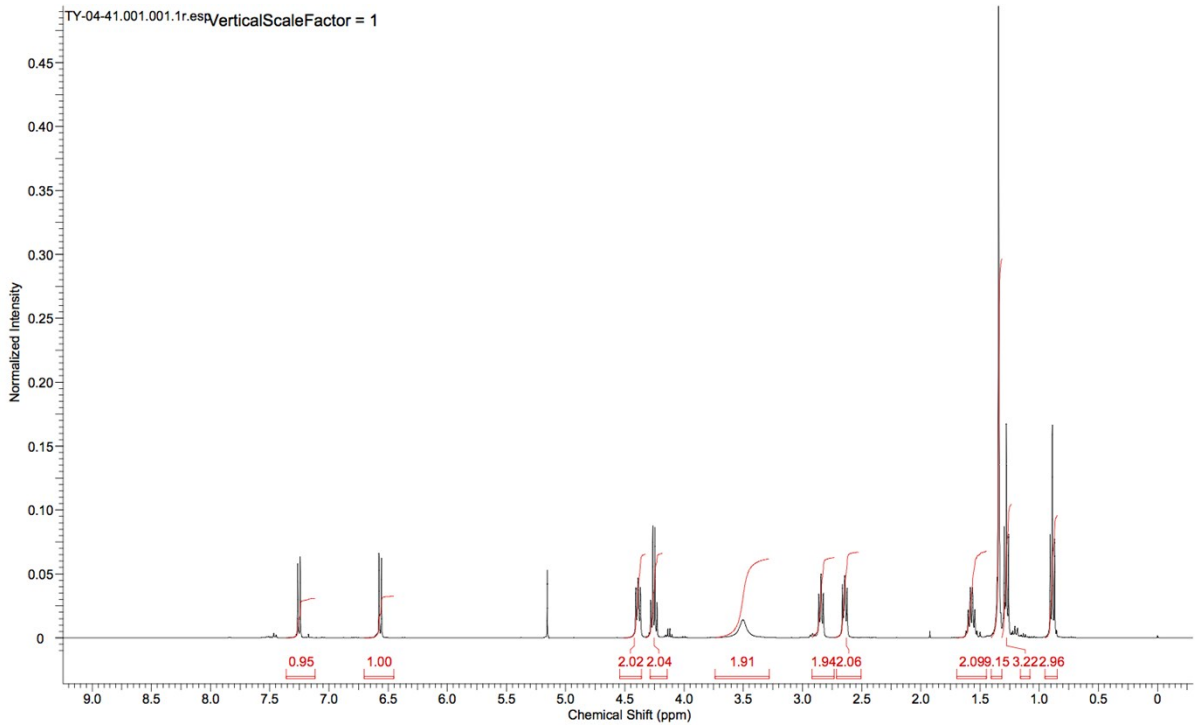


^{13}C, 101 MHz, $CDCl_3$

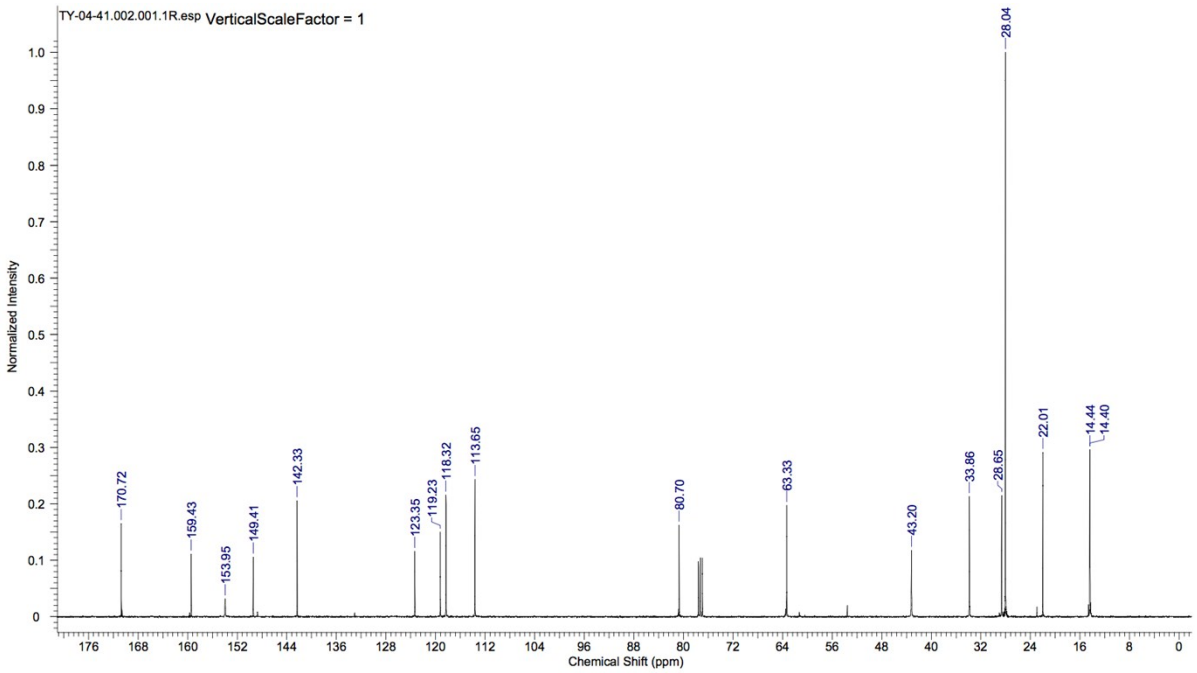


tert-Butyl 3-((5-amino-4-propylbenzo[d]thiazol-2-yl)(ethoxycarbonyl)amino)propanoate (13)

^{1}H, 400 MHz, $CDCl_3$

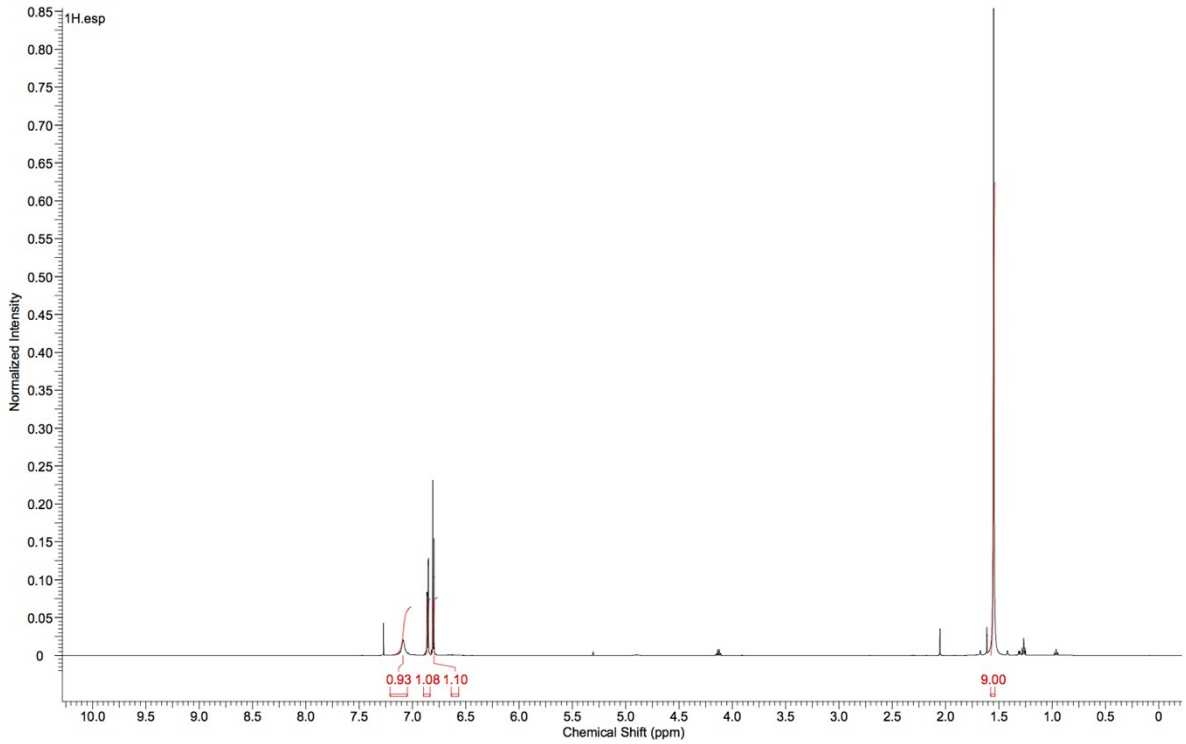


^{13}C, 101 MHz, $CDCl_3$

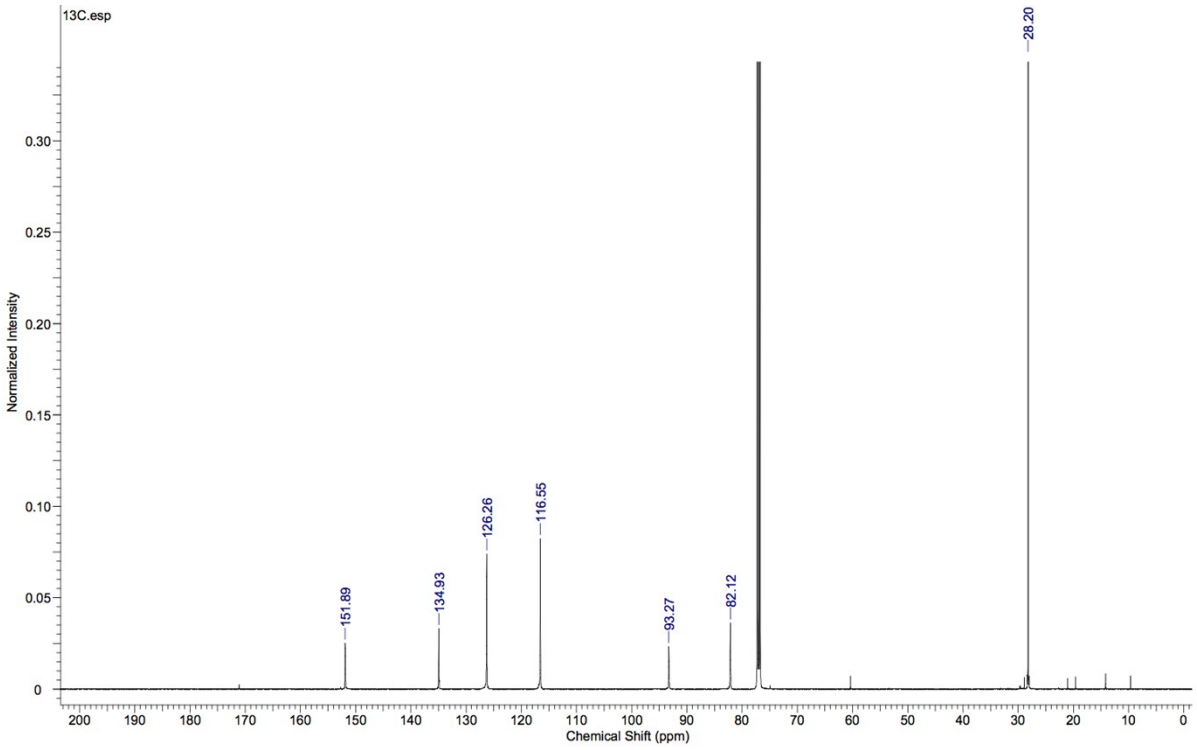


tert-Butyl (3-bromothiophen-2-yl)carbamate (36)

^{1}H, 500 MHz, $CDCl_3$

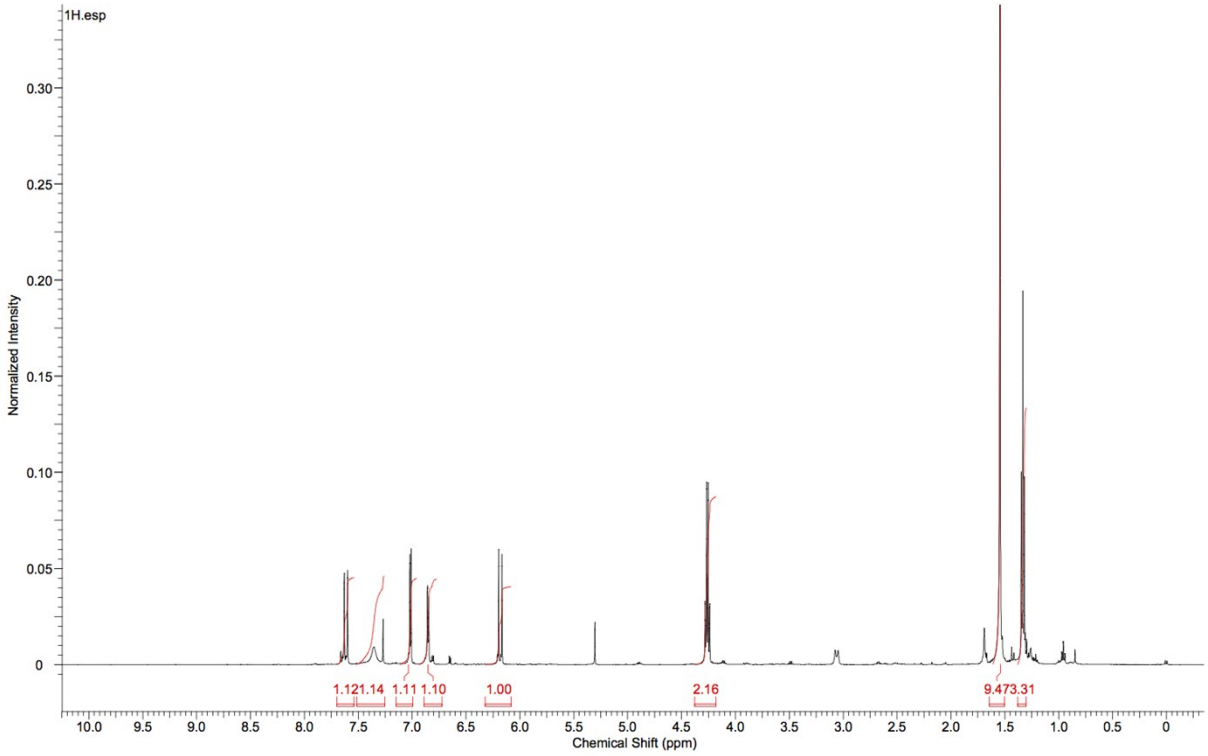


^{13}C, 126 MHz, $CDCl_3$

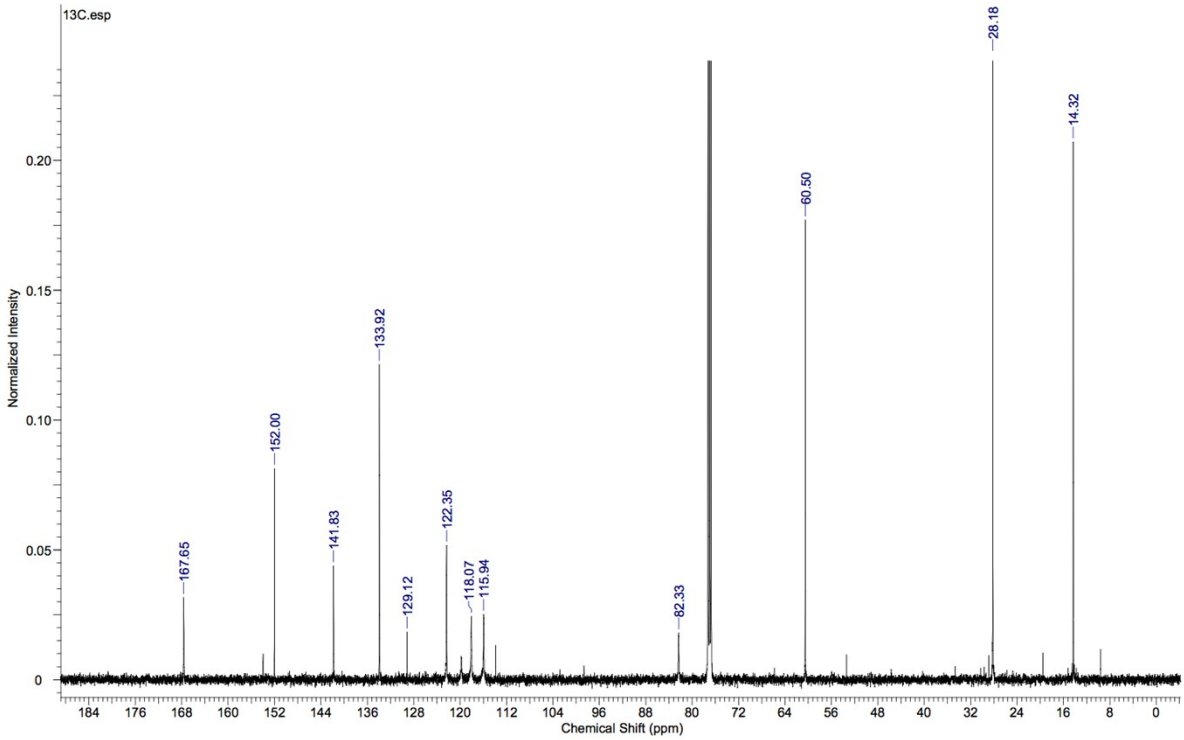


Ethyl (*E*)-3-(2-((*tert*-butoxycarbonyl)amino)thiophen-3-yl)acrylate (37)

^{1}H, 500 MHz, $CDCl_3$

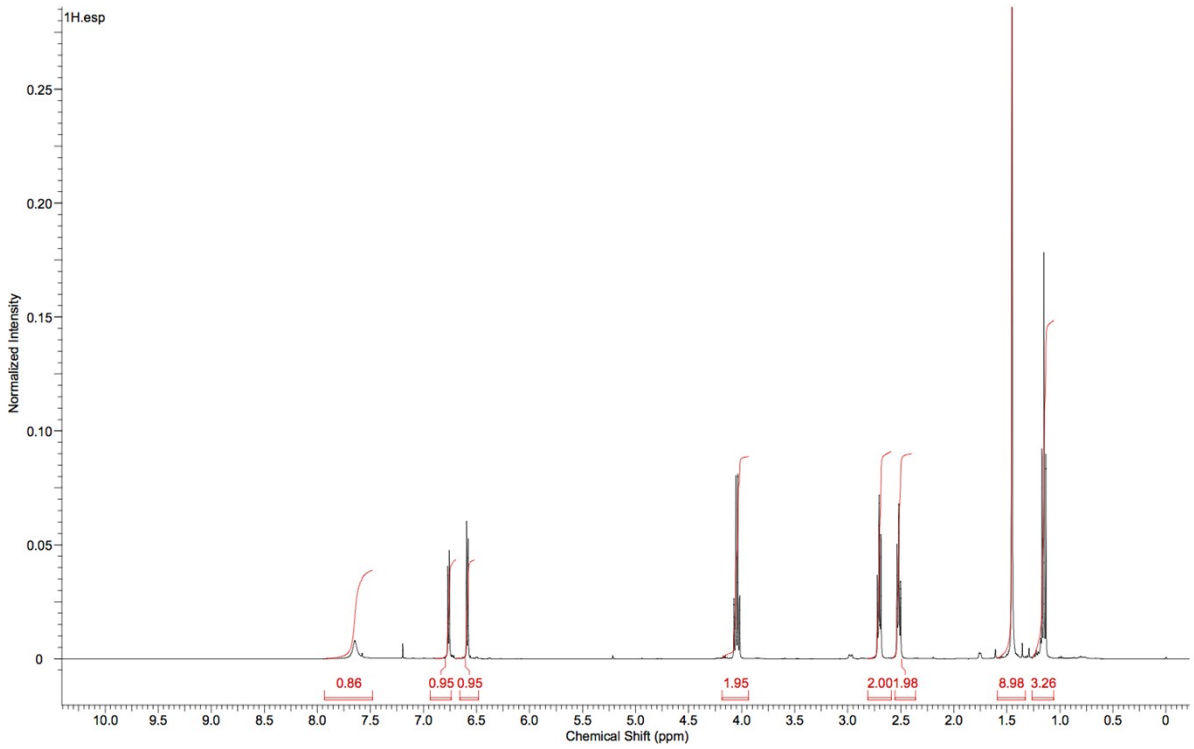


^{13}C, 126 MHz, $CDCl_3$

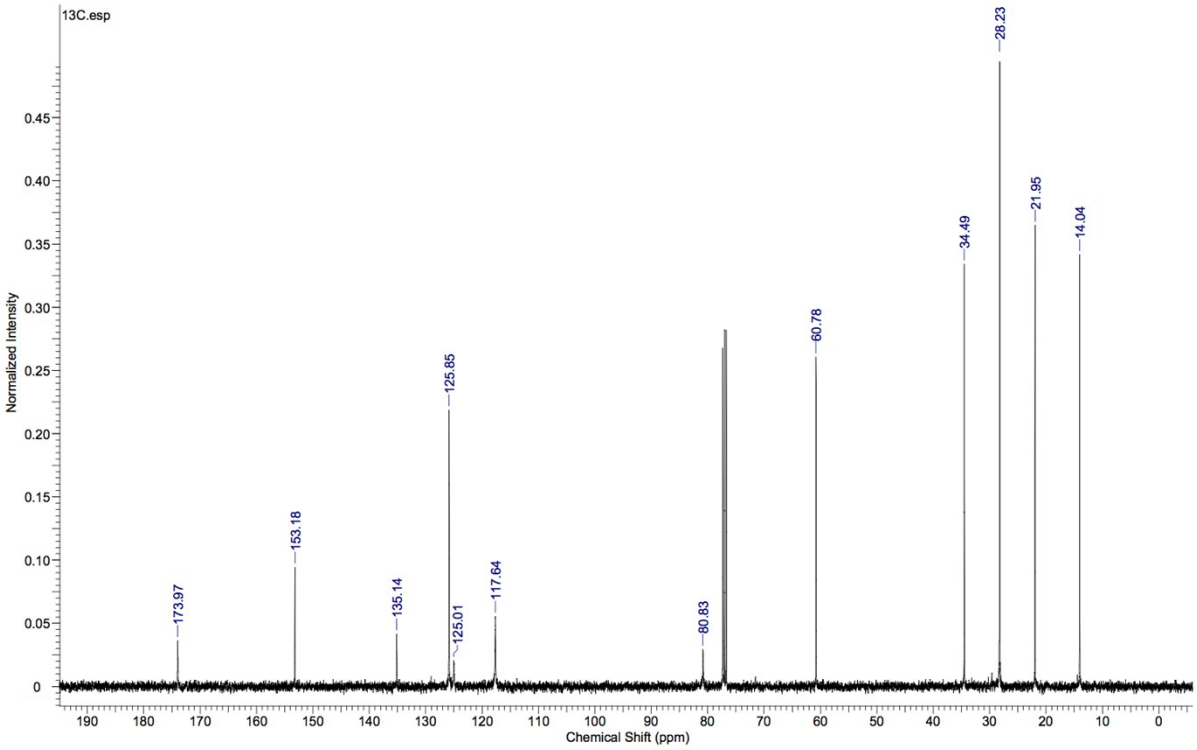


Ethyl 3-(2-((*tert*-butoxycarbonyl)amino)thiophen-3-yl)propanoate (38)

^{1}H, 400 MHz, $CDCl_3$

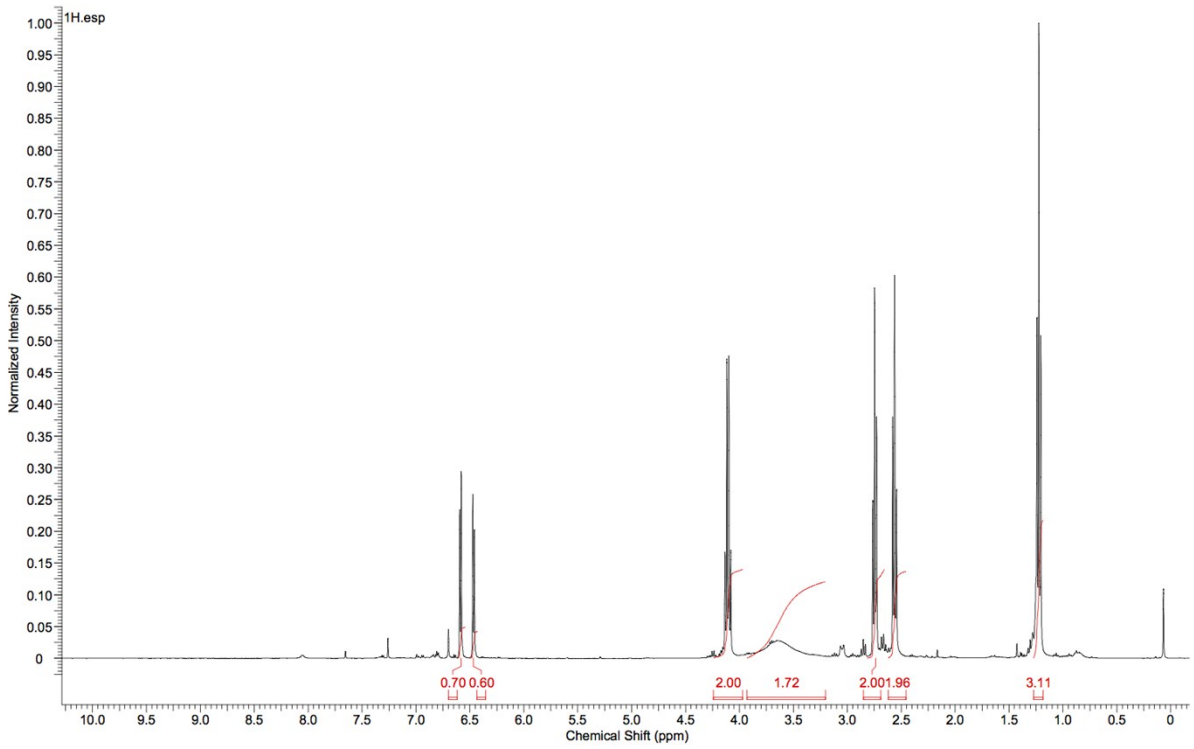


^{13}C, 101 MHz, $CDCl_3$

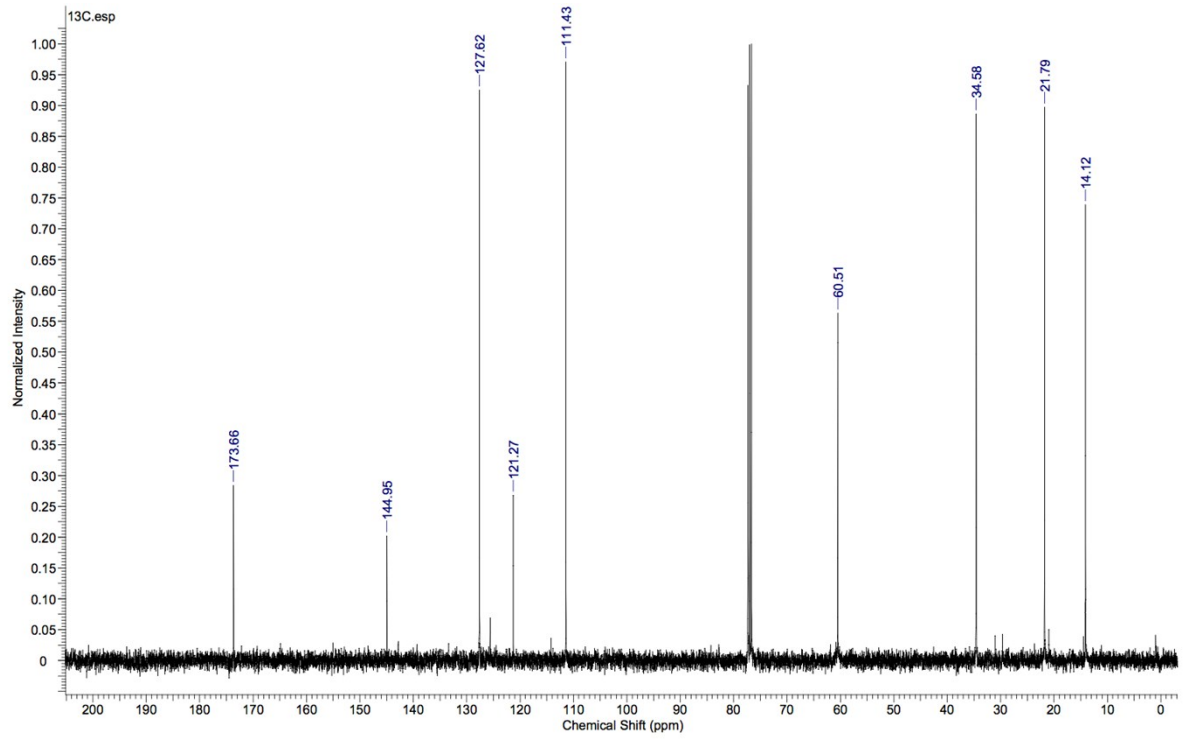


Ethyl 3-(2-aminothiophen-3-yl)propanoate (17)

^{1}H, 400 MHz, $CDCl_3$

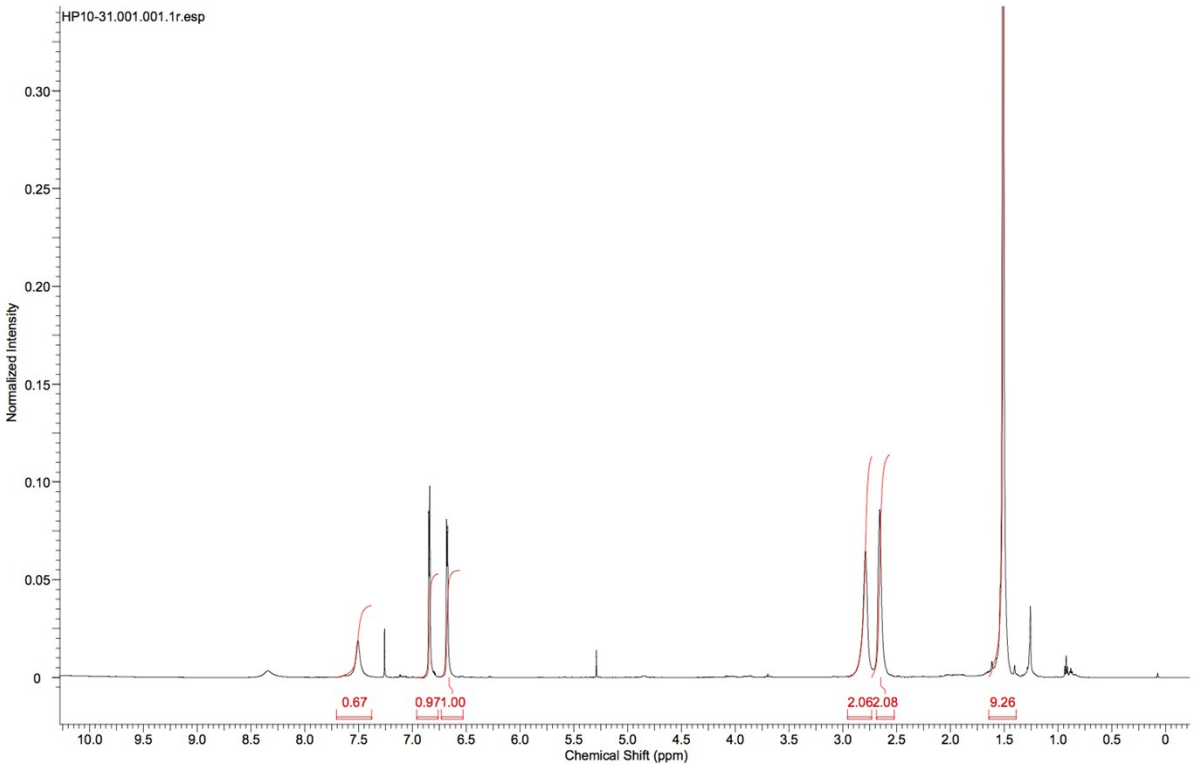


^{13}C, 101 MHz, $CDCl_3$

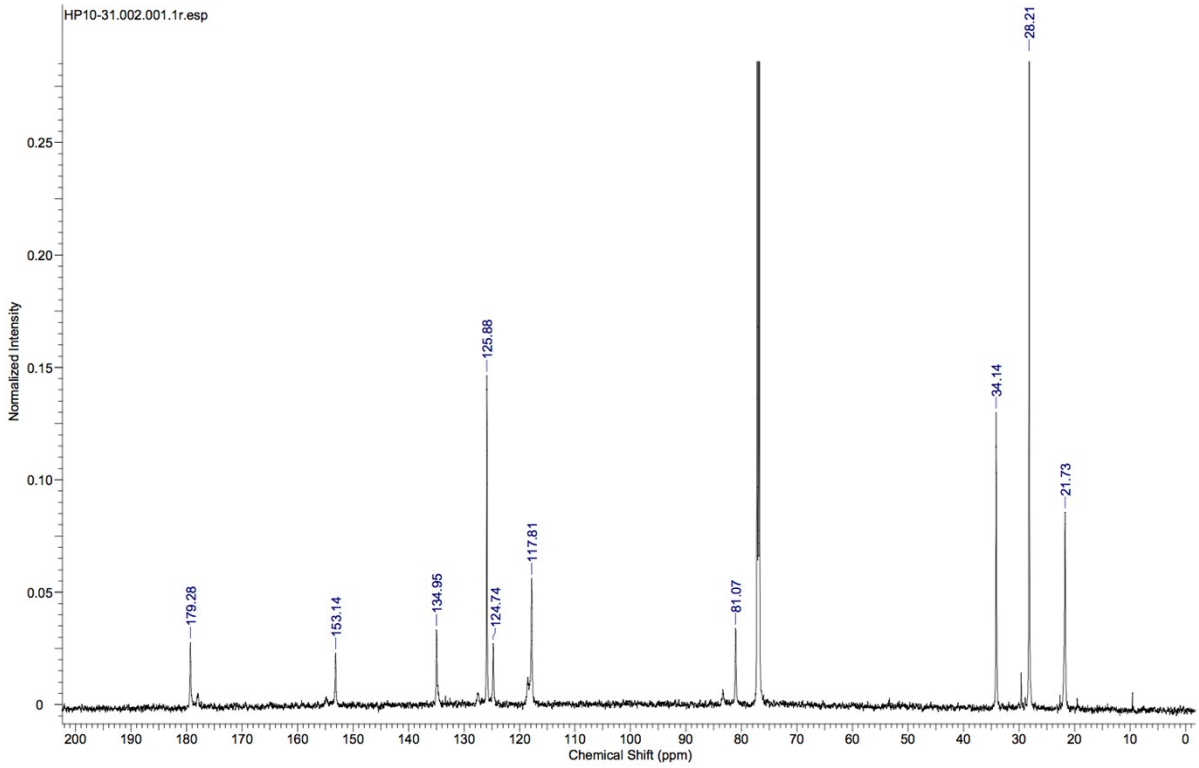


3-(2-((*tert*-Butoxycarbonyl)amino)thiophen-3-yl)propanoic acid (39)

^{1}H, 600 MHz, $CDCl_3$

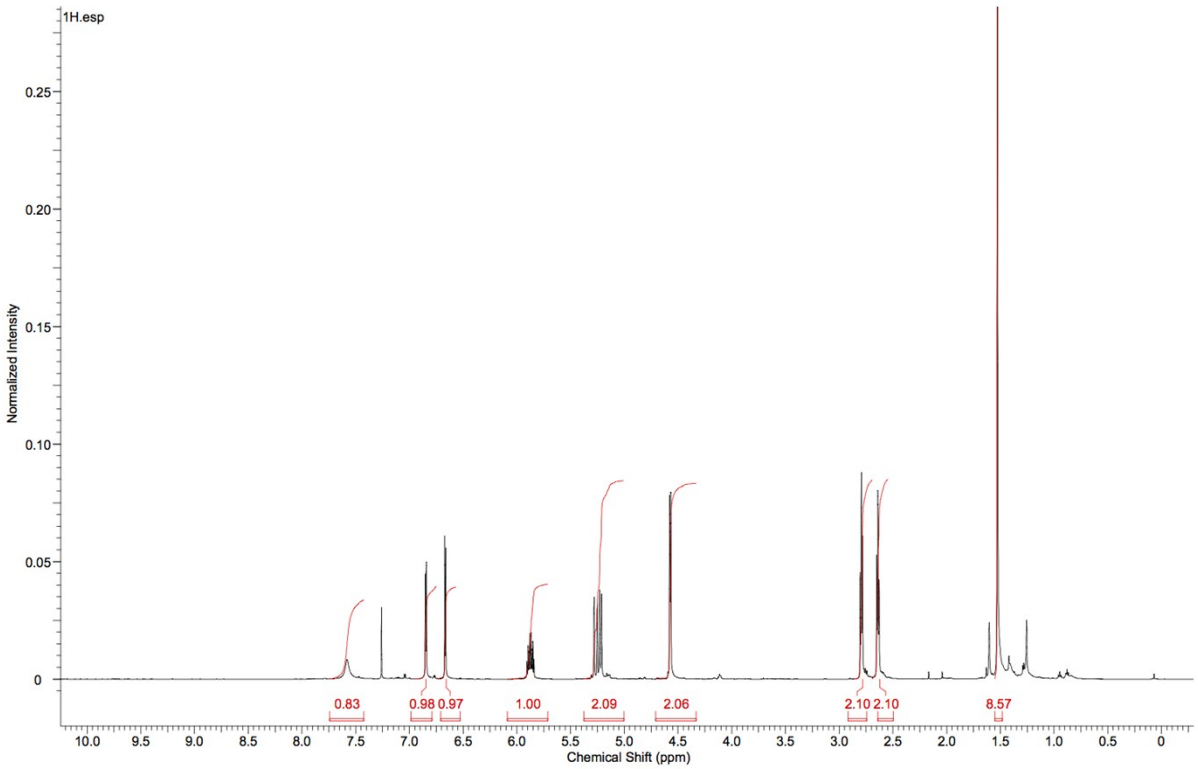


^{13}C, 151 MHz, $CDCl_3$

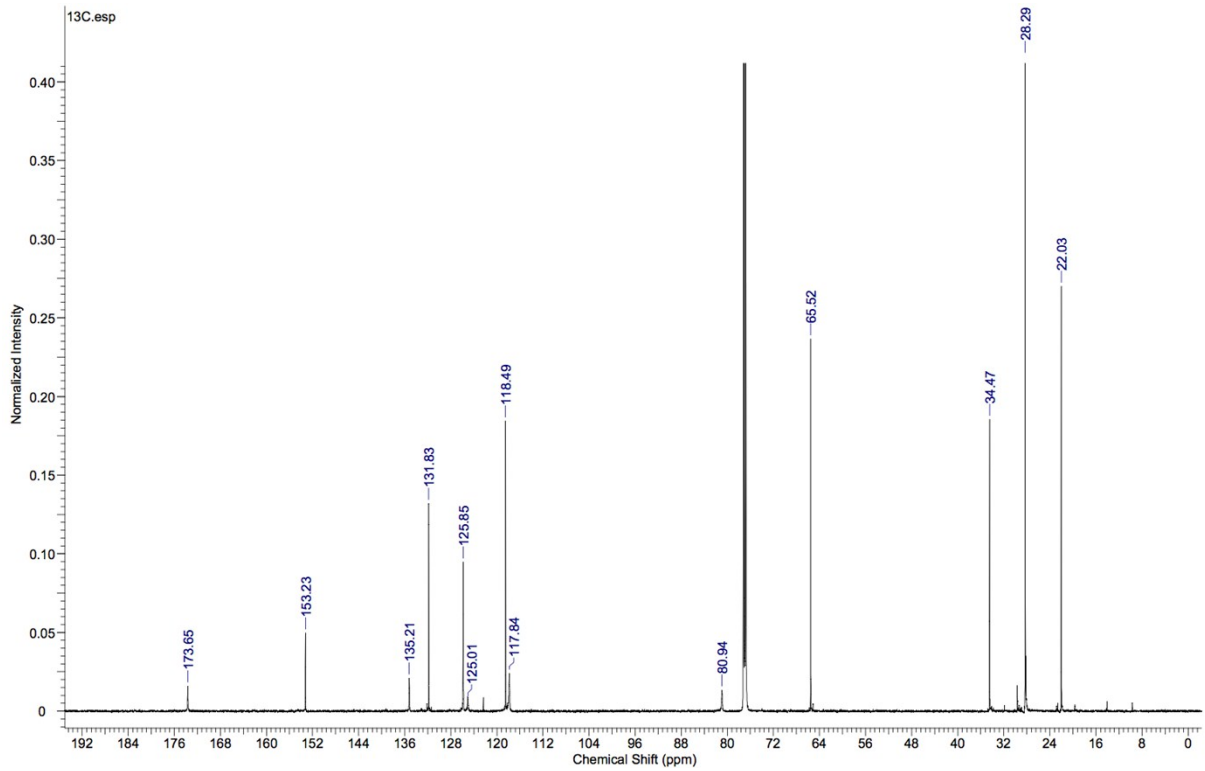


Allyl 3-(2-((*tert*-butoxycarbonyl)amino)thiophen-3-yl)propanoate (40)

^{1}H, 600 MHz, $CDCl_3$

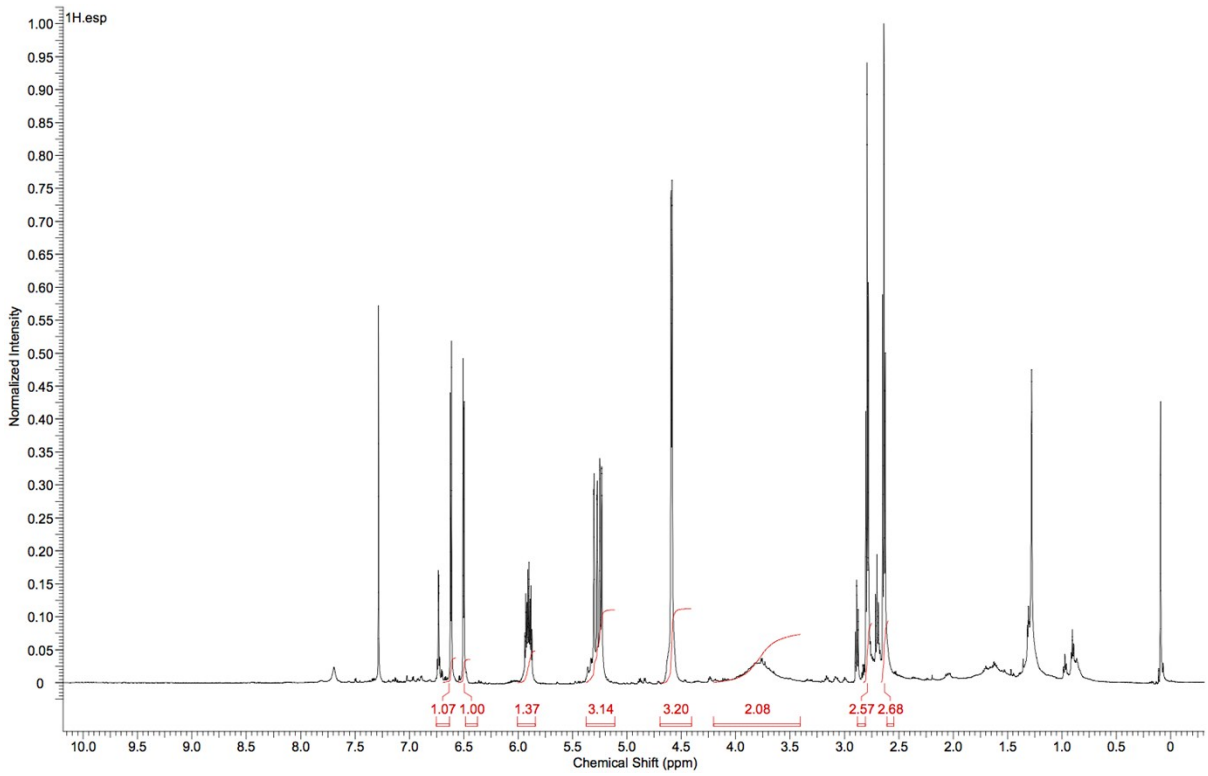


^{13}C, 151 MHz, $CDCl_3$



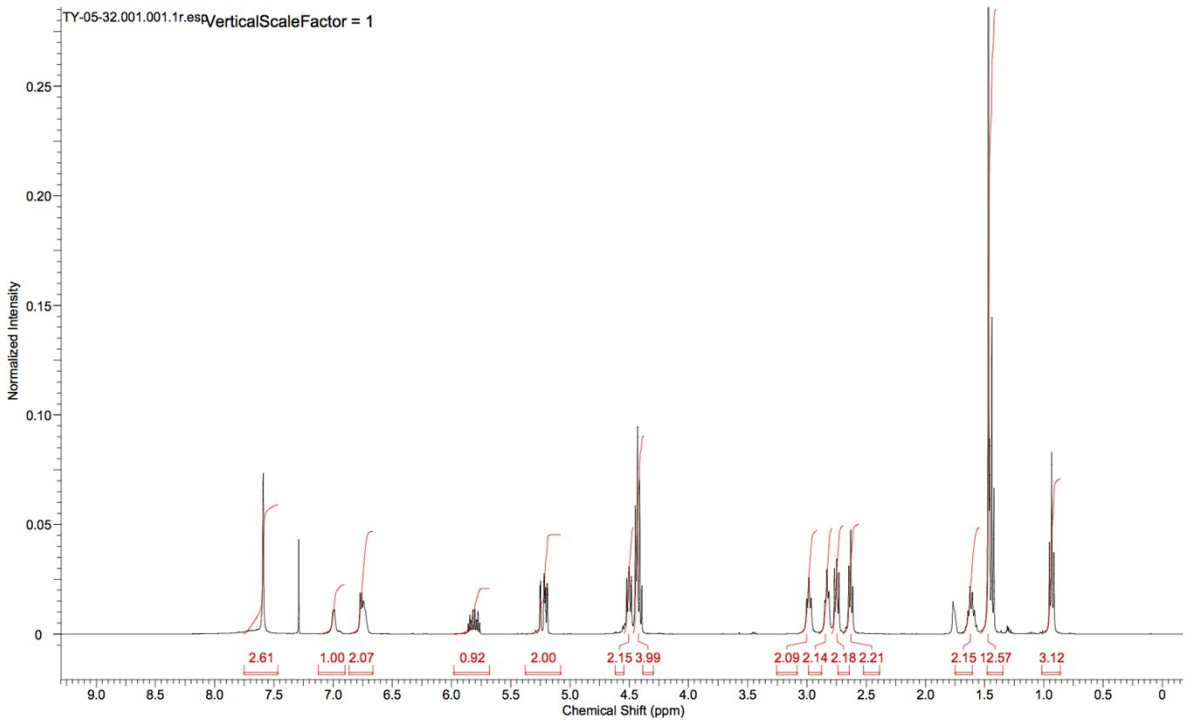
Allyl 3-(2-aminothiophen-3-yl)propanoate (18)

^{1}H, 600 MHz, $CDCl_3$

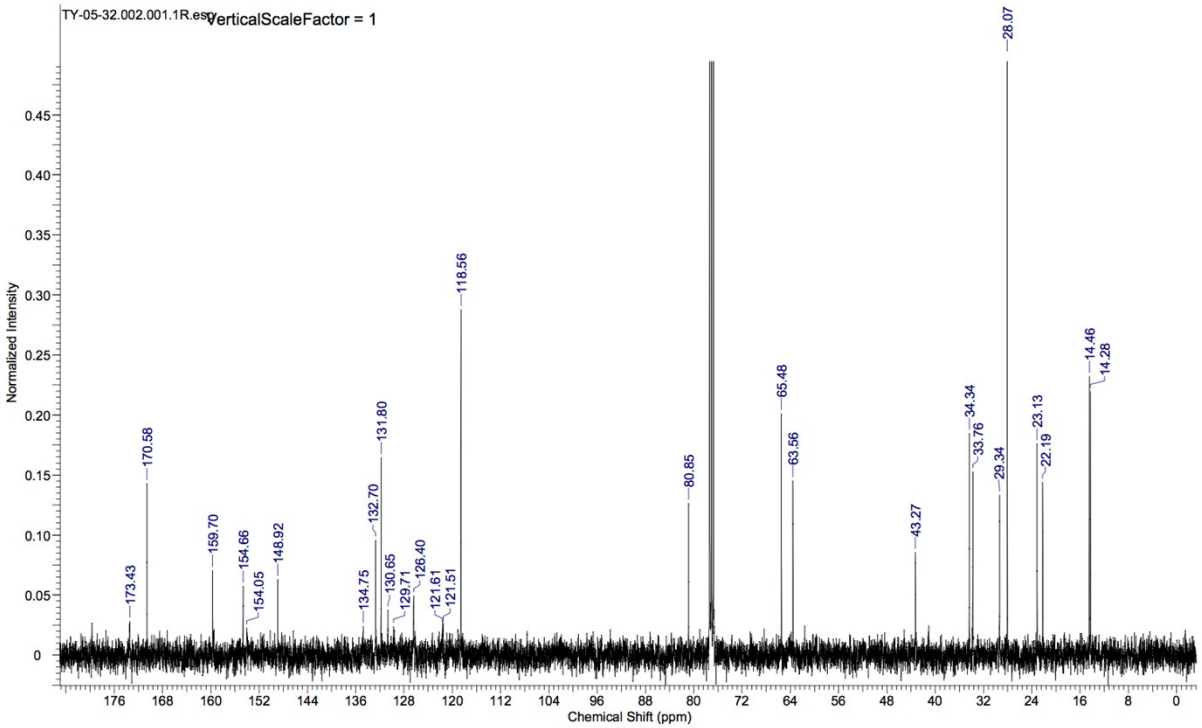


Allyl 3-(2-(3-(2-((3-(*tert*-butoxy)-3-oxopropyl)(ethoxycarbonyl)amino)-4-propylbenzo[d]thiazol-5-yl)ureido)thiophen-3-yl)propanoate (35)

^{1}H, 400 MHz, $CDCl_3$

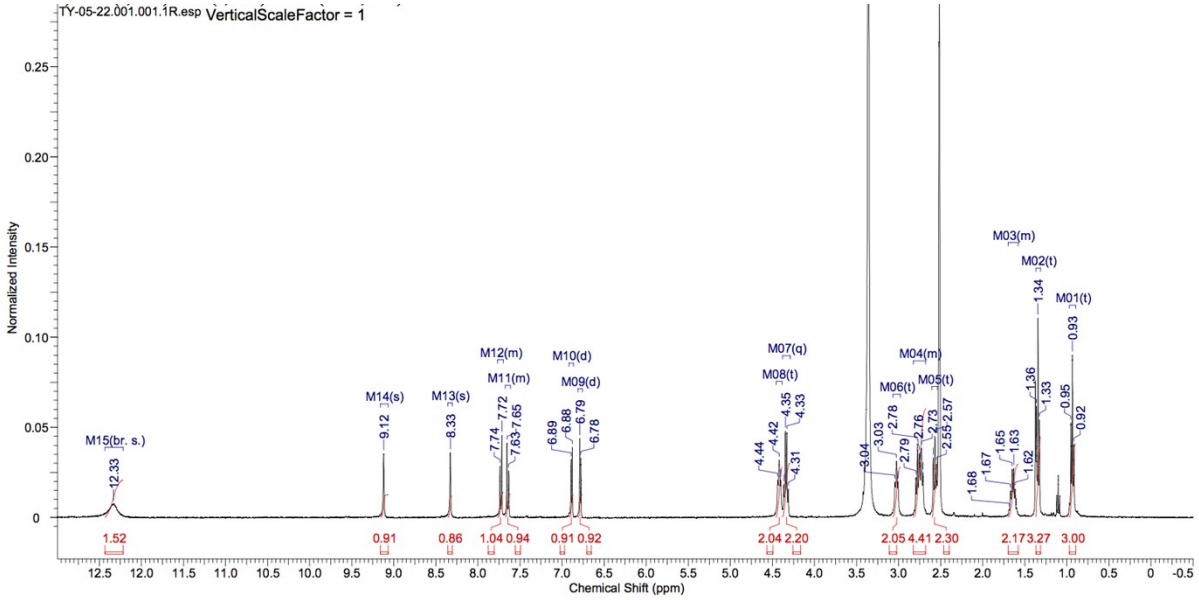


^{13}C, 101 MHz, $CDCl_3$

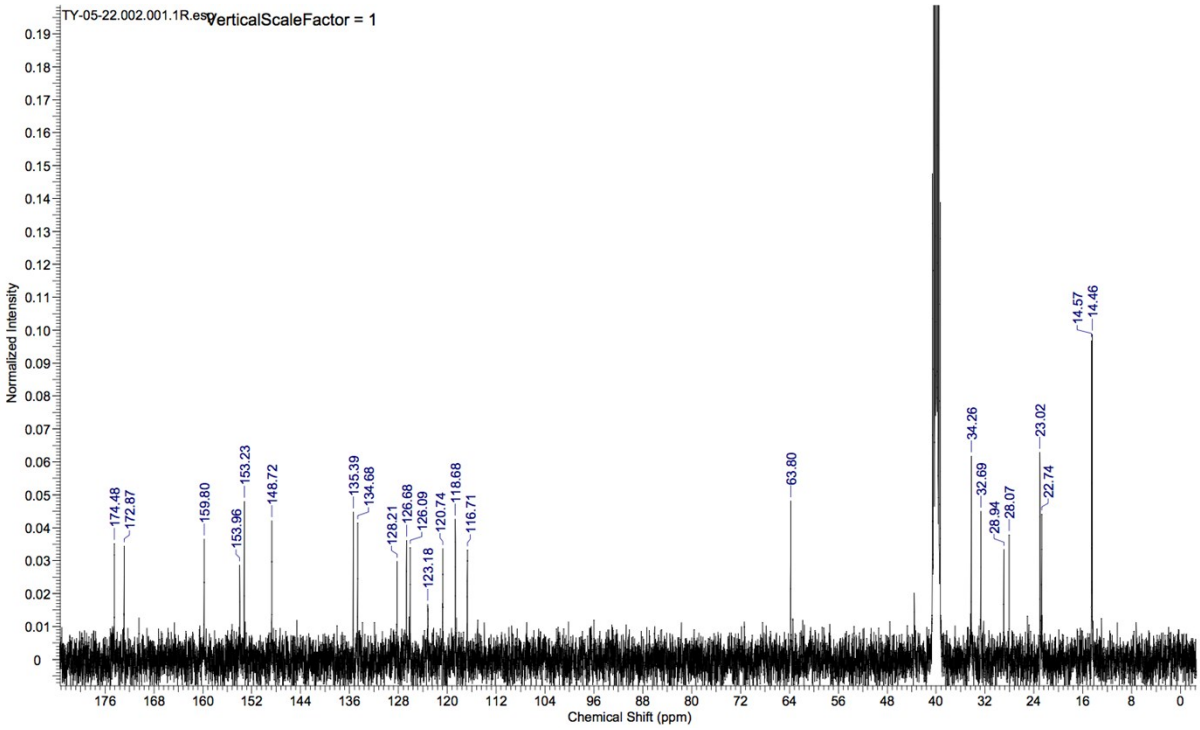


3-(2-(3-(2-((2-Carboxyethyl)(ethoxycarbonyl)amino)-4-propylbenzo[d]thiazol-5-yl)ureido)thiophen-3-yl)propanoic acid (22)

^{1}H, 400 MHz, $CDCl_3$

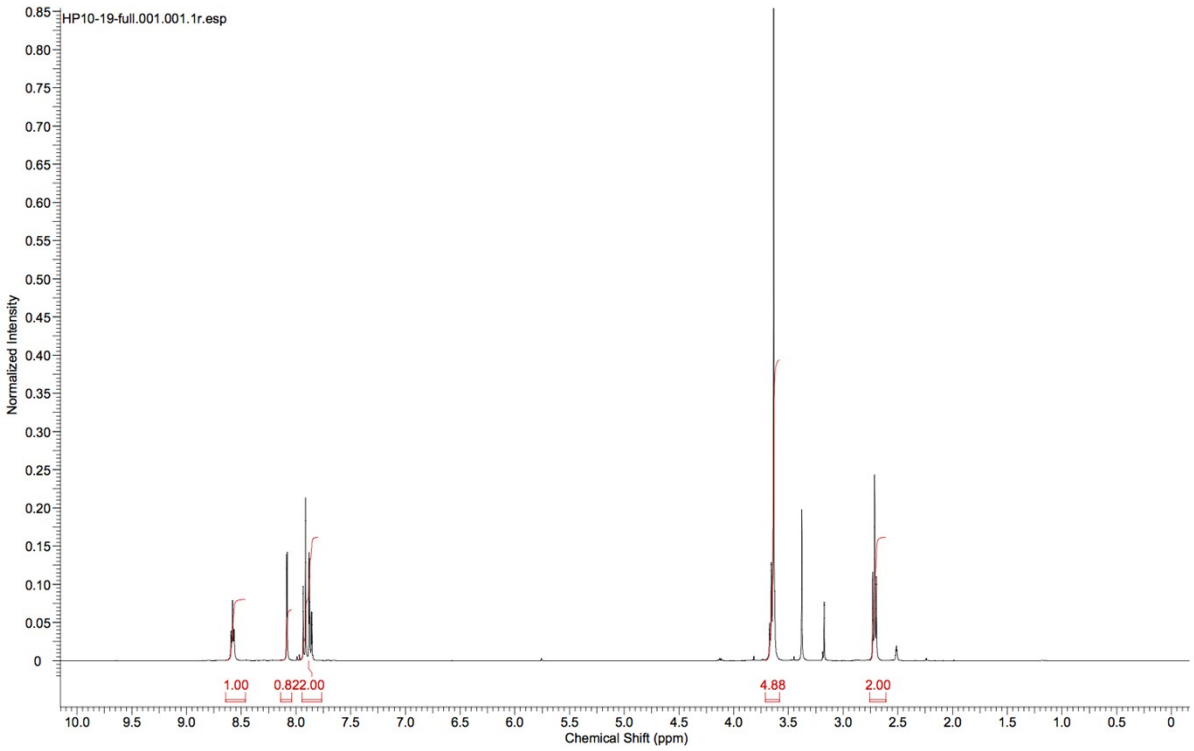


^{13}C, 101 MHz, $CDCl_3$

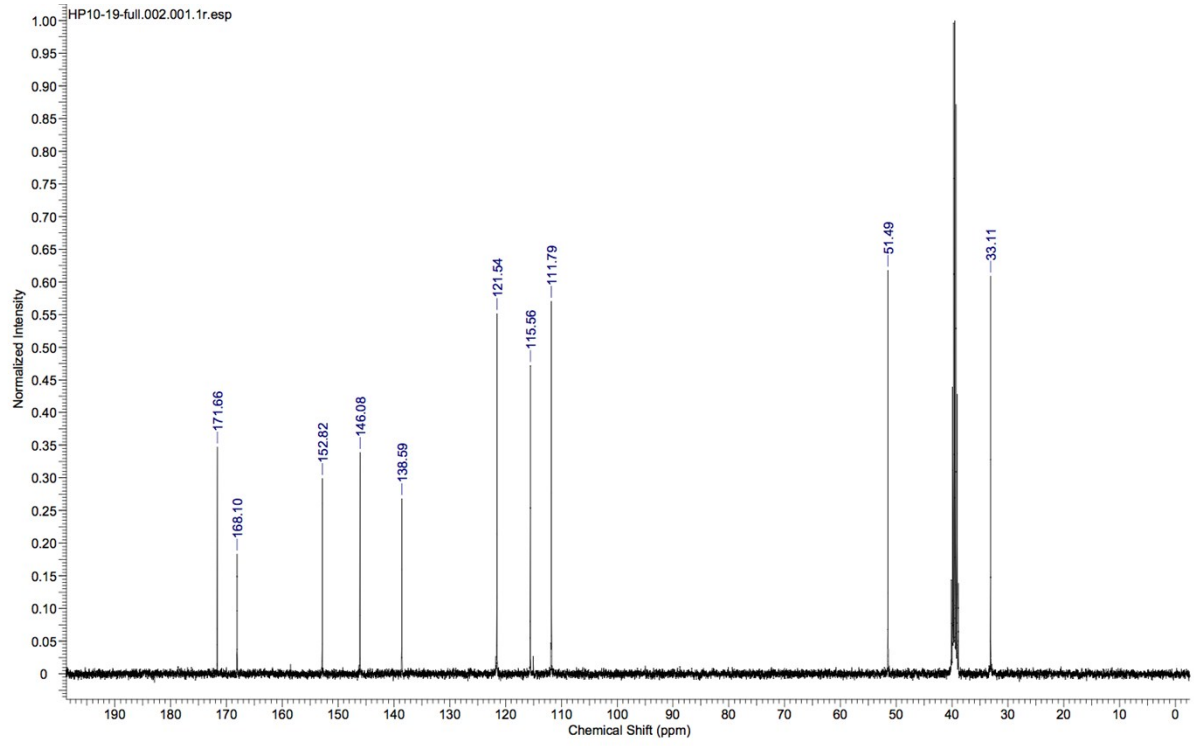


Methyl 3-((5-nitrobenzo[d]thiazol-2-yl)amino)propanoate (4)

^{1}H, 400 MHz, $CDCl_3$

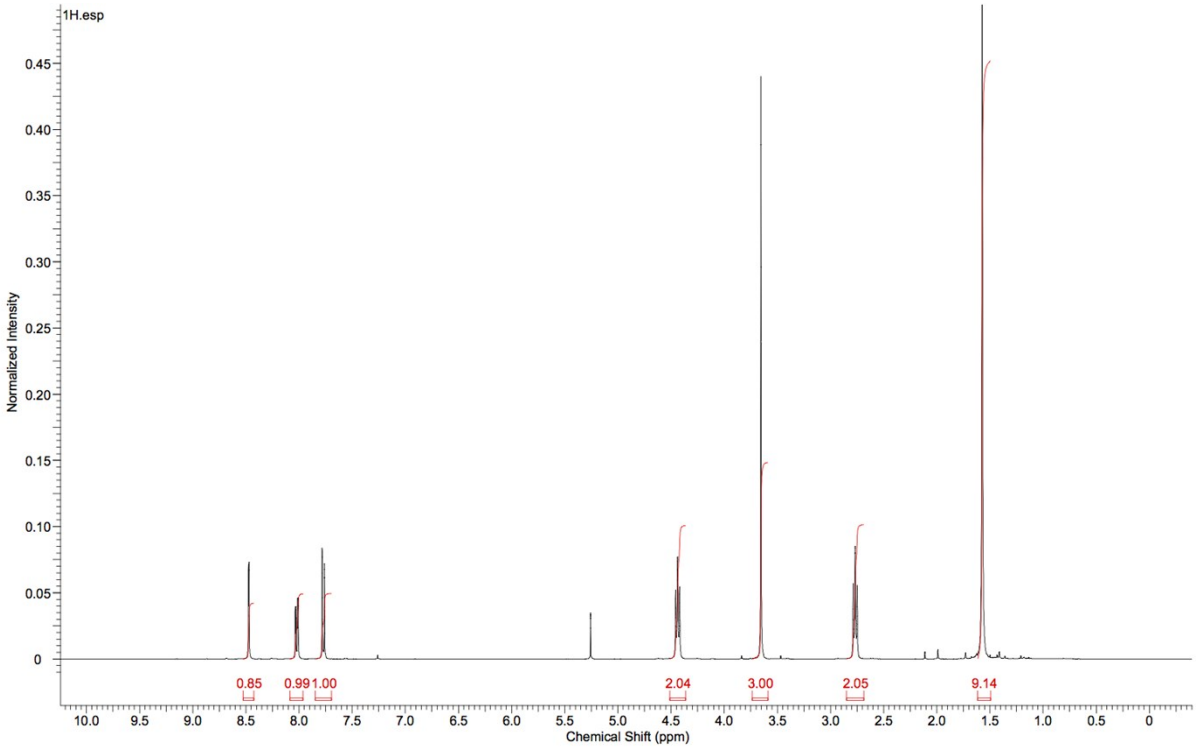


^{13}C, 101 MHz, $CDCl_3$

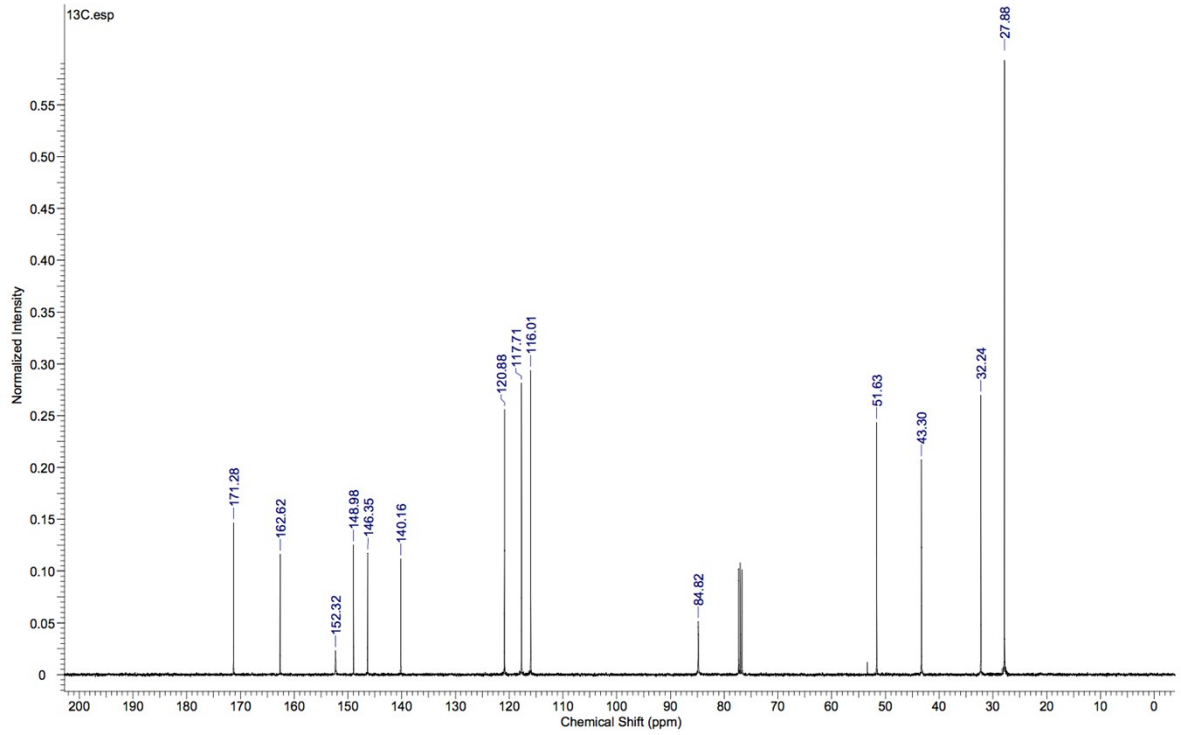


Methyl 3-((tert-butoxycarbonyl)(5-nitrobenzo[d]thiazol-2-yl)amino)propanoate (7)

^{1}H, 400 MHz, $CDCl_3$

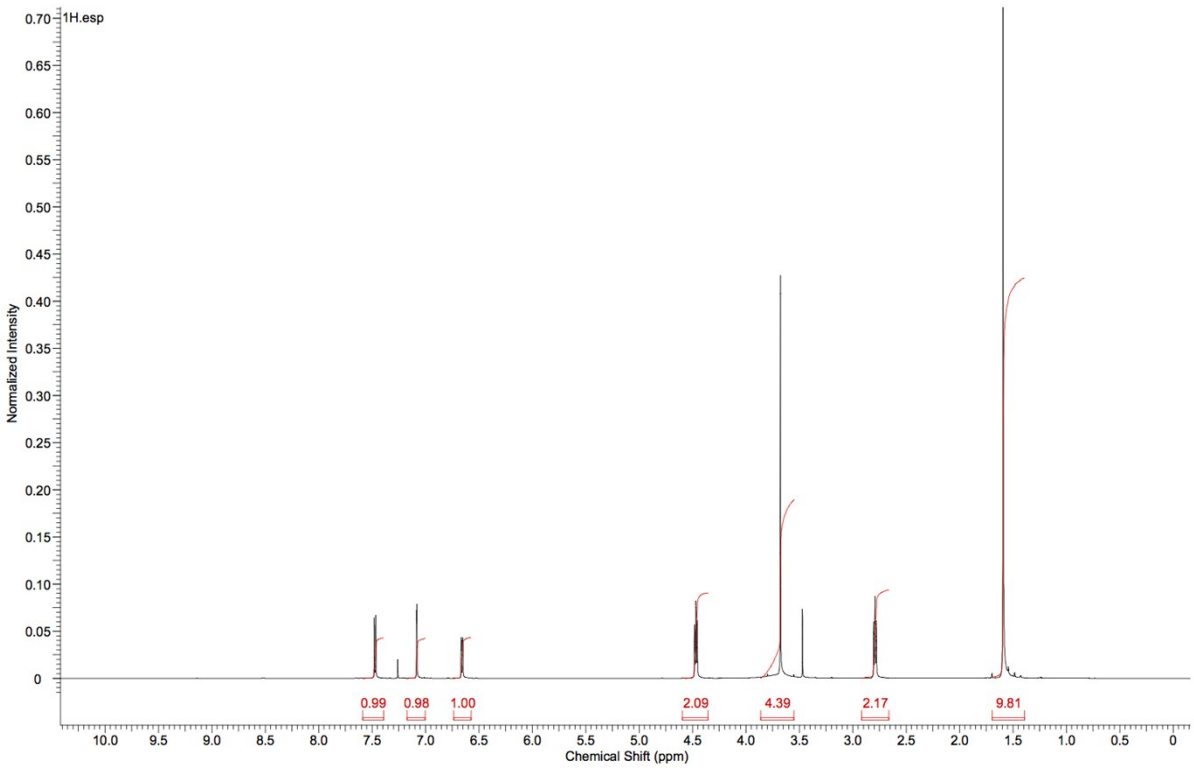


^{13}C, 101 MHz, $CDCl_3$

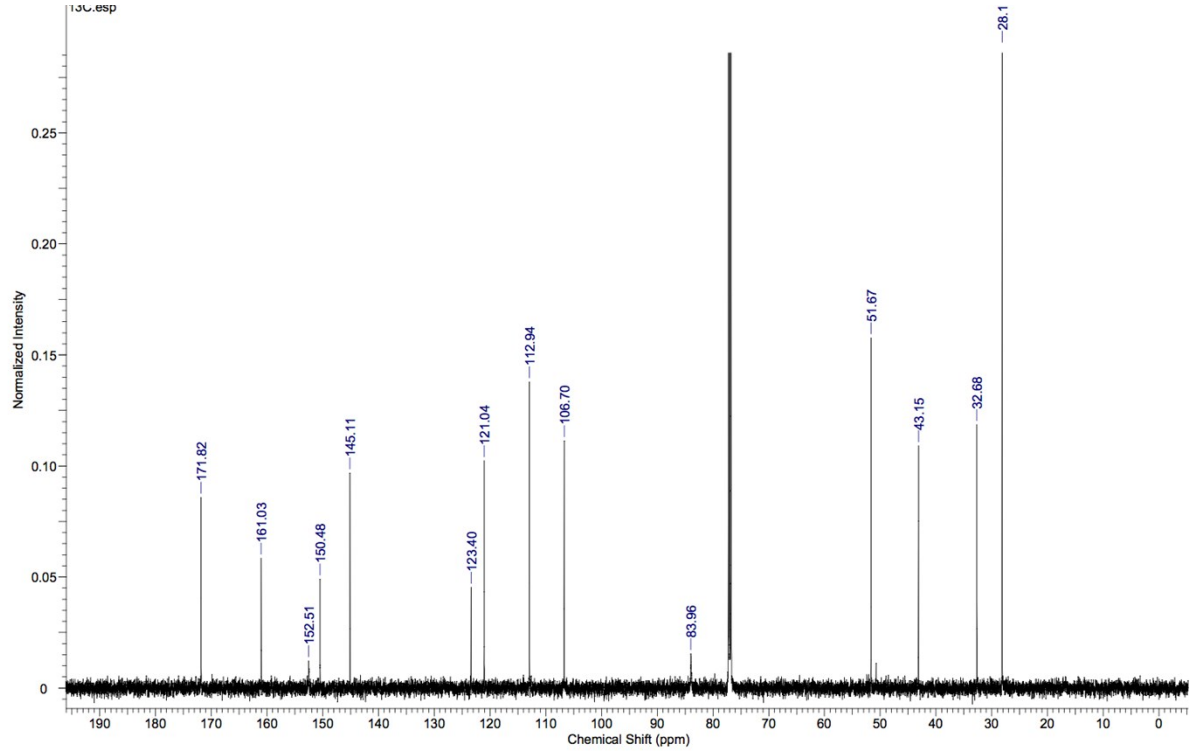


Methyl 3-((5-aminobenzo[d]thiazol-2-yl)(*tert*-butoxycarbonyl)amino)propanoate (41)

^{1}H, 600 MHz, $CDCl_3$

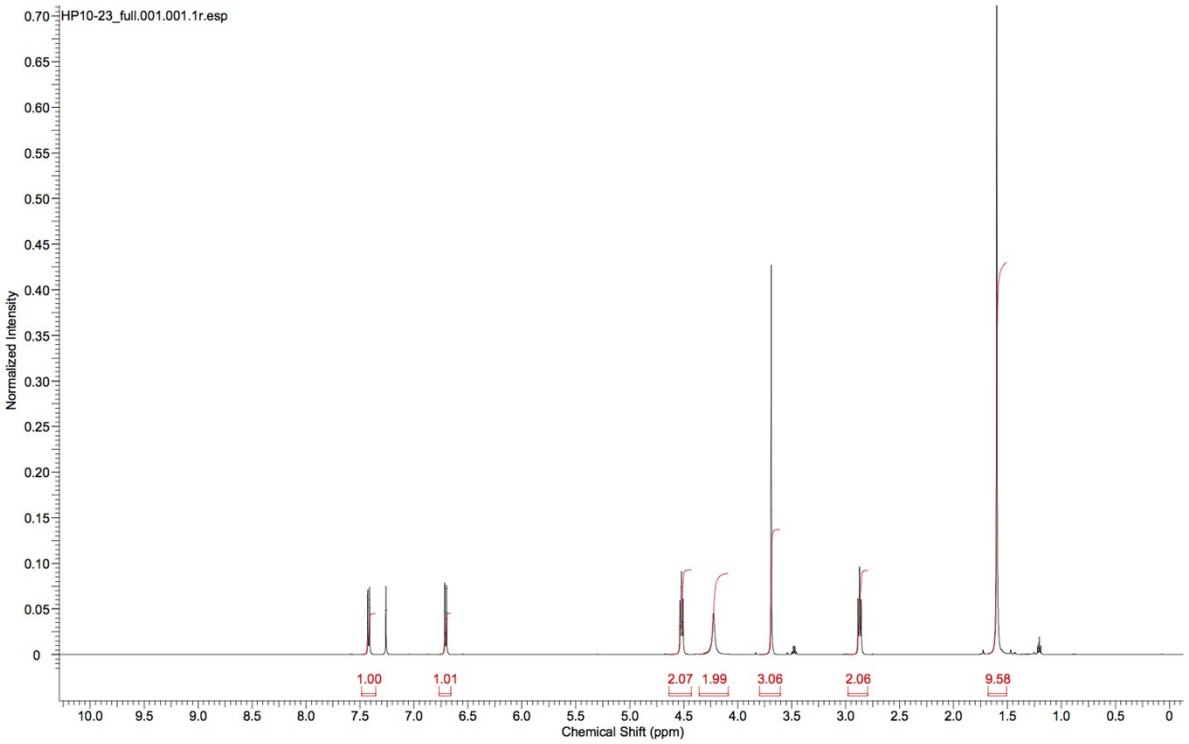


^{13}C, 151 MHz, $CDCl_3$

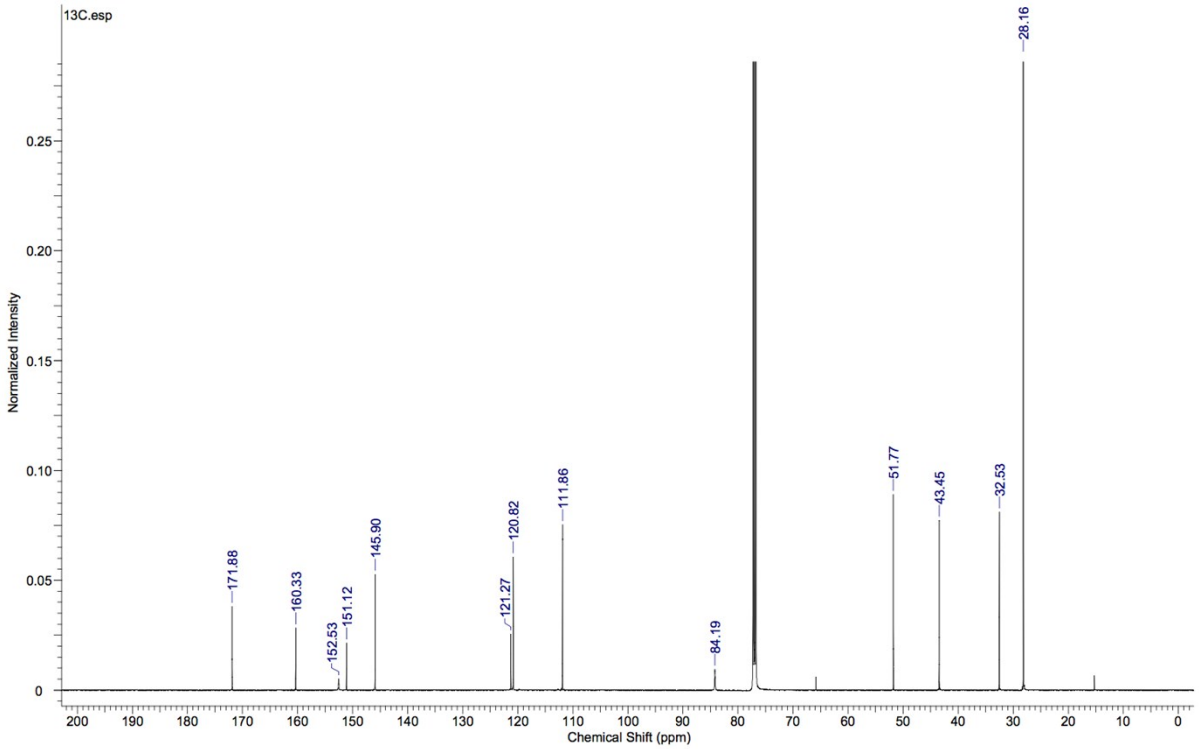


Methyl 3-((5-amino-4-iodobenzo[d]thiazol-2-yl)(*tert*-butoxycarbonyl)amino)propanoate (10)

^{1}H, 500 MHz, $CDCl_3$

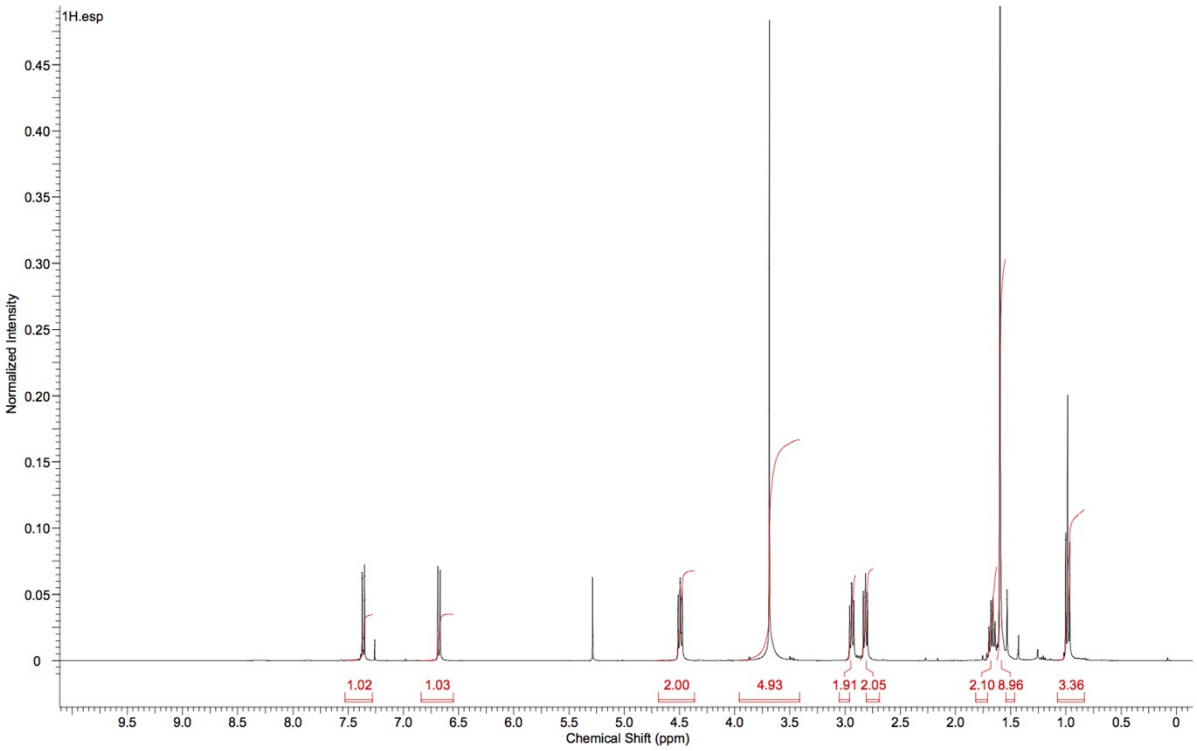


^{13}C, 126 MHz, $CDCl_3$

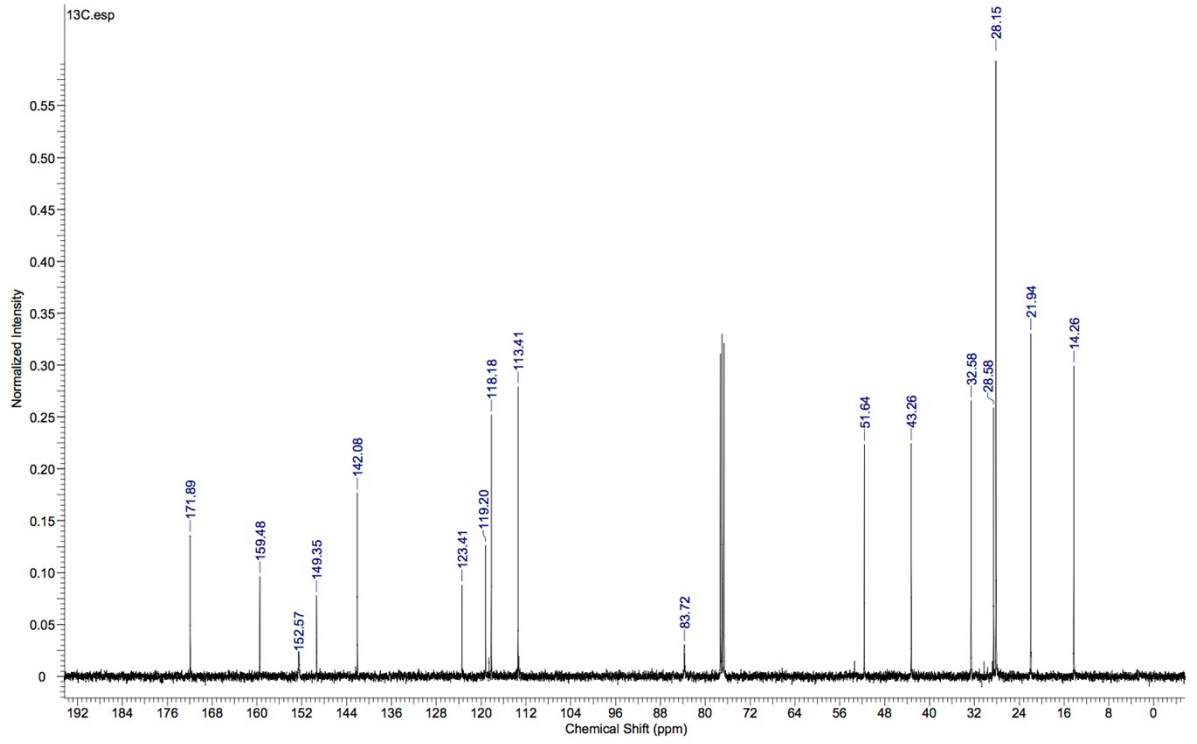


Methyl 3-((5-amino-4-propylbenzo[*d*]thiazol-2-yl)(*tert*-butoxycarbonyl)amino)propanoate (14)

^{1}H, 400 MHz, $CDCl_3$

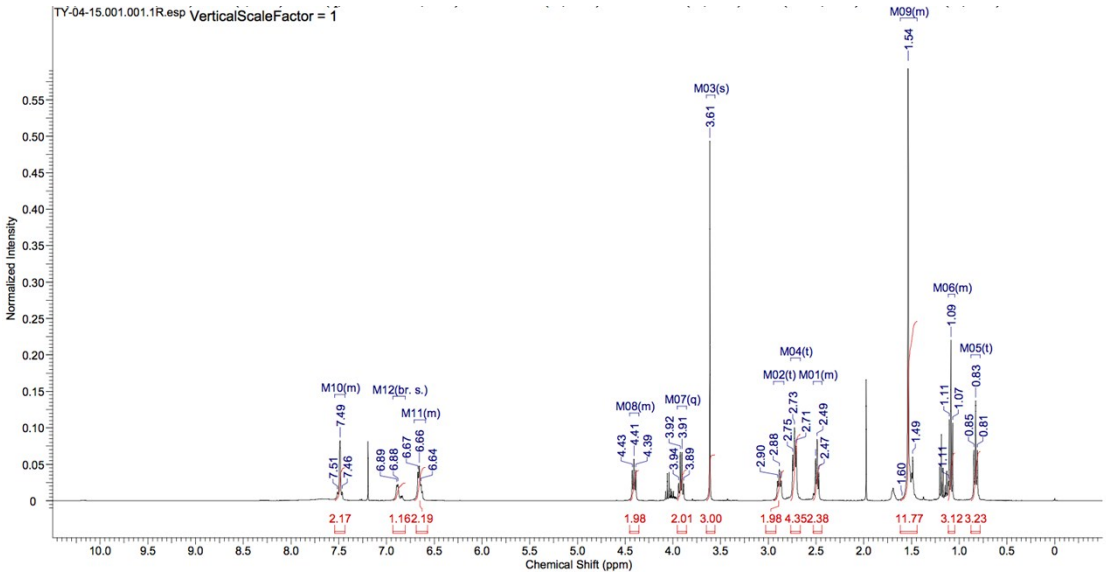


^{13}C, 101 MHz, $CDCl_3$

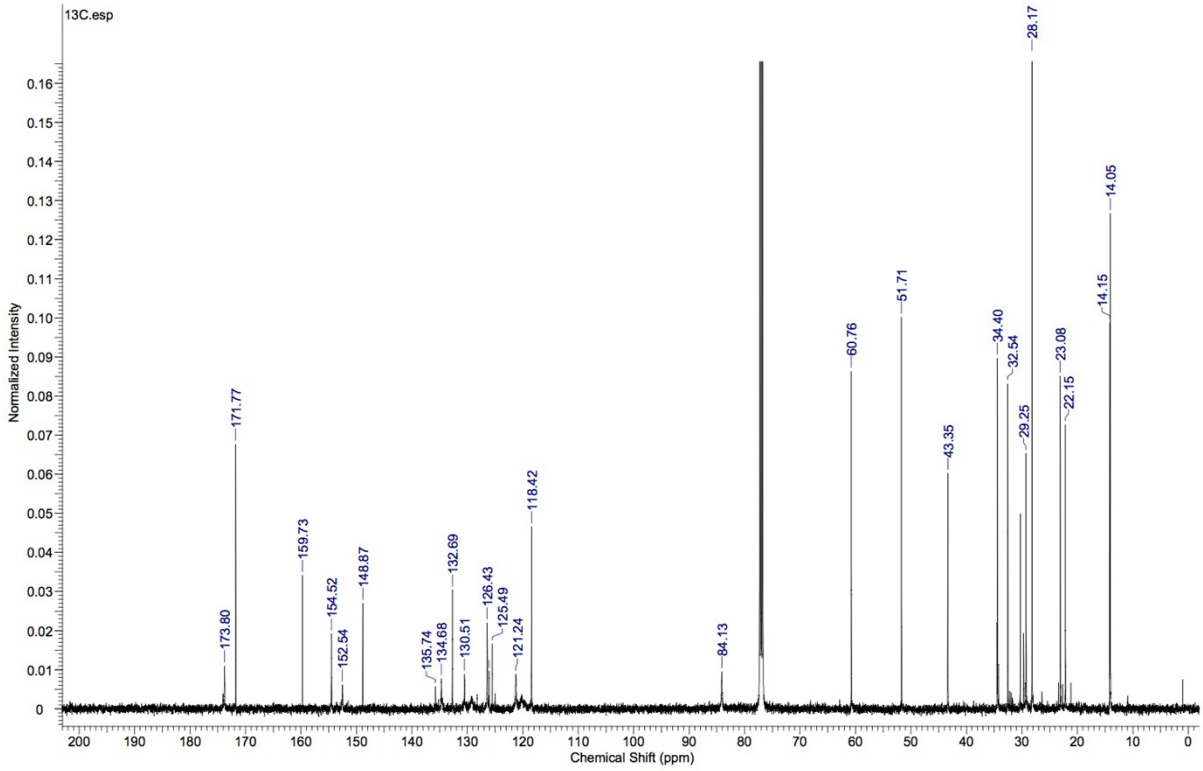


Ethyl 3-(2-(3-(2-((*tert*-butoxycarbonyl)(3-methoxy-3-oxopropyl)amino)-4-propylbenzo[d]thiazol-5-yl)ureido)thiophen-3-yl)propanoate (42)

^{1}H, 400 MHz, $CDCl_3$

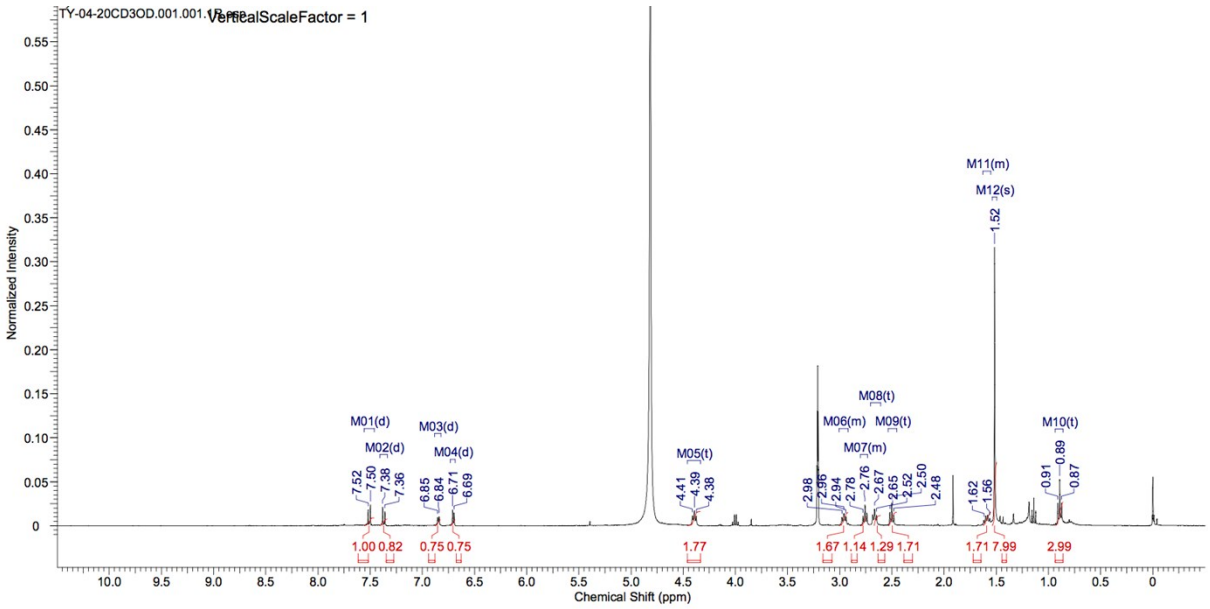


^{13}C, 126 MHz, $CDCl_3$

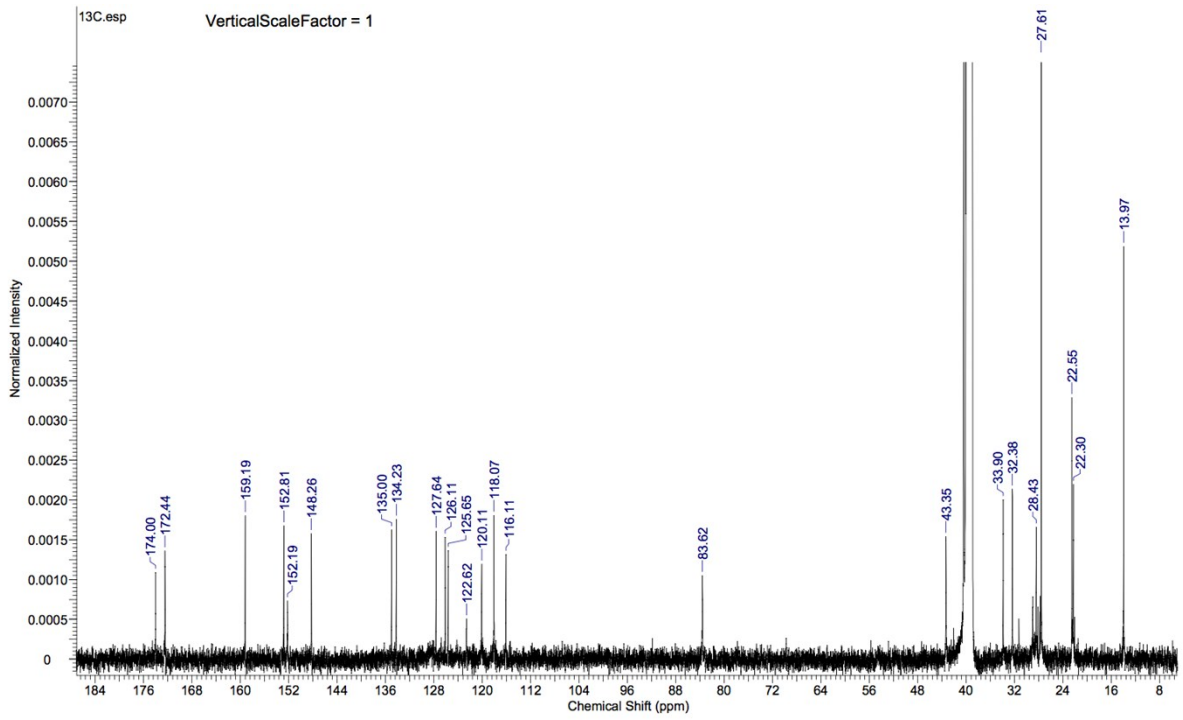


3-(2-(3-(2-((*tert*-Butoxycarbonyl)(2-carboxyethyl)amino)-4-propylbenzo[d]thiazol-5-yl)ureido)thiophen-3-yl)propanoic acid (19)

^{1}H, 400 MHz, CD_3OD

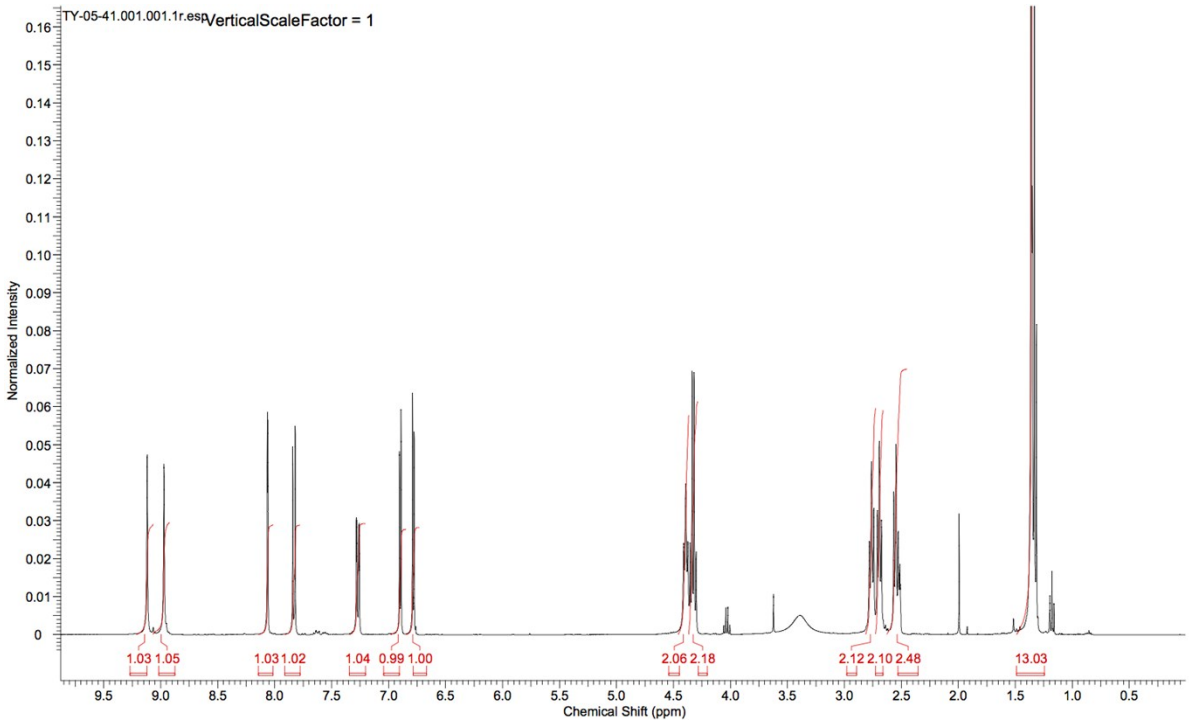


^{13}C, 101 MHz, CD_3OD

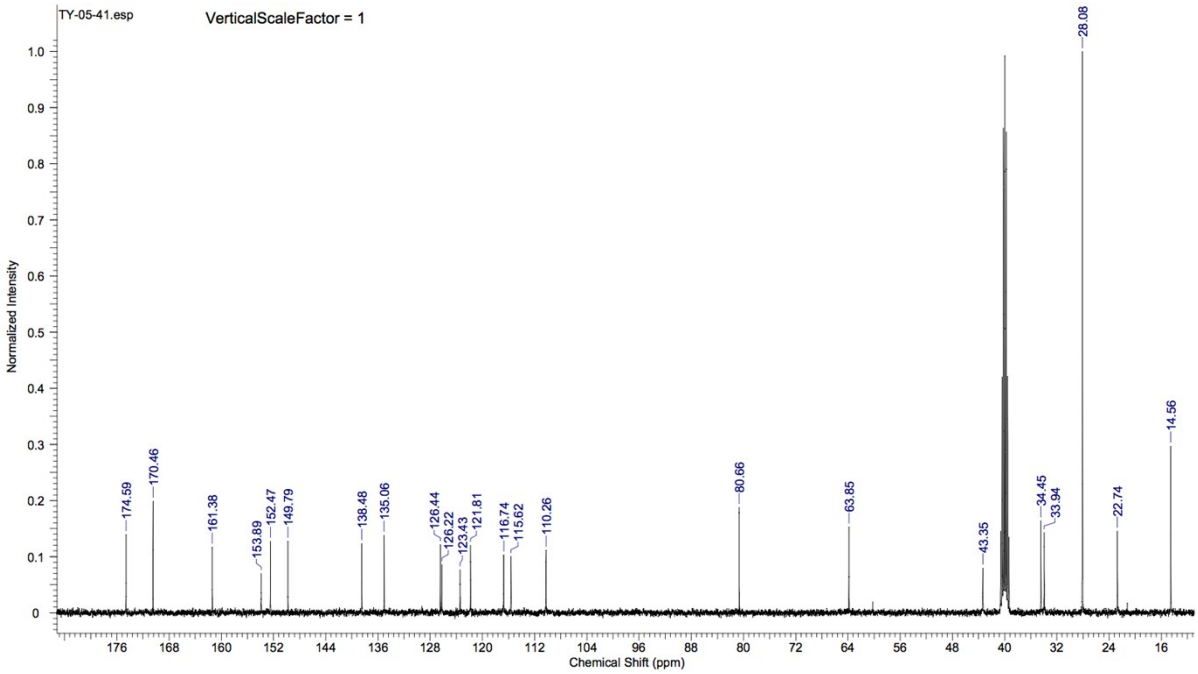


3-(2-(3-(2-((3-(*tert*-Butoxy)-3-oxopropyl)(ethoxycarbonyl)amino)benzo[d]thiazol-5-yl)ureido)thiophen-3-yl)propanoic acid (43)

^{1}H, 400 MHz, d_6-DMSO

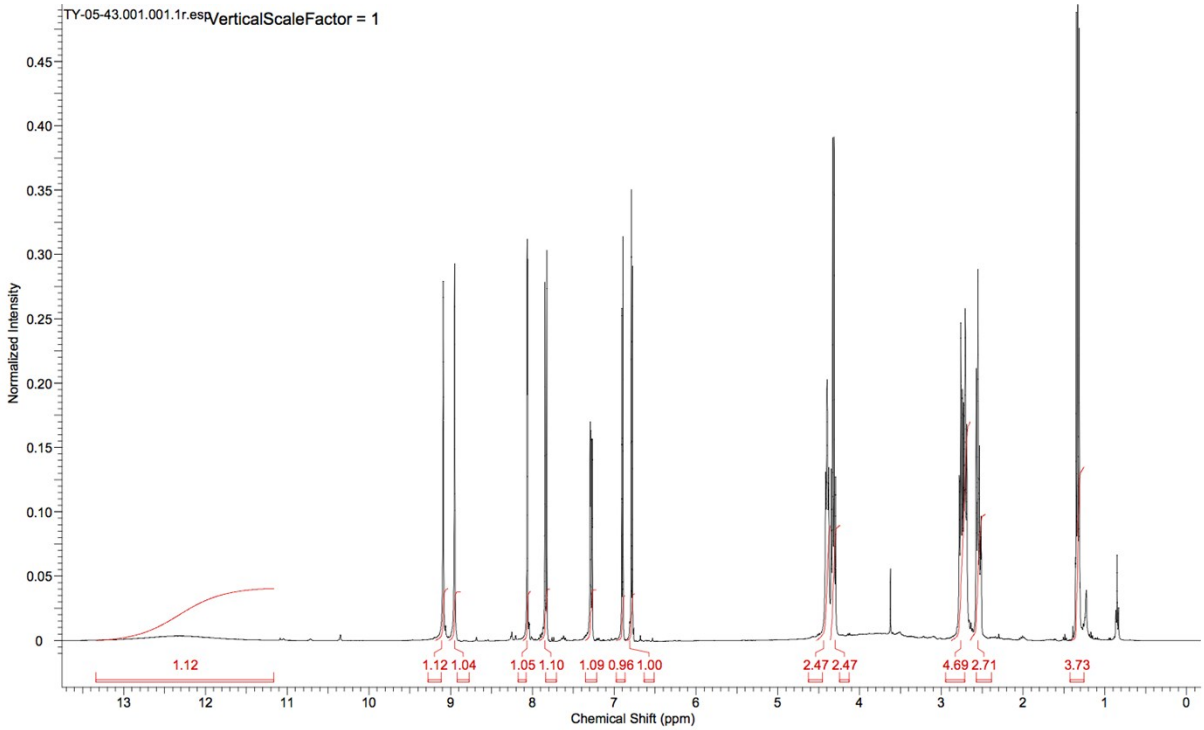


^{13}C, 101 MHz, d_6-DMSO

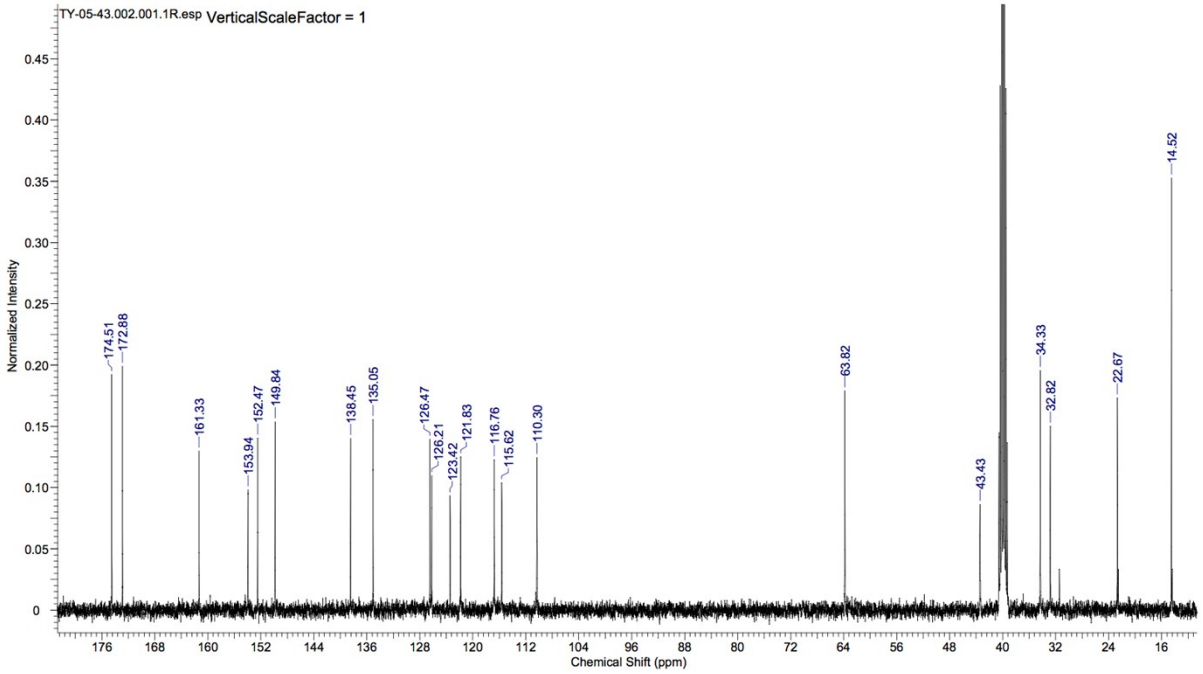


3-(2-(3-(2-((2-Carboxyethyl)(ethoxycarbonyl)amino)benzo[d]thiazol-5-yl)ureido)thiophen-3-yl)propanoic acid (23)

^{1}H, 400 MHz, d_6-DMSO

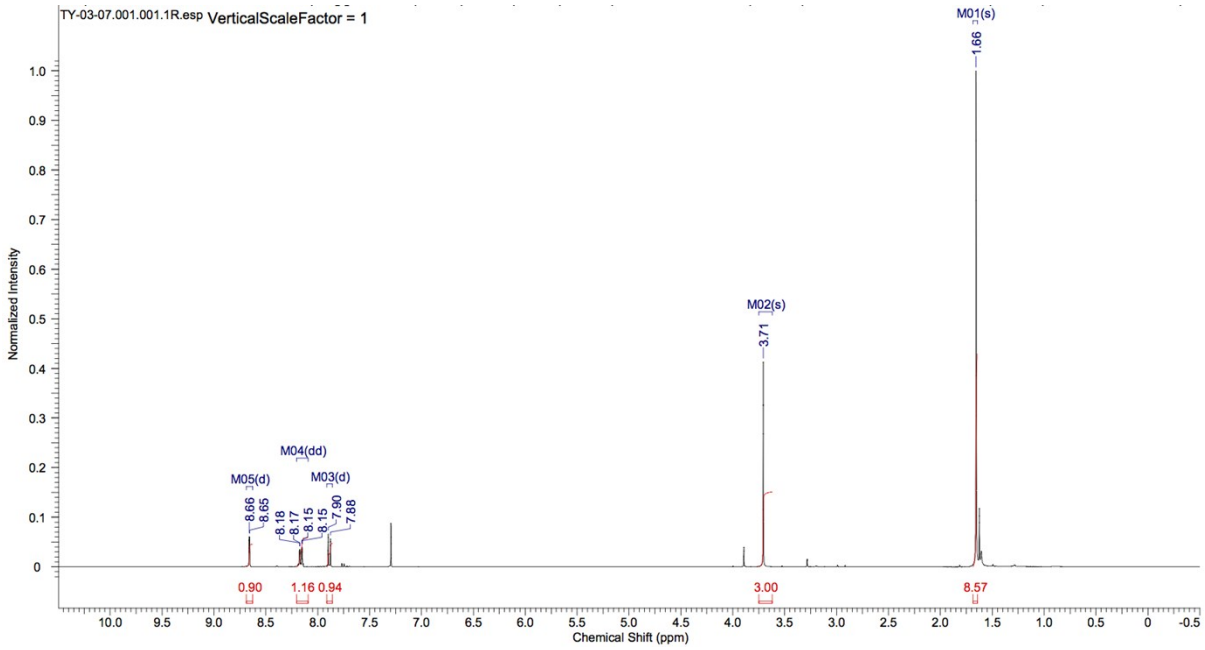


^{13}C, 101 MHz, d_6-DMSO

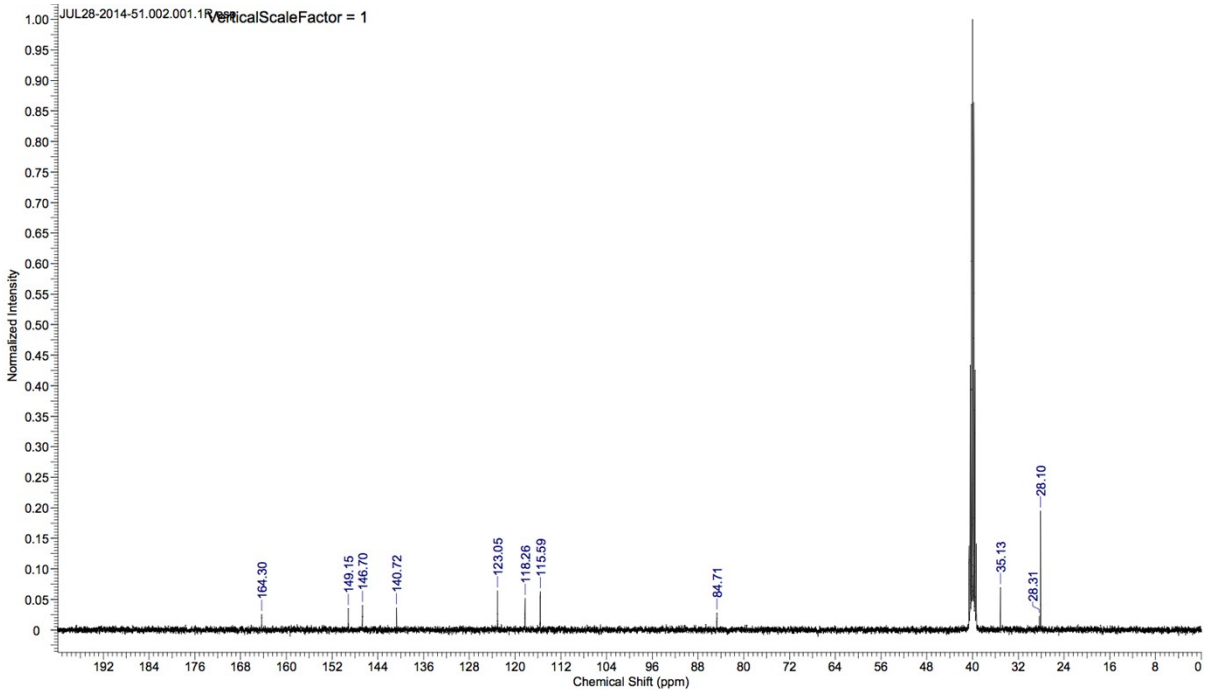


tert-Butyl (5-nitrobenzo[d]thiazol-2-yl)carbamate (45)

^{1}H, 400 MHz, $CDCl_3$

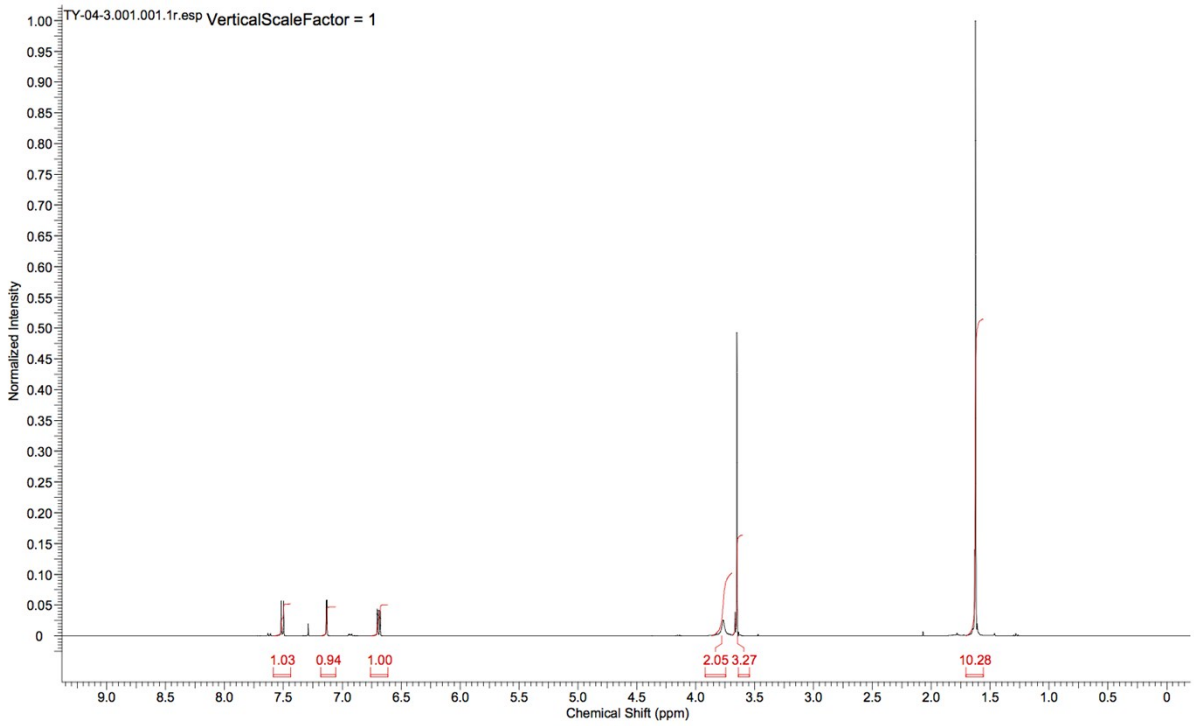


^{13}C, 101 MHz, d_6-DMSO

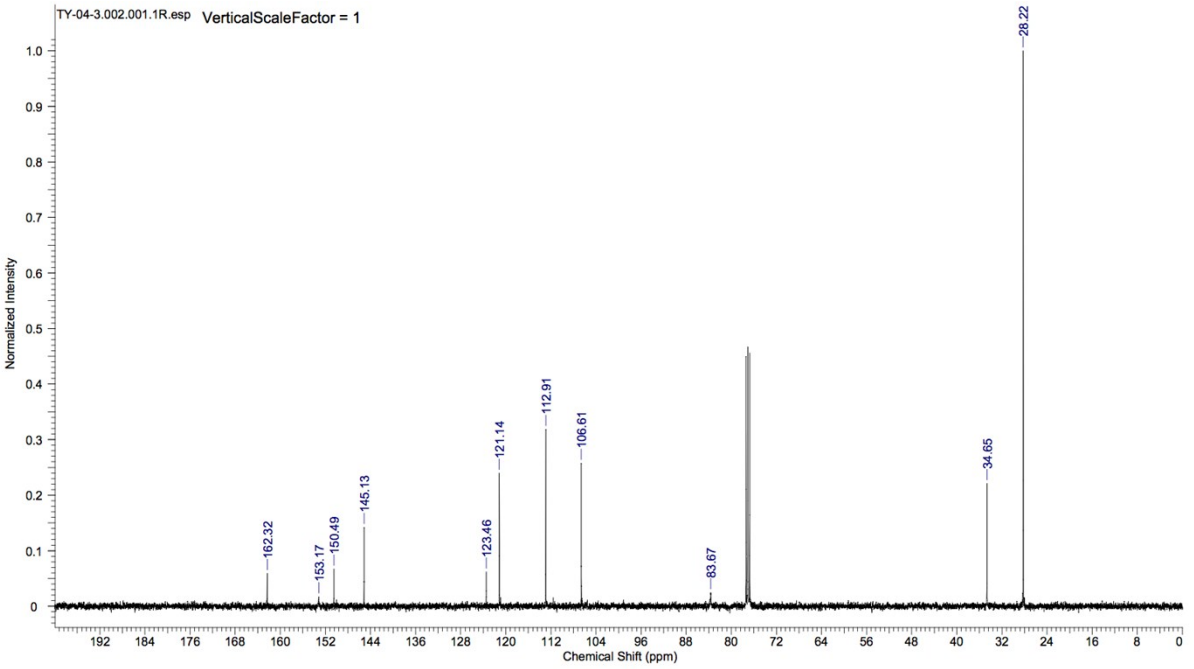


tert-Butyl (5-aminobenzo[d]thiazol-2-yl)(methyl)carbamate (46)

^{1}H, 400 MHz, $CDCl_3$

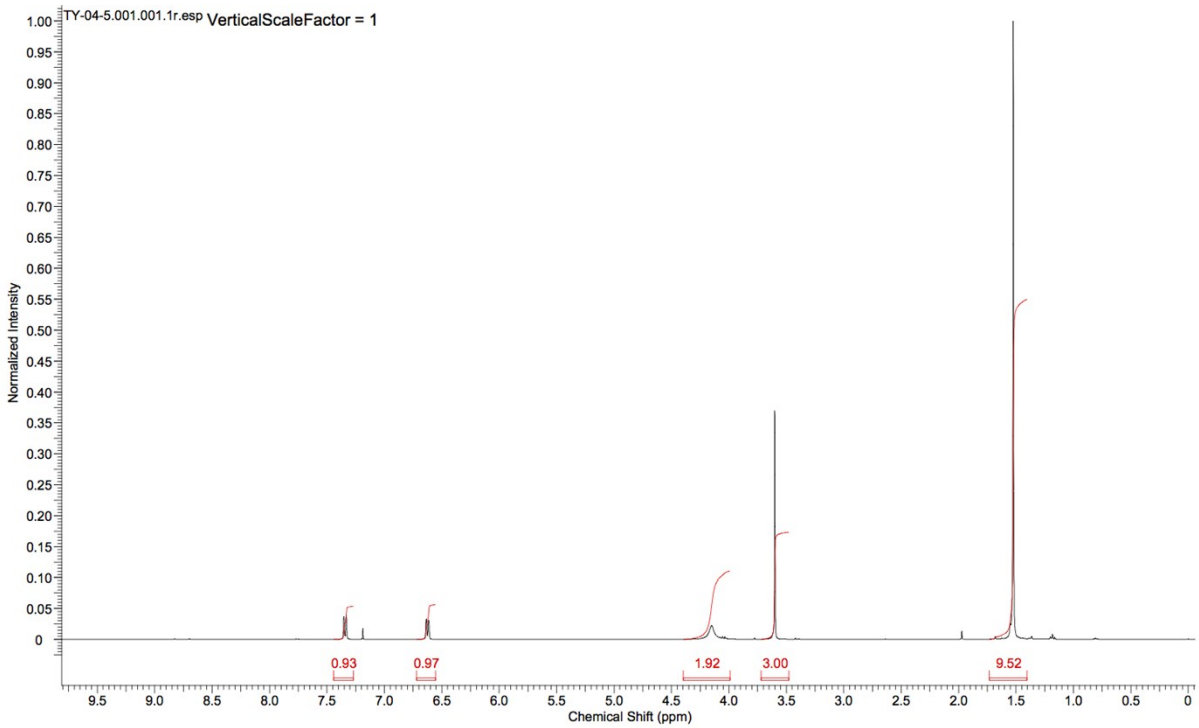


^{13}C, 101 MHz, $CDCl_3$

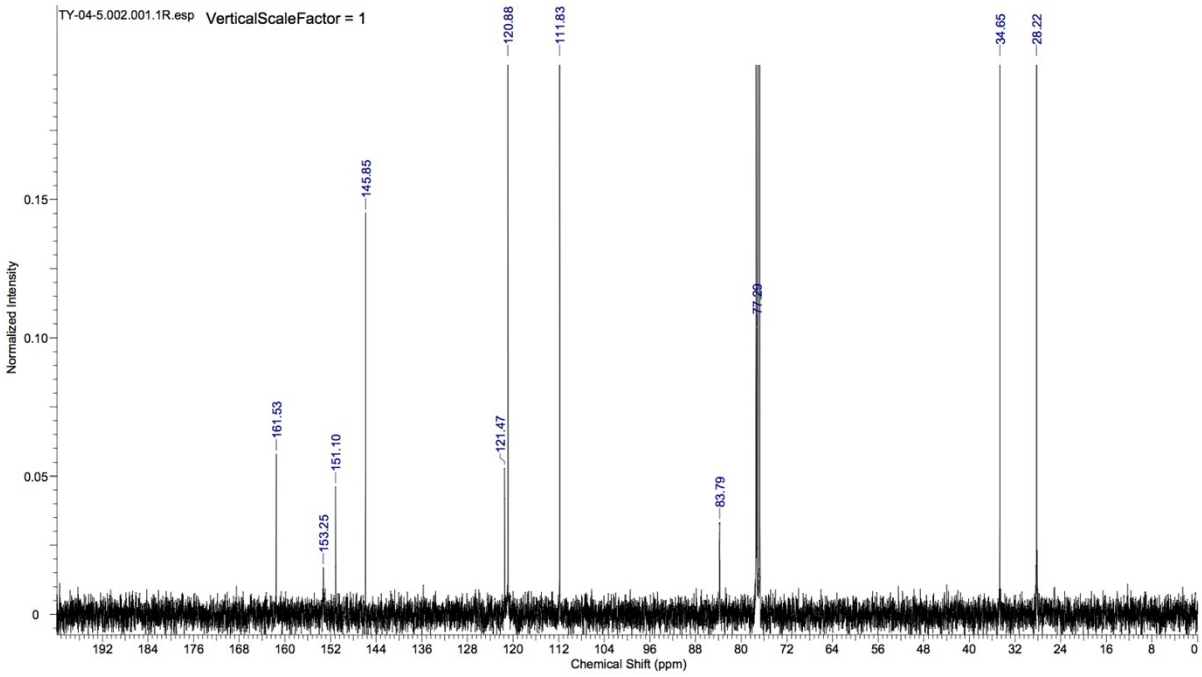


tert-Butyl (5-amino-4-iodobenzo[d]thiazol-2-yl)(methyl)carbamate (47)

^{1}H, 400 MHz, $CDCl_3$

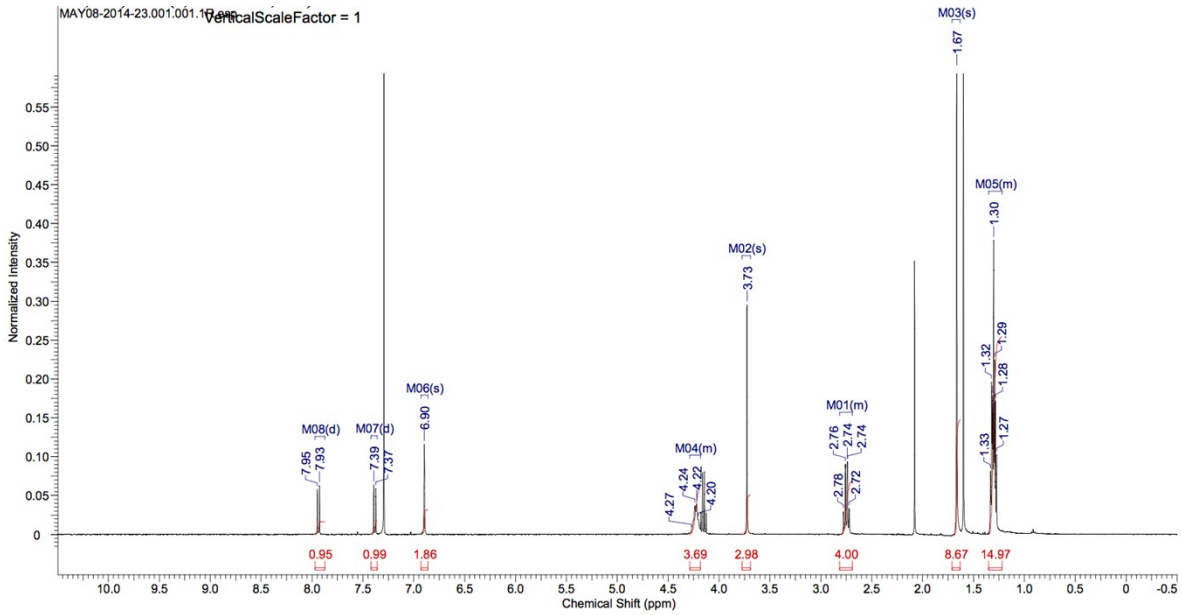


^{13}C, 101 MHz, $CDCl_3$

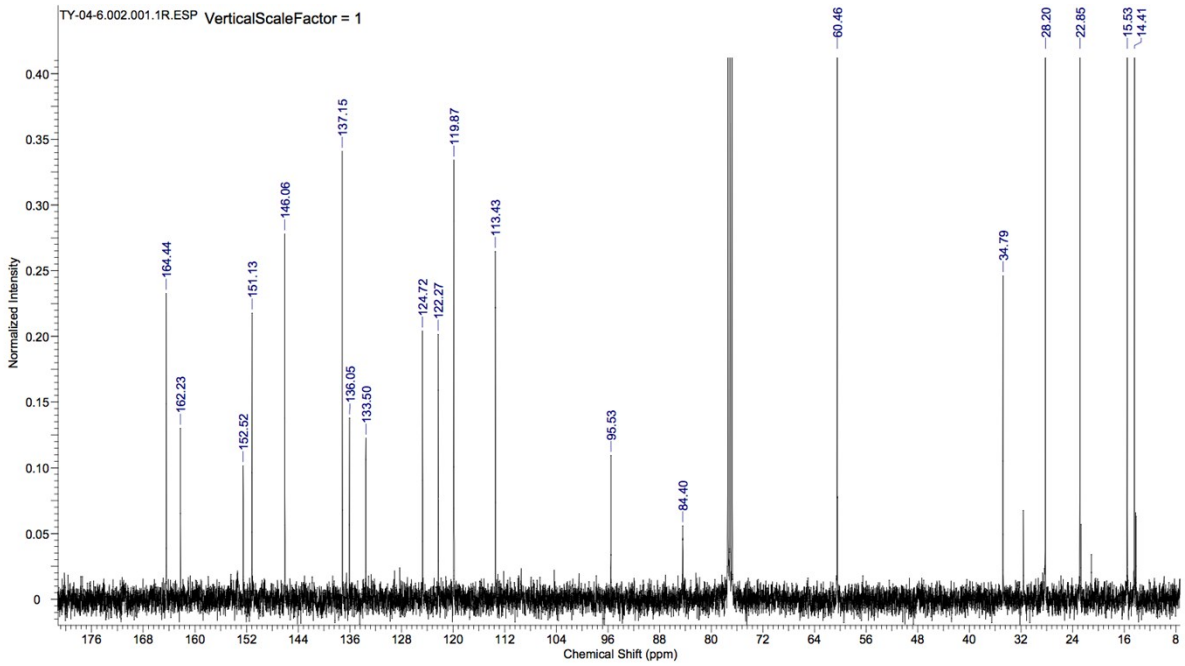


Diethyl 2,2'-((((2-((*tert*-butoxycarbonyl)(methyl)amino)-4-iodobenzo[*d*]thiazol-5-yl)azanediyl)bis(carbonyl))bis(azanediyl))bis(5-ethylthiophene-3-carboxylate) (49)

^{1}H, 400 MHz, $CDCl_3$

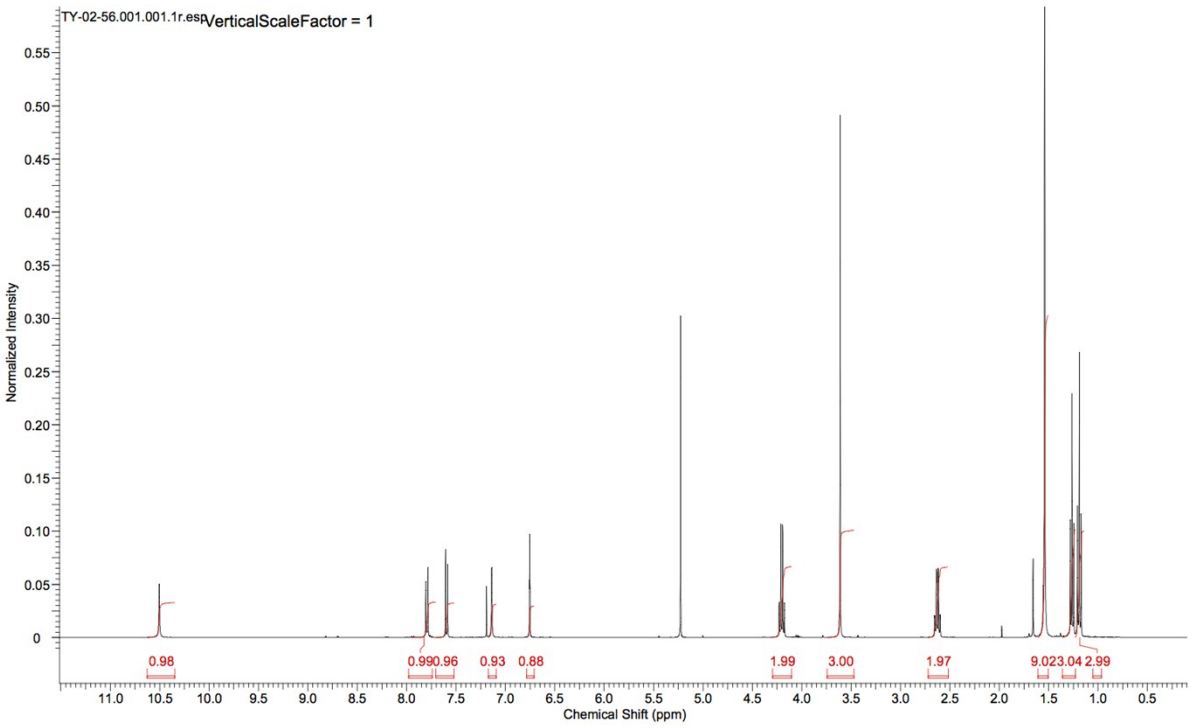


^{13}C, 101 MHz, $CDCl_3$

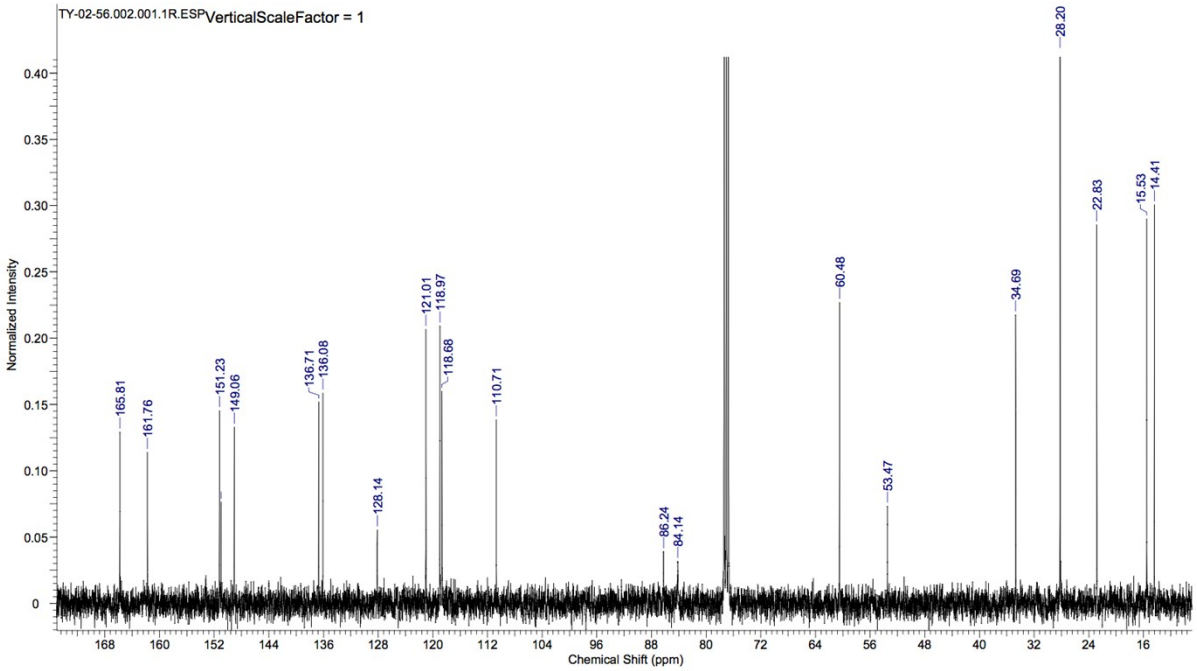


Ethyl 2-(3-(2-((*tert*-butoxycarbonyl)(methyl)amino)-4-iodobenzo[d]thiazol-5-yl)ureido)-5-ethylthiophene-3-carboxylate (24)

^{1}H, 400 MHz, $CDCl_3$



^{13}C, 101 MHz, $CDCl_3$



7. References

1 US Pat., 7514460B2, 2009.

2 H. Nowell, S. A. Barnett, K. E. Christensen, S. J. Teat and D. R. Allan, *J. Synchrotron Rad.*, 2012, **19**, 435–441.

3 L. Palatinus and G. Chapuis, *J. Appl. Cryst.*, 2007, **40**, 786–790.

4 P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout and D. J. Watkin, *J. Appl. Cryst.*, 2003, **36**, 1487–1487.

5 R. I. Cooper, A. L. Thompson and D. J. Watkin, *J. Appl. Cryst.*, 2010, **43**, 1100–1107.

6 J. Luo, C.-H. Yu, H. Yu, R. Borstnar, S. C. L. Kamerlin, A. Gräslund, J. P. Abrahams and S. K. T. S. Wärmländer, *ACS Chem. Neurosci.*, 2013, **4**, 454–462.

7 A. Savitzky and M. J. E. Golay, *Anal. Chem.*, 1964, **36**, 1627–1639.

8 Maestro, version 10.2, Schrödinger, LLC, New York, NY, 2015.

9 Jaguar, version 8.8, Schrödinger, LLC, New York, NY, 2015.

10 Y. Zhao and D. G. Truhlar, *Theor. Chem. Account*, 2007, **120**, 215–241.

11 W. J. Hehre, R. Ditchfield and J. A. Pople, *J. Chem. Phys.*, 1972, **56**, 2257–2261.

12 P. C. Hariharan and J. A. Pople, *Theoret. Chim. Acta*, 1973, **28**, 213–222.

13 R. J. Woods, M. Khalil, W. Pell, S. H. Moffat and V. H. Smith, *J. Comput. Chem.*, 1990, **11**, 297–310.