SUPPORTING INFORMATION

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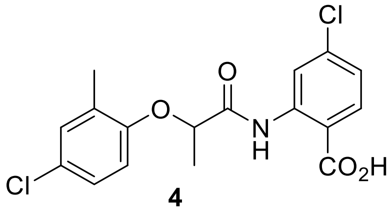
Chemistry

General remarks

Reagents and solvents were purchased from commercial sources and were used without further purification or drying. Automated column chromatography was performed on a TeledyneISCO CombiFlash Rf+ machine or an Interchim Puriflash 430 system on RediSepRf prepacked columns. Synthesis were followed by Alugram Xtra Sil G/UV254 with detection of the compounds by UV absorption at 214 nm. Preparative RP-HPLC was performed on a Xaters Prep LC4000 Chromatography system using a Reprospher 100 column from Dr. Maisch GmbH. A gradient from 100% A (milliQ deionised water with 0.1% TFA) to 60% A 40%D followed by 40% A 60% D and finally 100% D (HPLC-grade acetonitrile/milliQ deionised water 9/1 with 0.1% TFA) for 40 minutes was used. Compounds were analyzed by UPLC-MS and their purity assigned by analytical RP-UPLC. RP-UPLC spectra were obtained from a Dionex Ultimate 3000 RSLC System and a Dionex Acclaim RSLC 120 column. Three methods were used as follows: A gradient from 100% A (milliQ deionised water with 0.05% TFA) to 100% D (HPLC-grade acetonitrile/milliQ deionised water 9/1 with 0.05% TFA) was applied for 2.2 minutes (method A), 4.5 minutes (method B) or 7.5 minutes (method C), followed by 100% D washing (method A, B, C). Low-resolution mass spectra were acquired on a Thermo Scientific LCQ Fleet by electron spray ionization (ESI) in the positive mode. NMR spectra were recorded on different apparatus: BRUKER Advance 300 for ^{1}H-300 MHz; ^{13}C-75 MHz; ^{19}F-282 MHz measurements and BRUKER Advance II 400 for ^{1}H-400 MHz; ^{13}C-101 MHz measurements. Chemical shifts are given in parts per million (δ) referenced to TMS (δ = 0.00 ppm ^{1}H-, ^{13}C-NMR). Coupling constants are given in Hertz. High-resolution mass spectra measurements were performed by the “Service of Mass Spectrometry” at the University of Bern on a Thermo Scientific LTQ OritrapXL.

Commercial compounds

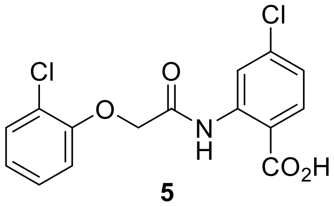
Compounds were purchased from Princeton Biomolecular Research as 1 mg solid and dissolved in DMSO to obtain 10 mM stock solutions suitable for biological testing. The hits were then repurchased from the same supplier as 25 mg solid, analyzed by UPLC-MS and ^{1}H-NMR and purified if needed.



4

(*rac*)-4-Chloro-2-(2-(4-chloro-2-methylphenoxy)propanamido)benzoic acid (**4**):

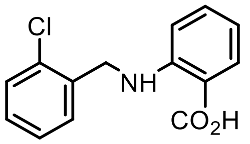
Supplier ID: OSSK_706302. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 12.02 (s, 1H), 8.75 (d, *J* = 2.1 Hz, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.26 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.18 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 5.07 – 4.94 (m, 1H), 2.32 (s, 3H), 1.54 (d, *J* = 6.7 Hz, 3H). LC-MS t_R 7.23 min (method C), *m/z* [M + H]$^+$ 367.77-369.82.



5

4-Chloro-2-(2-(2-chlorophenoxy)acetamido)benzoic acid (**5**):

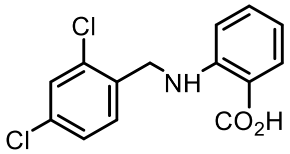
Supplier ID: OSSK_529112. ^{1}H-NMR (300 MHz, DMSO-*d*$_6$): *δ* 13.92 (br s, 1H), 11.94 (s, 1H), 8.76 (d, *J* = 2.1 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.48 (dd, *J* = 1.6, 7.8 Hz, 1H), 7.37 – 7.24 (m, 2H), 7.23 – 7.14 (m, 1H), 7.03 (td, *J* = 1.4, 7.8 Hz, 1H), 4.89 (s, 2H). LC-MS t_R 2.1 min (method B), *m/z* [M+H, Cl^{35}]$^+$ 339.89, [M+H, Cl^{37}]$^+$ 341.90.



8

2-((2-chlorobenzyl)amino)phenyl formate (8):

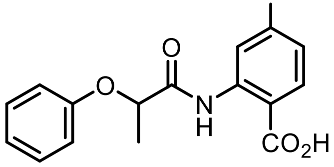
Supplier ID: OSSL_312244. ^{1}H NMR (400 MHz, DMSO-*d$_6$*) δ 12.72 (d, J = 81.4 Hz, 1H), 8.46 – 8.16 (m, 1H), 7.80 (s, 1H), 7.46 (d, J = 3.9 Hz, 1H), 7.40 – 7.33 (m, 1H), 7.33 – 7.25 (m, 79H), 6.56 (d, J = 0.8 Hz, 18H), 4.53 (d, J = 4.9 Hz, 1H). LC-MS t$_R$ 5.55 min (method C), *m/z* [M + H]$^+$ 261.94.



9

2-((2,4-dichlorobenzyl)amino)phenyl formate (9):

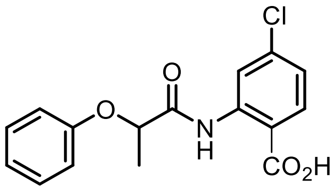
Supplier ID: OSSL_029456. ^{1}H NMR (300 MHz, DMSO- *d$_6$*) δ 12.73 (s, 1H), 8.34 (s, 1H), 7.82 (dd, J = 7.9, 1.6 Hz, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.34 (tdd, J = 8.7, 7.7, 1.9 Hz, 3H), 6.69 – 6.45 (m, 2H), 4.52 (d, J = 3.2 Hz, 2H). LC-MS t$_R$ 6.11 min (method C), *m/z* [M + H]$^+$ 295.90.



26

(*rac*)-4-Hydroxy-2-(2-phenoxypropanamido)benzoic acid (**26**):

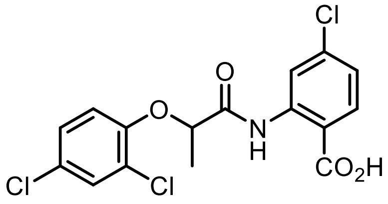
Supplier ID: OSSK_311951. LC-MS t$_R$ 4.00 min (method C), *m/z* [M+H]$^+$ 302.20.



33

(*rac*)-4-Chloro-2-(2-phenoxypropanamido)benzoic acid (**33**):

Supplier ID: OSSL_963487. LC-MS t_R 5.56 min (method C), *m/z* $[M+H]^+$ 320.01.

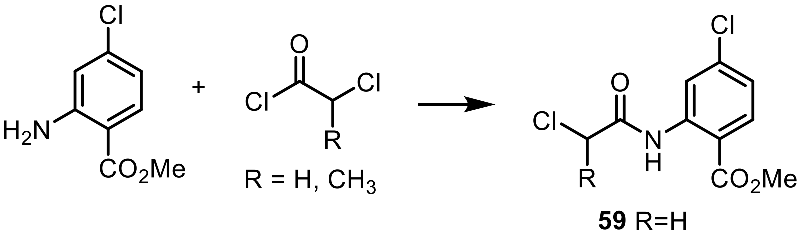


12

(*rac*)-4-Chloro-2-(2-(2,4-dichlorophenoxy)propanamido)benzoic acid (**12**):

Supplier ID: OSSK_705657. LC-MS t_R 6.31 min (method C), *m/z* $[M+H]^+$ 388.05.

Synthesis of common intermediates



59 R=H
60 R=CH$_3$

Methyl 4-chloro-2-(2-chloroacetamido)benzoate (**59**):

Methyl 2-amino-4-chlorobenzoate (20 mmol; 3.71 g) and potassium carbonate (40 mmol; 5.52 g) were dissolved in THF (300 mL) and stirred for 10 min at RT. The mixture was cooled to 0°C then the chloroacetyl chloride or 2-chloropropionyl chloride (40 mmol; 3.18 mL) was added dropwise in 5 min. The mixture was stirred at 0°C for further 15 min. Then the ice bath was removed and the mixture was stirred at RT for 3-4 hours (TLC Cyclohexane:EtOAc=4:1). When the reaction was complete, water (50 mL) was added and the pH was set to basic by the addition of solid K_2CO_3. The mixture was extracted with EtOAc (100 mL then 2 x 50 mL). The combined organics were washed with brine and dried with Na_2SO_4. After evaporation, the pure **59** intermediate was isolated as a pale pink solid (5.12 g; 98%).

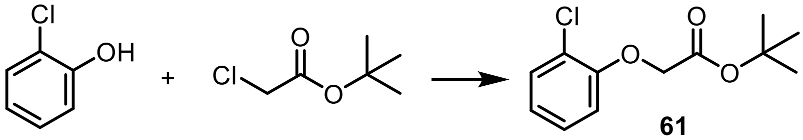
^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.44 (s, 1H), 8.53 (d, *J* = 2.1 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.34 (dd, *J* = 8.6, 2.1 Hz, 1H), 4.49 (s, 2H), 3.90 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.83 (s), 165.54 (s), 141.31 (s), 141.08 (s), 132.17 (s), 123.88 (s), 120.51 (s), 114.21 (s), 52.83 (s), 43.31 (s). HRMS *m/z* $[M + H]^+$ calcd for $C_{10}H_9Cl_2NO_3$ 262.0031, found: 262.0032.

(*rac*)-Methyl 4-chloro-2-(2-chloropropanamido)benzoate (**60**):

The methyl 2-amino-4-chlorobenzoate (5.39 mmol; 1.00 g) was acylated with 2-chloropropanoyl chloride (10.8 mmol; 1.05 mL) similarly to the synthesis of **59**. After evaporation of the solvents, a pink solid was obtained (1.50 g; 100%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.89 (s, 1H), 8.81 (d, *J* = 2.1 Hz, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.11 (dd, *J* = 8.6, 2.1 Hz, 1H), 4.54 (q, *J* = 7.0 Hz, 1H), 3.95 (s, 3H), 1.83 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR

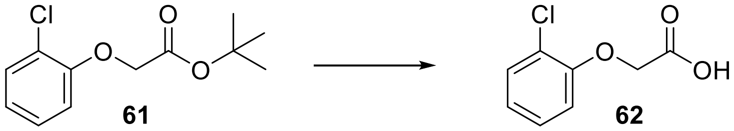
(101 MHz, CDCl3) δ 169.04 (s), 167.91 (s), 141.63 (s), 141.09 (s), 132.17 (s), 123.69 (s), 120.50 (s), 114.19 (s), 56.06 (s), 52.82 (s), 22.64 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{11}H_{12}Cl_2NO_3$ 276.0189, found: 276.0186.



tert-Butyl 2-(2-chlorophenoxy)acetate (**61**):

In a vial, 2 mL DMF was charged then 2-chlorophenol (5.0 mmol; 0.51 mL) and potassium carbonate (10 mmol; 1.38 g) were added and stirred for 10 min at RT. The *tert*-butyl chloroacetate (5.5 mmol; 0.79 mL) was added as a solid then the vial was closed and the mixture was heated to 80°C for 1 h (TLC Cyclohexane:EtOAc = 4:1). After full conversion, the hot mixture was poured into a mixture of crushed ice and water (~50 mL). The mixture was stirred for 30 min then the precipitate was filtered off, washed with water and dried over P_2O_5 in a vacuum desiccator. After drying the product still contained some water. The resulting white solid (1.251 g; 103%) was used without further treatment.

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 7.44 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.28 (ddd, *J* = 8.4, 7.4, 1.6 Hz, 1H), 7.12 - 6.86 (m, 2H), 4.79 (s, 2H), 1.43 (s, 9H).

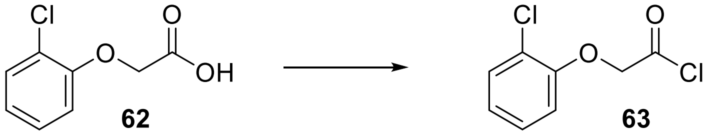


2-(2-Chlorophenoxy)acetic acid (**62**):

The ester **61** (2 mmol; 0.485 g) was dissolved in trifluoroacetic acid (2.0 mL) and stirred at RT for 1 hour. The mixture was poured on ice, stirred for 15 min then the product was extracted with DCM

(3x30ml). The combined organics were washed with brine, dried with Na_2SO_4 then evaporated to dryness. The acid **62** was isolated as a white powder (0.32 g; 87%).

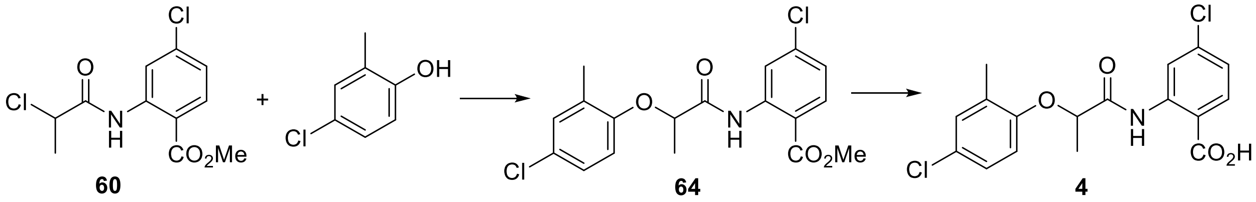
^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 13.11 (s, 1H), 7.44 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.28 (ddd, *J* = 9.0, 7.5, 1.6 Hz, 1H), 7.15 - 6.75 (m, 2H), 4.81 (s, 2H).



2-(2-Chlorophenoxy)acetyl chloride (63):

The acid **62** (1.71 mmol; 0.32 g) was dissolved in 30 mL DCM then $SOCl_2$ (17.1 mmol; 1.24 mL) was added. The mixture was refluxed for 4 h then the volatiles were removed by high vacuum. The intermediate **63** was used without further purification and characterization.

Synthetic procedures for tool compounds



(*rac*)-Methyl 4-chloro-2-(2-(4-chloro-2-methylphenoxy)propanamido)benzoate (64):

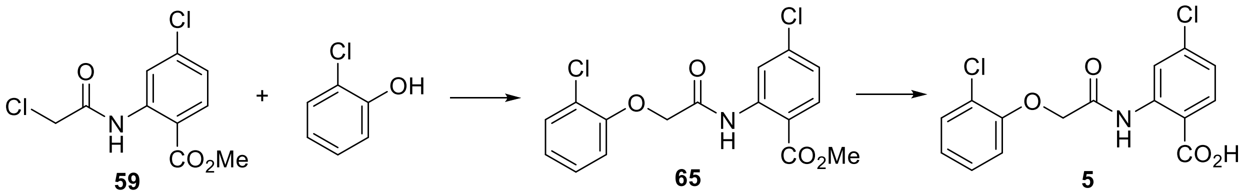
4-Chloro-2-methylphenol (1.99 mmol; 0.28 g) and potassium carbonate (3.62 mmol; 0.50 g) were dissolved in 1 mL DMF and were stirred for 10 minutes at RT. The intermediate **60** (1.81 mmol; 0.50 g) as well as another 4 mL of DMF were added to the reaction mixture, which was left to stir at 90°C under argon for 2h30 (TLC Hexane:EtOAc = 4:1). When the reaction was complete, it was poured into 120 mL of water and let to stir. Then it was extracted twice with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by automated flash chromatography on 24 g of silica gel (gradient from 80/20 Hexane/EtOAc to 100% EtOAc) to give a yellow oil (0.21 g; 30%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.85 (s, 1H), 8.87 (d, J = 2.0 Hz, 1H), 7.92 (d, J = 8.6 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 7.06 (ddd, J = 9.9, 6.0, 3.2 Hz, 2H), 6.71 (d, J = 8.7 Hz, 1H), 4.81 – 4.68 (m, 1H), 3.85 (d, J = 5.4 Hz, 3H), 2.39 (s, 3H), 1.68 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.78 (s), 167.58 (s), 153.81 (s), 141.56 (s), 140.93 (s), 132.03 (s), 131.05 (s), 130.00 (s), 126.59 (s), 123.44 (s), 120.58 (s), 116.16 (s), 114.20 (s), 113.20 (s), 75.70 (s), 52.50 (s), 19.07 (s), 16.48 (s). HRMS *m/z* $[M + H]^+$ calcd for $C_{18}H_{18}Cl_2NO_4$ 382.0607, found: 382.0612.

(*rac*)-4-Chloro-2-(2-(4-chloro-2-methylphenoxy)propanamido)benzoic acid (4):

Potassium hydroxide (7.11 mmol; 0.40 g) was added to a solution of **64** (0.55 mmol; 0.20 g) in methanol and water (12:1), which was then set to reflux for one day (TLC Hexane:EtOAc = 4:1). After completion of the reaction, the mixture was concentrated under reduced pressure and taken back in a 1 M aqueous solution of HCl. The formed precipitate was filtered to give a first batch of the compound as a yellow solid and the filtrate was extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. This crude was purified by automated flash chromatography on 12 g of silica gel (gradient from 80/20 Hexane/EtOAc to 100% EtOAc) to give a yellow solid, which was gathered with the first one (0.20 g; 83%).

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.07 (s, 1H), 8.74 (d, *J* = 2.1 Hz, 1H), 7.98 (d, *J* = 8.6 Hz, 1H), 7.24 (ddd, *J* = 9.6, 5.9, 2.3 Hz, 2H), 7.16 (td, *J* = 8.6, 2.6 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 5.00 (q, *J* = 6.6 Hz, 1H), 2.32 (s, 3H), 1.55 (s, 3H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 170.99 (s), 168.64 (s), 153.54 (s), 141.18 (s), 138.50 (s), 132.95 (s), 130.29 (s), 129.43 (s), 126.47 (s), 124.91 (s), 123.04 (s), 119.00 (s), 115.32 (s), 113.75 (s), 74.53 (s), 18.28 (s), 16.00 (s). HRMS *m/z* $[M + H]^+$ calcd for $C_{17}H_{16}Cl_2NO_4$ 368.0451, found: 368.0459.



Methyl 4-chloro-2-(2-(2-chlorophenoxy)acetamido)benzoate (**65**):

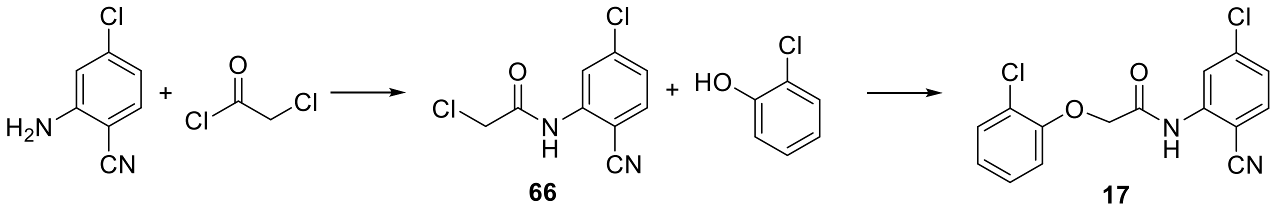
2-Chlorophenol (2.2 mmol; 0.224 mL) and intermediate **59** (2.0 mmol; 0.524 g) were reacted according to the synthesis of **61**. The product was isolated as a whitish powder (0.590 g; 83%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.49 (s, 1H), 8.67 (d, J = 2.1 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.51 (dd, J = 7.9, 1.5 Hz, 1H), 7.33 (ddd, J = 5.4, 4.3, 2.4 Hz, 2H), 7.22 (dd, J = 8.3, 1.2 Hz, 1H), 7.05 (td, J = 7.8, 1.3 Hz, 1H), 4.90 (s, 2H), 3.85 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.69 (s), 167.01 (s), 140.81 (s), 139.21 (s), 132.95 (s), 130.71 (s), 128.84 (s), 124.02 (s), 123.36 (s), 120.45 (s), 117.49 (s), 115.70 (s), 115.24 (s), 96.45 (s), 68.68 (s), 53.14 (s). HRMS m/z $[M + H]^+$ calcd for $C_{16}H_{13}Cl_2NO_4$ 354.0294, found: 354.0301.

4-Chloro-2-(2-(2-chlorophenoxy)acetamido)benzoic acid (**5**):

The ester **65** (1.65 mmol; 0.585 g) was dissolved in the necessary amount of MeOH (100 mL) and water (20 mL) was added. Then potassium hydroxide (4.95 mmol; 0.278 g) was added as a powder. The mixture was refluxed for 1 h (TLC Cyclohexane:EtOAc = 4:1), cooled and the volatiles evaporated. The mixture was treated with saturated aq. NH_4Cl (50 mL). The suspension was extracted with EtOAc (3 x 50 mL) then the combined organics were merged, washed with brine and dried with Na_2SO_4. Volatiles were evaporated under vacuum. After evaporation, the product was recrystallized from acetonitrile to give yellow crystals (0.465 g; 83%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 13.93 (s, 1H), 11.95 (s, 1H), 8.77 (d, J = 2.1 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.48 (dd, J = 7.9, 1.5 Hz, 1H), 7.31 (ddd, J = 8.4, 7.3, 1.8 Hz, 2H), 7.24 - 7.15 (m, 1H), 7.10 - 6.99 (m, 1H), 4.89 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.93 (s), 167.85 (s), 153.18 (s), 141.48 (s), 138.98 (s), 133.41 (s), 130.68 (s), 128.83 (s), 123.69 (s), 123.22 (s), 122.23 (s), 119.86 (s), 115.77 (s), 114.90 (s), 68.67 (s). HRMS *m/z* [M + Na]$^+$ calcd for $C_{15}H_{11}Cl_2NO_4Na$ 361.9957, found: 361.9954.



66

17

2-Chloro-N-(5-chloro-2-cyanophenyl)acetamide (**66**):

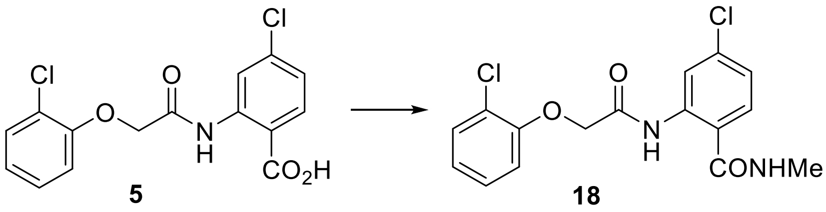
Intermediate **66** was synthesized from 2-amino-4-chlorobenzonitrile (7.0 mmol; 1.064 g) similarly to **59**. After evaporation, a pale-yellow solid was obtained (1.565 g; 98%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 10.63 (s, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 2.0 Hz, 1H), 7.50 (dd, *J* = 8.4, 2.1 Hz, 1H), 4.40 (s, 2H). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 166.20 (s), 141.27 (s), 138.89 (s), 135.43 (s), 126.68 (s), 125.38 (s), 116.27 (s), 105.95 (s), 43.37 (s).

N-(5-Chloro-2-cyanophenyl)-2-(2-chlorophenoxy)acetamide (**17**):

The intermediate **66** (1.0 mmol; 0.229 g) was reacted with 2-chlorophenol (1.1 mmol; 0.112 mL) according the method of **61**. The dried solid was further purified by automated flash chromatography (gradient from 100% Cyclohexane to 20/80 Cyclohexane/EtOAc). The merged fractions were evaporated to dryness to yield a yellow solid (0.130 g; 40%).

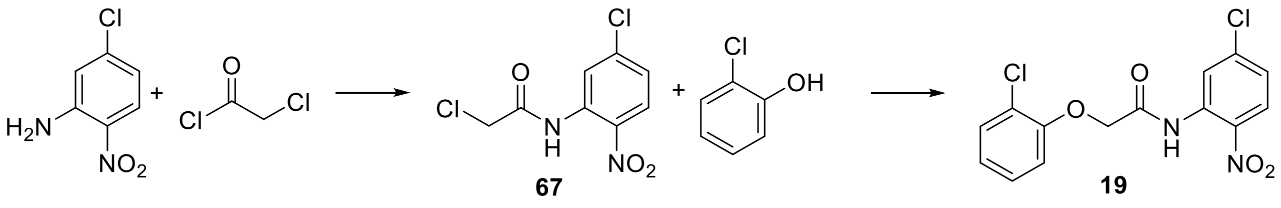
^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 10.31 (s, 1H), 7.96 (d, *J* = 2.0 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.49 (t, *J* = 1.6 Hz, 1H), 7.48 - 7.45 (m, 1H), 7.37 - 7.27 (m, 1H), 7.15 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.02 (td, *J* = 7.7, 1.3 Hz, 1H), 4.95 (s, 2H). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 167.60 (s), 152.59 (s), 137.12 (s), 135.39 (s), 133.22 (s), 130.55 (s), 128.76 (s), 126.30 (s), 124.53 (s), 122.88 (s), 118.15 (s), 114.75 (s), 105.06 (s), 67.88 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{15}H_{11}Cl_2N_2O_2$ 343.0012, found: 343.0019.



4-Chloro-2-(2-(2-chlorophenoxy)acetamido)-N-methylbenzamide (**18**):

The 4-chloro-2-(2-(2-chlorophenoxy)acetamido)benzoic acid **5** (0.41mmol; 0.138 g) was dissolved in a mixture of DCM (30 mL) and THF (30 mL) with one drop of DMF. Oxalyl chloride (4.1 mmol; 0.352 mL) was added to the mixture then it was kept at 50°C for 2.5 h. Then the volume was reduced to half under vacuum and the remaining solution was cooled to 0°C. A solution of methylamine (2M in THF; 4.1 mmol; 8.2 mL) was added slowly in 2 min. The mixture was stirred at 0°C for 30 min then water (30 mL) was added. The two layers were separated then the aqueous phase was extracted with EtOAc (2x50ml). The combined organics were washed with brine, dried with Na_2SO_4 and was evaporated to dryness. The crude was purified by automated flash chromatography (gradient from 100% Cyclohexane to 100% EtOAc). The merged fractions were evaporated to dryness to yield a white solid (0.020 g; 14%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.94 (s, 1H), 8.75 (d, *J* = 4.0 Hz, 1H), 8.60 (d, *J* = 2.1 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.49 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.30 (ddd, *J* = 8.5, 6.8, 2.0 Hz, 2H), 7.17 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.10 - 6.96 (m, 1H), 4.85 (s, 2H), 2.74 (d, *J* = 4.5 Hz, 3H). HRMS *m/z* [M + H]$^+$ calcd for $C_{16}H_{15}Cl_2N_2O_3$ 375.0274, found: 375.0258.



2-Chloro-N-(5-chloro-2-nitrophenyl)acetamide (**67**):

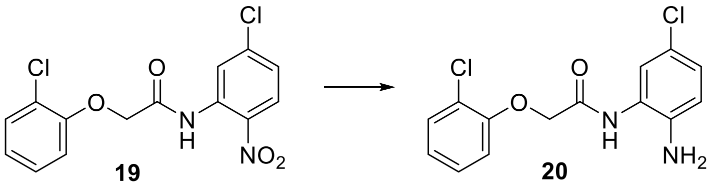
2-Nitro-4-chlorobenzonitrile (5.0 mmol; 0.863 g) was acylated according to the method described for **59**. After evaporation, a yellow solid was obtained (1.231 g; 99%).

^{1}H NMR (300 MHz, DMSO-*d$_6$*) δ 10.78 (s, 1H), 8.10 (d, *J* = 8.9 Hz, 1H), 8.00 (d, *J* = 2.3 Hz, 1H), 7.50 (dd, *J* = 8.9, 2.3 Hz, 1H), 4.43 (s, 2H). ^{13}C NMR (75 MHz, DMSO-*d$_6$*) δ 165.98 (s), 140.20 (s), 139.16 (s), 132.97 (s), 127.64 (s), 125.84 (s), 124.44 (s), 43.53 (s).

N-(5-Chloro-2-nitrophenyl)-2-(2-chlorophenoxy)acetamide (**19**):

The intermediate **67** (4.88 mmol; 0.229 g) was reacted with 2-chlorophenol (5.37 mmol; 0.548 mL) similarly to the synthesis of **61**. The product was recrystallized from acetonitrile to give a light brown solid (0.668 g; 40%).

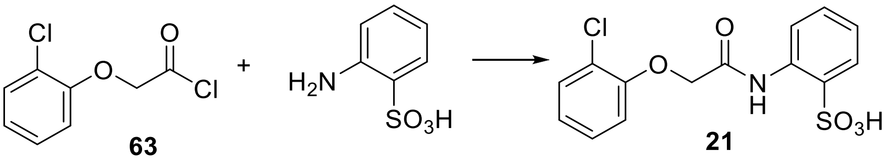
^{1}H NMR (300 MHz, DMSO-*d$_6$*) δ 10.91 (s, 1H), 8.43 (d, *J* = 2.3 Hz, 1H), 8.19 (d, *J* = 9.0 Hz, 1H), 7.58 - 7.40 (m, 2H), 7.40 - 7.27 (m, 1H), 7.20 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.05 (td, *J* = 7.7, 1.4 Hz, 1H), 4.93 (s, 2H). ^{13}C NMR (75 MHz, DMSO-*d$_6$*) δ 167.65 (s), 157.98 (s), 156.92 (s), 139.89 (s), 135.36 (s), 130.65 (s), 128.85 (s), 127.96 (s), 125.10 (s), 123.19 (s), 123.07 (s), 117.49 (s), 114.86 (s), 68.12 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{14}H_{11}Cl_2N_2O_4$ 342.1845, found: 342.1841.



N-(2-Amino-5-chlorophenyl)-2-(2-chlorophenoxy)acetamide (**20**):

The N-(5-chloro-2-nitrophenyl)-2-(2-chlorophenoxy)acetamide **19** (0.2 mmol; 0.061 g) was suspended in MeOH (30 mL). The mixture was stirred for 30 min at 50°C. Then water (7.5 mL), iron powder (1.4 mmol; 0.077 g) and ammonium formate (4.0 mmol; 0.255 g) were added. The solution was refluxed for 1.5 h. The hot solution was filtered through Celite and washed with hot MeOH (50 mL). The volatiles were evaporated. The residue was diluted with sat. aq. $NaHCO_3$ (50 mL) and extracted with EtOAc (3x75 mL). The combined organics were washed with brine and dried with Na_2SO_4. After evaporation, the residue was purified by automated flash chromatography (gradient from 100% Cyclohexane to 100% EtOAc). The merged fractions were evaporated to dryness to yield a yellow solid (0.034 g; 55%).[3]

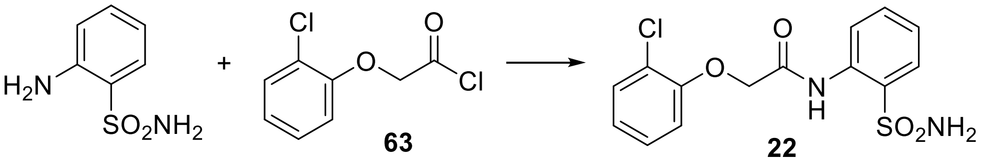
^{1}H NMR (300 MHz, DMSO-d_6) δ 9.29 (s, 1H), 7.46 (dd, J = 7.9, 1.6 Hz, 1H), 7.38 - 7.26 (m, 2H), 7.13 (d, J = 7.2 Hz, 1H), 7.06 - 6.92 (m, 2H), 6.74 (d, J = 8.6 Hz, 1H), 5.14 (s, 2H), 4.86 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.73 (s), 153.88 (s), 141.33 (s), 130.52 (s), 128.72 (s), 127.35 (s), 126.29 - 126.00 (m), 124.89 (s), 122.57 (s), 119.36 (s), 118.32 (s), 117.26 (s), 114.59 (s), 67.94 (s). HRMS m/z $[M + H]^+$ calcd for $C_{14}H_{13}Cl_2N_2O_2$ 311.0355, found: 311.0349.



2-(2-(2-Chlorophenoxy)acetamido)benzenesulfonic acid (**21**):

2-Aminobenzenesulfonic acid (0.7 mmol; 0.121 g) and K_2CO_3 (2.1 mmol; 0.290 g) were dissolved in THF (10 mL) and stirred for 15 min at RT. Then the intermediate **63** (0.77 mmol; 0.158 g) was added in one portion. The reaction mixture was stirred at RT for 1.5 h. Water was added and the pH was set to 5-6 with 1 M HCl solution then it was extracted with EtOAc (3x30 mL). The combined organics were washed with brine, dried with Na_2SO_4 and evaporated to dryness. The residue was purified by automated flash chromatography (gradient from 100% Cyclohexane to 100% EtOAc). The collected fractions were evaporated to dryness to yield a white solid (0.006 g; 3%).

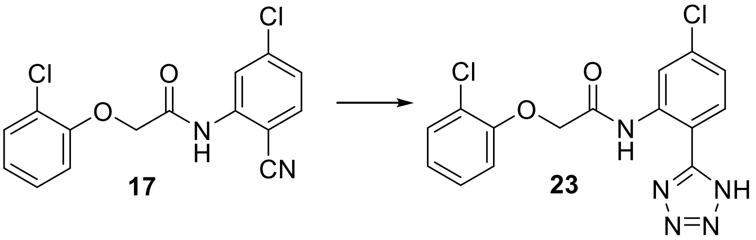
^{1}H NMR (300 MHz, MeOD) δ 10.57 (s, 1H), 8.18 (dd, J = 8.2, 1.0 Hz, 1H), 7.80 (dd, J = 7.8, 1.5 Hz, 1H), 7.40 - 7.25 (m, 2H), 7.14 (dqd, J = 11.4, 7.5, 1.4 Hz, 3H), 6.91 (ddd, J = 7.9, 7.2, 1.8 Hz, 1H), 4.65 (s, 2H). ^{13}C NMR (75 MHz, MeOD) δ 167.55 (s), 157.84 (s), 134.02 (s), 130.52 (s), 130.06 (s), 127.70 (s), 127.08 (s), 123.72 (s), 123.55 (s), 122.88 (s), 122.16 (s), 117.49 (s), 115.66 (s), 68.93 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{14}H_{13}ClNO_5S$ 340.0052, found: 340.0055.



2-(2-Chlorophenoxy)-N-(2-sulfamoylphenyl)acetamide (**22**):

Compound **22** was synthesized similarly to **21** from 2-aminobenzenesulfonamide (0.7 mmol; 0.12 g) and **63** (0.77 mmol; 0.158 g). After evaporation of the collected fractions, the residue was recrystallized from acetonitrile to give a white powder (0.081 g; 34%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 10.00 (s, 1H, exch. with D_2O), 8.21 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 7.1 Hz, 1H), 7.72 - 7.56 (m, 3H, 2H exch. with D_2O then 7.62(t, *J* = 7.4 Hz, 1H)), 7.48 (d, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 12.6, 4.9 Hz, 2H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 4.87 (s, 2H). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 167.00 (s), 153.23 (s), 134.49 (s), 133.26 (s), 130.63 (s), 128.77 (s), 128.12 (s), 124.95 (s), 123.93 (s), 123.10 (s), 114.98 (s), 68.42 (s). Two quaternary carbons are hidden. HRMS *m/z* [M + H]$^+$ calcd for $C_{14}H_{14}ClN_2O_4S$ 341.0357, found: 341.0358.

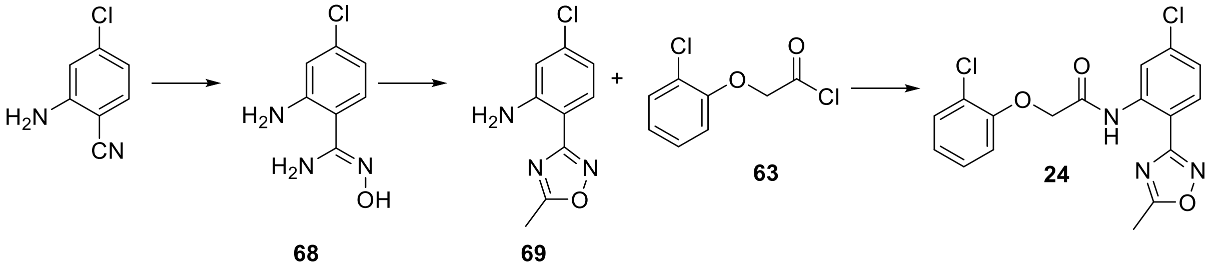


N-(5-Chloro-2-(1H-tetrazol-5-yl)phenyl)-2-(2-chlorophenoxy)acetamide (**23**):

The N-(5-chloro-2-cyanophenyl)-2-(2-chlorophenoxy)acetamide **17** (0.09 mmol; 0.030 g) was dissolved in THF (2 mL) then water (2 mL) and 2-propanol (1 mL) were added. Sodium azide (0.1 mmol; 0.007 g) and $ZnCl_2$ (0.1 mmol; 0.014 g) were added as solid. The mixture was refluxed for

30h. The THF was evaporated then the residue was diluted with 1M HCl (5 mL) and extracted with EtOAc (3x15 mL). The combined organics were washed with brine, dried with Na_2SO_4 and evaporated to dryness. The title compound was isolated as a white solid (0.006 g; y= 18%).[4]

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (s, 1H, exchange with D_2O), 8.67 (d, J = 2.1 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.56 - 7.36 (m, 2H), 7.35 - 7.25 (m, 1H), 7.20 (dd, J = 8.3, 1.4 Hz, 1H), 7.02 (td, J = 7.8, 1.4 Hz, 1H), 4.93 (s, 2H), (1.24 (s, exchange with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.26 (s), 167.83 (s), 138.97 (s), 137.68 (s), 136.16 (s), 130.68 (s), 130.63 (s), 128.70 (s), 124.73 (s), 123.11 (s), 121.41 (s), 117.49 (s), 114.98 (s), 68.59 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{15}H_{12}Cl_2N_5O_2$ 364.0363, found: 364.0358.



(Z)-2-Amino-4-chloro-N'-hydroxybenzimidamide (**68**):

A hot solution of 2-amino-4-chloro-benzonitrile (10 mmol; 1.530 g) in 96% EtOH (40 mL) was added to a stirring solution of hydroxyl amine hydrochloride (20 mmol; 1.390 g) and $NaHCO_3$ (25 mmol; 2.100 g) in water (20 mL). The mixture was refluxed for 24 h then an additional 0.5 eq hydroxylamine HCl and $NaHCO_3$ were added (0.346 g and 0.420 g, respectively). It was refluxed for further 7 more hours. Then the volatiles were evaporated. The residue was suspended in water. The precipitate was filtered and washed with water. A white cotton-like solid was obtained (1.454 g; 79%).[5]

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.66 (s, 1H), 7.37 (d, J = 8.5 Hz, 1H), 6.71 (d, J = 1.8 Hz, 1H), 6.55 (s, 2H), 6.53 (d, J = 9.0 Hz, 1H), 5.78 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.70 (s), 148.67 (s), 129.38 (s), 117.49 (s), 114.71 (s), 114.62 (s), 113.34 (s).

5-Chloro-2-(5-methyl-1,2,4-oxadiazol-3-yl)aniline (**69**):

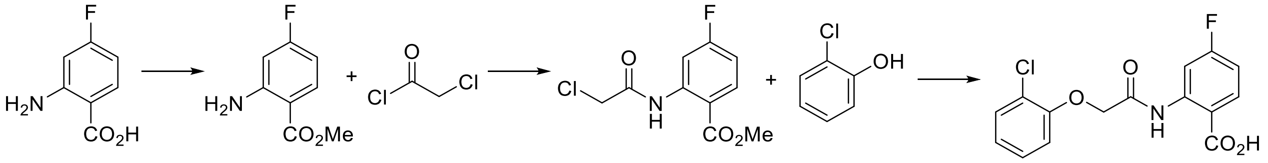
Amid-oxime **68** (1.0 mmol; 0.186 g) was dissolved in abs. EtOH (10 mL) then sodium ethylate (10.0 mmol; 0.68 g) and anhydrous EtOAc (2.0 mmol; 0.587 mL) were added, respectively. The mixture was refluxed for 24 h then the volatiles were evaporated. The residue was suspended in water (30 mL) and the precipitate was filtered and dried. A brown solid was obtained (0.138 g; 66%).[5]

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 7.85 (d, *J* = 8.5 Hz, 1H), 6.94 (d, *J* = 2.1 Hz, 1H), 6.69 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.53 (s, 2H), 2.66 (s, 3H). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 176.19 (s), 167.57 (s), 149.09 (s), 136.84 (s), 131.42 (s), 115.92 (s), 115.23 (s), 107.03 (s), 12.31 (s). HRMS *m/z* $[M + H]^+$ calcd for $C_9H_9ClN_3O$ 232.0248, found: 232.0252.

N-(5-Chloro-2-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)-2-(2-chlorophenoxy)acetamide (**24**):

The aniline **69** (0.66 mmol; 0.138 g) was dissolved in THF (10 mL) then K_2CO_3 was added. The mixture was stirred for 30 min at RT then the acid chloride **63** (0.72 mmol, 0.148 g) was added as a THF solution (10 mL). The mixture was stirred at RT for 18 h. Water was added then it was extracted with EtOAc (3x30 mL). The combined organics were washed with brine, dried with Na_2SO_4 then evaporated to dryness to give pale-yellow flakes (0.232 g; 93%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 10.87 (s, 1H), 8.65 (d, *J* = 2.1 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.51 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.42 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.36 - 7.28 (m, 1H), 7.21 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.05 (td, *J* = 7.8, 1.3 Hz, 1H), 4.92 (s, 2H), 2.65 (s, 3H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 153.67 (s), 146.44 (s), 140.30 (s), 135.64 (s), 130.58 (s), 128.68 (s), 125.30 (s), 122.59 (s), 121.71 (s), 119.29 (s), 118.20 (s), 114.99 (s), 114.53 (s), 114.35 (s), 89.89 (s), 66.77 (s), 29.47 (s). HRMS *m/z* $[M + H]^+$ calcd for $C_{17}H_{14}Cl_2N_3O_3$ 378.0407, found: 378.0407.



70 **71** **25**

Methyl 2-amino-4-fluorobenzoate (70):

Sulfuric acid (64.5 mmol; 3.51 mL) was added to a solution of 2-amino-4-fluorobenzoic acid (3.22 mmol; 0.50 g) in 11 mL methanol and was refluxed for seven days (TLC Hexane:EtOAc = 4:1). When the reaction was complete, the reaction mixture was concentrated under reduced pressure, and then the residue was dissolved in water. The obtained solution was set to basic pH with a 25% solution of NaOH to allow the formation of a precipitate, which was filtered and dried to give a brown solid (0.37 g; 68%).[6]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.8, 6.6 Hz, 1H), 6.38 – 6.28 (m, 2H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.99 (d, *J* = 7.5 Hz), 165.46 (s), 152.71 (d, *J* = 12.6 Hz), 134.05 (d, *J* = 11.5 Hz), 107.53 (d, *J* = 1.7 Hz), 104.44 (d, *J* = 22.7 Hz), 102.28 (d, *J* = 24.5 Hz), 97.06 (d, *J* = 25.7 Hz), 51.68 (s).

Methyl 2-(2-chloroacetamido)-4-fluorobenzoate (71):

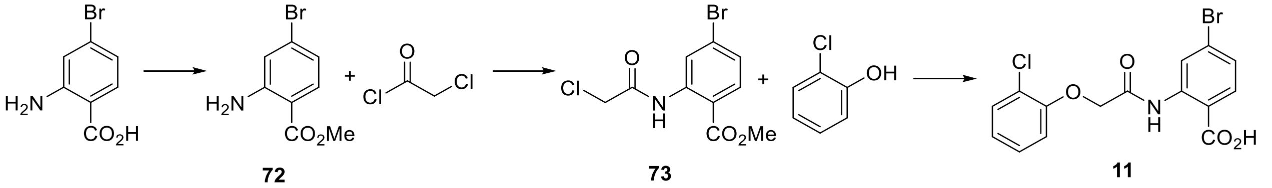
Intermediate **70** (1.77 mmol; 0.30 g) and potassium carbonate (3.55 mmol; 0.49 g) were dissolved in 30 mL THF and were stirred for 10 min at RT. The mixture was cooled to 0°C then chloroacetyl chloride (3.55 mmol; 0.28 mL) was added dropwise for 5 min. The mixture was stirred at 0°C for further 15 min. Then the ice bath was removed and the mixture was stirred at RT for the next 3 hours (TLC Hexane:EtOAc = 4:1). When the reaction was complete, 15 mL of water was added then the pH was set to basic by the addition of solid K_2CO_3. The mixture was extracted three times with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give an orange solid (0.41 g; 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.04 (s, 1H), 8.53 (dd, *J* = 11.7, 2.6 Hz, 1H), 8.08 (dd, *J* = 8.9, 6.5 Hz, 1H), 6.89 – 6.78 (m, 1H), 4.21 (s, 2H), 3.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.79 (s), 167.55 (s), 165.35 (d, *J* = 64.6 Hz), 142.61 (d, *J* = 13.0 Hz), 133.43 (d, *J* = 10.7 Hz), 117.17 (dd, *J* = 116.1, 21.6 Hz), 110.90 (d, *J* = 22.3 Hz), 107.86 (d, *J* = 28.5 Hz), 52.74 (s), 43.31 (s).

2-(2-(2-Chlorophenoxy)acetamido)-4-fluorobenzoic acid (**25**)**:**

2-Chlorophenol (1.34 mmol; 0.14 mL) and potassium carbonate (2.44 mmol; 0.34 g) were dissolved in 1 mL DMF and were stirred for 10 minutes at RT. The intermediate **71** (1.22 mmol; 0.30 g) as well as another 4 mL of DMF were added to the reaction mixture which was left to stir at 90°C under argon for 3h (TLC Hexane:EtOAc = 4:1). After completion of the reaction, it was cooled down to RT. Potassium carbonate (6.11 mmol; 3.43 g) was added to the reaction mixture then it was refluxed for 1h. After hydrolysis of the ester, the reaction mixture was cooled down to RT. 15 mL of water was added to the mixture then the pH was set to acidic by concentrated HCl. The formed precipitate was filtered and then recrystallized from a mixture of toluene/EtOAc to give orange crystals (0.21 g; 54%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 8.50 (dd, *J* = 12.2, 2.6 Hz, 1H), 8.08 (dd, *J* = 8.8, 6.9 Hz, 1H), 7.47 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.36 – 7.26 (m, 1H), 7.23 – 7.11 (m, 1H), 7.10 – 6.98 (m, 2H), 4.89 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.44 (s), 167.44 (s), 164.85 (d, *J* = 249.6 Hz), 152.72 (s), 142.09 (d, *J* = 12.9 Hz), 133.97 (d, *J* = 10.9 Hz), 130.21 (s), 128.34 (s), 122.74 (s), 121.80 (s), 113.71 (d, *J* = 144.5 Hz), 110.29 (d, *J* = 22.1 Hz), 106.65 (d, *J* = 28.4 Hz), 68.22 (s). HRMS *m/z* $[M + H]^+$ calcd for $C_{15}H_{12}ClFNO_4$ 324.0433, found: 324.0432.



Methyl 2-amino-4-bromobenzoate (**72**)**:**

Sulfuric acid (27.72 mmol; 1.51 mL) was added to a solution of 2-amino-4-bromobenzoic acid (2.31 mmol; 0.50 g) in 11 mL methanol and was left to stir to reflux for three days (TLC Hexane:EtOAc = 4:1). When the reaction was complete, the reaction mixture was concentrated under reduced pressure and taken back in water. The obtained solution was set to basic pH with a 25% solution of NaOH to allow the formation of a precipitate, which was filtered and dried. The precipitate was further purified by automated flash chromatography on 24 g of silica gel (gradient from 90/10 Hexane/EtOAc to 100% EtOAc) to give a white solid (0.17 g; 31%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.6 Hz, 1H), 6.83 (d, *J* = 1.9 Hz, 1H), 6.74 (dd, *J* = 8.6, 1.9 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.20 (s), 151.32 (s), 132.71 (s), 128.82 (s), 119.64 (s), 119.13 (s), 109.74 (s), 51.78 (s).

Methyl 4-bromo-2-(2-chloroacetamido)benzoate (73):

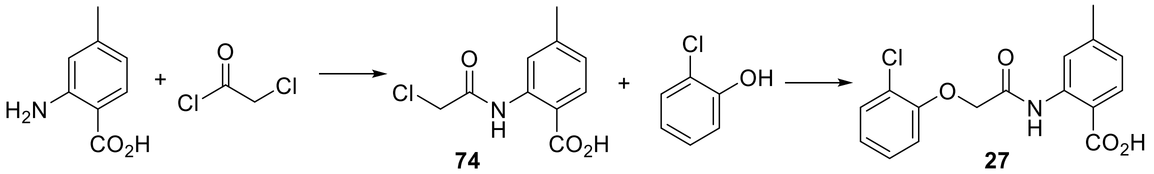
The aniline **72** (0.59 mmol; 0.14 g) was acylated with chloroacetyl chloride (1.17 mmol; 0.09 mL) according to **71**. Volatiles were evaporated under reduced pressure to give a white solid (0.17 g; 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.91 (s, 1H), 8.96 (d, *J* = 1.9 Hz, 1H), 7.90 (t, *J* = 6.3 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 4.21 (s, 2H), 3.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.96 (s), 165.50 (s), 141.22 (s), 132.17 (s), 129.71 (s), 126.89 (s), 123.45 (s), 114.64 (s), 52.86 (s), 43.31 (s).

4-Bromo-2-(2-(2-chlorophenoxy)acetamido)benzoic acid (11):

2-Chlorophenol (0.52 mmol; 0.05 mL) was alkylated with intermediate **73** (0.47 mmol; 0.15 g) under the same conditions as compound **25** was prepared. After recrystallization from toluene/EtOAc, yellow crystals were isolated (0.13 g; 72%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.92 (s, 1H), 11.91 (s, 1H), 8.91 (d, *J* = 1.9 Hz, 1H), 7.98 – 7.88 (m, 1H), 7.47 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.41 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.35 – 7.25 (m, 1H), 7.24 – 7.13 (m, 1H), 7.02 (tt, *J* = 7.3, 3.6 Hz, 1H), 4.88 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.57 (s), 167.32 (s), 152.71 (s), 140.96 (s), 132.93 (s), 130.20 (s), 128.34 (s), 127.54 (s), 126.15 (s), 122.73 (s), 122.34 (s), 121.77 (s), 115.63 (s), 114.43 (s), 68.20 (s). HRMS *m/z* $[M + H]^+$ calcd for $C_{15}H_{12}BrClNO_4$ 383.9633, found: 383.9627.



2-(2-Chloroacetamido)-4-methylbenzoic acid (74):

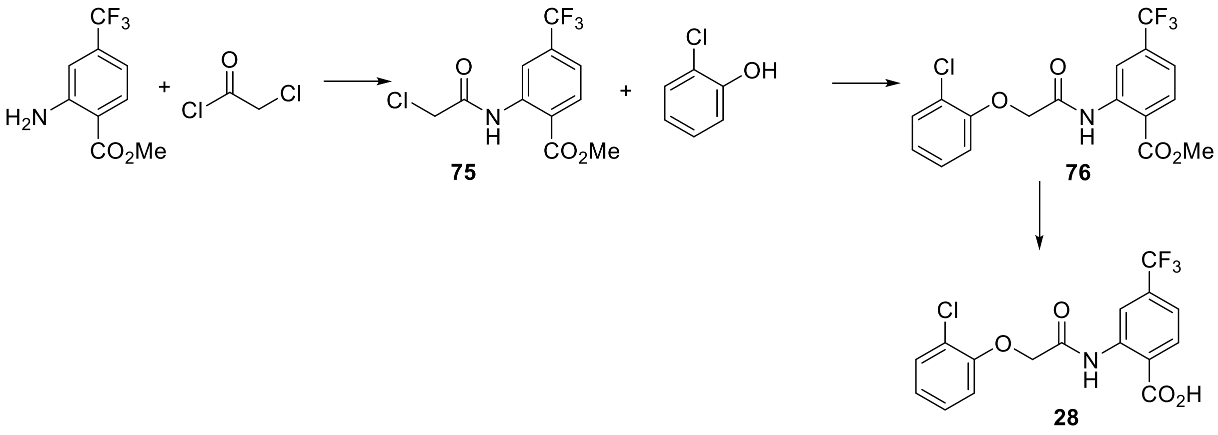
2-Amino-4-methylbenzoicacid (3.31 mmol; 0.50 g) and potassium carbonate (6.62 mmol; 0.91 g) were dissolved in 10 mL THF and were stirred for 10 min at RT. The mixture was cooled to 0°C then chloroacetyl chloride (6.62 mmol; 0.53 mL) was added dropwise for 5 min. The mixture was stirred at 0°C for further 15 min. Then the ice bath was removed and the mixture was stirred at RT overnight (TLC Hexane:EtOAc = 4:1). When the reaction was complete, 50 mL of EtOAc was added then the mixture was washed three times with a solution of 0.1M NaOH. The pH of the aqueous was set to acid by addition of a 2M solution of HCl. The mixture was then extracted three times with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give a white solid (0.66 g; 87%).

^1H NMR (400 MHz, DMSO-d_6) δ 13.58 (s, 1H), 11.83 (s, 1H), 8.39 (s, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.03 (d, J = 8.6 Hz, 1H), 4.44 (s, 2H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.32 (s), 165.17 (s), 144.71 (s), 140.01 (s), 131.17 (s), 124.20 (s), 120.03 (s), 114.03 (s), 43.46 (s), 21.60 (s). HRMS *m/z* $[M - H]^-$ calcd for $C_{10}H_{10}ClNO_3$ 226.0276, found: 226.0271.

2-(2-(2-Chlorophenoxy)acetamido)-4-methylbenzoic acid (27):

The intermediate **74** (0.88 mmol; 0.20 g), 2-chlorophenol (7.85 mmol; 0.88 mL) and potassium carbonate (1.08 mmol; 0.15 g) were dissolved in 4 mL DMF and left to stir at 90°C under argon overnight (TLC Hexane:EtOAc = 1:1). When the reaction was complete, the reaction mixture was concentrated under reduced pressure then taken back in toluene and concentrated again. The pH of the residue was set to acid with a 1M solution of HCl then extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by automated flash chromatography on 24 g of silica gel (gradient from 50/50 Hexane/EtOAc to 100% EtOAc) to give an orange solid (0.03 g; 10%).[7]

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.48 (s, 1H), 11.86 (s, 1H), 8.52 (s, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.47 (dd, J = 7.9, 1.5 Hz, 1H), 7.38 – 7.24 (m, 1H), 7.16 (dd, J = 8.2, 0.9 Hz, 1H), 7.03 (dd, J = 10.8, 4.4 Hz, 2H), 4.85 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.10 (s), 166.76 (s), 152.81 (s), 144.59 (s), 140.01 (s), 131.15 (s), 130.17 (s), 128.30 (s), 123.99 (s), 122.63 (s), 121.78 (s), 120.26 (s), 114.36 (s), 113.86 (s), 68.30 (s), 21.59 (s). HRMS m/z [M + H]$^+$ calcd for $C_{16}H_{14}ClNO_4$ 320.0684, found: 320.0683.



Methyl 2-(2-chloroacetamido)-4-(trifluoromethyl)benzoate (**75**):

Methyl 2-amino-4-trifluoromethyl-benzoate (1.0 mmol; 0.219 g) and chloroacetyl chloride (2.0 mmol; 0.160 mL) were reacted according to the synthesis of **59**. After evaporation, a white solid was obtained (0.28 g; 95%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.37 (s, 1H), 8.71 (d, J = 0.9 Hz, 1H), 8.17 (d, J = 8.2 Hz, 1H), 7.63 (dd, J = 8.3, 1.2 Hz, 1H), 4.49 (s, 2H), 3.93 (s, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -62.20

(s). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 166.87 (s), 166.29 (s), 139.77 (s), 133.98 (s), 133.55 (s), 132.51 (s), 121.67 (s), 120.77 (d, *J* = 3.7 Hz), 117.71 (d, *J* = 4.2 Hz), 53.51 (s), 43.79 (s).

Methyl 2-(2-(2-chlorophenoxy)acetamido)-4-(trifluoromethyl)benzoate (**76**):

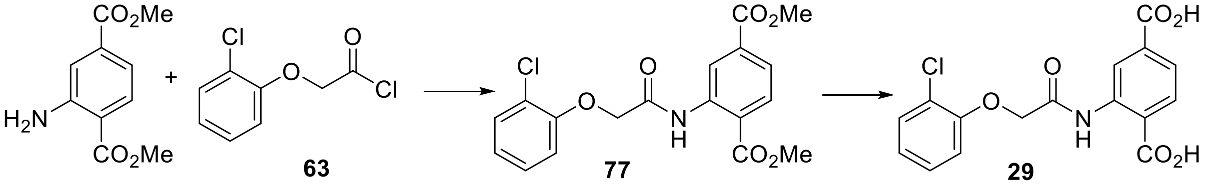
The intermediate **75** (0.3 mmol; 0.089 g) was reacted with 2-chlorophenol (0.33 mmol; 0.034 mL) according to synthesis of **61**. The product was isolated as a white solid (0.041 g; 35%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.44 (s, 1H), 8.90 (s, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 7.62 (d, *J* = 7.1 Hz, 1H), 7.51 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.39 - 7.28 (m, 1H), 7.23 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.12 - 7.00 (m, 1H), 4.91 (s, 2H), 3.89 (s, 3H). ^{19}F NMR (282 MHz, DMSO-*d*$_6$) δ -62.18 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{17}H_{14}ClF_3NO_4$ 410.0377, found: 410.0371.

2-(2-(2-Chlorophenoxy)acetamido)-4-(trifluoromethyl)benzoic acid (**28**):

The methyl ester **76** (0.09 mmol; 0.035 g) was hydrolyzed similarly to **5**. After evaporation, the product was recrystallized from acetonitrile to give a white solid (0.016 g; 48%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 14.19 (s, 1H), 11.99 (s, 1H), 9.05 (s, 1H), 8.21 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 1H), 7.04 (t, *J* = 7.4 Hz, 1H), 4.91 (s, 2H). ^{19}F NMR (282 MHz, DMSO-*d*$_6$) δ -62.14 (s). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 168.60 (s), 168.03 (s), 153.18 (s), 140.77 (s), 137.18 (s), 132.95 (s), 130.68 (s), 128.84 (s), 123.23 (s), 122.22 (s), 120.72 (s), 120.30 - 119.95 (m), 117.49 (s), 117.05 - 116.60 (m), 114.93 (s), 68.65 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{16}H_{12}ClF_3NO_4$ 396.0221, found: 396.0224.



Dimethyl 2-(2-(2-chlorophenoxy)acetamido)terephthalate (**77**):

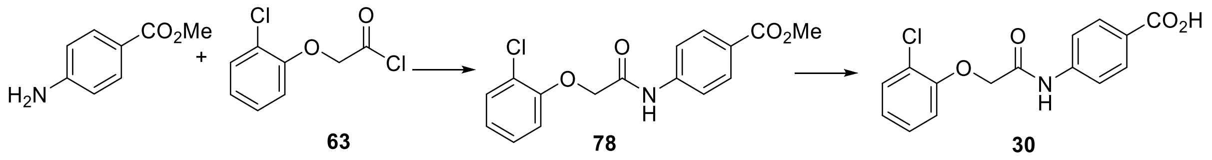
Dimethyl 2-aminoterephthalate (0.7 mmol; 0.146 g) and K_2CO_3 (1.4 mmol; 0.193 g) were dissolved in THF (10 mL) and stirred for 15 min at RT. Then intermediate **63** (0.77 mmol; 0.158 g) was added at once. The reaction mixture was stirred at RT for 2.5 h. Water was added then it was extracted with EtOAc (3x30 mL). The combined organics were washed with brine, dried with Na_2SO_4 and evaporated to dryness. The residue was recrystallized from MeCN to give the pure product as a white solid (0.179 g; 68%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.33 (s, 1H), 9.10 (d, *J* = 1.5 Hz, 1H), 8.09 (d, *J* = 8.3 Hz, 1H), 7.79 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.51 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.39 - 7.28 (m, 1H), 7.22 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.05 (td, *J* = 7.8, 1.4 Hz, 1H), 4.90 (s, 2H), 3.91 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 167.47 (s), 167.03 (s), 165.74 (s), 153.20 (s), 139.51 (s), 134.58 (s), 131.66 (s), 130.70 (s), 128.84 (s), 124.36 (s), 123.28 (s), 121.89 (s), 121.24 (s), 115.15 (s), 68.61 (s), 53.27 (s), 53.15 (s). HRMS *m/z* $[M + H]^+$ calcd for $C_{18}H_{17}ClNO_6$ 378.0739, found: 378.0742.

2-(2-(2-Chlorophenoxy)acetamido)terephthalic acid (**29**):

The methyl ester **77** (0.35 mmol; 0.134 g) was hydrolyzed similarly to **5**. After evaporation, the product was isolated as a white solid (0.085 g; 69%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 14.01 (s, 1H), 13.38 (s, 1H), 11.92 (s, 1H), 9.24 (d, *J* = 1.5 Hz, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.72 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.49 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.39 - 7.26 (m, 1H), 7.20 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.04 (td, *J* = 7.7, 1.4 Hz, 1H), 4.89 (s, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 168.95 (s), 167.40 (s), 167.03 (s), 153.37 (s), 147.49 (s), 140.28 (s), 131.88 (s), 130.66 (s), 130.58 (s), 128.80 (s), 124.02 (s), 123.14 (s), 122.31 (s), 121.28 (s), 114.99 (s), 68.83 (s). HRMS *m/z* $[M + H]^+$ calcd for $C_{16}H_{13}ClNO_6$ 350.0426, found: 350.0429.



Methyl 4-(2-(2-chlorophenoxy)acetamido)benzoate (**78**):

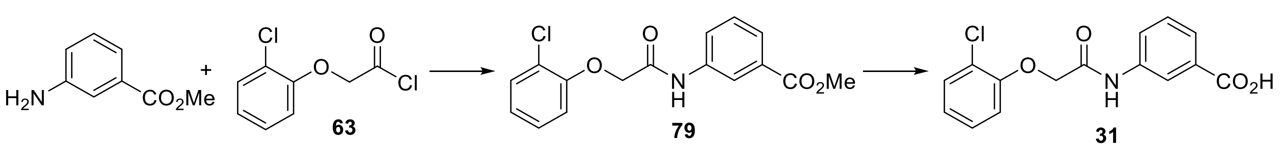
Methyl 4-aminobenzoate (0.7 mmol; 0.106 g) and intermediate **63** (0.77 mmol, 0.158 g) were reacted similarly to the synthesis of **77**. The amide was isolated as a white solid (0.202 g; 90%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 10.52 (s, 1H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.47 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.39 - 7.21 (m, 1H), 7.09 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.00 (td, *J* = 7.8, 1.3 Hz, 1H), 4.89 (s, 2H), 3.83 (s, 3H). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 167.07 (s), 166.23 (s), 153.86 (s), 143.26 (s), 130.83 (s), 130.58 (s), 128.74 (s), 124.83 (s), 122.62 (s), 121.88 (s), 119.26 (s), 114.51 (s), 68.03 (s), 52.40 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{16}H_{15}ClNO_4$ 320.0684, found: 320.0689.

4-(2-(2-Chlorophenoxy)acetamido)benzoic acid (**30**):

The methyl ester **78** (0.36 mmol; 0.114 g) was hydrolyzed similarly to **5**. After evaporation, the residue was recrystallized from MeCN to give a light brown solid (0.011 g; 10%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 12.73 (s, 1H), 10.47 (s, 1H), 7.92 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 4.88 (s, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 167.32 (s), 166.95 (s), 153.89 (s), 142.85 (s), 130.91 (s), 130.57 (s), 128.73 (s), 126.12 (s), 122.64 (s), 121.93 (s), 119.17 (s), 114.58 (s), 68.13 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{15}H_{13}ClNO_4$ 306.0528, found: 306.0530.



Methyl 3-(2-(2-chlorophenoxy)acetamido)benzoate (**79**):

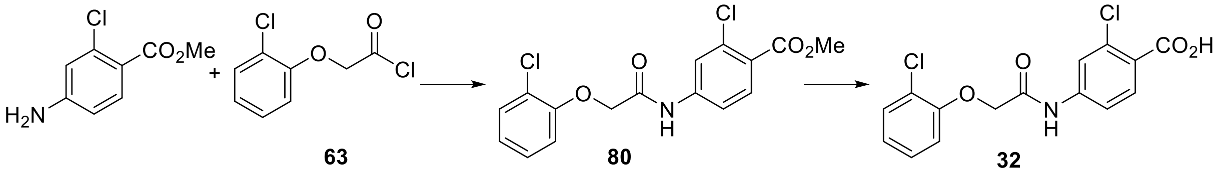
Methyl 3-aminobenzoate (0.7 mmol; 0.106 g) and intermediate **63** (0.77 mmol, 0.158 g) were reacted similarly to the synthesis of **77**. The amide was isolated as a white solid (0.218 g; 97%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.42 (s, 1H), 8.32 (t, *J* = 1.7 Hz, 1H), 7.91 - 7.77 (m, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.56 - 7.40 (m, 2H), 7.37 - 7.23 (m, 1H), 7.09 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.00 (td, *J* = 7.7, 1.3 Hz, 1H), 4.87 (s, 2H), 3.86 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.83 (s), 166.47 (s), 153.90 (s), 139.25 (s), 130.66 (s), 130.57 (s), 129.82 (s), 128.74 (s), 124.75 (s), 124.36 (s), 122.61 (s), 121.91 (s), 120.35 (s), 114.51 (s), 68.02 (s), 52.70 (s). HRMS *m/z* $[M + H]^+$ calcd for $C_{16}H_{15}ClNO_4$ 320.0684, found: 320.0688.

3-(2-(2-Chlorophenoxy)acetamido)benzoic acid (**31**):

The methyl ester **79** (0.59 mmol; 0.19 g) was hydrolyzed similarly to **5**. After evaporation, the product was isolated as a pale yellow solid (0.165 g; 91%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.99 (s, 1H), 10.36 (s, 1H), 8.26 (t, *J* = 1.6 Hz, 1H), 7.91 - 7.79 (m, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.55 - 7.41 (m, 2H), 7.38 - 7.25 (m, 1H), 7.09 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.00 (td, *J* = 7.7, 1.3 Hz, 1H), 4.86 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.52 (s), 166.74 (s), 153.92 (s), 139.08 (s), 131.86 (s), 130.57 (s), 129.57 (s), 128.74 (s), 124.94 (s), 124.00 (s), 122.61 (s), 121.92 (s), 120.64 (s), 114.54 (s), 68.09 (s). HRMS *m/z* $[M + H]^+$ calcd for $C_{15}H_{13}ClNO_4$ 306.0528, found: 306.0531.



Methyl 2-chloro-4-(2-(2-chlorophenoxy)acetamido)benzoate (**80**):

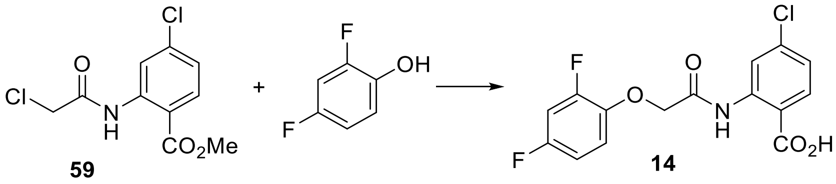
Methyl 4-amino-2-chlorobenzoate (0.7 mmol; 0.13 g) and intermediate **63** (0.77 mmol, 0.158 g) were reacted similarly to the synthesis of **77**. After evaporation, the residue was recrystallized from MeCN to give the pure product as a white solid (0.139 g; 56%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.63 (s, 1H), 7.94 (d, *J* = 2.0 Hz, 1H), 7.88 (d, *J* = 8.6 Hz, 1H), 7.62 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.47 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.35 - 7.25 (m, 1H), 7.09 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.00 (td, *J* = 7.7, 1.3 Hz, 1H), 4.89 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 167.45 (s), 165.16 (s), 153.39 (s), 142.94 (s), 133.59 (s), 132.99 (s), 130.59 (s), 128.75 (s), 124.17 (s), 122.68 (s), 120.97 (s), 117.89 (s), 117.50 (s), 114.57 (s), 67.96 (s), 52.77 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{16}H_{14}Cl_2NO_4$ 354.0294, found: 354.0301.

2-Chloro-4-(2-(2-chlorophenoxy)acetamido)benzoic acid (**32**):

The methyl ester **80** (0.68 mmol; 0.24 g) was hydrolyzed similarly to **5**. After evaporation, the residue was recrystallized from MeCN to give a light-brown solid (0.098 g; 42%).

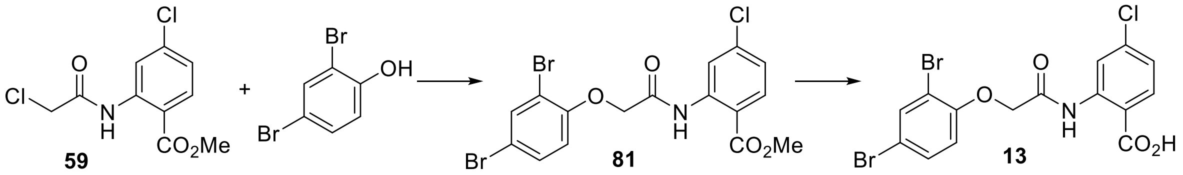
^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 13.16 (s, 1H), 10.59 (s, 1H), 7.91 (d, *J* = 2.0 Hz, 1H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.58 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.47 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.35 - 7.24 (m, 1H), 7.09 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.00 (td, *J* = 7.8, 1.3 Hz, 1H), 4.89 (s, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 167.32 (s), 166.35 (s), 153.85 (s), 142.42 (s), 133.45 (s), 132.85 (s), 130.92 (s), 130.58 (s), 128.74 (s), 122.70 (s), 121.97 (s), 120.97 (s), 117.83 (s), 114.65 (s), 68.07 (s). HRMS *m/z* [M - H]$^-$ calcd for $C_{15}H_{10}Cl_2NO_4$ 337.9992, found: 337.9989.



4-Chloro-2-(2-(2,4-difluorophenoxy)acetamido)benzoic acid (**14**):

2,4-Difluorophenol (0.84 mmol; 0.11 g) was alkylated with intermediate **59** (0.76 mmol; 0.20 g) under the same conditions as compound **25** was prepared. The product was obtained after recrystallization from toluene/EtOAc as yellow crystals (0.03 g; 10%).

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.12 (s, 1H), 8.76 (d, *J* = 2.1 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.33 (ddd, *J* = 11.3, 7.2, 2.7 Hz, 1H), 7.30 – 7.23 (m, 2H), 7.13 – 6.94 (m, 1H), 4.84 (s, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 168.70 (s), 167.27 (s), 157.48 (d, *J* = 10.5 Hz), 155.09 (d, *J* = 10.4 Hz), 152.71 (d, *J* = 12.6 Hz), 150.24 (d, *J* = 12.6 Hz), 141.89 (dd, *J* = 10.8, 3.4 Hz), 141.08 (s), 138.60 (s), 132.94 (s), 123.14 (s), 119.07 (s), 116.55 – 116.10 (m), 115.07 (s), 110.91 (dd, *J* = 22.6, 3.9 Hz), 105.32 (s), 105.07 (d, *J* = 5.3 Hz), 104.82 (s), 68.61 (s). ^{19}F NMR (282 MHz, DMSO-*d*$_6$) δ -118.93 (d, *J* = 2.6 Hz), -128.40 (t, *J* = 9.8 Hz). HRMS *m/z* [M + H]$^+$ calcd for $C_{15}H_{11}ClF_2NO_4$ 342.0339, found: 342.0338.



Methyl 4-chloro-2-(2-(2,4-dibromophenoxy)acetamido)benzoate (81):

The intermediate **59** (0.76 mmol; 0.20 g), 2,4-dibromophenol (0.55 mmol; 0.14 g) and potassium carbonate (1.14 mmol; 0.16 g) were dissolved in 4 mL DMF and left to stir at 90°C under argon for 6 h (TLC Hexane:EtOAc = 4:1). When the reaction was complete, the reaction mixture was concentrated under reduced pressure then crystallized in methanol to give a pink solid (0.15 g; 40%).

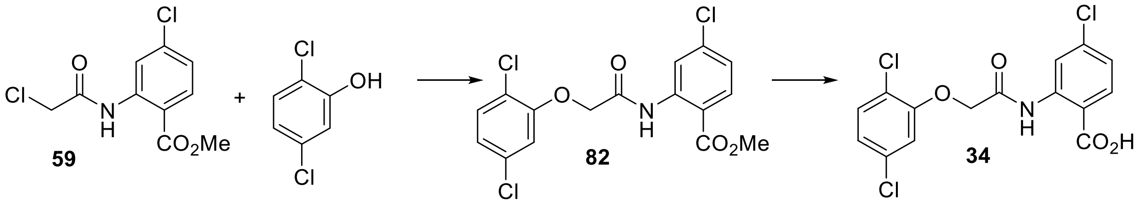
^{1}H NMR (400 MHz, CDCl$_3$) δ 11.73 (s, 4H), 8.70 (d, *J* = 2.1 Hz, 12H), 7.87 (d, *J* = 8.6 Hz, 13H), 7.63 (d, *J* = 2.4 Hz, 12H), 7.29 (dd, *J* = 8.7, 2.4 Hz, 11H), 7.02 (dd, *J* = 8.6, 2.1 Hz, 14H), 6.76 (d, *J* = 8.8 Hz, 16H), 4.59 (s, 27H), 3.79 (s, 37H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 167.02 (s), 166.47 (s), 153.33 (s), 140.60 (s), 140.41 (s), 135.90 (s), 131.93 (s), 131.39 (s), 123.58 (s), 120.65 (s), 115.69 (s), 114.99 (s), 114.42 (s), 113.60 (s), 69.24 (s), 52.43 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{16}H_{13}Br_2ClNO_4$ 475.8894, found: 475.8897.

4-Chloro-2-(2-(2,4-dibromophenoxy)acetamido)benzoic acid (13):

The desired anthranilic acid was purified from the filtrate of the crystallization in the previous step (**81**) by automated flash chromatography on 12 g of silica gel (gradient from 80/20 Hexane/EtOAc to 100% EtOAc) to give a white solid (0,08 g; 22%).

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.07 (s, 1H), 8.71 (d, *J* = 2.1 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.85 (d, *J* = 2.4 Hz, 1H), 7.53 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.26 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.11 (d, *J* =

8.9 Hz, 1H), 4.90 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.41 (s), 166.99 (s), 153.39 (s), 140.93 (s), 138.17 (s), 134.93 (s), 132.91 (s), 131.66 (s), 123.15 (s), 119.33 (s), 116.08 (s), 113.52 (s), 112.48 (s), 68.61 (s). One quaternary carbon was not observed and is expected to be close to the baseline. HRMS *m/z* [M - H]$^-$ calcd for $C_{15}H_9Br_2ClNO_4$ 459.8592, found: 459.8592.



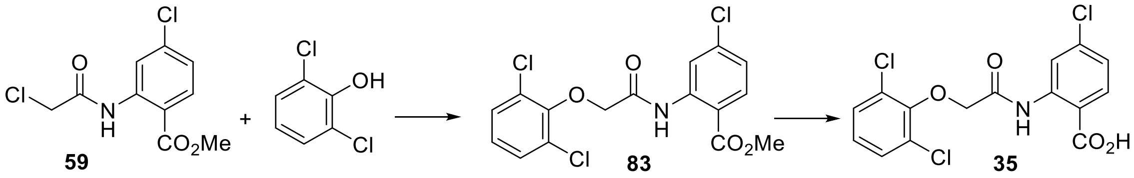
Methyl 4-chloro-2-(2-(2,5-dichlorophenoxy)acetamido)benzoate (**82**):

The intermediate **59** (0.76 mmol; 0.20 g), 2,5-dichlorophenol (0.92 mmol; 0.15 g) and potassium carbonate (1.14 mmol; 0.16 g) were dissolved in 4 mL DMF and left to stir at 90°C under argon for 4 h (TLC Hexane:EtOAc = 4:1). When the reaction was complete, the reaction mixture was concentrated under reduced pressure then purified by automated flash chromatography on 12 g of silica gel (gradient from 80/20 Hexane/EtOAc to 100% EtOAc) to give a white solid (0.21 g; 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.92 (s, 1H), 8.86 (d, *J* = 2.1 Hz, 1H), 7.98 (d, *J* = 8.6 Hz, 1H), 7.40 – 7.32 (m, 1H), 7.13 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.03 – 6.97 (m, 2H), 4.70 (s, 2H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.51 (s), 166.50 (s), 153.64 (s), 141.10 (s), 140.90 (s), 133.40 (s), 132.10 (s), 131.43 (s), 123.86 (s), 123.42 (s), 122.38 (s), 121.06 (s), 115.36 (s), 114.60 (s), 69.21 (s), 52.66 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{16}H_{13}Cl_3NO_4$ 387.9905, found: 387.9907.

4-Chloro-2-(2-(2,5-dichlorophenoxy)acetamido)benzoic acid (**34**):

A 1.4 M aq ueous solution of lithium hydroxide (0.77 mmol; 0.55 mL) was added to a solution of **82** (0.55 mmol; 0.21 g) in 1 mL dioxane and let to stir at RT for 1 h (TLC Hexane:EtOAc = 1:1). When the reaction was complete, the reaction mixture was quenched with 0.3 mL of a 1 M HCl solution and concentrated under reduced pressure. The crude was purified by automated flash chromatography on 12 g of silica gel (gradient from 50/50 Hexane/EtOAc to 100% EtOAc) The evaporated fractions were then recrystallized from a mixture of toluene/EtOAc to give a white solid (0.05 g; 25%).[8]

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.75 (d, J = 1.9 Hz, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.36 (d, J = 2.1 Hz, 1H), 7.29 (dd, J = 8.6, 2.0 Hz, 1H), 7.11 (dd, J = 8.5, 2.1 Hz, 1H), 4.96 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.45 (s), 166.84 (s), 153.30 (s), 140.96 (s), 138.46 (s), 132.94 (s), 132.32 (s), 131.14 (s), 123.24 (s), 122.50 (s), 120.68 (s), 119.43 (s), 115.39 (s), 114.82 (s), 68.25 (s). HRMS m/z [M + H]$^+$ calcd for $C_{15}H_{11}Cl_3NO_4$ 373.9748, found: 373.9751.



Methyl 4-chloro-2-(2-(2,6-dichlorophenoxy)acetamido)benzoate (83):

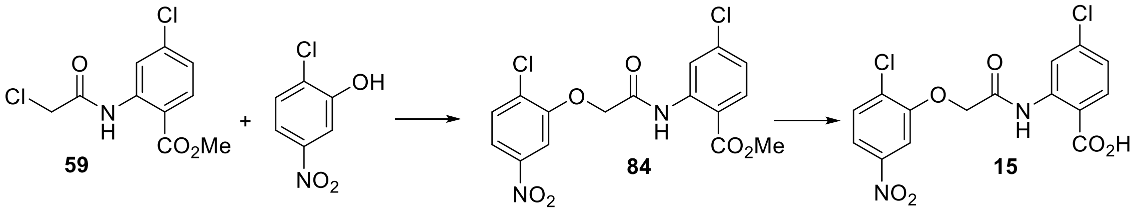
The intermediate **59** (0.76 mmol; 0.20 g), 2,6-dichlorophenol (0.92 mmol; 0.15 g) and potassium carbonate (1.14 mmol; 0.16 g) were dissolved in 4 mL DMF and left to stir at 90°C under argon for 4 h (TLC Hexane:EtOAc = 4:1). When the reaction was complete, the reaction mixture was concentrated under reduced pressure then purified by automated flash chromatography on 12 g of silica gel (gradient from 80/20 Hexane/EtOAc to 100% EtOAc) to give a yellow solid (0.30 g; 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.11 (s, 1H), 8.94 (d, J = 2.1 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.36 (s, 1H), 7.34 (s, 1H), 7.13 (dd, J = 8.6, 2.1 Hz, 1H), 7.11 – 7.05 (m, 1H), 4.65 (s, 2H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.37 (s), 167.08 (s), 150.26 (s), 141.24 (s), 140.84 (s), 133.43 (s), 132.22 (s), 129.62 (s), 129.27 (s), 128.66 (s), 126.33 (s), 123.63 (s), 120.88 (s), 114.67 (s), 71.54 (s), 52.72 (s). HRMS m/z [M + H]$^+$ calcd for $C_{16}H_{13}Cl_3NO_4$ 387.9905, found: 387.9910; [M + Na]$^+$ calcd for $C_{16}H_{12}Cl_3NO_4Na$ 409.9724, found: 409.9728.

4-Chloro-2-(2-(2,6-dichlorophenoxy)acetamido)benzoic acid (**35**):

The methyl ester **83** (0.62 mmol; 0.24 g) was hydrolyzed similarly to the preparation of **34**. After evaporation of the merged fractions, a white solid (0.18 g; 79%) was obtained.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 13.97 (s, 1H), 8.70 (d, *J* = 2.1 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.24 (t, *J* = 8.1 Hz, 1H), 7.15 (dd, *J* = 8.4, 2.2 Hz, 1H), 4.59 (s, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 168.13 (s), 166.27 (s), 149.62 (s), 140.91 (s), 135.70 (s), 132.85 (s), 129.35 (s), 128.43 (s), 126.73 (s), 122.28 (s), 118.43 (s), 71.49 (s). One quaternary carbon was not observed and is expected to be close to the baseline. HRMS *m/z* $[M - H]^-$ calcd for $C_{15}H_9Cl_3NO_4$ 371.9603, found: 371.9602.



Methyl 4-chloro-2-(2-(2-chloro-5-nitrophenoxy)acetamido)benzoate (**84**):

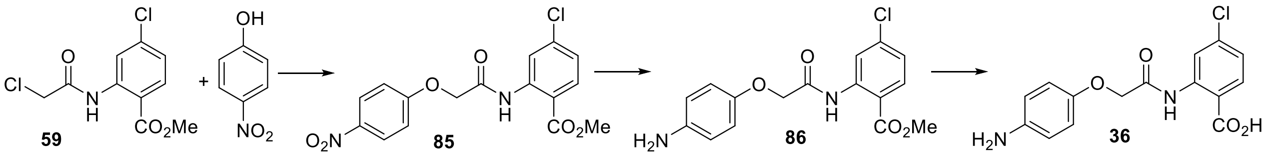
The intermediate **59** (1.0 mmol; 0.262 g) was reacted with 2-chloro-5-nitrophenol (1.1 mmol; 0.191 g) according to the synthesis of **61**. The dried light-brown powder is the expected product (0.348 g; 87%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.45 (s, 1H), 8.63 (d, *J* = 2.0 Hz, 1H), 8.04 (d, *J* = 2.4 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.94 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.35 (dd, *J* = 8.6, 2.1 Hz, 1H), 5.14 (s, 2H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 167.10 (s), 166.96 (s), 153.53 (s), 147.55 (s), 140.72 (s), 139.20 (s), 132.93 (s), 131.48 (s), 129.76 (s), 124.15 (s), 120.63 (s), 118.09 (s), 115.97 (s), 109.85 (s), 68.86 (s), 53.14 (s). HRMS *m/z* $[M + H]^+$ calcd for $C_{16}H_{13}Cl_2N_2O_6$ 399.0145, found: 399.0147.

4-Chloro-2-(2-(2-chloro-5-nitrophenoxy)acetamido)benzoic acid (**15**):

The methyl ester **84** (0.5 mmol; 0.200 g) was hydrolyzed similarly to the method of **5**. After evaporation, the product was isolated as a yellow solid (0.160 g; 83%).

^{1}H NMR (300 MHz, DMSO-*d$_6$*) δ 14.40 (bs, 1H), 8.61 (s, 1H), 8.03 - 7.92 (m, 2H), 7.89 (d, J = 8.7 Hz, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 5.07 (s, 2H). ^{13}C NMR (101 MHz, DMSO-*d$_6$*) δ 168.58 (s), 166.49 (s), 154.11 (s), 147.43 (s), 141.50 (s), 135.63 (s), 133.25 (s), 131.35 (s), 129.86 (s), 122.55 (s), 118.82 (s), 117.66 (s), 109.47 (s), 69.10 (s). HRMS *m/z* [M + Na]$^{+}$ calcd for $C_{15}H_{10}Cl_2N_2O_6Na$ 406.9808, found: 406.9810.



Methyl 4-chloro-2-(2-(4-nitrophenoxy)acetamido)benzoate (**85**):

The intermediate **59** (2.0 mmol; 0.524 g) was reacted with 4-nitrophenol (2.2 mmol; 0.306 g) according to the synthesis of **61**. The expected product was isolated as a pale-yellow powder (0.63 g; 86%).

^{1}H NMR (300 MHz, DMSO-*d$_6$*) δ 11.76 (s, 1H), 8.70 (d, *J* = 1.9 Hz, 1H), 8.31 (d, *J* = 9.2 Hz, 2H), 8.05 (d, *J* = 8.6 Hz, 1H), 7.50 - 7.15 (m, 3H), 4.99 (s, 2H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, DMSO-*d$_6$*) δ 166.91 (s), 166.63 (s), 162.01 (s), 141.75 (s), 140.45 (s), 138.90 (s), 132.56 (s), 125.97 (s, 2C), 123.47 (s), 119.49 (s), 115.54 (s, 2C), 114.89 (s), 67.60 (s), 52.80 (s). HRMS *m/z* [M + H]$^{+}$ calcd for $C_{16}H_{15}ClN_2O_6$ 365.0535, found: 365.0534.

Methyl 2-(2-(4-aminophenoxy)acetamido)-4-chlorobenzoate (**86**):

The methyl 4-chloro-2-(2-(4-nitrophenoxy)acetamido)benzoate **85** (1.0 mmol; 0.365 g) was dissolved in the mixture of MeOH (100 mL) and DCM (100 mL). The flask was evacuated then under Ar atmosphere, palladium catalyst (5% on charcoal; 0.04 g) and hydrazine hydrate (25%wt; 2

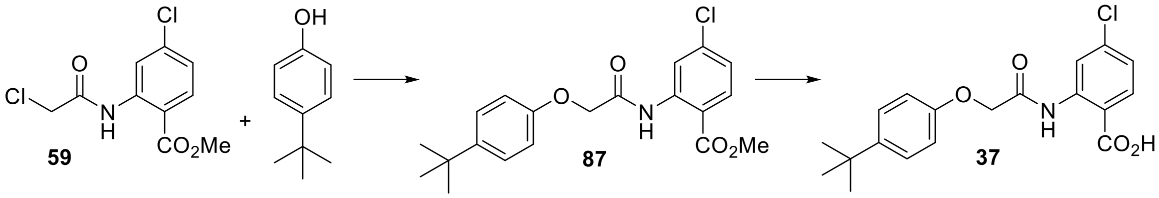
mL) was added to the solution. The mixture was vigorously stirred for 25 h. The catalyst was filtered off on a Celite pad. The filtrate was evaporated. The residue was partitioned between water and EtOAc (50-50 mL). The aq. layer was further extracted with EtOAc (2x50 mL). The combined organics were washed with brine, dried with Na_2SO_4 and evaporated to dryness to give a yellow solid (0.328 g; 98%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.80 (s, 1H), 8.77 (d, *J* = 2.1 Hz, 1H), 8.05 (d, *J* = 8.6 Hz, 1H), 7.33 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.56 (d, *J* = 8.8 Hz, 2H), 4.60 (s, 2H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 168.33 (s), 166.74 (s), 164.33 (s), 148.34 (s), 143.60 (s), 140.68 (s), 138.91 (s), 132.60 (s), 123.21 (s), 119.22 (s), 115.88 (s), 114.75 (s), 68.32 (s), 52.75 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{16}H_{16}ClN_2O_4$ 335.0793, found: 335.0803.

2-(2-(4-Aminophenoxy)acetamido)-4-chlorobenzoic acid (**36**):

The methyl ester **86** (0.08 mmol; 0.028 g) was hydrolyzed similarly to the synthesis of **5**. The protocol was slightly modified. The pH was carefully set to 7 by the addition of sat. aq, NH_4Cl. After evaporation, the product was isolated as a brown solid (0.022 g; 82%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 12.58 (s, 1H), 8.76 (s, 1H), 8.02 (s, 1H), 7.23 (s, 1H), 6.81 (s, 2H), 6.54 (s, 2H), 4.56 (s, 2H). HRMS *m/z* [M + H]$^+$ calcd for $C_{15}H_{14}ClN_2O_4$ 321.0637, found: 321.0632.



Methyl 2-(2-(4-(*tert*-butyl)phenoxy)acetamido)-4-chlorobenzoate (87):

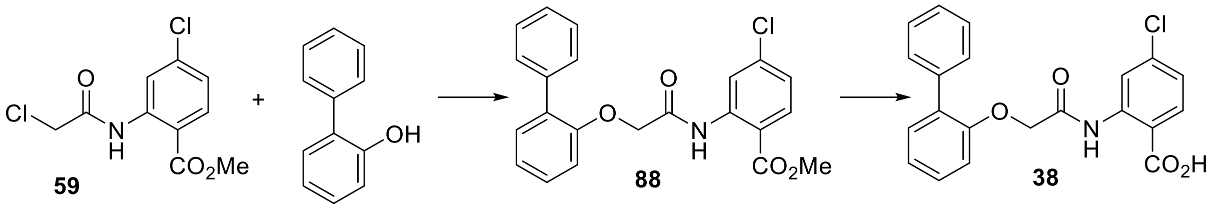
The intermediate **59** (0.76 mmol; 0.20 g), 4-*tert*-butylphenol (0.92 mmol; 0.14 g) and potassium carbonate (1.14 mmol; 0.16 g) were dissolved in 4 mL DMF and left to stir at 90°C under argon for 4h (TLC Hexane/EtOAc = 8:2). When the reaction was complete, the reaction mixture was concentrated under reduced pressure then purified by automated flash chromatography on 12 g of silica gel (gradient from 80/20 Hexane/EtOAc to 100% EtOAc) to give a yellow solid (0.13 g; 44%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.79 (s, 1H), 8.72 (d, *J* = 2.1 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.41 – 7.32 (m, 2H), 7.30 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.08 – 6.98 (m, 2H), 4.72 (s, 2H), 3.90 (s, 3H), 1.24 (d, *J* = 15.7 Hz, 10H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.81 (s), 166.79 (s), 154.83 (s), 144.06 (s), 140.63 (s), 138.89 (s), 132.54 (s), 126.27 (s), 123.24 (s), 119.32 (s), 114.64 (s), 114.42 (s), 67.44 (s), 52.71 (s), 31.26 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{20}H_{23}ClNO_4$ 376.1310, found: 376.1316.

2-(2-(4-(*tert*-Butyl)phenoxy)acetamido)-4-chlorobenzoic acid (**37**):

The methyl ester **87** (0.33 mmol; 0.12 g) was hydrolyzed similarly to the preparation of **34**. After evaporation of the merged fractions, a white solid was obtained (0.09 g; 74%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.45 (s, 1H), 8.78 (d, *J* = 2.2 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.38 – 7.31 (m, 2H), 7.26 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.05 – 6.95 (m, 2H), 4.71 (s, 2H), 1.25 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.66 (s), 167.86 (s), 154.89 (s), 143.92 (s), 141.15 (s), 138.30 (s), 133.01 (s), 126.23 (s), 122.90 (s), 118.75 (s), 115.68 (s), 114.30 (s), 67.35 (s), 33.85 (s), 31.29 (s). HRMS *m/z* [M - H]$^-$ calcd for $C_{19}H_{19}ClNO_4$ 360.1008, found: 360.1005.



Methyl 2-(2-([1,1'-biphenyl]-2-yloxy)acetamido)-4-chlorobenzoate (**88**):

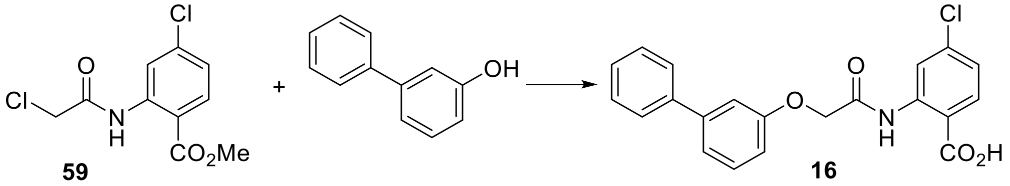
The intermediate **59** (0.31 mmol; 0.08 g) was reacted with 2-phenylphenol (0.34 mmol; 0.058 g) according to the synthesis of **61**. After evaporation, a yellow oil was obtained which was used without further purification (0.108 g; y= 88%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.36 (s, 1H), 8.65 (d, *J* = 2.1 Hz, 1H), 7.98 (d, *J* = 8.6 Hz, 1H), 7.69 - 7.59 (m, 2H), 7.46 - 7.27 (m, 6H), 7.15 (d, *J* = 8.7 Hz, 2H), 4.76 (s, 2H), 3.75 (s, 3H). HRMS *m/z* $[M + Na]^+$ calcd for $C_{22}H_{18}ClNO_4Na$ 418.0817, found: 418.0816.

2-(2-([1,1'-Biphenyl]-2-yloxy)acetamido)-4-chlorobenzoic acid (**38**):

The methyl ester **88** (0.25 mmol; 0.10 g) was hydrolyzed according to the synthesis of **5**. After evaporation, the product was recrystallized from MeCN and isolated as a pale-yellow solid (0.036 g; 38%).

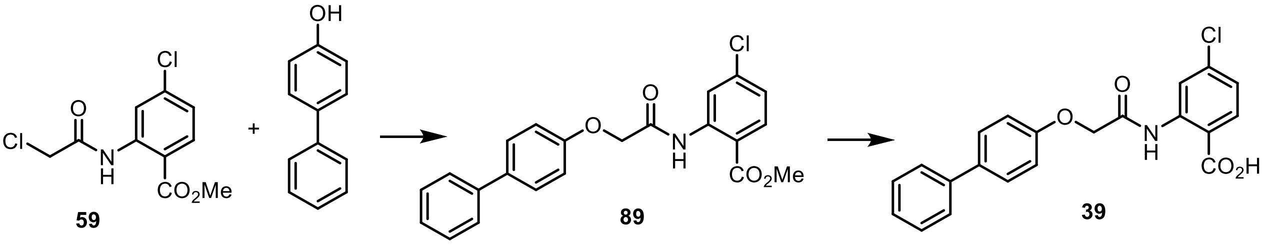
^{1}H NMR (300 MHz, DMSO-d_6) δ 13.90 (s, 1H), 11.90 (s, 1H), 8.73 (s, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.65 (d, *J* = 7.4 Hz, 2H), 7.35 (m, 6H), 7.13 (m, 2H), 4.72 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.97 (s), 168.62 (s), 155.13 (s), 141.53 (s), 139.00 (s), 138.19 (s), 133.44 (s), 131.42 (s), 131.32 (s), 129.92 (s), 129.44 (s), 128.50 (s), 127.51 (s), 123.61 (s), 122.93 (s), 119.74 (s), 115.68 (s), 114.75 (s), 69.77 (s). HRMS *m/z* $[M - H]^-$ calcd for $C_{21}H_{15}ClNO_4$ 380.0693, found: 380.0685.



2-(2-([1,1'-Biphenyl]-3-yloxy)acetamido)-4-chlorobenzoic acid (**16**):

The intermediate **59** (0.25 mmol; 0.066 g) was reacted with 3-phenylphenol (0.28 mmol; 0.048 g) according to the synthesis of **61**. After evaporation, a yellow oil was crystallized from MeCN. The yellow solid gave the ester of **16**. Accidently some water was added to the filtrate. After one weekend at RT, a white precipitate was formed. It was filtered off and proved to be the targeted compound **16** (0.025 g; 26%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.48 (s, 1H), 8.80 (s, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 7.4 Hz, 2H), 7.58 - 7.18 (m, 7H), 7.11 (d, *J* = 7.3 Hz, 1H), 4.86 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.22 (s), 168.16 (s), 158.02 (s), 142.41 (s), 141.60 (s), 140.30 (s), 138.86 (s), 133.56 (s), 130.62 (s), 129.40 (s), 128.20 (s), 127.34 (s), 123.43 (s), 120.71 (s), 119.26 (s), 114.99 (s), 114.41 (s), 113.67 (s), 67.78 (s). HRMS *m/z* $[M + H]^+$ calcd for $C_{21}H_{17}ClNO_4$ 382.0841, found: 382.0845.



59 **89** **39**

Methyl 2-(2-([1,1'-biphenyl]-4-yloxy)acetamido)-4-chlorobenzoate (**89**):

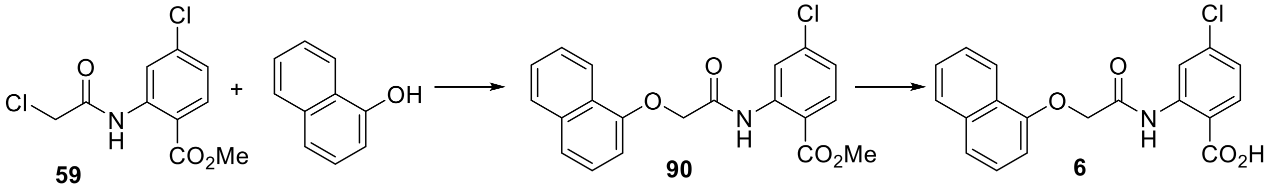
The intermediate **59** (0.25 mmol; 0.066 g) was reacted with 4-phenylphenol (0.28 mmol; 0.048 g) according to the synthesis of **61**. After evaporation, the product was purified by recrystallization from MeCN. The ester **89** was obtained as a yellow solid (0.054 g; 55%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.85 (s, 1H), 8.76 (d, *J* = 2.1 Hz, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.74 - 7.59 (m, 4H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.38 - 7.29 (m, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 4.83 (s, 2H), 3.93 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.12 (s), 167.37 (s), 157.11 (s), 141.13 (s), 139.43 (s), 134.34 (s), 133.10 (s), 129.37 (s), 128.44 (s), 127.43 (s), 126.78 (s), 123.83 (s), 119.82 (s), 117.48 (s), 115.87 (s), 115.13 (s), 67.88 (s), 53.30 (s). HRMS *m/z* $[M + H]^+$ calcd for $C_{22}H_{19}ClNO_4$ 396.0997, found: 396.1007.

2-(2-([1,1'-Biphenyl]-4-yloxy)acetamido)-4-chlorobenzoic acid (**39**):

The methyl ester **89** (0.13 mmol; 0.050 g) was hydrolyzed according to synthesis of **5**. The desired compound was isolated as a yellow powder (0.039 g; 79%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 13.07 (s, 1H), 8.76 (d, *J* = 2.1 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.64 (dd, *J* = 7.9, 6.4 Hz, 4H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.26 - 7.12 (m, 3H), 4.79 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.05 (s), 168.03 (s), 157.31 (s), 141.59 (s), 140.11 (s), 137.84 (s), 134.14 (s), 133.47 (s), 129.35 (s), 128.34 (s), 127.38 (s), 126.77 (s), 123.12 (s), 119.02 (s), 115.83 (s), 109.75 (s), 67.91 (s). HRMS *m/z* $[M + H]^+$ calcd for $C_{21}H_{17}ClNO_4$ 382.0841, found: 382.0844.



Methyl 4-chloro-2-(2-(naphthalen-1-yloxy)acetamido)benzoate (**90**):

The intermediate **59** (0.25 mmol; 0.066 g) was reacted with 1-hydroxynaphthaline (0.28 mmol; 0.040 g) according to the synthesis of **61**. The ester **90** was obtained as a yellow solid (0.079 g; 85%).

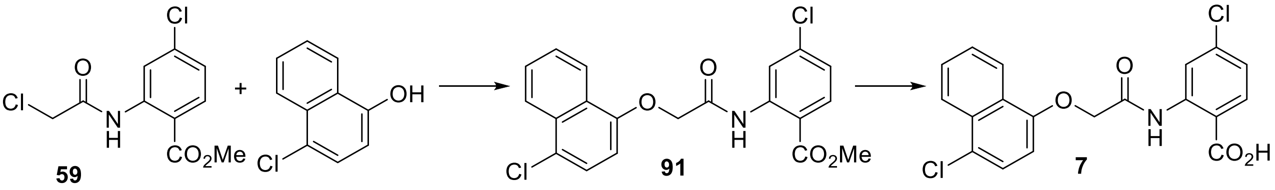
^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.91 (s, 1H), 8.82 (d, *J* = 2.1 Hz, 1H), 8.72 (d, *J* = 9.3 Hz, 1H), 8.06 (d, *J* = 8.6 Hz, 1H), 8.00 - 7.84 (m, 1H), 7.69 - 7.52 (m, 3H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.35 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 4.97 (s, 2H), 3.92 (s, 3H). HRMS *m/z* $[M + H]^+$ calcd for $C_{20}H_{17}ClNO_4$ 370.0841, found: 370.0843.

4-Chloro-2-(2-(naphthalen-1-yloxy)acetamido)benzoic acid (**6**):

The methyl ester **90** (0.2 mmol; 0.074 g) was hydrolyzed according to the synthesis of **5**. The desired compound was obtained after recrystallization from MeCN as a purple powder (0.038 g; 53%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 14.09 (s, 1H), 12.95 (s, 1H), 8.82 (d, *J* = 1.8 Hz, 1H), 8.75 - 8.62 (m, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.97 - 7.83 (m, 1H), 7.65 - 7.50 (m, *J* = 7.3 Hz, 3H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.25 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 4.93 (s, 2H). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 169.18 (s), 167.88 (s), 153.22 (s), 141.63 (s), 134.55 (s), 133.73 (s), 133.44 (s), 127.81 (s), 127.05 (s), 126.45 (s), 126.07 (s), 125.24 (s), 123.29 (s), 122.73 (s), 121.63 (s), 119.50

(s), 117.48 (s), 106.49 (s), 68.29 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{19}H_{15}ClNO_4$ 354.0539, found: 354.0525.



Methyl 4-chloro-2-(2-((4-chloronaphthalen-1-yl)oxy)acetamido)benzoate (**91**):

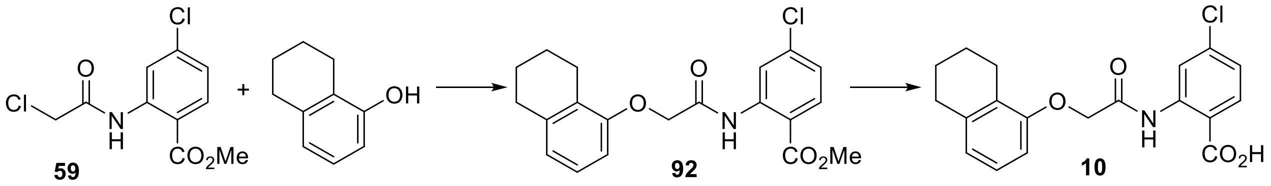
The intermediate **59** (0.25 mmol; 0.066 g) was reacted with 1-hydroxynaphthaline (0.28 mmol; 0.050 g) according to the synthesis of **61**. The ester **91** was obtained as a yellow solid (0.061 g; 60%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.89 (s, 1H), 8.87 - 8.74 (m, 2H), 8.17 (dd, *J* = 7.3, 1.9 Hz, 1H), 8.06 (d, *J* = 8.6 Hz, 1H), 7.82 - 7.70 (m, 2H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.36 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 5.00 (s, 2H), 3.92 (s, 3H). HRMS *m/z* [M + Na]$^+$ calcd for $C_{20}H_{15}Cl_2NO_4Na$ 426.0270, found: 426.0270.

4-Chloro-2-(2-((4-chloronaphthalen-1-yl)oxy)acetamido)benzoic acid (**7**):

The methyl ester **91** (0.14 mmol; 0.056 g) was hydrolyzed according to the synthesis of **5**. The desired compound was obtained as an off-white powder (0.054 g; 99%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 15.24 (s, 1H), 9.02 (d, *J* = 8.0 Hz, 1H), 8.70 (d, *J* = 1.7 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 8.02 (d, *J* = 8.3 Hz, 1H), 7.75 (t, *J* = 7.3 Hz, 1H), 7.72 - 7.64 (m, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.16 (s, 1H), 7.05 (t, *J* = 9.9 Hz, 2H), 4.86 (s, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 168.52 (s), 167.00 (s), 153.03 (s), 141.44 (s), 134.36 (s), 133.26 (s), 130.91 (s), 128.57 (s), 127.00 (s), 126.55 (s), 126.50 (s), 124.39 (s), 123.67 (s), 123.02 (s), 122.16 (s), 118.60 (s), 114.94 (s), 106.61 (s), 68.55 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{19}H_{14}Cl_2NO_4$ 390.0294, found: 390.0289.



Methyl 4-chloro-2-(2-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)acetamido)benzoate (**92**):

The intermediate **59** (0.25 mmol; 0.066 g) was reacted with 5,6,7,8-tetrahydronaphthalen-1-ol (0.28 mmol; 0.041 g) according to the synthesis of **61**. After evaporation, the product was purified by recrystallization from MeCN. The ester **92** was obtained as a brown solid (0.028 g; 31%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.60 (s, 1H), 8.75 (d, *J* = 2.1 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.32 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.05 (t, *J* = 7.9 Hz, 1H), 6.76 (t, *J* = 8.0 Hz, 2H), 4.74 (s, 2H), 3.86 (s, 3H), 2.87 (t, *J* = 6.1 Hz, 2H), 2.72 (t, *J* = 5.9 Hz, 2H), 1.92 - 1.59 (m, 4H).

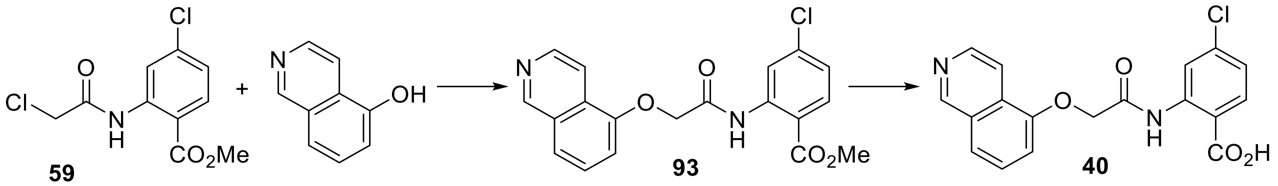
^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 168.45 (s), 166.00 (s), 157.63 (s), 141.13 (s), 139.38 (s), 138.66 (s), 132.93 (s), 126.26 (s), 126.17 (s), 123.83 (s), 122.90 (s), 120.03 (s), 115.13 (s), 109.08 (s), 67.91 (s), 53.08 (s), 29.52 (s), 23.16 (s), 22.84 (s), 22.80 (s). HRMS *m/z* $[M + H]^+$ calcd for $C_{20}H_{21}ClNO_4$ 374.1154, found: 374.1154.

4-Chloro-2-(2-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)acetamido)benzoic acid (**10**):

The methyl ester **92** (0.06 mmol; 0.024 g) was hydrolyzed according to the synthesis of **5**. The desired compound was obtained as a pale brown powder (0.022 g; 96%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 14.91 (s, 1H, exch. with D_2O), 8.61 (d, *J* = 1.7 Hz, 1H), 7.96 (d, *J* = 8.3 Hz, 1H), 7.14 (bs, 1H, exch. with D_2O), 7.06 - 6.95 (m, 2H), 6.69 (d, *J* = 7.9 Hz, 2H), 4.61 (s, *J* = 506.7 Hz, 2H), 2.83 (t, *J* = 5.2 Hz, 2H), 2.71 (t, *J* = 5.8 Hz, 2H), 1.88 - 1.57 (m, *J* = 5.2 Hz, 4H).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 169.42 (s), 168.35 (s), 155.62 (s), 140.58 (s), 138.71 (s), 134.82 (s), 133.32 (s), 126.48 (s), 126.10 (s), 124.18 (s), 122.63 (s), 122.57 (s), 118.63 (s), 108.56 (s), 68.15 (s), 29.50 (s), 22.93 (s), 22.71 (s). HRMS *m/z* $[M + H]^+$ calcd for $C_{19}H_{19}ClNO_4$ 360.0997, found: 360.0999.



Methyl 4-chloro-2-(2-(isoquinolin-5-yloxy)acetamido)benzoate (**93**):

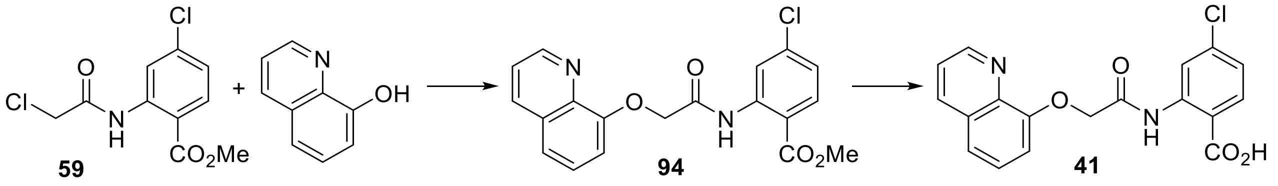
The intermediate **59** (0.25 mmol; 0.066 g) was reacted with 4-hydroxyisoquinoline (0.28 mmol; 0.041 g) according to the synthesis of **61**. After evaporation, the product was purified by recrystallization from MeCN. The ester **93** was obtained as a brown solid (0.053 g; 57%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.94 (s, 1H), 9.34 (s, 1H), 8.81 (d, *J* = 2.1 Hz, 1H), 8.62 (s, 1H), 8.56 (d, *J* = 5.8 Hz, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.64 (t, *J* = 8.0 Hz, 1H), 7.42 - 7.32 (m, 2H), 5.02 (s, 2H), 3.94 (s, 3H). HRMS *m/z* $[M + H]^+$ calcd for $C_{19}H_{16}ClN_2O_4$ 371.0793, found: 371.0795.

4-Chloro-2-(2-(isoquinolin-5-yloxy)acetamido)benzoic acid (**40**):

The methyl ester **93** (0.13 mmol; 0.048 g) was hydrolyzed according to the synthesis of **5**. The desired compound was obtained as an off-white powder (0.042 g; 90%).

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 15.46 (s, 1H), 9.29 (s, 1H), 8.86 (s, 1H), 8.71 (d, *J* = 2.1 Hz, 1H), 8.55 (d, *J* = 5.7 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 4.88 (s, 2H). HRMS *m/z* $[M + H]^+$ calcd for $C_{18}H_{14}ClN_2O_4$ 357.0637, found: 357.0634.



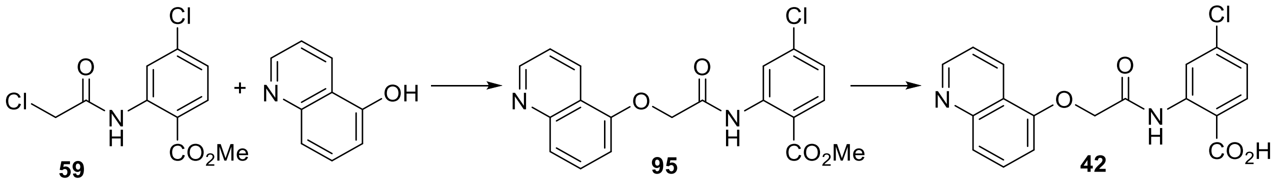
Methyl 4-chloro-2-(2-(quinolin-8-yloxy)acetamido)benzoate (**94**):

The intermediate **59** (0.25 mmol; 0.066 g) was reacted with 8-hydroxyquinoline (0.28 mmol; 0.040 g) according to the synthesis of **61**. The ester **94** was obtained as a pale brown solid (0.088 g; 95%). ^{1}H NMR (300 MHz, DMSO-*d$_6$*) δ 11.61 (s, 1H), 8.92 (s, 1H), 8.68 (s, 1H), 8.39 (s, 1H), 7.98 (s, 1H), 7.62 (m, 3H), 7.38 (m, 2H), 5.04 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (75 MHz, DMSO-*d$_6$*) δ 168.54 (s), 166.85 (s), 153.81 (s), 149.92 (s), 140.69 (s), 139.13 (s), 136.50 (s), 133.08 (s), 129.76 (s), 127.16 (s), 123.97 (s), 122.51 (s), 120.52 (s), 117.61 - 117.14 (m), 116.06 (s), 113.76 (s), 113.31 (s), 70.32 (s), 53.11 (s). HRMS *m/z* [M + Na]$^+$ calcd for $C_{19}H_{15}ClN_2O_4Na$ 393.0613, found: 393.0607.

4-Chloro-2-(2-(quinolin-8-yloxy)acetamido)benzoic acid (**41**):

The methyl ester **94** (0.22 mmol; 0.080 g) was hydrolyzed according to the synthesis of **5**. The desired compound was obtained as a yellow solid (0.014 g; 18%).

^{1}H NMR (300 MHz, DMSO-*d$_6$*) δ 12.27 (s, 1H), 8.91 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.78 (d, *J* = 2.1 Hz, 1H), 8.38 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.59 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.27 (dd, *J* = 8.5, 2.1 Hz, 1H), 5.05 (s, 2H). ^{13}C NMR (101 MHz, DMSO-*d$_6$*) δ 168.86 (s), 168.71 (s), 153.98 (s), 149.87 (s), 141.57 (s), 140.45 (s), 138.73 (s), 136.54 (s), 133.38 (s), 129.77 (s), 127.13 (s), 123.48 (s), 122.44 (s), 122.32 (s), 119.70 (s), 116.30 (s), 113.46 (s), 70.43 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{18}H_{14}ClN_2O_4$ 357.0637, found: 357.0637.



Methyl 4-chloro-2-(2-(quinolin-5-yloxy)acetamido)benzoate (**95**):

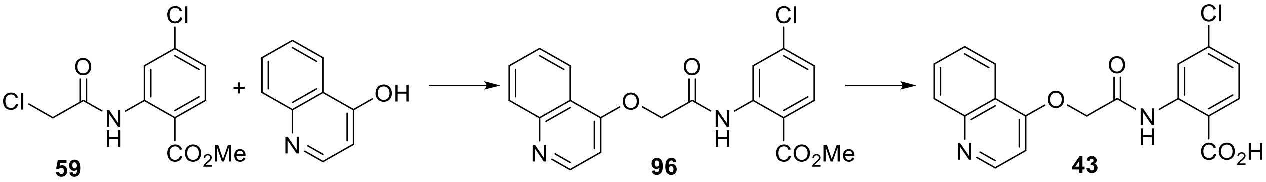
The intermediate **59** (0.25 mmol; 0.066 g) was reacted with 5-hydroxyquinoline (0.28 mmol; 0.040 g) according to the synthesis of **61**. The ester **95** was obtained as a pale brown solid (0.066 g; 71%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.92 (s, 1H), 9.11 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.96 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.80 (d, *J* = 2.1 Hz, 1H), 8.06 (d, *J* = 8.6 Hz, 1H), 7.77 - 7.67 (m, 2H), 7.63 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.35 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.20 (dd, *J* = 6.0, 2.8 Hz, 1H), 5.01 (s, 2H), 3.92 (s, 3H). HRMS *m/z* [M + H]$^+$ calcd for $C_{19}H_{16}ClN_2O_4$ 371.0793, found: 371.0793.

4-Chloro-2-(2-(quinolin-5-yloxy)acetamido)benzoic acid (**42**):

The methyl ester **95** (0.16 mmol; 0.060 g) was hydrolyzed according to the synthesis of **5**. The desired compound was obtained after recrystallization from MeCN as a purple powder (0.018 g; 32%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 13.47 (s, 1H), 9.19 (dd, *J* = 8.3, 0.7 Hz, 1H), 8.92 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.79 (d, *J* = 2.1 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.74 - 7.63 (m, 2H), 7.57 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.21 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.15 (dd, *J* = 6.4, 2.3 Hz, 1H), 4.93 (s, 2H). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 169.42 (s), 167.42 (s), 152.99 (s), 151.26 (s), 148.96 (s), 141.51 (s), 137.39 (s), 133.48 (s), 131.59 (s), 129.87 (s), 123.11 (s), 122.57 (s), 121.45 (s), 120.49 (s), 119.27 (s), 117.70 (s), 106.86 (s), 68.29 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{18}H_{14}ClN_2O_4$ 357.0637, found: 357.0637.



Methyl 4-chloro-2-(2-(quinolin-4-yloxy)acetamido)benzoate (**96**):

The intermediate **59** (0.25 mmol; 0.066 g) was reacted with 4-hydroxyisoquinoline (0.28 mmol; 0.041 g) according to the synthesis of **61**. After evaporation, the product was purified by recrystallization from MeCN. The ester **96** was obtained as a yellow solid (0.019 g; 20%).

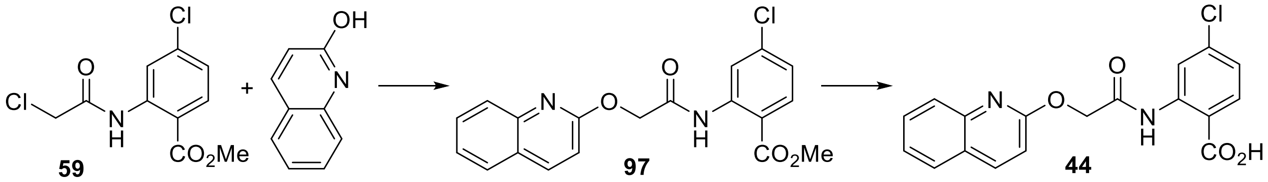
^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.88 (s, 1H), 8.84 - 8.69 (m, 3H), 8.06 (d, *J* = 8.6 Hz, 1H), 8.01 (d, *J* = 8.3 Hz, 1H), 7.80 (dd, *J* = 11.1, 4.2 Hz, 1H), 7.68 (t, *J* = 7.1 Hz, 1H), 7.36 (dd, *J* = 8.6, 2.2

Hz, 1H), 7.16 (d, *J* = 5.2 Hz, 1H), 5.09 (s, 2H), 3.94 (s, 3H). HRMS *m/z* [M + H]$^+$ calcd for $C_{19}H_{16}ClN_2O_4$ 371.0793, found: 371.0788.

4-Chloro-2-(2-(quinolin-4-yloxy)acetamido)benzoic acid (**43**):

The methyl ester **96** (0.04 mmol; 0.016 g) was hydrolyzed according to the synthesis of **5**. The desired compound was obtained as an off-white powder (0.009 g; 3%).

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 15.05 (s, 1H), 8.92 (d, *J* = 8.2 Hz, 1H), 8.75 (d, *J* = 5.2 Hz, 1H), 8.70 (d, *J* = 2.1 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.84 - 7.73 (m, 1H), 7.65 - 7.55 (m, 1H), 7.13 (bs, 1H), 7.12 - 7.01 (m, 2H), 4.97 (s, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 168.53 (s), 166.55 (s), 160.24 (s), 156.06 (s), 151.83 (s), 149.28 (s), 141.46 (s), 133.29 (s), 130.31 (s), 128.73 (s), 126.35 (s), 123.66 (s), 122.39 (s), 121.14 (s), 118.72 (s), 114.99 (s), 102.62 (s), 68.19 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{18}H_{14}ClN_2O_4$ 357.0637, found: 357.0639.



Methyl 4-chloro-2-(2-(quinolin-2-yloxy)acetamido)benzoate (**97**):

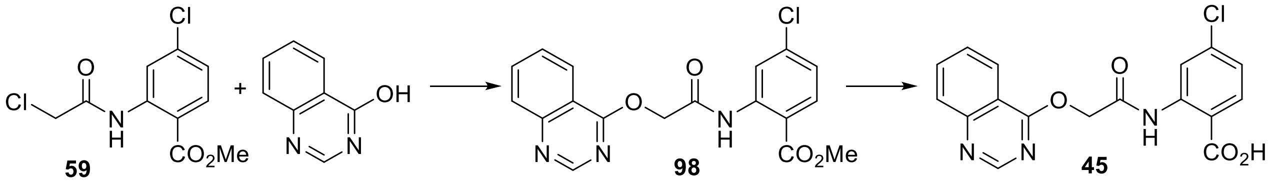
The intermediate **59** (0.25 mmol; 0.066 g) was reacted with 2-hydroxyquinoline (0.28 mmol; 0.040 g) according to the synthesis of **61**. The ester **97** was obtained as a brown solid (0.062 g; 71%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 10.98 (s, 1H), 8.35 (d, *J* = 2.1 Hz, 1H), 8.03 (d, *J* = 9.5 Hz, 1H), 7.93 (d, *J* = 8.6 Hz, 1H), 7.78 (d, *J* = 6.5 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.48 (s, 1H), 7.30 (dd, *J* = 8.5, 2.2 Hz, 2H), 6.70 (d, *J* = 9.5 Hz, 1H), 5.23 (s, 2H), 3.81 (s, 3H). HRMS *m/z* [M + Na]$^+$ calcd for $C_{19}H_{15}ClN_2O_4Na$ 393.0613, found: 393.0615.

4-Chloro-2-(2-(quinolin-2-yloxy)acetamido)benzoic acid (**44**):

The methyl ester **97** (0.14 mmol; 0.016 g) was hydrolyzed according to the synthesis of **5**. The desired compound was obtained after recrystallization from MeCN as a pale yellow solid (0.010 g; 20%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 13.71 (s, 1H), 8.53 (s, 1H), 7.98 (t, *J* = 9.1 Hz, 2H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.27 (t, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 9.4 Hz, 1H), 5.14 (s, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 166.65 (s), 161.72 (s), 151.30 (s), 141.82 (s), 140.61 (s), 140.05 (s), 139.66 (s), 133.27 (s), 131.29 (s), 129.39 (s), 125.38 (s), 122.57 (s), 121.27 (s), 120.77 (s), 118.45 (s), 116.20 (s), 115.00 (s), 46.62 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{18}H_{14}ClN_2O_4$ 357.0637, found: 357.0637.



Methyl 4-chloro-2-(2-(quinazolin-4-yloxy)acetamido)benzoate (**98**):

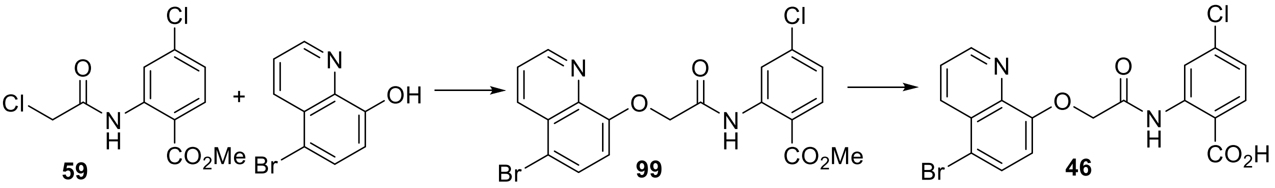
The intermediate **59** (0.5 mmol; 0.132 g) was reacted with 4-hydroxyquinazoline (0.56 mmol; 0.082 g) according to the synthesis of **61**. After evaporation, the product was purified by recrystallization from MeCN. The ester **98** was obtained as a white solid (0.054 g; 29%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 10.94 (s, 1H), 8.40 (s, 1H), 8.28 (d, *J* = 2.1 Hz, 1H), 8.16 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.93 (d, *J* = 8.6 Hz, 1H), 7.88 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H), 7.74 (d, *J* = 7.7 Hz, 1H), 7.63 - 7.54 (m, 1H), 7.32 (dd, *J* = 8.6, 2.2 Hz, 1H), 4.96 (s, 2H), 3.82 (s, 3H). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 167.14 (s), 166.77 (s), 160.77 (s), 148.69 (s), 148.51 (s), 140.28 (s), 138.79 (s), 135.11 (s), 132.87 (s), 127.79 (s), 127.75 (s), 126.51 (s), 124.28 (s), 121.90 (s), 121.31 (s), 117.48 (s), 53.09 (s), 49.94 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{18}H_{15}ClN_3O_4$ 372.0746, found: 372.0739.

4-Chloro-2-(2-(quinazolin-4-yloxy)acetamido)benzoic acid (45):

The methyl ester **98** (0.13 mmol; 0.048 g) was hydrolyzed according to the synthesis of **5**. The desired compound was obtained as a white powder (0.018 g; 39%).

^{1}H NMR (300 MHz, DMSO-*d$_6$*) δ 15.36 (s, 1H), 8.45 (s, 1H), 8.40 (s, 1H), 8.15 (d, *J* = 6.4 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.87 (t, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 6.1 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.18 (s, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 4.85 (s, 2H). ^{13}C NMR (101 MHz, DMSO-*d$_6$*) δ 168.64 (s), 165.84 (s), 160.81 (s), 148.58 (s), 141.83 (s), 134.91 (s), 134.46 (s), 133.15 (s), 127.75 (s), 127.56 (s), 126.51 (s), 122.02 (s), 121.87 (s), 118.04 (s), 50.18 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{17}H_{13}ClN_3O_4$ 358.0589, found: 358.0592.



Methyl 2-(2-((5-bromoquinolin-8-yl)oxy)acetamido)-4-chlorobenzoate (**99**):

The intermediate **59** (0.25 mmol; 0.066 g) was reacted with 5-bromo-8-hydroxyquinoline (0.28 mmol; 0.063 g) according to the synthesis **61**. After evaporation, the product was purified by recrystallization from MeCN. The ester **99** was obtained as a white solid (0.061 g; 54%). It contains two rotameres (1:2). They were used without further purification.

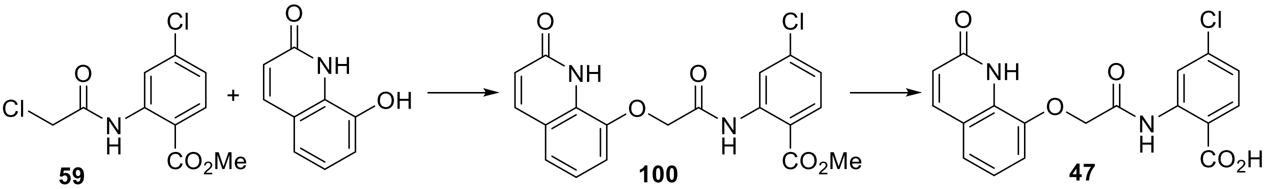
^{1}H NMR of the major isomer (300 MHz, DMSO-*d$_6$*) δ 11.54 (s, 1H), 9.01 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.67 (d, *J* = 2.1 Hz, 1H), 8.51 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.77 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.38 – 7.30 (m, 2H), 5.07 (s, 2H), 3.77 (s, 3H).

2-(2-((5-Bromoquinolin-8-yl)oxy)acetamido)-4-chlorobenzoic acid (**46**):

The methyl ester **99** (0.12 mmol; 0.056 g) was hydrolyzed according to the synthesis of **5**. The desired compound was obtained as a pale brown solid (0.052 g; 99%).

^{1}H NMR (300 MHz, DMSO-*d$_6$*) δ 15.04 (s, 1H), 8.98 (d, *J* = 2.8 Hz, 1H), 8.60 (s, 1H), 8.48 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.75 (dd, *J* = 8.6, 3.6 Hz, 1H), 7.32

(d, *J* = 8.2 Hz, 1H), 7.15 (s, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 4.99 (s, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 167.53 (s), 167.48 (s), 154.68 (s), 150.43 (s), 141.57 (s), 141.36 (s), 141.34 (s), 135.31 (s), 133.20 (s), 130.78 (s), 128.10 (s), 123.84 (s), 122.04 (s), 118.41 (s), 113.90 (s), 112.88 (s), 109.41 (s), 70.47 (s). HRMS *m/z* [M - H]$^-$ calcd for $C_{18}H_{11}BrClN_2O_4$ 434.9742, found: 434.9736.



Methyl 4-chloro-2-(2-((2-oxo-1,2-dihydroquinolin-8-yl)oxy)acetamido)benzoate (**100**):

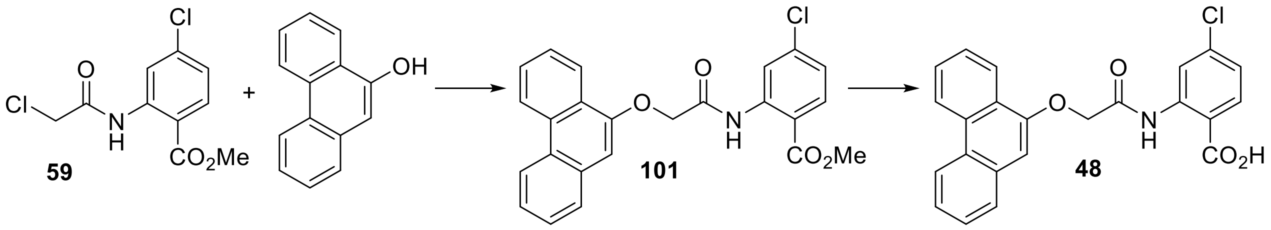
The intermediate **59** (0.25 mmol; 0.045 g) was reacted with quinolin-2,8-diol (0.28 mmol; 0.063 g) according to the synthesis of **61**. The product was further purified by recrystallization from MeCN. The ester **100** was obtained as a white solid (0.045 g; 47%). It contains two rotameres (1:3). They were used without further purification.

^{1}H NMR of the major isomer (300 MHz, DMSO-*d*$_6$) δ 15.58 (s, 1H), 11.30 (s, 1H), 8.60 (s, 1H), 8.02 (dd, *J* = 16.8, 8.6 Hz, 1H), 7.96 – 7.85 (m, 1H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.20 (dt, *J* = 15.6, 7.7 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.56 (d, *J* = 9.7 Hz, 1H), 4.73 (s, 2H), 4.00 (s, 3H). HRMS *m/z* [M + H]$^+$ calcd for $C_{19}H_{16}ClN_2O_5$ 387.0742, found: 387.0745.

4-Chloro-2-(2-((2-oxo-1,2-dihydroquinolin-8-yl)oxy)acetamido)benzoic acid (**47**):

The methyl ester **100** (0.1 mmol; 0.041 g) was hydrolyzed according to the synthesis of **5**. The desired compound was obtained as a white solid (0.031 g; 83%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 15.54 (s, 1H), 11.26 (s, 1H), 8.60 (d, *J* = 1.7 Hz, 1H), 8.04 (d, J = 8.3 Hz, 1H), 7.92 (d, *J* = 9.6 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.28 - 7.12 (m, *J* = 15.6, 7.7 Hz, 2H), 7.07 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.56 (d, *J* = 9.5 Hz, 1H), 4.74 (s, 2H). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 168.80 (s), 166.24 (s), 162.42 (s), 143.78 (s), 141.18 (s), 140.90 (s), 134.72 (s), 133.48 (s), 124.26 (s), 123.06 - 122.97 (m), 122.35 (s), 122.26 (s), 121.52 (s), 121.17 (s), 120.55 (s), 118.02 (s), 112.86 (s), 68.14 (s). HRMS *m/z* $[M - H]^-$ calcd for $C_{18}H_{12}ClN_2O_5$ 371.0440, found: 371.0441.



Methyl 4-chloro-2-(2-(phenanthren-9-yloxy)acetamido)benzoate (**101**):

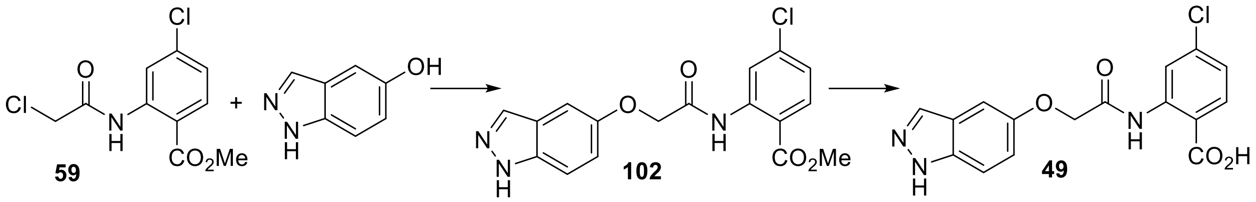
The intermediate **59** (0.31 mmol; 0.08 g) was reacted with 9-phenanthrol (0.34 mmol; 0.066 g) according to the synthesis of **61**. The product was further purified by recrystallization from MeCN. The ester **101** was obtained as a white solid (0.033 g; 25%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.94 (s, 1H), 8.84 (s, 2H), 8.76 (d, *J* = 6.8 Hz, 1H), 8.07 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 6.2 Hz, 1H), 7.85 - 7.71 (m, 2H), 7.66 - 7.50 (m, 2H), 7.42 (s, 1H), 7.36 (d, *J* = 9.5 Hz, 1H), 5.08 (s, 2H), 3.94 (s, 3H). HRMS *m/z* $[M + H]^+$ calcd for $C_{24}H_{19}ClNO_4$ 420.0997, found: 420.1006.

4-Chloro-2-(2-(phenanthren-9-yloxy)acetamido)benzoic acid (**48**):

The methyl ester **101** (0.07 mmol; 0.03 g) was hydrolyzed according to the synthesis of **5**. The desired compound was obtained after recrystallization from MeCN as a white solid (0.014 g; 49%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 14.00 (bs, 1H), 12.44 (bs, 1H), 8.91 - 8.81 (m, 2H), 8.76 (s, 1H), 8.74 (s, 1H), 8.06 (d, *J* = 8.6 Hz, 1H), 7.91 (d, *J* = 7.2 Hz, 1H), 7.84 - 7.68 (m, 2H), 7.65 - 7.50 (m, 2H), 7.39 (s, 1H), 7.30 (dd, *J* = 8.5, 2.1 Hz, 1H), 5.07 (s, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 169.26 (s), 167.89 (s), 151.22 (s), 141.69 (s), 138.74 (s), 136.01 (s), 133.47 (s), 132.59 (s), 131.29 (s), 128.14 (s), 128.05 (s), 127.66 (s), 127.32 (s), 126.75 (s), 125.90 (s), 125.47 (s), 123.56 (s), 123.36 (s), 123.20 (s), 123.17 (s), 119.75 (s), 104.73 (s), 68.26 (s). HRMS *m/z* $[M - H]^-$ calcd for $C_{23}H_{15}ClNO_4$ 404.0695, found: 404.0679.



Methyl 2-(2-((1*H*-indazol-5-yl)oxy)acetamido)-4-chlorobenzoate (**102**):

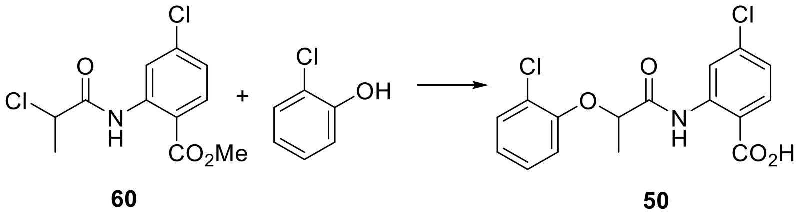
The intermediate **59** (0.25 mmol; 0.066 g) was reacted with 5-hydroxy-1*H*-indazol (0.28 mmol; 0.038 g) according to the synthesis of **61**. The product was further purified by automated flash chromatography (gradient from 100% Cyclohexane to 80/20 Cyclohexane/EtOAc in 20 min then isocratic for 20 min, then to 50% - 50% in 5 min). The merged fractions were evaporated then suspended in DEE. The product was finally filtered off to give a pale-yellow solid (0.011 g; 12%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 11.89 (s, 1H), 8.77 (d, *J* = 2.1 Hz, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.99 (s, 1H), 7.56 (d, *J* = 9.0 Hz, 1H), 7.36 – 7.30 (m, *J* = 8.7, 2.2 Hz, 2H), 7.24 (dd, *J* = 8.9, 2.2 Hz, 1H), 4.79 (s, 2H), 3.92 (s, 3H). HRMS *m/z* [M + Na]$^+$ calcd for $C_{17}H_{14}ClN_3O_4Na$ 382.0565, found: 382.0565.

2-(2-((1*H*-Indazol-5-yl)oxy)acetamido)-4-chlorobenzoic acid (**49**):

The methyl ester **102** (0.02 mmol; 0.008 g) was hydrolyzed according to the synthesis of **5**. The desired compound was obtained as a grey powder (0.006 g; 79%).

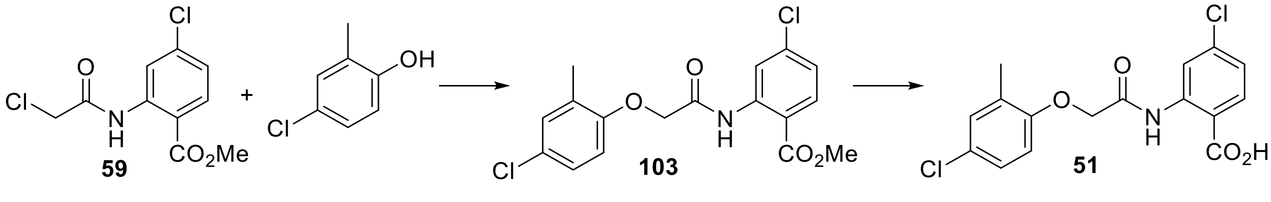
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H, exch. with D_2O), 12.33 (s, 1H, exch. with D_2O), 8.82 (d, *J* = 2.0 Hz, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.99 (s, 1H), 7.53 (d, *J* = 9.0 Hz, 1H), 7.37 - 7.24 (m, 2H), 7.21 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.14 (s, 0.5H, exch. with D_2O), 7.01 (s, 0.5H, exch. with D_2O), 4.78 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.21 (s), 168.40 (s), 151.98 (s), 141.68 (s), 139.15 (s), 133.53 (s), 123.49 (s), 123.40 (s), 119.29 (s), 118.33 (s), 115.42 (s), 115.00 (s), 111.90 (s), 102.30 (s), 68.25 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{16}H_{13}ClN_3O_4$ 346.0589, found: 346.0590.



(*rac*)-4-Chloro-2-(2-(2-chlorophenoxy)propanamido)benzoic acid (**50**):

2-Chlorophenol (1.99 mmol; 0.20 mL) and potassium carbonate (3.62 mmol; 0.50 g) were dissolved in 1 mL DMF and were stirred for 10 minutes at RT. The intermediate **60** (1.81 mmol; 0.50 g) as well as another 4 mL of DMF were added to the reaction mixture which was left to stir at 90°C under argon for 4h (TLC Hexane/EtOAc = 8:2). When the reaction was complete, it was poured into 120 mL of water and let to stir. Then it was extracted twice with EtOAc. The aqueous phase was freeze-dried before purification by RP-HPLC to give a white lyophilisate (0.05 g; 8%).

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.05 (s, 1H), 8.72 (d, J = 2.1 Hz, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.47 (dd, J = 7.9, 1.6 Hz, 1H), 7.34 – 7.21 (m, 2H), 7.14 (dd, J = 8.3, 1.1 Hz, 1H), 7.02 (td, J = 7.7, 1.3 Hz, 1H), 5.05 (q, J = 6.7 Hz, 1H), 1.57 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 170.61 (s), 168.50 (s), 152.30 (s), 141.09 (s), 138.47 (s), 132.90 (s), 130.30 (s), 128.35 (s), 123.16 (s), 122.95 (s), 122.63 (s), 119.23 (s), 115.60 (s), 115.45 (s), 75.78 (s), 18.32 (s). HRMS *m/z* [M + Na]$^+$ calcd for $C_{16}H_{13}Cl_2NO_4Na$ 376.0114, found: 376.0108.



Methyl 4-chloro-2-(2-(4-chloro-2-methylphenoxy)acetamido)benzoate (**103**):

4-Chloro-2-methylphenol (2.10 mmol; 0.30 g) and potassium carbonate (3.82 mmol; 0.53 g) were dissolved in 1 mL DMF and were stirred for 10 minutes at RT. The intermediate **59** (1.91 mmol; 0.50 g) as well as another 4 mL of DMF were added to the reaction mixture which was left to stir at

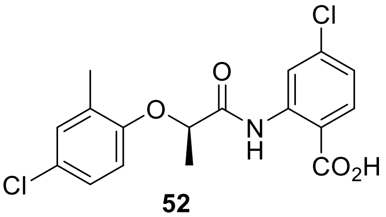
90°C under argon for 4h (TLC Hexane/EtOAc = 8:2). When the reaction was complete, it was poured into 120 mL of water and let to stir. The precipitate that formed was filtered to give a yellow solid (0.52 g; 74%).

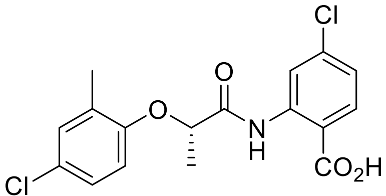
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.95 (s, 1H), 8.89 (d, *J* = 1.9 Hz, 1H), 7.96 (d, *J* = 8.6 Hz, 1H), 7.18 (d, *J* = 2.2 Hz, 1H), 7.11 (dt, *J* = 8.5, 2.7 Hz, 2H), 6.74 (d, *J* = 8.7 Hz, 1H), 4.63 (s, 2H), 3.89 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.59 (s), 167.56 (s), 154.17 (s), 141.33 (s), 140.95 (s), 132.01 (s), 131.14 (s), 129.56 (s), 126.79 (s), 126.63 (s, *J* = 16.0 Hz), 123.65 (s), 120.84 (s), 114.26 (s), 112.41 (s), 68.23 (s), 52.54 (s), 16.47 (s). HRMS *m/z* $[M + H]^+$ calcd for $C_{17}H_{16}Cl_2NO_4$ 368.0451, found: 368.0456.

4-Chloro-2-(2-(4-chloro-2-methylphenoxy)acetamido)benzoic acid (**51**):

Potassium hydroxide (2.04 mmol; 0.11 g) was added to a solution of **103** (0.68 mmol; 0.25 g) in methanol and water (14:1), which was then set to reflux for 4h (TLC Hexane:EtOAC = 4:1). After completion of the reaction, the mixture was concentrated under reduced pressure and taken back in a 1M aqueous solution of HCl. The formed precipitate was filtered to give a first batch of the compound as a yellow solid and the filtrate was extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was triturated in diethyl ether. After filtration, the yellow solid was merged with the first batch (0.24 g; 100%).

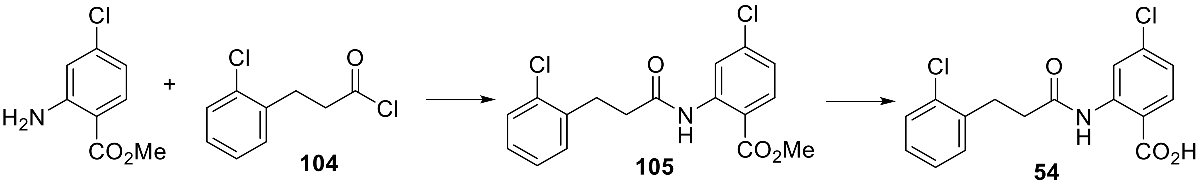
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.06 (s, 1H), 8.78 (d, *J* = 1.9 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.25 (dd, *J* = 5.7, 2.4 Hz, 2H), 7.19 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 1H), 4.77 (s, 2H), 4.77 (s, 2H), 2.36 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.62 (s), 167.55 (s), 154.04 (s), 141.11 (s), 138.49 (s), 132.97 (s), 130.19 (s), 128.85 (s), 126.44 (s), 124.94 (s), 123.09 (s), 119.18 (s), 115.28 (s), 113.17 (s), 67.65 (s), 16.03 (s). HRMS *m/z* $[M - H]^-$ calcd for $C_{16}H_{12}Cl_2NO_4$ 352.0149, found: 352.0162.


52


53

(*R*) and **(*S*)-4-chloro-2-(2-(4-chloro-2-methylphenoxy)propanamido)benzoic acid** (**52**/**53**):

Chiral separation was done by the Novartis Institutes for Biomedical Research using a Gilson Trilution Prep HPLC and a Chiralpak AD-H (5µm 25x250 mm) column. Eluent 95% Heptane, 8% isopropanol and 0.1% TFA was used to elute the compound. The same system on a Shimadzu Prominence system was used to analyze the compound and the fractions obtained. Before the chiral column an achiral preparative HPLC was performed by the company. Two white solids were obtained with more than 99% ee for both isomers. The absolute configuration of the two isomers was not determined. The samples were tested without further characterisation.



3-(2-Chlorophenyl)propanoyl chloride (**104**):

3-(2-Chlorophenyl)propanoic acid (1.07 mmol; 0.20 g) was transformed to acid chloride **104** similarly to the synthesis of **63**. The acid chloride was used without further purification.

Methyl 4-chloro-2-(3-(2-chlorophenyl)propanamido)benzoate (**105**):

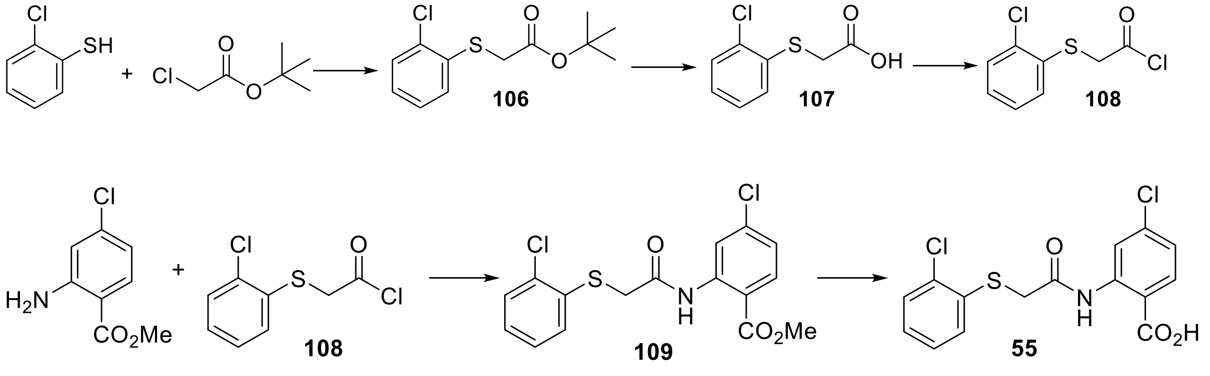
Methyl 2-amino-4-chlorobenzoate (0.54 mmol; 0.099 g) was dissolved in THF (4 mL) then K_2CO_3 (1.07 mmol; 0.148 g) was added. The mixture was stirred for 30 min at RT then the acid chloride **104** (ca 1.07 mmol) was added as THF solution (4 mL). The mixture was stirred at RT for 1.5 h. Water was added then it was extracted with EtOAc (3x30 mL). The combined organics were washed with brine, dried with Na_2SO_4 then evaporated to dryness. The product was further purified by automated flash chromatography (gradient from 100% Cyclohexane to 70/30 Cyclohexane/EtOAc). The merged fractions were evaporated to give a pale-yellow solid (0.153 g; 80%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.68 (s, 1H), 8.39 (d, *J* = 2.1 Hz, 1H), 7.92 (d, *J* = 8.6 Hz, 1H), 7.41 (ddd, *J* = 12.4, 6.8, 1.8 Hz, 2H), 7.35 – 7.11 (m, 3H), 3.85 (s, 3H), 3.04 (t, *J* = 7.6 Hz, 2H), 2.74 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.02 (s), 167.28 (s), 141.14 (s), 138.84 (s), 138.32 (s), 133.38 (s), 132.77 (s), 131.08 (s), 129.74 (s), 128.65 (s), 127.82 (s), 123.58 (s), 120.80 (s), 116.62 (s), 53.09 (s), 37.17 (s), 28.82 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{17}H_{17}O_3NCl_2$ 352.0502, found: 352.0489.

4-Chloro-2-(3-(2-chlorophenyl)propanamido)benzoic acid (**54**):

The methyl ester **105** (0.43 mmol; 0.15 g) was hydrolyzed according to the synthesis of **5**. The desired compound was obtained as a dark-yellow powder (0.117 g; 81%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 14.51 (s, 1H), 8.52 (d, *J* = 2.2 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.48 – 7.34 (m, 2H), 7.31 – 7.18 (m, 2H), 6.97 (dd, *J* = 8.3, 2.2 Hz, 1H), 3.11 – 2.95 (m, 2H), 2.63 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.31 (s), 168.62 (s), 148.07 (s), 142.20 (s), 138.71 (s), 133.38 (s), 133.19 (s), 131.04 (s), 129.70 (s), 128.53 (s), 127.79 (s), 121.41 (s), 118.01 (s), 113.46 (s), 37.75 (s), 29.01 (s). HRMS *m/z* [M + H]$^+$ calcd for $C_{16}H_{15}O_3NCl_2$ 338.0339, found: 338.0345.



***tert*-Butyl 2-((2-chlorophenyl)thio)acetate** (**106**):

2-Chlorothiophenol (1 mmol; 0.113 mL) and *tert*-butyl chloroacetate (1.1 mmol; 0.158 mL) were reacted according to the synthesis of **61**. After drying the product still contained some water. The resulting yellow liquid (0.12 g; 46%) was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (ddd, *J* = 7.9, 6.6, 1.6 Hz, 2H), 7.11 (dtd, *J* = 21.1, 7.4, 1.6 Hz, 2H), 3.53 (s, 2H), 1.33 (s, 9H).

Methyl 4-chloro-2-(2-((2-chlorophenyl)thio)acetamido)benzoate (**109**):

The *t*Bu ester **106** (0.46 mmol; 0.12 g) was dissolved in DCM (20 mL), TFA (0.5mL) was added then the mixture was stirred at RT for 24 h. Water (20 mL) was added to the mixture. The aq. layer was extracted with DCM (2x30 mL). The combined organics were washed with brine, dried with Na_2SO_4 and evaporated to dryness. Although the 2-((2-chlorophenyl)thio)acetic acid (**107**) contained some *t*-butanol and TFA, it was used without further treatment. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (t, *J* = 1.6 Hz, 1H), 7.32 (t, *J* = 1.5 Hz, 1H), 7.21 – 7.07 (m, 2H), 3.66 (s, 2H). The 2-((2-chlorophenyl)thio)acetic acid (**107**) was then transformed to acid chloride **108** similarly to the synthesis of **63**. The acid chloride (0.095 g) was used without further purification. Methyl 2-amino-4-chlorobenzoate (0.39 mmol; 0.095 g) was dissolved in THF (30 mL) then K_2CO_3 (1.17 mmol; 0.161 g) was added. The mixture was stirred for 30 min at RT then the acid chloride **108** (ca 0.43 mmol; 0.095 g) was added as a THF solution (30 mL). The mixture was stirred at RT for 1.5 h. Water was added then it was extracted with EtOAc (3x30 mL). The combined organics were washed with 1 M HCl, brine and dried with Na_2SO_4. After evaporation, the product was further purified by flash chromatography (from Cyclohexane to 20% EtOAc). The merged fractions were evaporated to give a yellow solid (0.037 g; 22% for 3 steps from **106**).

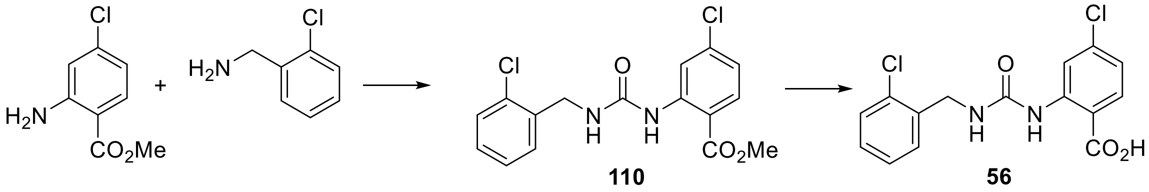
^{1}H NMR (300 MHz, $CDCl_3$) δ 11.73 (s, 1H), 8.70 (d, *J* = 2.1 Hz, 1H), 7.87 (d, *J* = 8.6 Hz, 1H), 7.35 - 7.24 (m, 2H), 7.11 (ddd, *J* = 11.0, 7.5, 1.7 Hz, 2H), 7.00 (dd, *J* = 8.6, 2.1 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.52 (s), 167.32 (s), 157.91 (s), 141.49 (s), 140.81

(s), 133.81 (s), 131.97 (s), 129.92 (s), 128.78 (s), 127.62 (s), 127.57 (s), 123.36 (s), 120.47 (s), 113.99 (s), 63.15 (s), 52.59 (s). HRMS *m/z* $[M + H]^+$ calcd for $C_{16}H_{14}Cl_2NO_3S$ 370.0066, found: 370.0062.

4-Chloro-2-(2-((2-chlorophenyl)thio)acetamido)benzoic acid (**55**):

The methyl ester **109** (0.09 mmol; 0.032 g) was hydrolyzed according to the synthesis of **5**. The desired compound was obtained as a yellow powder (0.030 g; 98%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 13.35 (s, 1H), 8.55 (d, *J* = 2.1 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.47 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.39 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.32 (td, *J* = 7.7, 1.1 Hz, 1H), 7.20 (td, *J* = 7.8, 1.5 Hz, 1H), 7.14 (dd, *J* = 8.5, 2.1 Hz, 1H), 4.06 (s, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 173.65 (s), 172.18 (s), 146.58 (s), 140.10 (s), 138.06 (s), 136.19 (s), 134.71 (s), 133.12 (s), 132.54 (s), 132.11 (s), 129.23 (s), 127.50 (s), 123.67 (s), 111.86 (s), 64.97 (s). HRMS *m/z* $[M - H]^-$ calcd for $C_{15}H_{10}Cl_2NO_3S$ 353.9764, found: 353.9771.



Methyl 4-chloro-2-(3-(2-chlorobenzyl)ureido)benzoate (**110**):

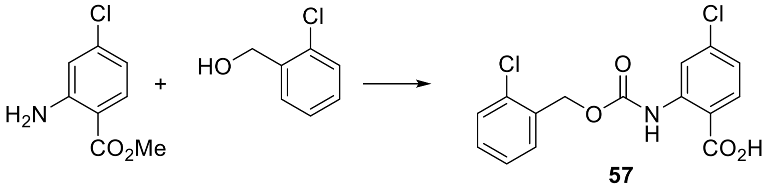
To a solution of the 2-chlorobenzylamine (0.5 mmol; 0.061 mL) and diisopropylethylamine (0.3 mmol; 0.523 mL) in $CHCl_3$ (10 mL), triphosgene (0.5 mmol; 0.149 g) was added portionwise in 5 min. The mixture was stirred for 20 min at RT then the methyl 2-amino-4-chlorobenzoate (0.5 mmol; 0.093 g) was added in one portion. After 20 h stirring at RT, sat. $NaHCO_3$ solution (10 mL) was added. The product was extracted with CH_2Cl_2 (3x30 mL). The combined organics were washed with brine, dried with Na_2SO_4 and evaporated to dryness. The crude product was purified by automated flash chromatography on 12 g of silica gel (gradient from 100% Cyclohexane to 100% EtOAc) to give a white solid (0.005 g; 3%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 10.03 (s, 1H), 8.54 (d, *J* = 2.2 Hz, 1H), 8.33 - 8.23 (m, 1H), 7.92 (d, *J* = 8.6 Hz, 1H), 7.52 - 7.40 (m, 2H), 7.40 - 7.21 (m, 2H), 7.08 (dd, *J* = 8.6, 2.2 Hz, 1H), 4.37 (d, *J* = 5.9 Hz, 2H), 3.88 (s, 3H).

4-Chloro-2-(3-(2-chlorobenzyl)ureido)benzoic (**56**):

The ester **110** (0.02 mmol; 0.007 g) was dissolved in MeOH (10 mL) then water (1 mL) was added. Then potassium hydroxide (0.06 mmol; 0.003 g) was added as a powder. The mixture was refluxed for 1 h (TLC Cyclohexane:EtOAc = 4:1). The mixture was cooled then the volatiles were evaporated. The mixture was treated with saturated aq. NH_4Cl (50 mL). The suspension was filtered and then, the product was recrystallized from MeOH to give white crystals (0.006 g; 88%).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.74 (s, 1H, exch. with D_2O), 7.96 (d, *J* = 8.2 Hz, 1H), 7.49 (d, *J* = 7.4 Hz, 1H), 7.37 - 7.17 (m, 5H, 1H exch. with D_2O), 7.06 (d, *J* = 7.6 Hz, 1H), 5.12 (s, 2H). One H is missing (COOH). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 161.84 (s), 150.50 (s), 141.22 (s), 140.06 (s), 134.36 (s), 131.97 (s), 130.11 (s), 129.69 (s), 129.03 (s), 127.83 (s), 127.20 (s), 123.34 (s), 115.16 (s), 113.19 (s), 41.85 (s). HRMS *m/z* $[M – H_2O]^-$ calcd for $C_{15}H_9Cl_2N_2O_2$ 319.0036, found: 319.0059.

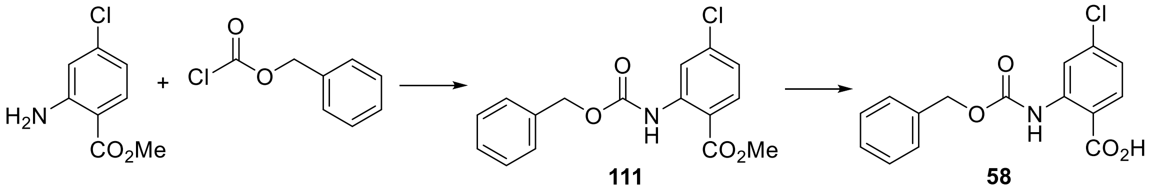


57

4-Chloro-2-((((2-chlorobenzyl)oxy)carbonyl)amino)benzoic acid (**57**):

To a solution of the methyl 2-amino-4-chlorobenzoate (0.5 mmol; 0.093 g) and potassium carbonate (5.0 mmol; 0.690 g) in MeCN (10 mL), triphosgene (0.5 mmol; 0.149 g) was added portionwise in 5 min. The mixture was stirred for 30 min at RT then the 2-chlorobenzylalcohol (0.5 mmol; 0.071 g) was added in one portion. After 24 h stirring at RT, sat. $NaHCO_3$ solution (10 mL) was added. The product was extracted with CH_2Cl_2 (3x30 mL). The combined organics were washed with brine, dried with Na_2SO_4 and evaporated to dryness. The crude product was purified by automated flash chromatography on 12 g of silica gel (gradient from 100% Cyclohexane to 100% EtOAc) to give a white solid (0.005 g; 3%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.73 (d, J = 8.7 Hz, 1H), 7.62 - 7.49 (m, 2H), 7.46 - 7.35 (m, 2H), 6.90 (s, 2H, exch. with D_2O), 6.87 (d, J = 2.1 Hz, 1H), 6.56 (dd, J = 8.7, 2.1 Hz, 1H), 5.37 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.70 (s), 152.93 (s), 139.38 (s), 134.08 (s), 133.16 (s), 133.04 (s), 130.79 (s), 130.58 (s), 129.94 (s), 127.94 (s), 115.81 (s), 115.39 (s), 107.70 (s), 63.58 (s). One quaternary C is missing. HRMS: the molecular ion wasn't detected, the fragmentation couldn't be deconvoluted.



Methyl 2-(((benzyloxy)carbonyl)amino)-4-chlorobenzoate (**111**):

To a stirring solution of the methyl 2-amino-4-chlorobenzoate (2.0 mmol; 0.37 g) and potassium carbonate (4.0 mmol; 0.552 g) in THF (40 mL), the benzyl chloroformate (2.2 mmol; 0.314 mL) was added in one portion. The mixture was stirred at RT for 3.5 h then sat. $NaHCO_3$ solution (10 mL) was added. The product was extracted with EtOAc (3x30 mL). The combined organics were washed with brine, dried with Na_2SO_4 and evaporated to dryness. The crude product was used without further purification (contains benzyl alcohol).

2-(((Benzyloxy)carbonyl)amino)-4-chlorobenzoic acid (**58**):

The ester **111** (0.06 mmol; 0.020 g) was dissolved in MeOH (10 mL) then water (1 mL) was added. Then potassium hydroxide (0.18 mmol; 0.010 g) was added as a powder. The mixture was refluxed for 1 h (TLC Cyclohexane:EtOAc = 4:1). The mixture was cooled then the volatiles were evaporated. The mixture was treated with saturated aq. NH_4Cl (50 mL). The suspension was filtered to give a white solid (0.014 g; 76%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 14.19 (s, 1H, exch. with D_2O), 8.19 (d, *J* = 2.1 Hz, 1H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.45 - 7.38 (m, 4H), 7.36 (dd, *J* = 6.9, 4.3 Hz, 1H), 7.17 (s, 1H, it integrates as 3H and exch. with D_2O), 6.93 (dd, *J* = 8.3, 2.2 Hz, 1H), 5.14 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.59 (s), 153.59 (s), 142.31 (s), 137.22 (s), 134.64 (s), 133.28 (s), 128.92 (s), 128.51 (s), 128.46 (s), 121.79 (s), 120.67 (s), 116.54 (s), 66.09 (s). HRMS *m/z* $[M + Na]^+$ calcd for $C_{15}H_{12}ClNO_4Na$ 328.0347, found: 328.0348.

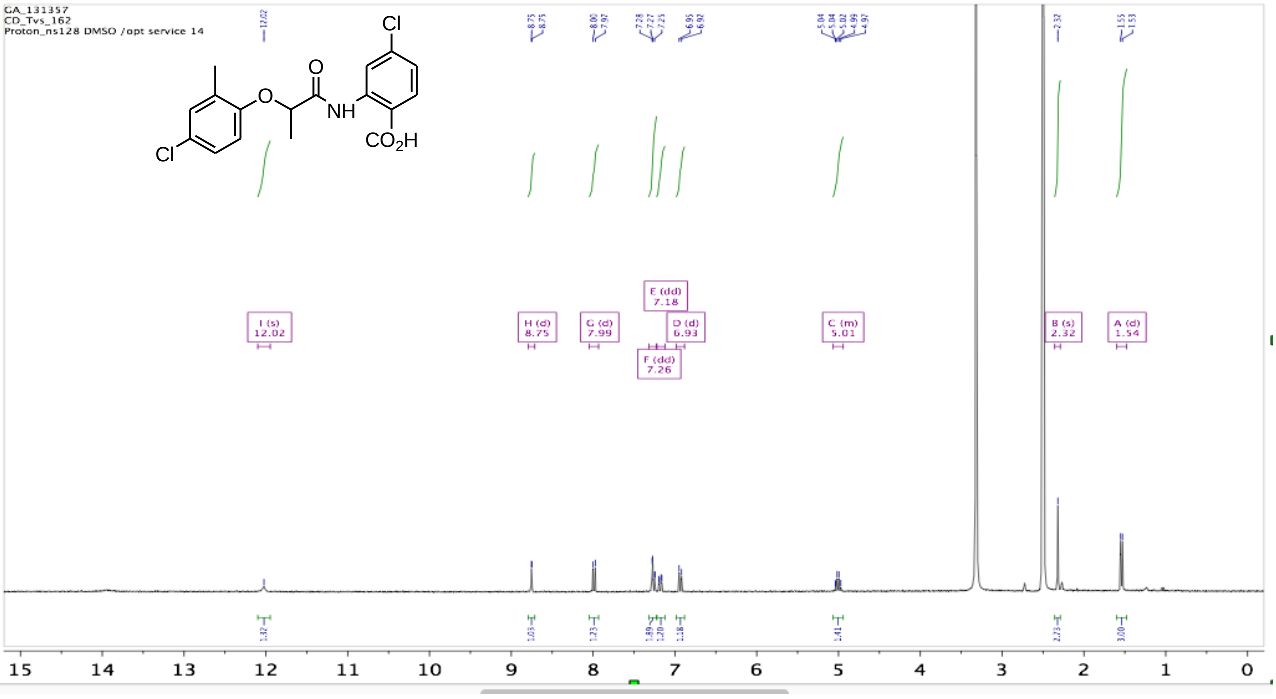
UPLC Purity

Compound	UHPLC purity[a] (%)	Compound	UHPLC purity[a] (%)
18	/[b]	38	95%
19	> 99%	16	86%
20	/[c]	39	96%
21	98%	6	> 99%
22	98%	7	92%
23	/[c]	10	> 99%
24	> 99%	40	/[c]
25	96%	41	92%
11	97%	42	> 99%
26	99%	43	> 99%
27	97%	44	/[b]
28	94%	45	99%
29	> 99%	46	99%
30	> 99%	47	98%
31	98%	48	94%
32	98%	49	90%
33	99%	50	94%
12	99%	51	> 99%
14	97%	52	> 99%
13	97%	53	> 99%
34	98%	54	> 99%
35	95%	55	81%
15	92%	56	> 99%
36	92%	57	99%
37	98%	58	98%

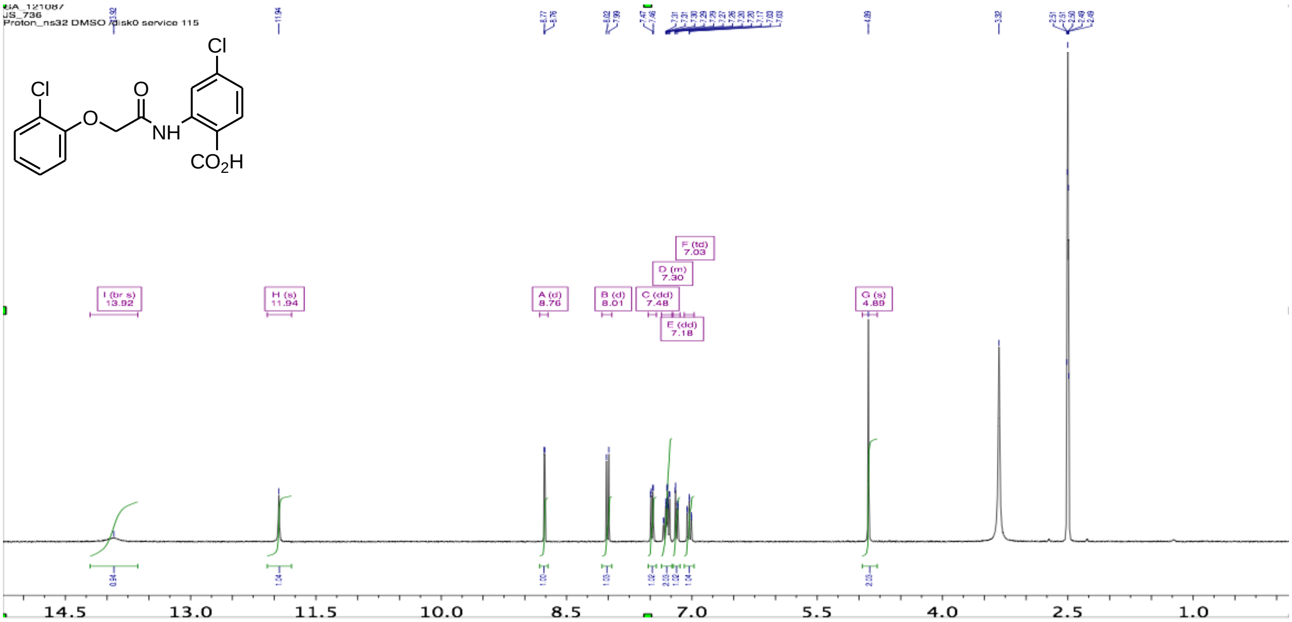
Table S5: Analytical RP-UPLC purity. a) The spectra were obtained according to method B (see description in general remarks). b) A partial decomposition of the compound was observed preventing any purity analysis. c) Any UPLC trace could be obtained due to either too few material or precipitation in UPLC solvents. NMR purity was considered (> 90%).

Copy of ^{1}H & ^{13}C-NMR spectra

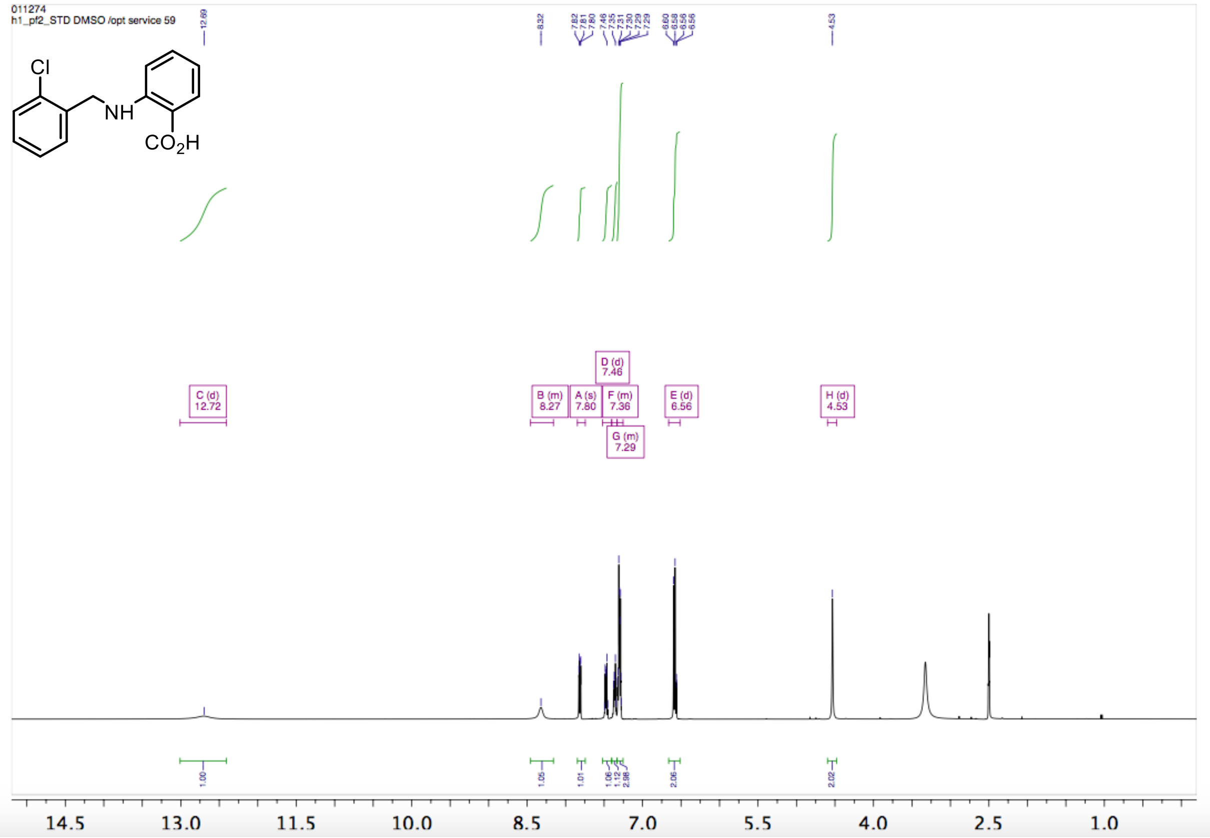
(*rac*)-4-Chloro-2-(2-(4-chloro-2-methylphenoxy)propanamido)benzoic acid (4):



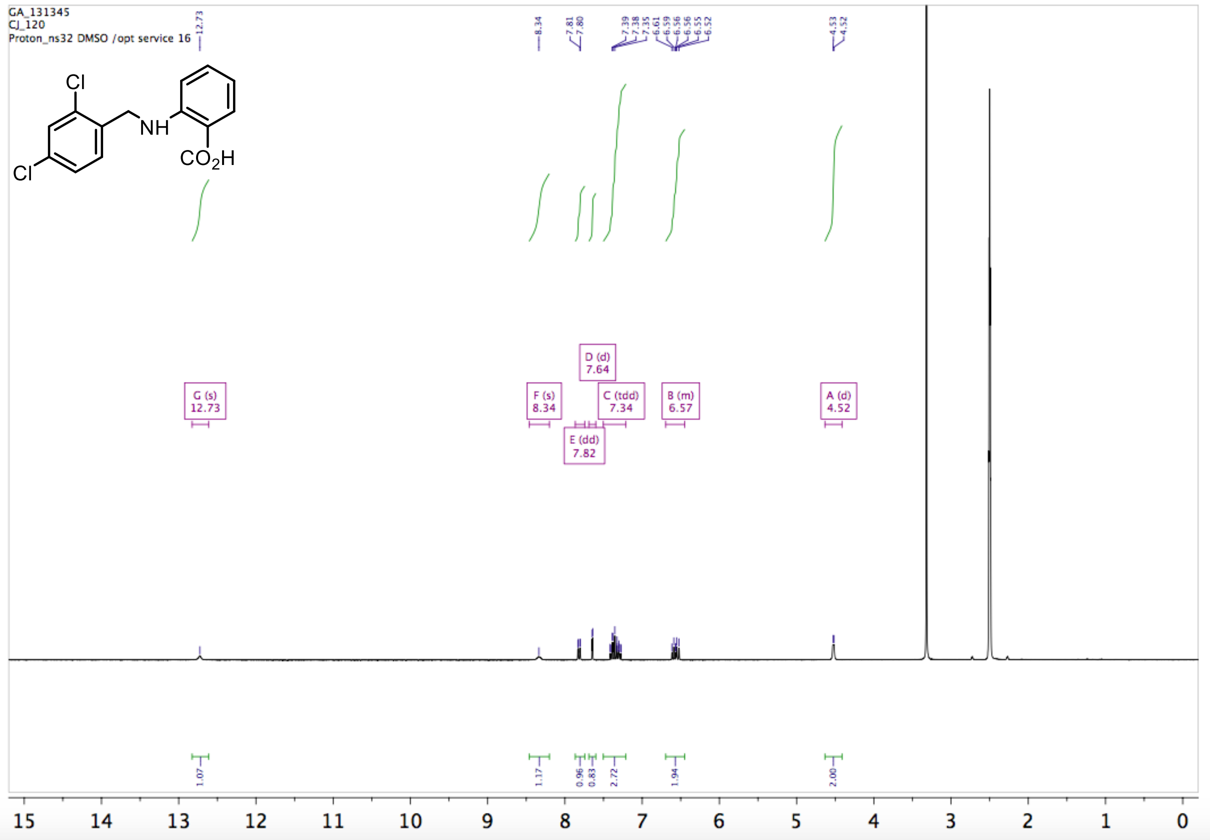
4-Chloro-2-(2-(2-chlorophenoxy)acetamido)benzoic acid (5) :



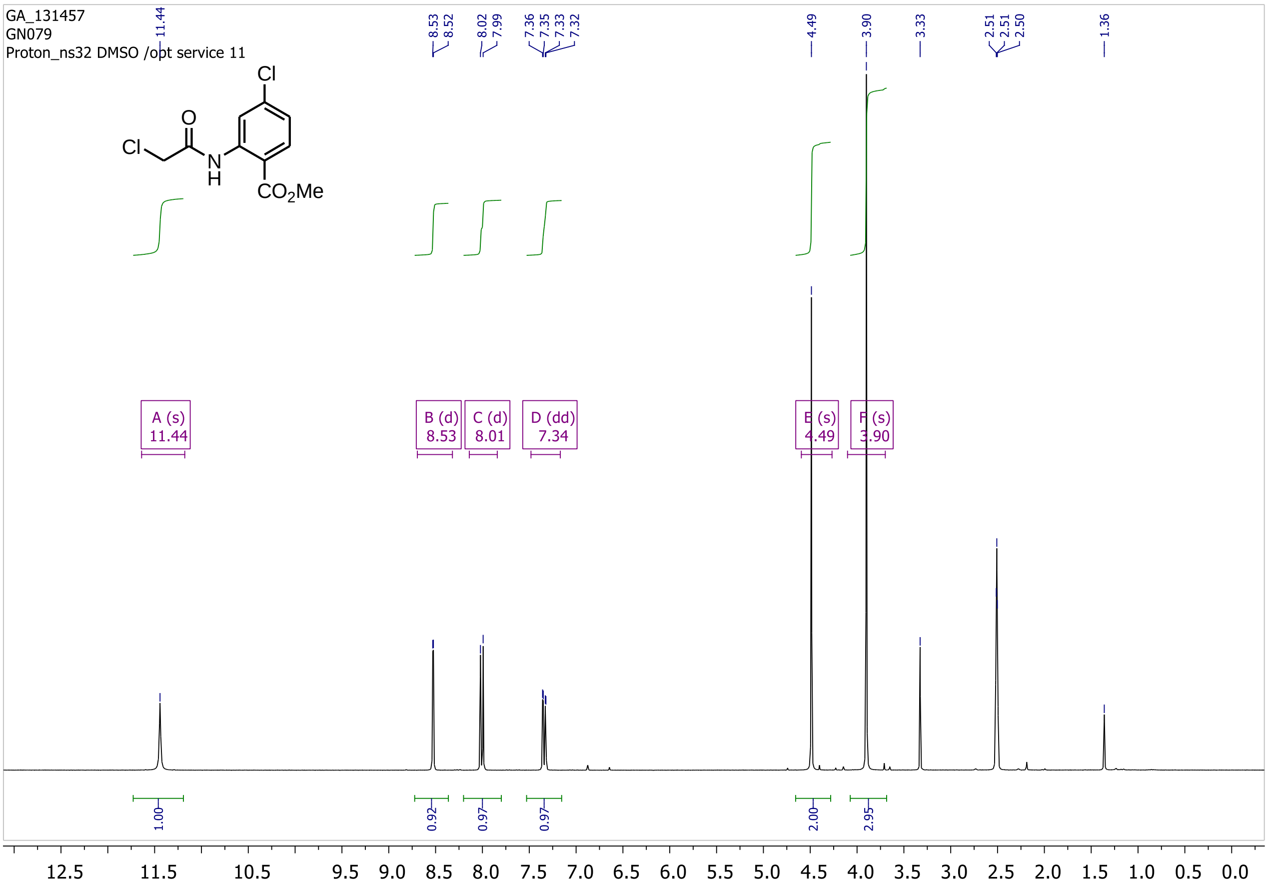
2-((2-chlorobenzyl)amino)phenyl formate (8):

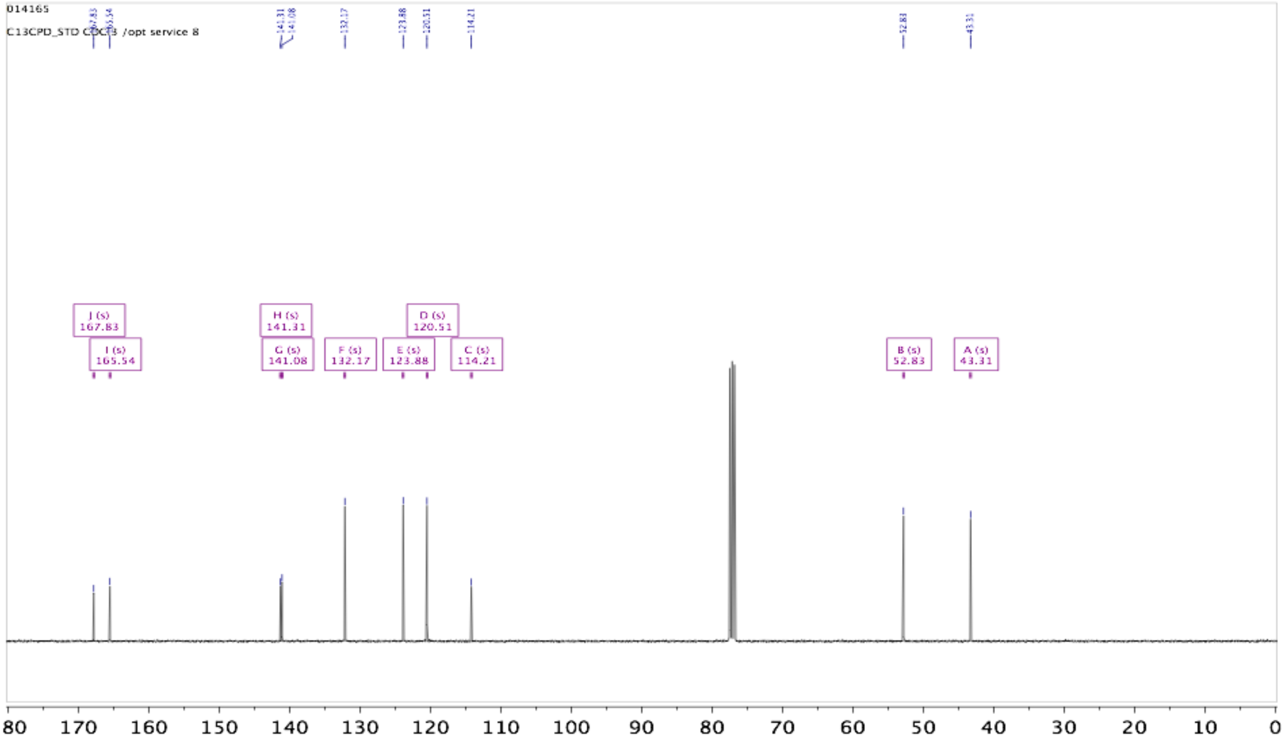


2-((2,4-dichlorobenzyl)amino)phenyl formate (9):

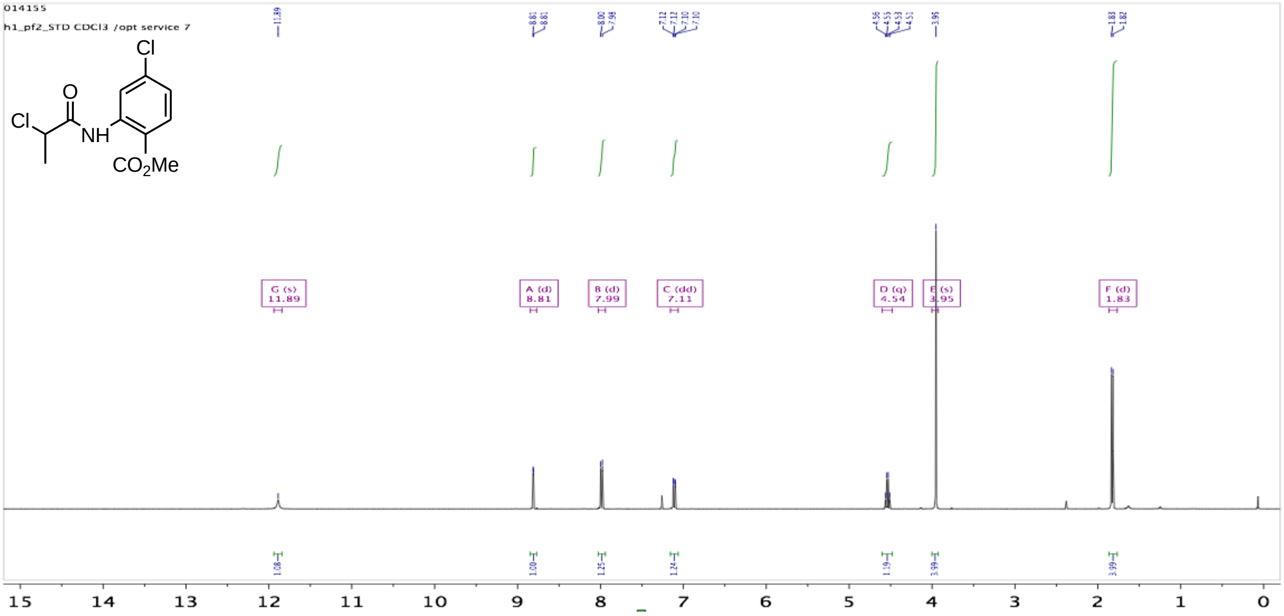


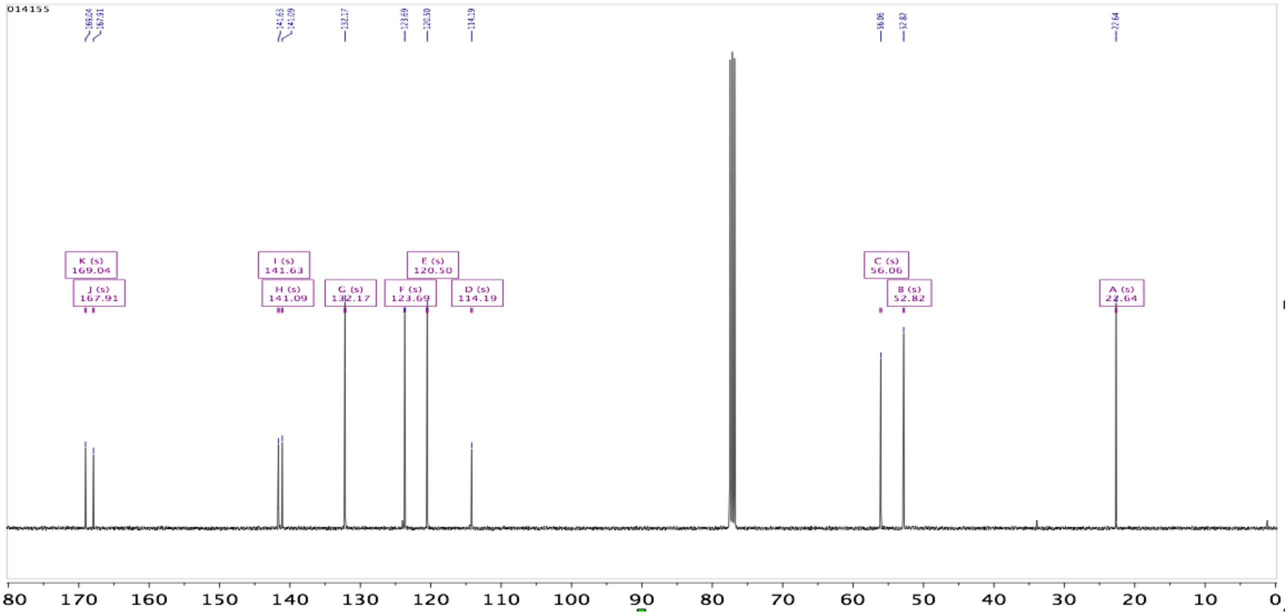
Methyl 4-chloro-2-(2-chloroacetamido)benzoate (**59**):



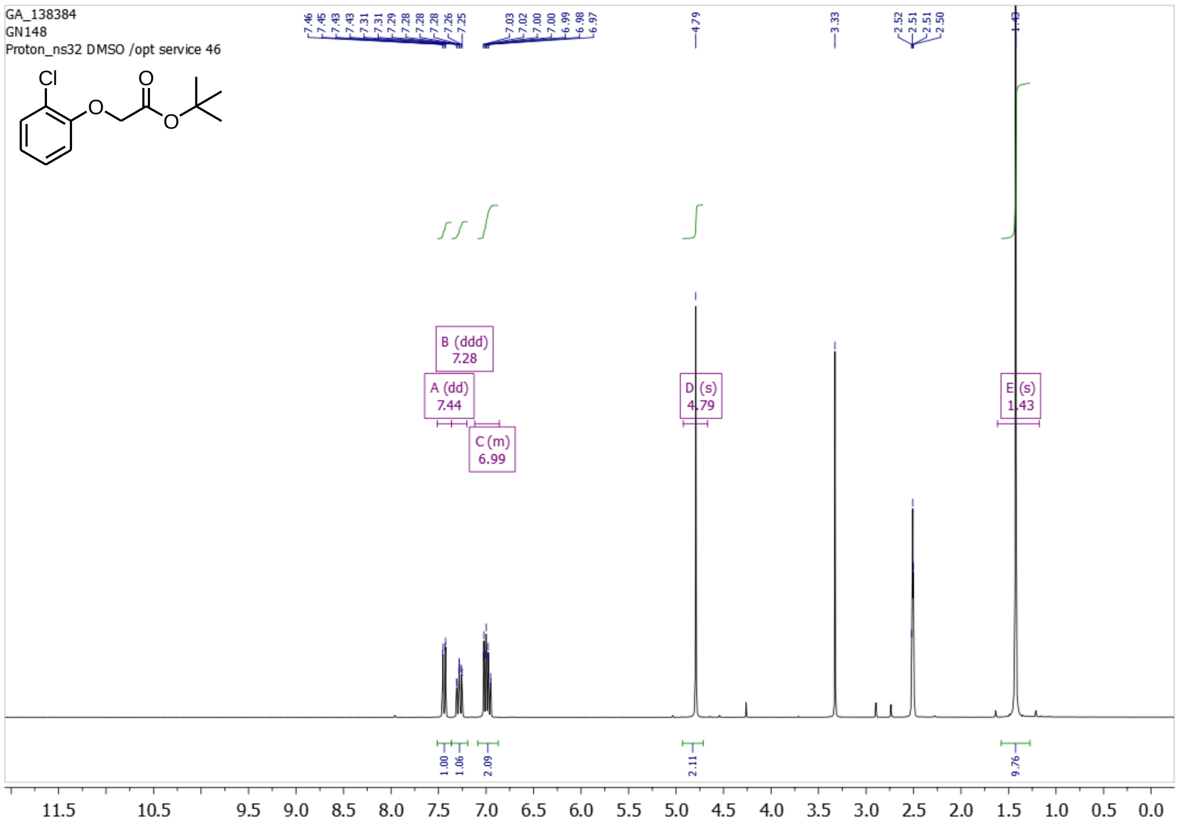


(*rac*)-Methyl 4-chloro-2-(2-chloropropanamido)benzoate (60):

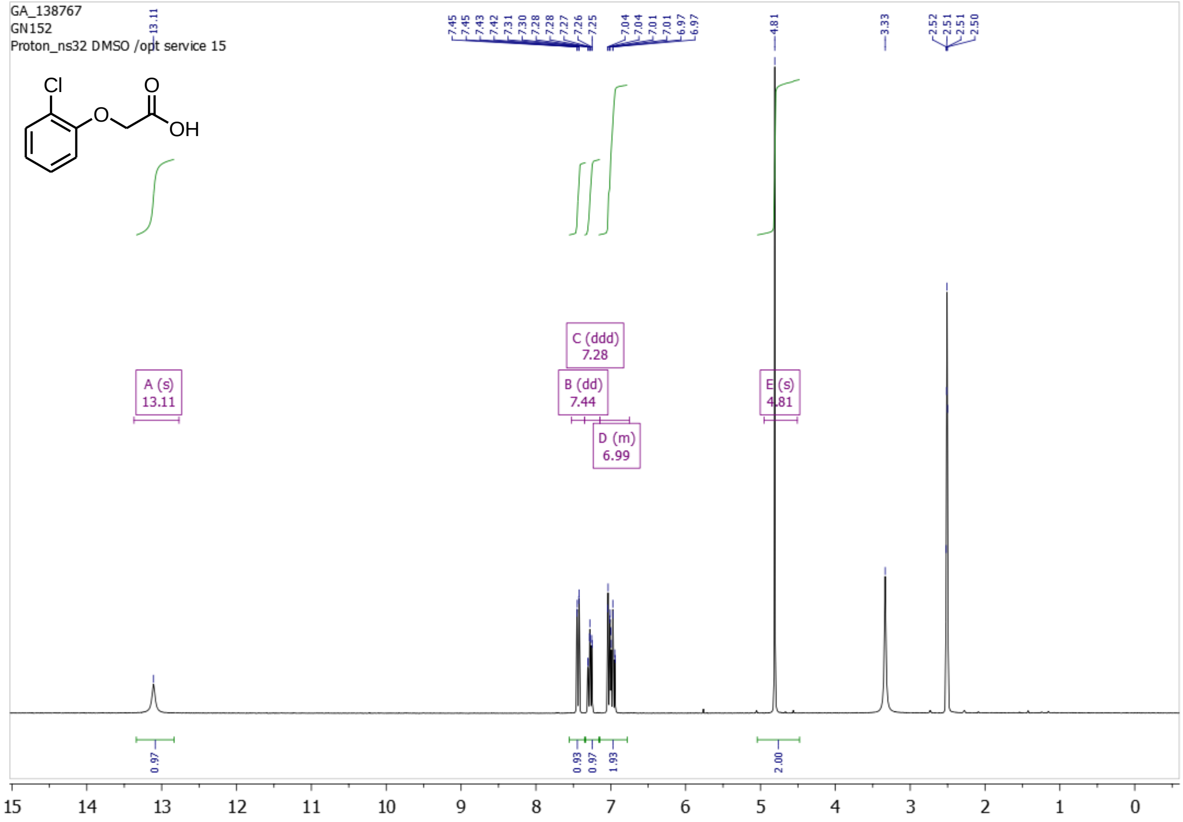




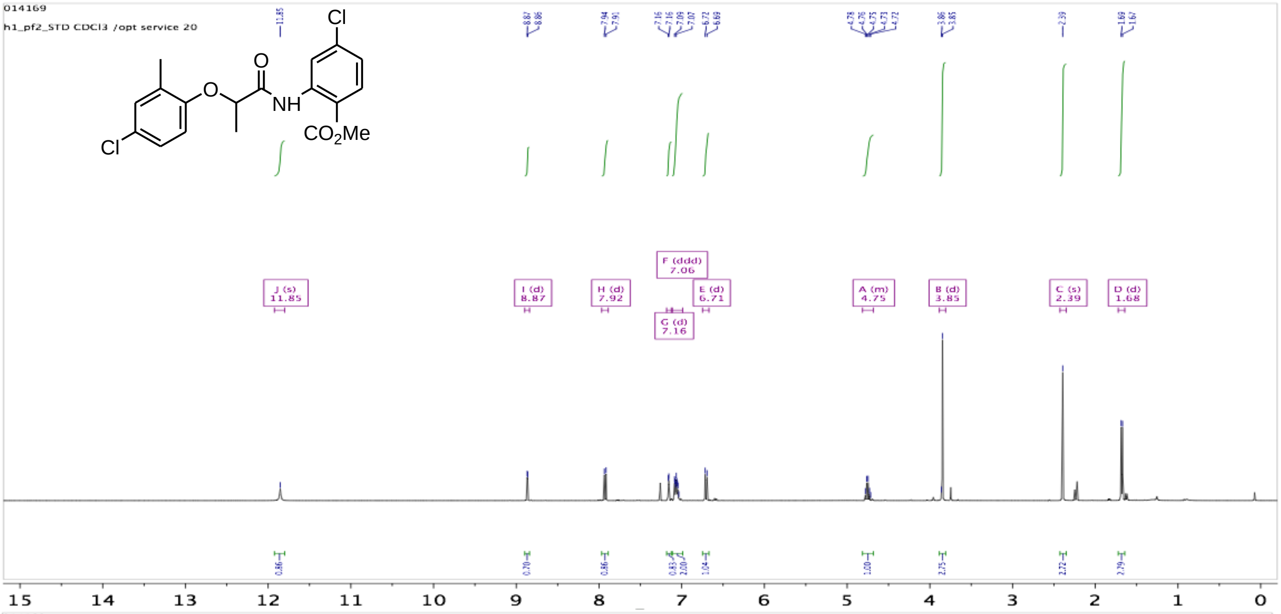
***tert*-Butyl 2-(2-chlorophenoxy)acetate (61):**

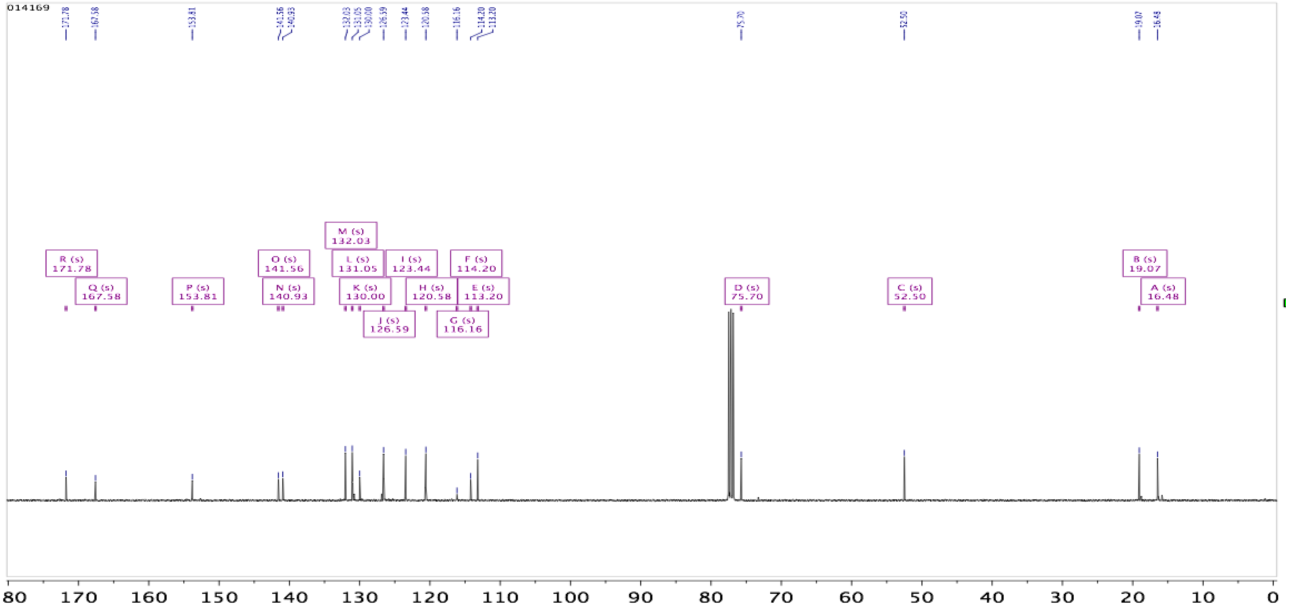


2-(2-Chlorophenoxy)acetic acid (62):

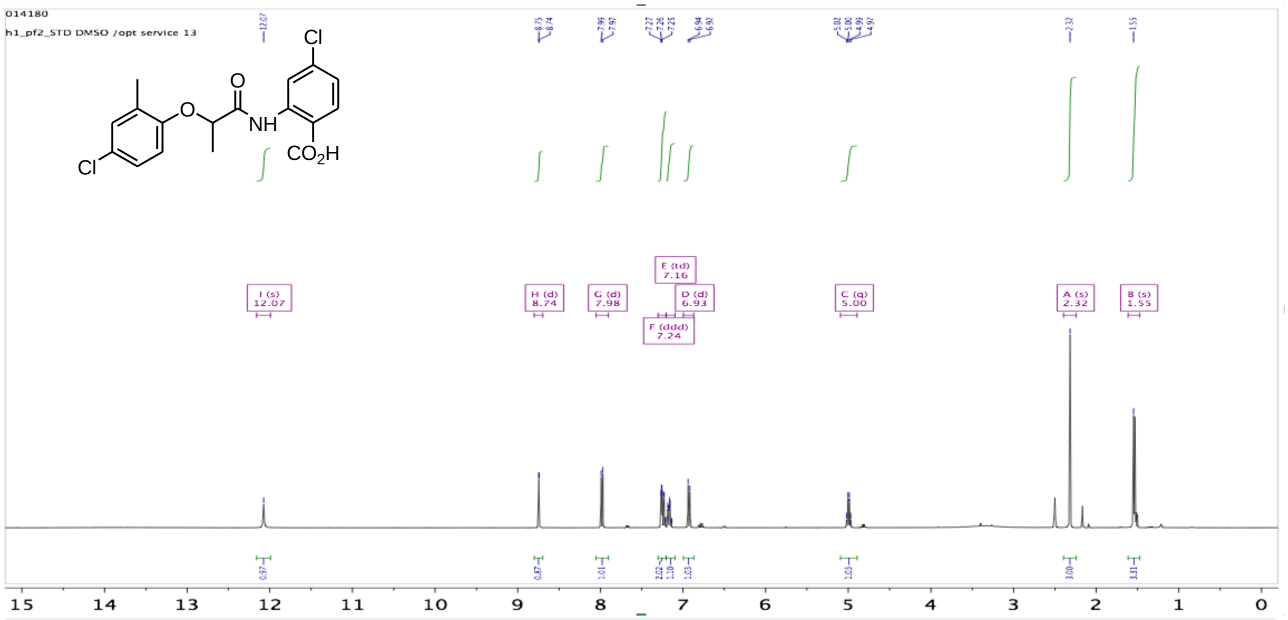


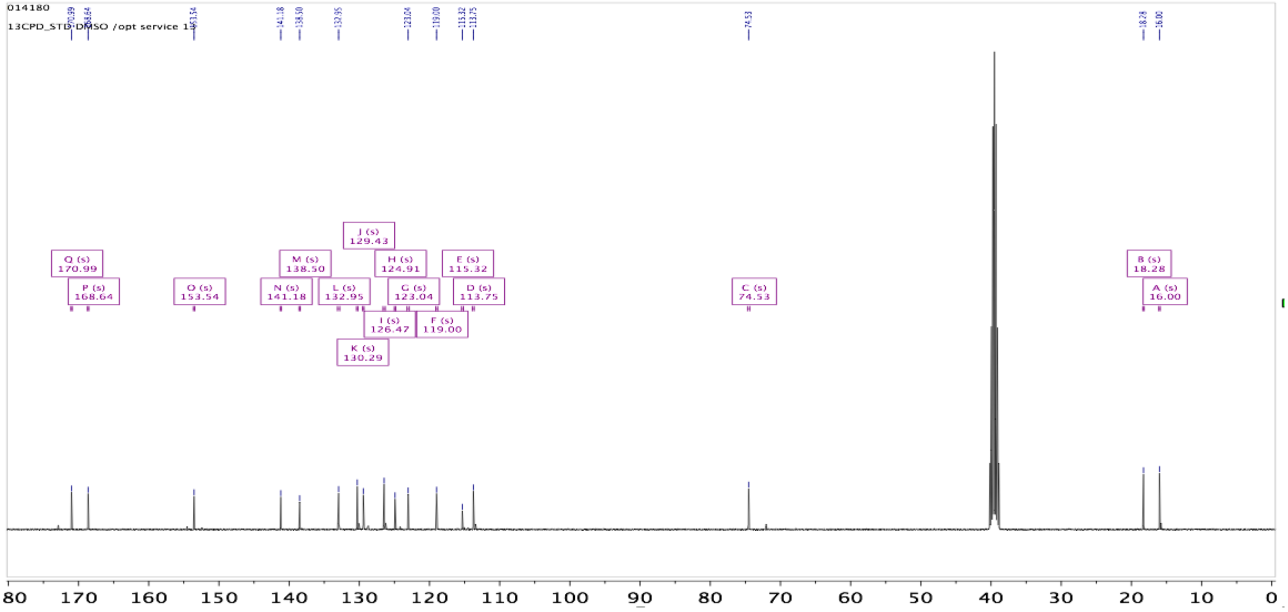
(*rac*)-Methyl 4-chloro-2-(2-(4-chloro-2-methylphenoxy)propanamido)benzoate (64):



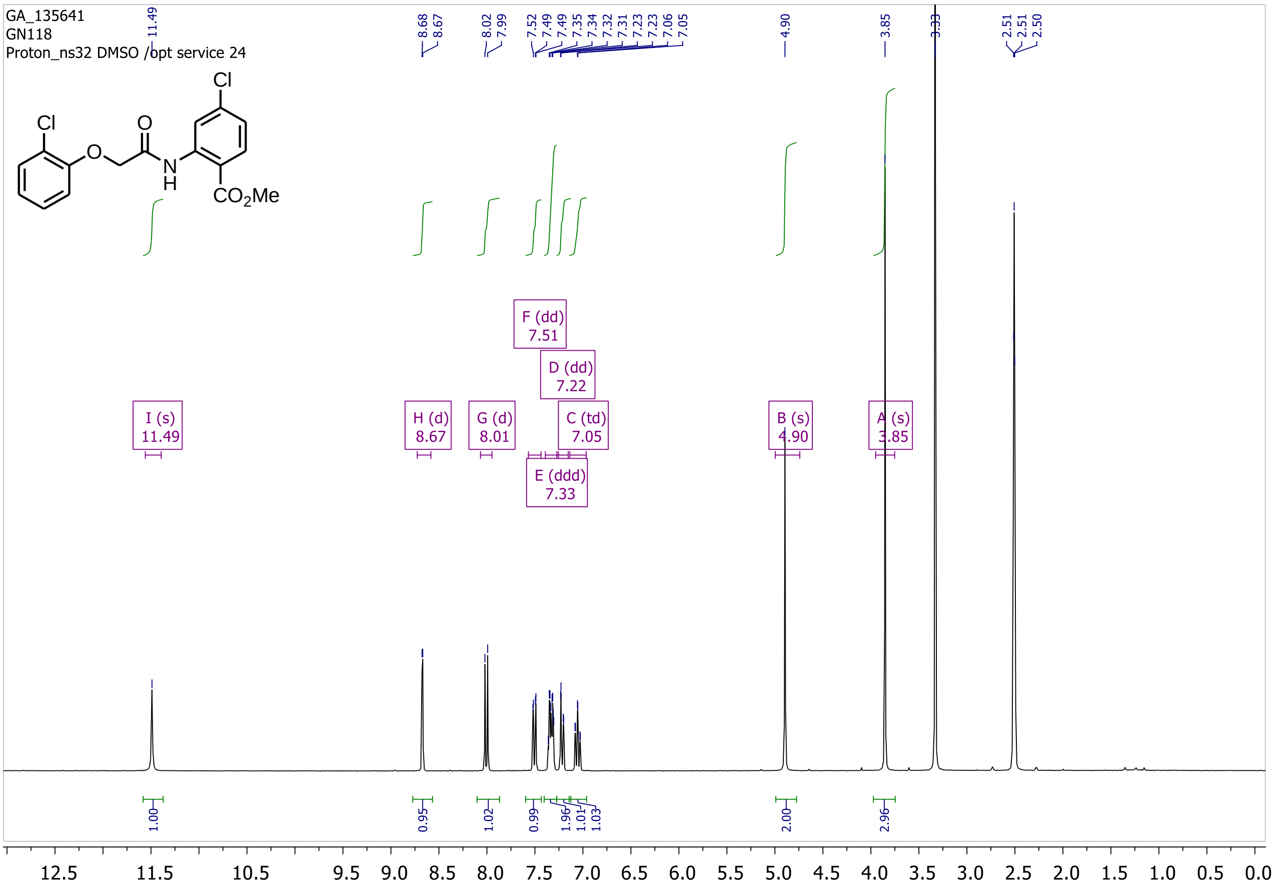


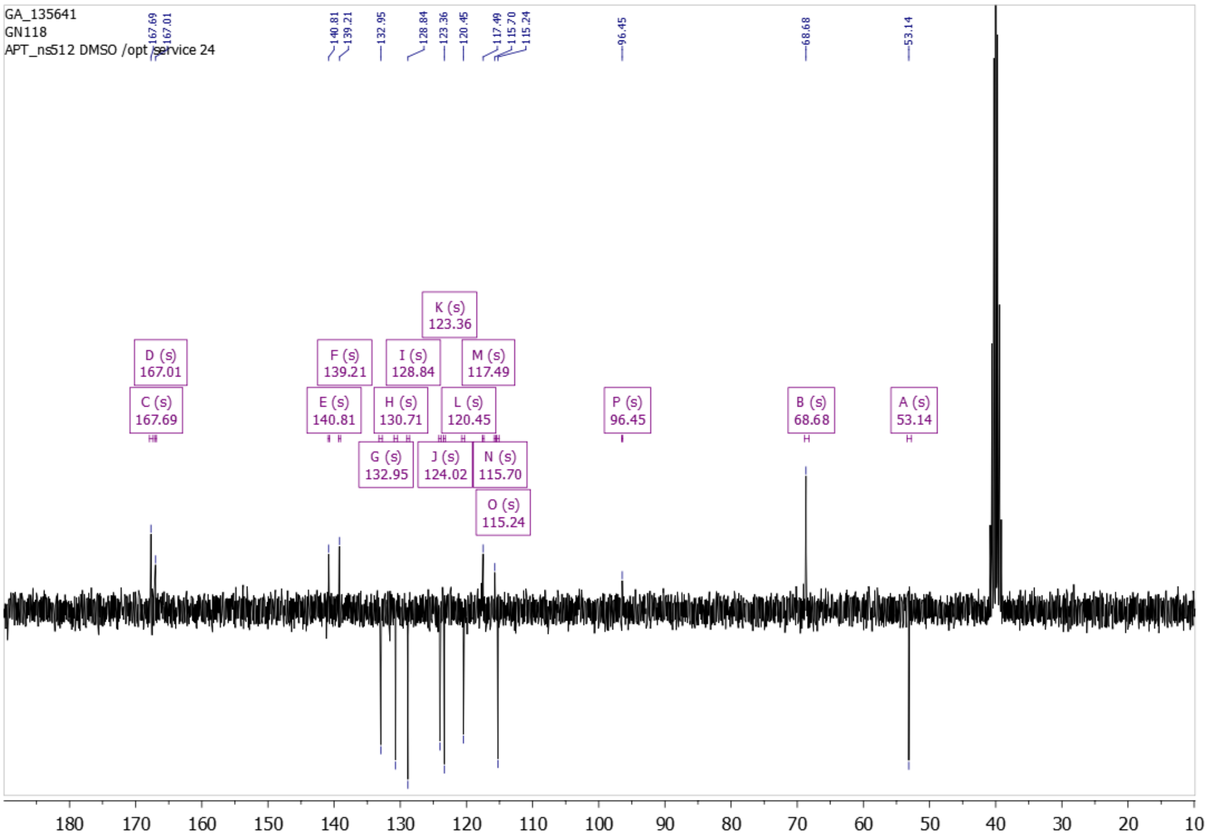
(*rac*)-4-Chloro-2-(2-(4-chloro-2-methylphenoxy)propanamido)benzoic acid (4):



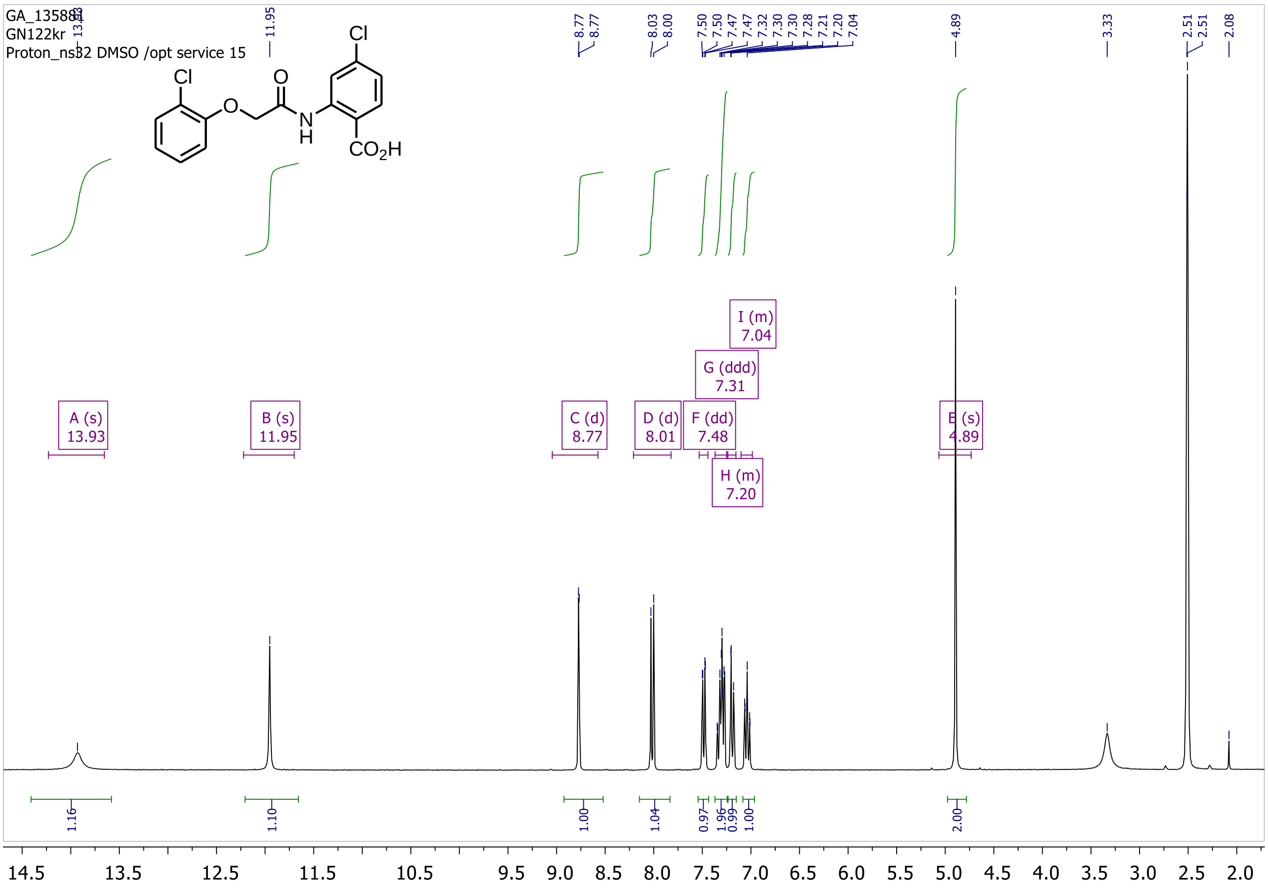


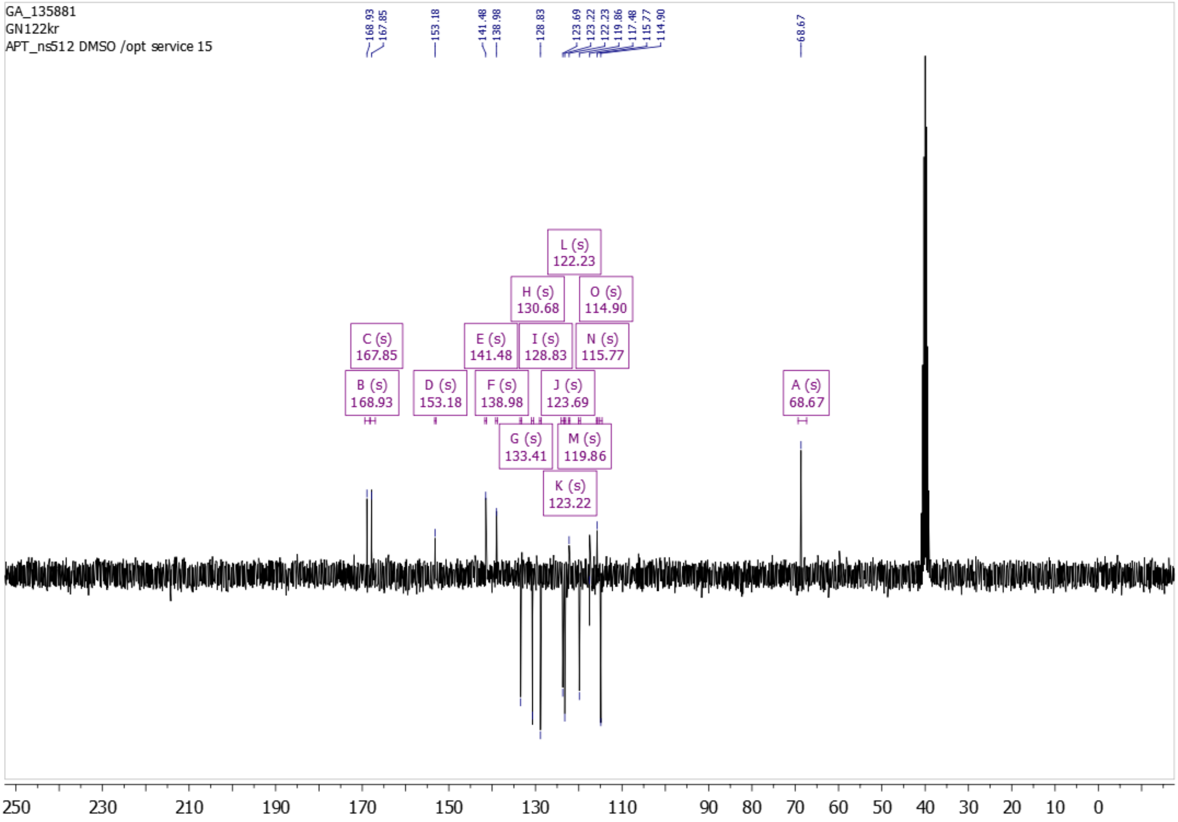
Methyl 4-chloro-2-(2-(2-chlorophenoxy)acetamido)benzoate (65):



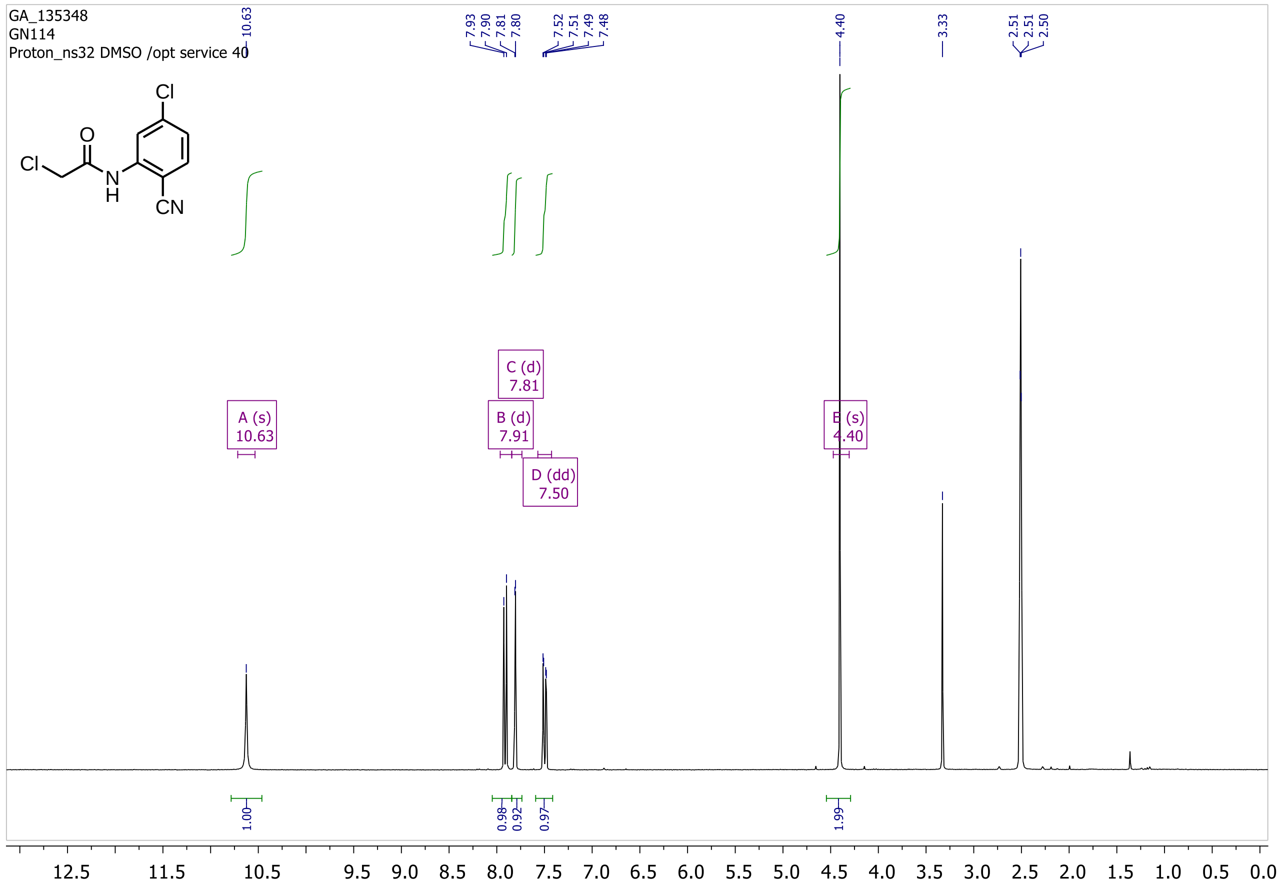


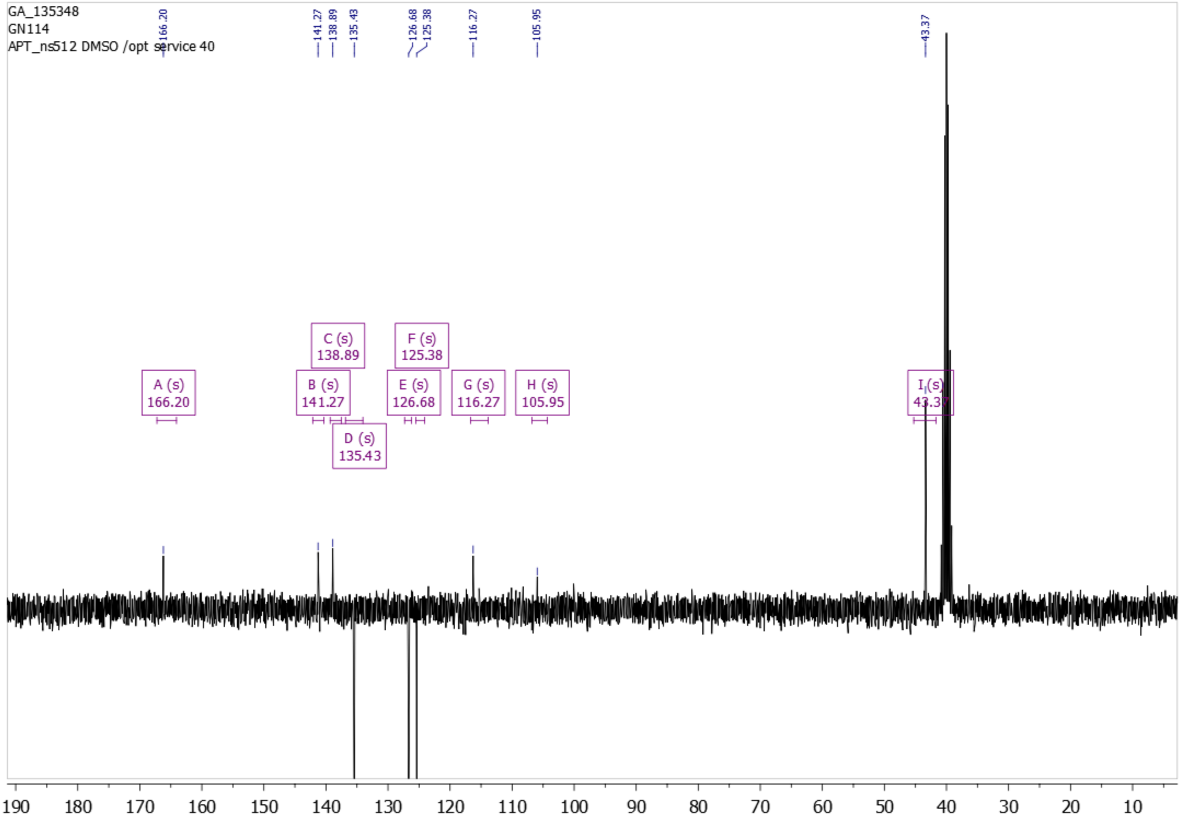
4-Chloro-2-(2-(2-chlorophenoxy)acetamido)benzoic acid (5):



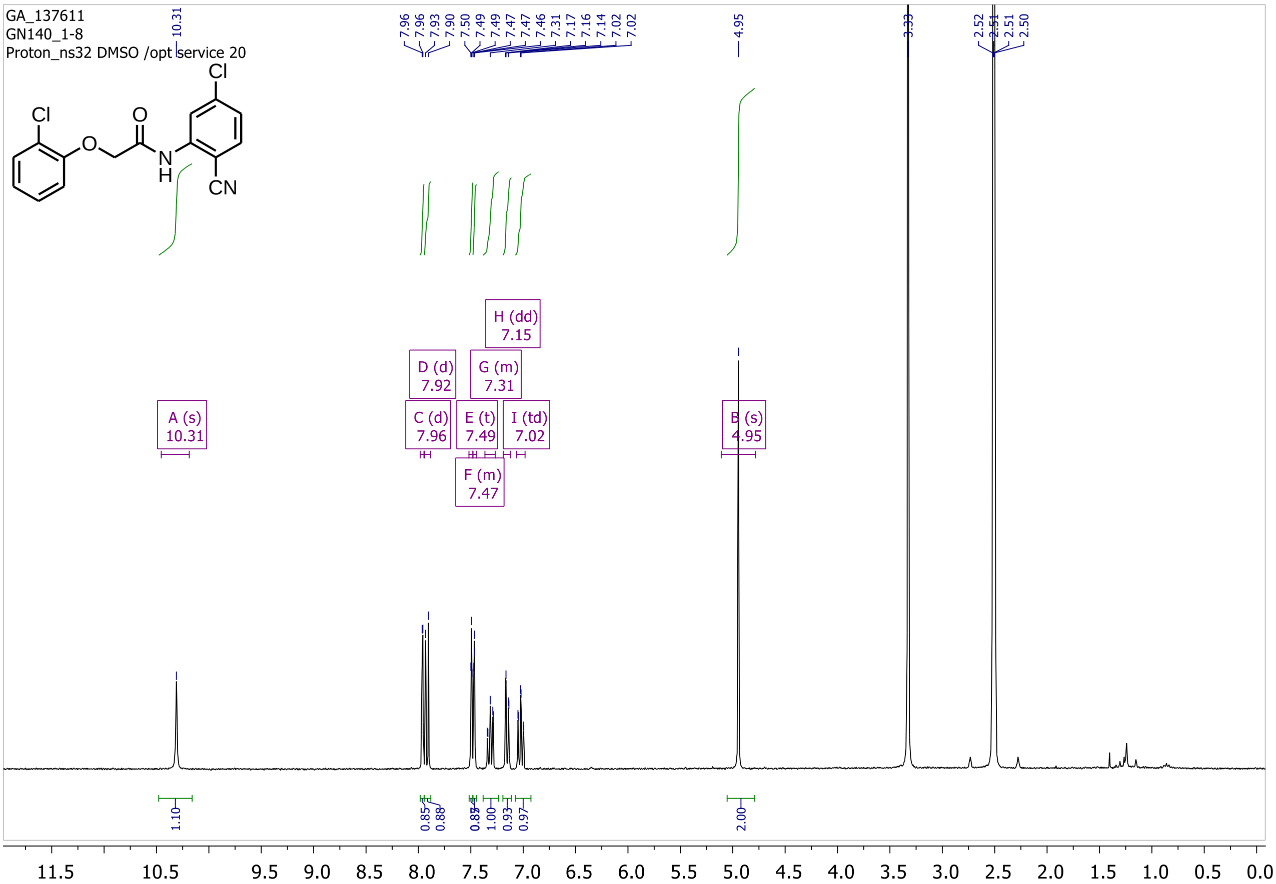


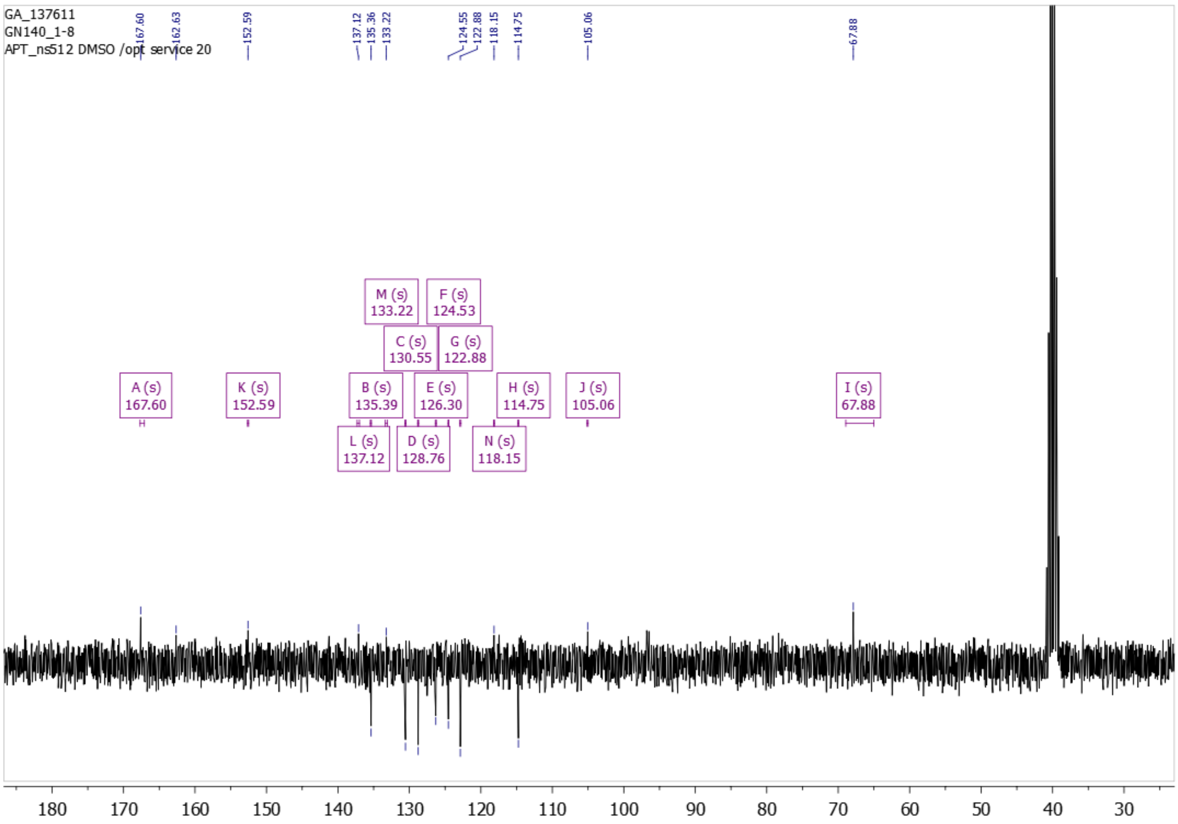
2-Chloro-N-(5-chloro-2-cyanophenyl)acetamide (**66**):



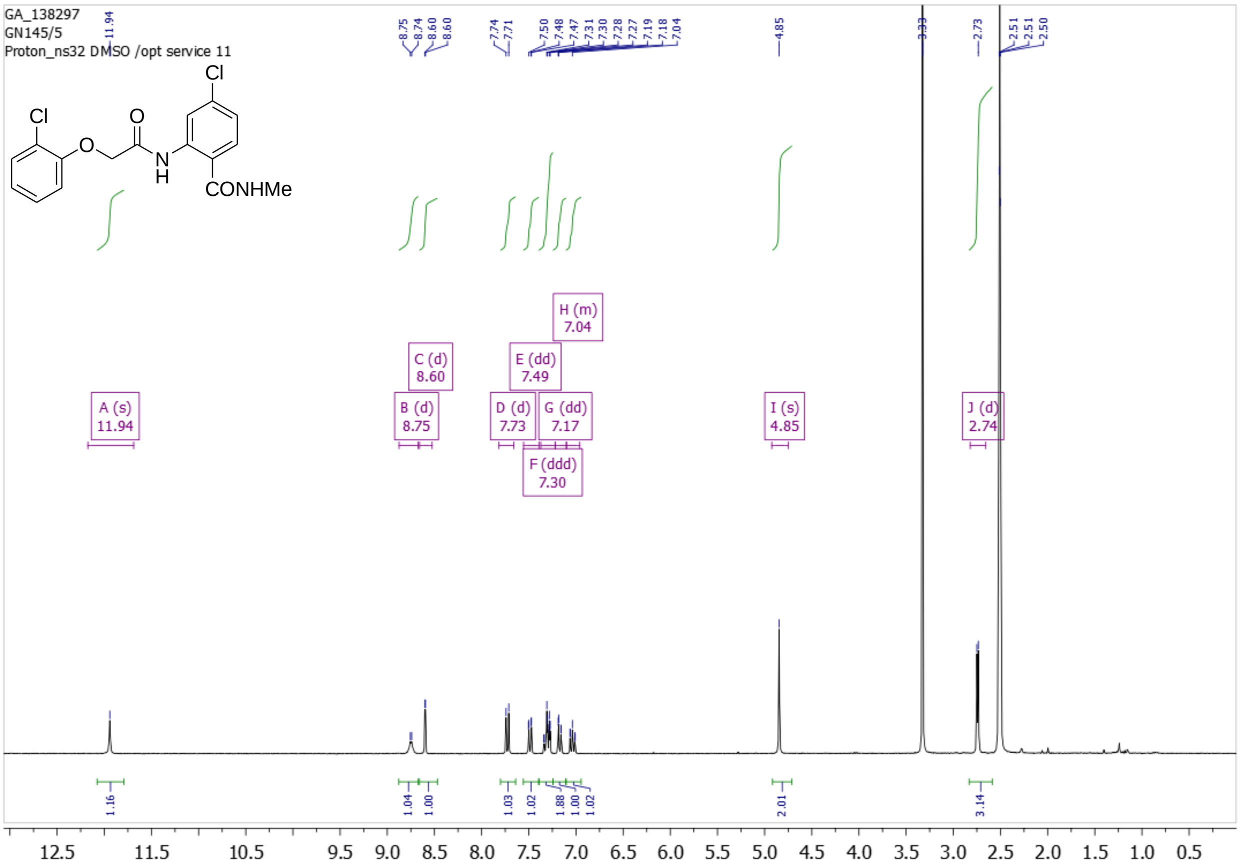


N-(5-Chloro-2-cyanophenyl)-2-(2-chlorophenoxy)acetamide (17):

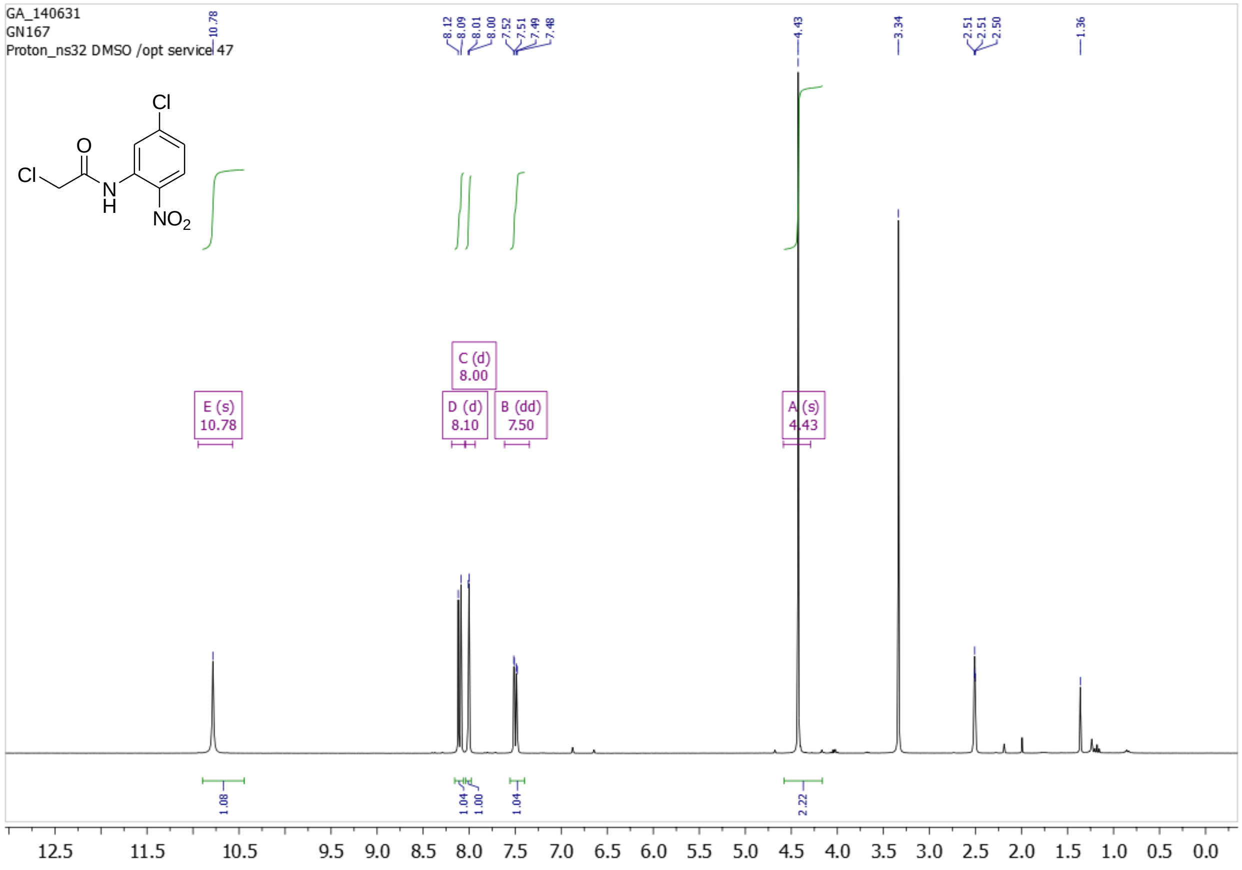


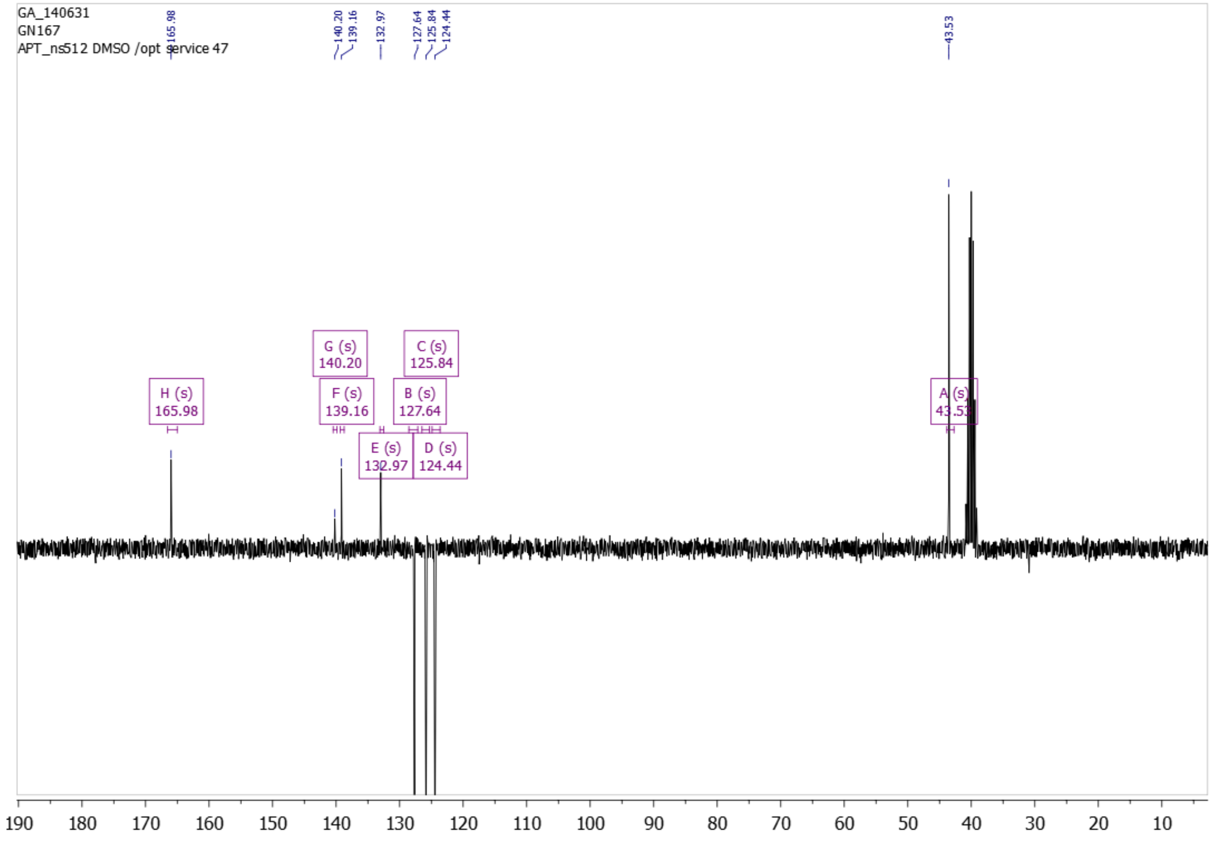


4-Chloro-2-(2-(2-chlorophenoxy)acetamido)-N-methylbenzamide (**18**):

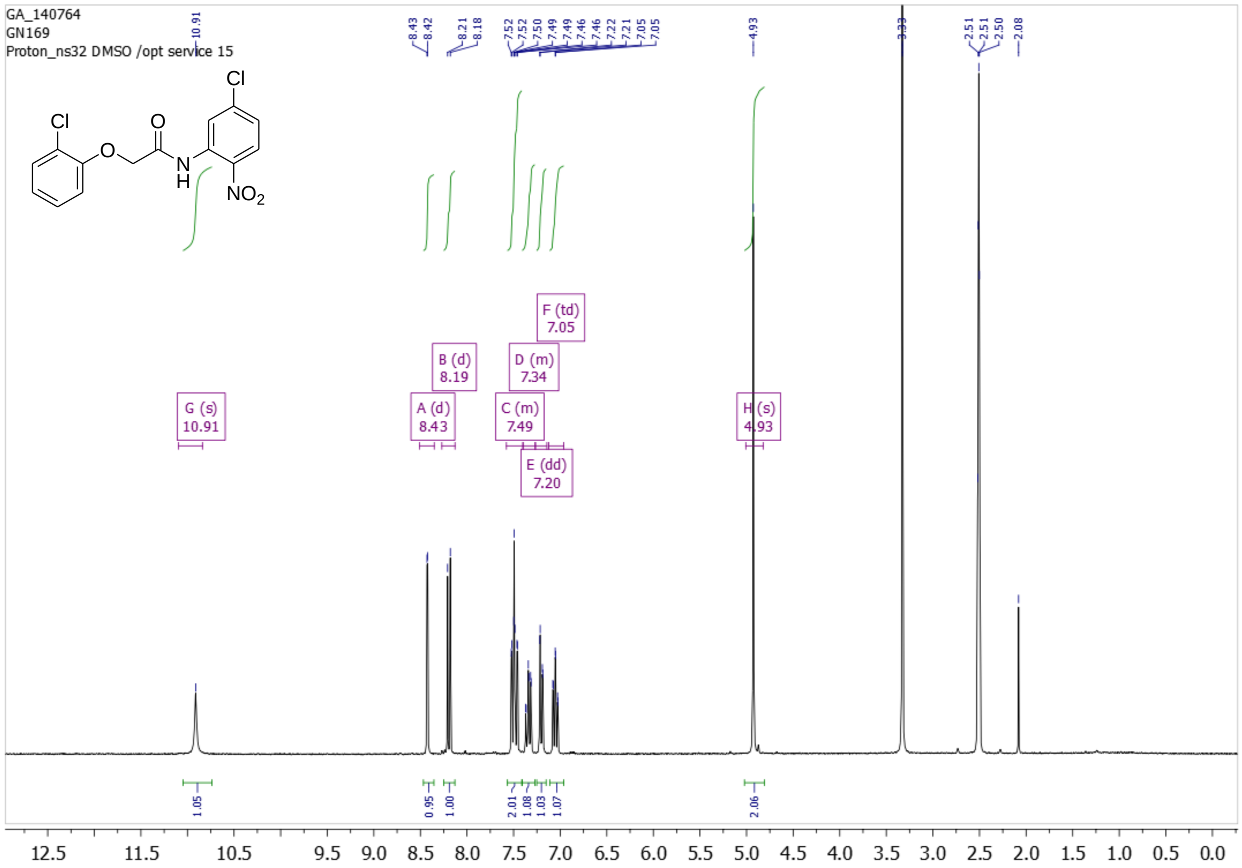


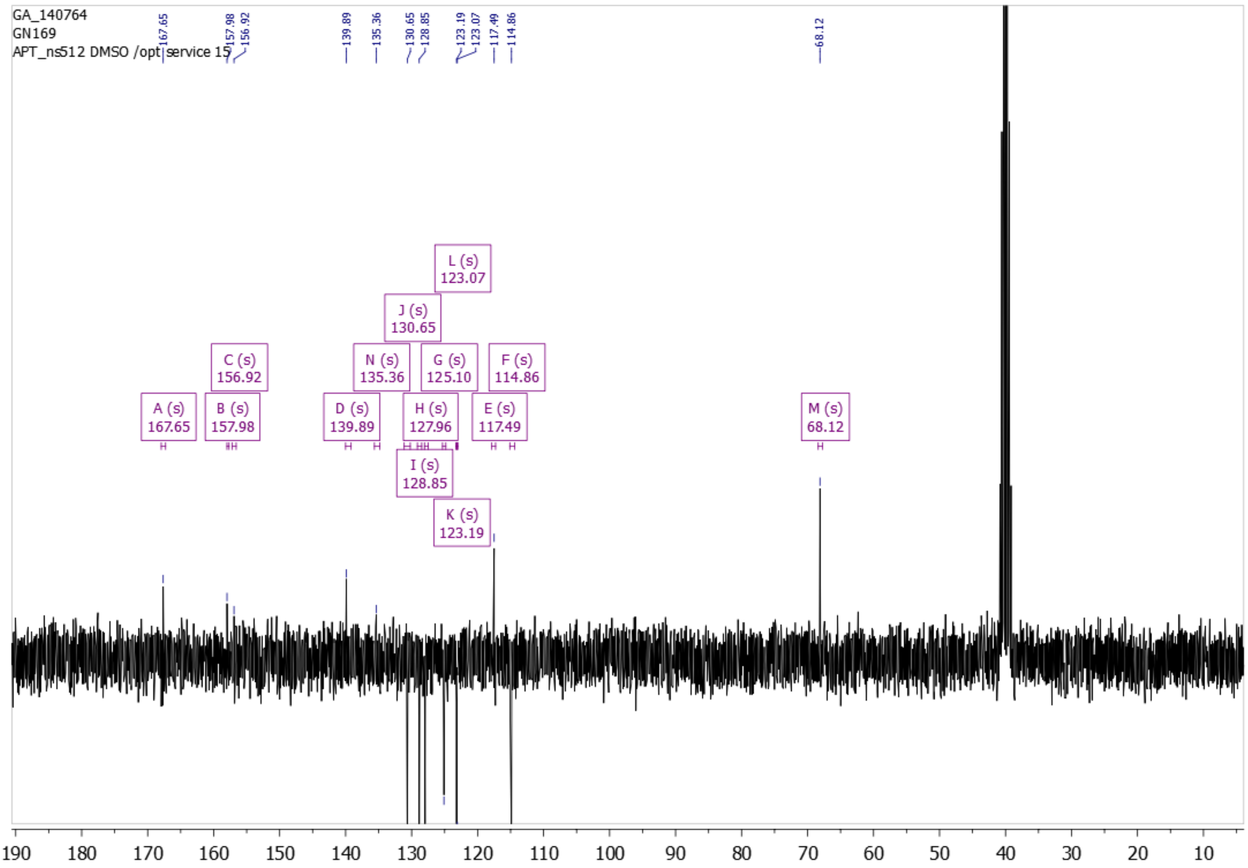
2-Chloro-N-(5-chloro-2-nitrophenyl)acetamide (67):



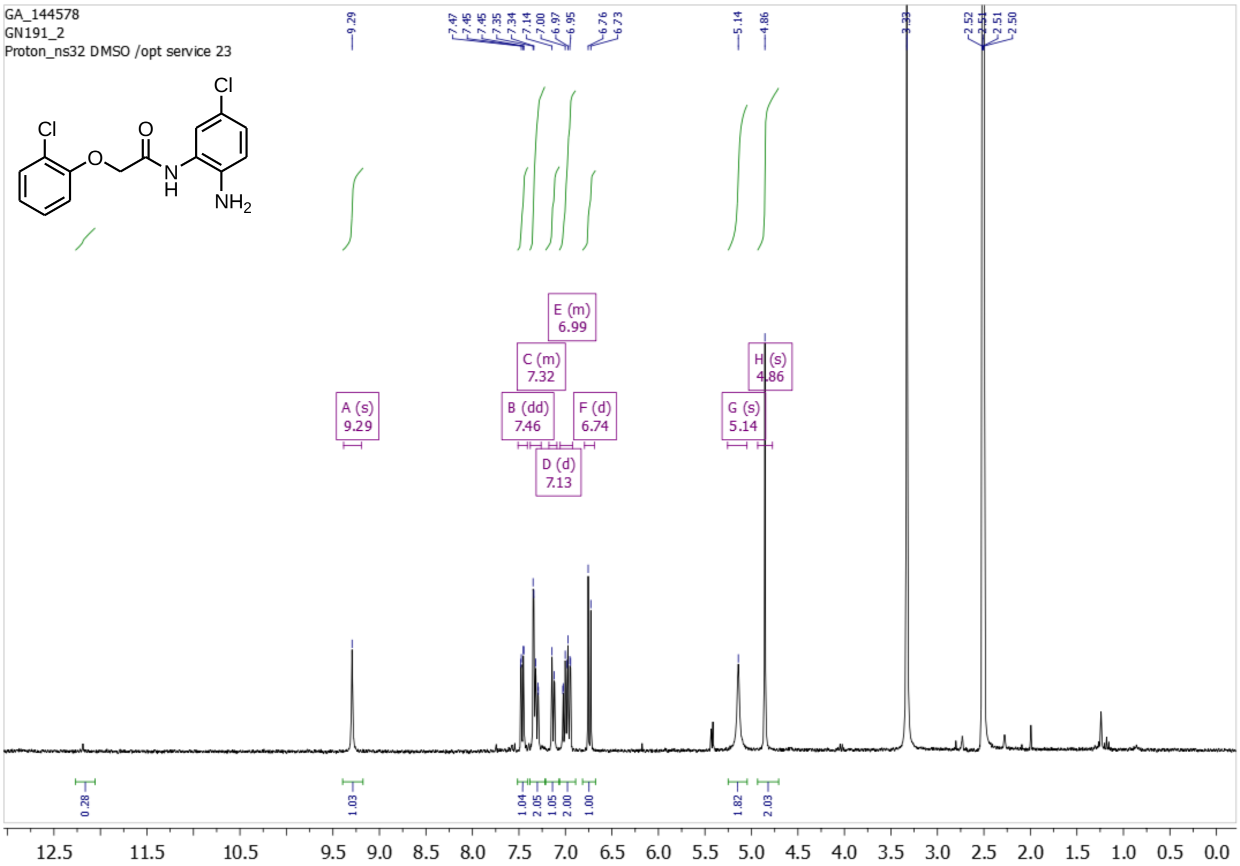


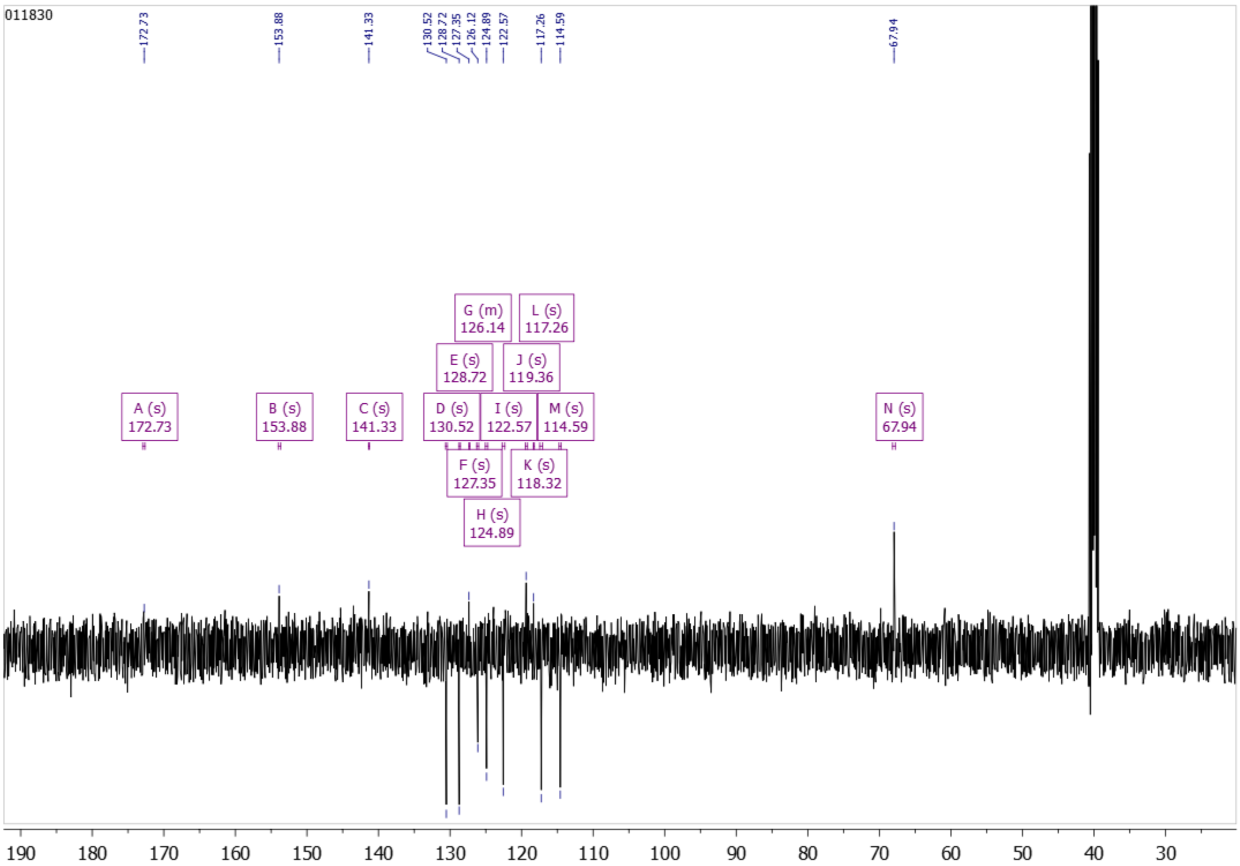
N-(5-Chloro-2-nitrophenyl)-2-(2-chlorophenoxy)acetamide (19):



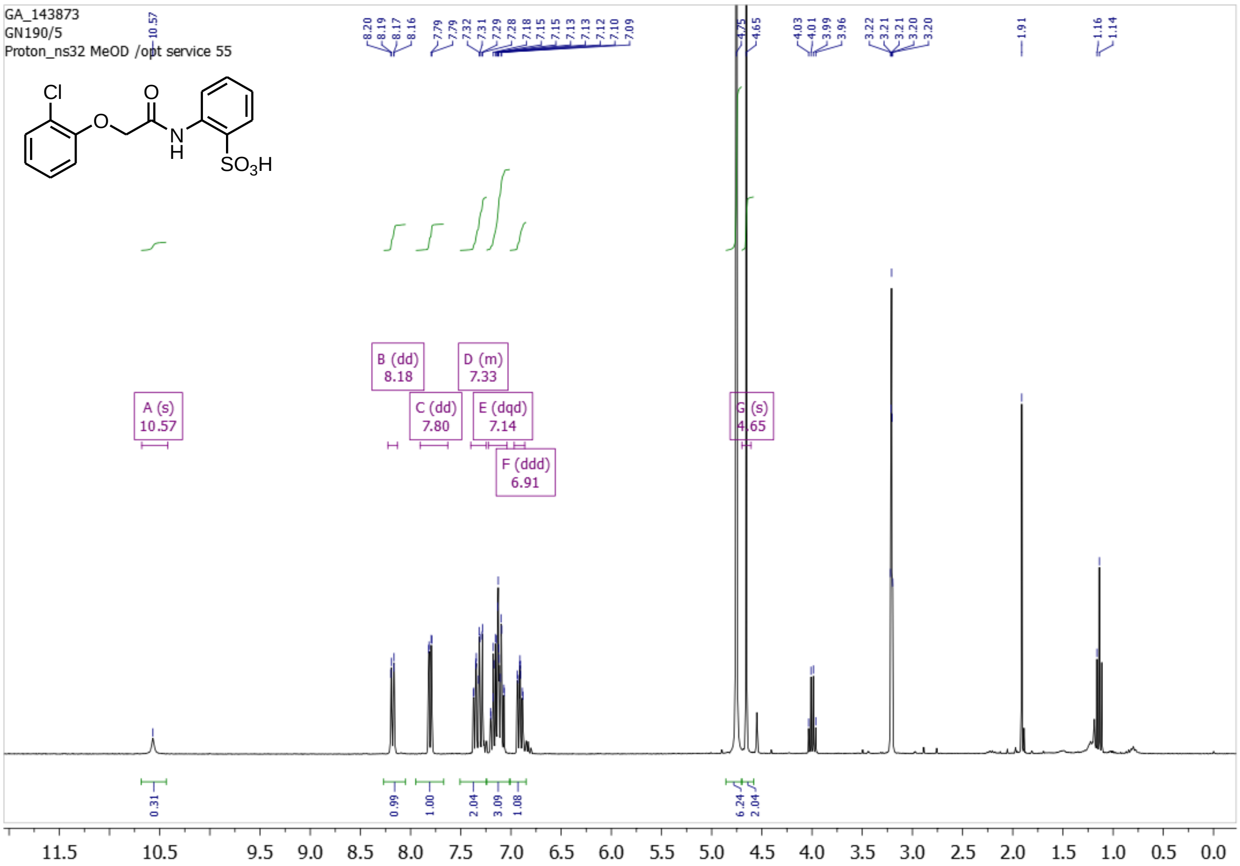


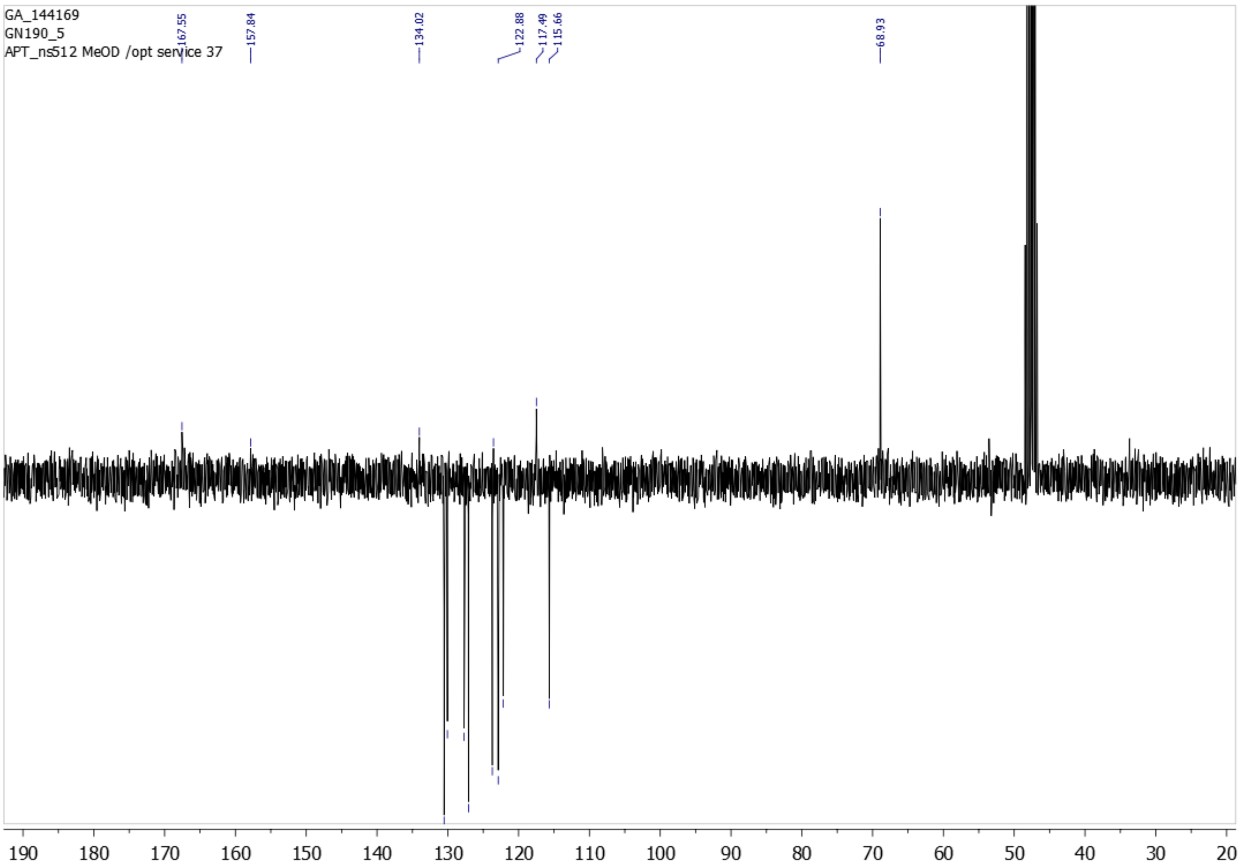
N-(2-Amino-5-chlorophenyl)-2-(2-chlorophenoxy)acetamide (**20**):



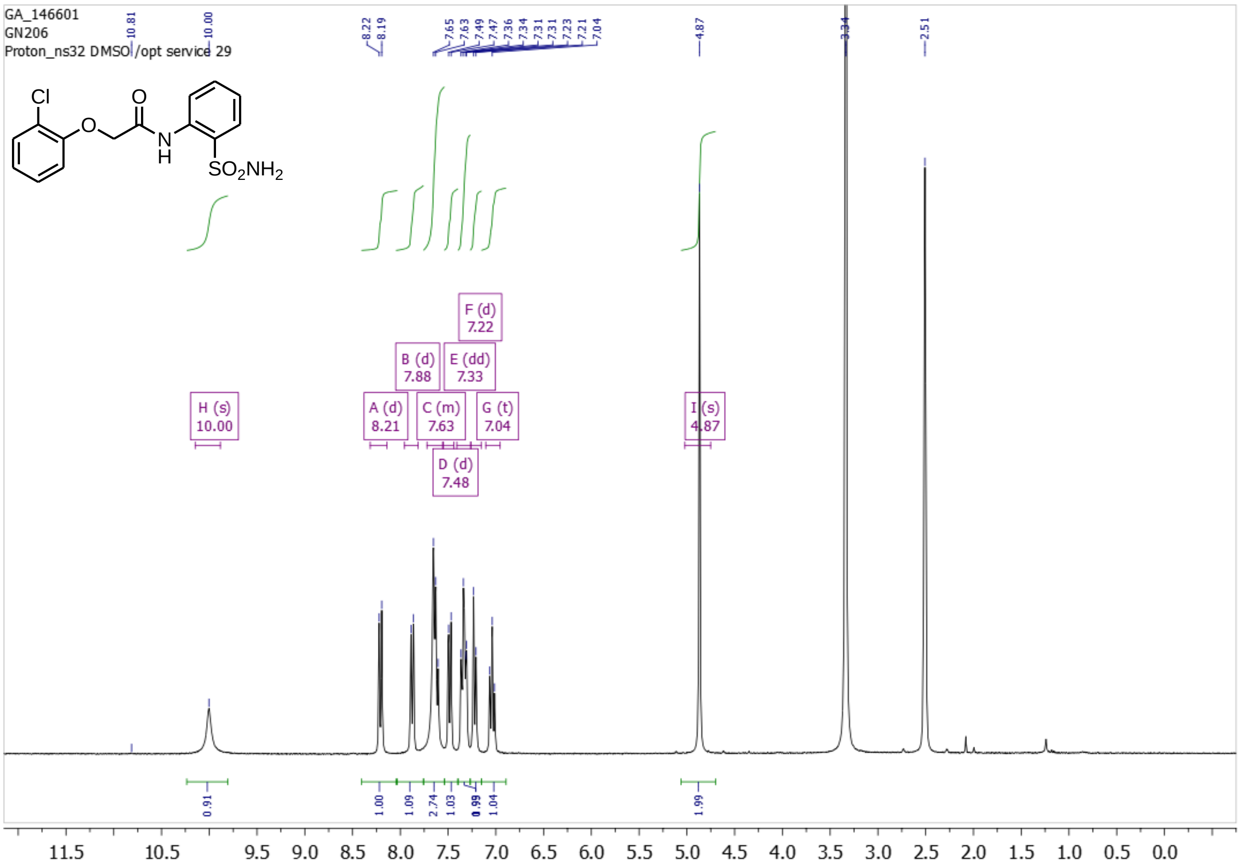


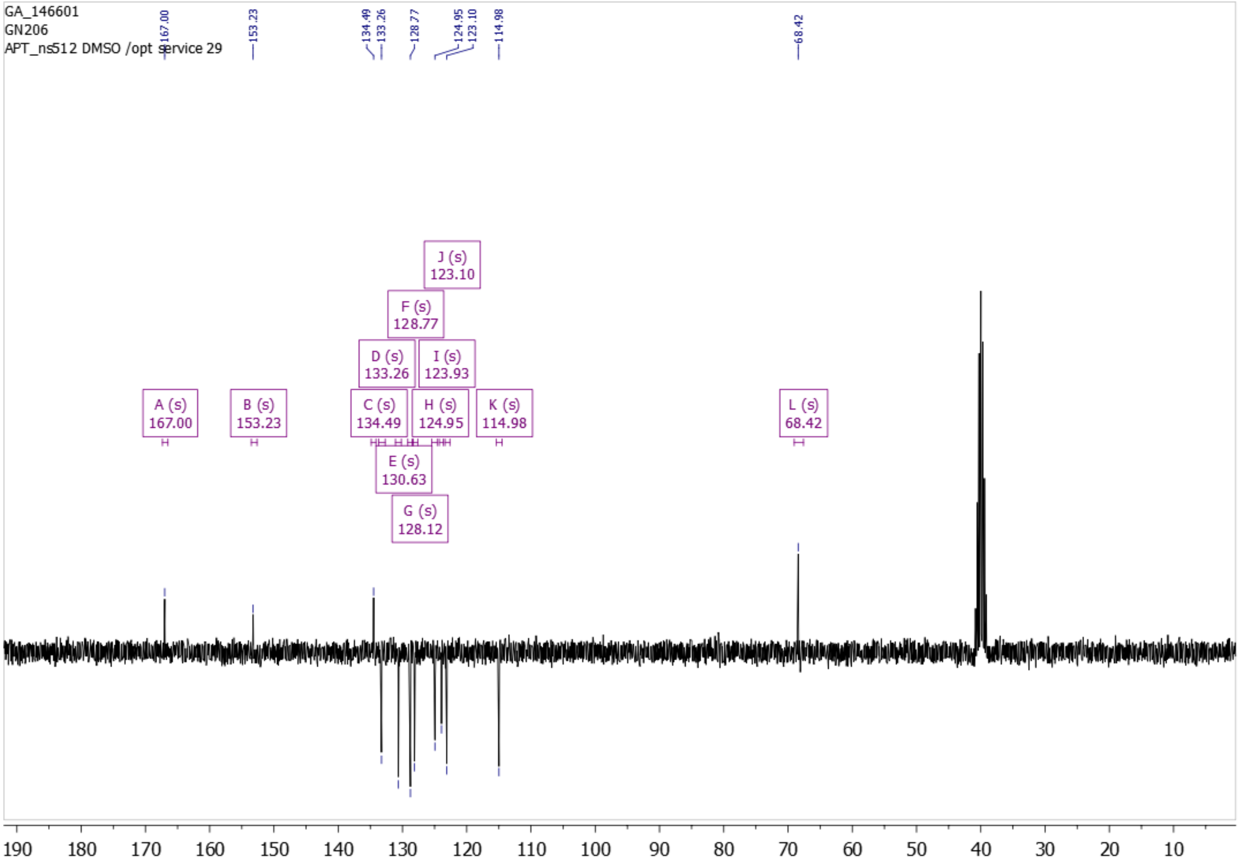
2-(2-(2-Chlorophenoxy)acetamido)benzenesulfonic acid (21):



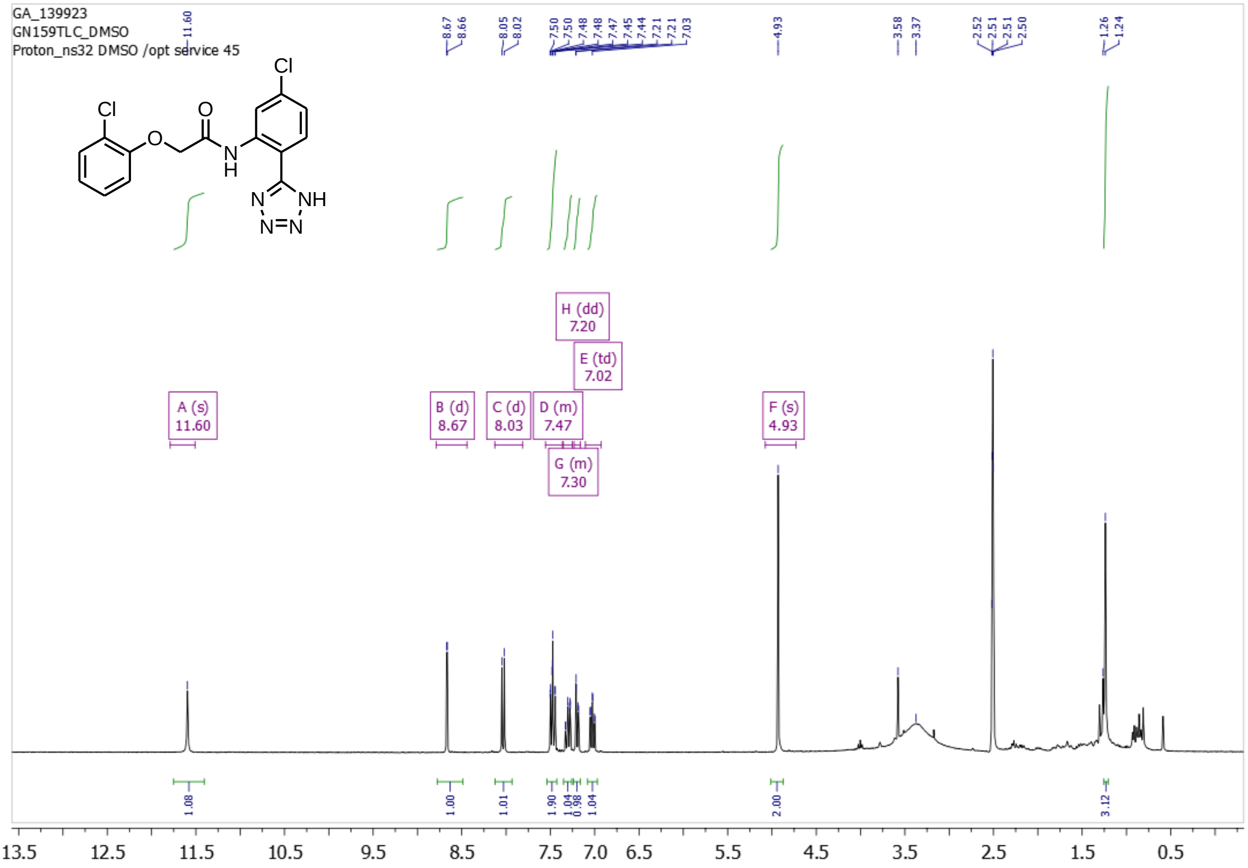


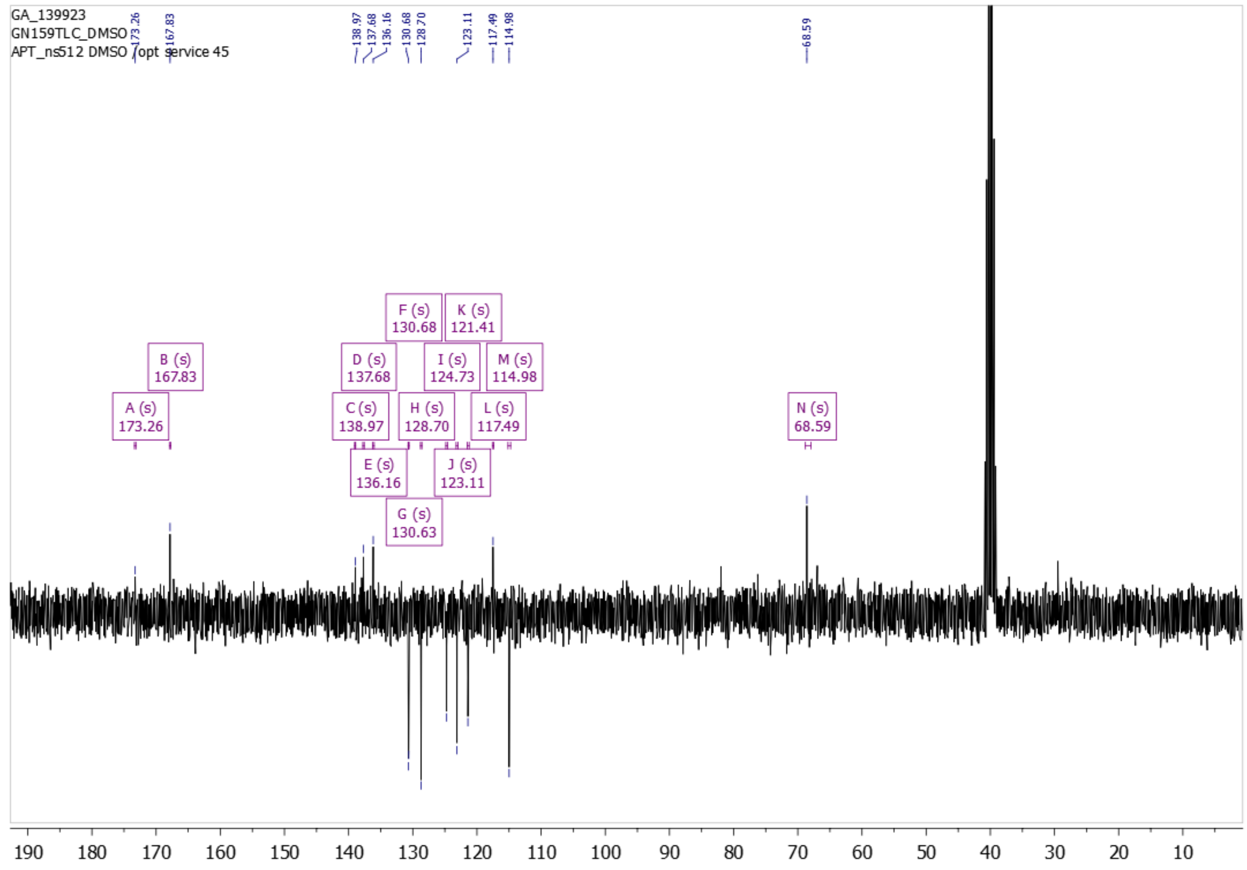
2-(2-Chlorophenoxy)-N-(2-sulfamoylphenyl)acetamide (22):



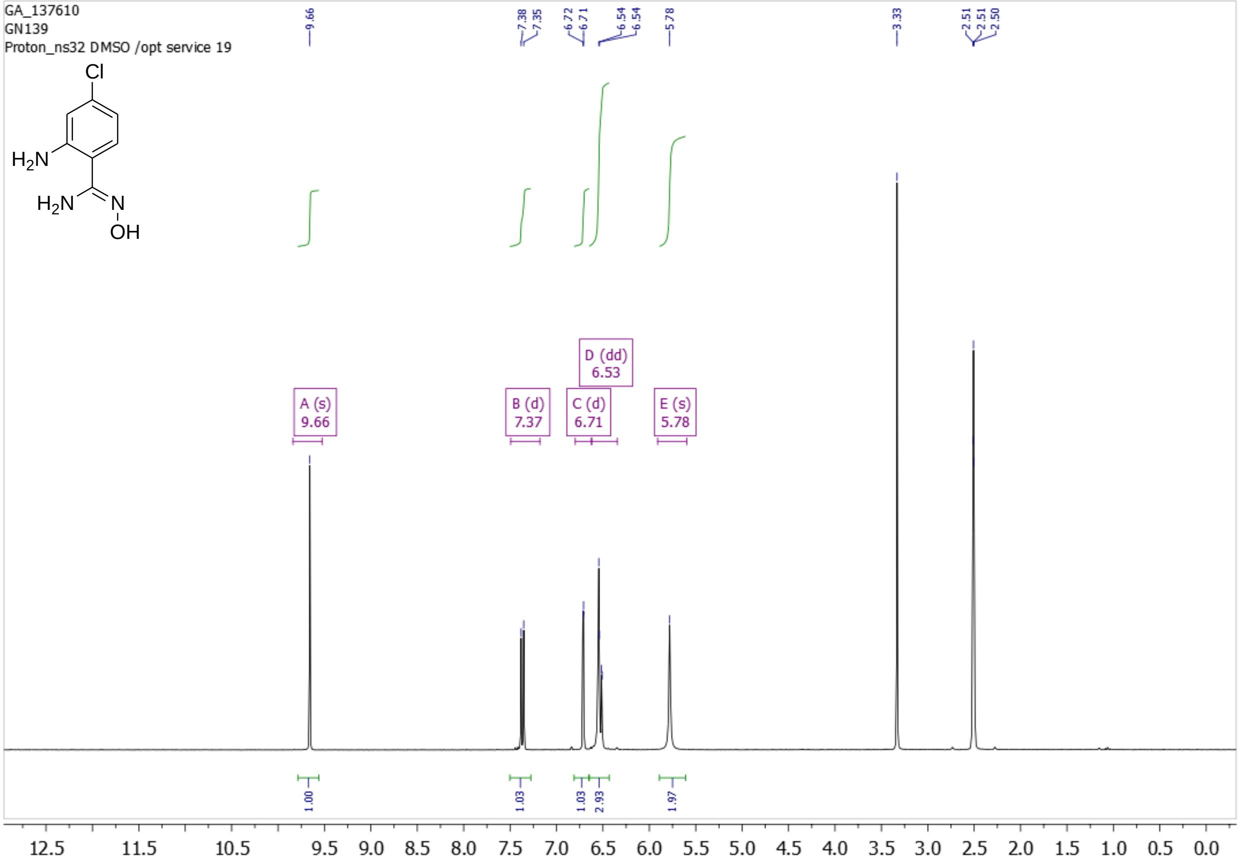


N-(5-Chloro-2-(1H-tetrazol-5-yl)phenyl)-2-(2-chlorophenoxy)acetamide (23):

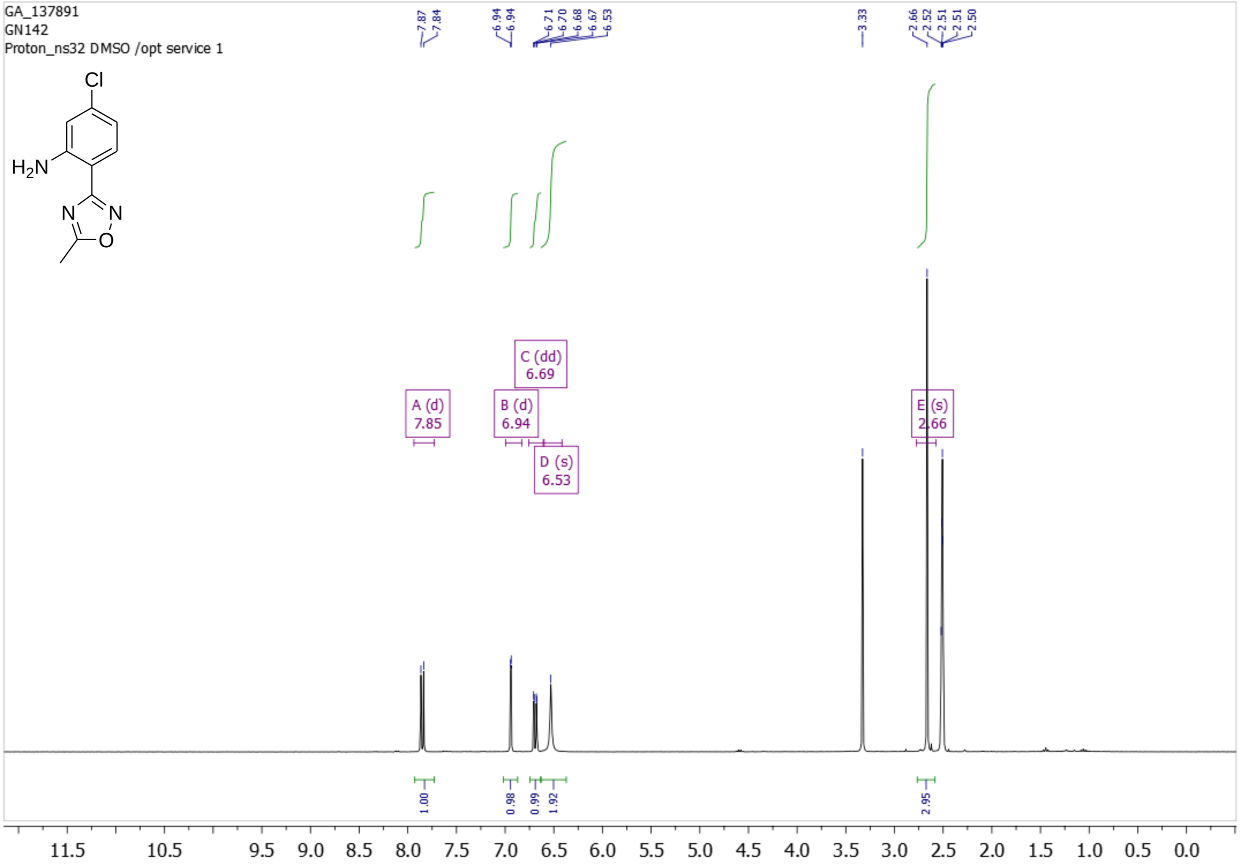


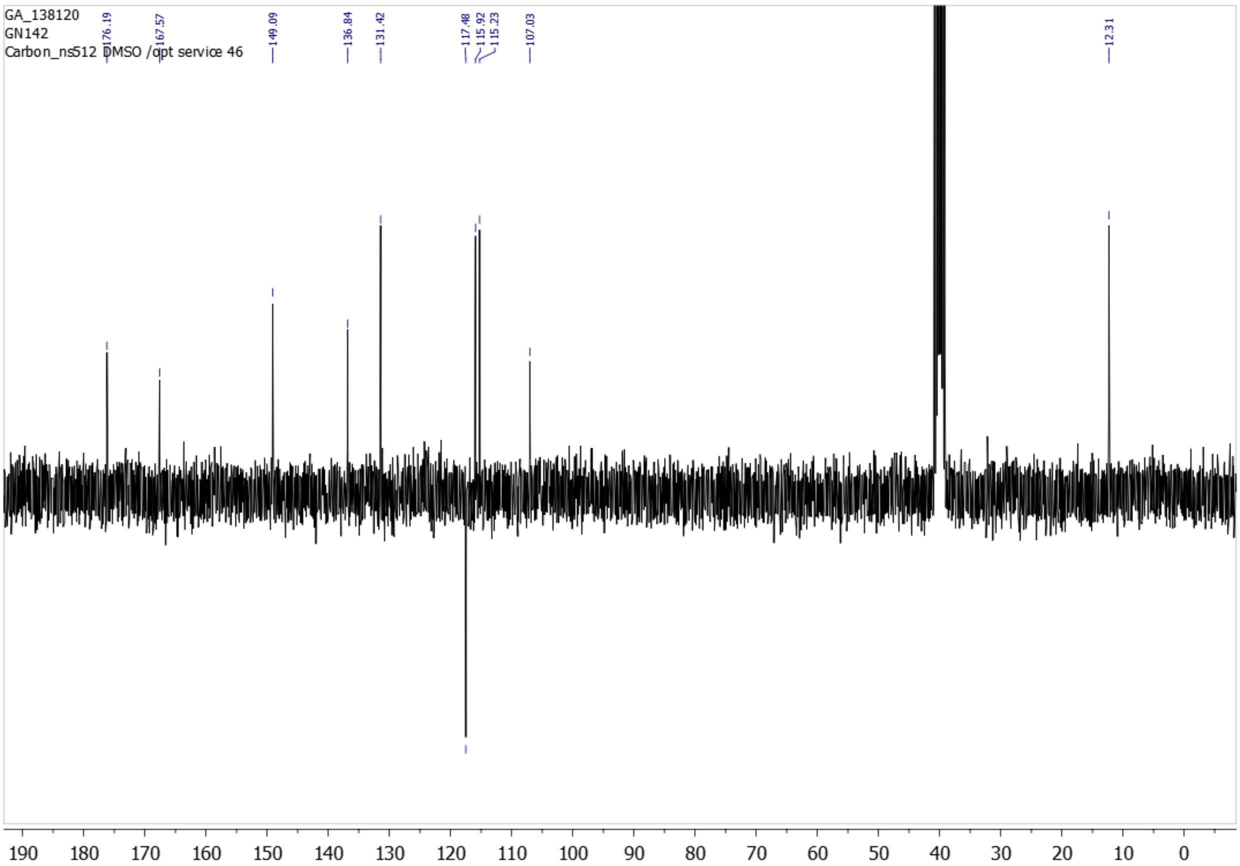


(Z)-2-Amino-4-chloro-N'-hydroxybenzimidamide (68):

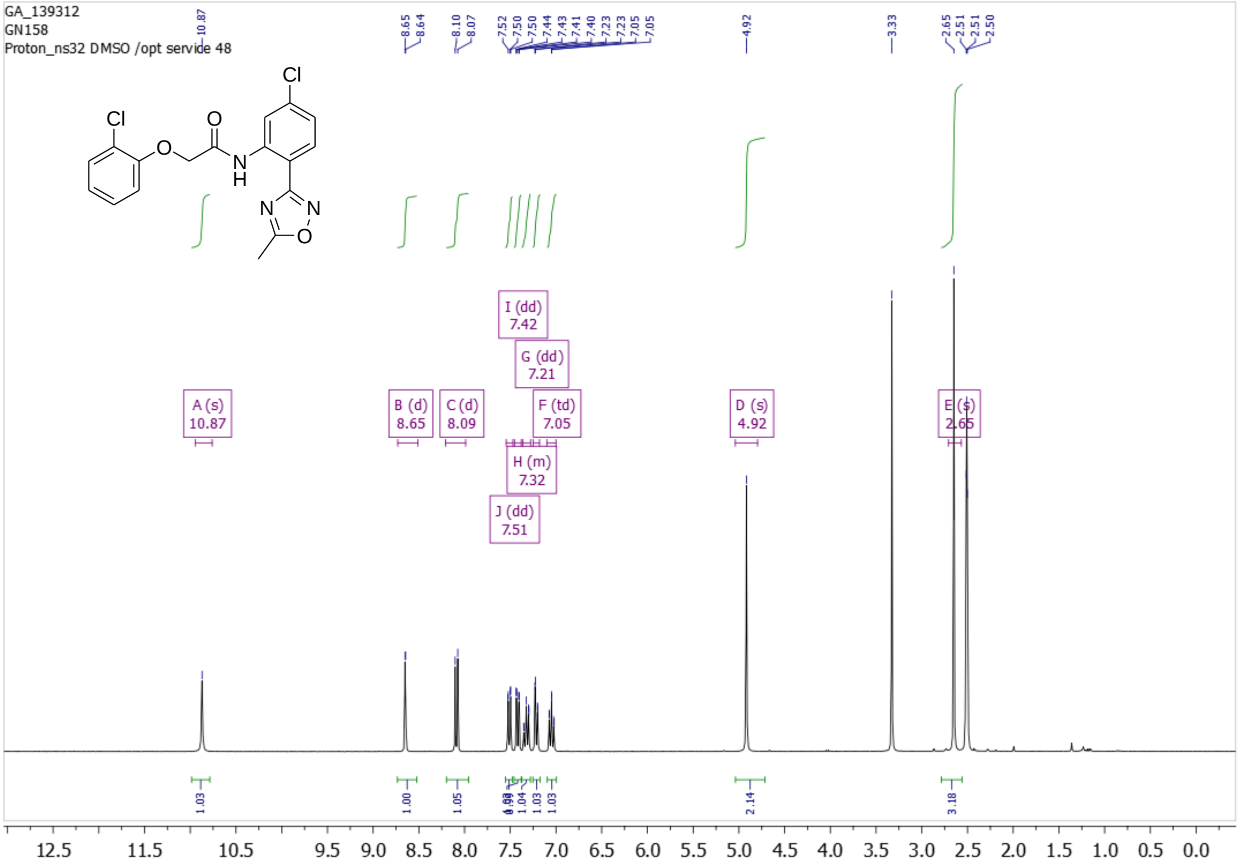


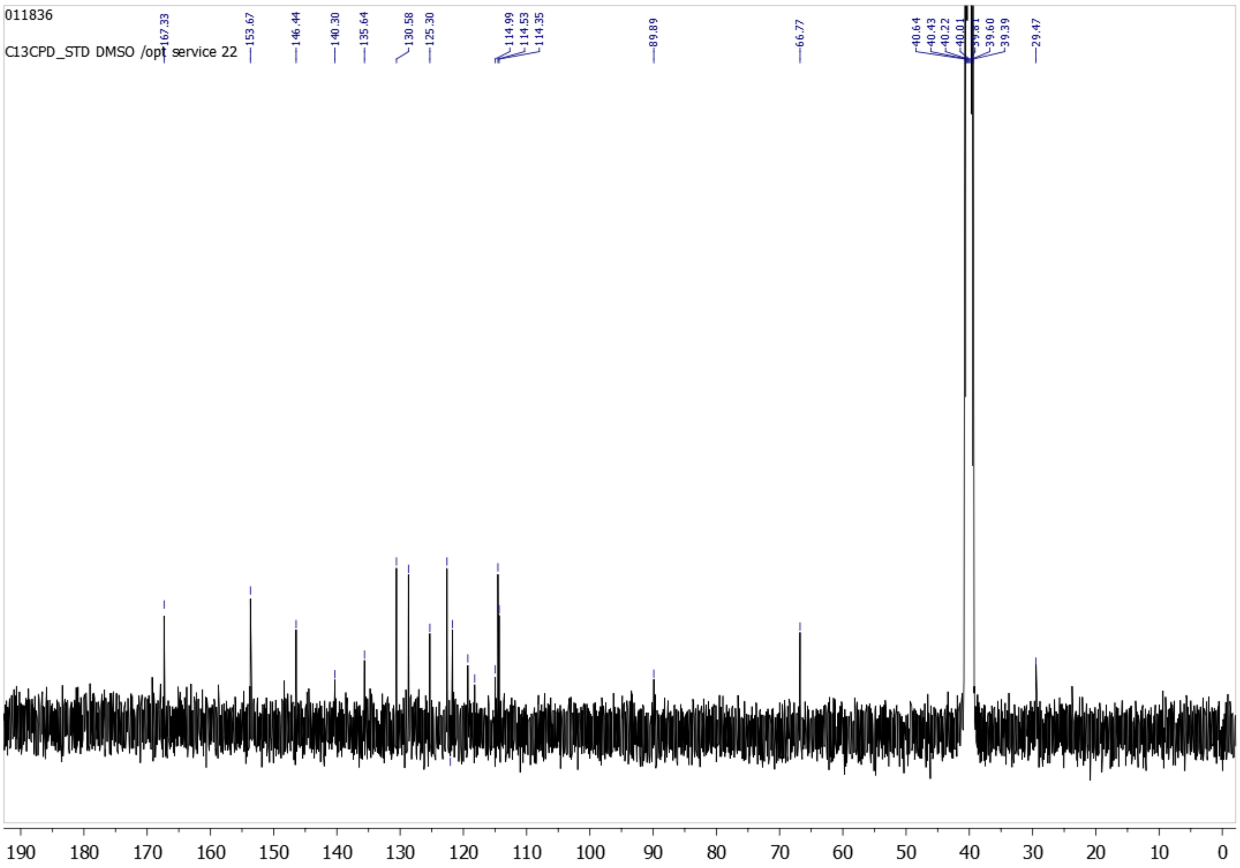
5-Chloro-2-(5-methyl-1,2,4-oxadiazol-3-yl)aniline (**69**):



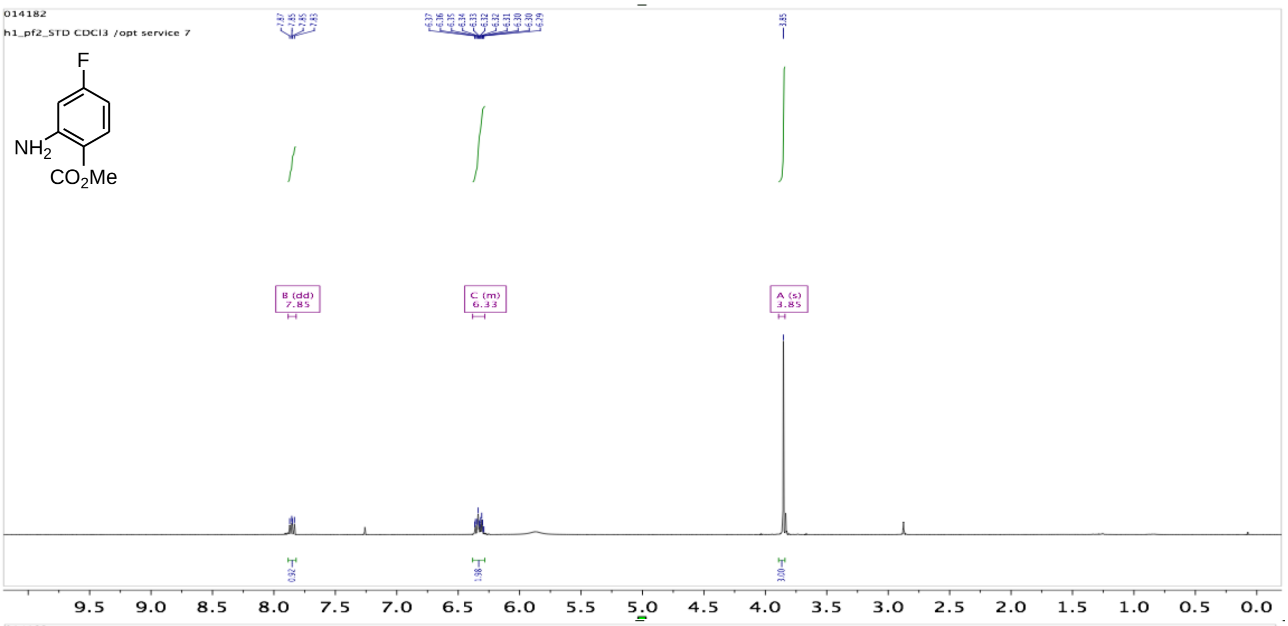


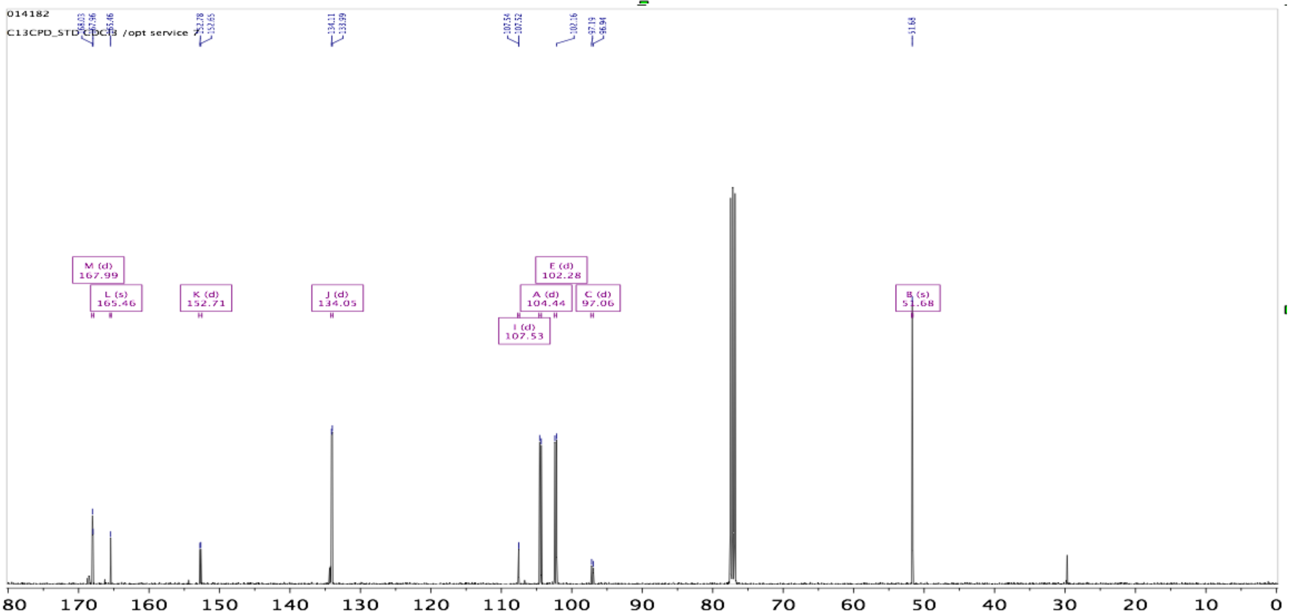
N-(5-Chloro-2-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)-2-(2-chlorophenoxy)acetamide (24):



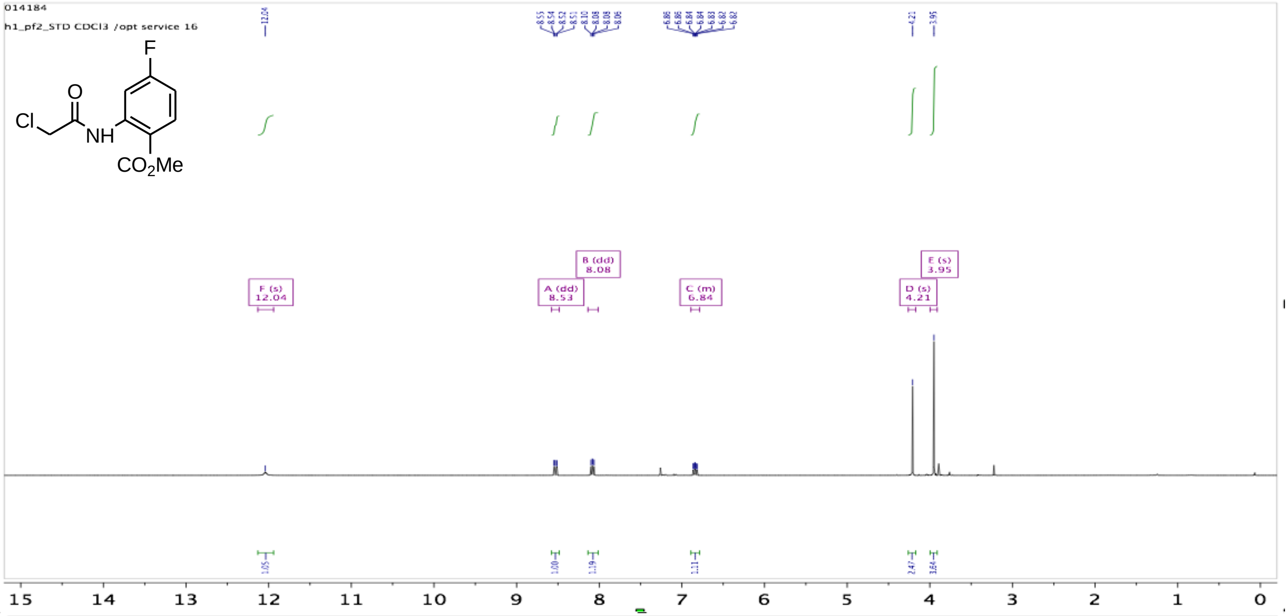


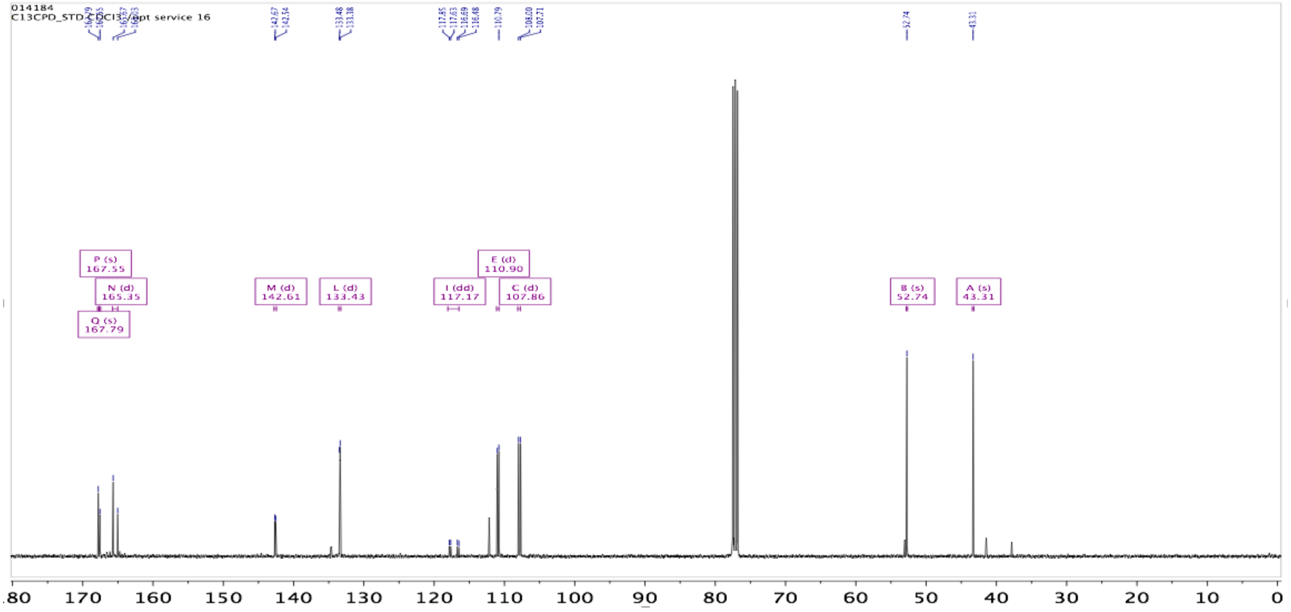
Methyl 2-amino-4-fluorobenzoate (70):



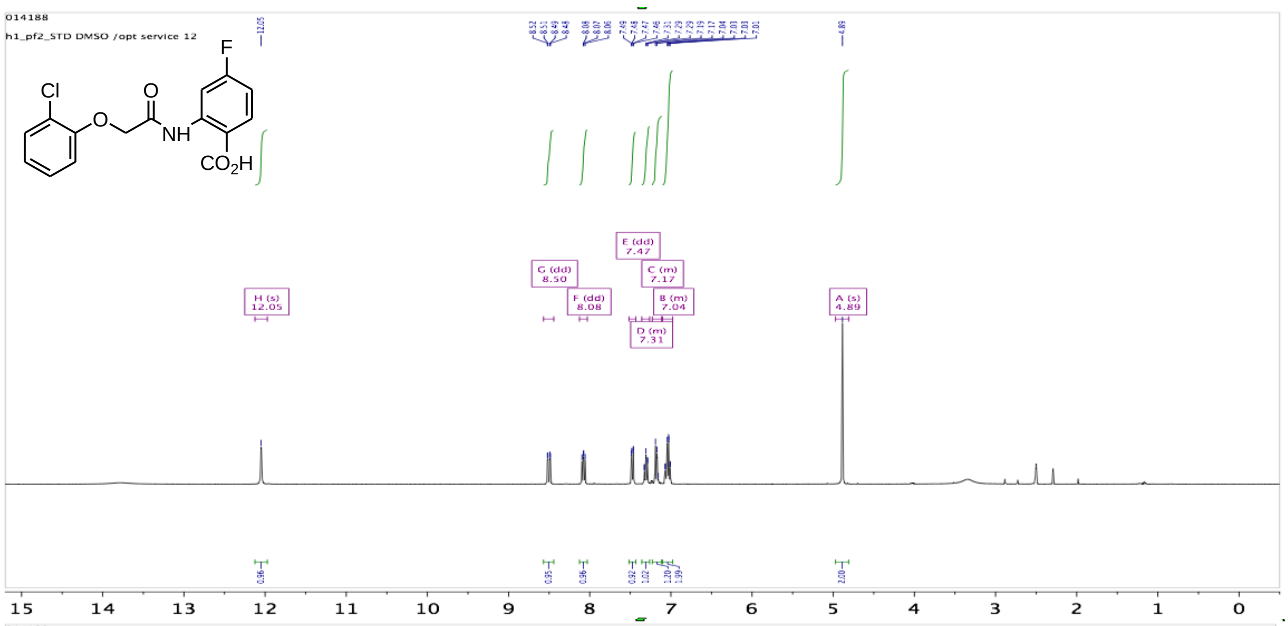


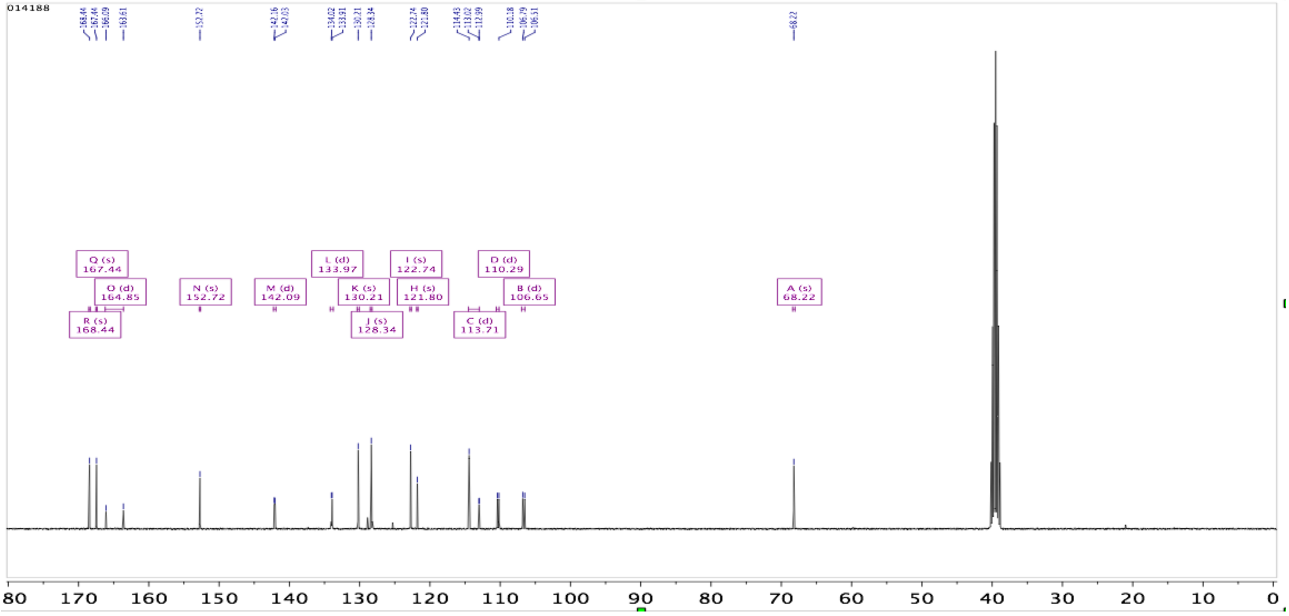
Methyl 2-(2-chloroacetamido)-4-fluorobenzoate (71):



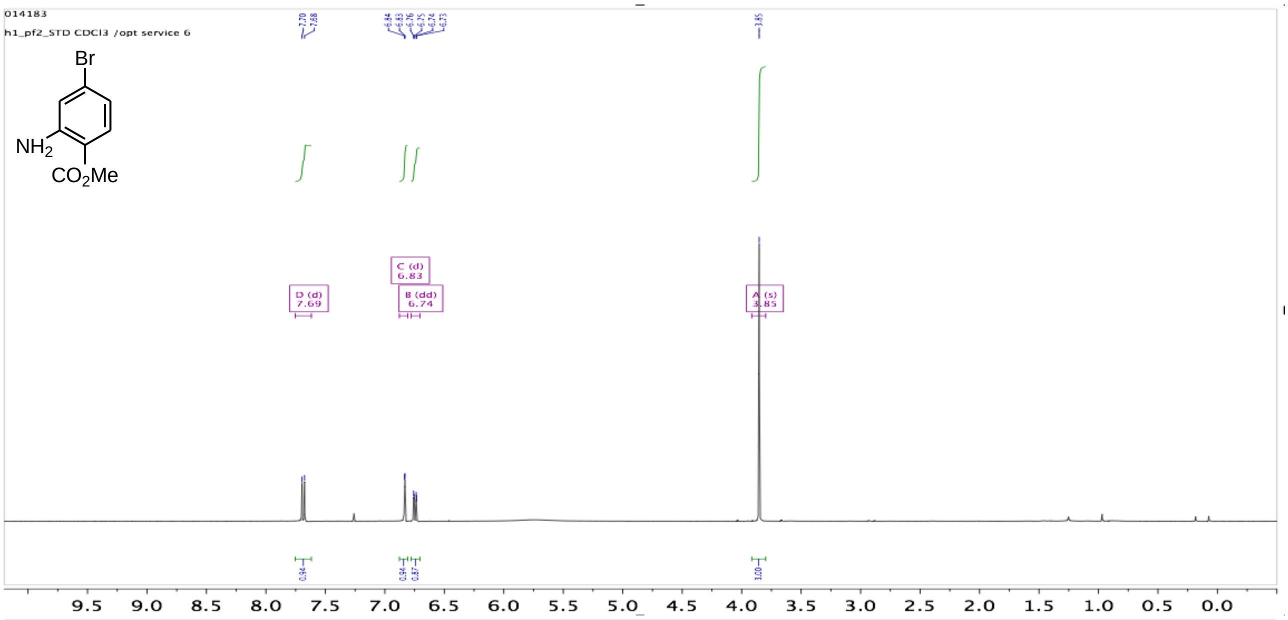


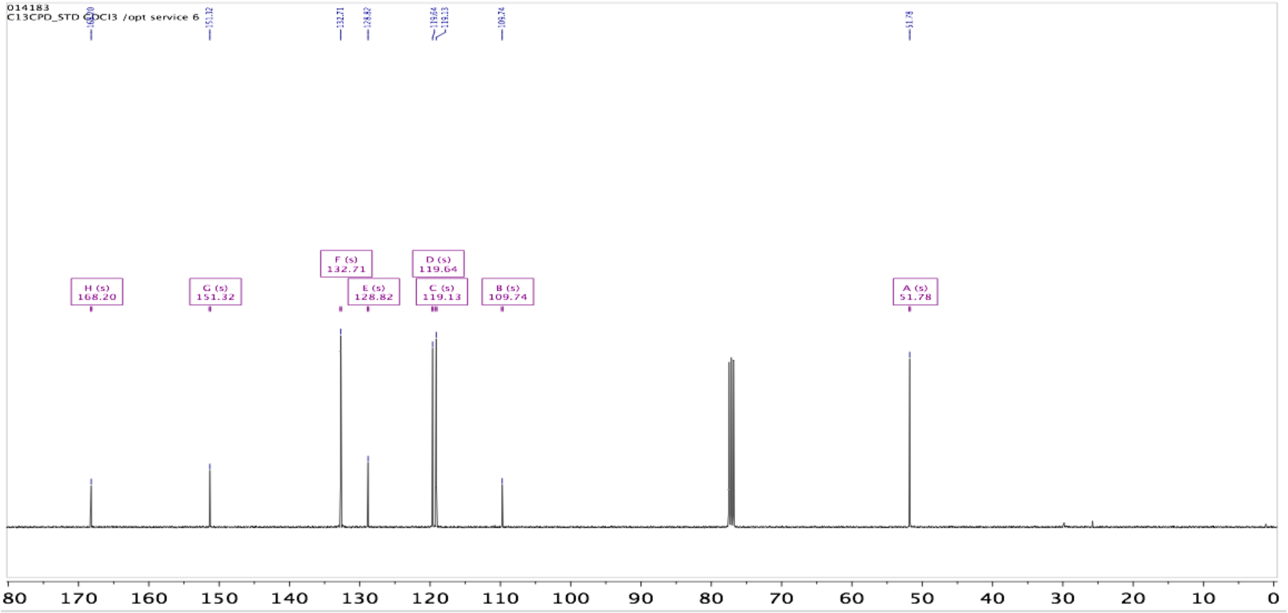
2-(2-(2-Chlorophenoxy)acetamido)-4-fluorobenzoic acid (25)**:**



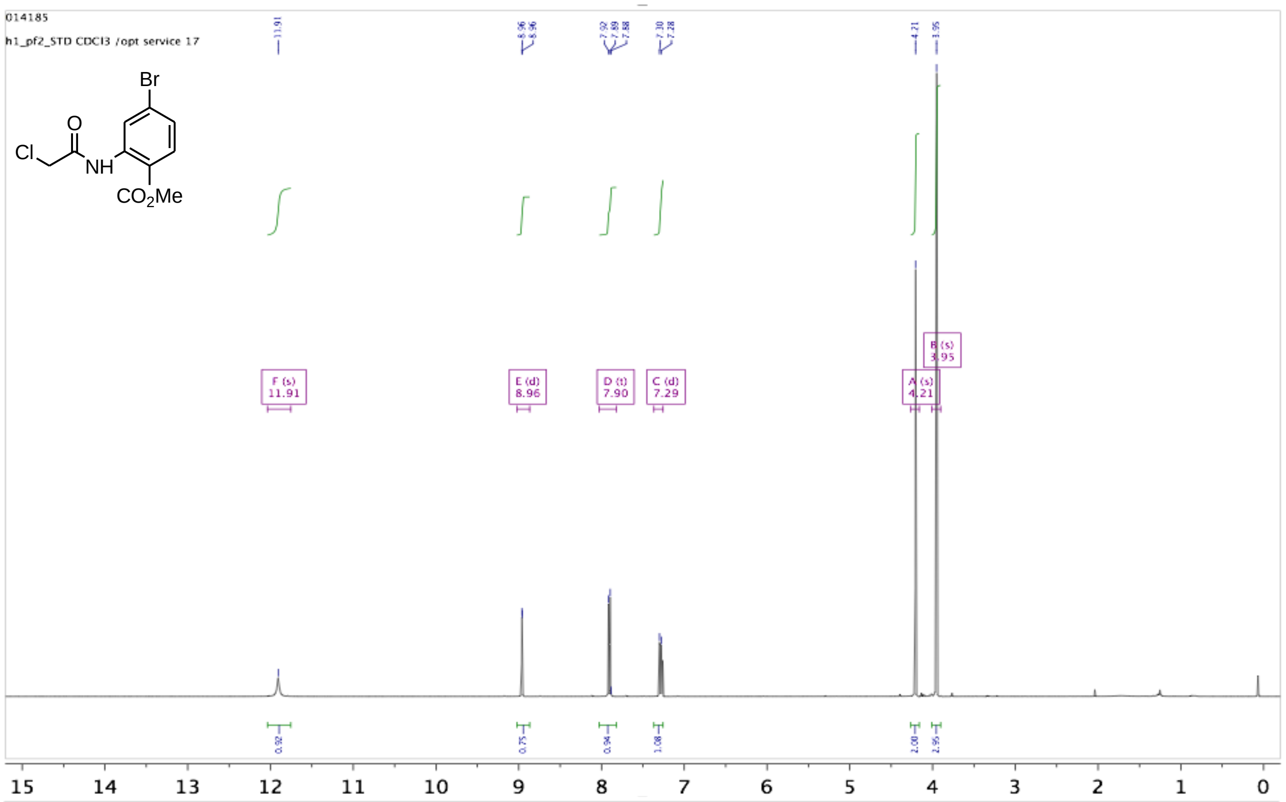


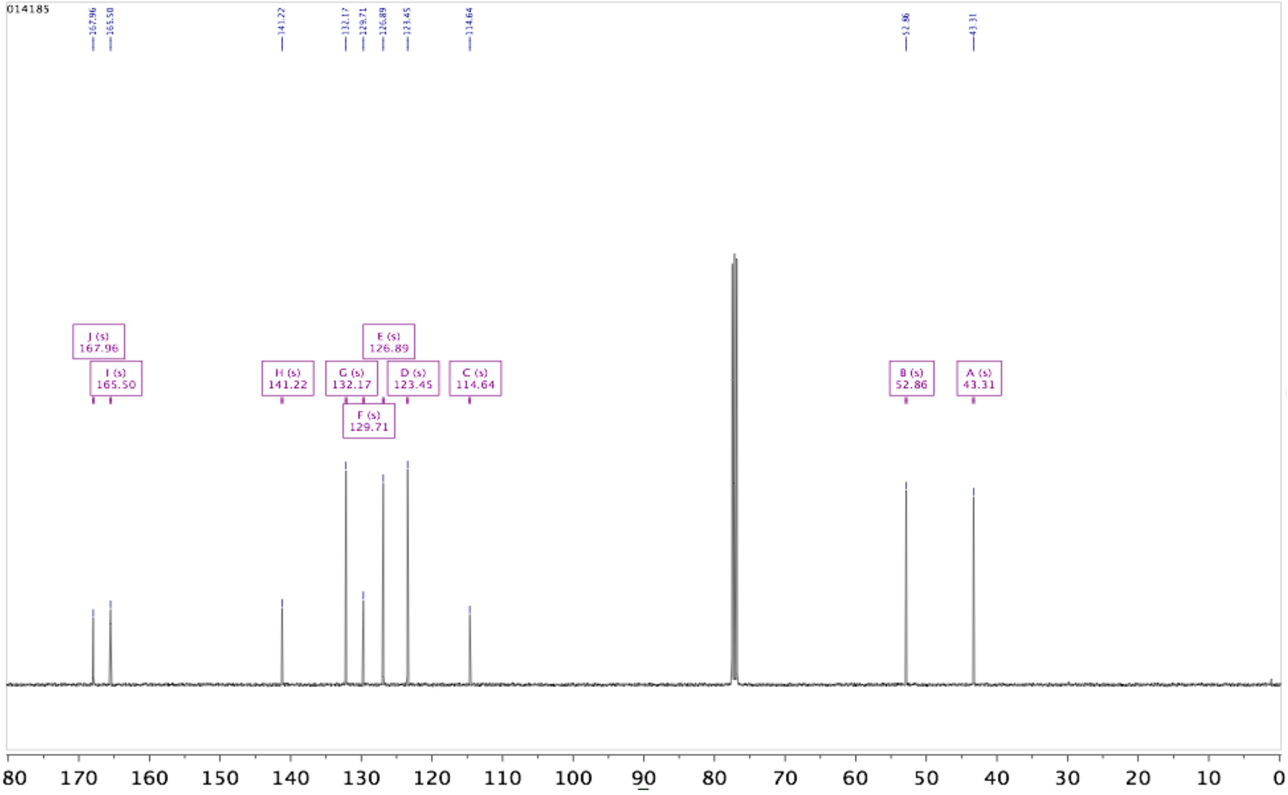
Methyl 2-amino-4-bromobenzoate (72):



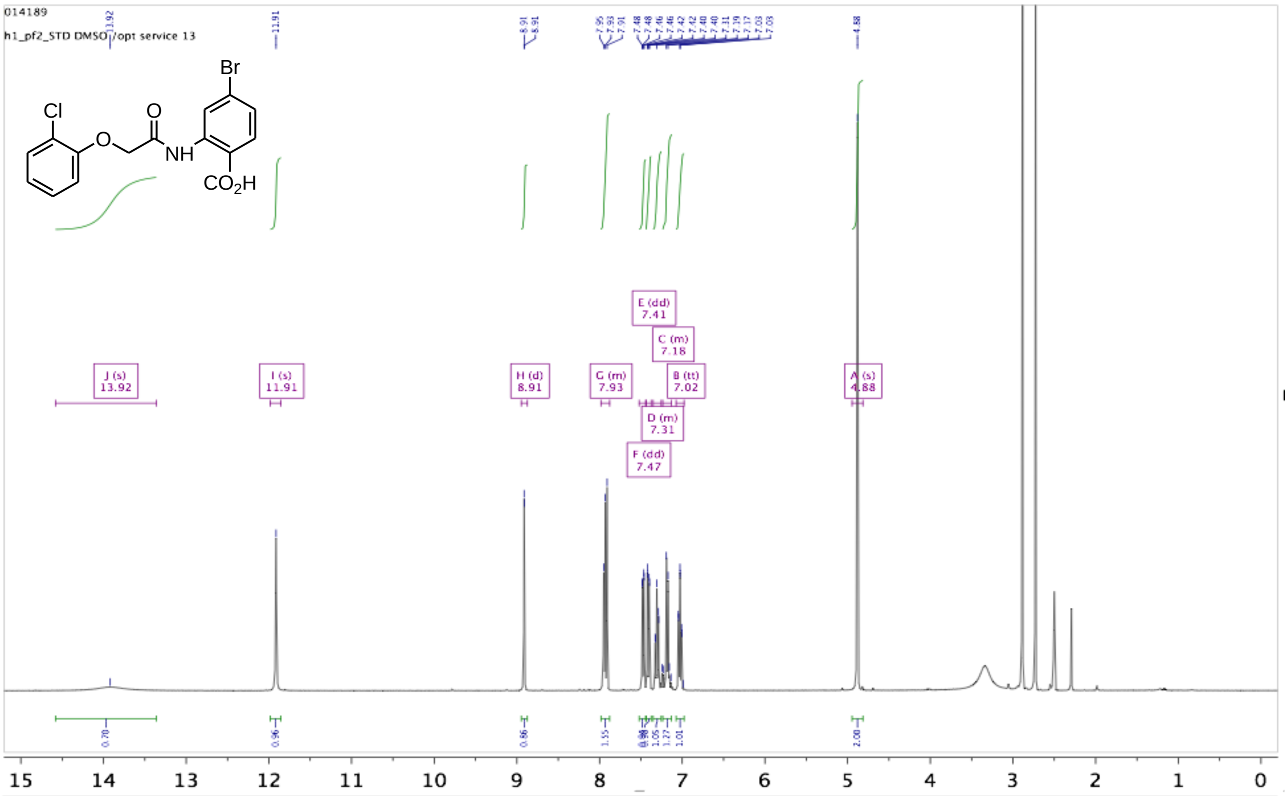


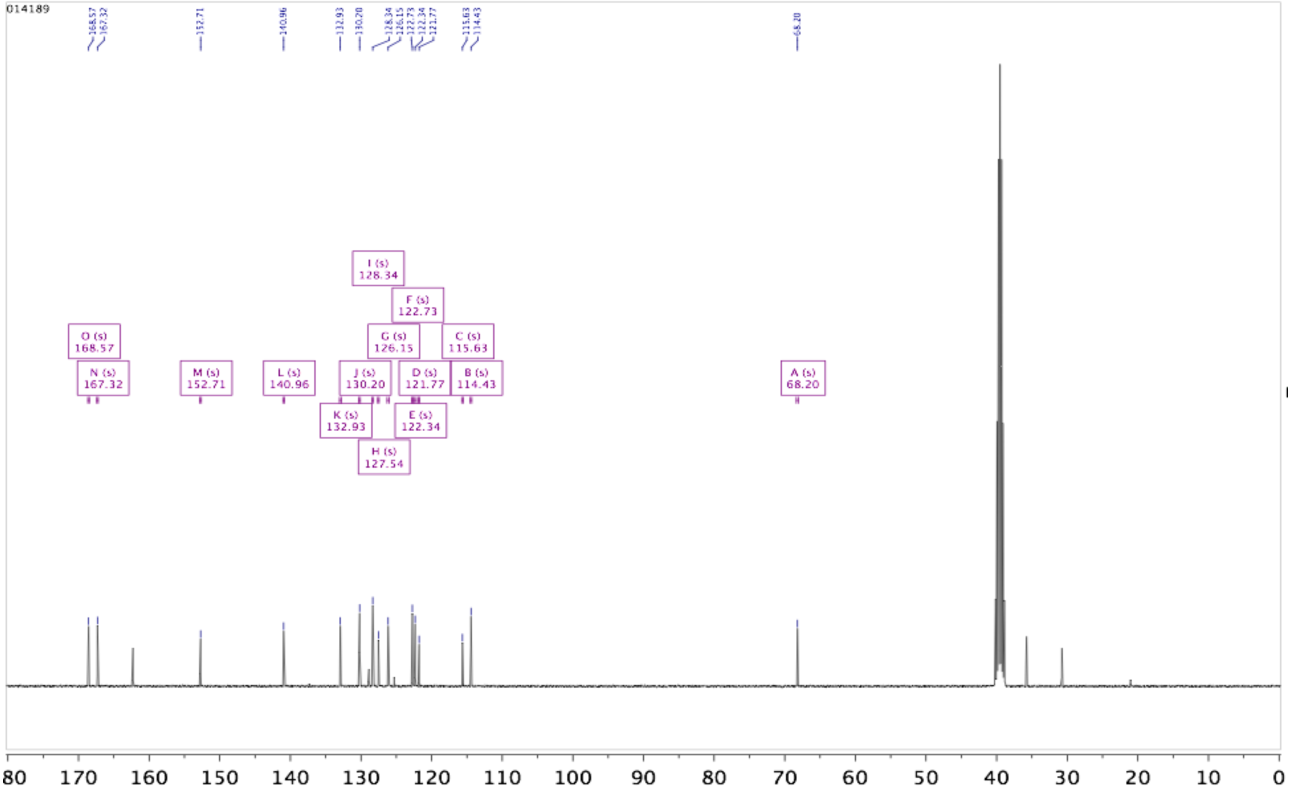
Methyl 4-bromo-2-(2-chloroacetamido)benzoate (73):



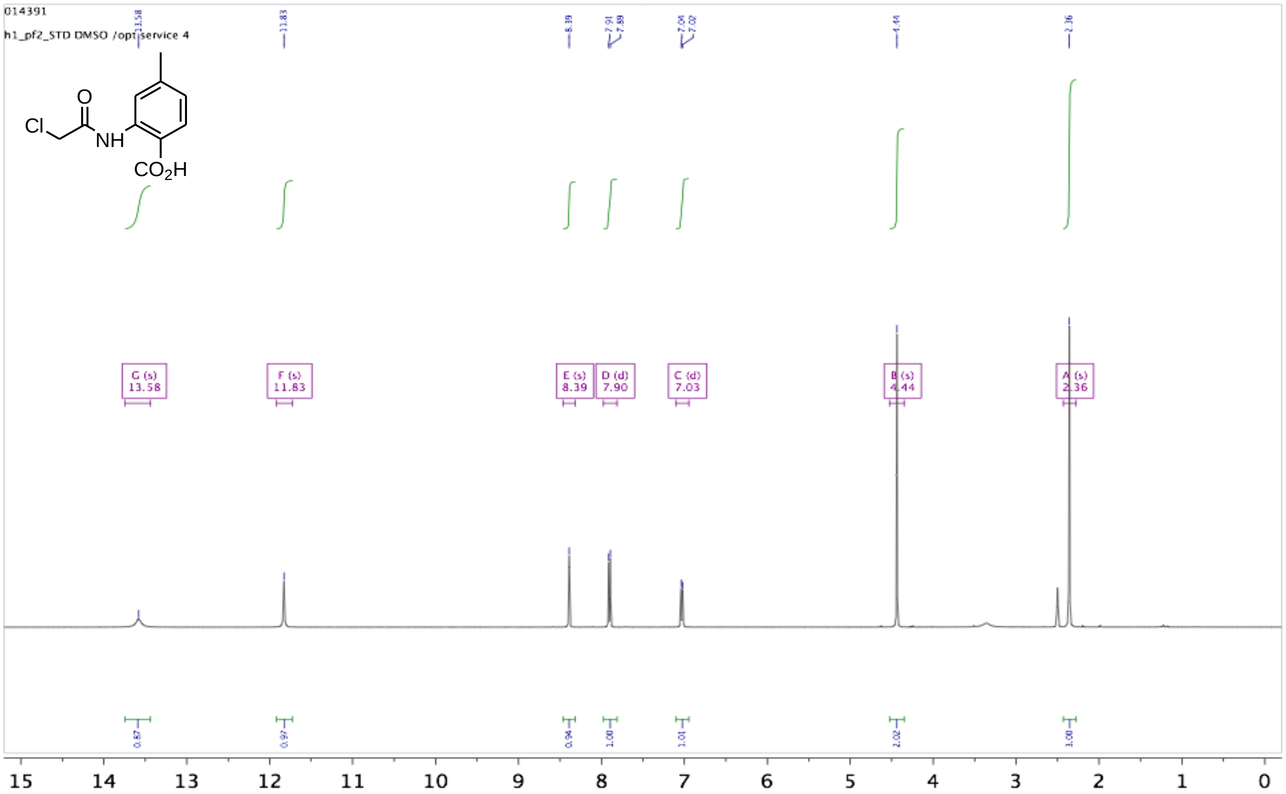


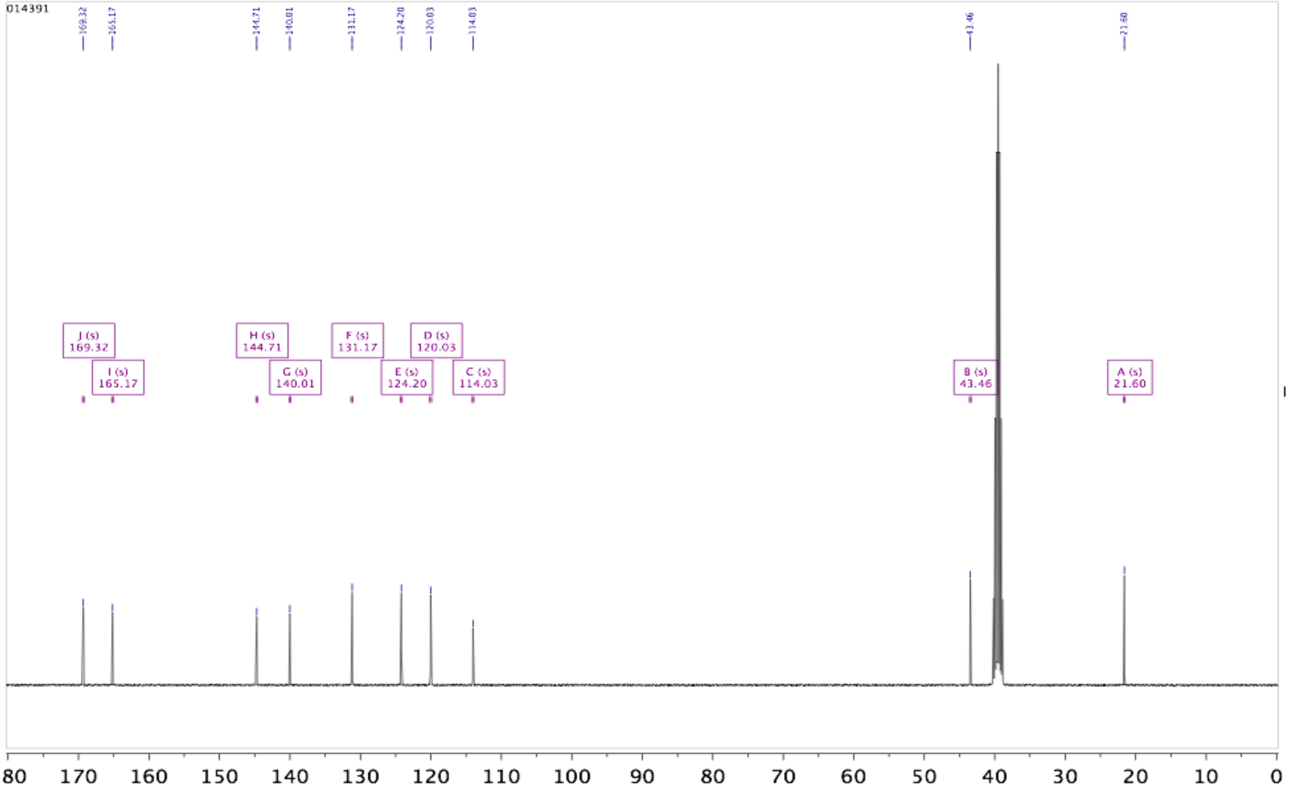
4-Bromo-2-(2-(2-chlorophenoxy)acetamido)benzoic acid (**11**):



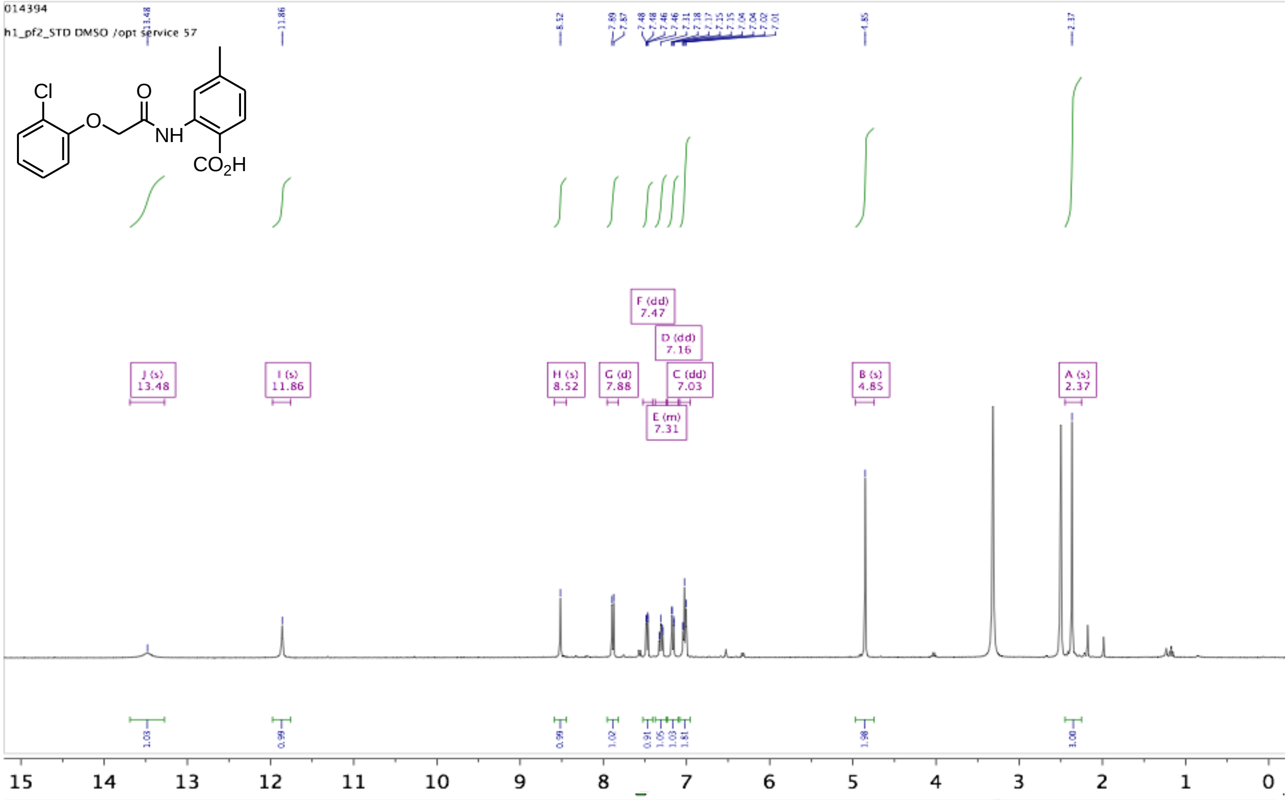


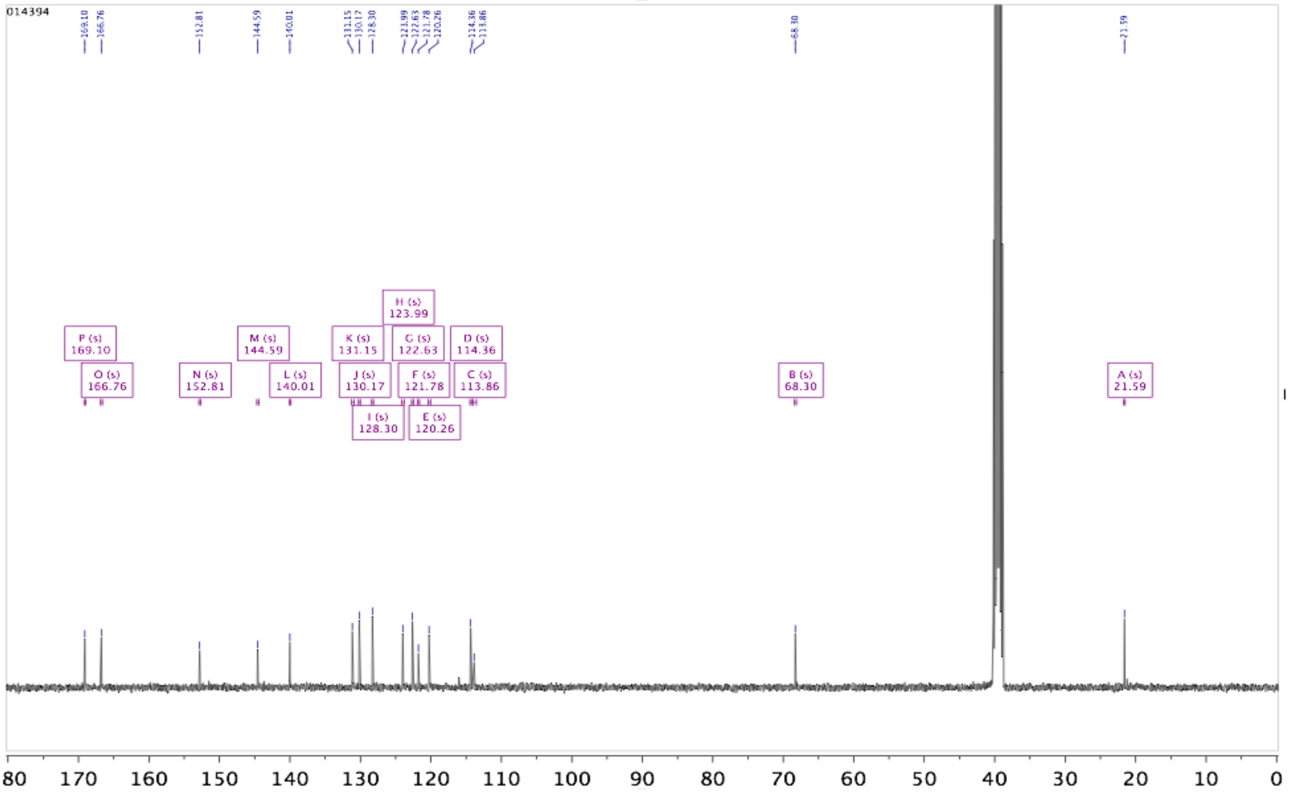
2-(2-Chloroacetamido)-4-methylbenzoic acid (74):



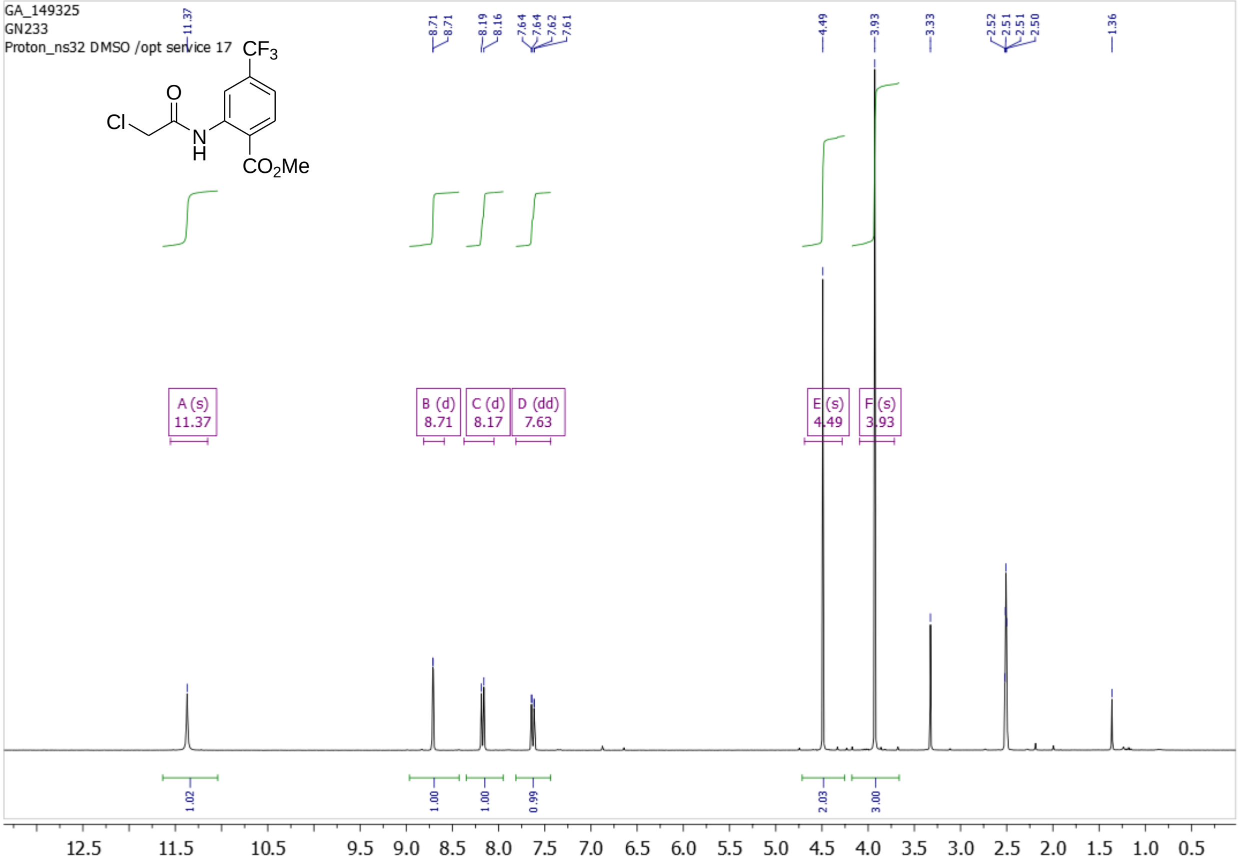


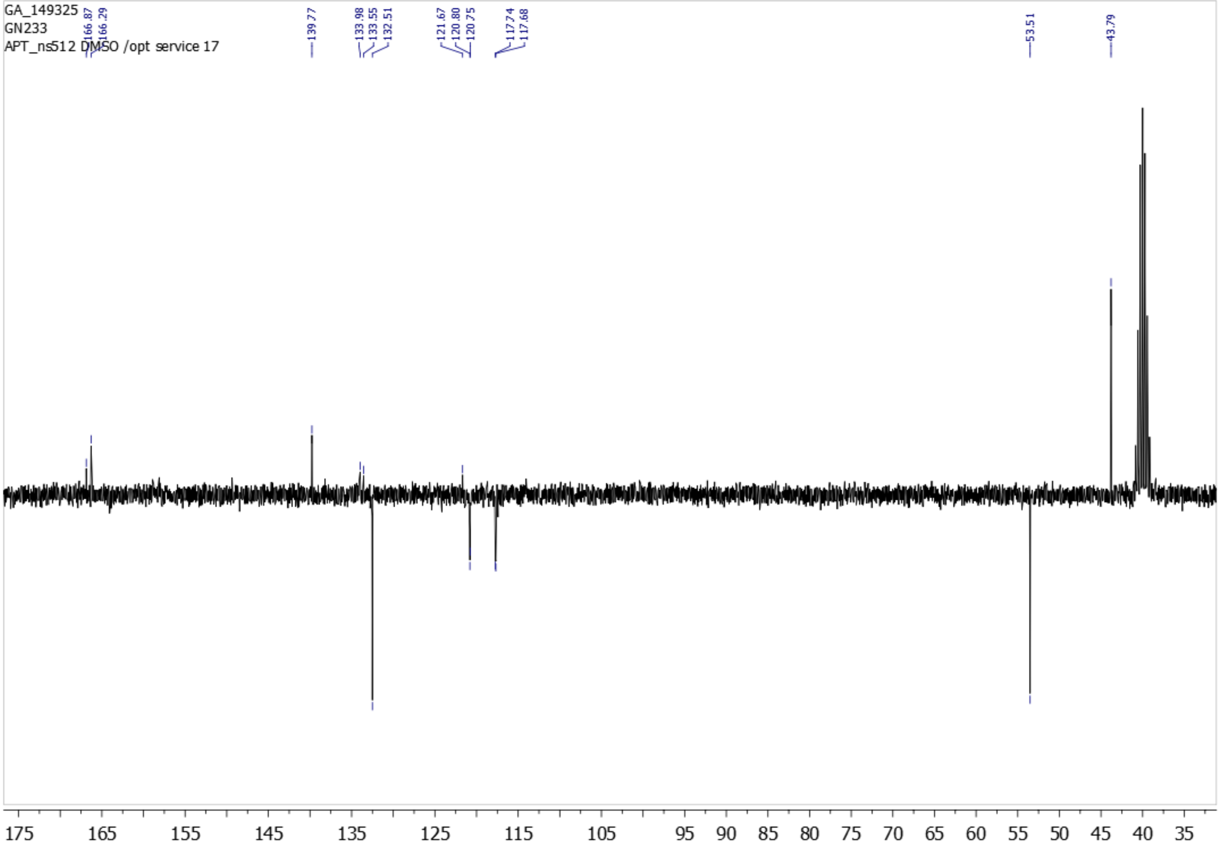
2-(2-(2-Chlorophenoxy)acetamido)-4-methylbenzoic acid (27):



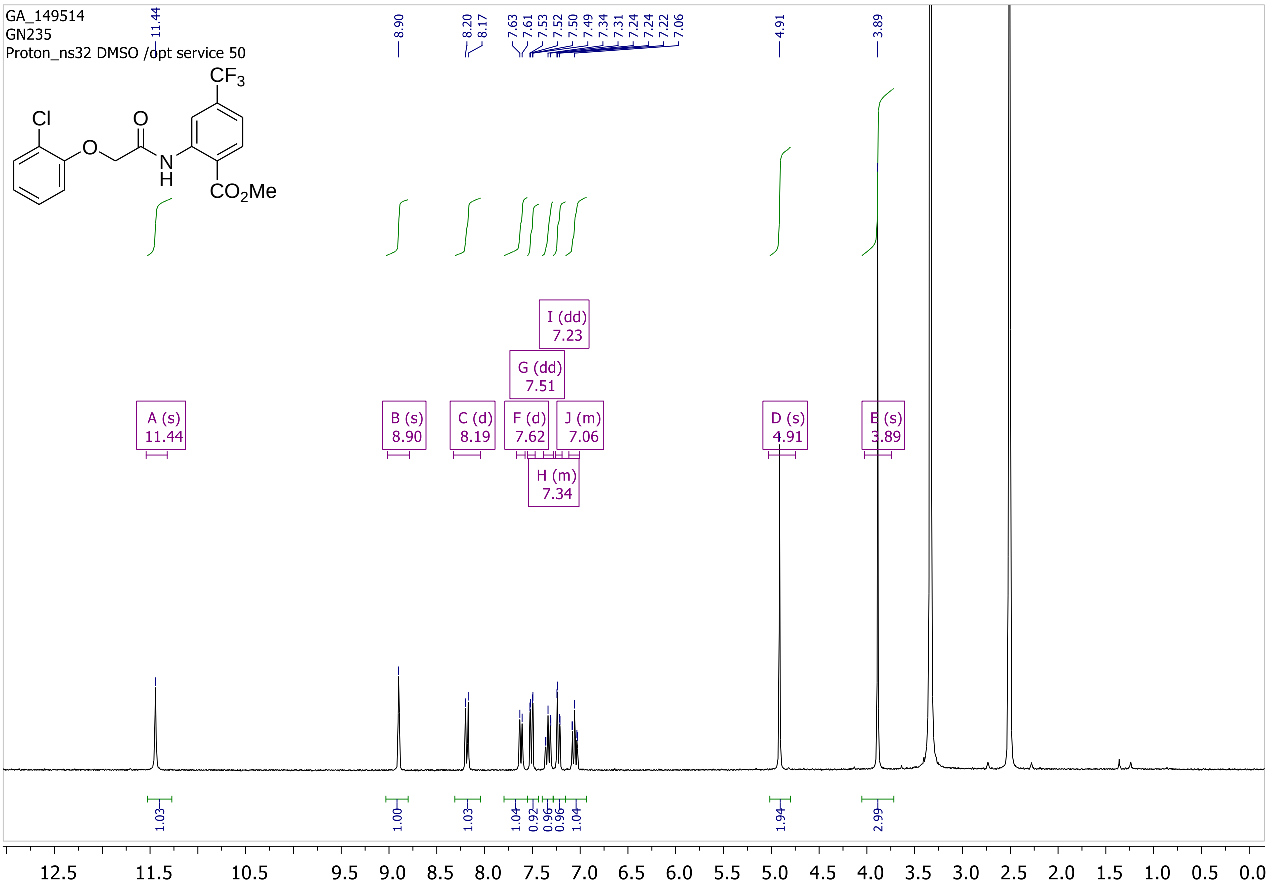


Methyl 2-(2-chloroacetamido)-4-(trifluoromethyl)benzoate (75):

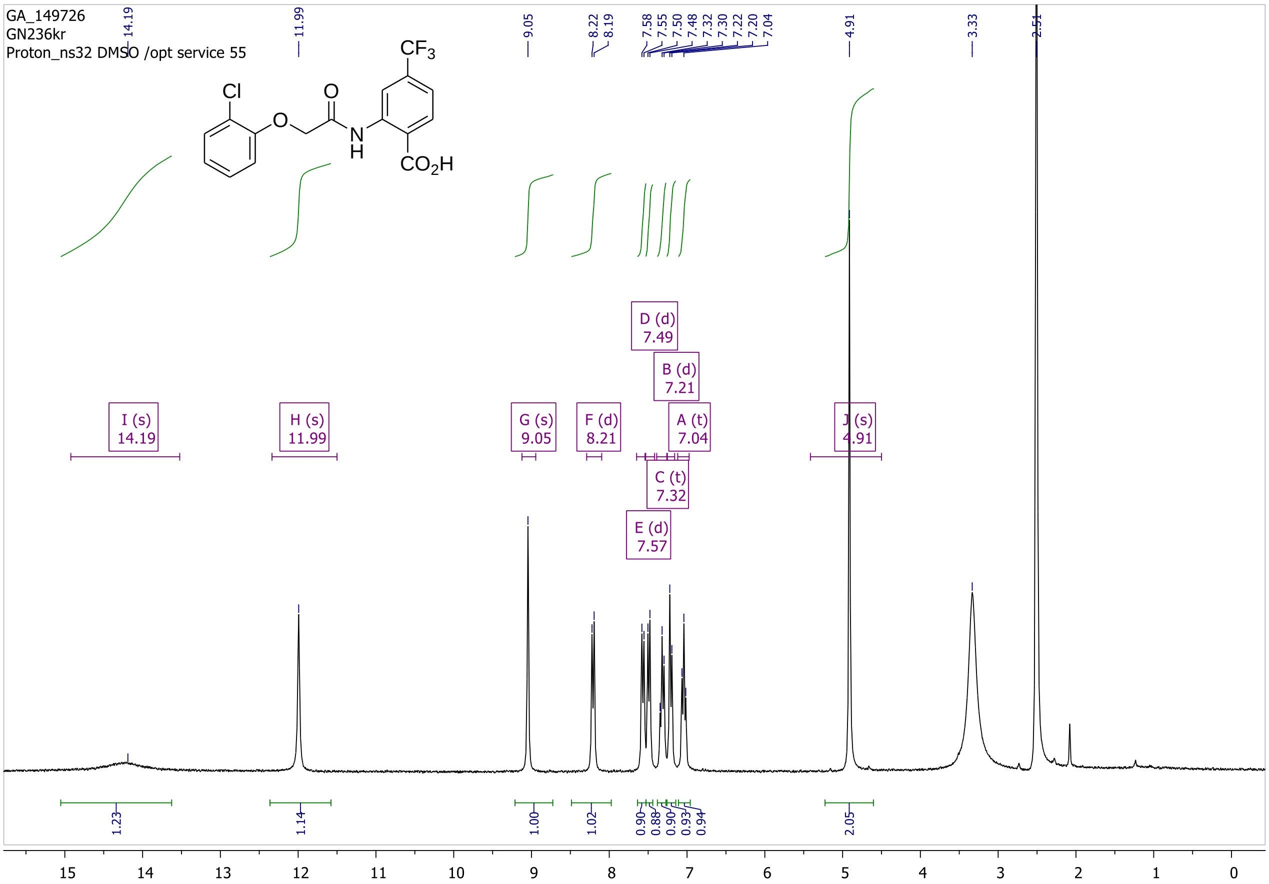


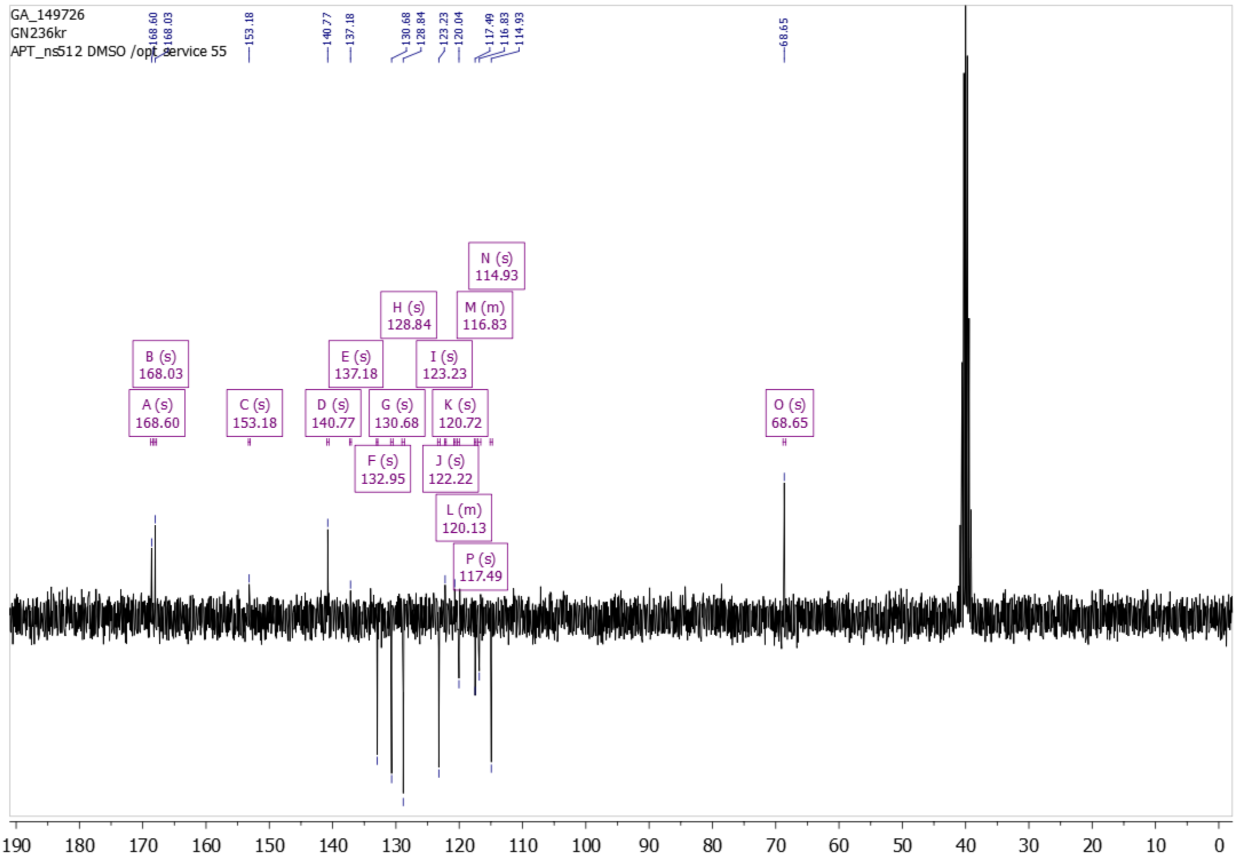


Methyl 2-(2-(2-chlorophenoxy)acetamido)-4-(trifluoromethyl)benzoate (76):

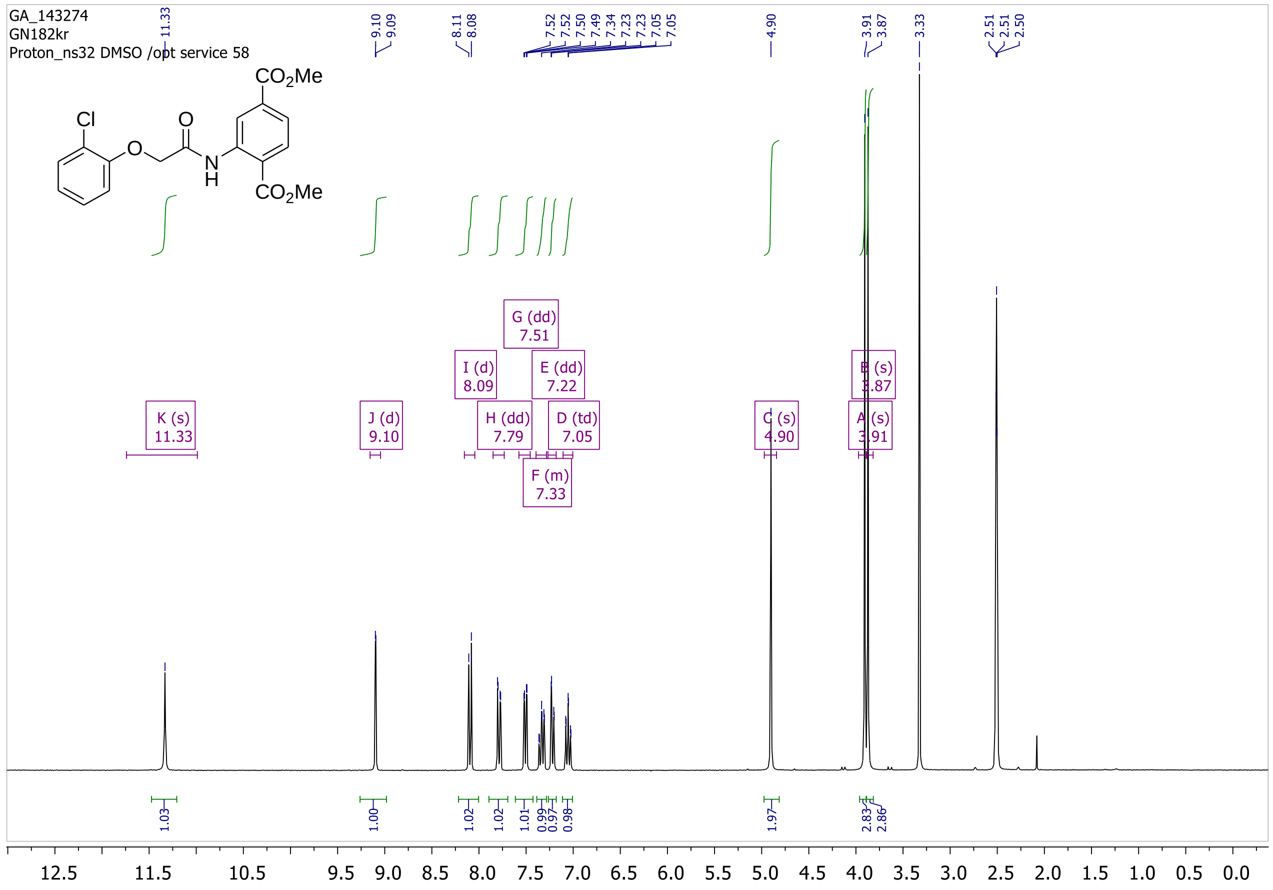


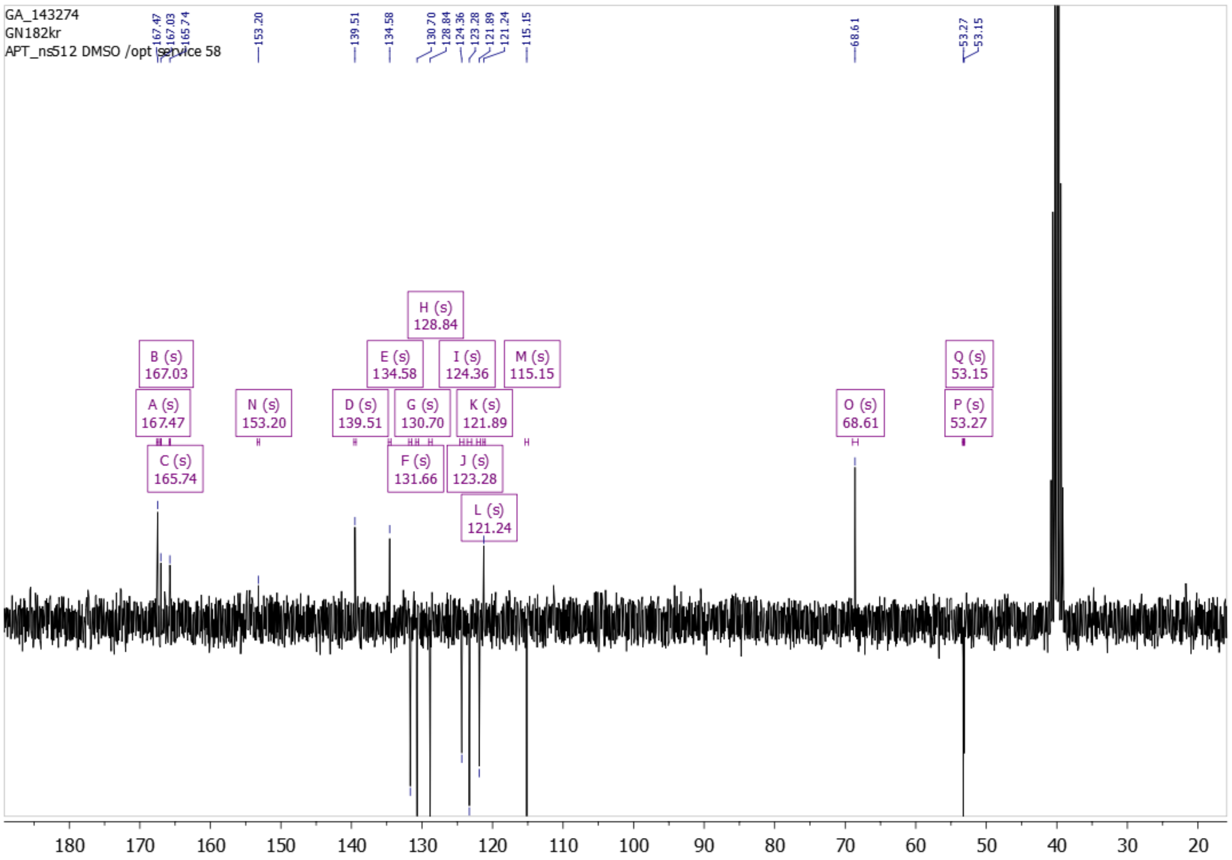
2-(2-(2-Chlorophenoxy)acetamido)-4-(trifluoromethyl)benzoic acid (28):



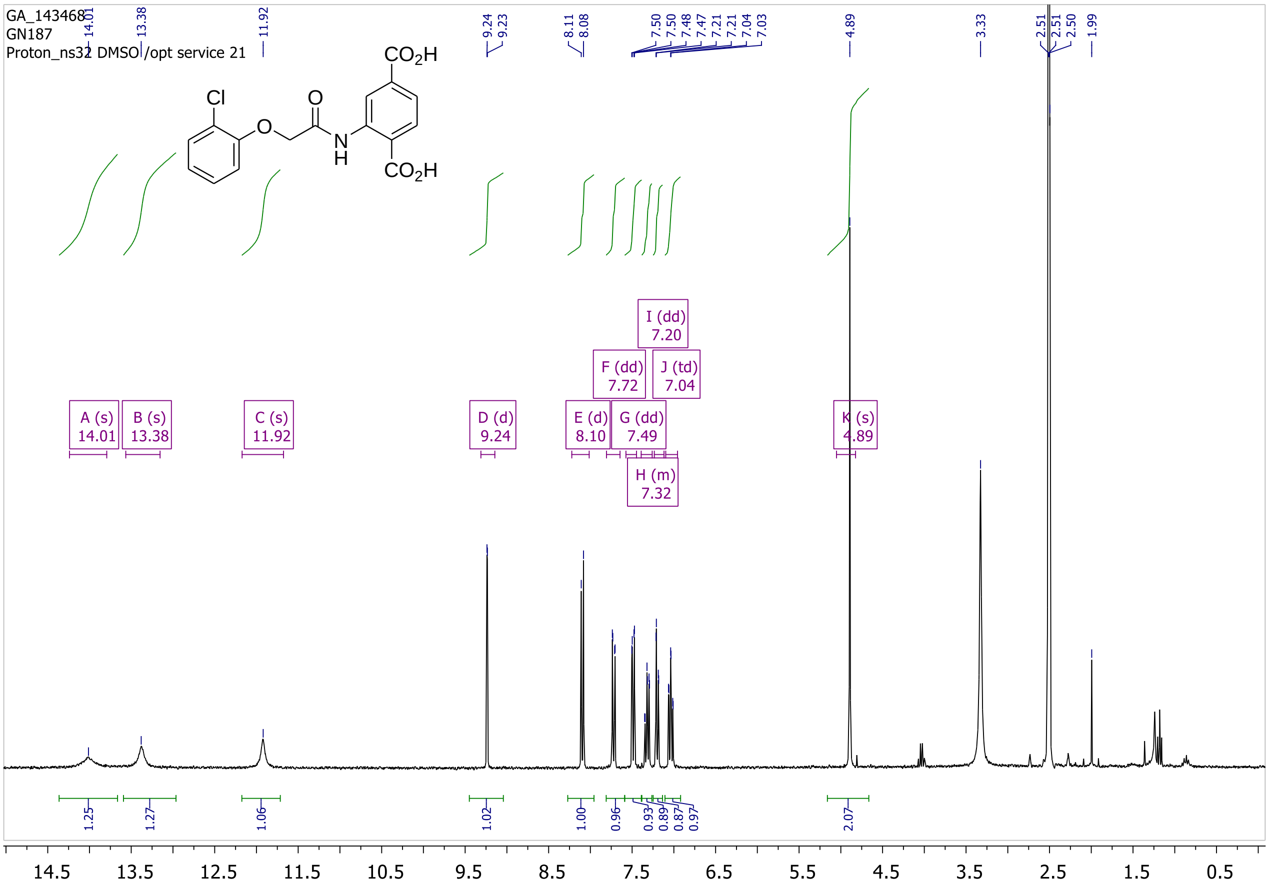


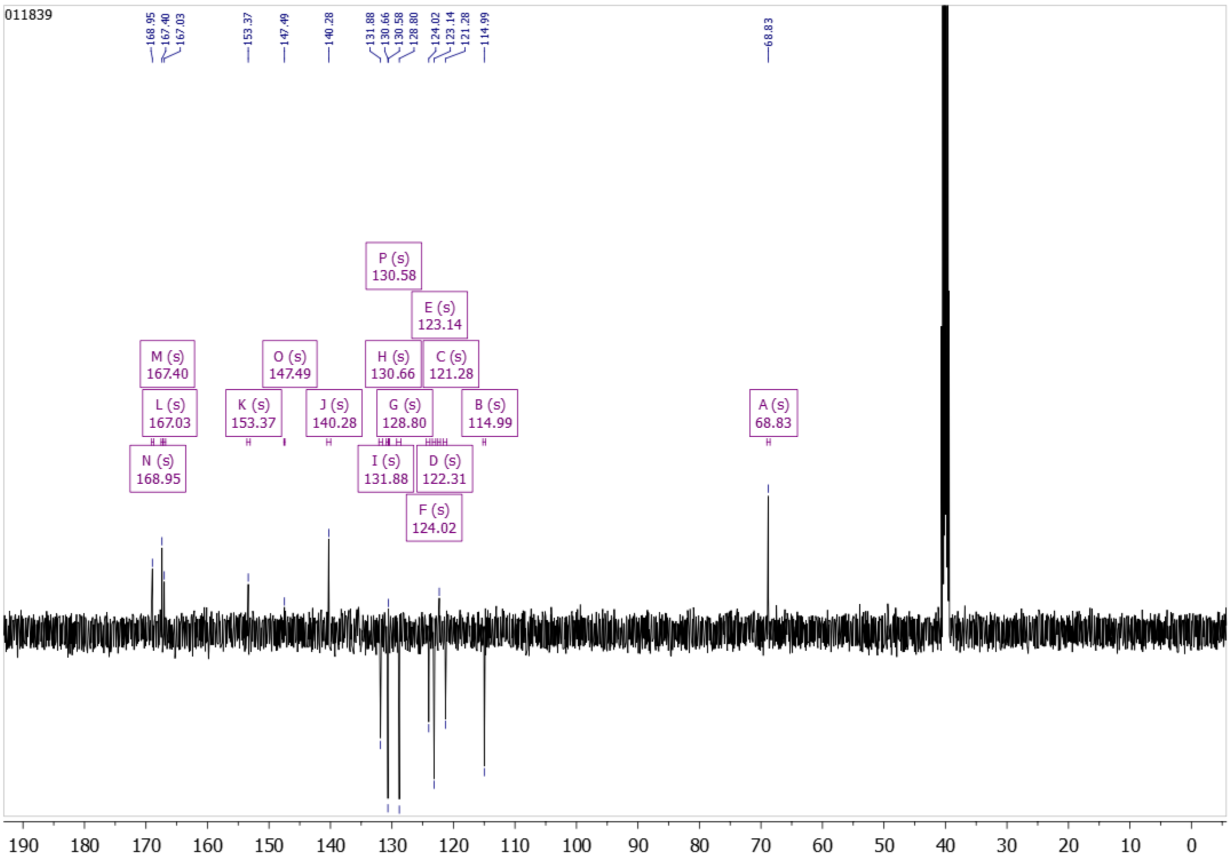
Dimethyl 2-(2-(2-chlorophenoxy)acetamido)terephthalate (**77**):



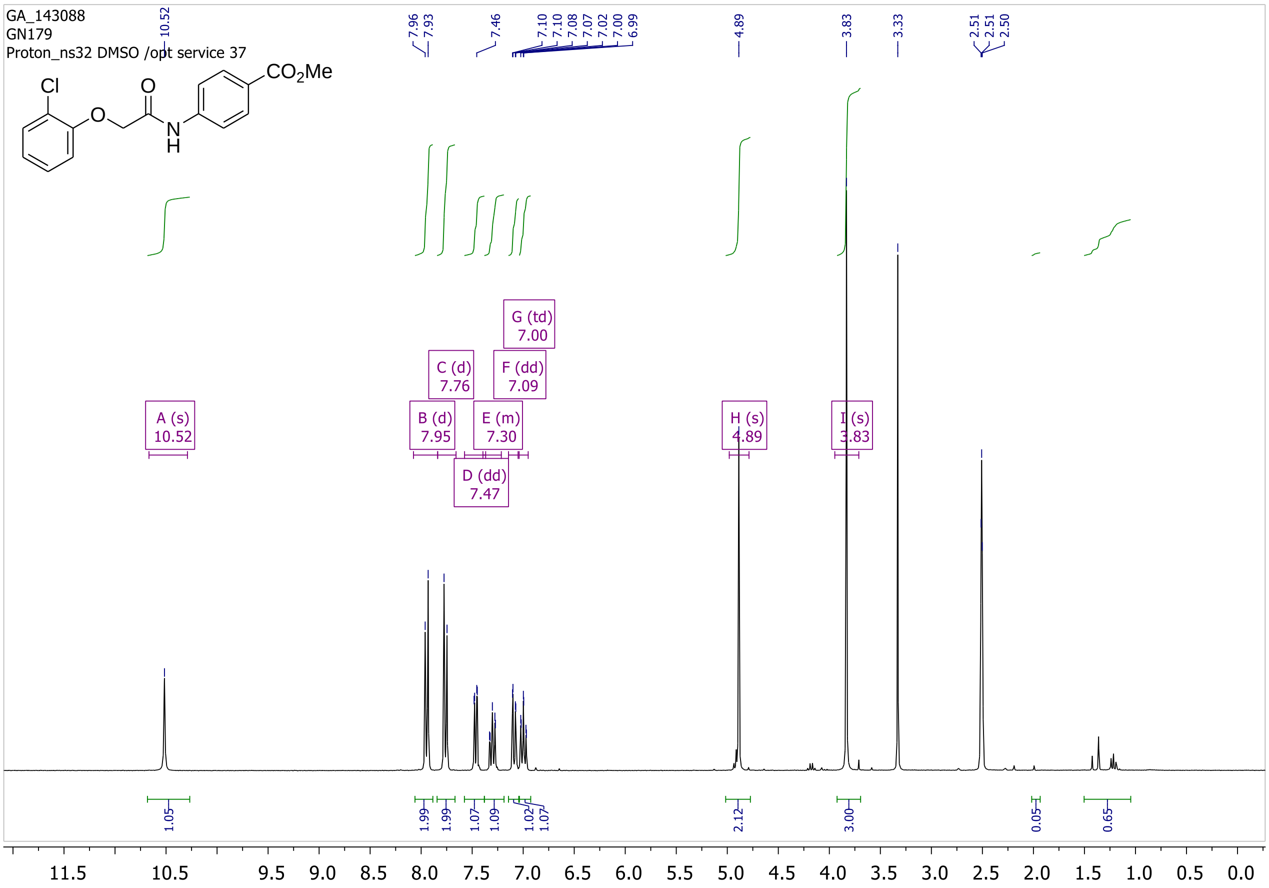


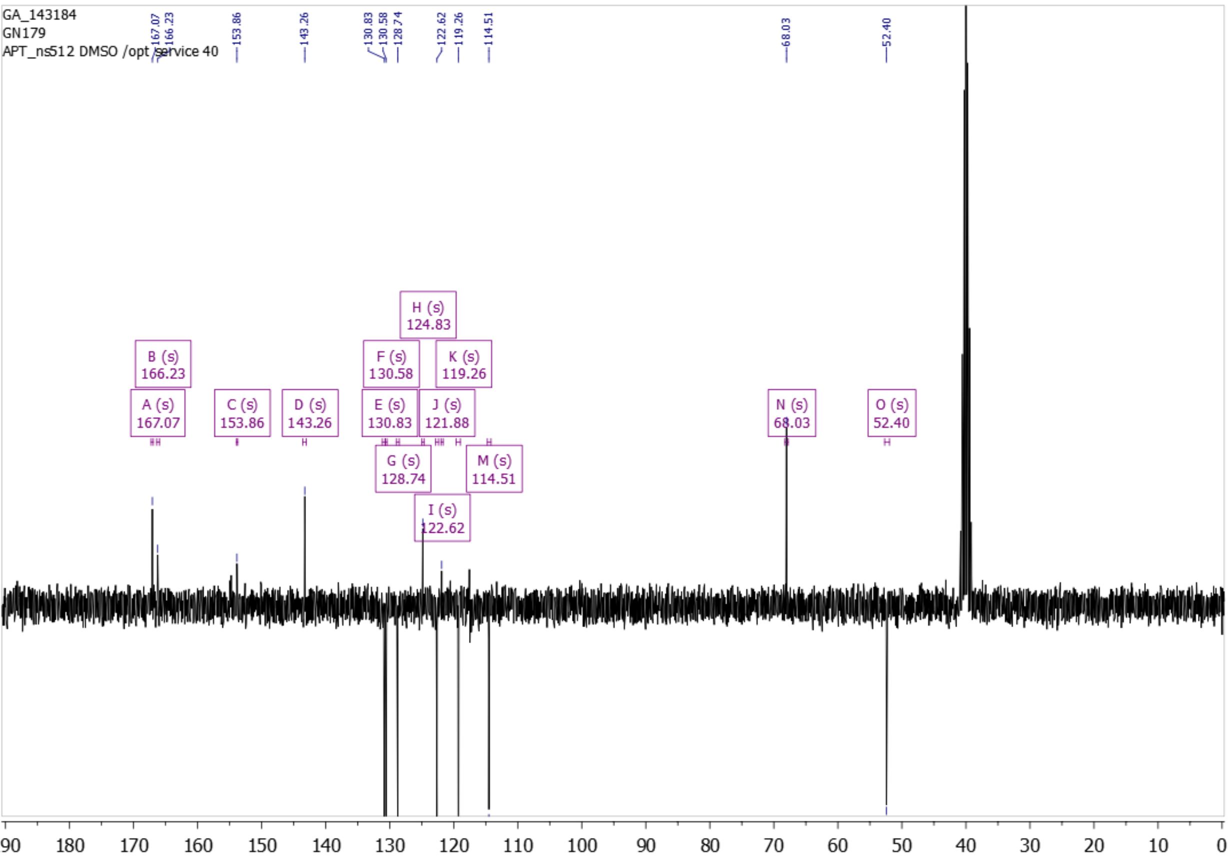
2-(2-(2-Chlorophenoxy)acetamido)terephthalic acid (29):



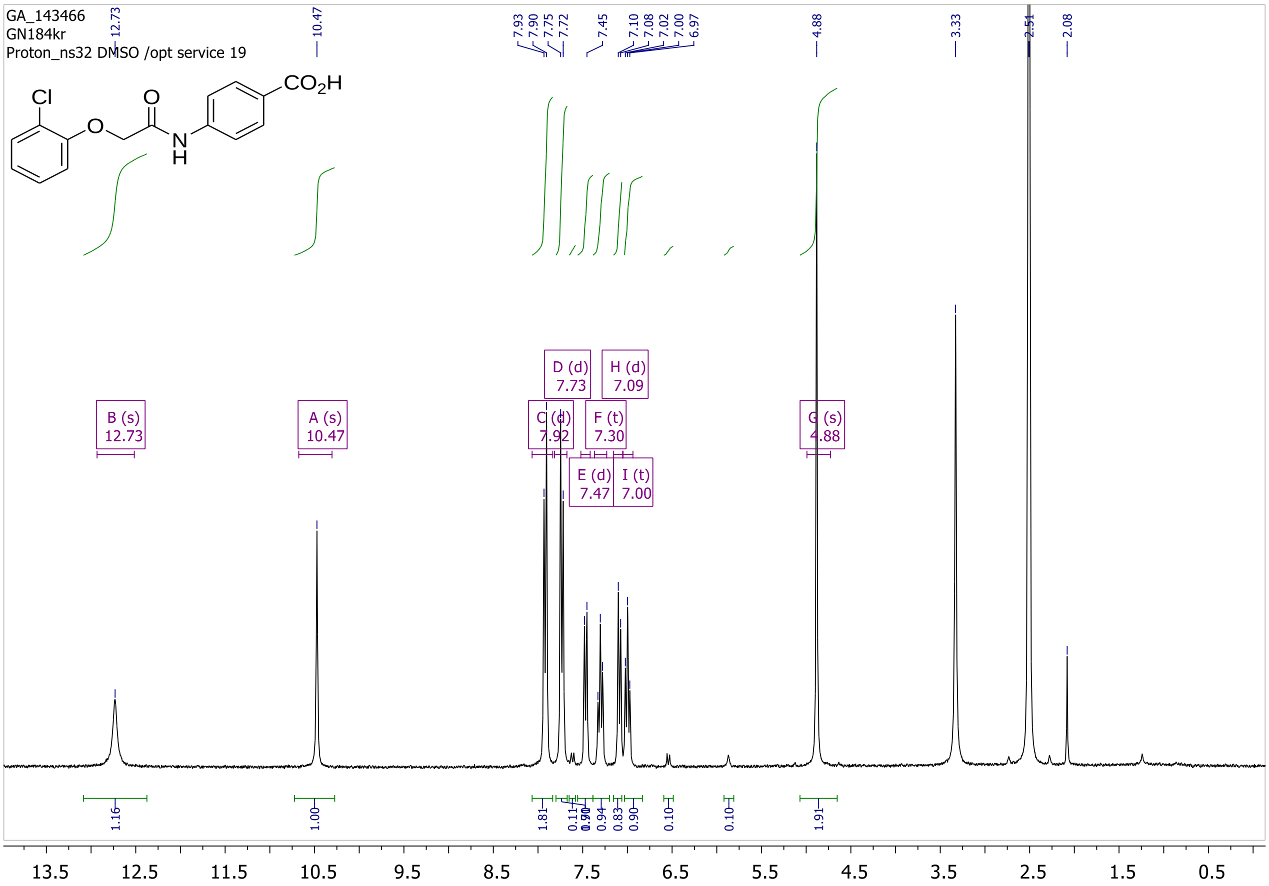


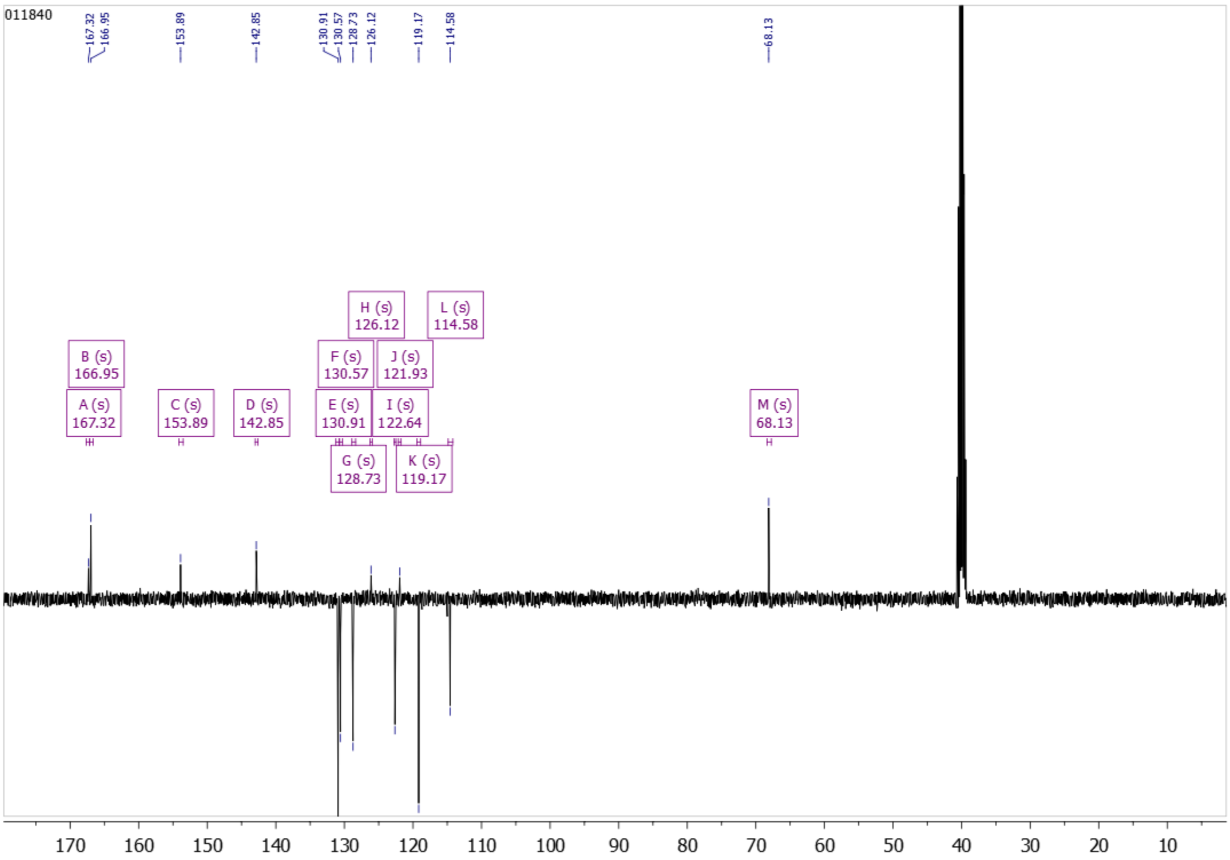
Methyl 4-(2-(2-chlorophenoxy)acetamido)benzoate (78):



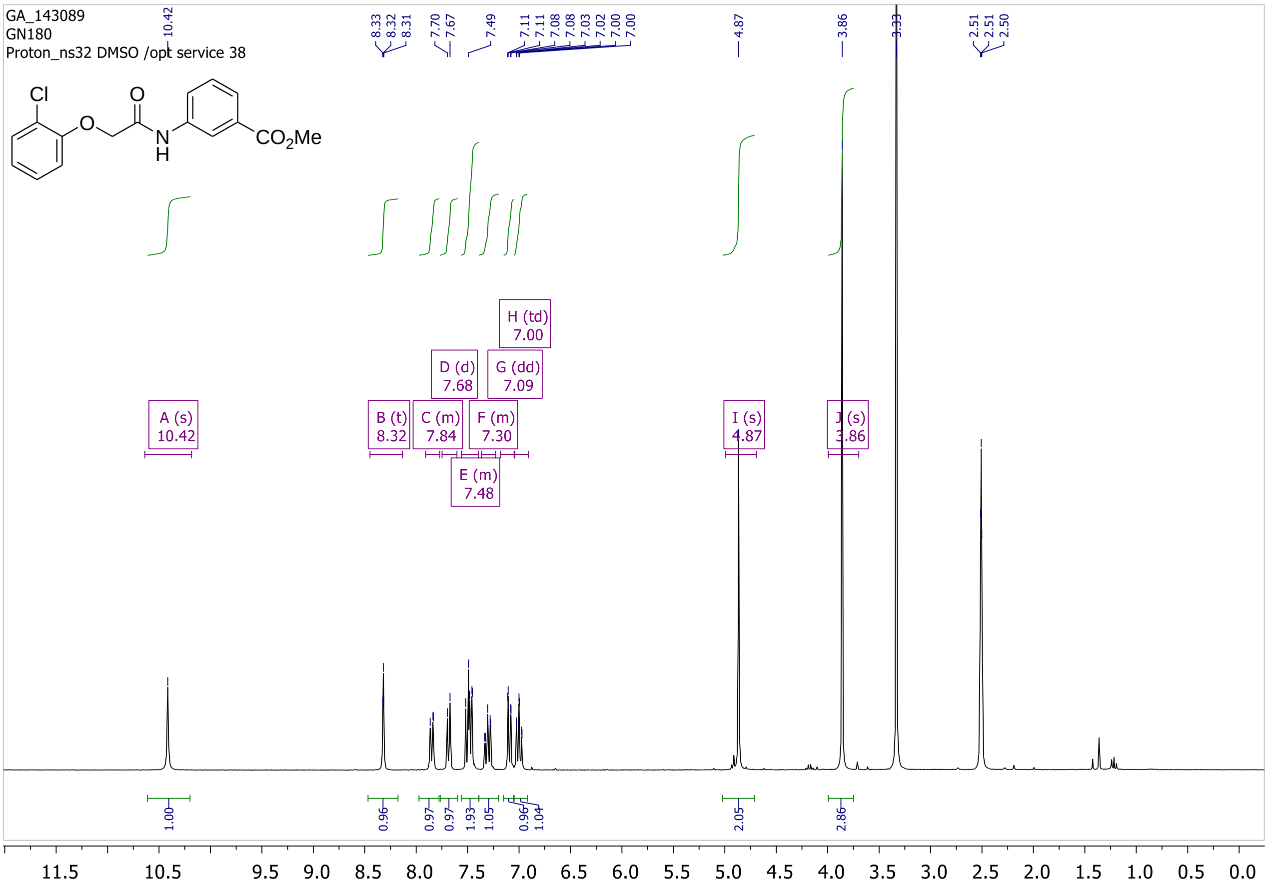


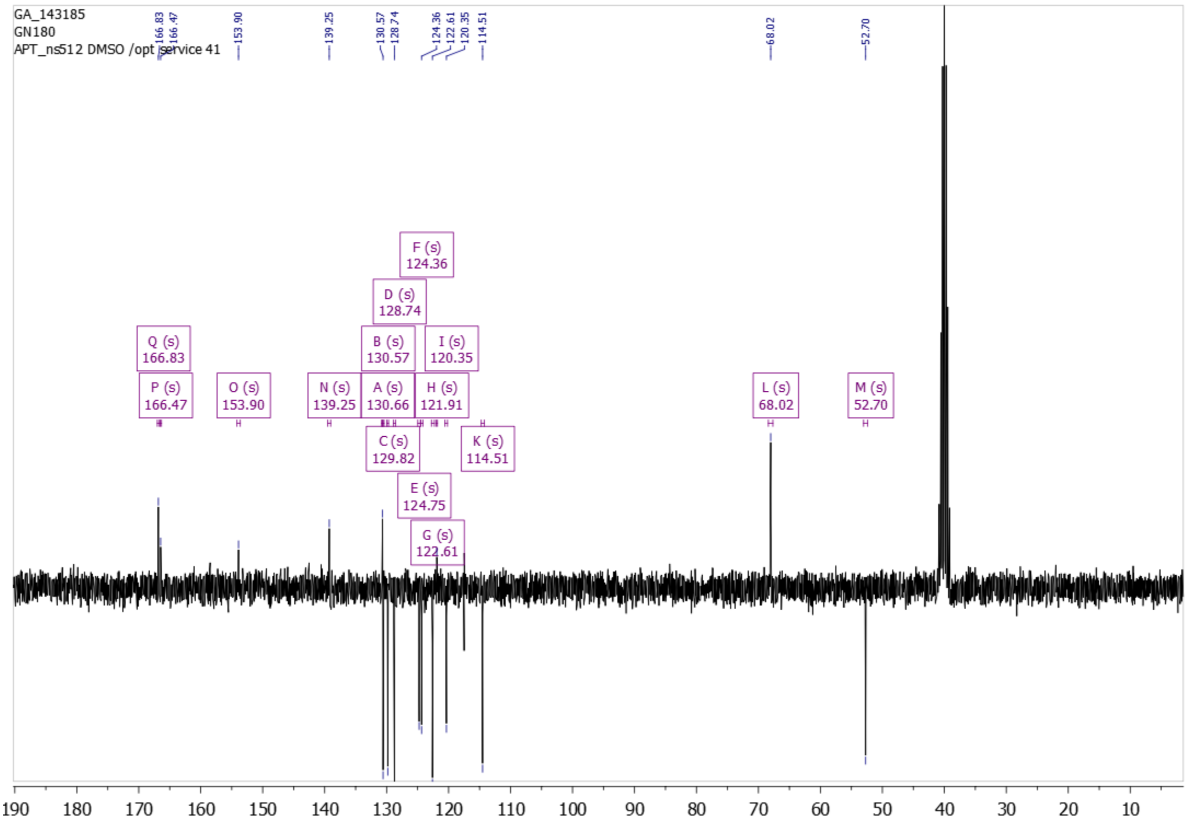
4-(2-(2-Chlorophenoxy)acetamido)benzoic acid (**30**):



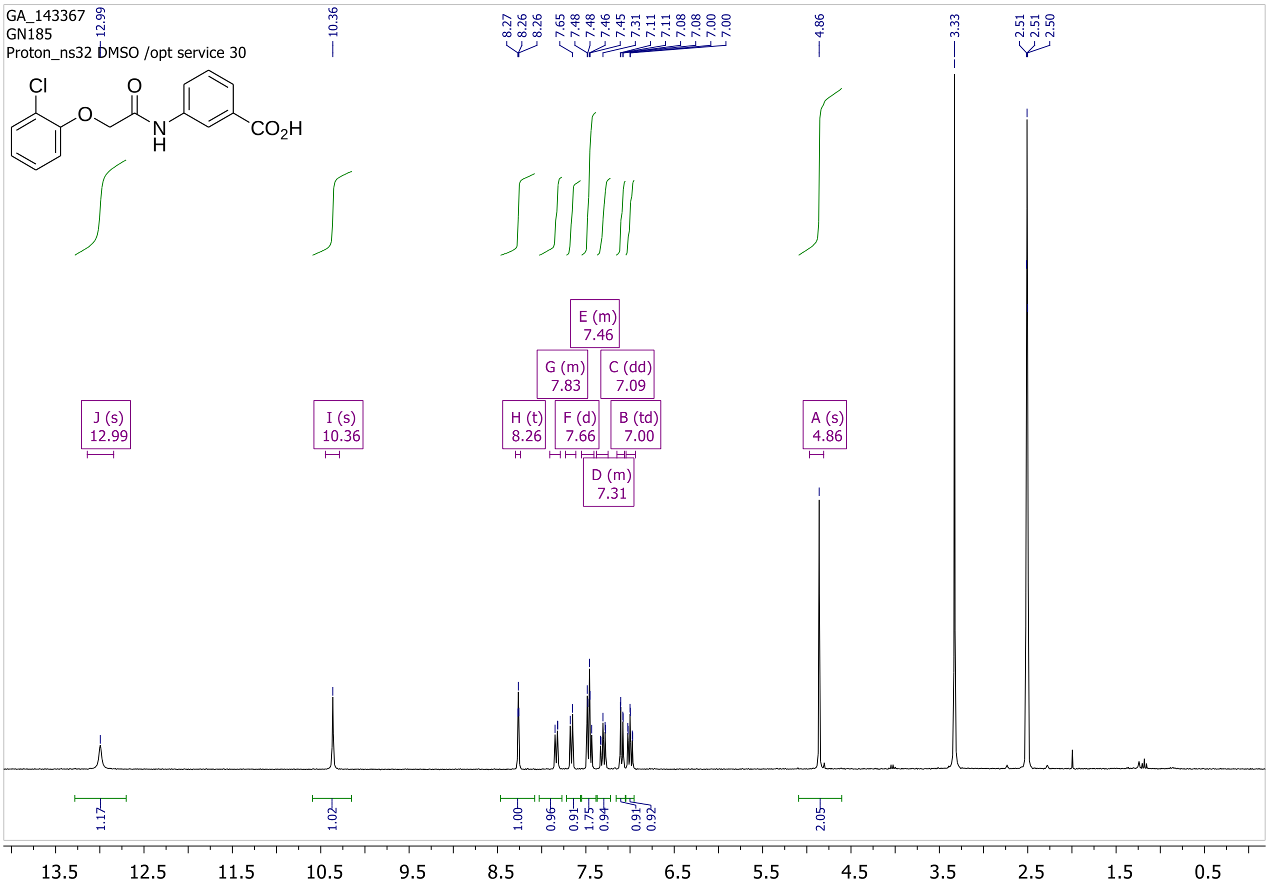


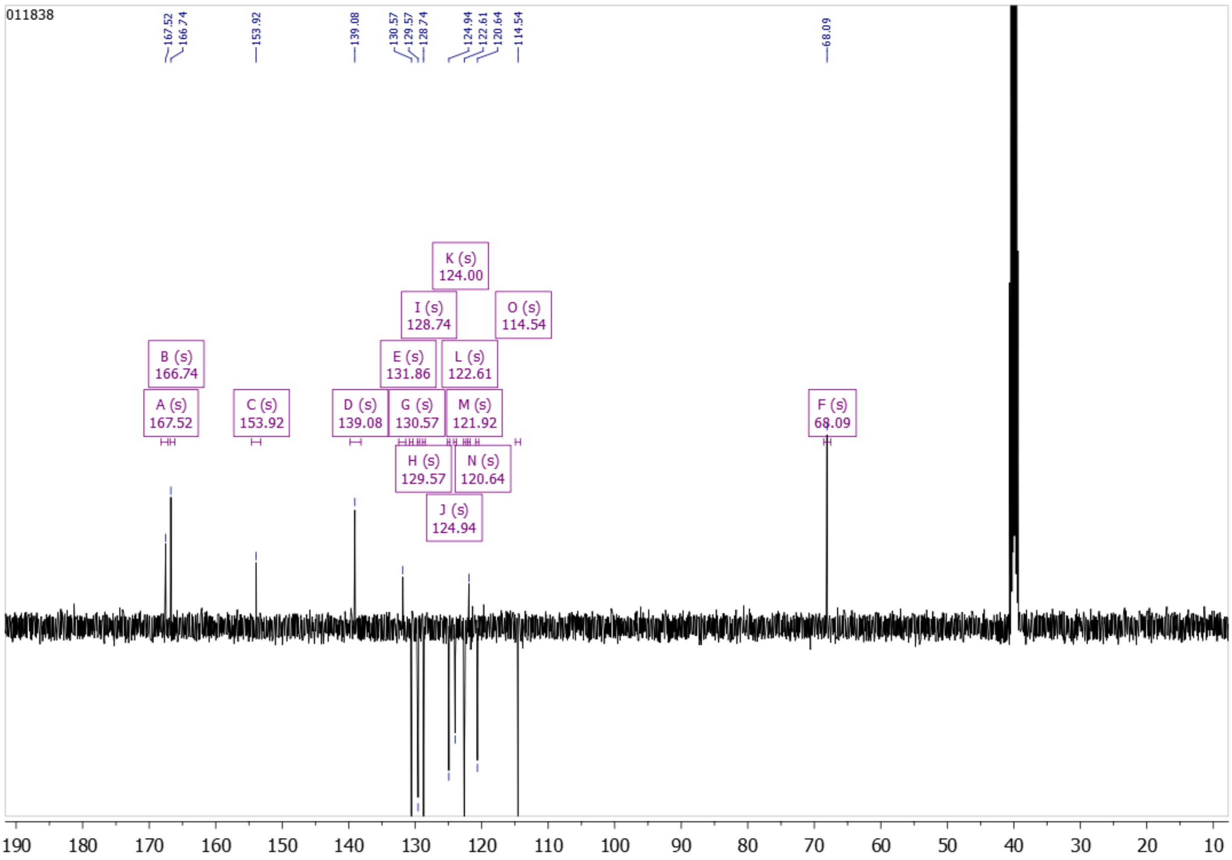
Methyl 3-(2-(2-chlorophenoxy)acetamido)benzoate (79):



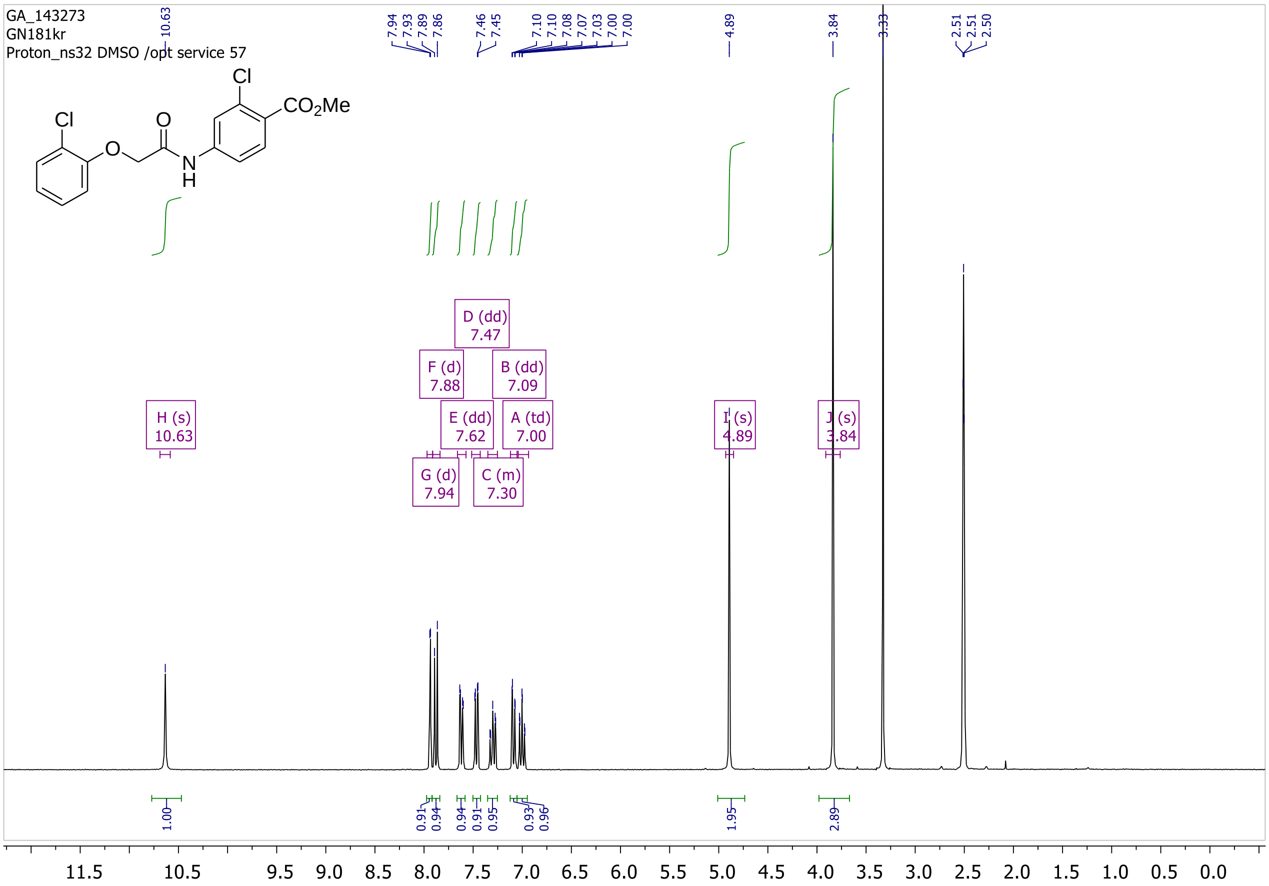


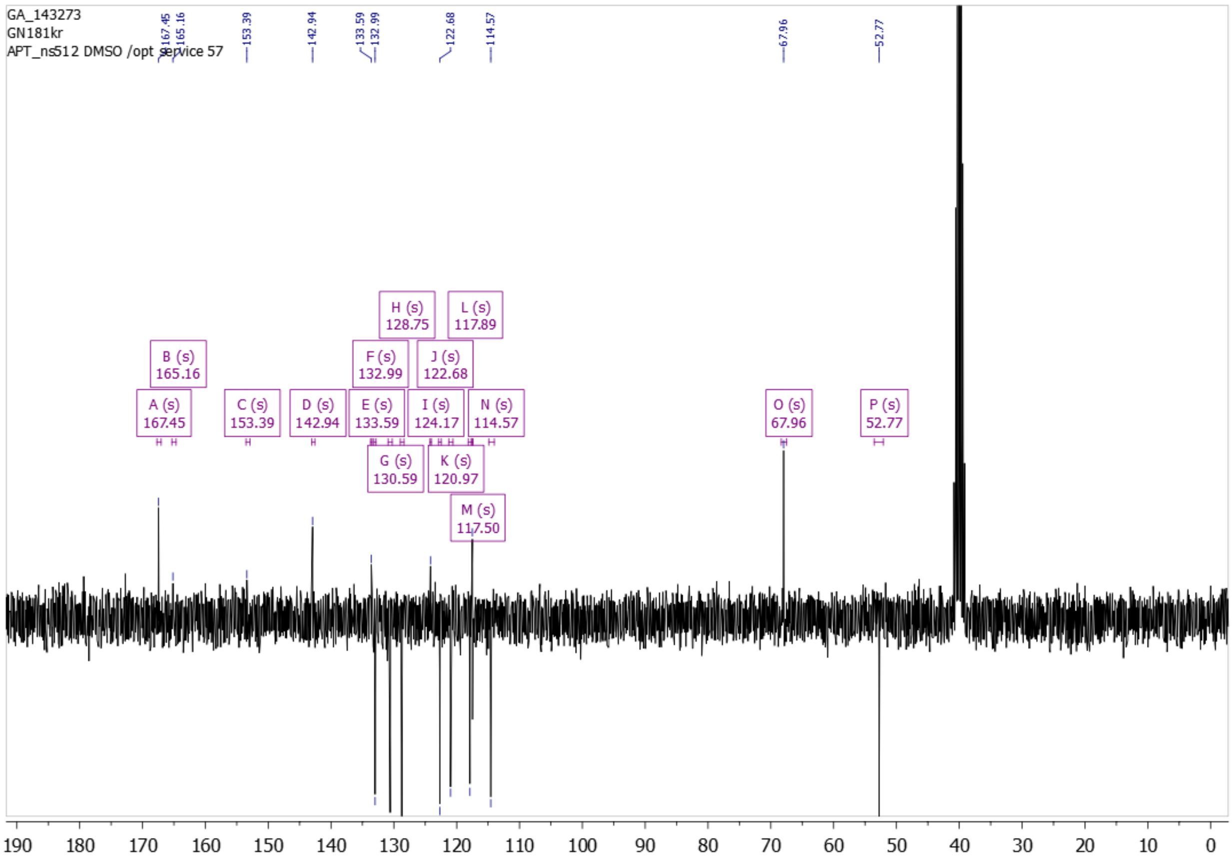
3-(2-(2-Chlorophenoxy)acetamido)benzoic acid (31):



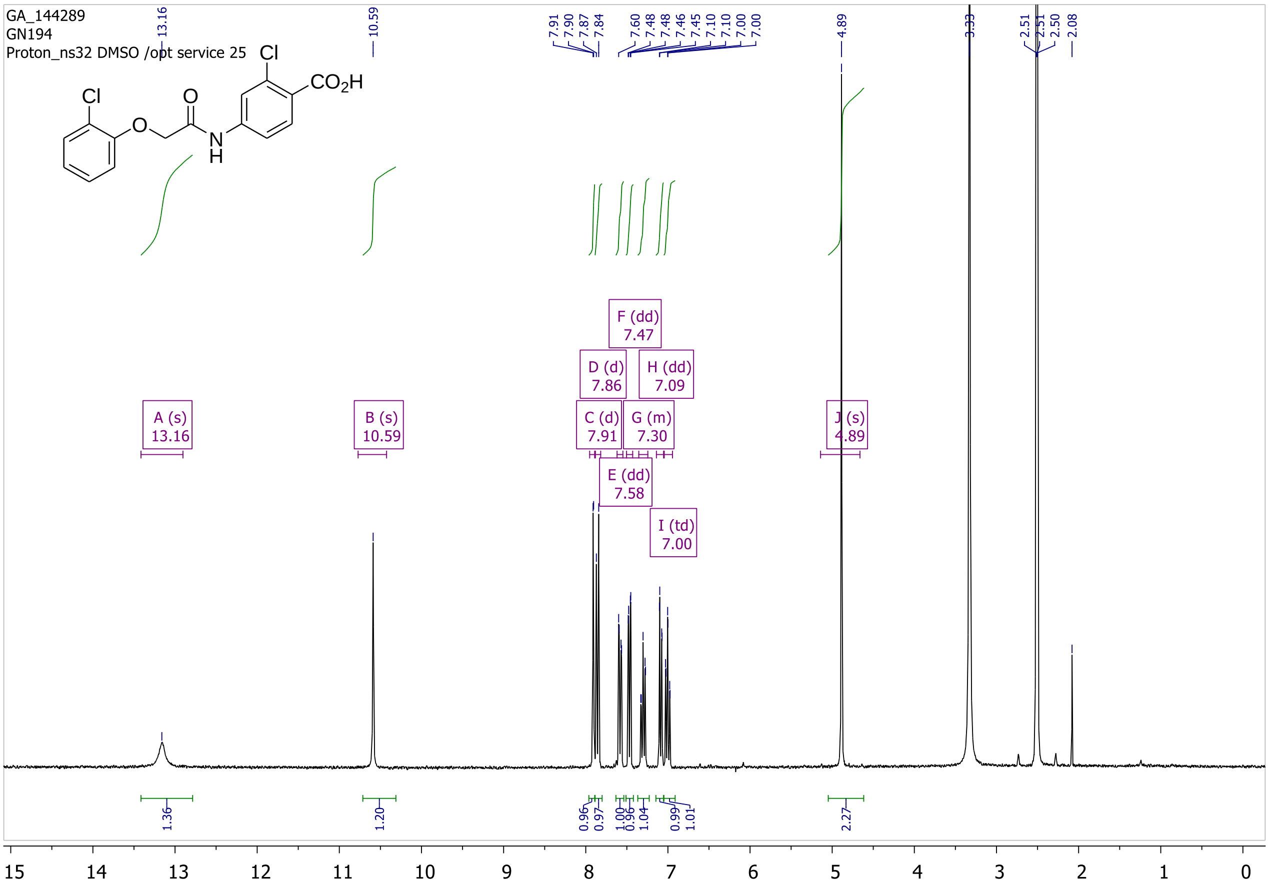


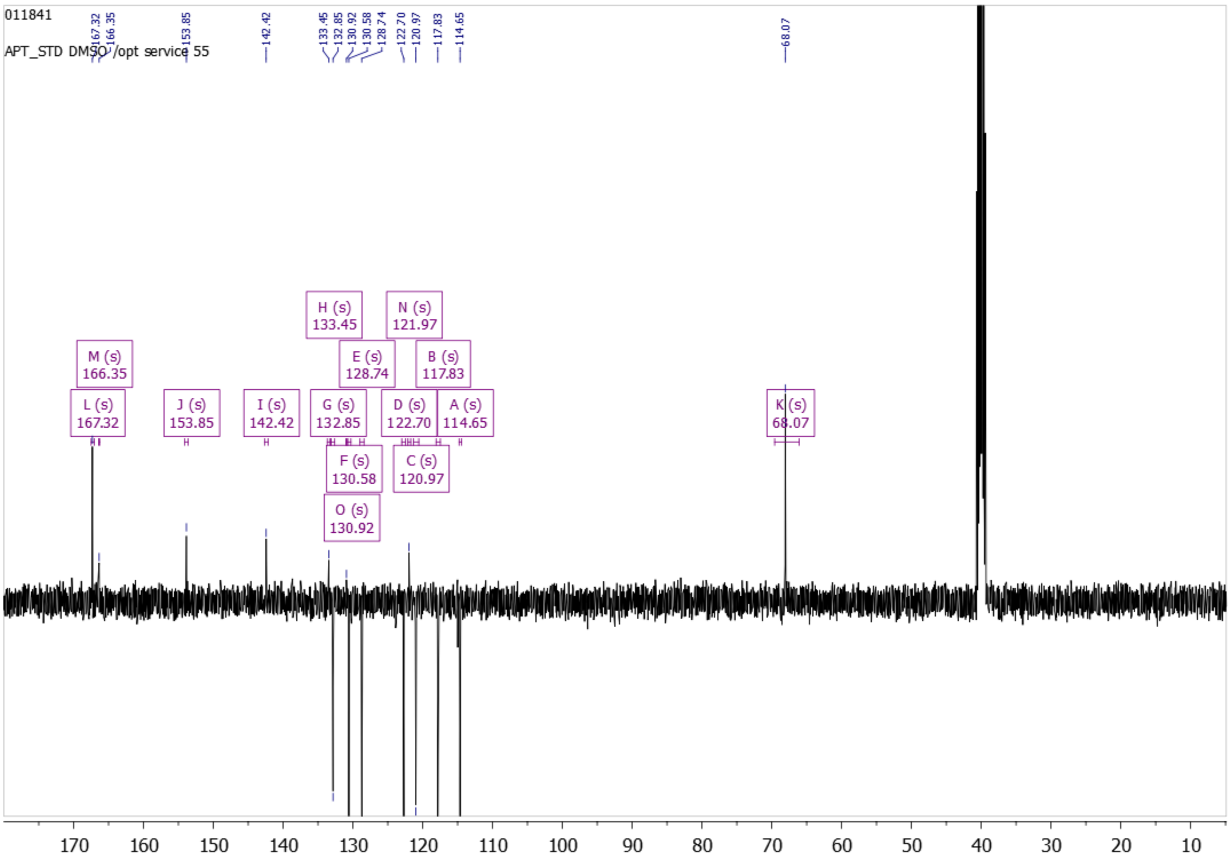
Methyl 2-chloro-4-(2-(2-chlorophenoxy)acetamido)benzoate (80):



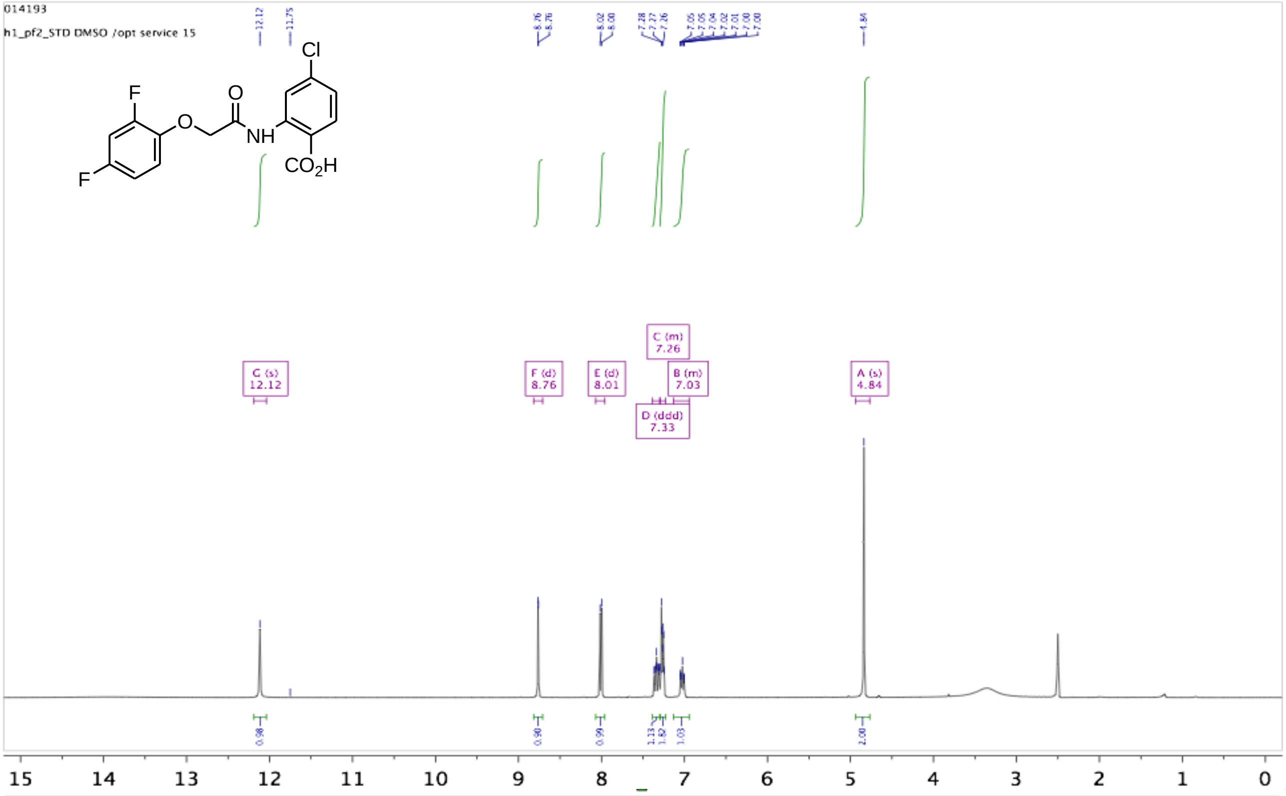


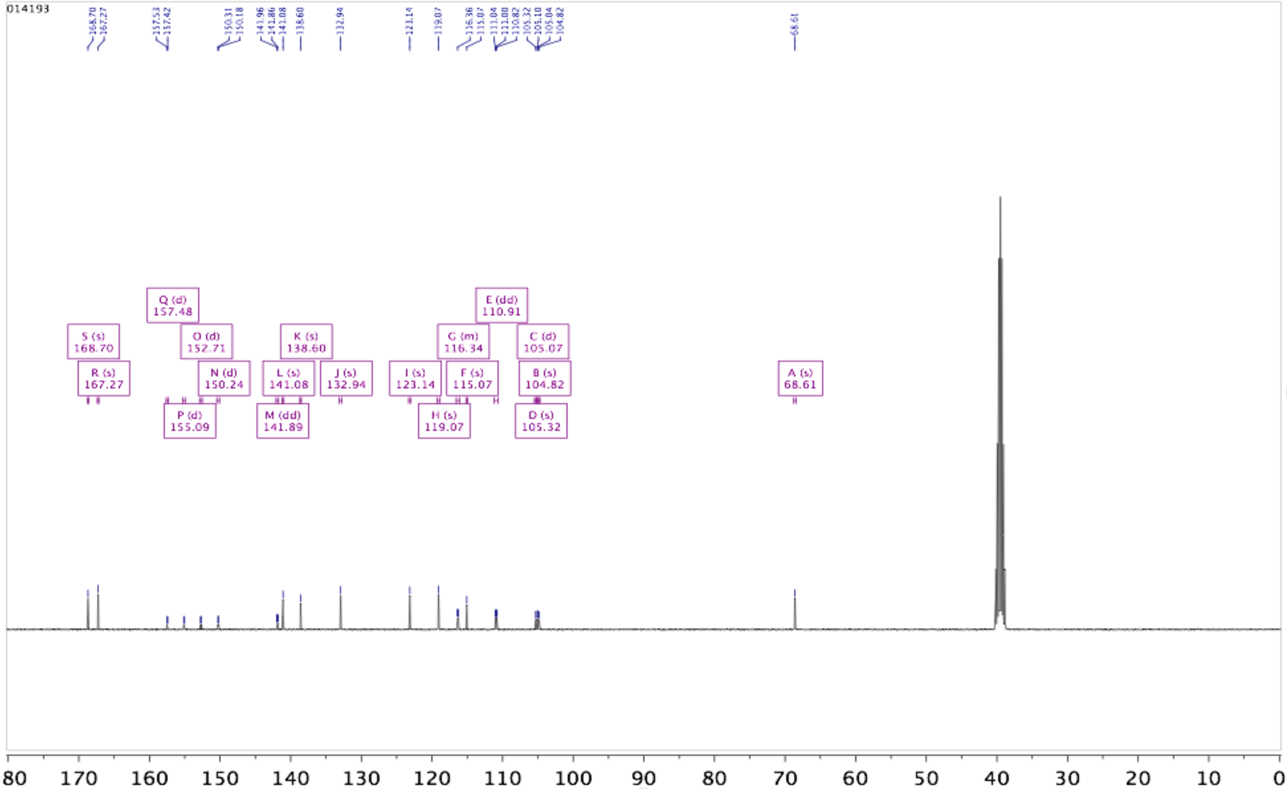
2-Chloro-4-(2-(2-chlorophenoxy)acetamido)benzoic acid (32):



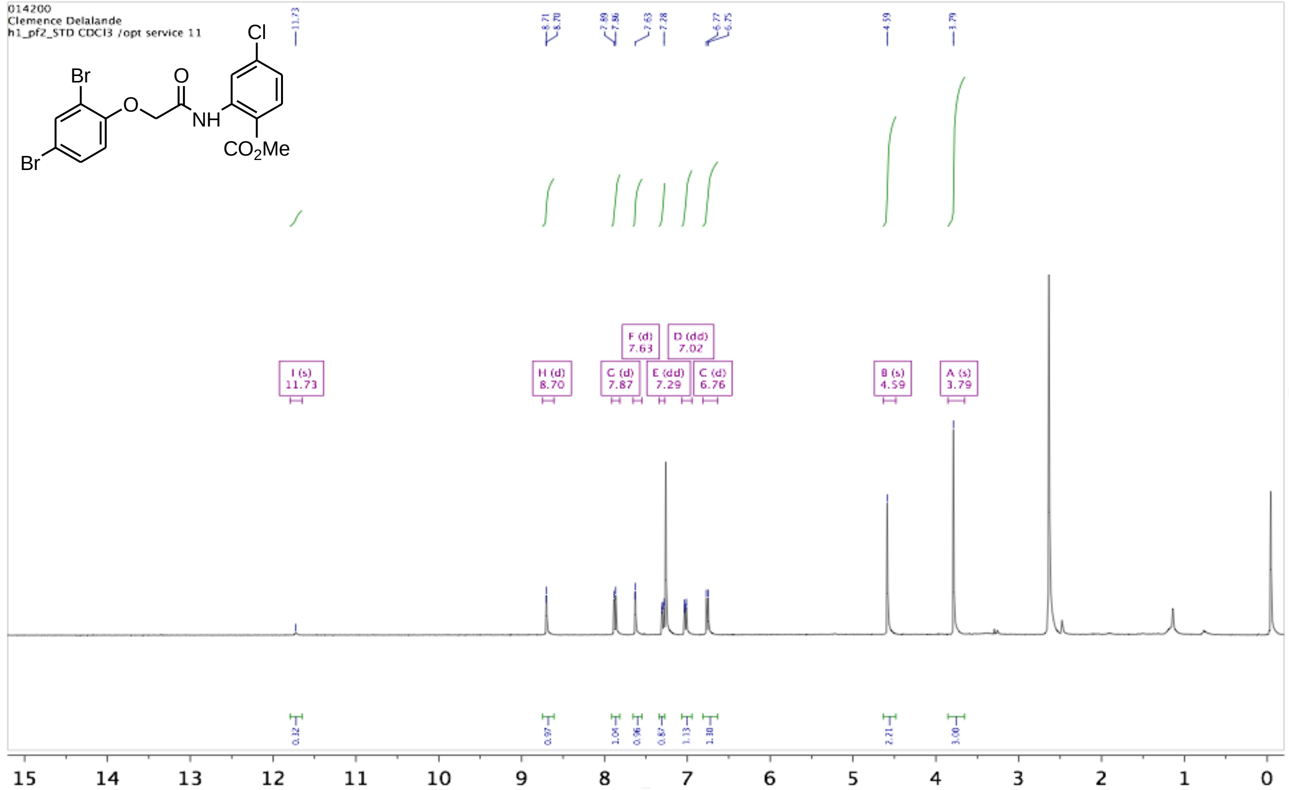


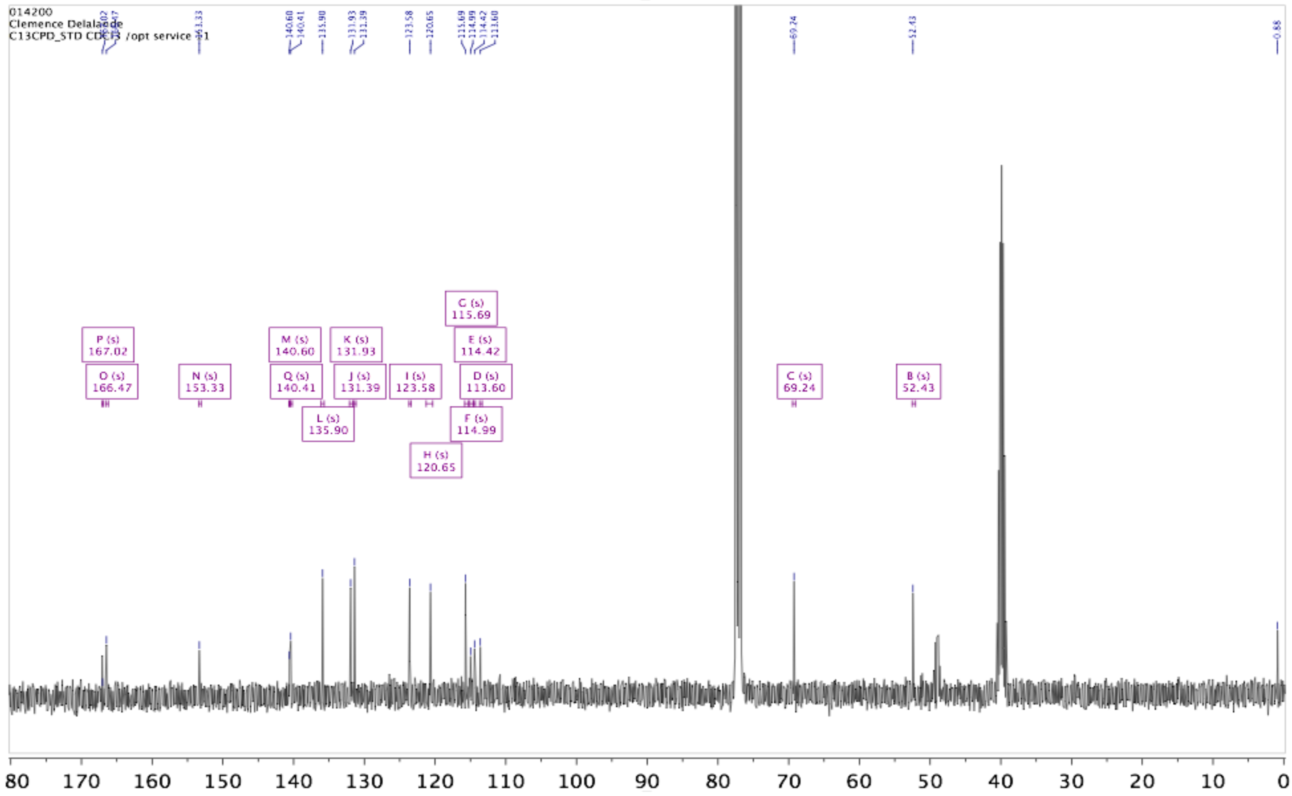
4-Chloro-2-(2-(2,4-difluorophenoxy)acetamido)benzoic acid (14):



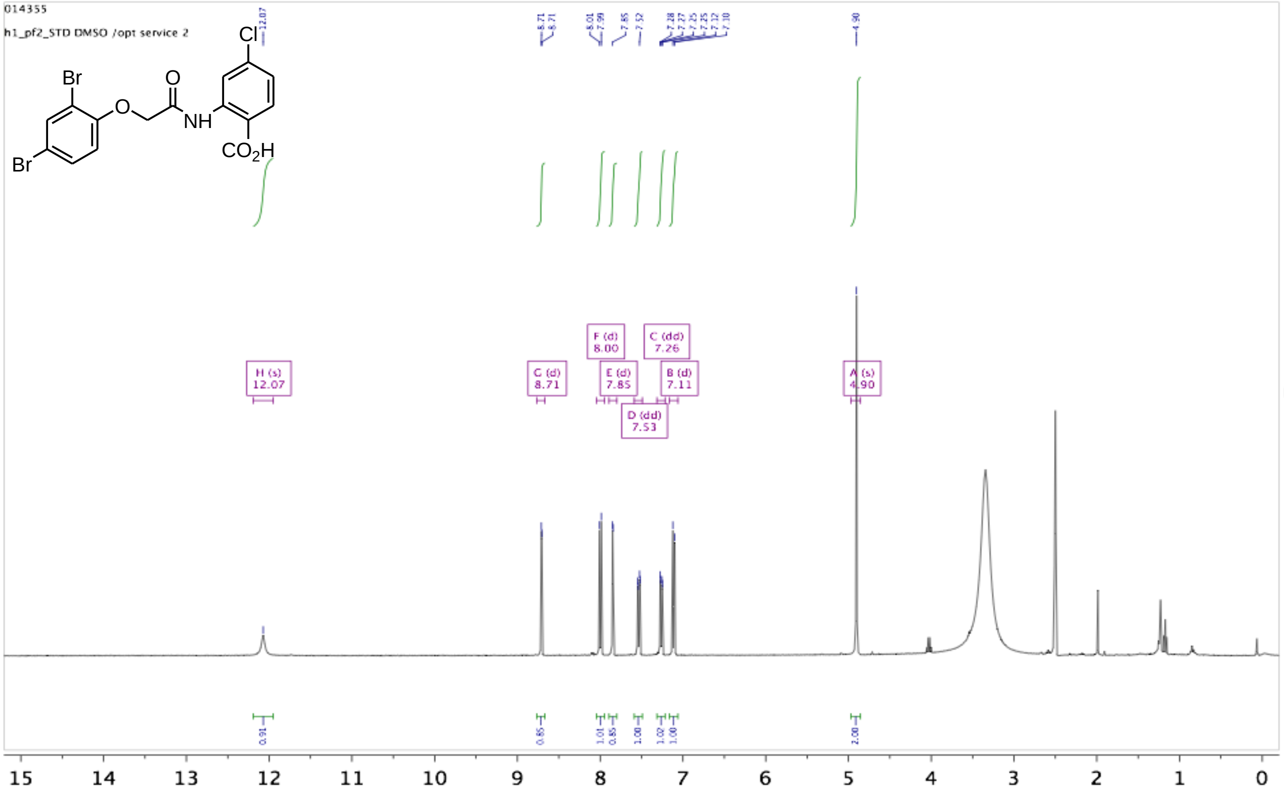


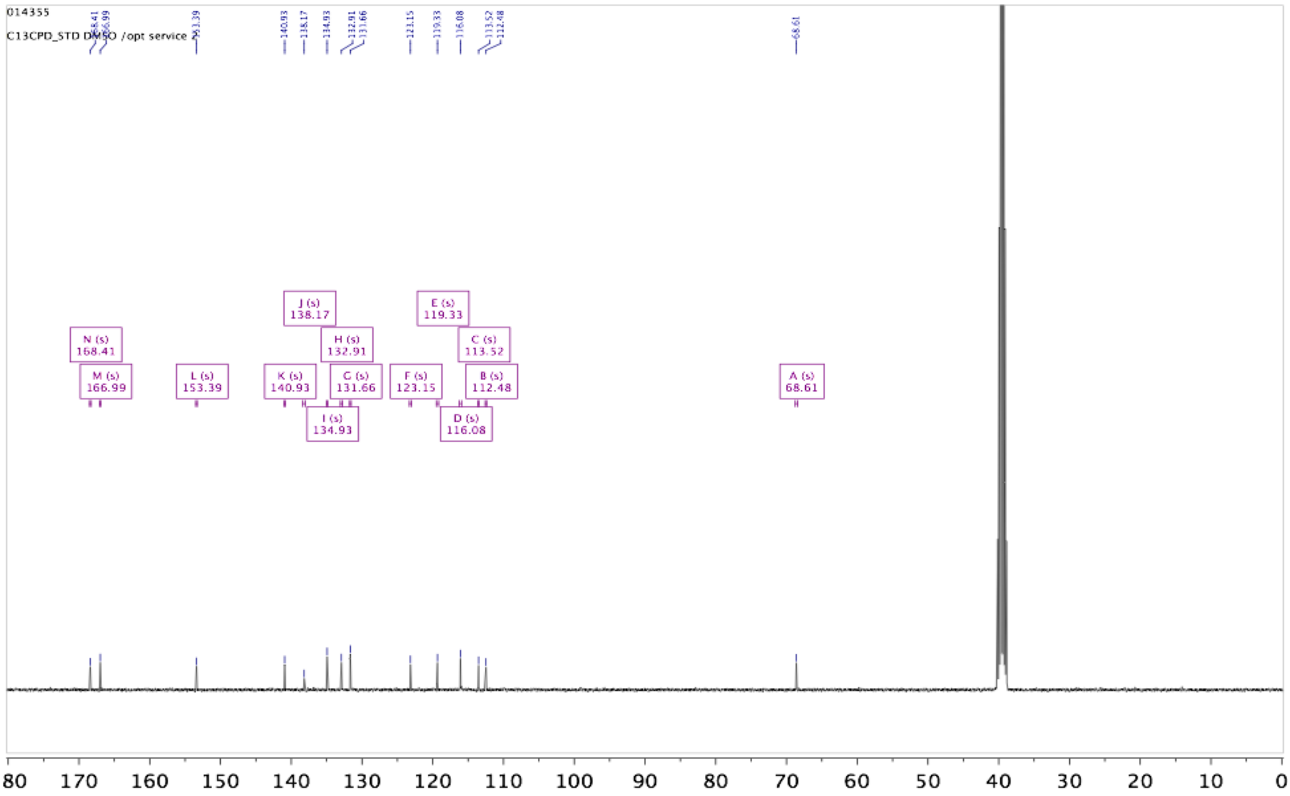
Methyl 4-chloro-2-(2-(2,4-dibromophenoxy)acetamido)benzoate (81):



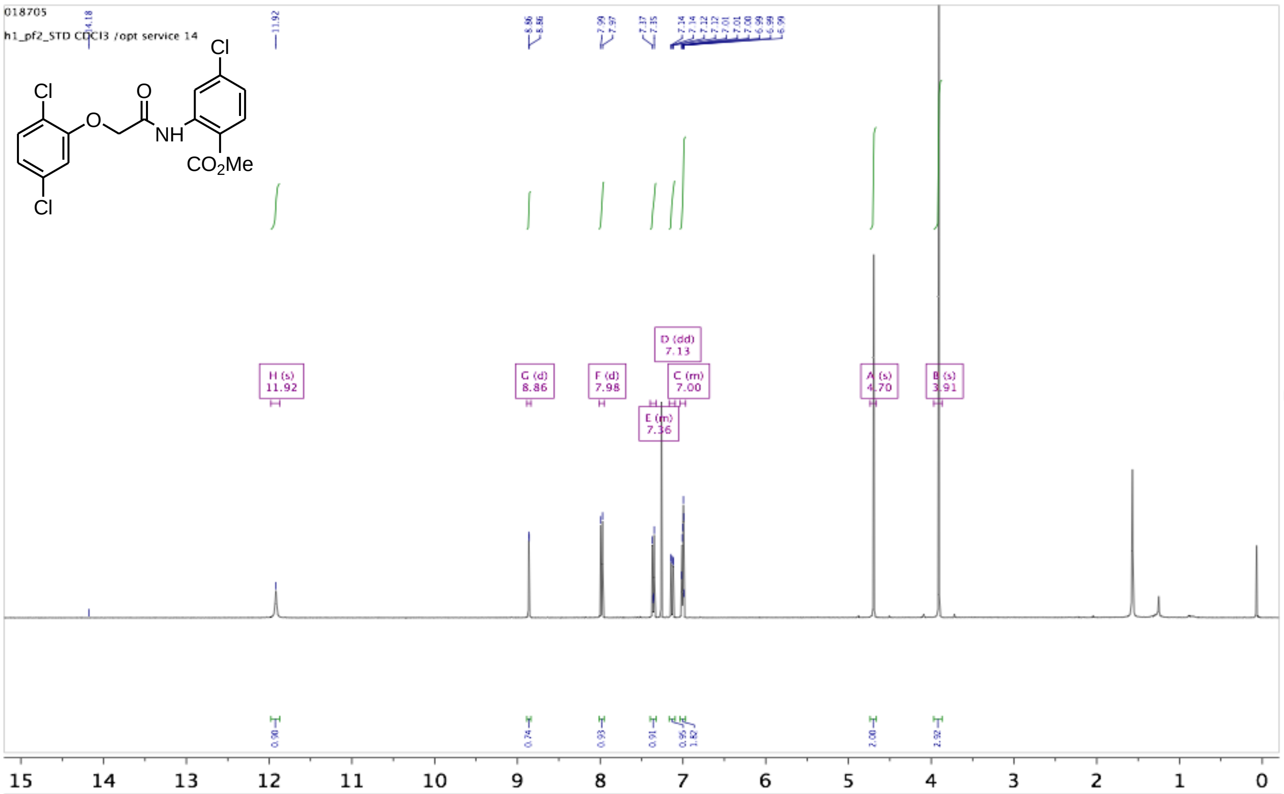


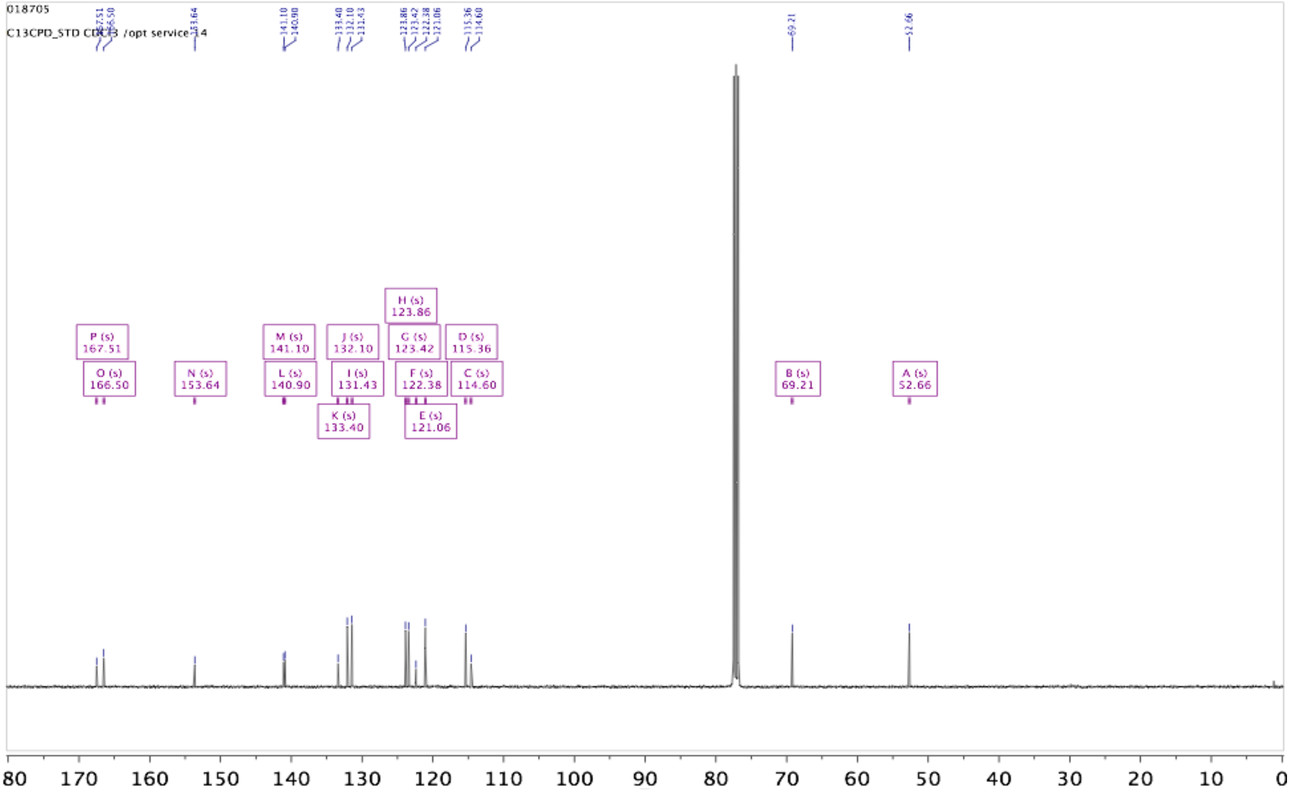
4-Chloro-2-(2-(2,4-dibromophenoxy)acetamido)benzoic acid (13):



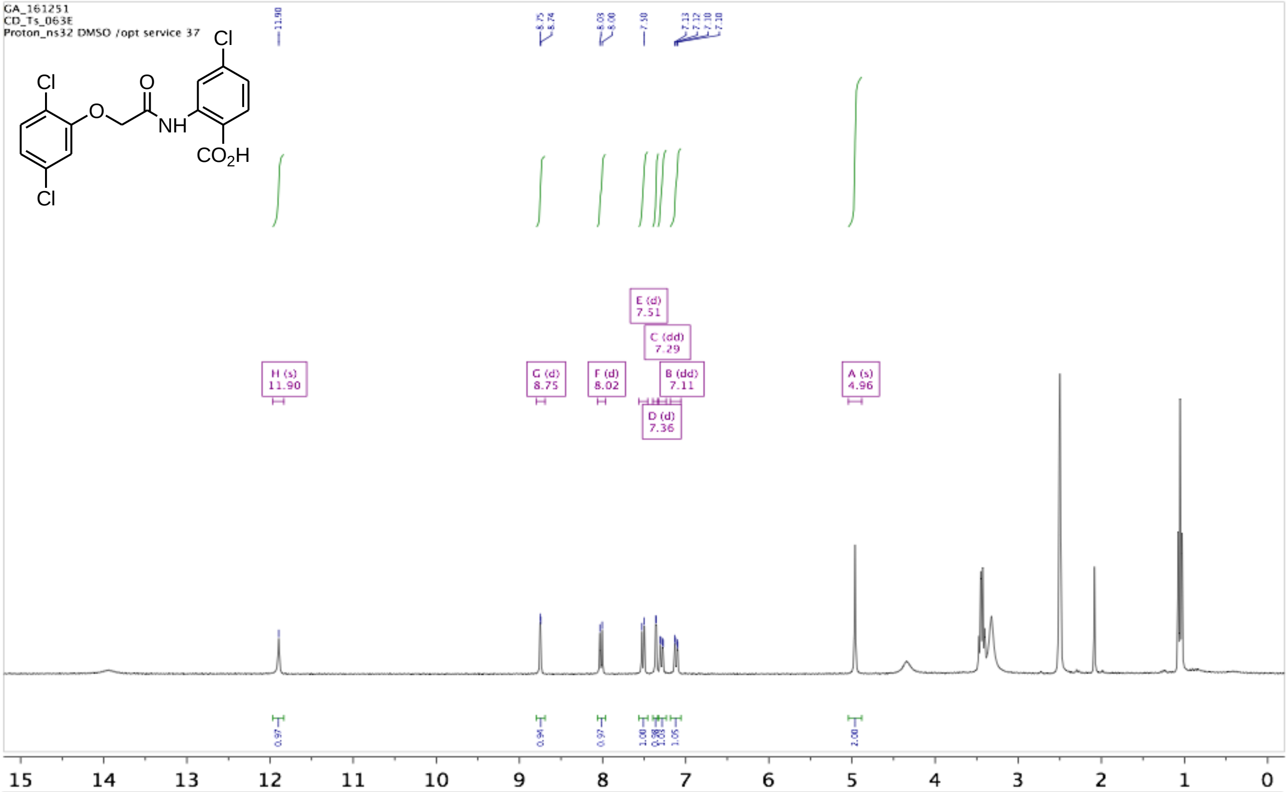


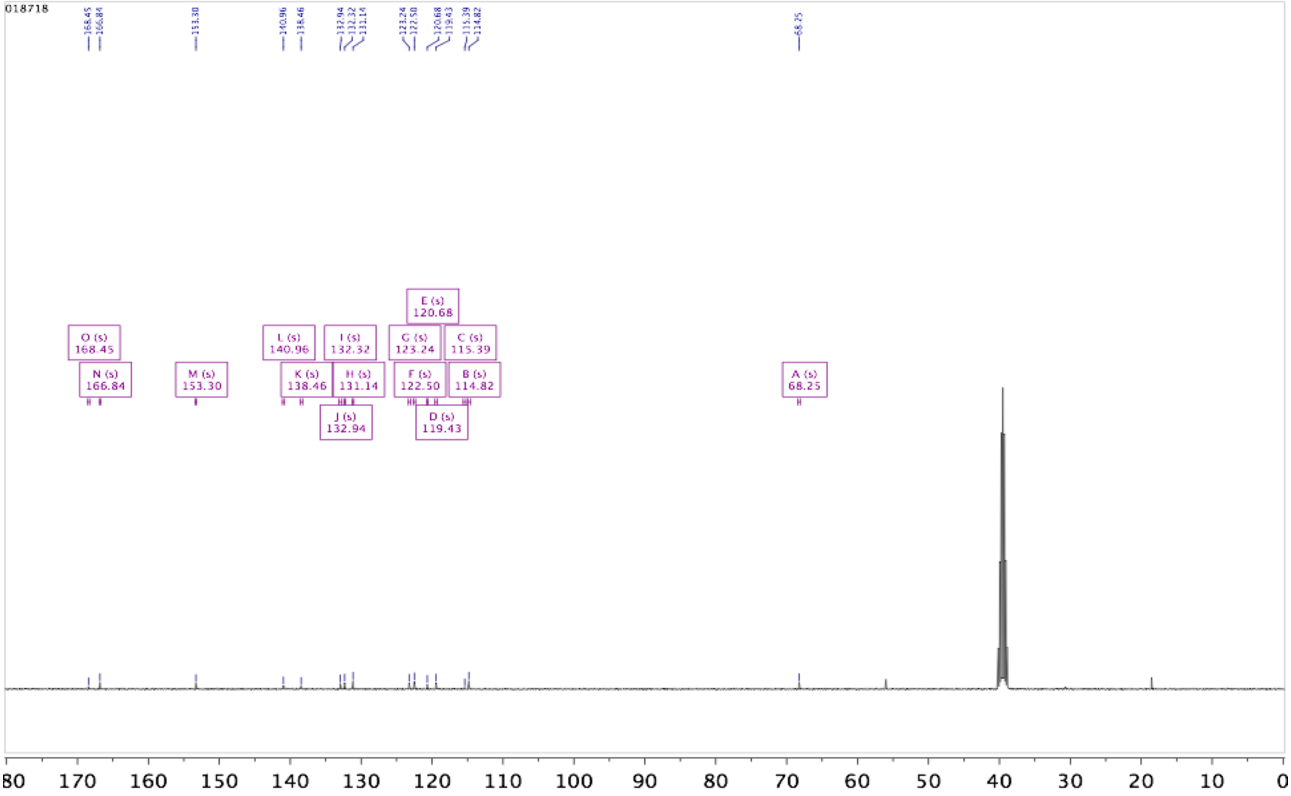
Methyl 4-chloro-2-(2-(2,5-dichlorophenoxy)acetamido)benzoate (82):



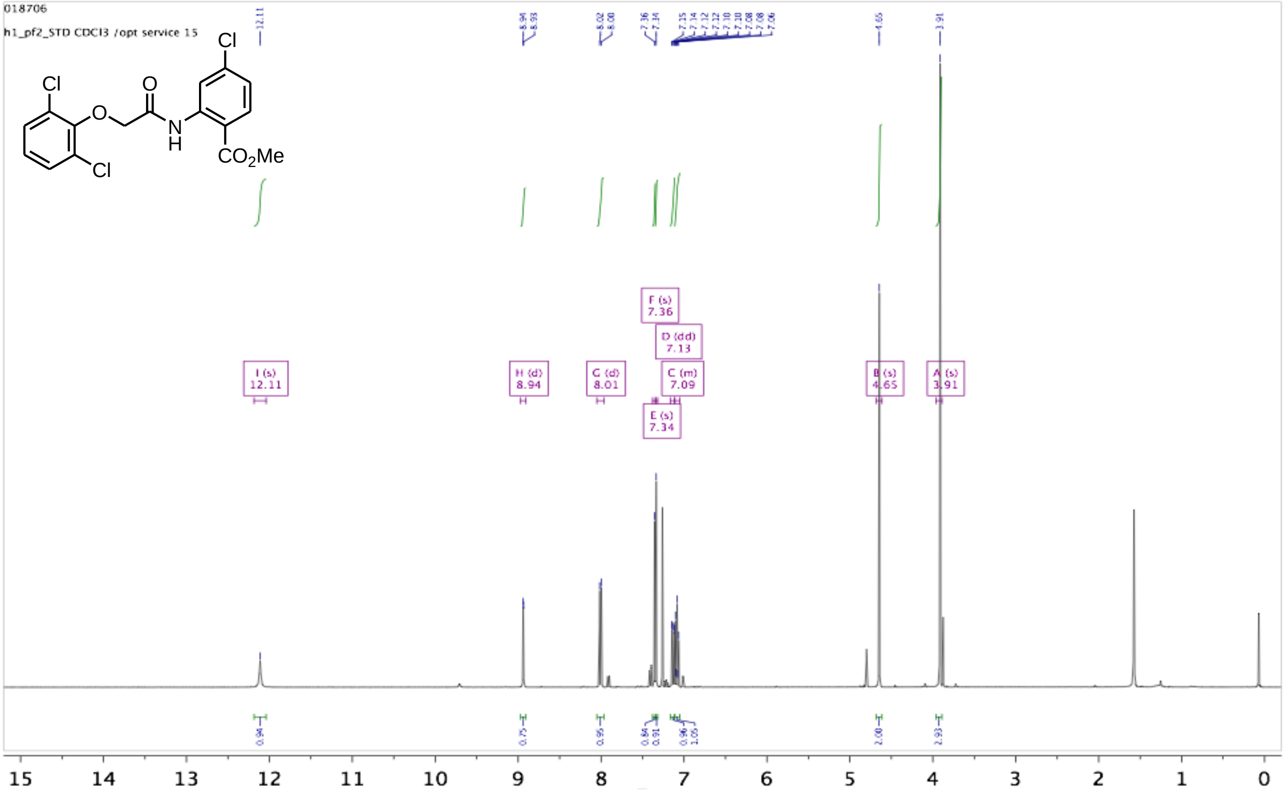


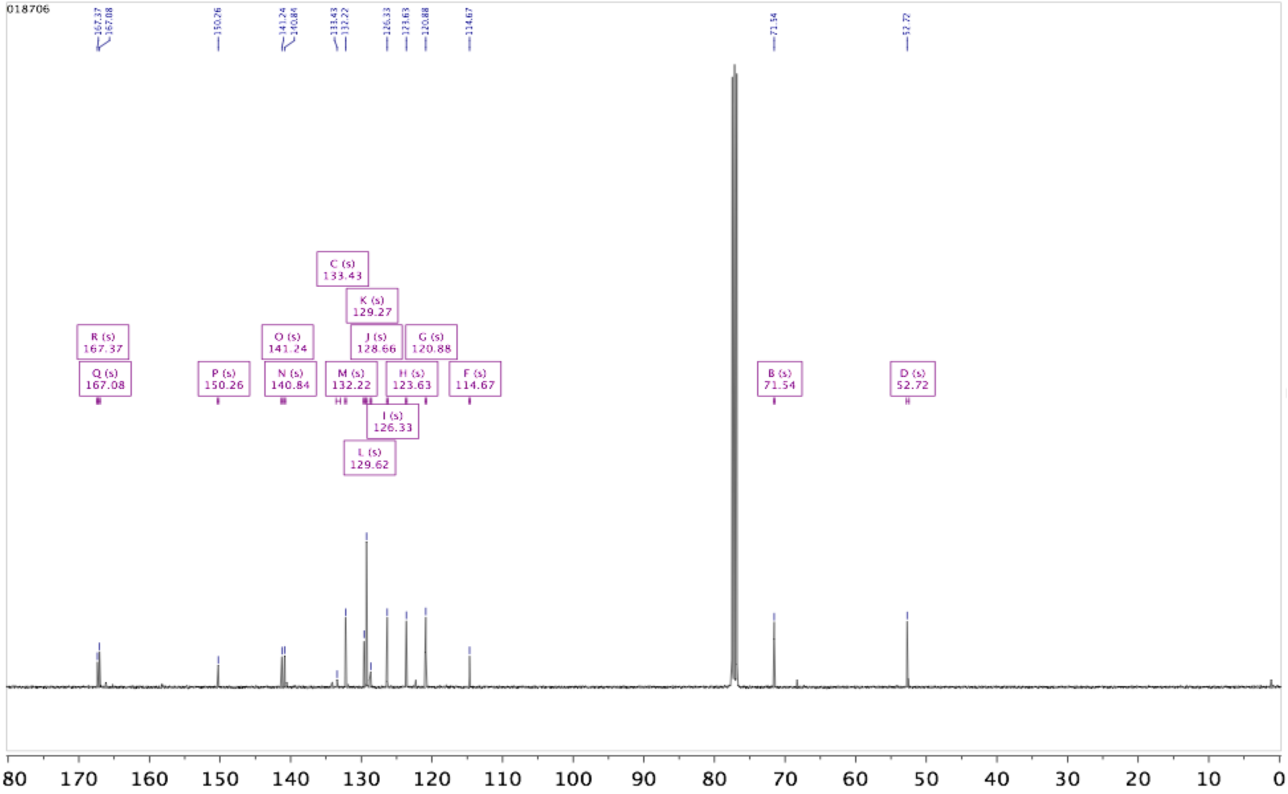
4-Chloro-2-(2-(2,5-dichlorophenoxy)acetamido)benzoic acid (**34**):



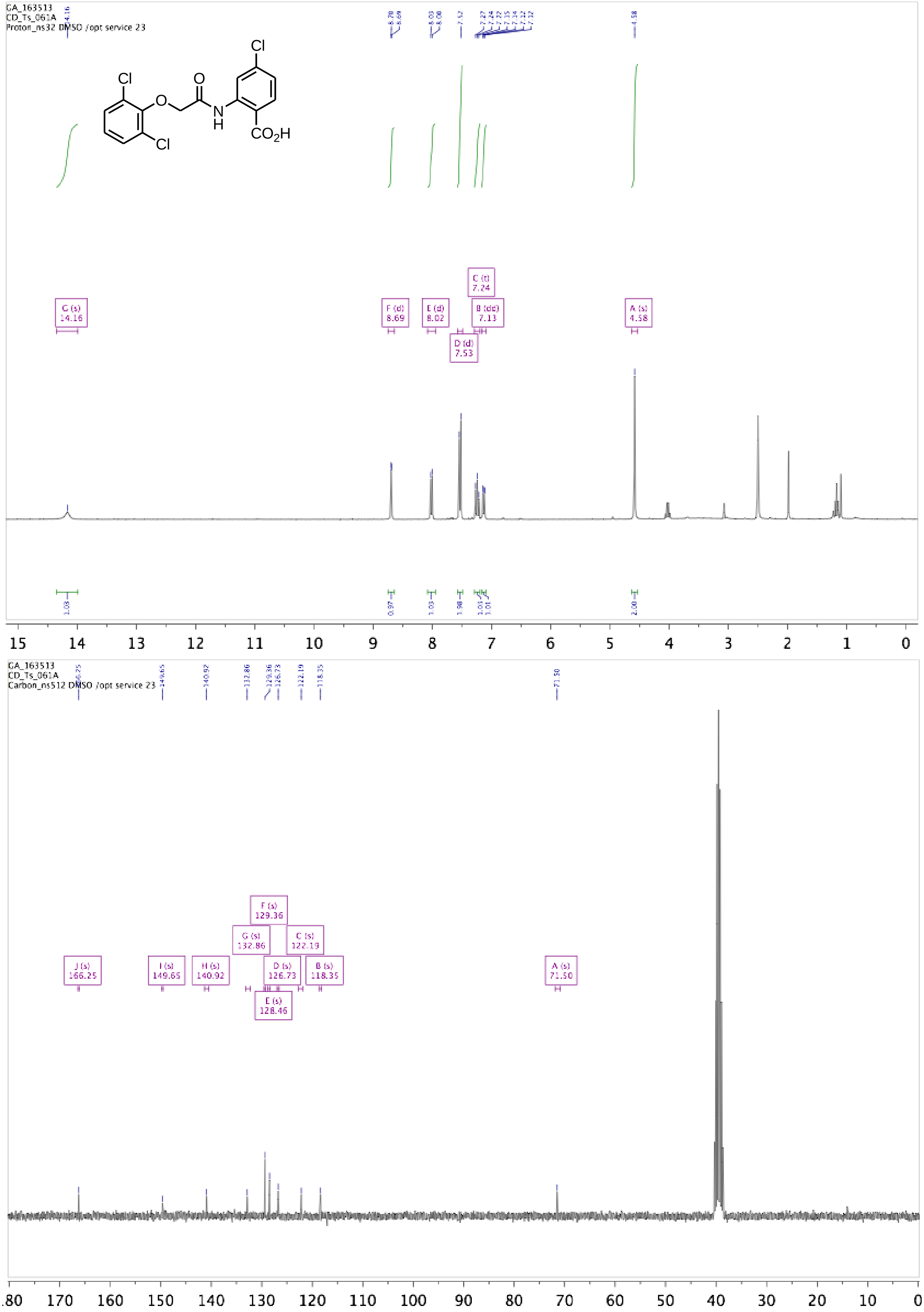


Methyl 4-chloro-2-(2-(2,6-dichlorophenoxy)acetamido)benzoate (83):

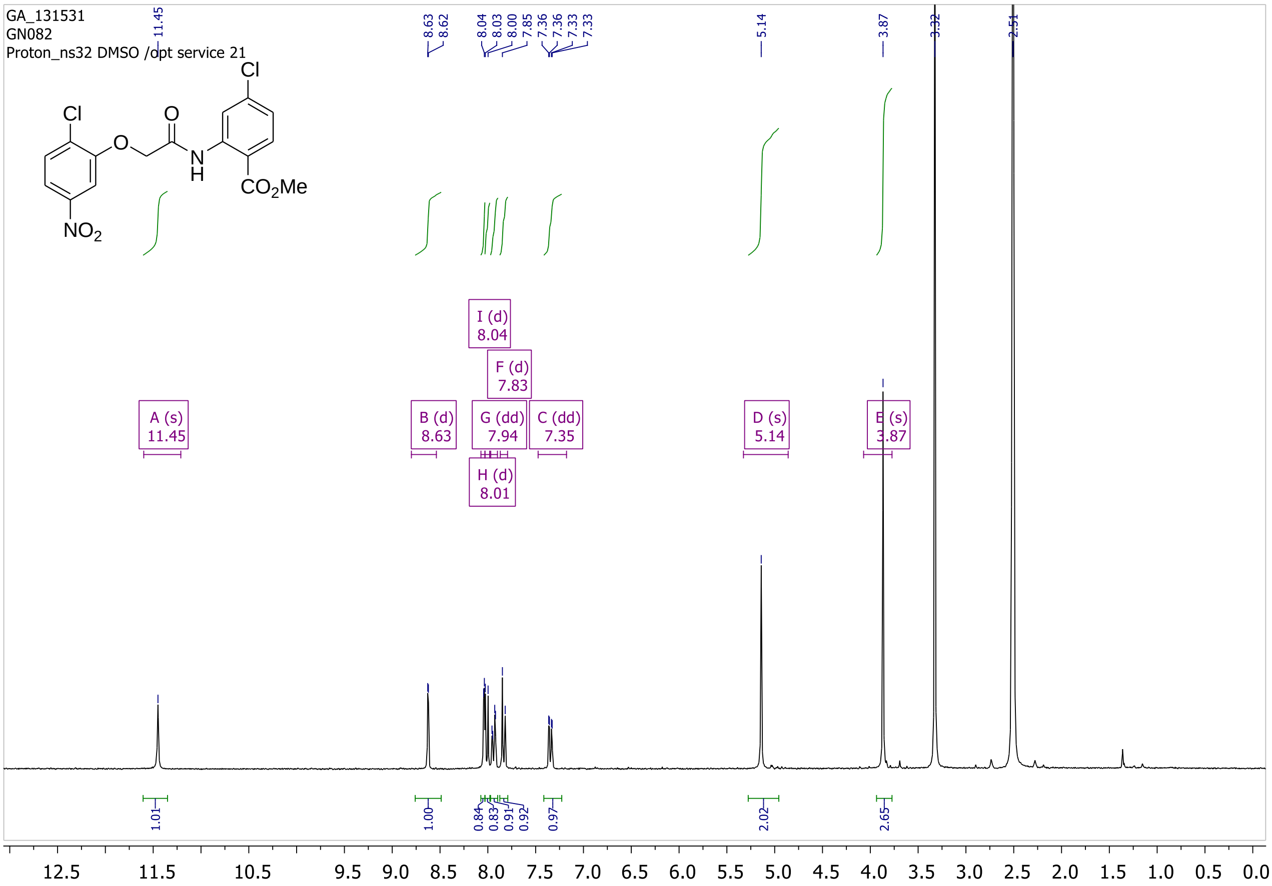


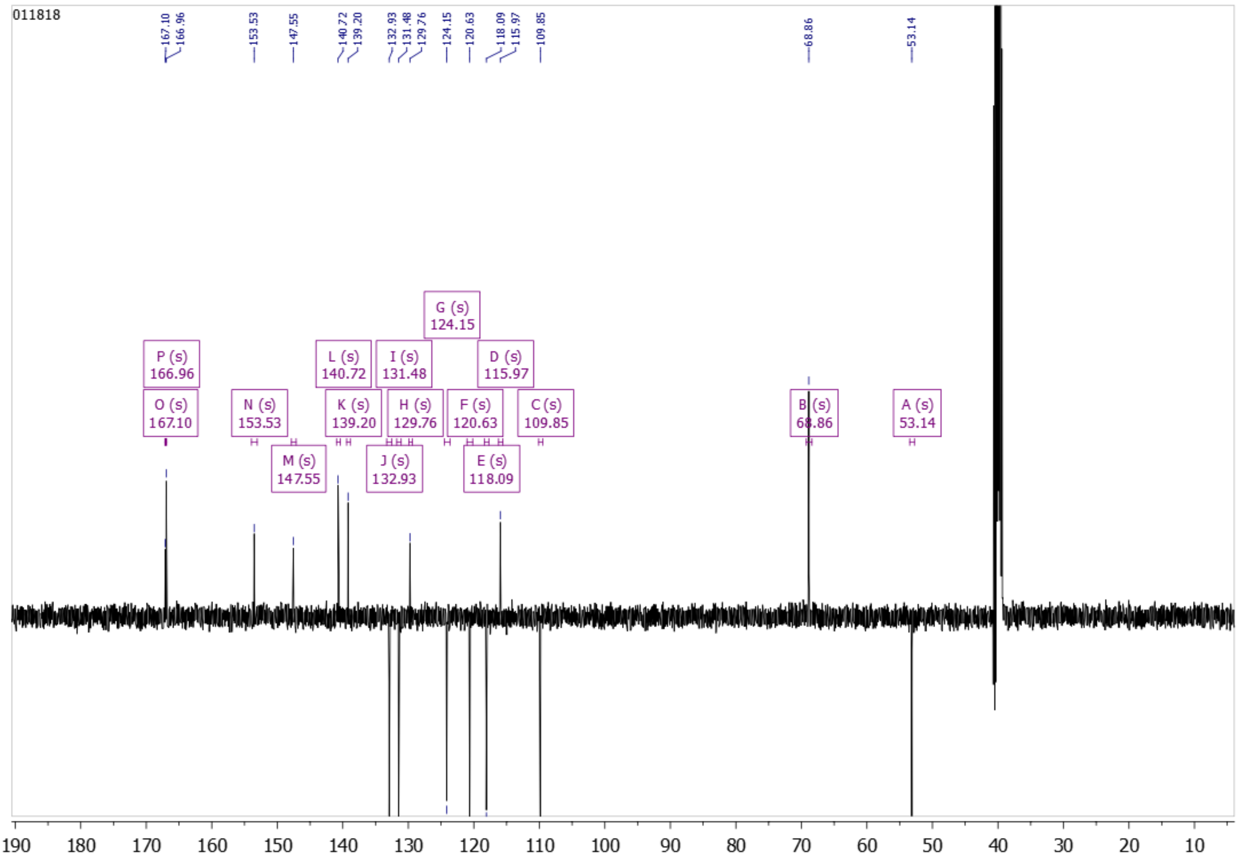


4-Chloro-2-(2-(2,6-dichlorophenoxy)acetamido)benzoic acid (35):

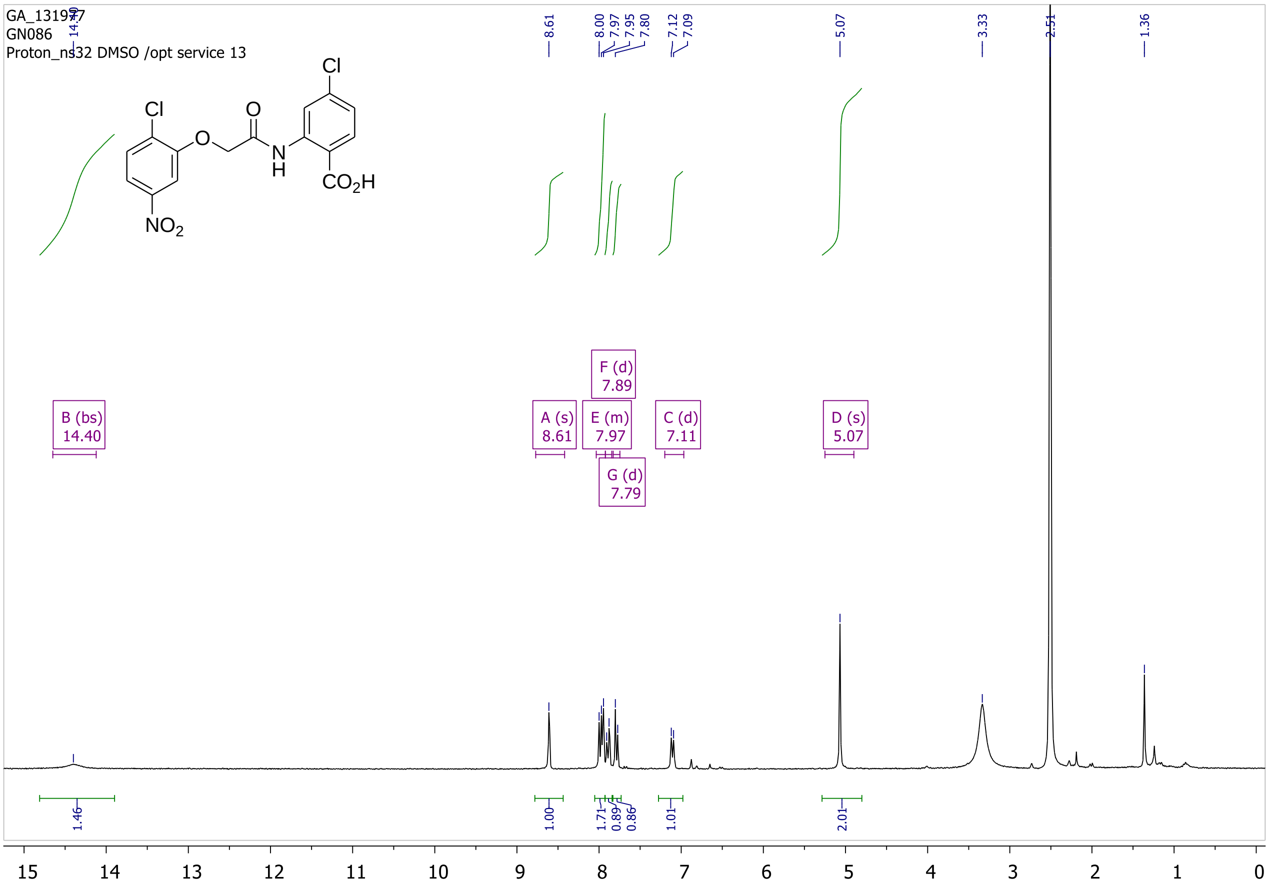


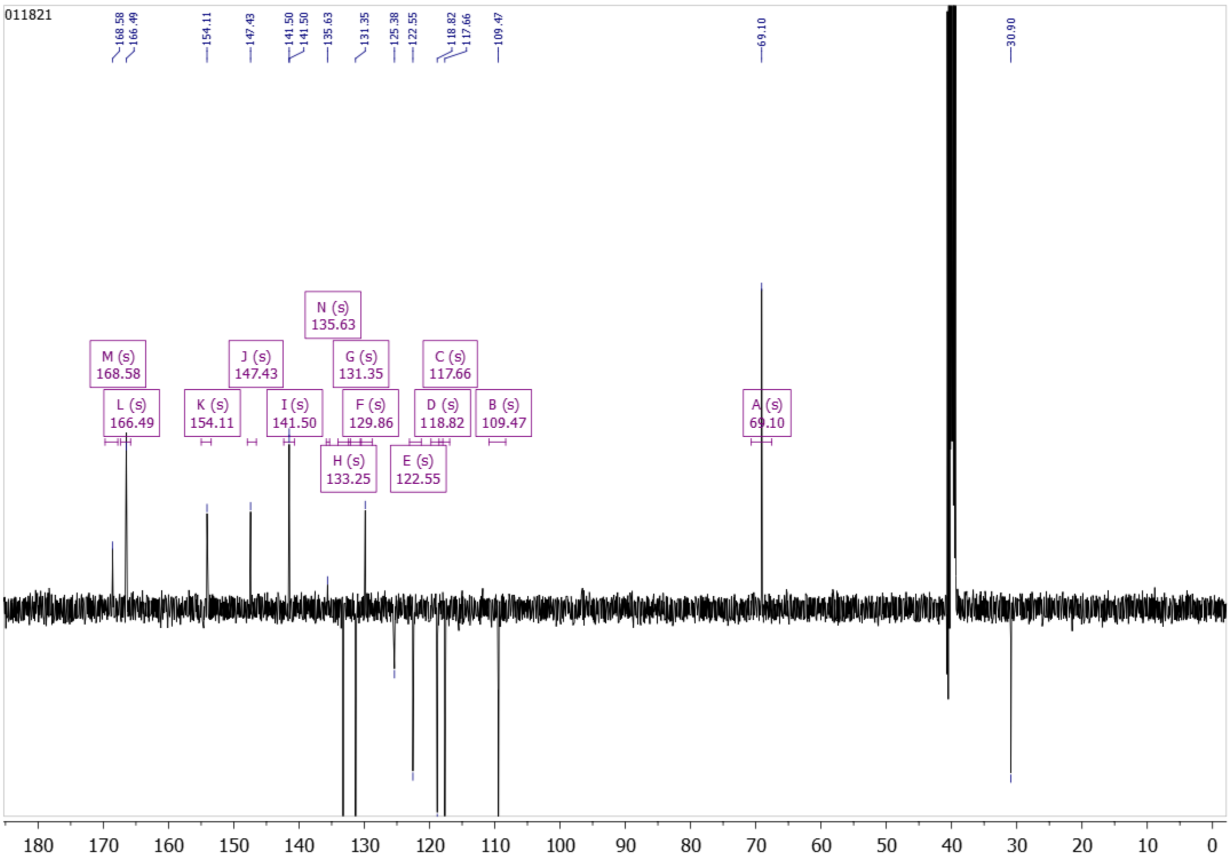
Methyl 4-chloro-2-(2-(2-chloro-5-nitrophenoxy)acetamido)benzoate (84):



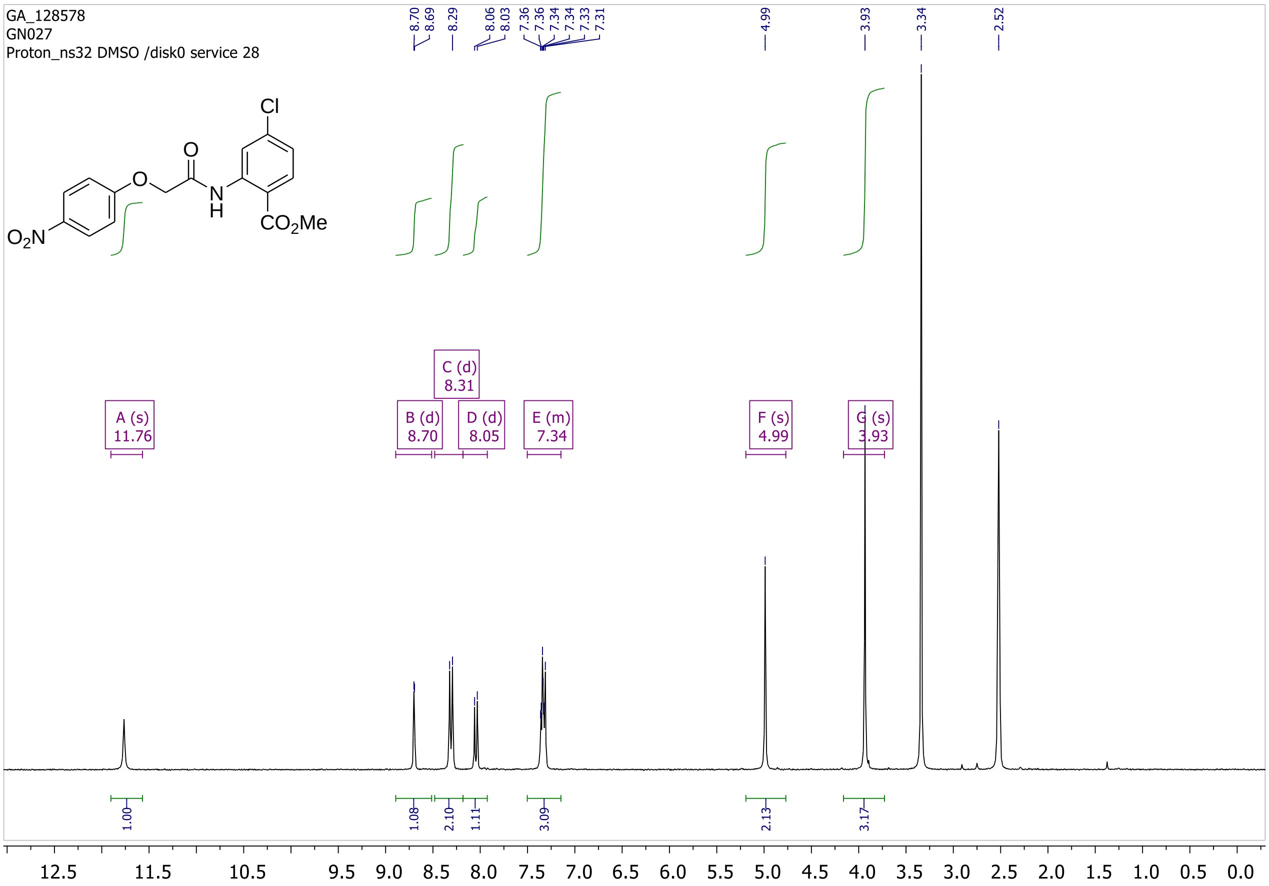


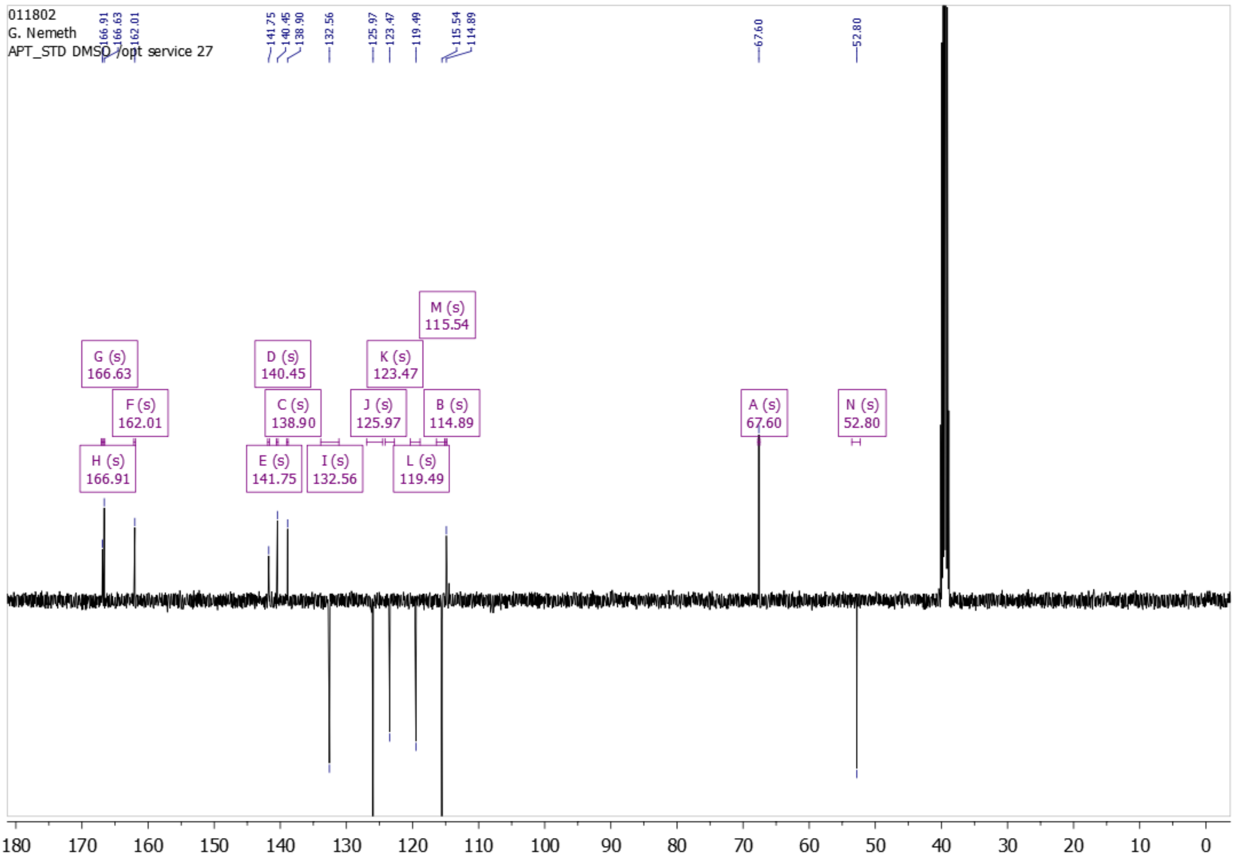
4-Chloro-2-(2-(2-chloro-5-nitrophenoxy)acetamido)benzoic acid (**15**):



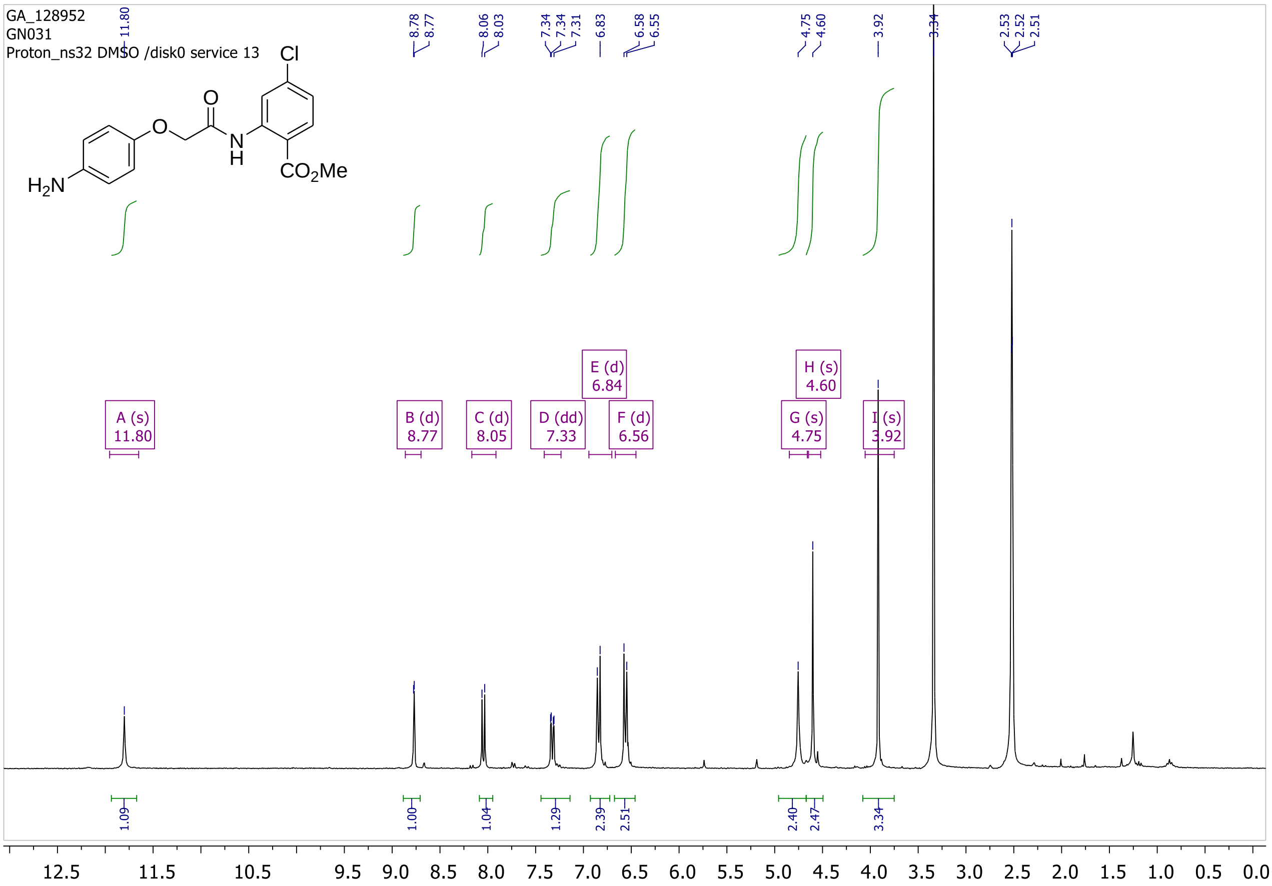


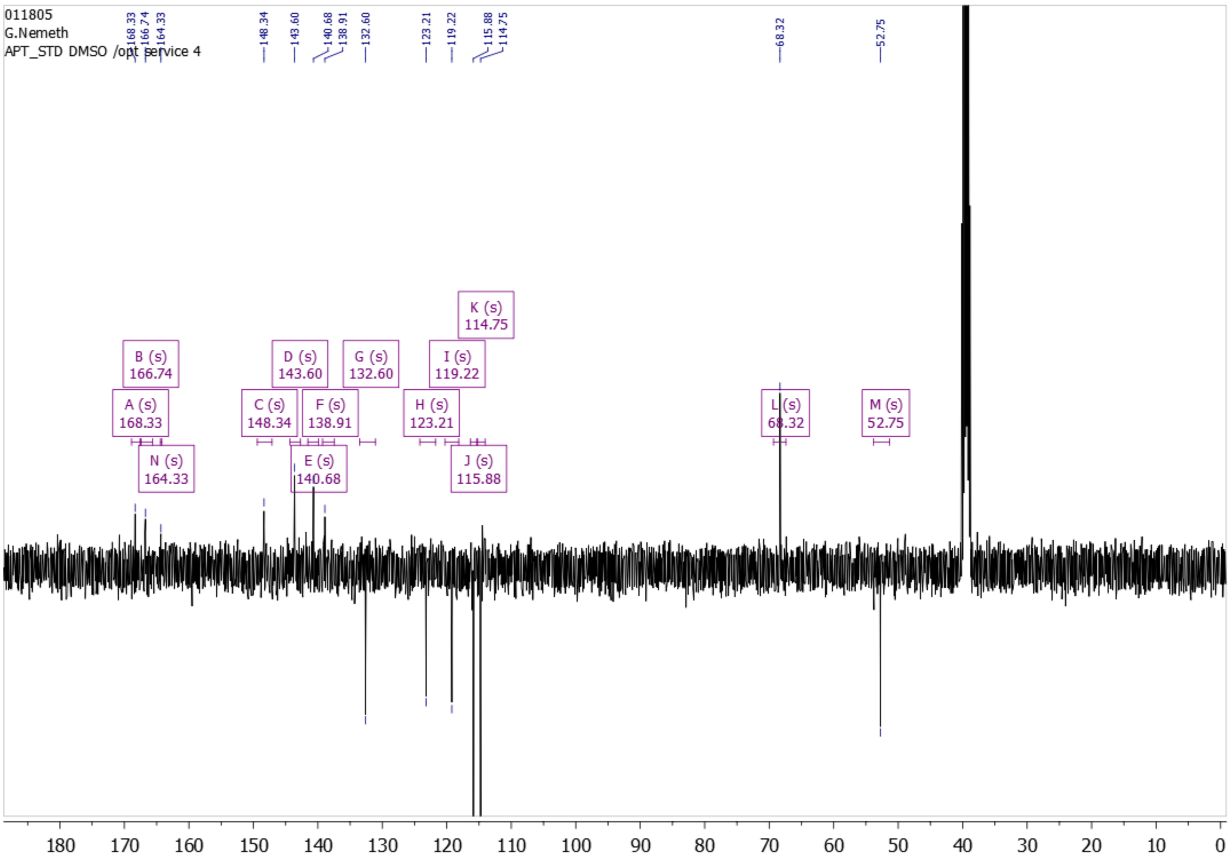
Methyl 4-chloro-2-(2-(4-nitrophenoxy)acetamido)benzoate (**85**):



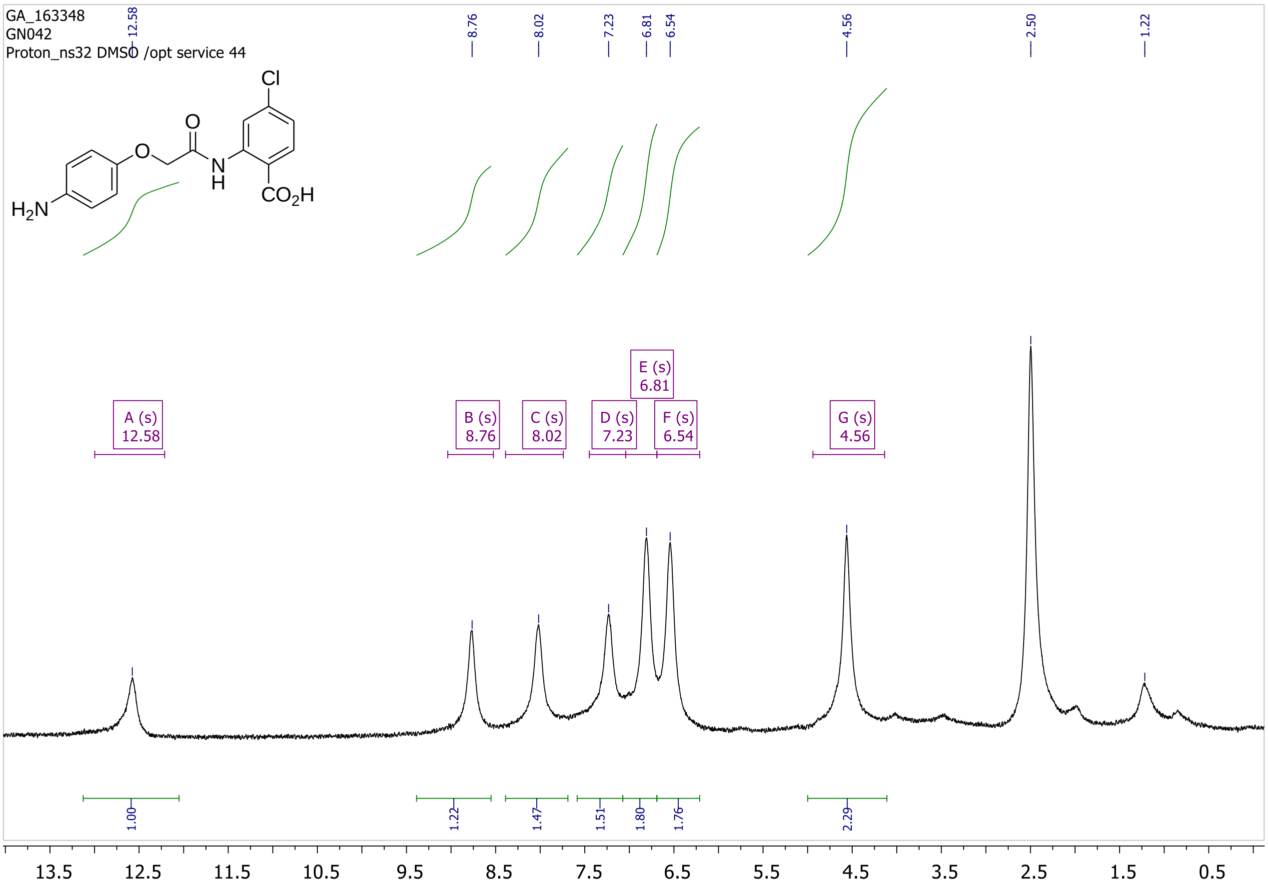


Methyl 2-(2-(4-aminophenoxy)acetamido)-4-chlorobenzoate (86):

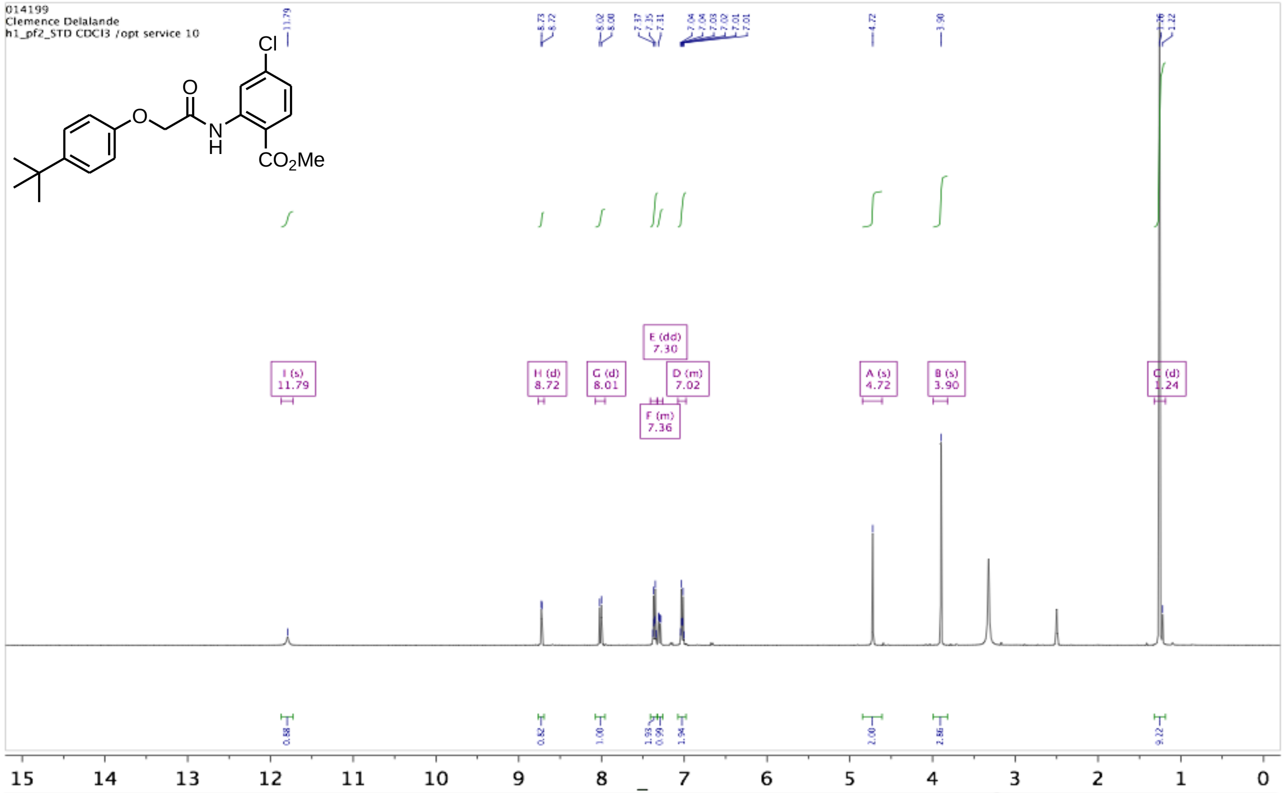


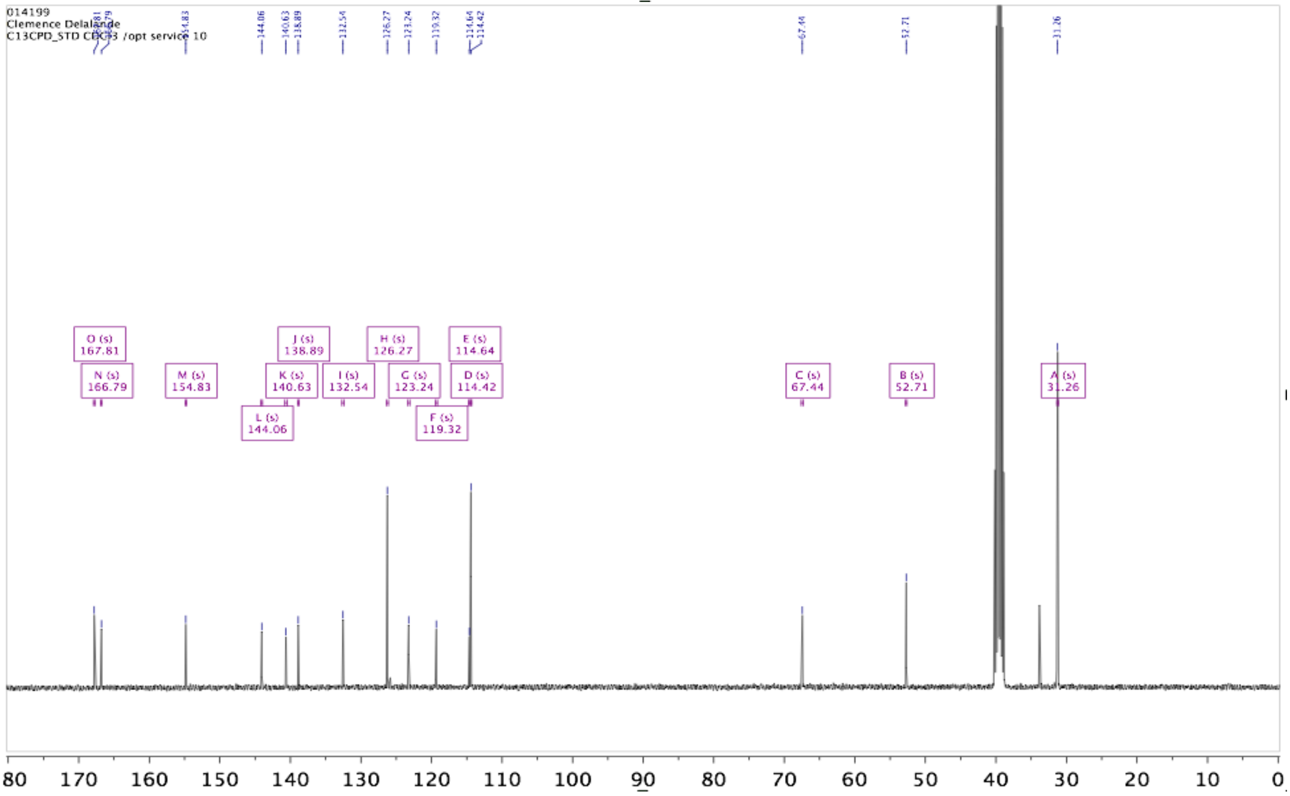


2-(2-(4-Aminophenoxy)acetamido)-4-chlorobenzoic acid (36):

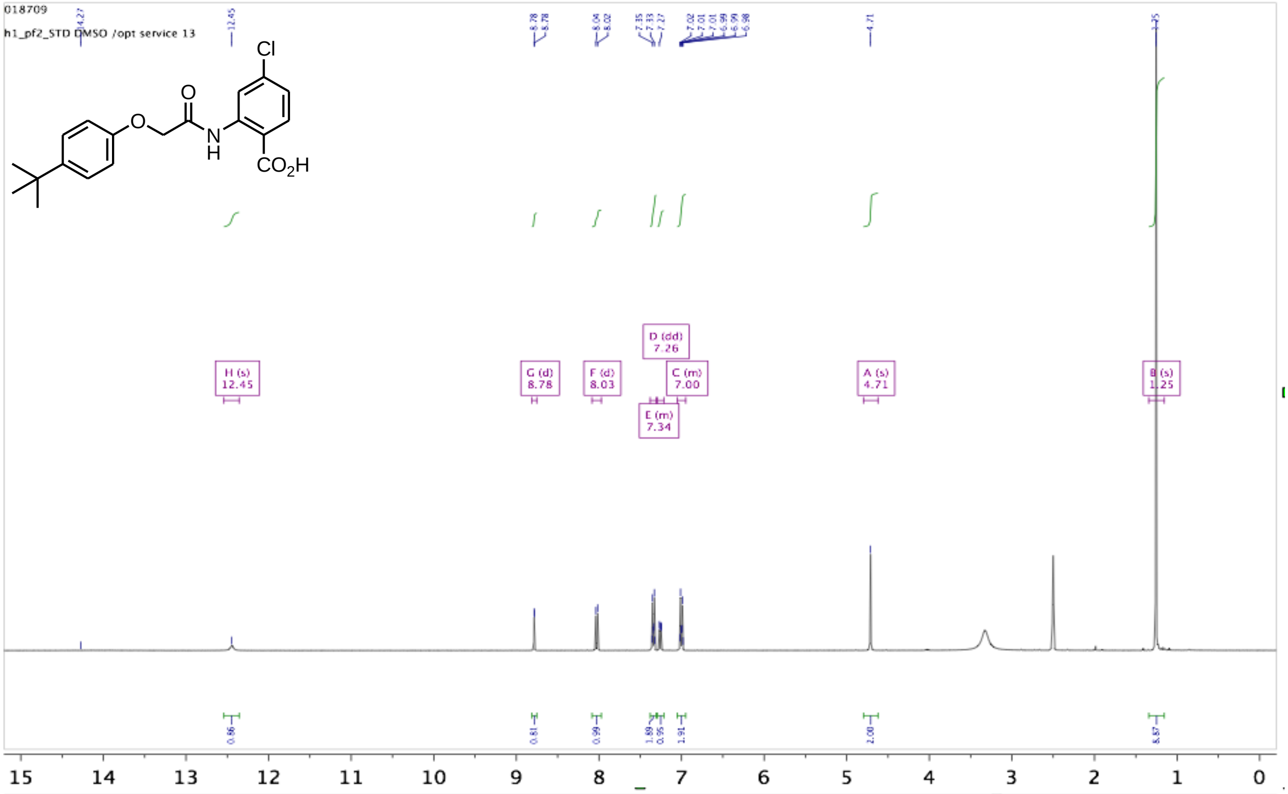


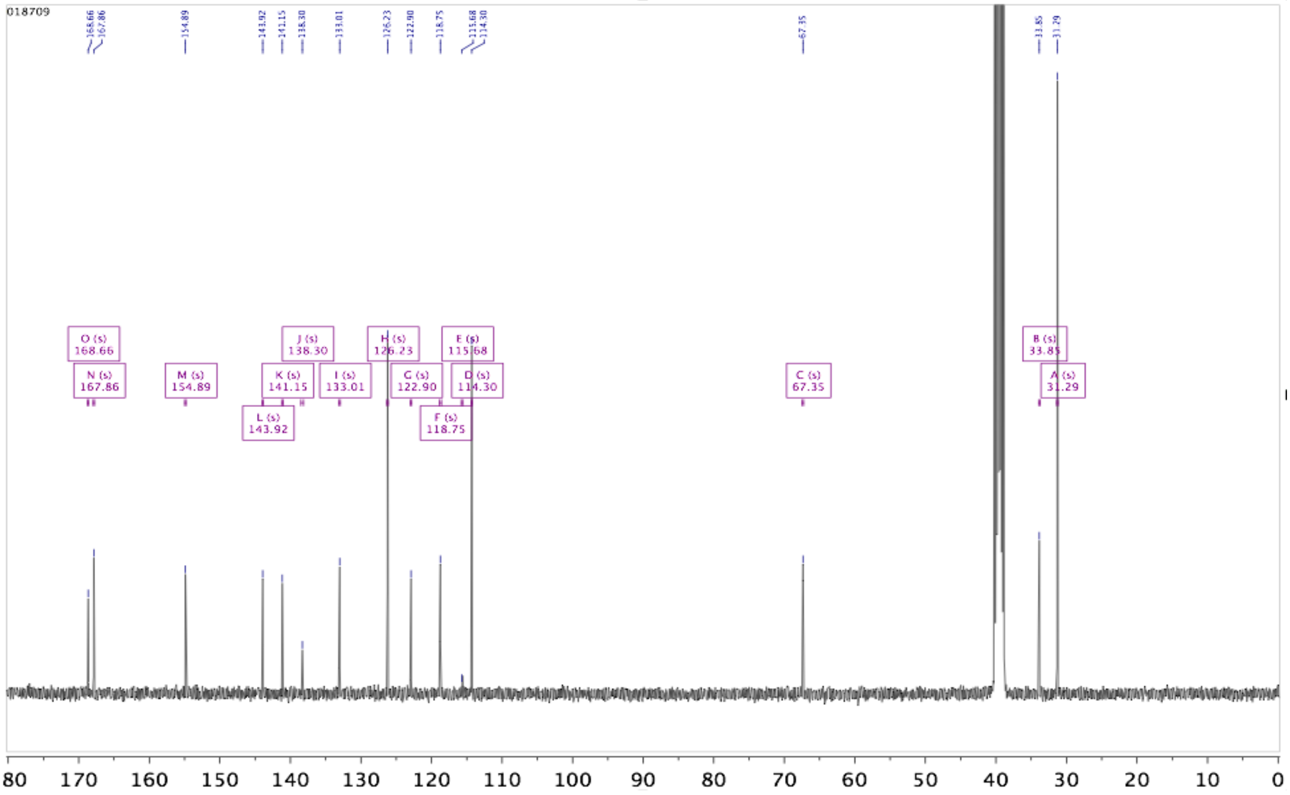
Methyl 2-(2-(4-(tert-butyl)phenoxy)acetamido)-4-chlorobenzoate (87):



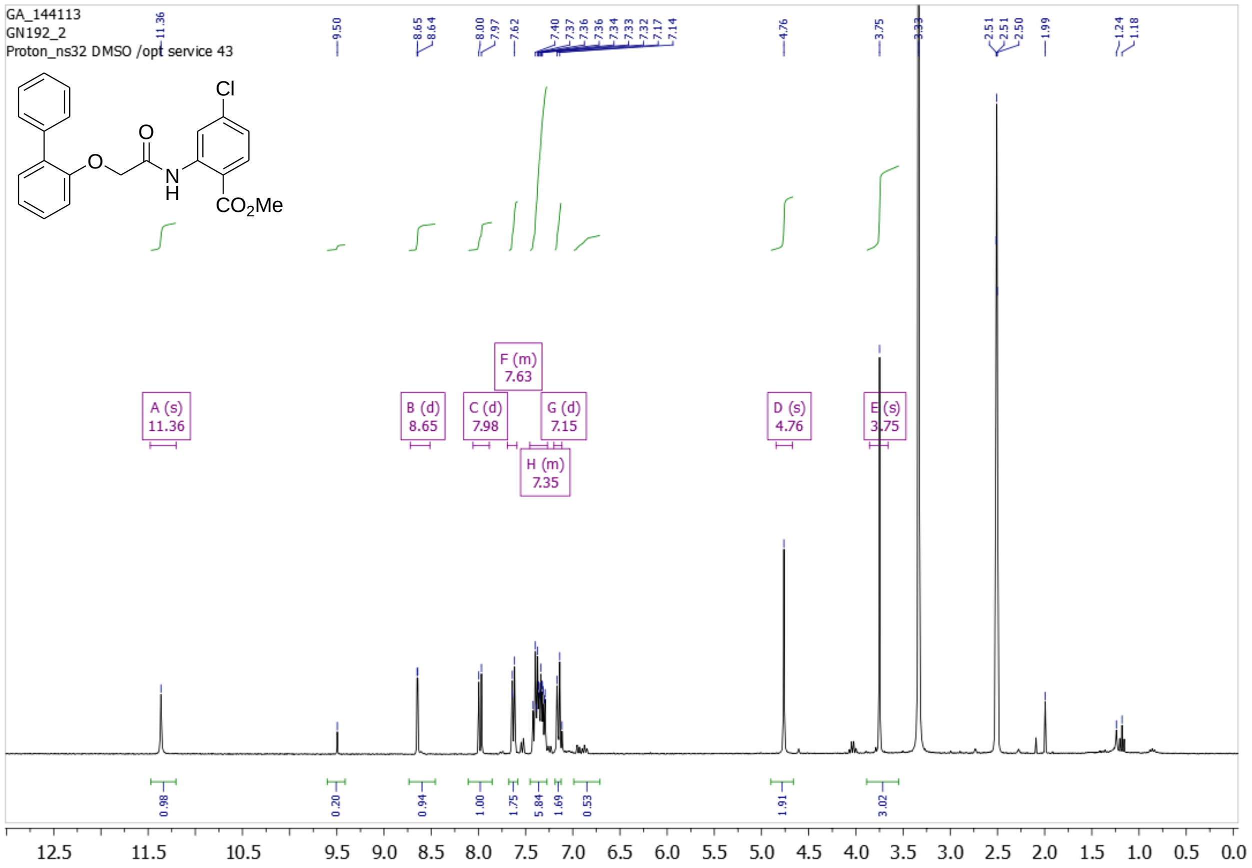


2-(2-(4-(*tert*-Butyl)phenoxy)acetamido)-4-chlorobenzoic acid (37):

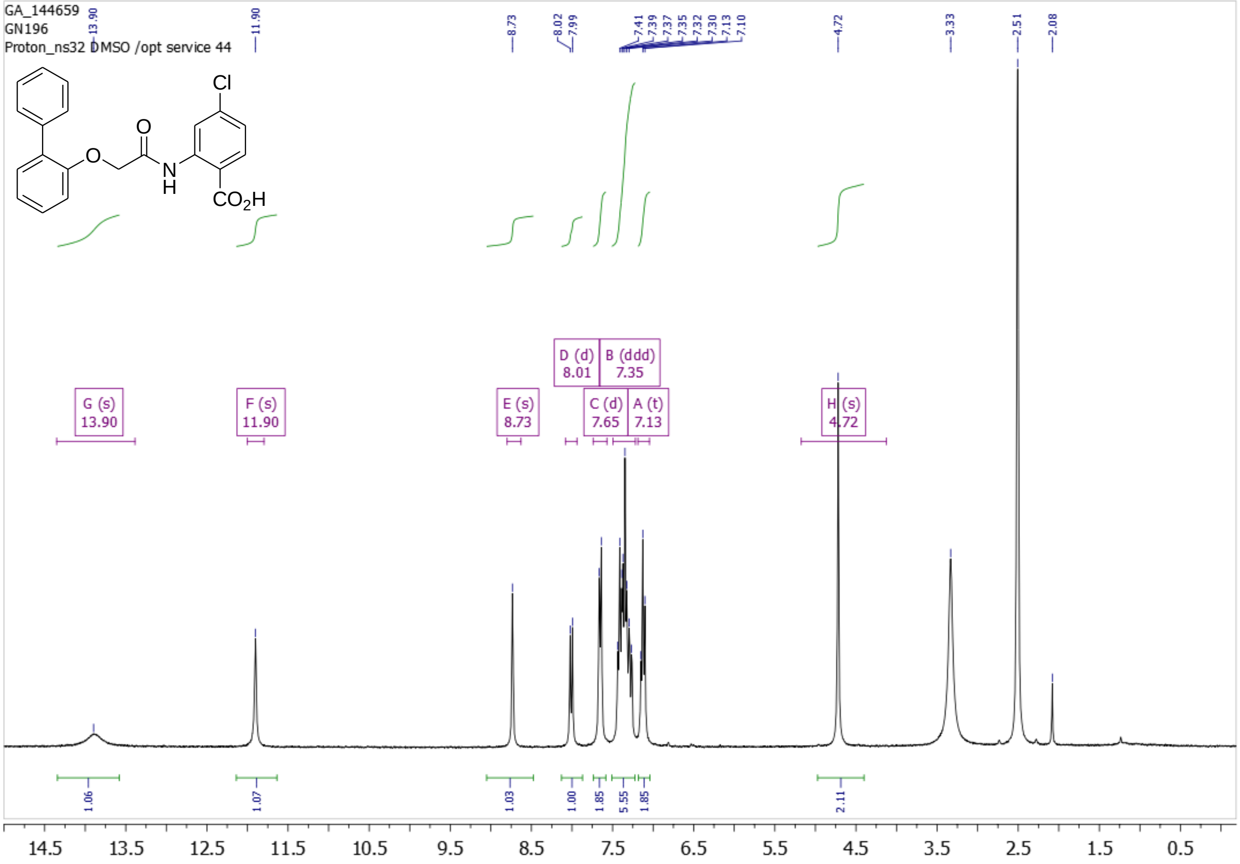


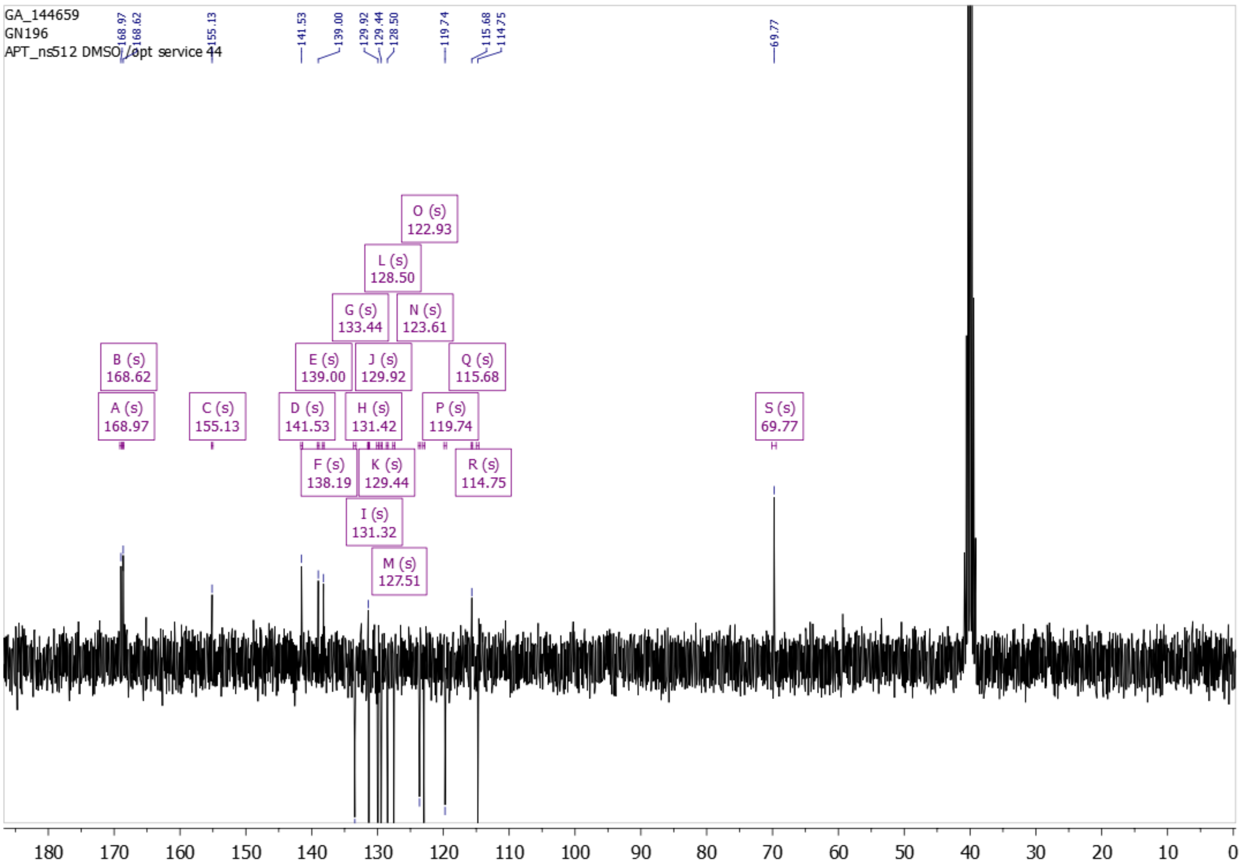


Methyl 2-(2-([1,1'-biphenyl]-2-yloxy)acetamido)-4-chlorobenzoate (88):

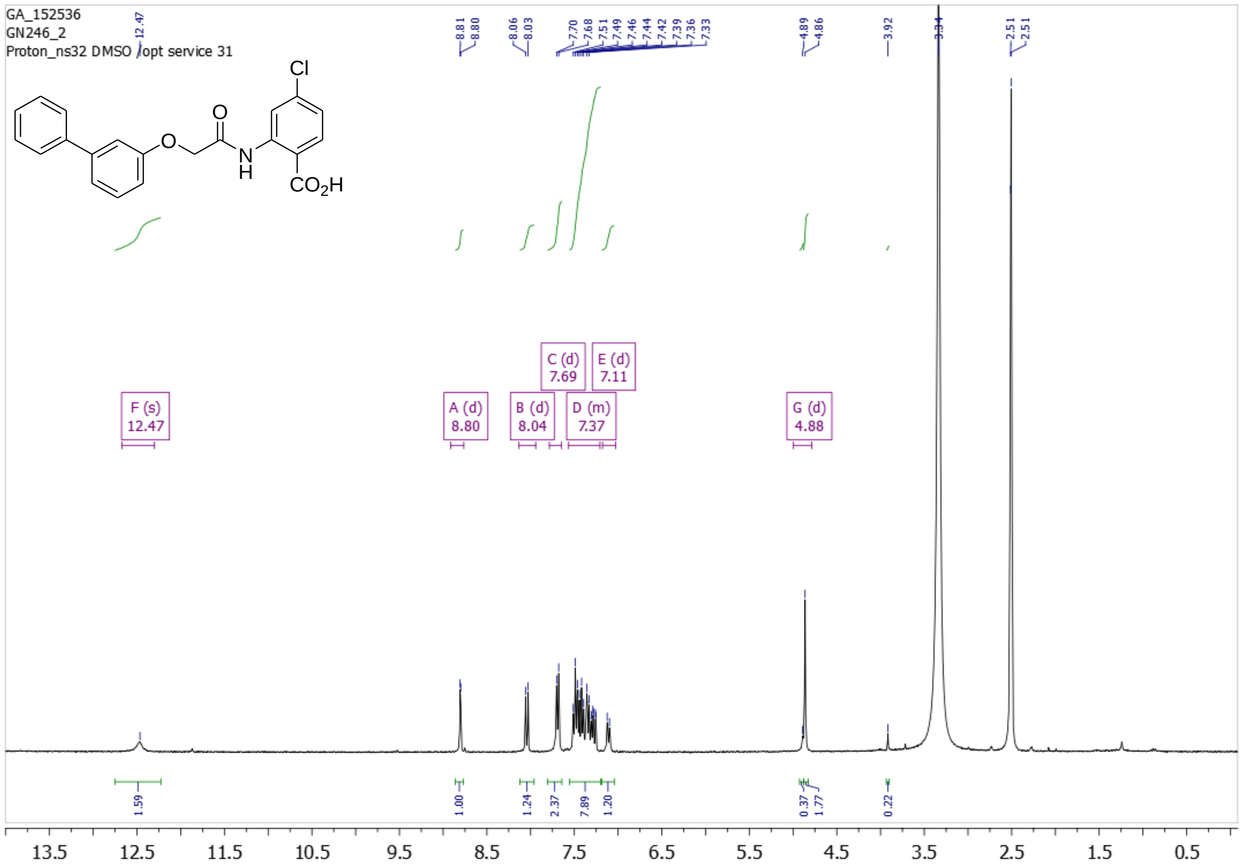


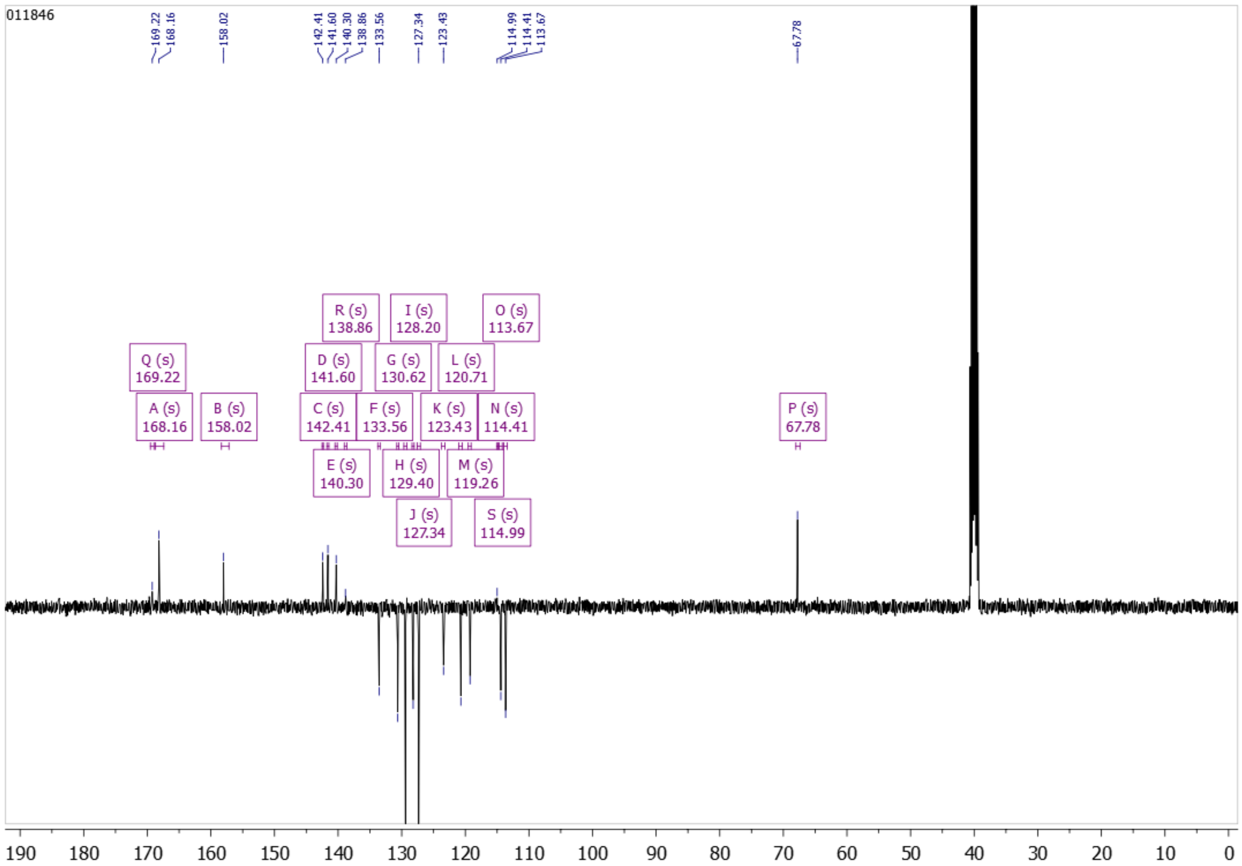
2-(2-([1,1'-Biphenyl]-2-yloxy)acetamido)-4-chlorobenzoic acid (**38**):



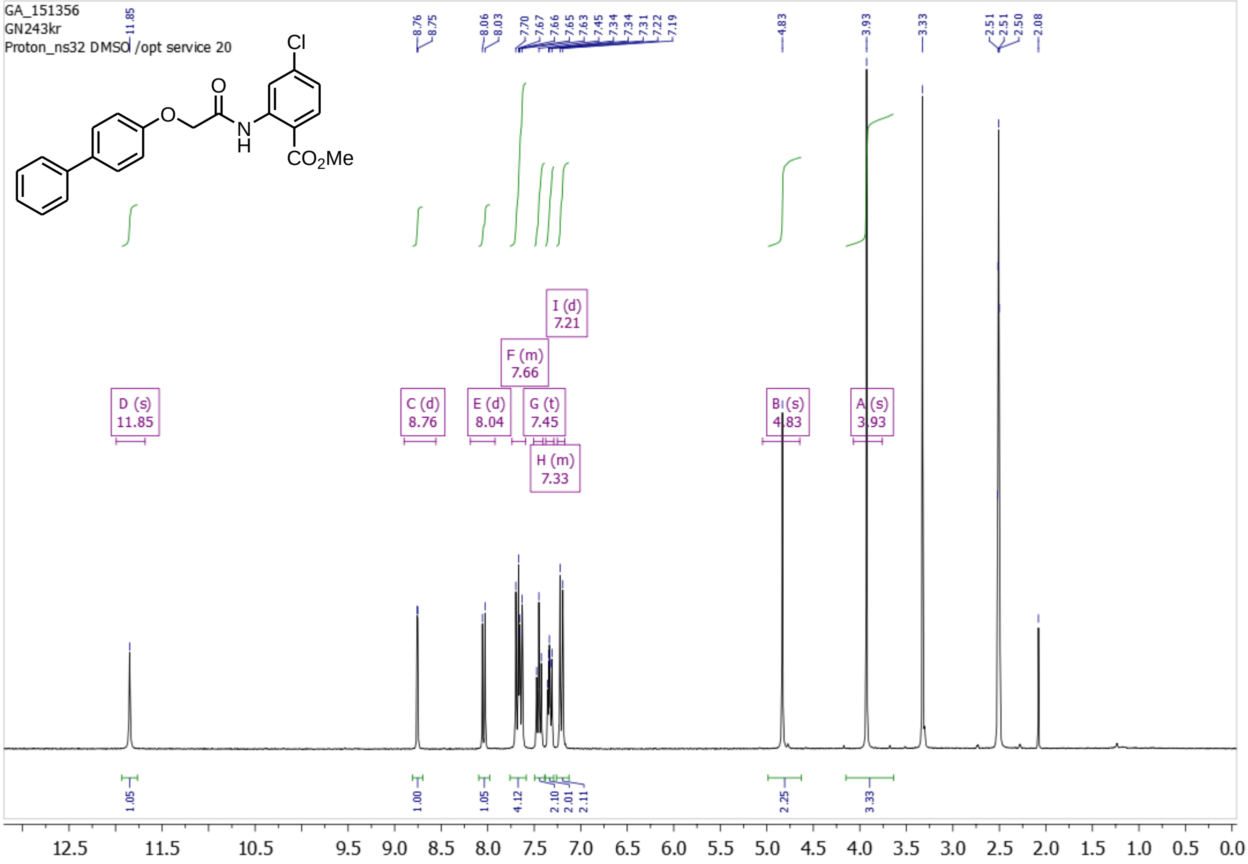


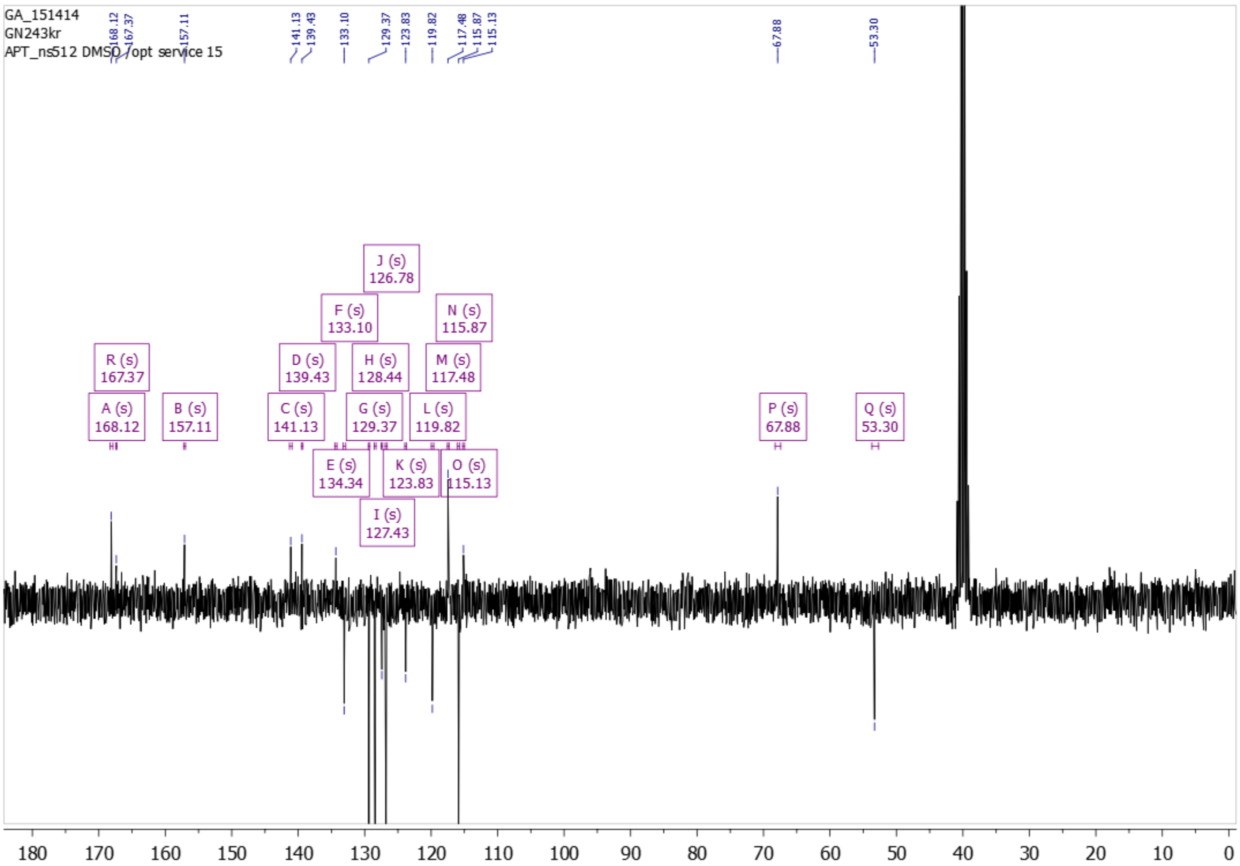
2-(2-([1,1'-Biphenyl]-3-yloxy)acetamido)-4-chlorobenzoic acid (16):



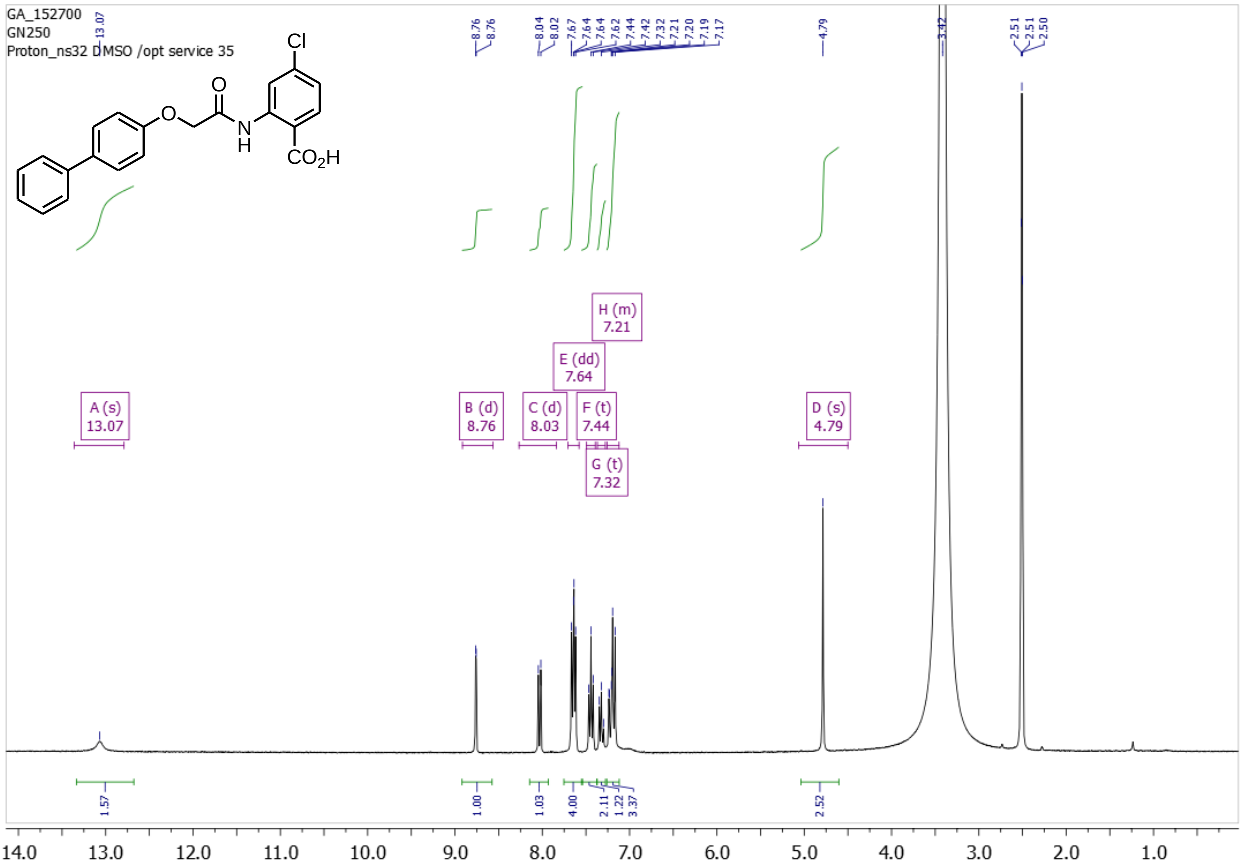


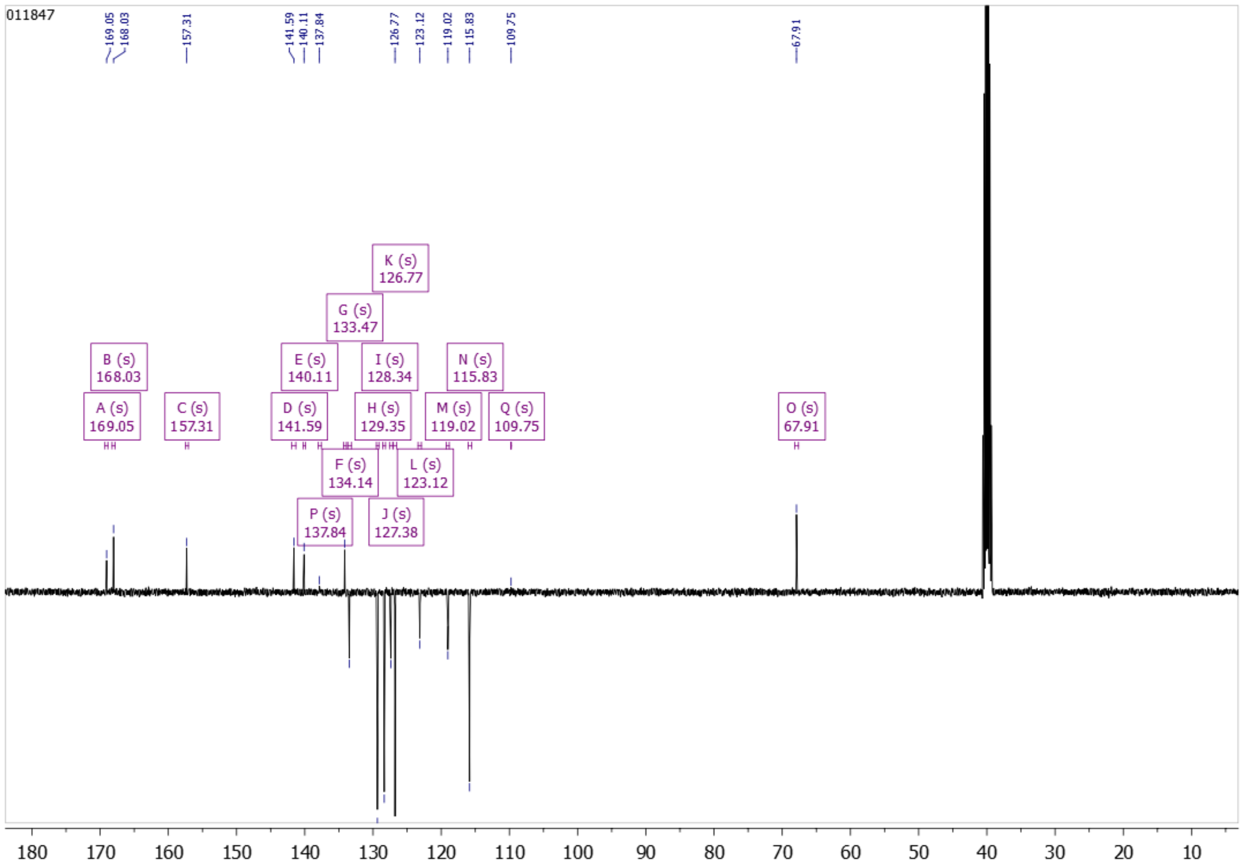
Methyl 2-(2-([1,1'-biphenyl]-4-yloxy)acetamido)-4-chlorobenzoate (**89**):



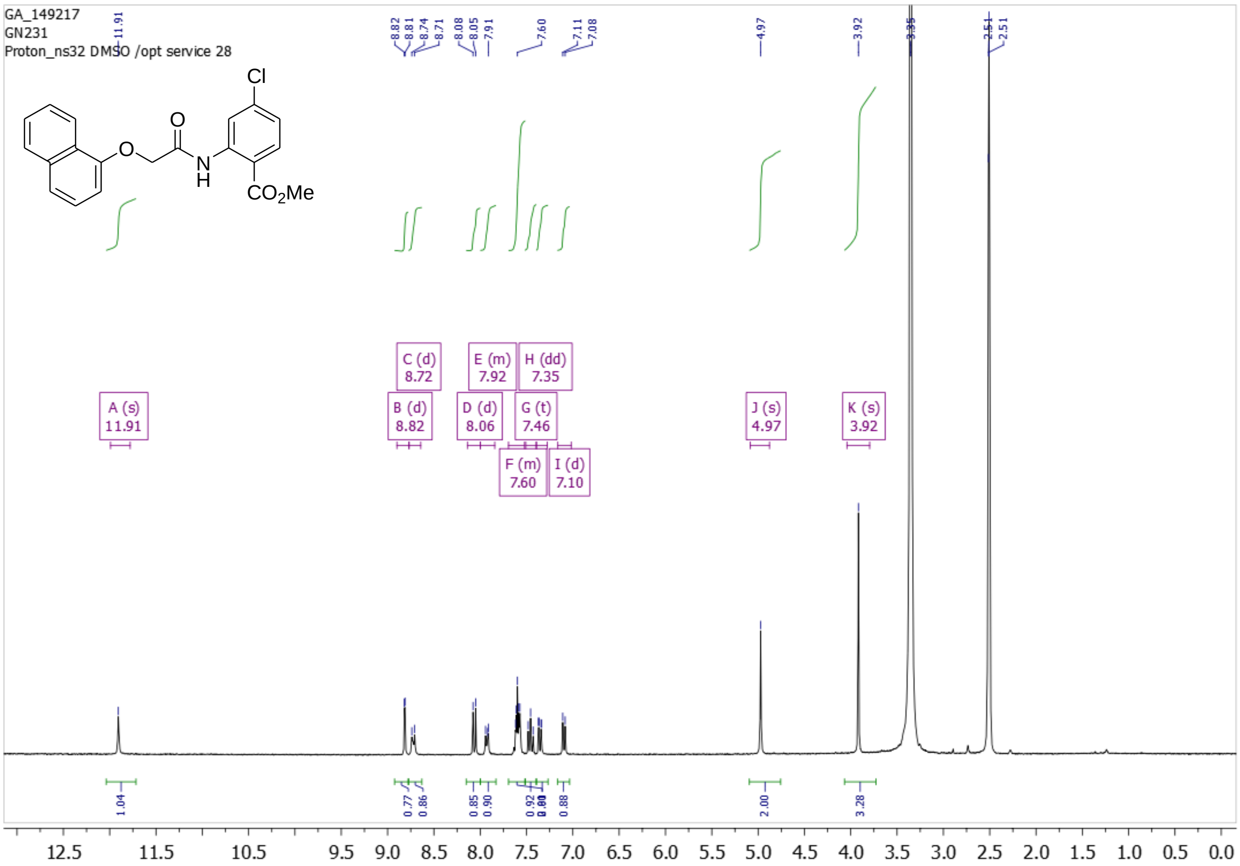


2-(2-([1,1'-Biphenyl]-4-yloxy)acetamido)-4-chlorobenzoic acid (39):

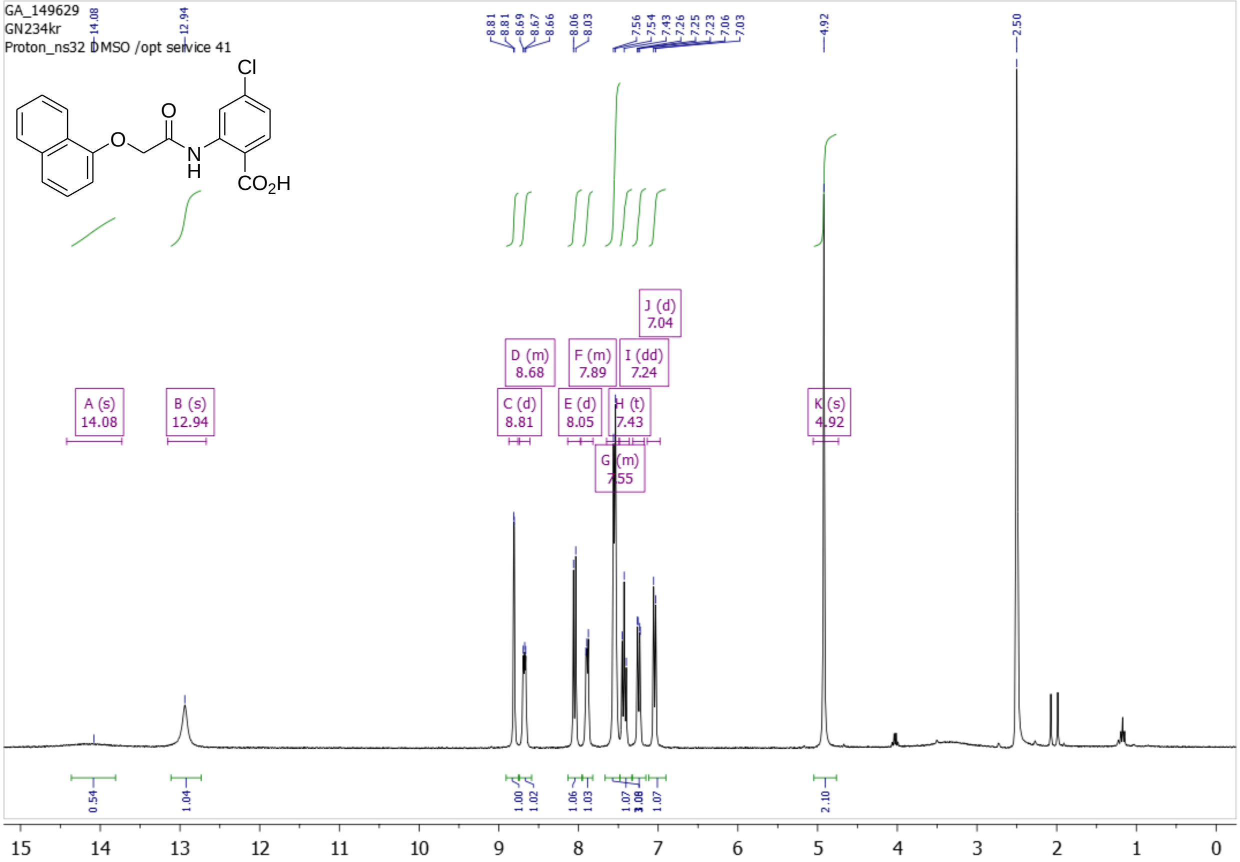


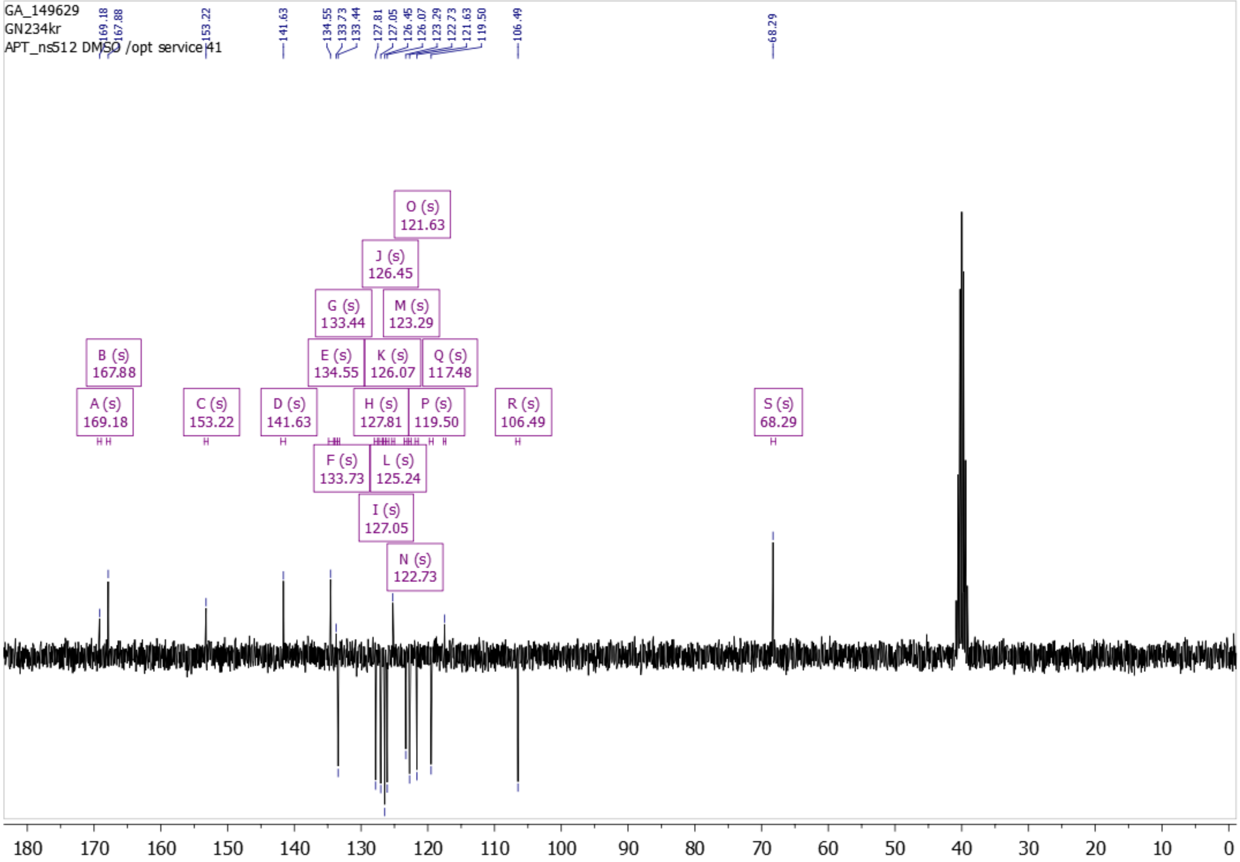


Methyl 4-chloro-2-(2-(naphthalen-1-yloxy)acetamido)benzoate (90):

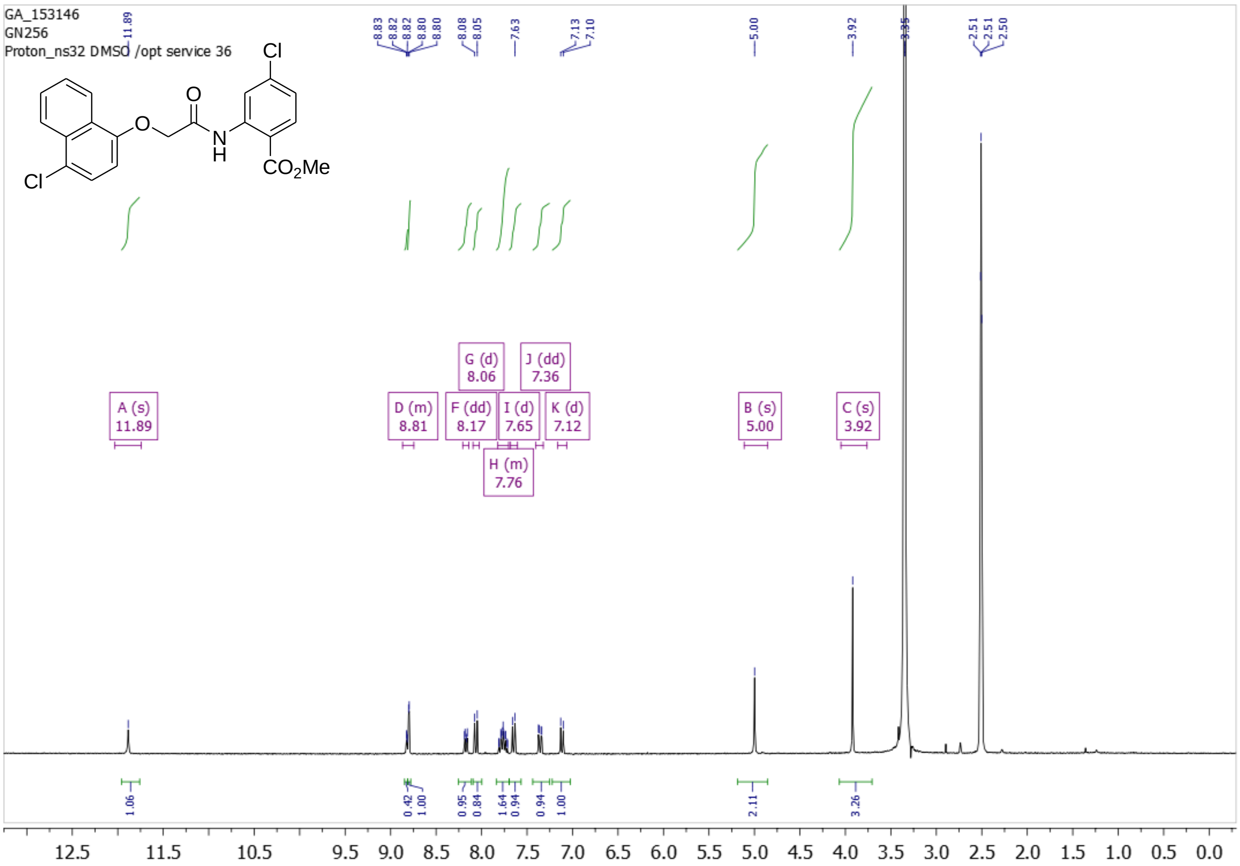


4-Chloro-2-(2-(naphthalen-1-yloxy)acetamido)benzoic acid (6):

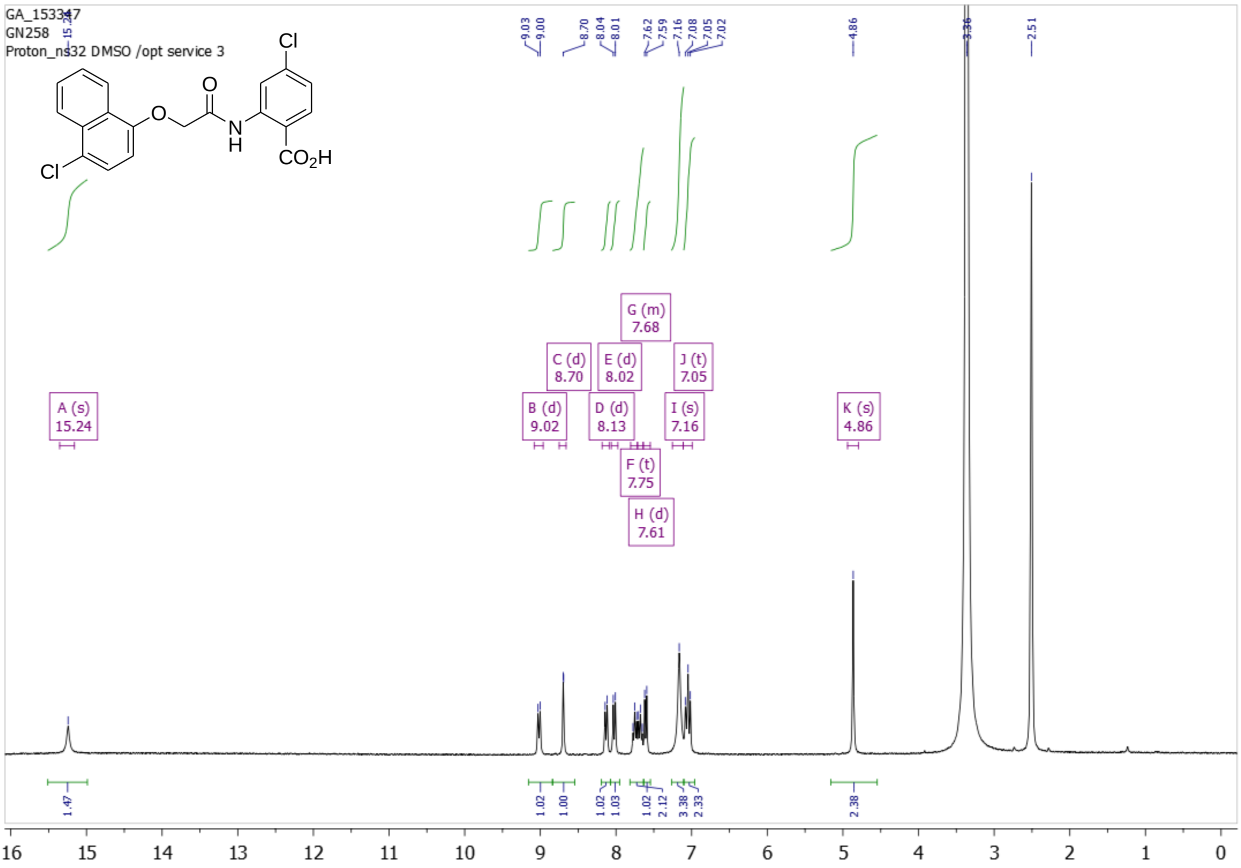


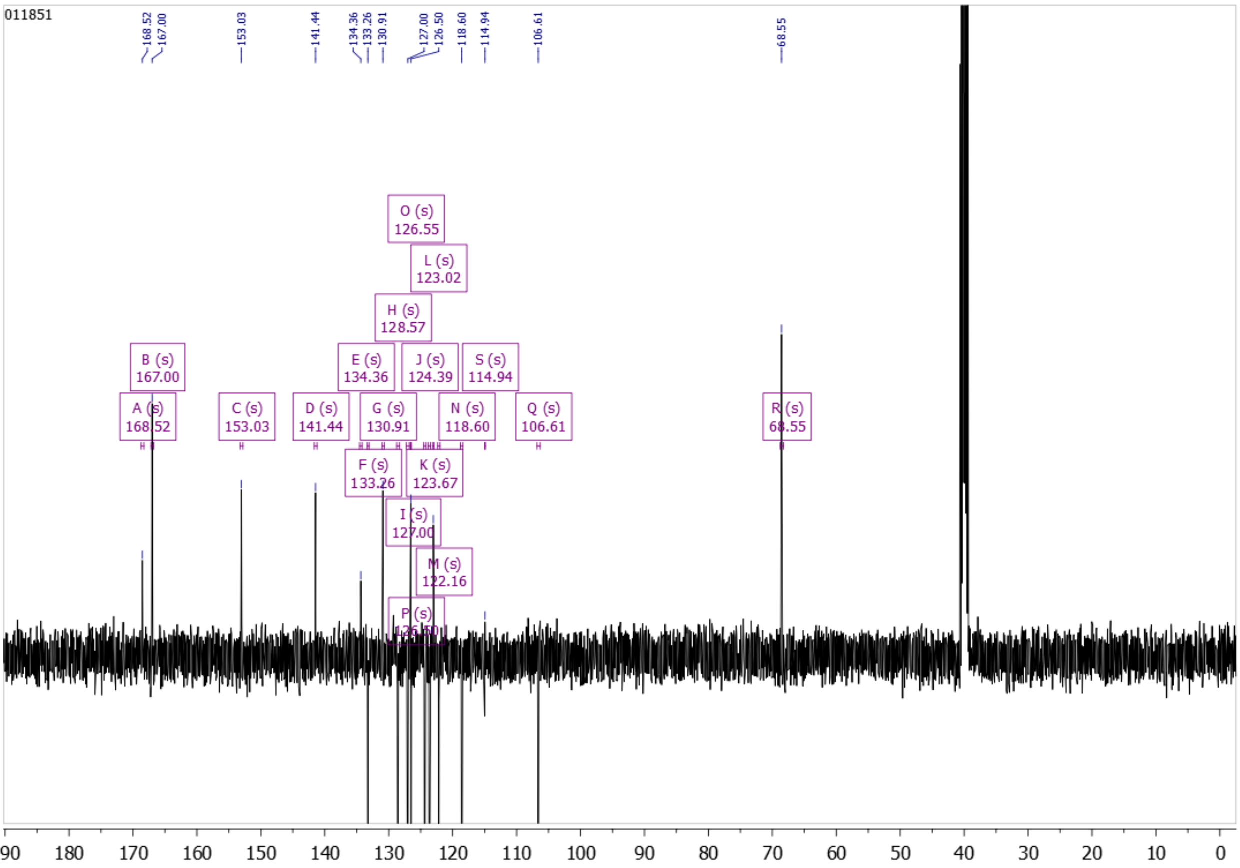


Methyl 4-chloro-2-(2-((4-chloronaphthalen-1-yl)oxy)acetamido)benzoate (91):

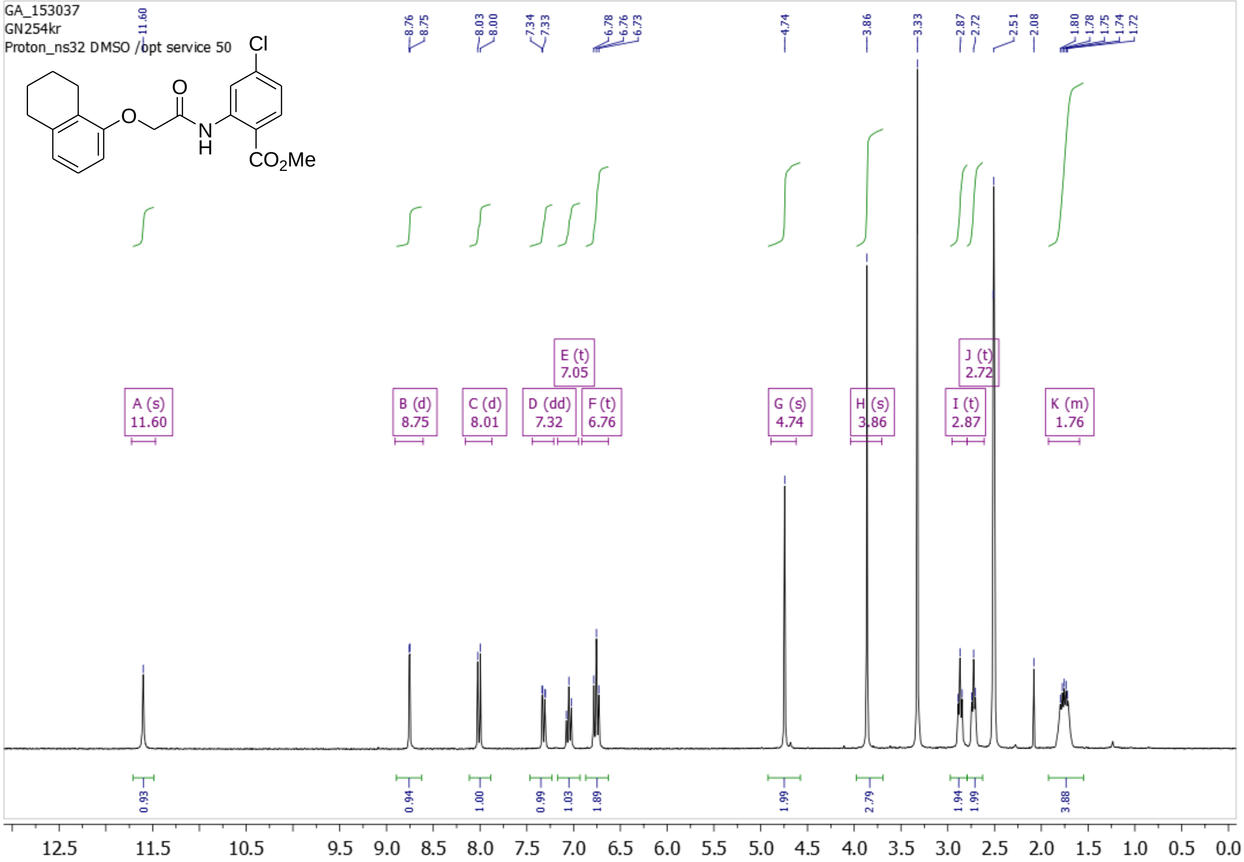


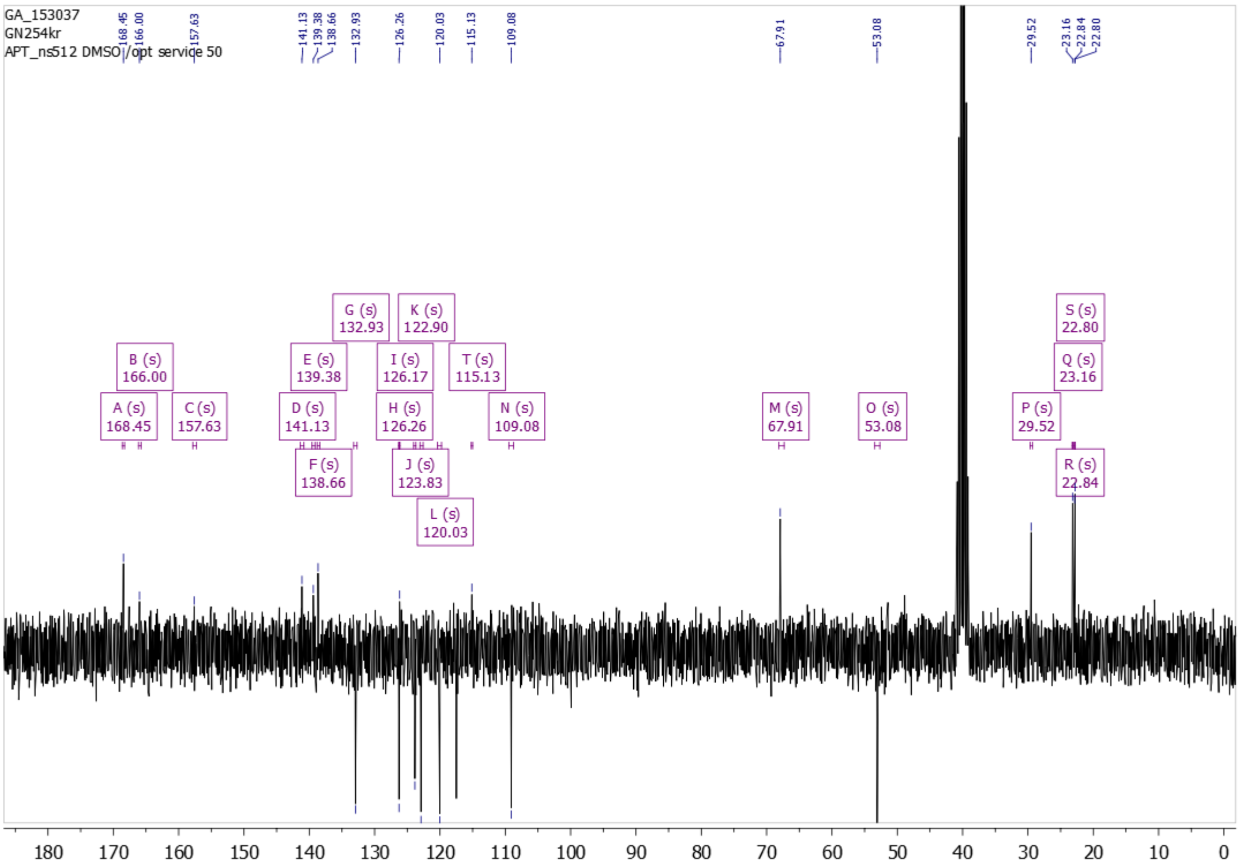
4-Chloro-2-(2-((4-chloronaphthalen-1-yl)oxy)acetamido)benzoic acid (7):



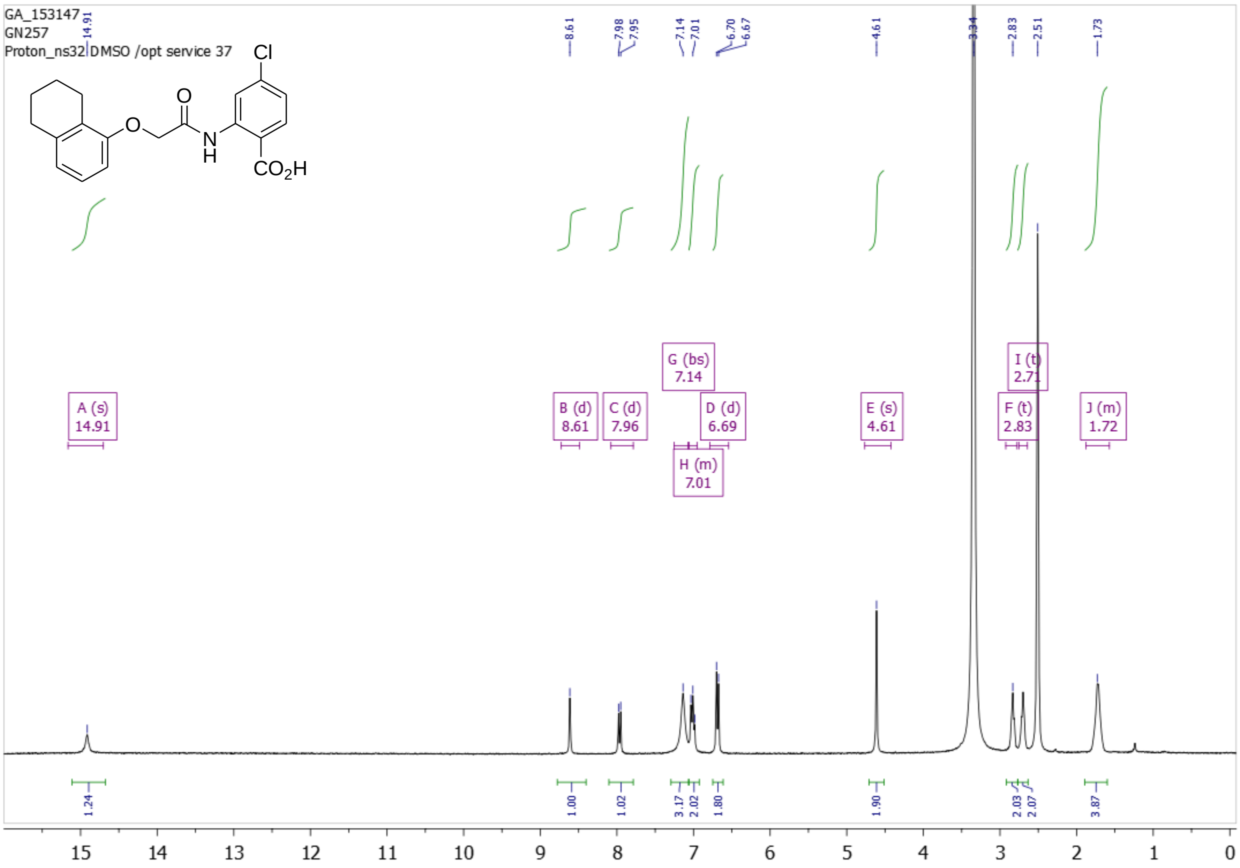


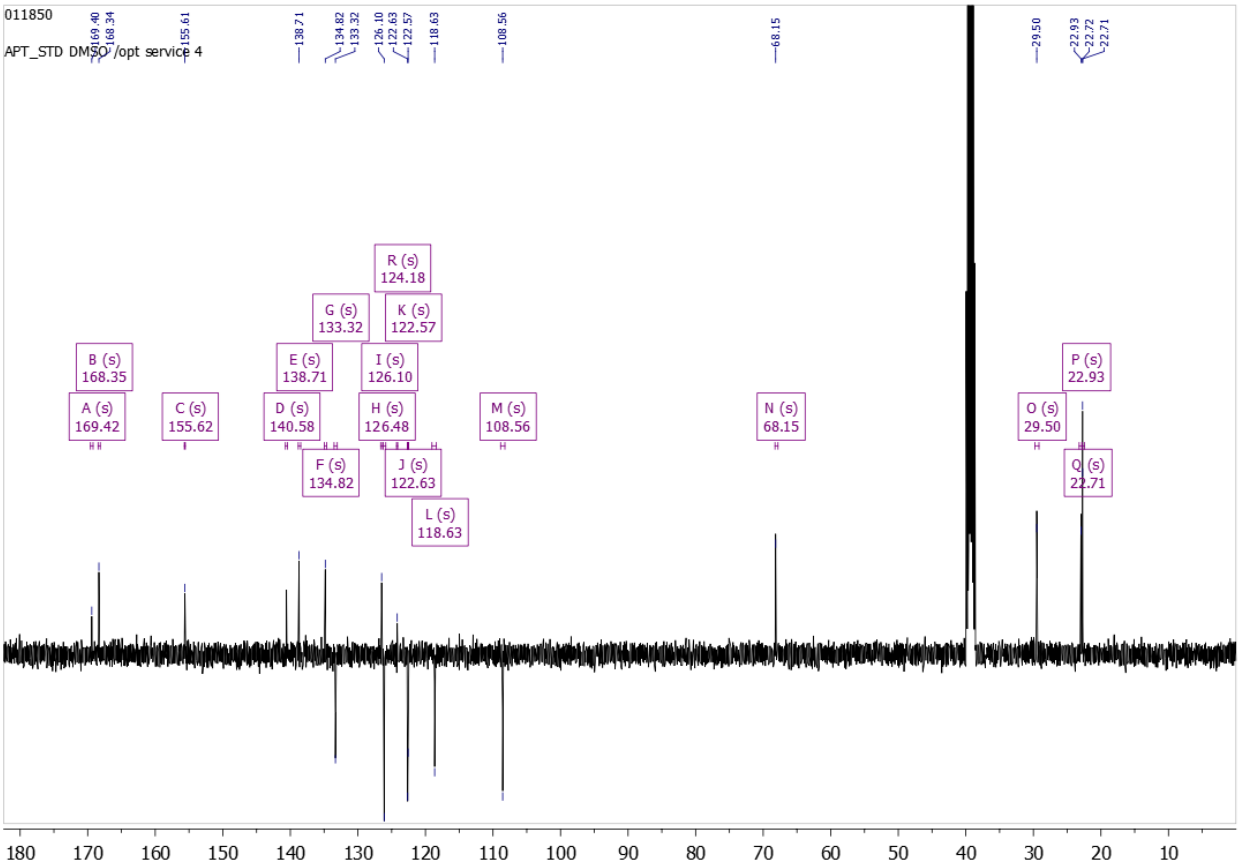
Methyl 4-chloro-2-(2-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)acetamido)benzoate (92):



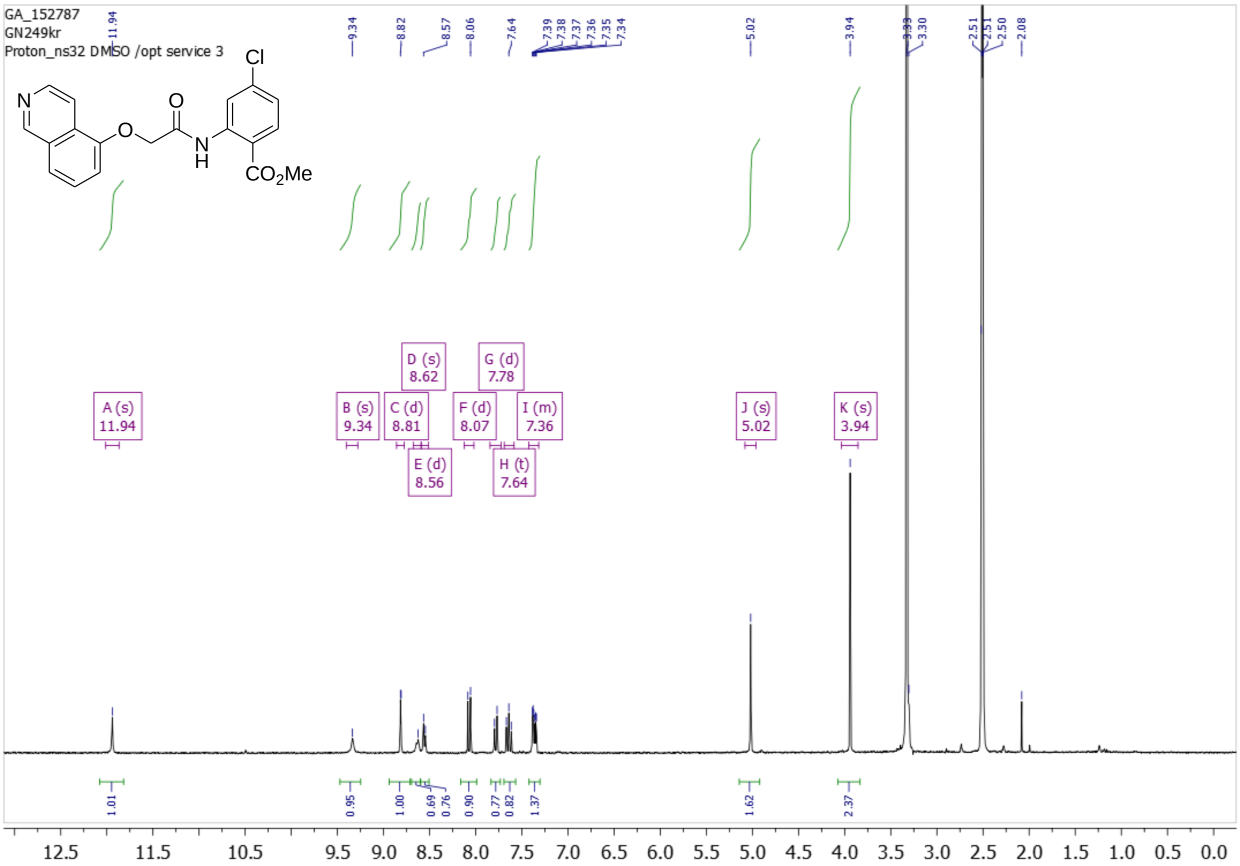


4-Chloro-2-(2-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)acetamido)benzoic acid (10):

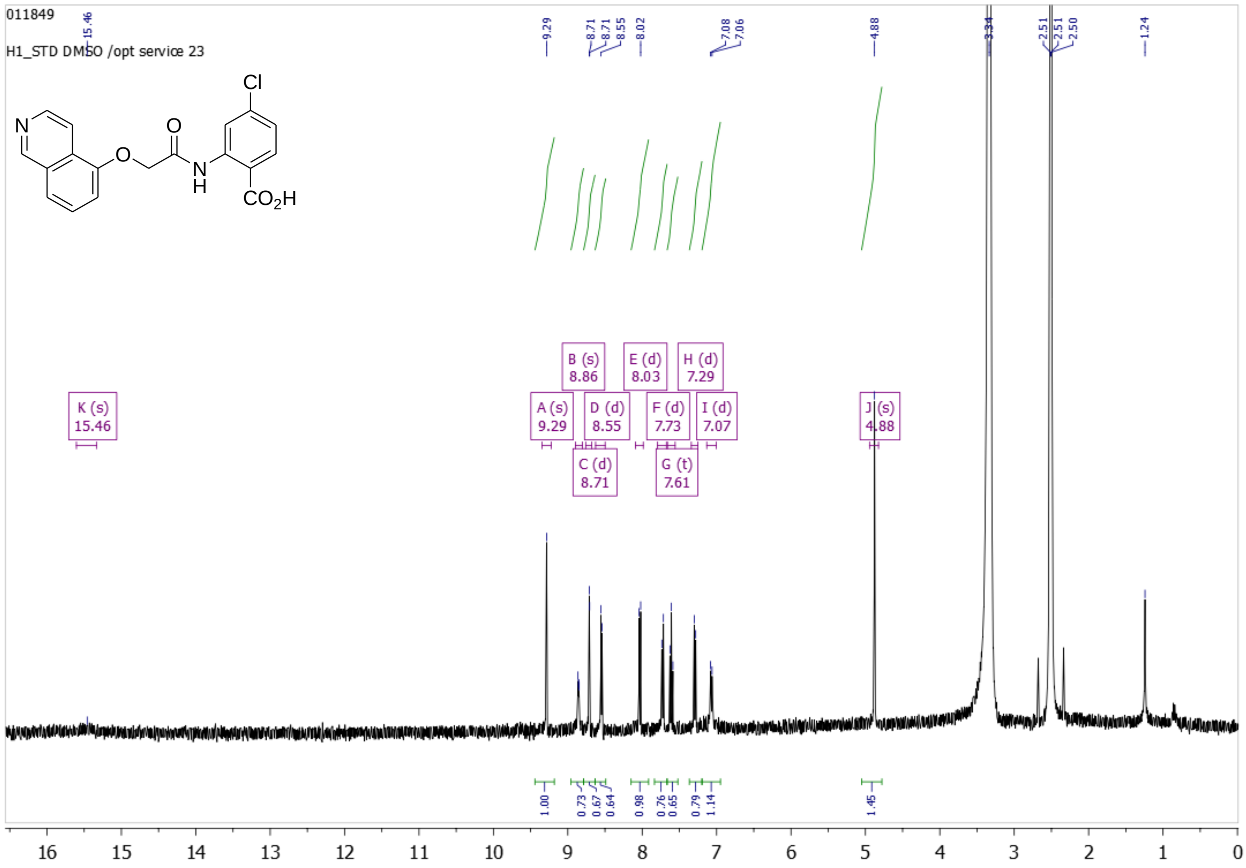




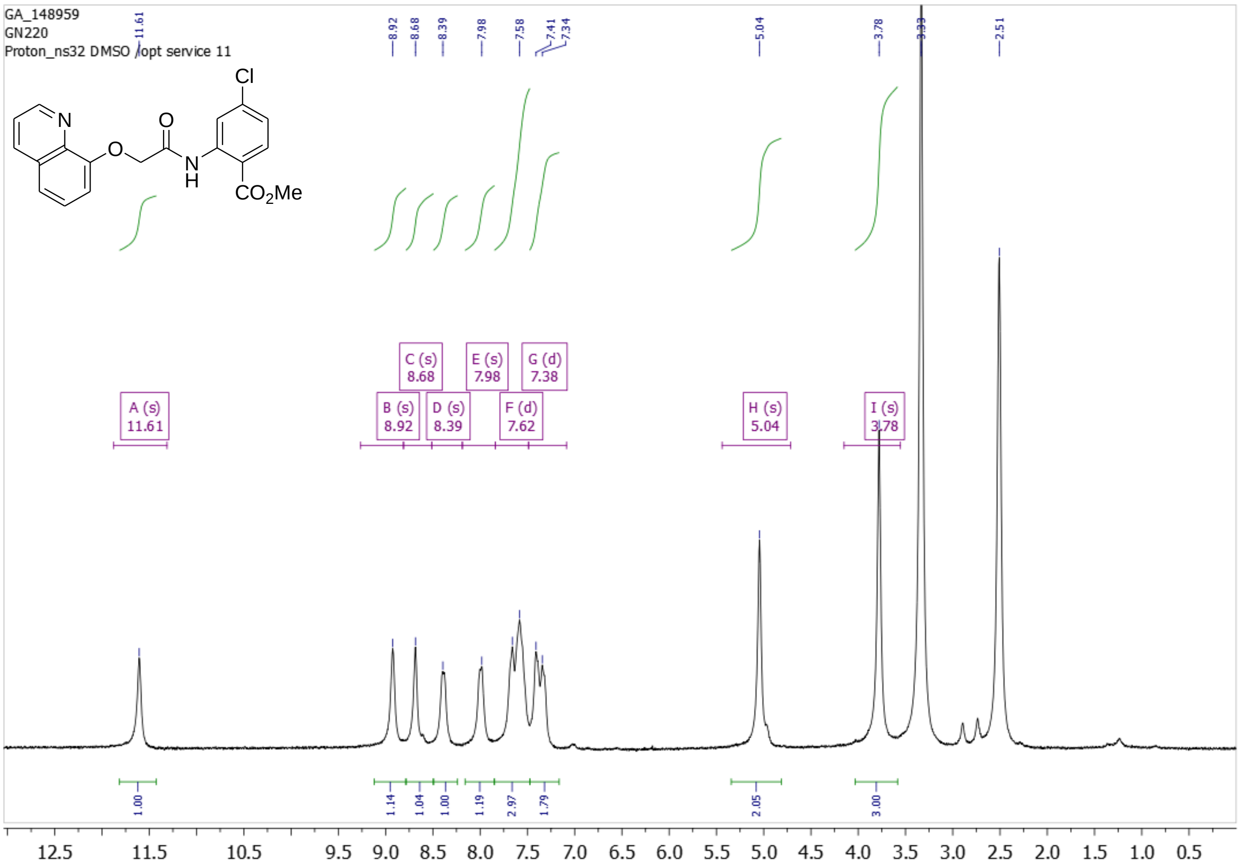
Methyl 4-chloro-2-(2-(isoquinolin-5-yloxy)acetamido)benzoate (93):

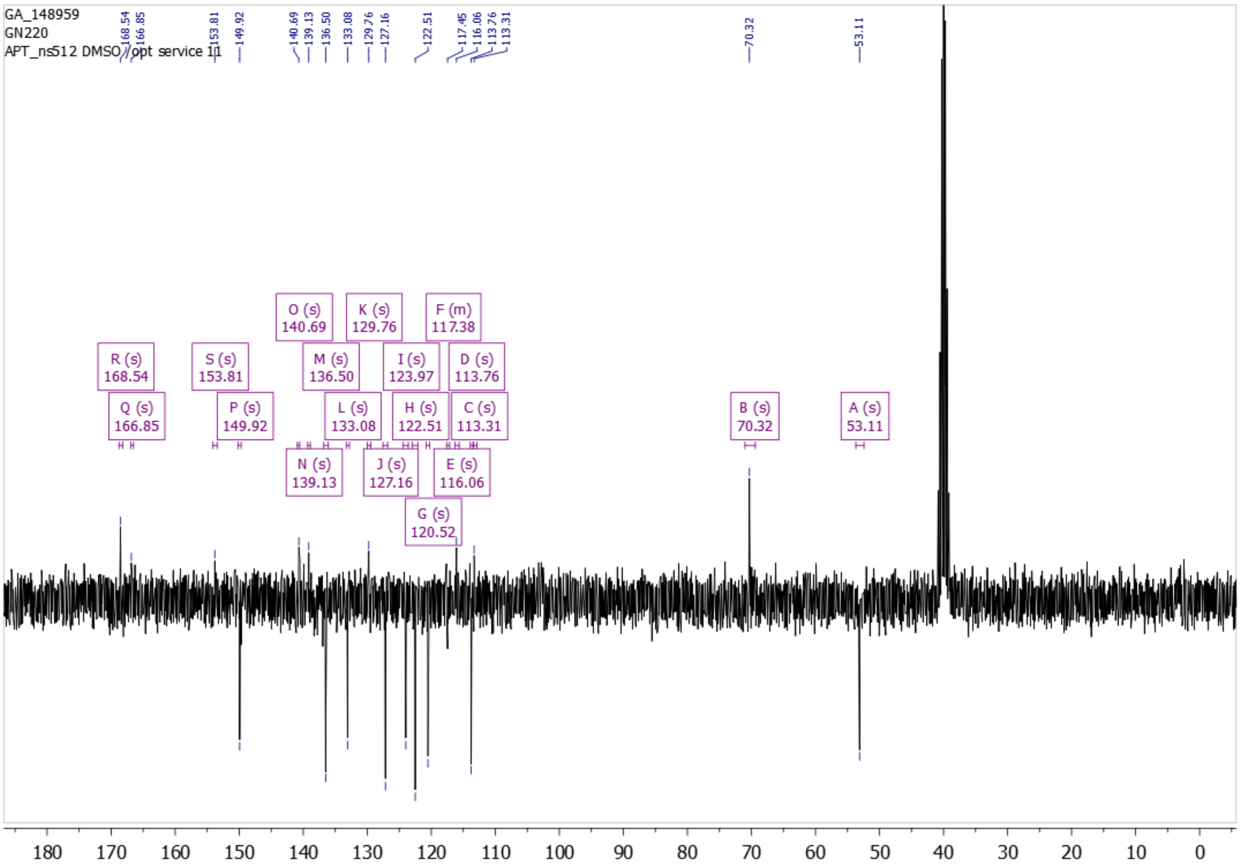


4-Chloro-2-(2-(isoquinolin-5-yloxy)acetamido)benzoic acid (**40**):

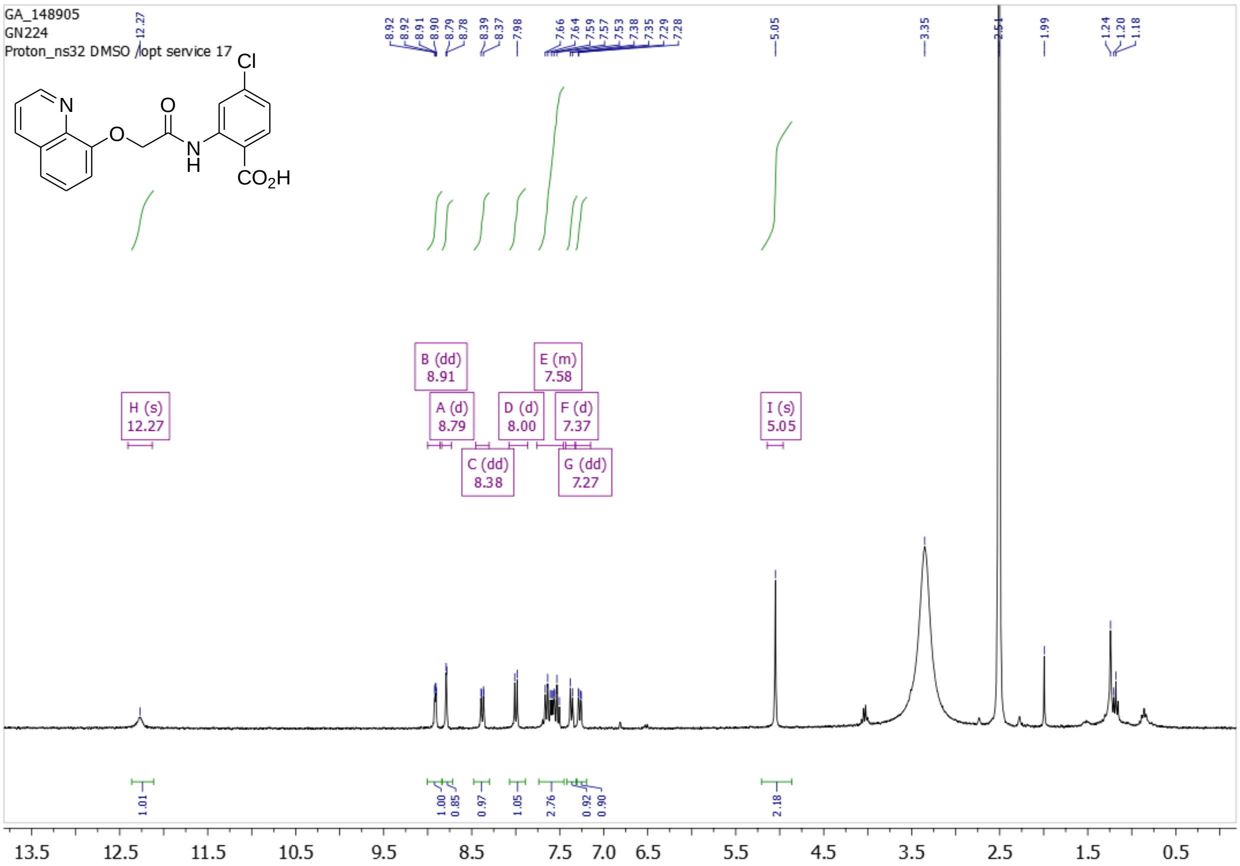


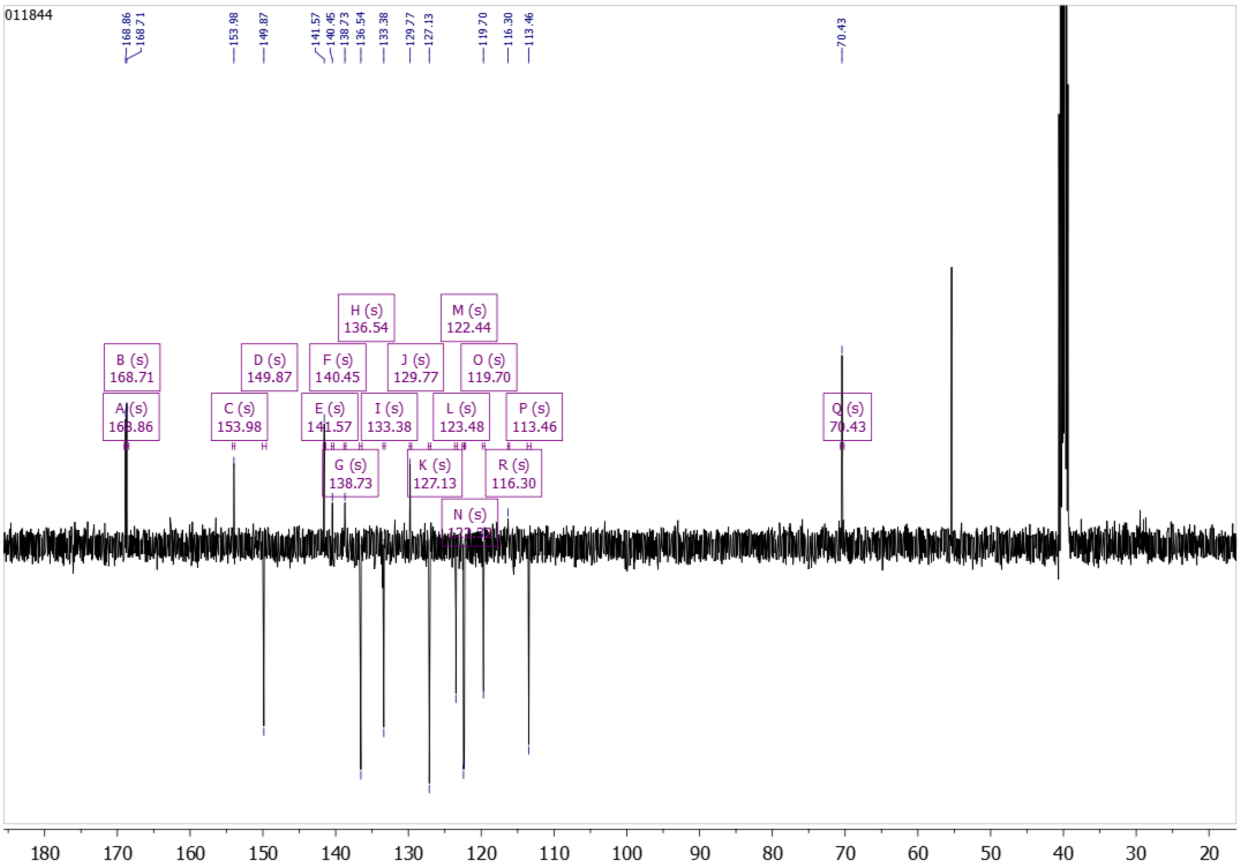
Methyl 4-chloro-2-(2-(quinolin-8-yloxy)acetamido)benzoate (94):



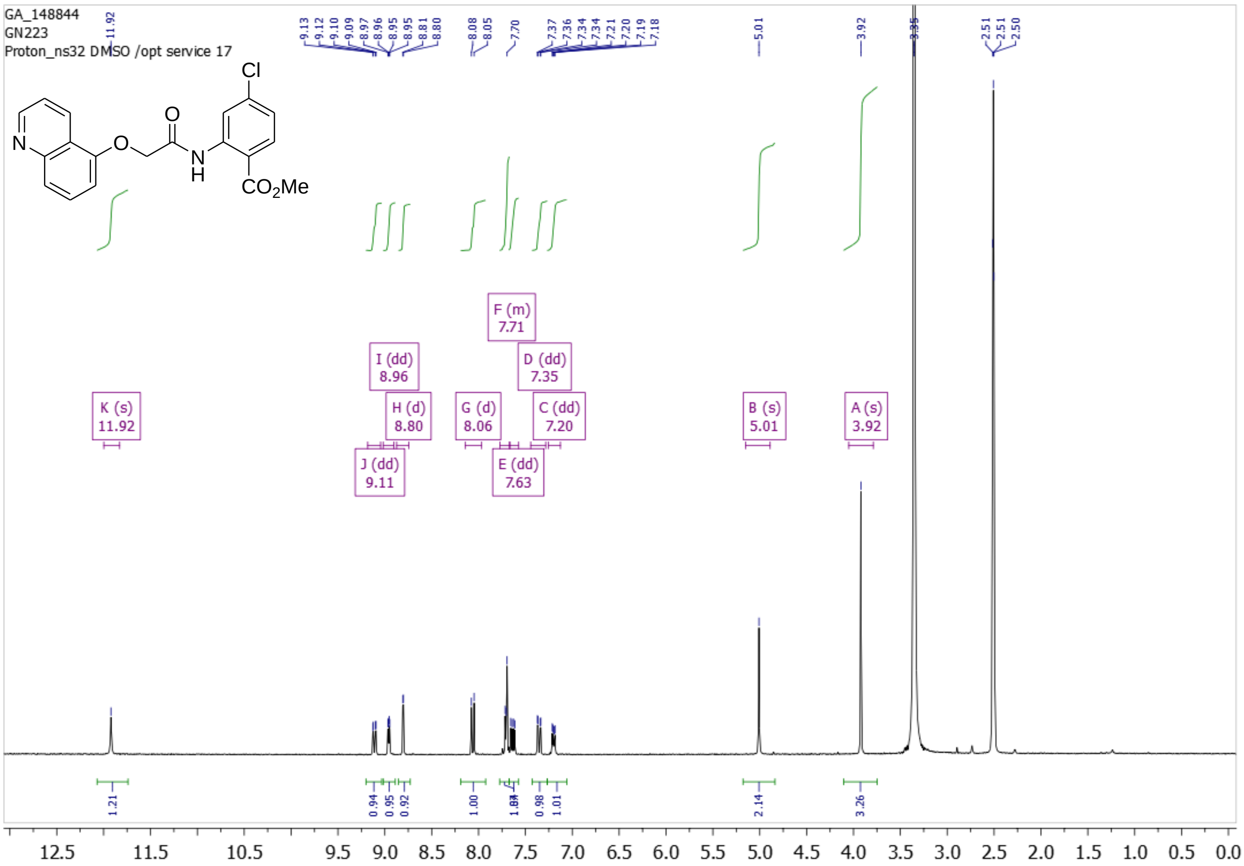


4-Chloro-2-(2-(quinolin-8-yloxy)acetamido)benzoic acid (**41**):

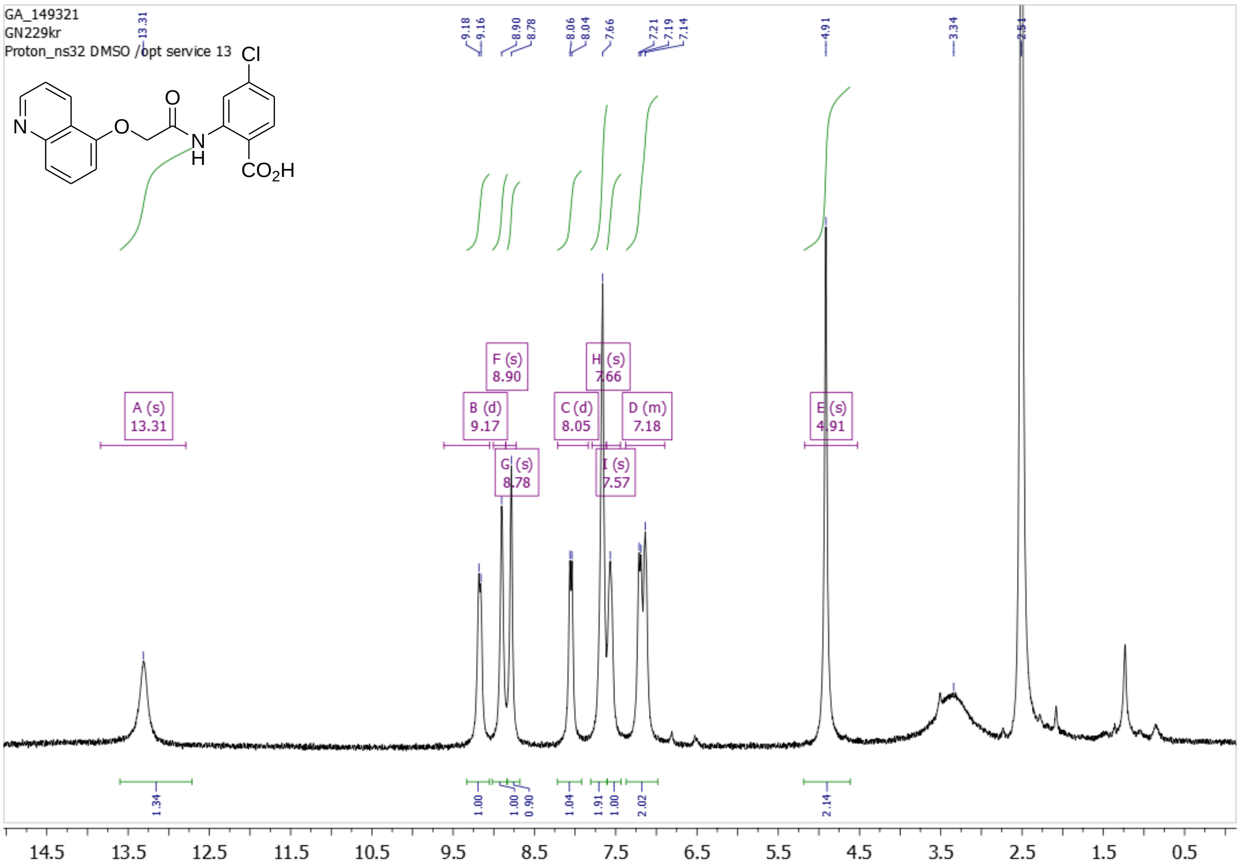


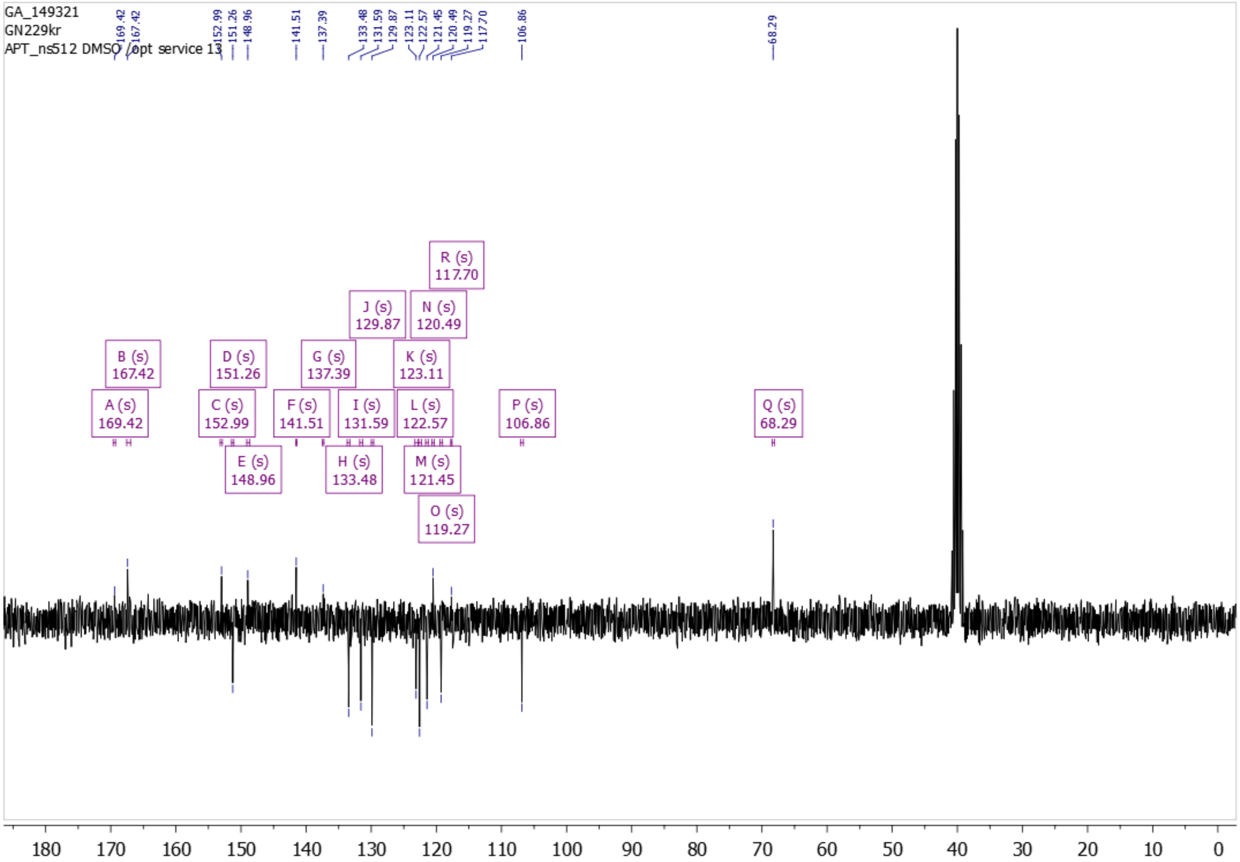


Methyl 4-chloro-2-(2-(quinolin-5-yloxy)acetamido)benzoate (**95**):

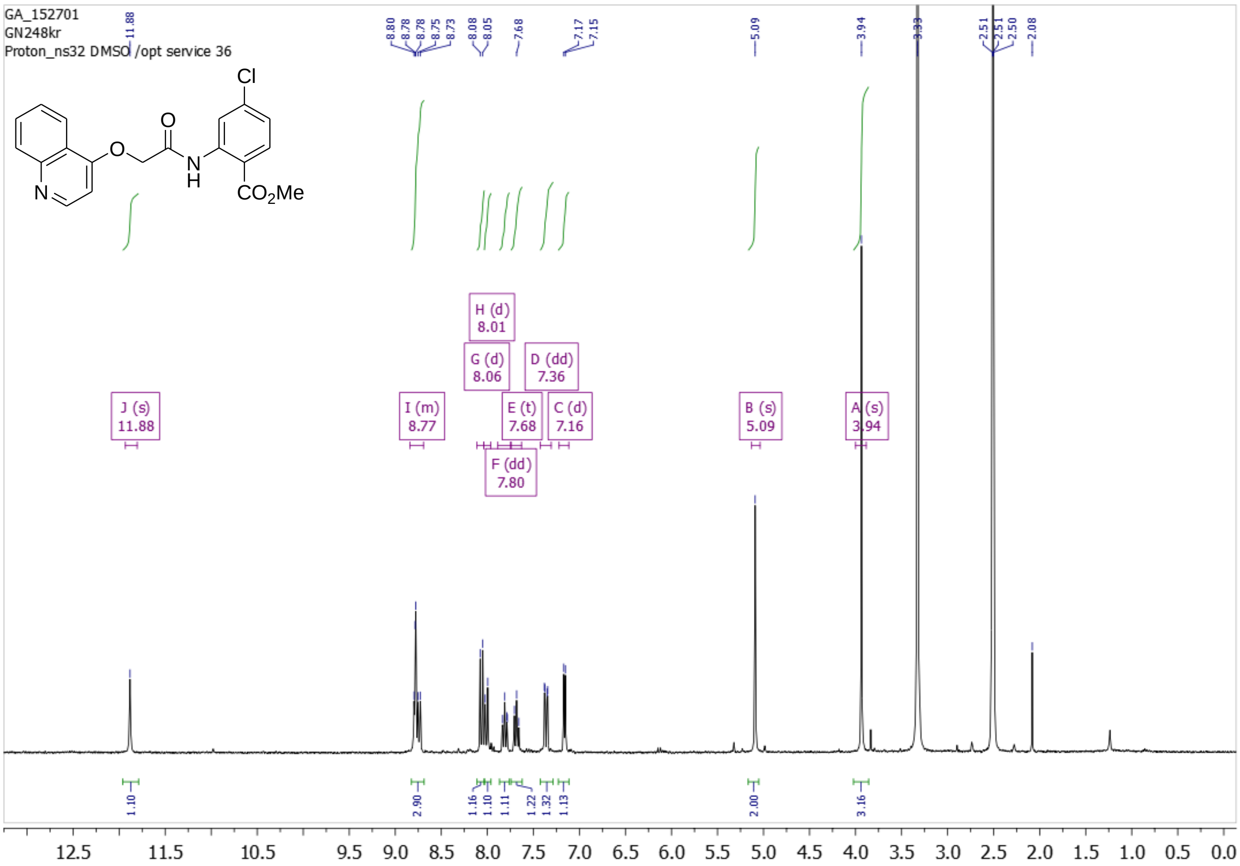


4-Chloro-2-(2-(quinolin-5-yloxy)acetamido)benzoic acid (42):

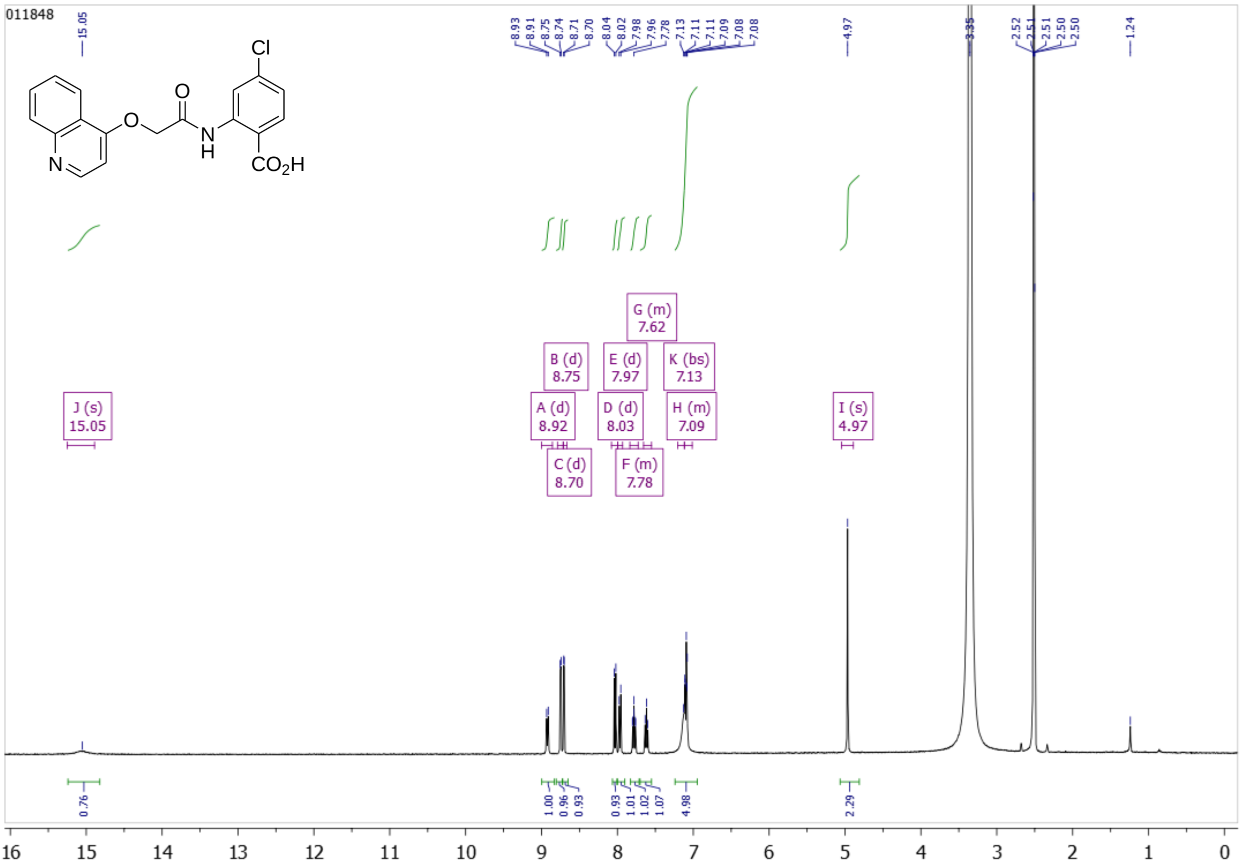


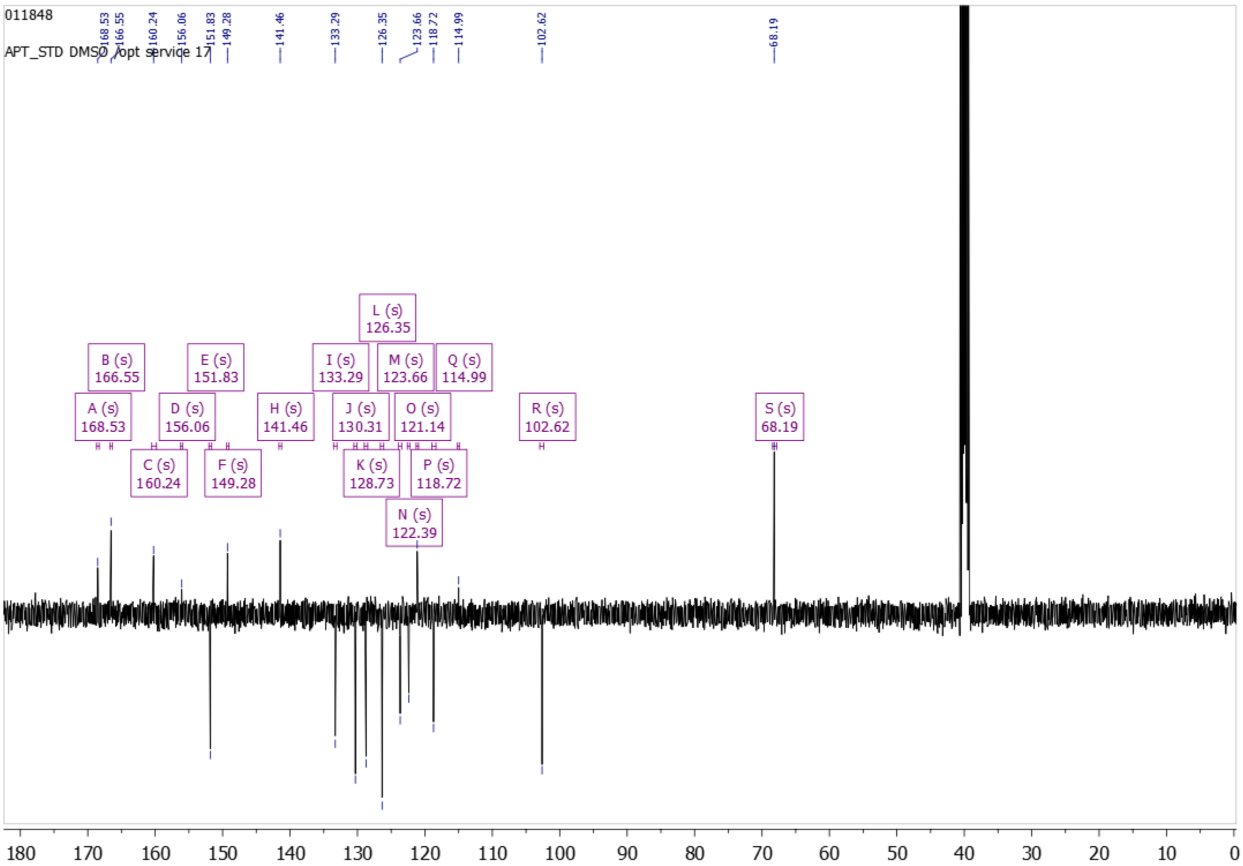


Methyl 4-chloro-2-(2-(quinolin-4-yloxy)acetamido)benzoate (**96**):

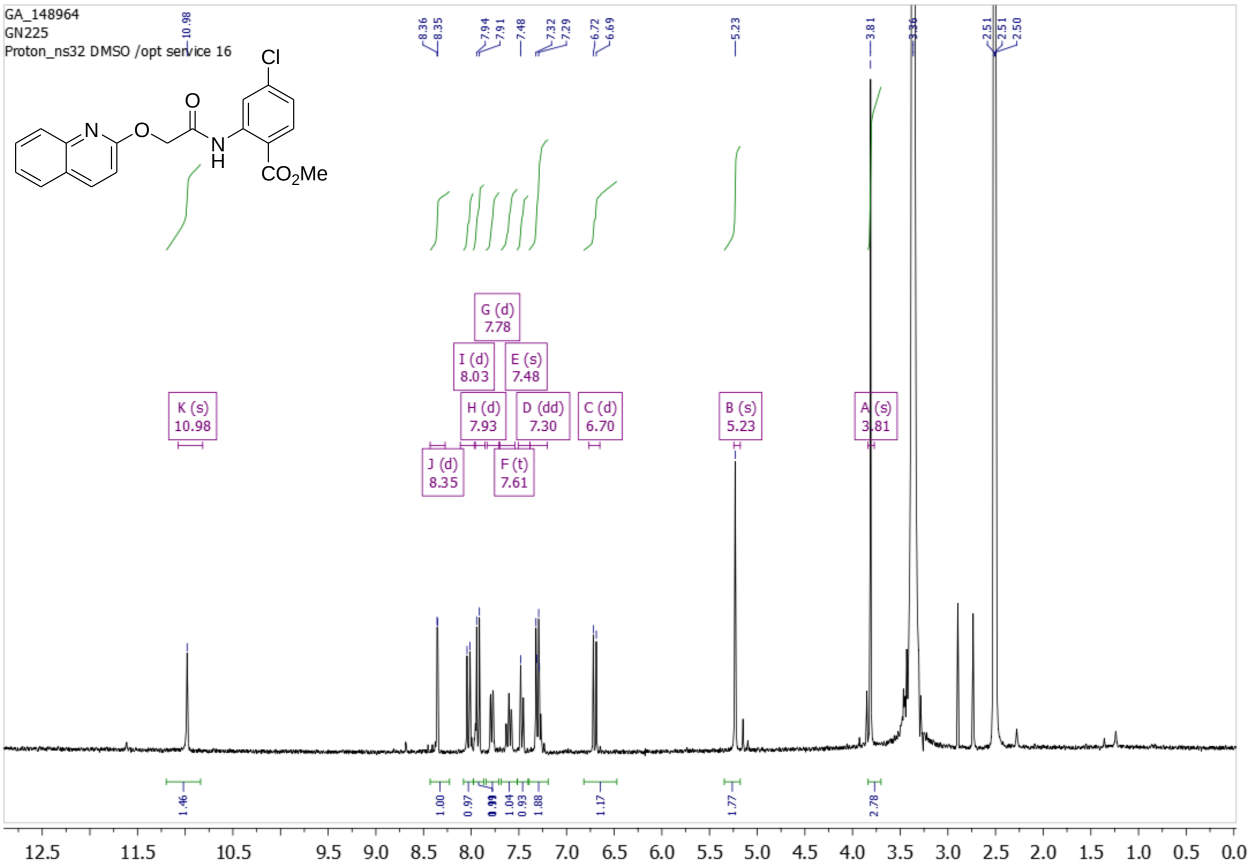


4-Chloro-2-(2-(quinolin-4-yloxy)acetamido)benzoic acid (43):

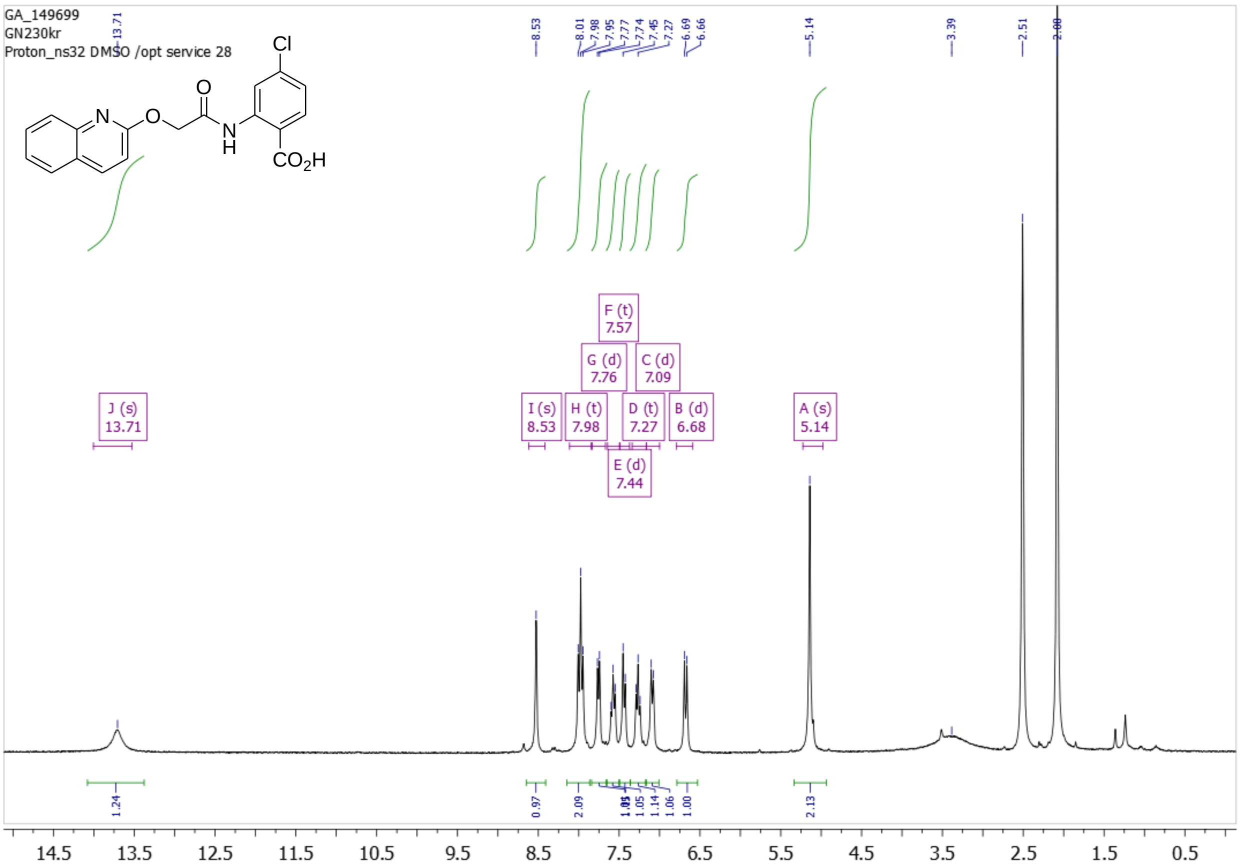


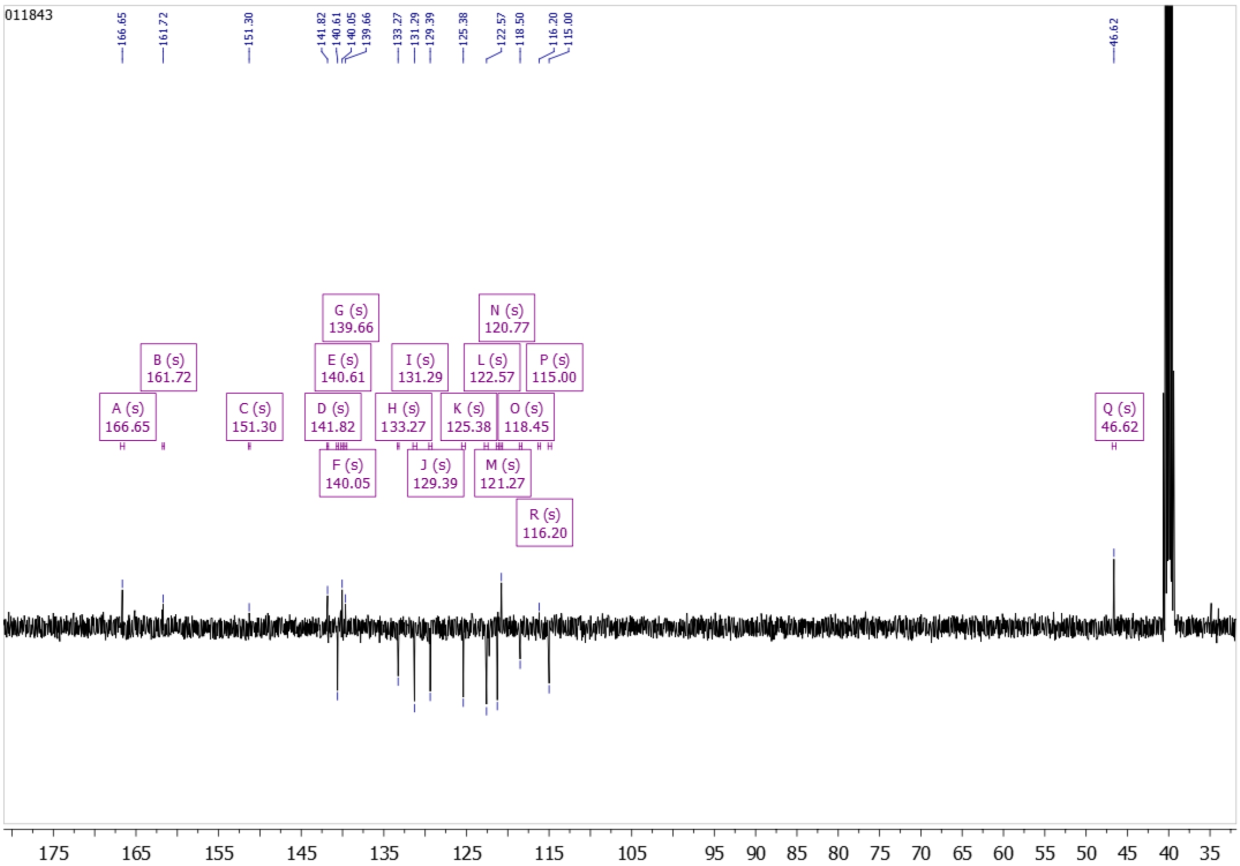


Methyl 4-chloro-2-(2-(quinolin-2-yloxy)acetamido)benzoate (97):

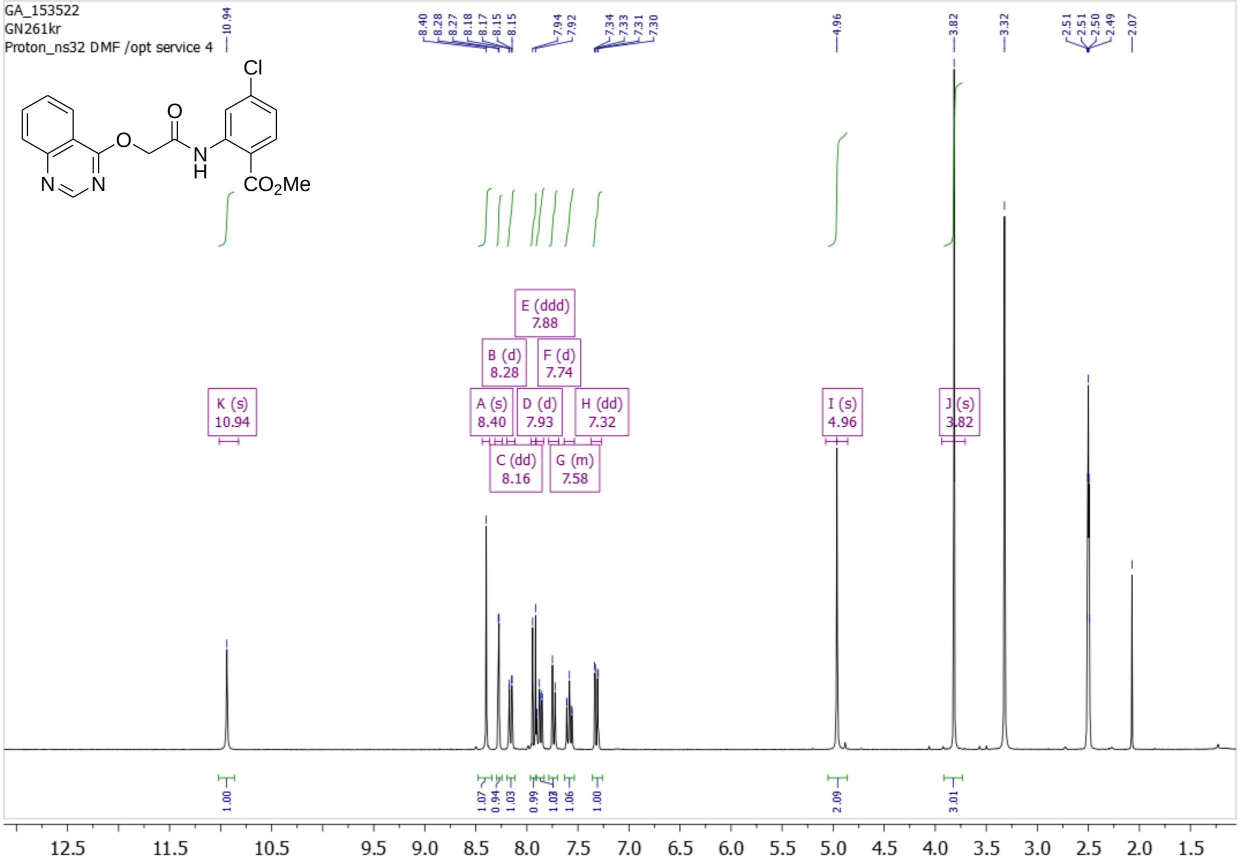


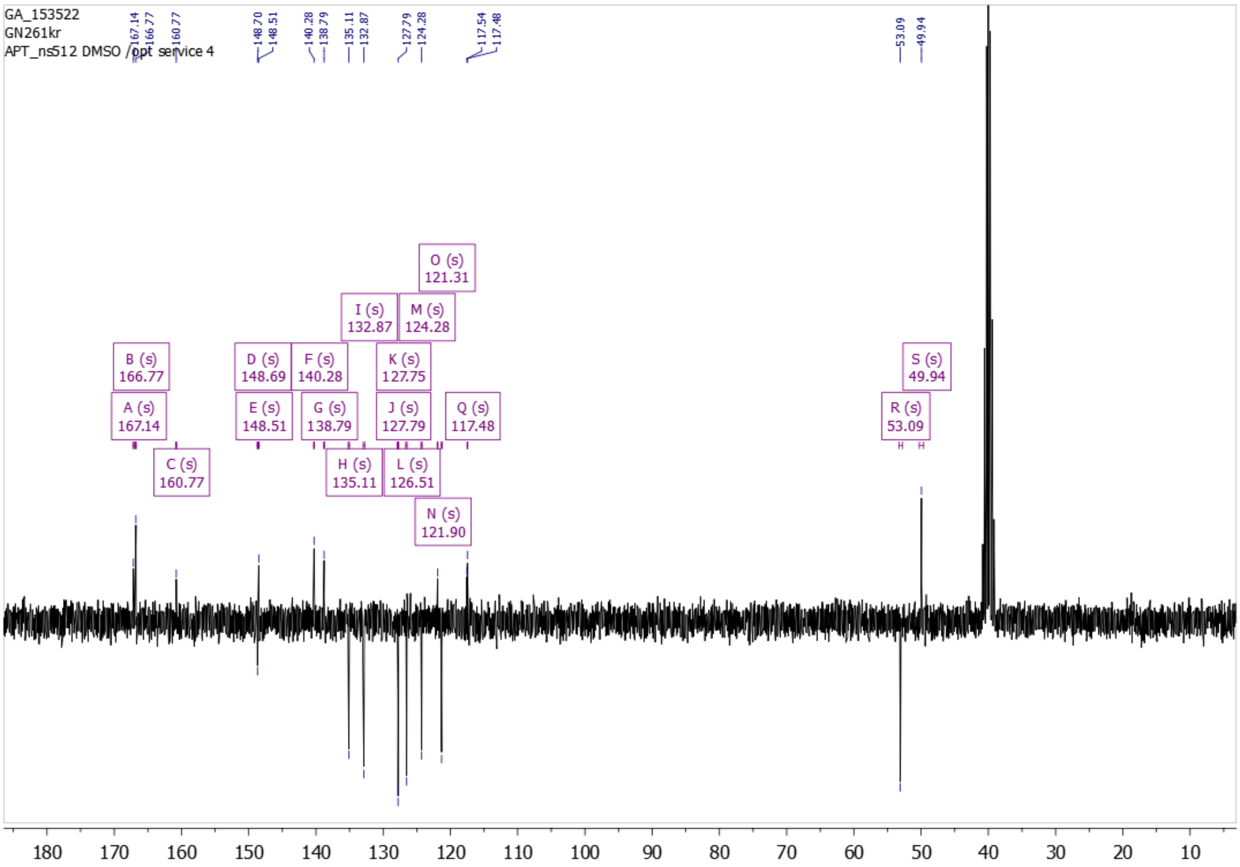
4-Chloro-2-(2-(quinolin-2-yloxy)acetamido)benzoic acid (44):



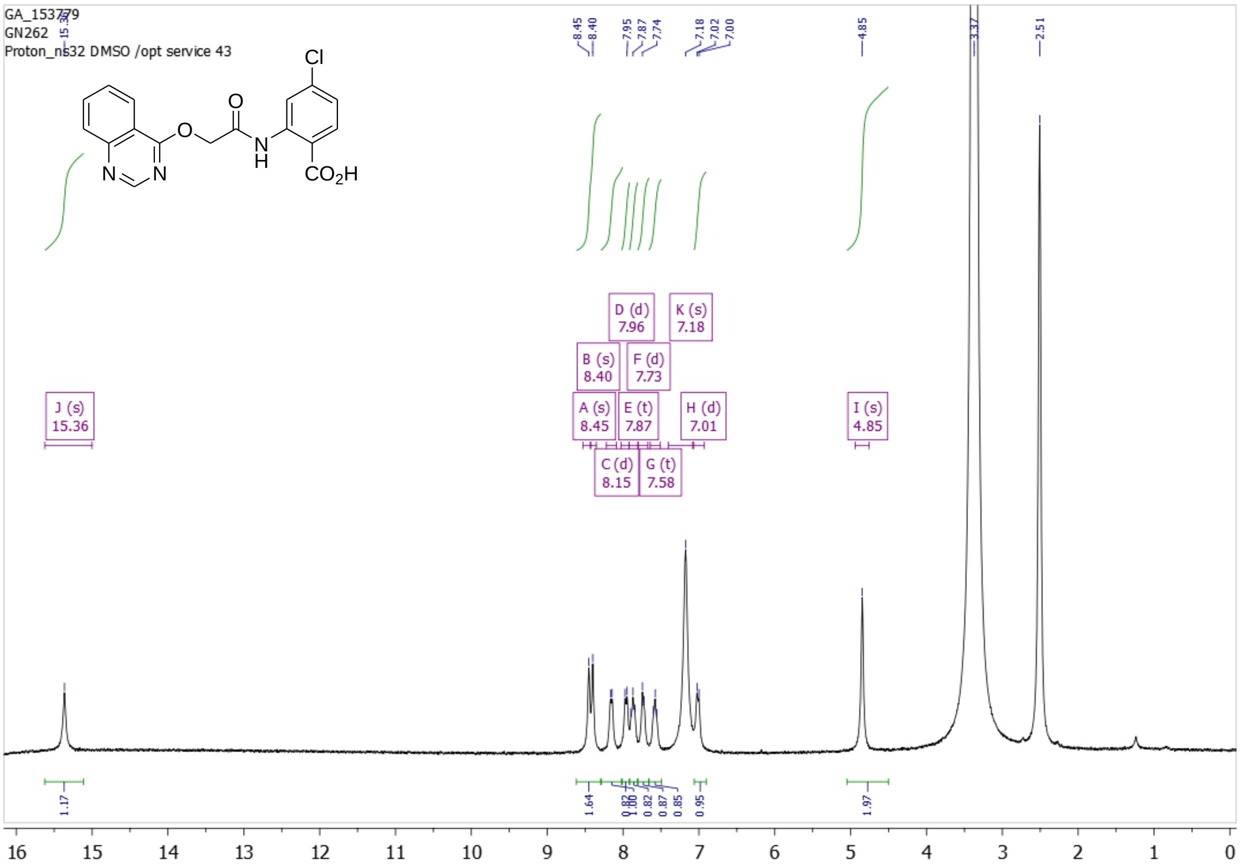


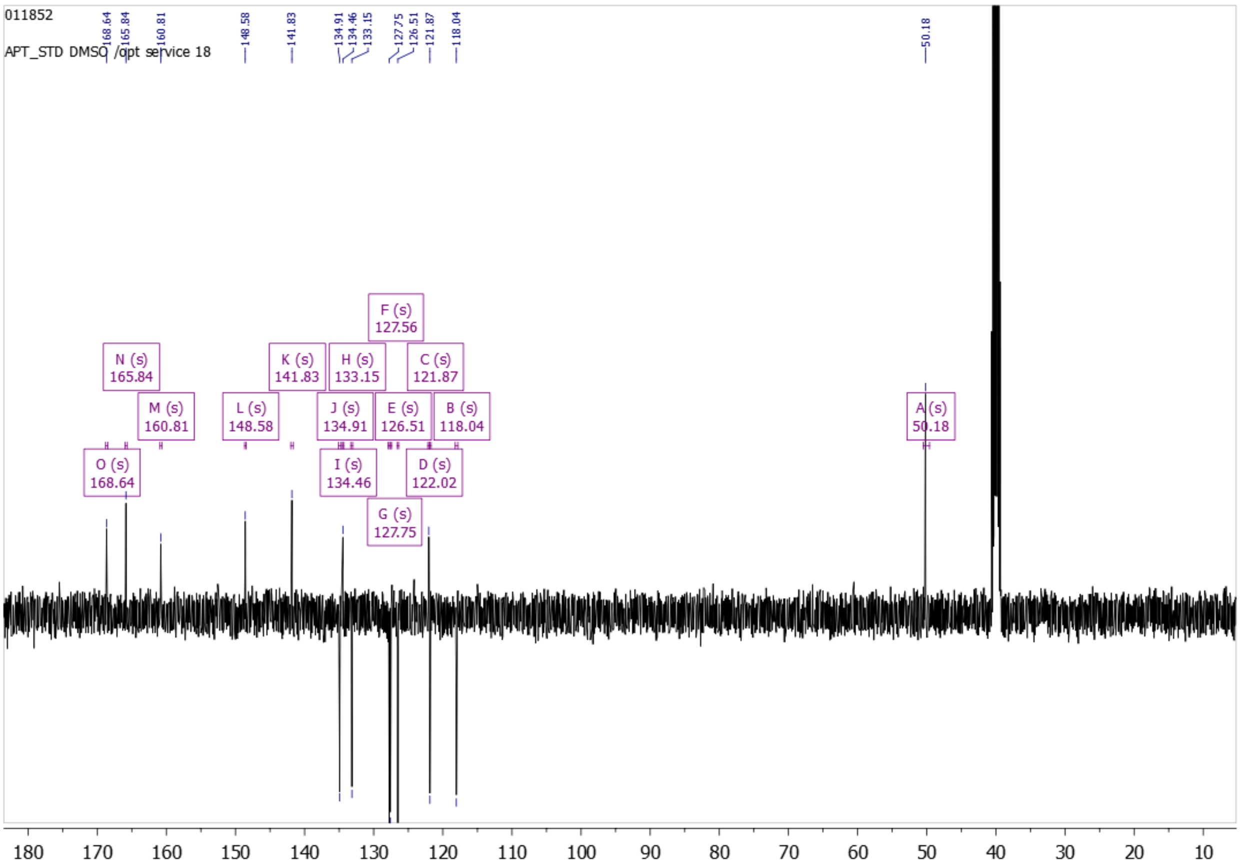
Methyl 4-chloro-2-(2-(quinazolin-4-yloxy)acetamido)benzoate (**98**):



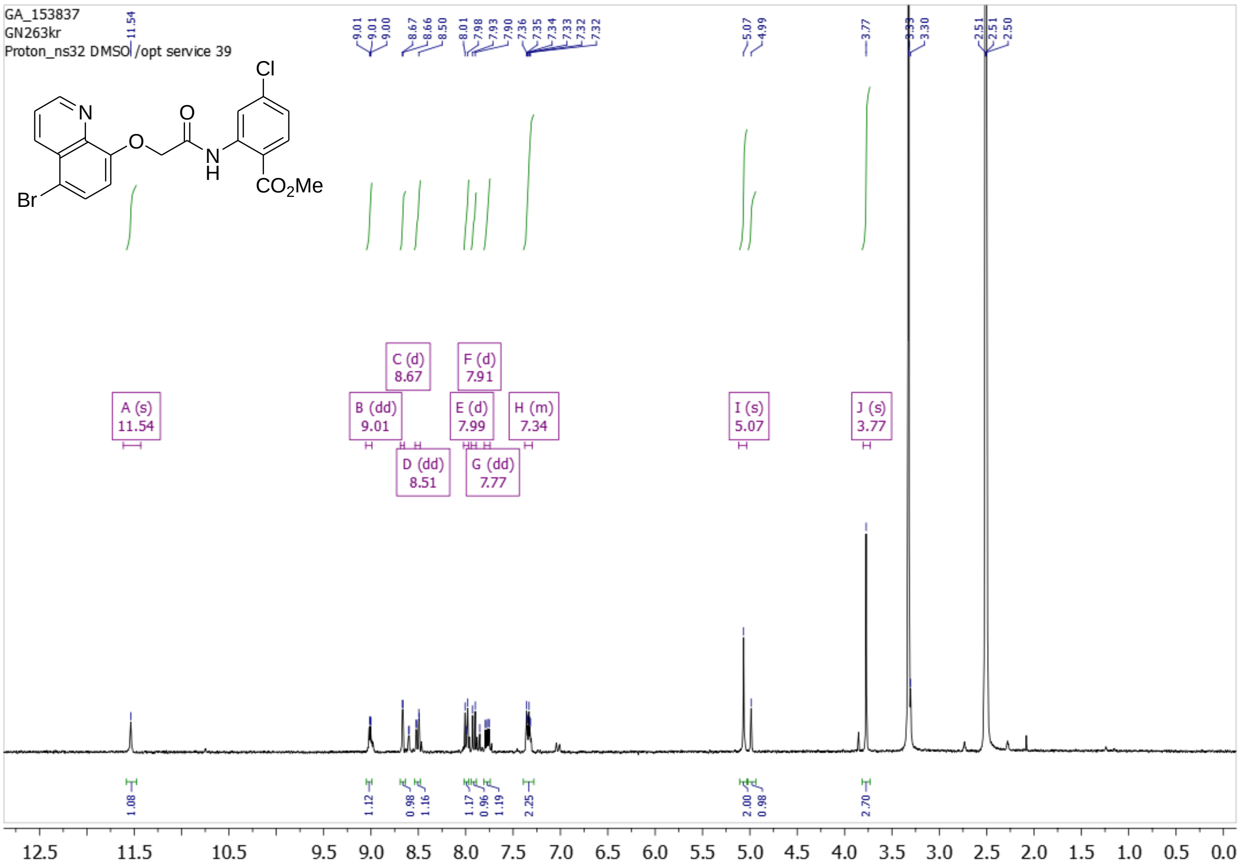


4-Chloro-2-(2-(quinazolin-4-yloxy)acetamido)benzoic acid (**45**):

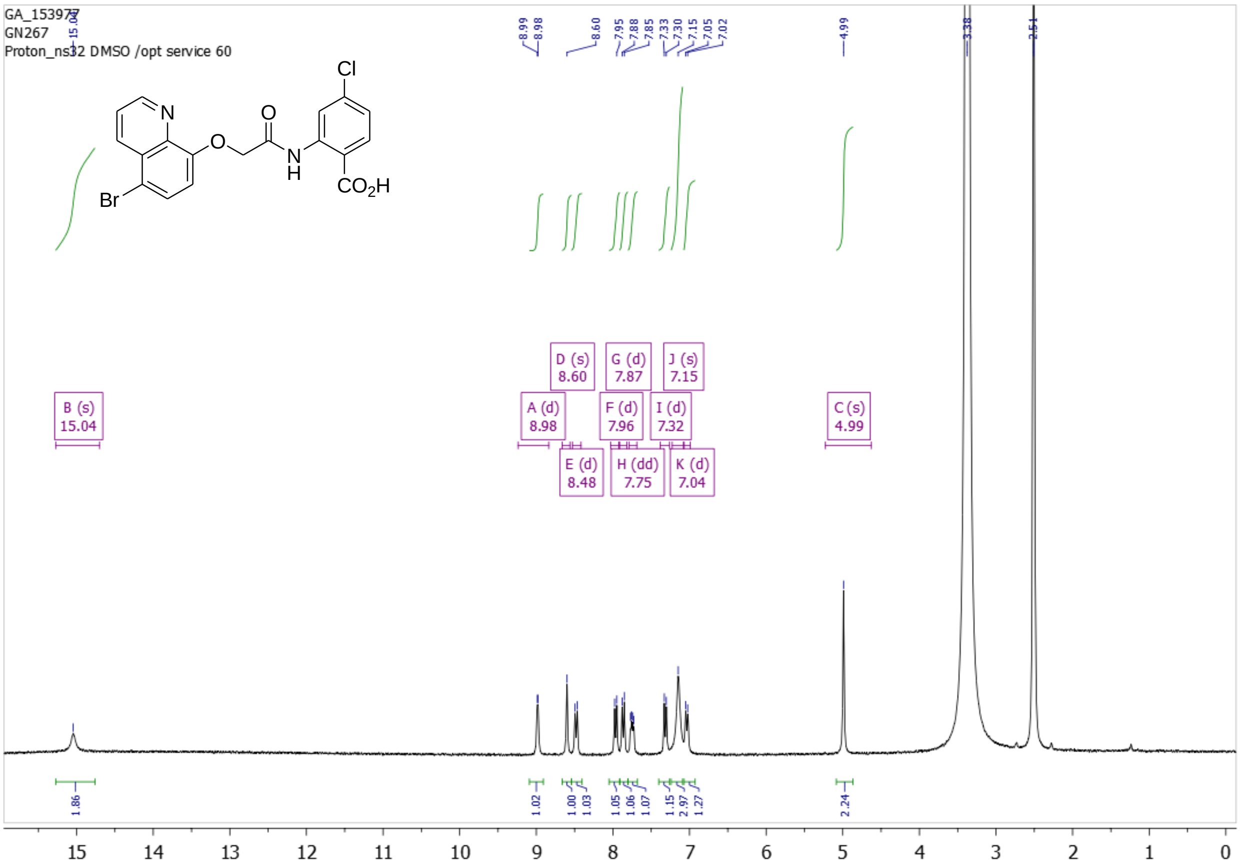


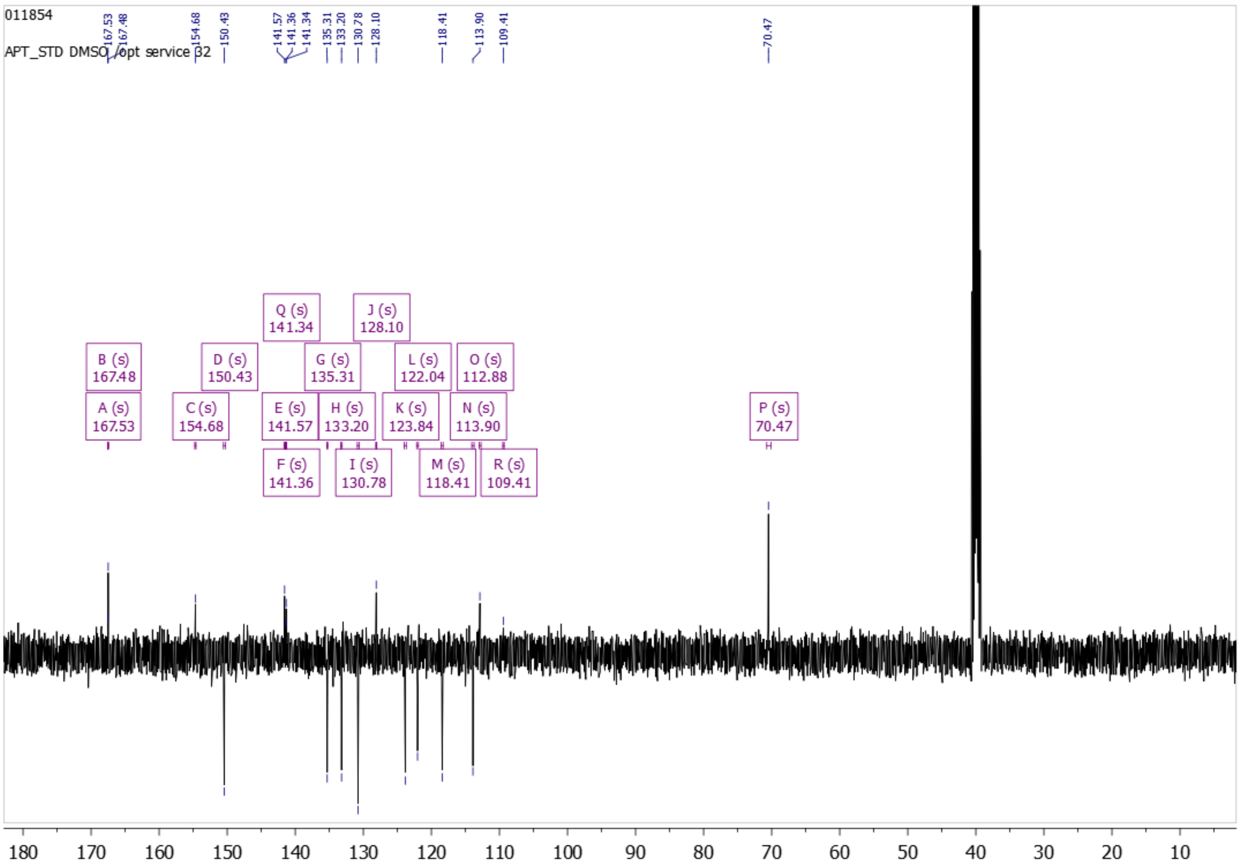


Methyl 2-(2-((5-bromoquinolin-8-yl)oxy)acetamido)-4-chlorobenzoate (**99**):

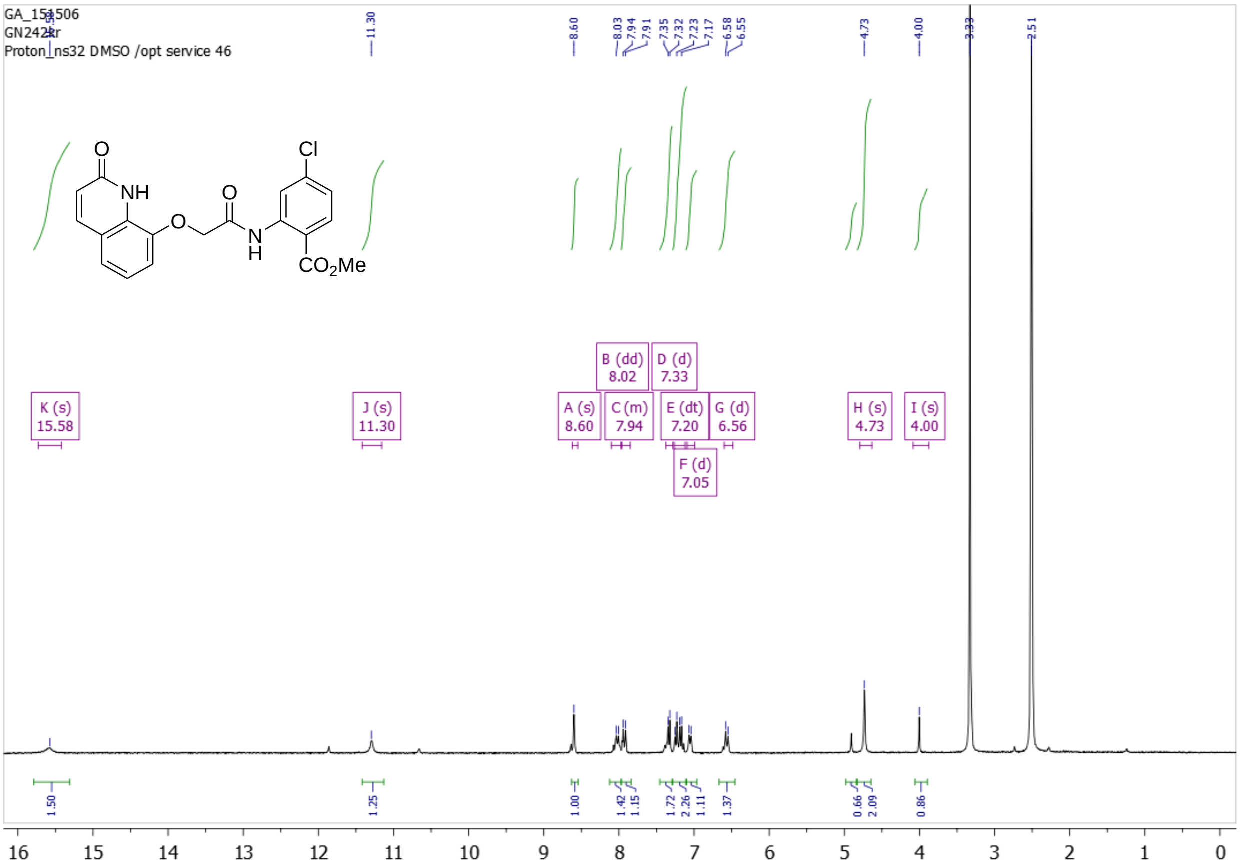


2-(2-((5-Bromoquinolin-8-yl)oxy)acetamido)-4-chlorobenzoic acid (46):

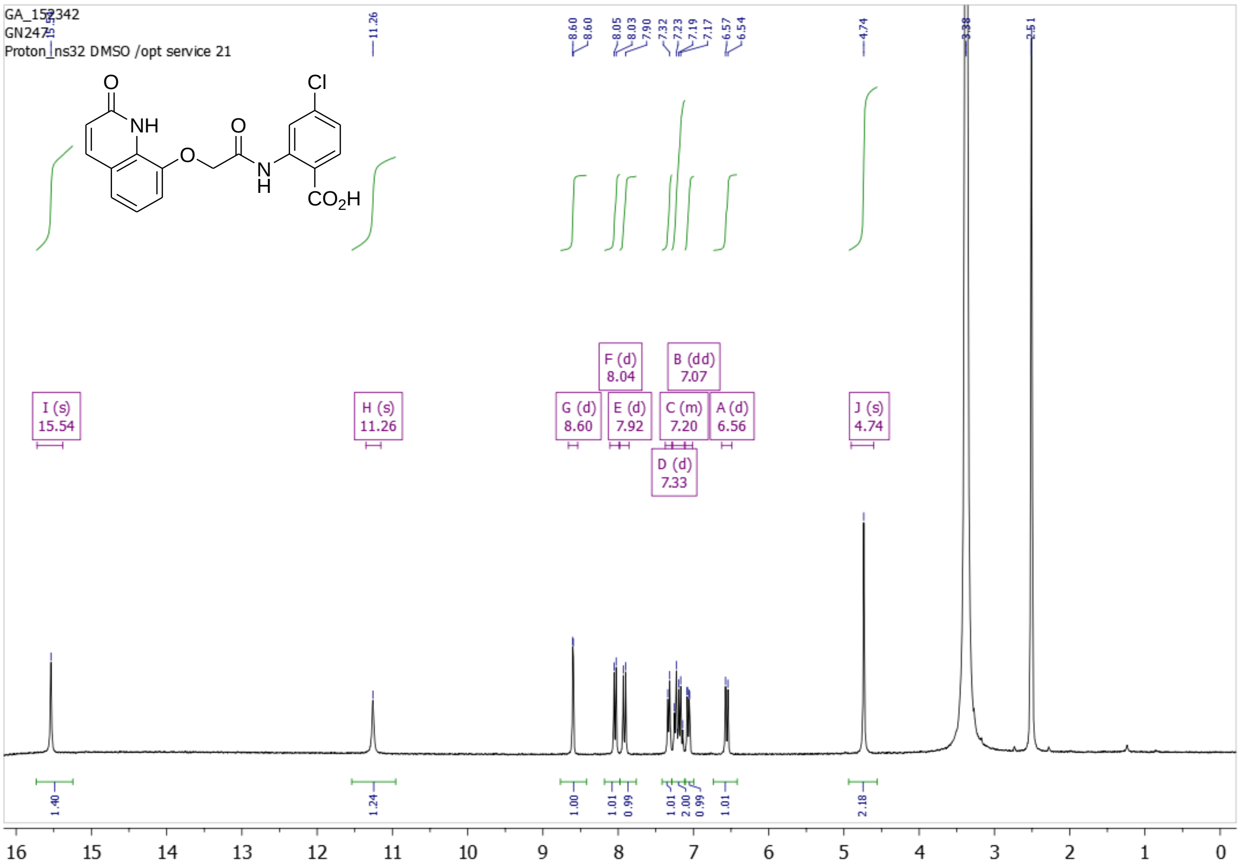


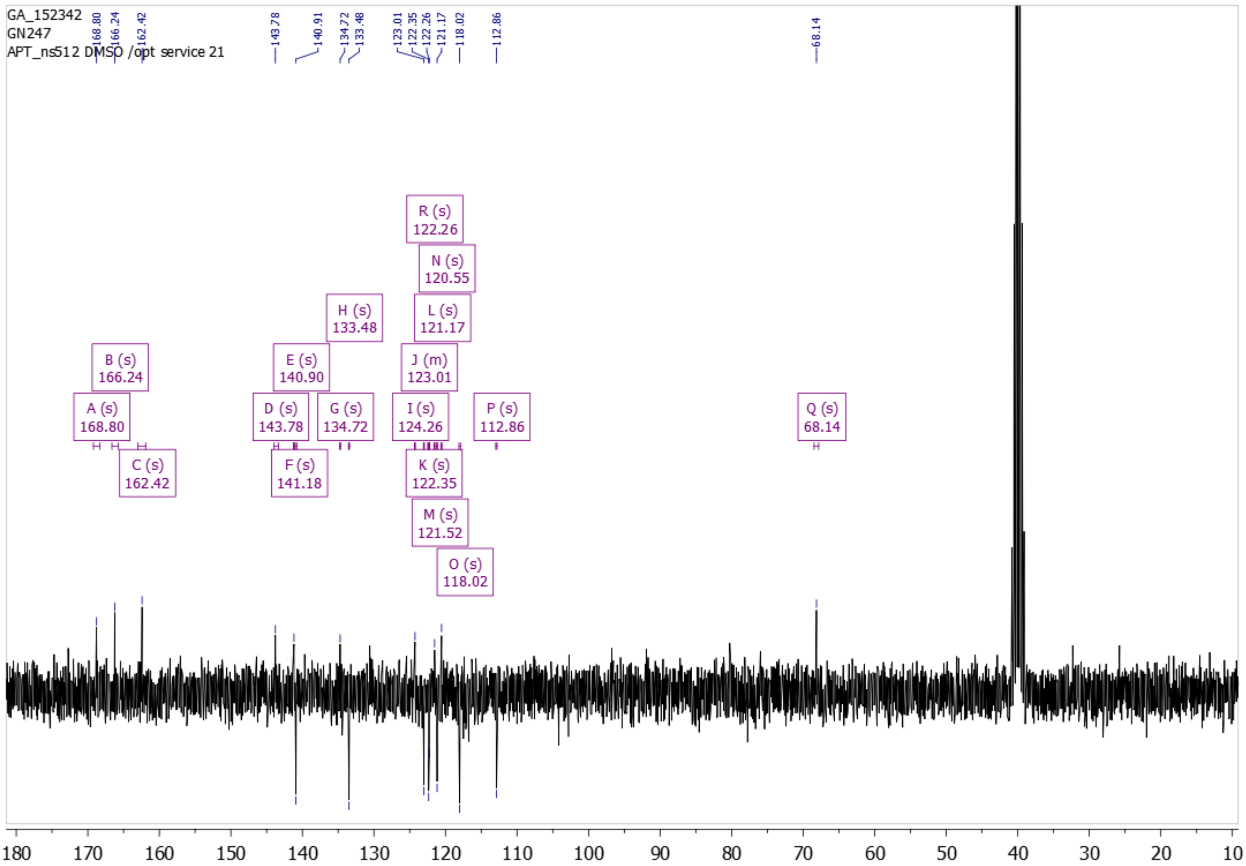


Methyl 4-chloro-2-(2-((2-oxo-1,2-dihydroquinolin-8-yl)oxy)acetamido)benzoate (100):

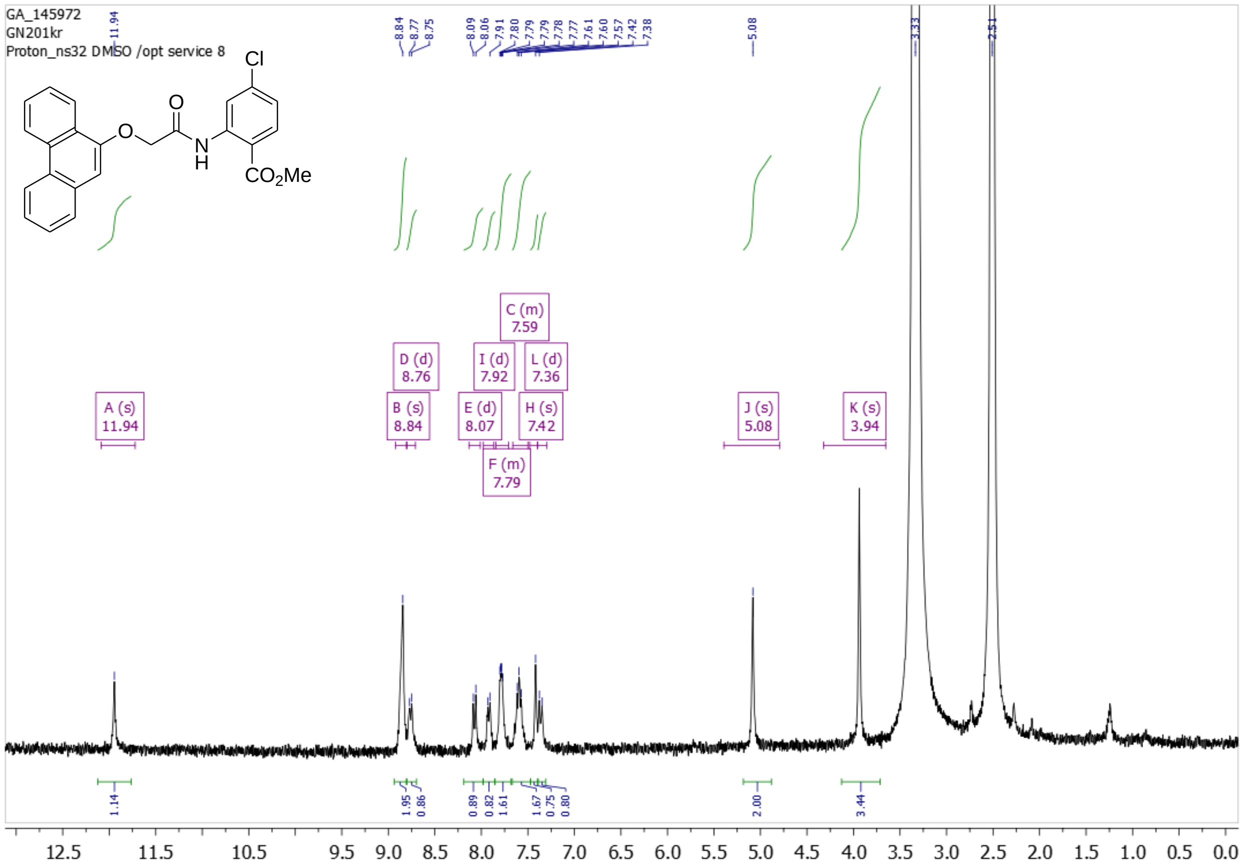


4-Chloro-2-(2-((2-oxo-1,2-dihydroquinolin-8-yl)oxy)acetamido)benzoic acid (**47**):

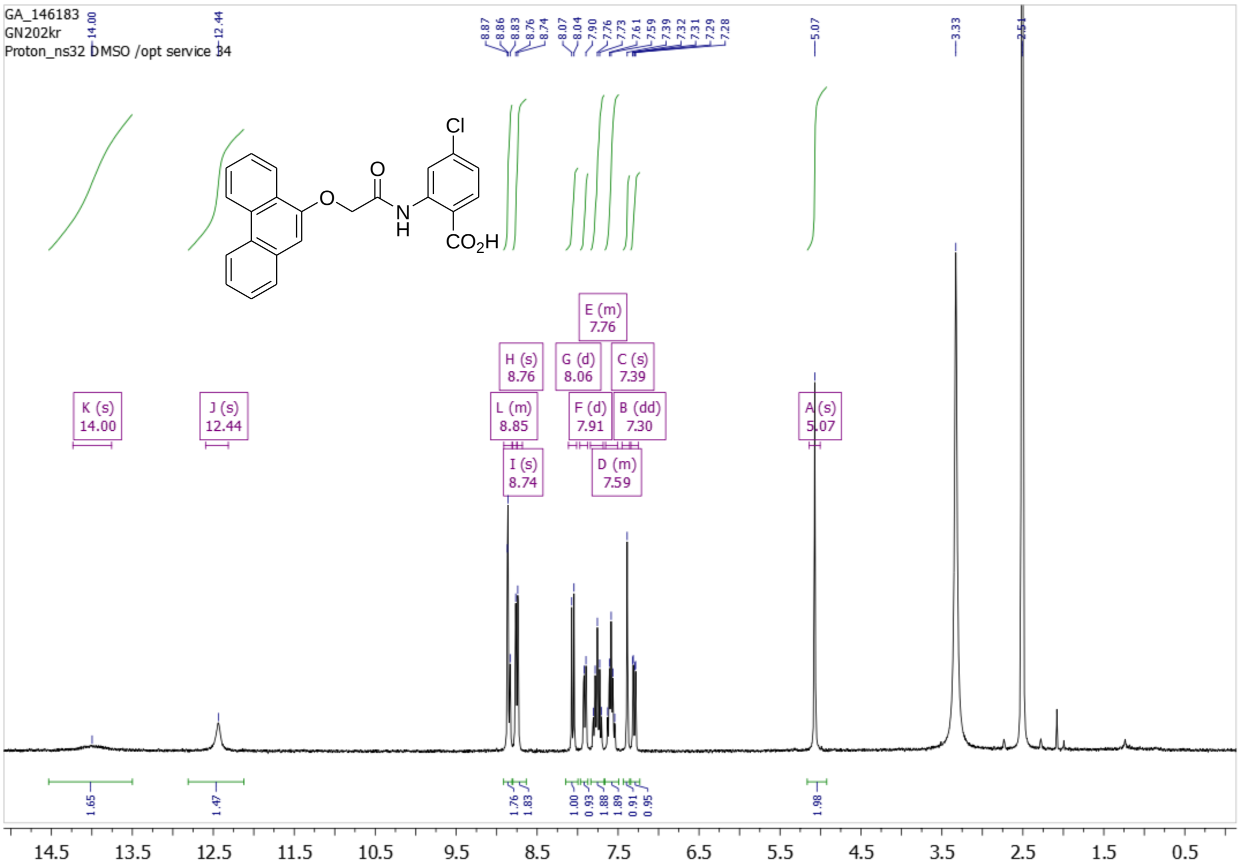


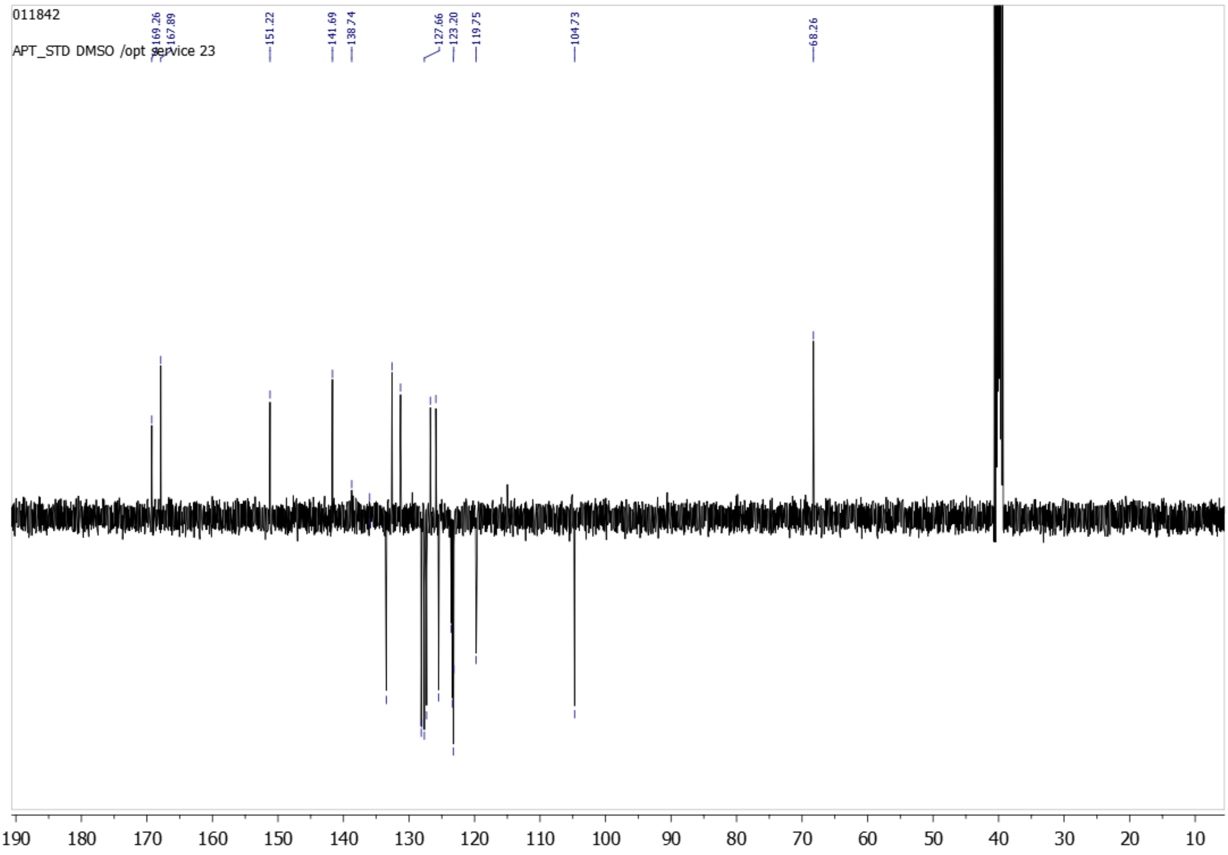


Methyl 4-chloro-2-(2-(phenanthren-9-yloxy)acetamido)benzoate (101):

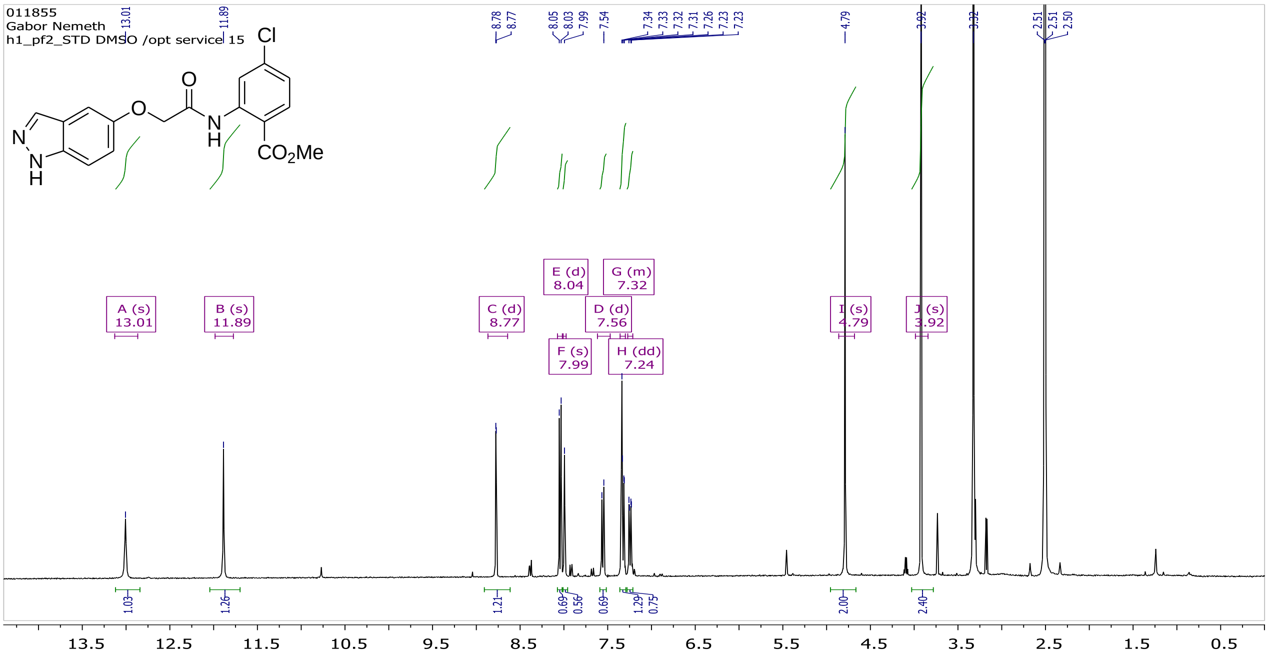


4-Chloro-2-(2-(phenanthren-9-yloxy)acetamido)benzoic acid (48):

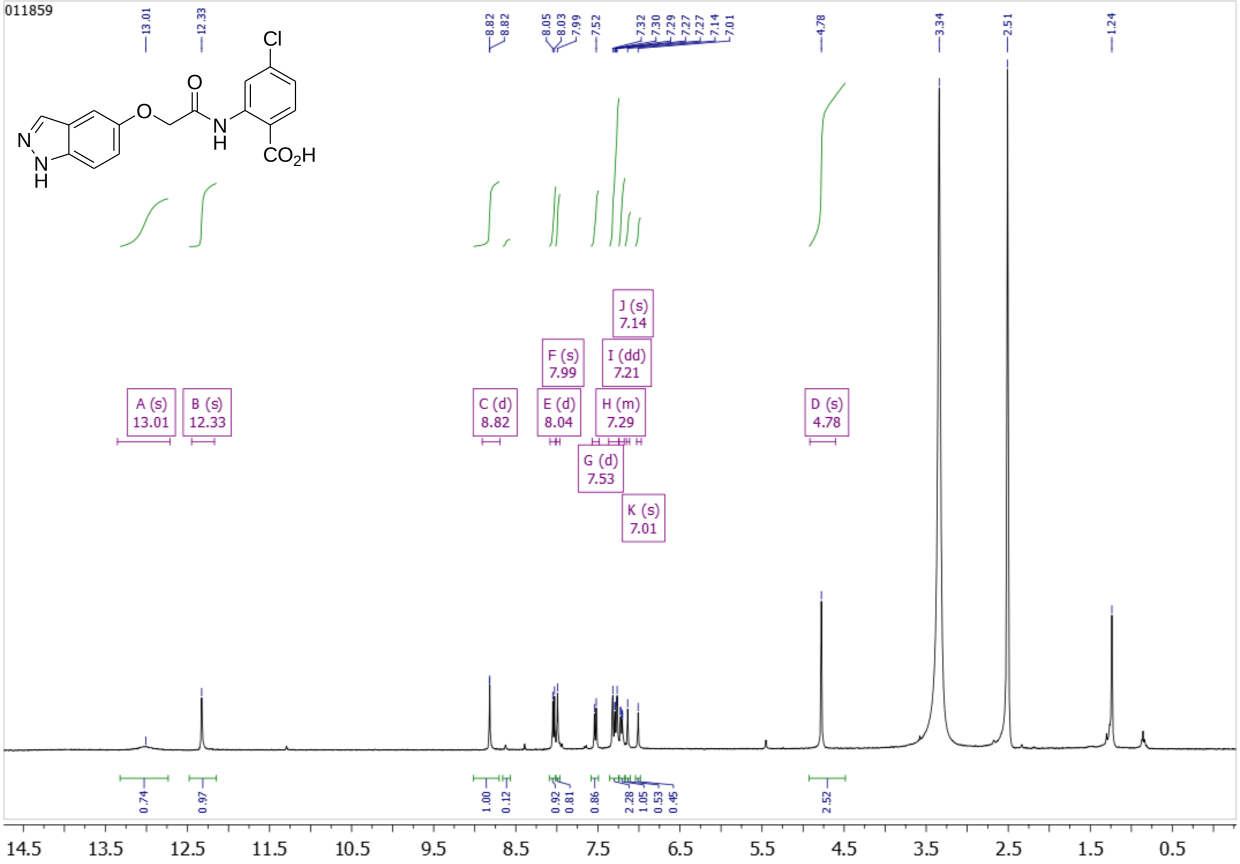


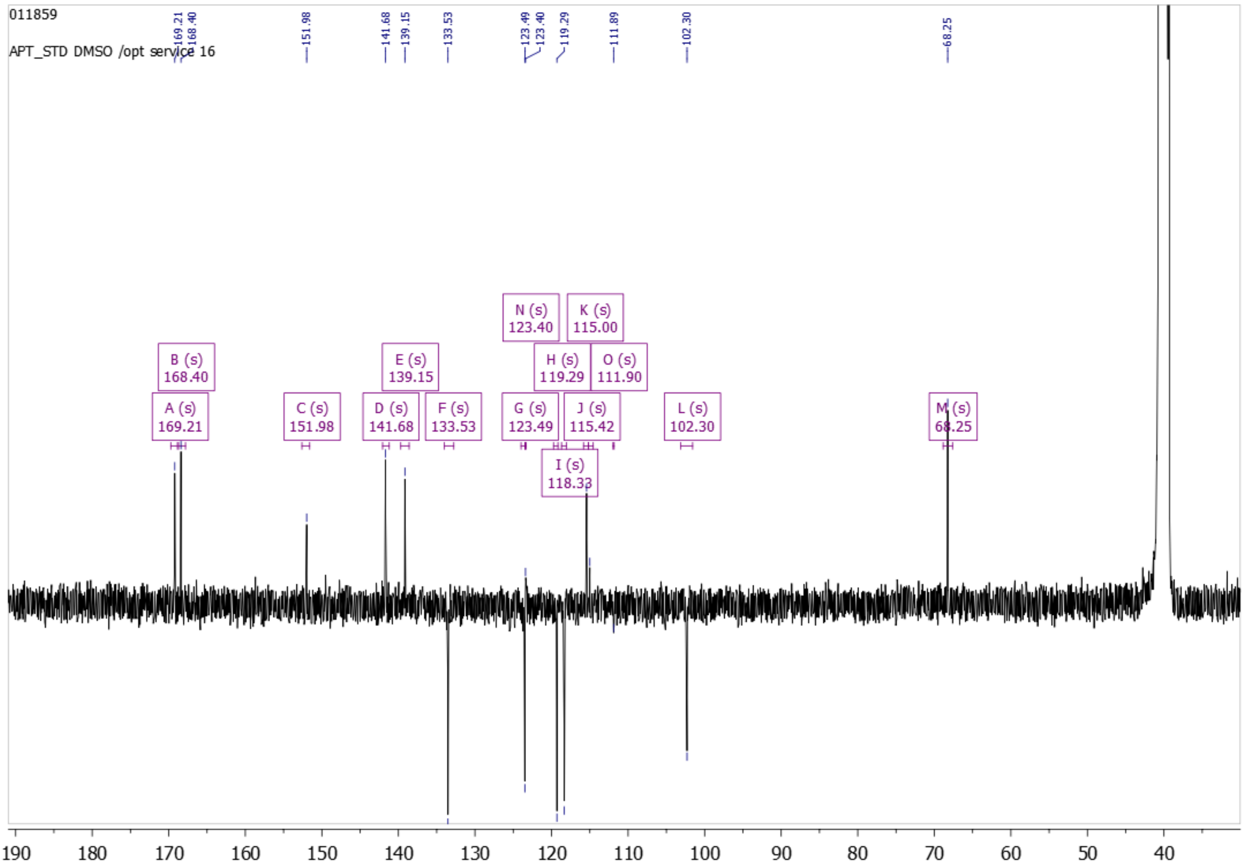


Methyl 2-(2-((1*H*-indazol-5-yl)oxy)acetamido)-4-chlorobenzoate (102):

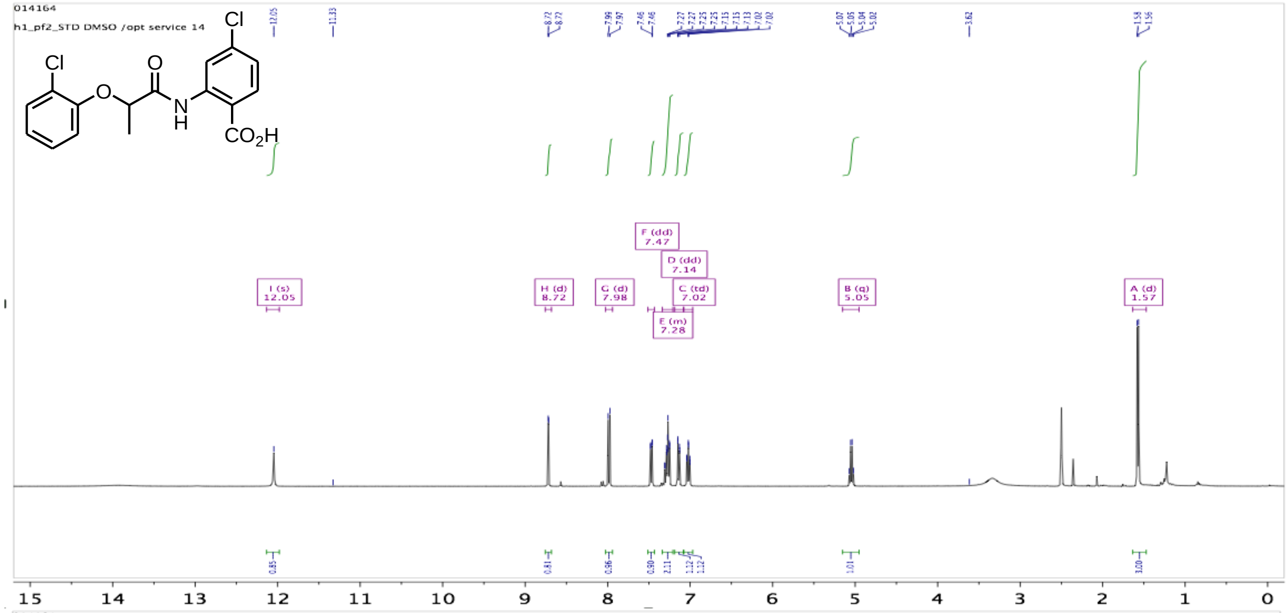


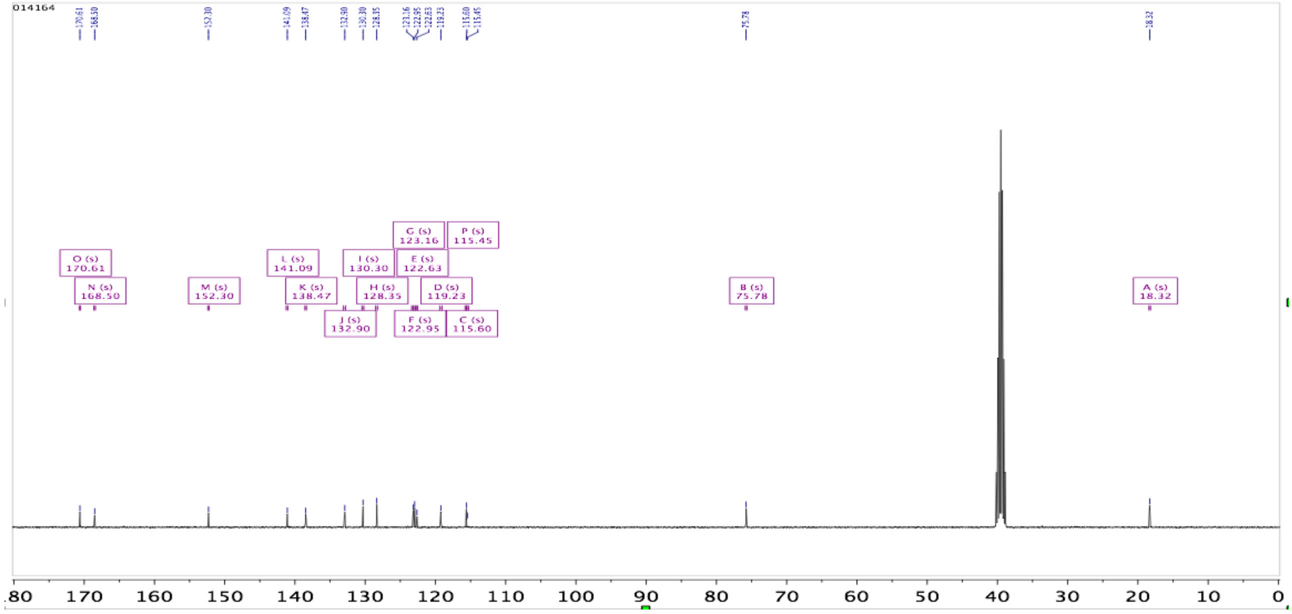
2-(2-((1*H*-Indazol-5-yl)oxy)acetamido)-4-chlorobenzoic acid (49):



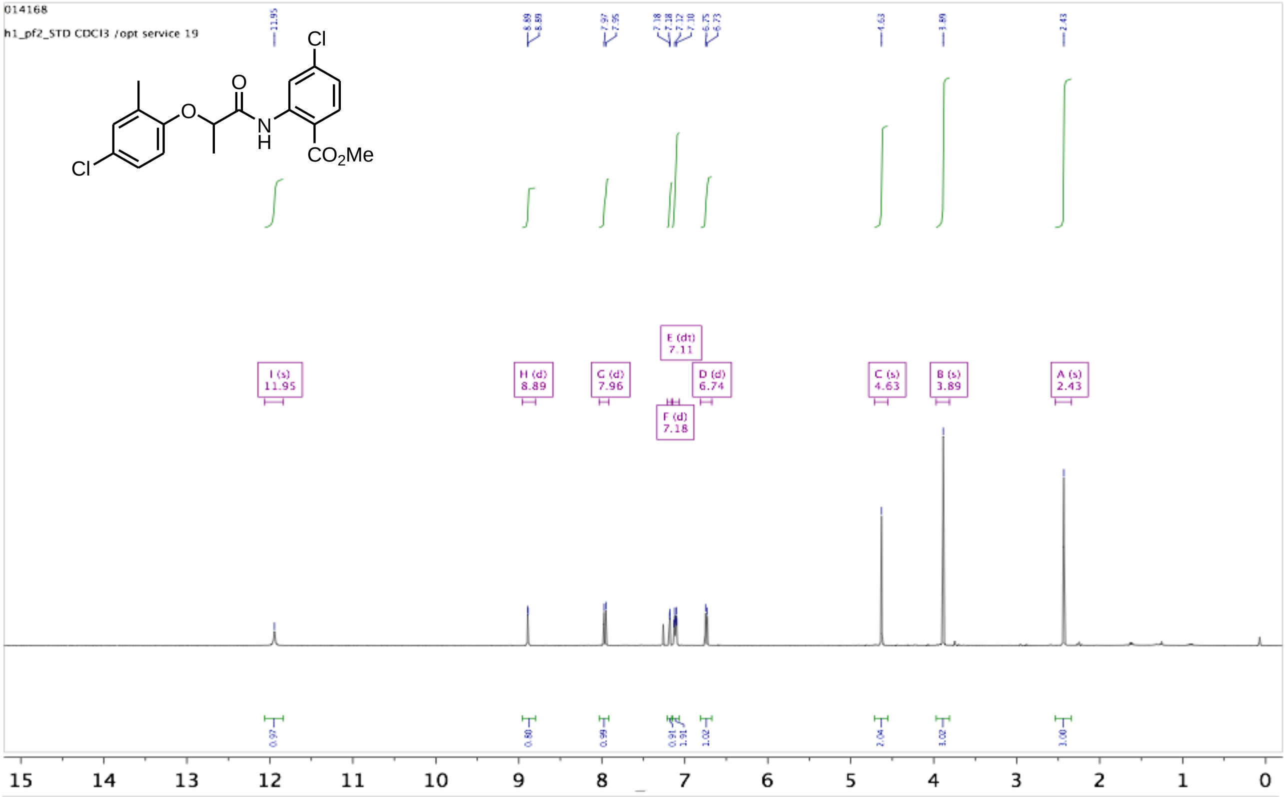


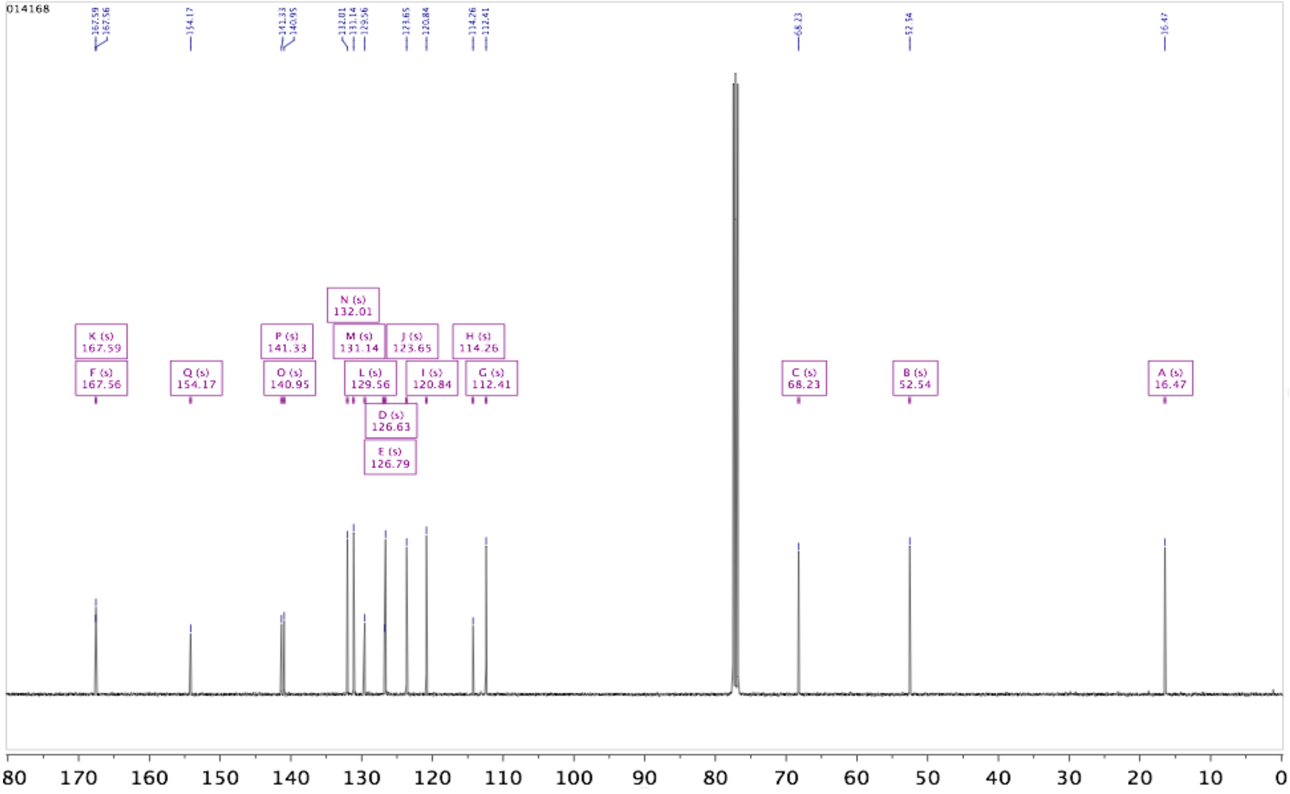
(*rac*)-4-Chloro-2-(2-(2-chlorophenoxy)propanamido)benzoic acid (50):



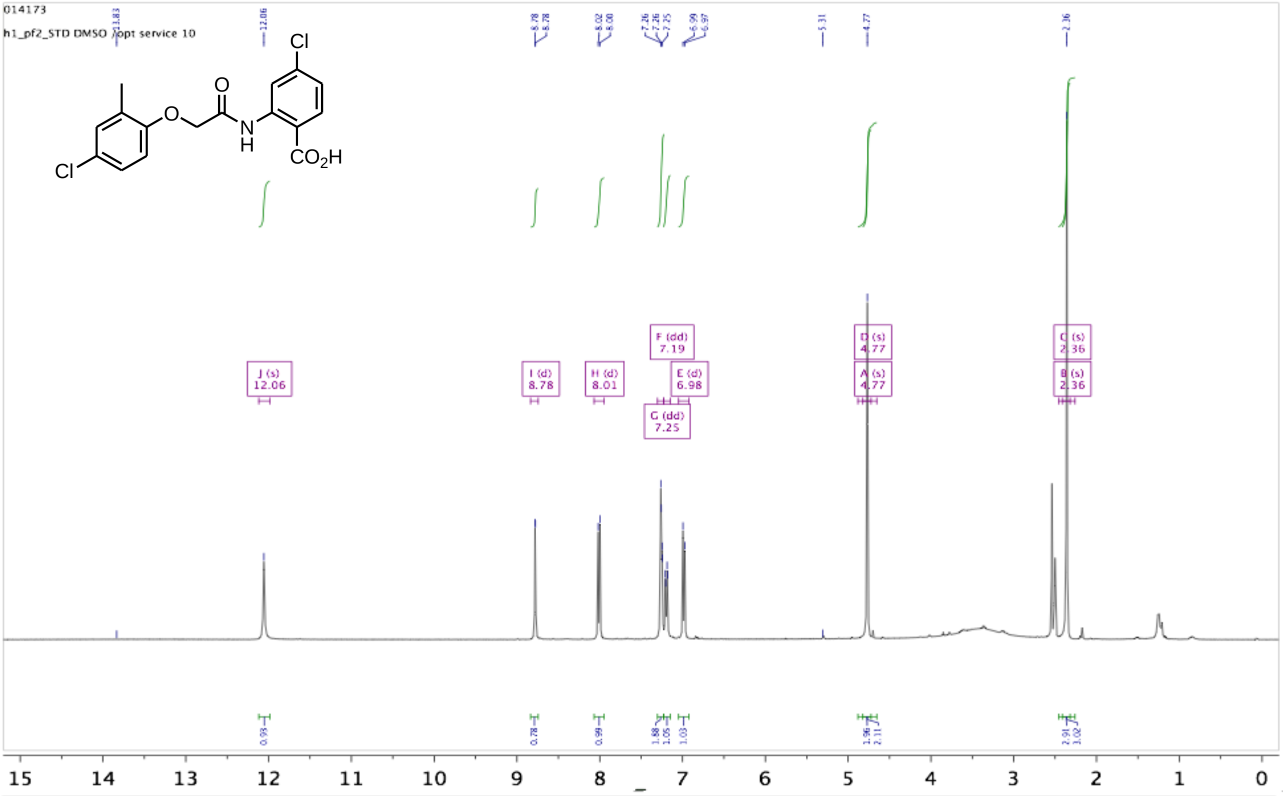


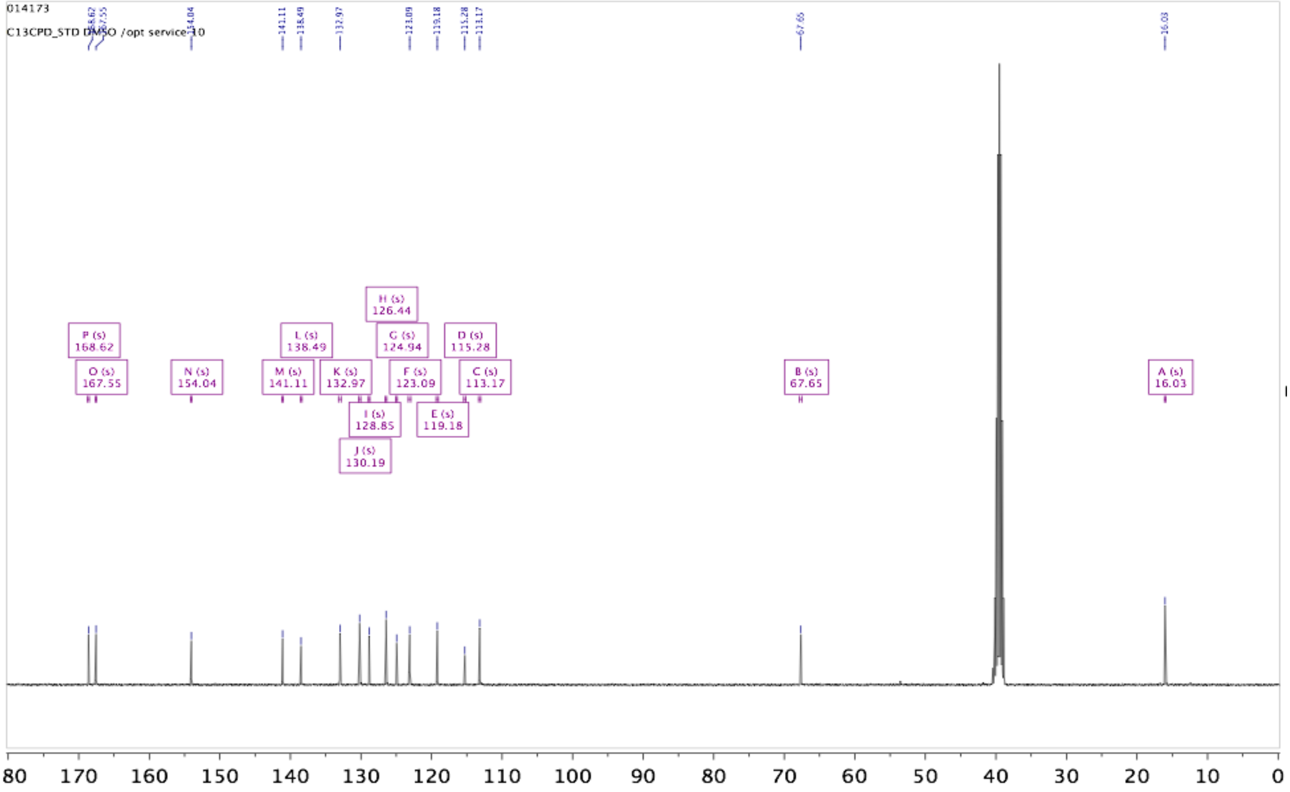
Methyl 4-chloro-2-(2-(4-chloro-2-methylphenoxy)acetamido)benzoate (103):



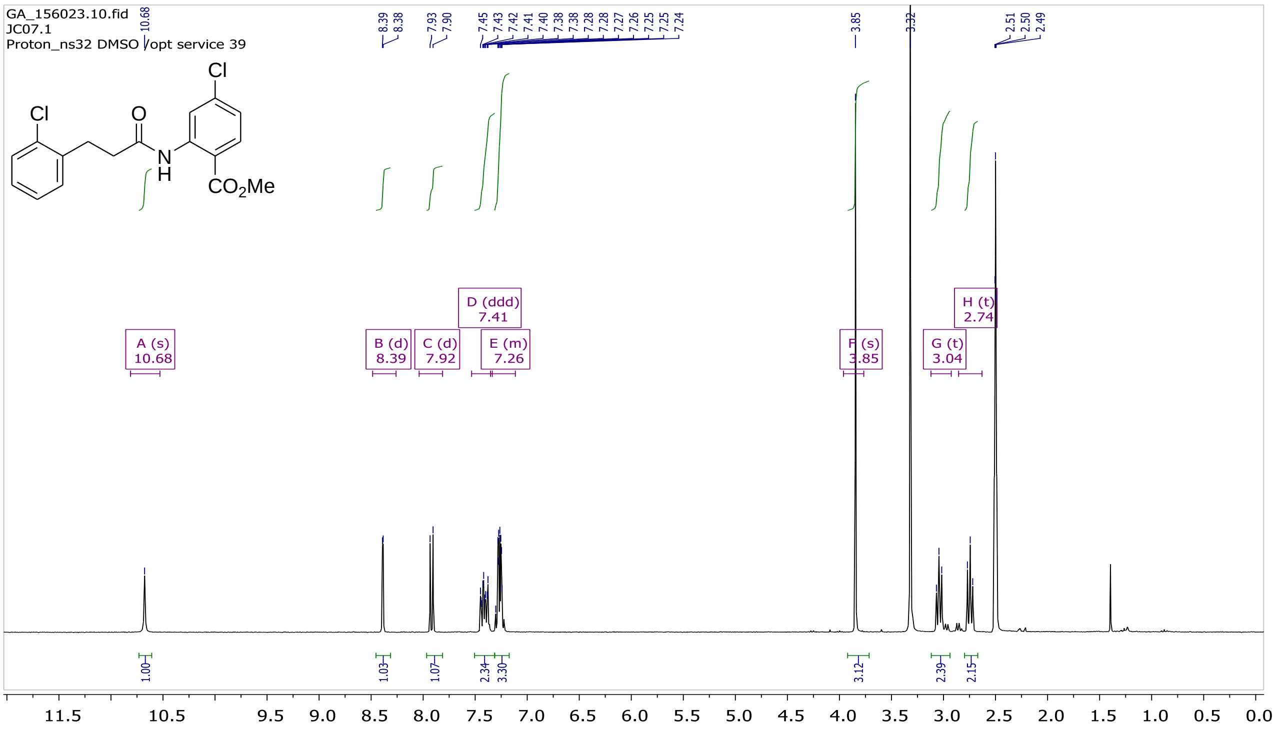


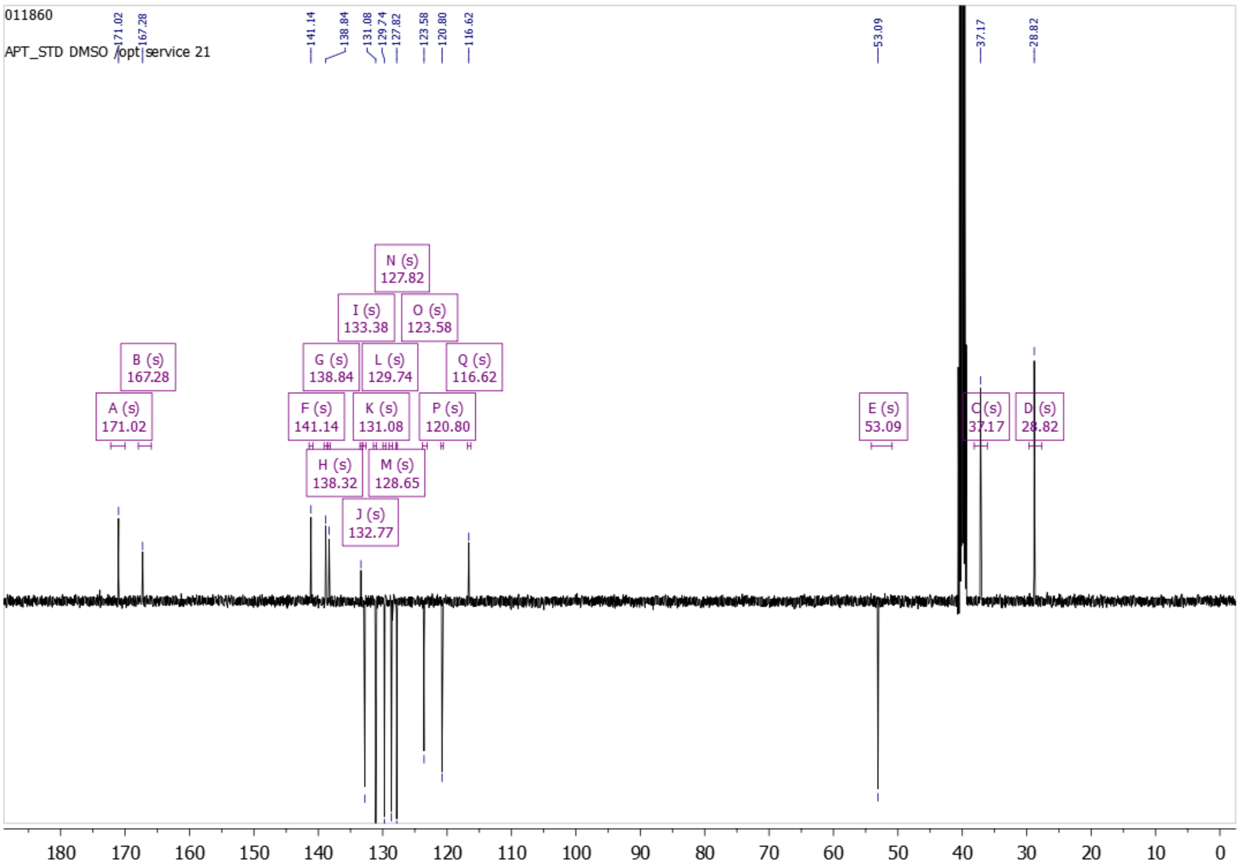
4-Chloro-2-(2-(4-chloro-2-methylphenoxy)acetamido)benzoic acid (**51**):



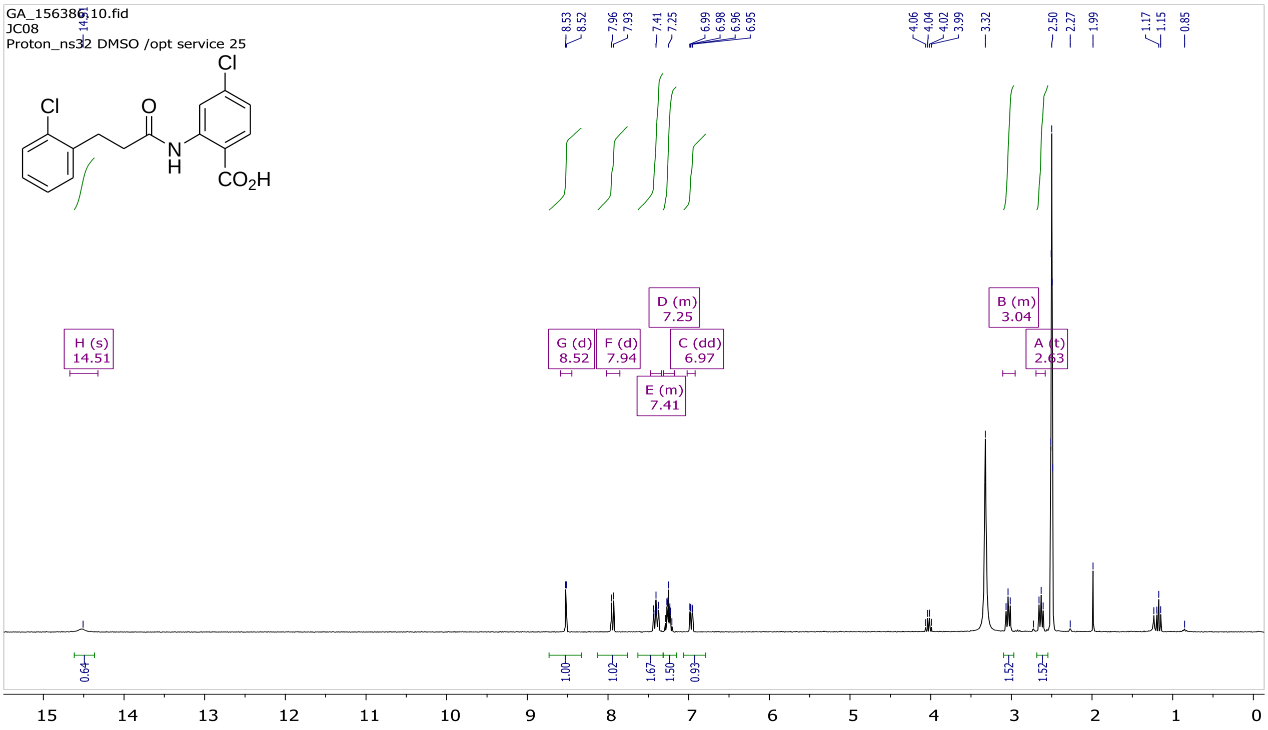


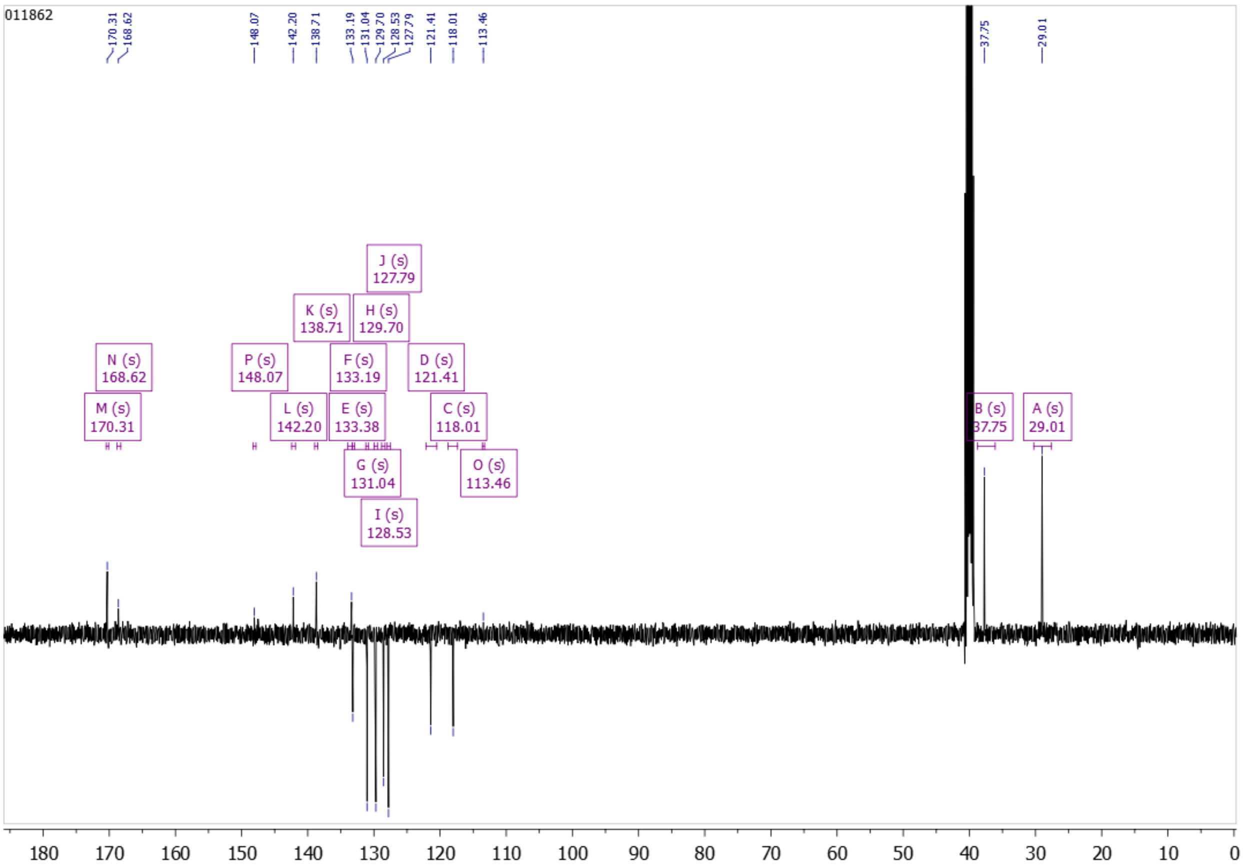
Methyl 4-chloro-2-(3-(2-chlorophenyl)propanamido)benzoate (105):



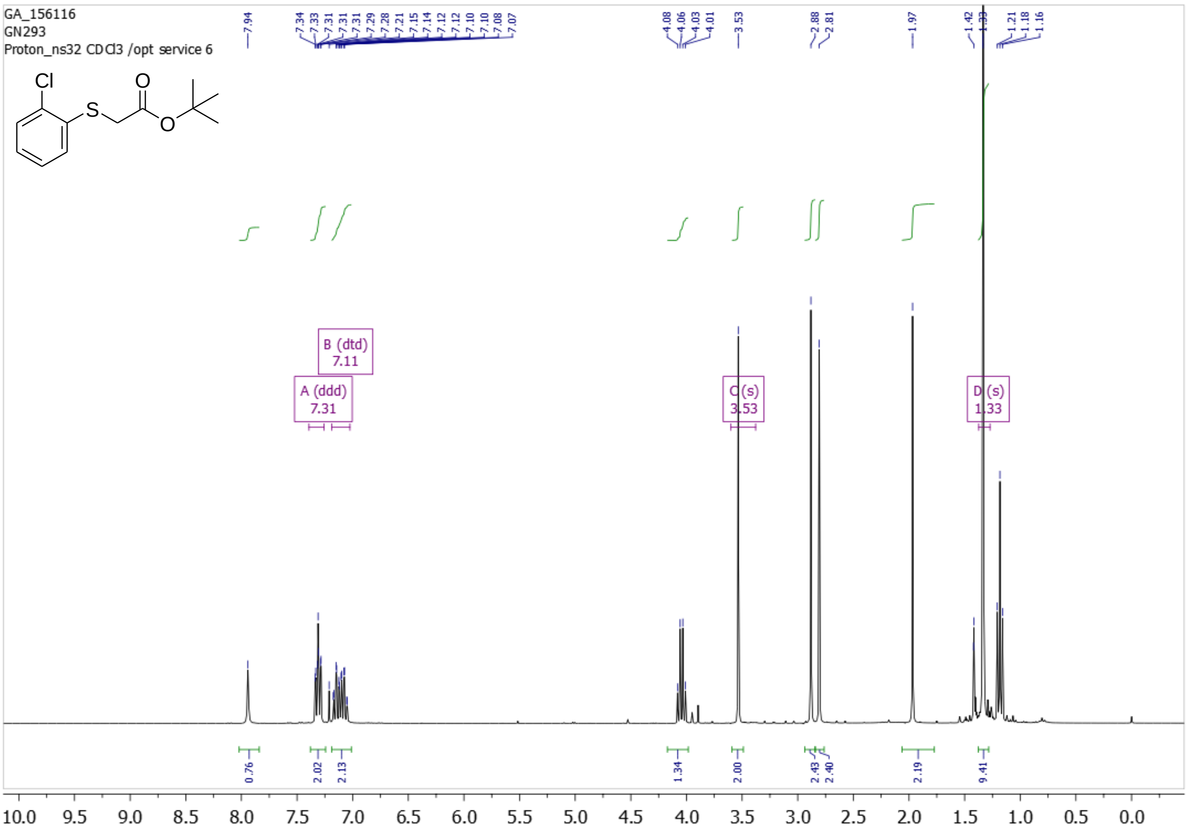


4-Chloro-2-(3-(2-chlorophenyl)propanamido)benzoic acid (**54**):

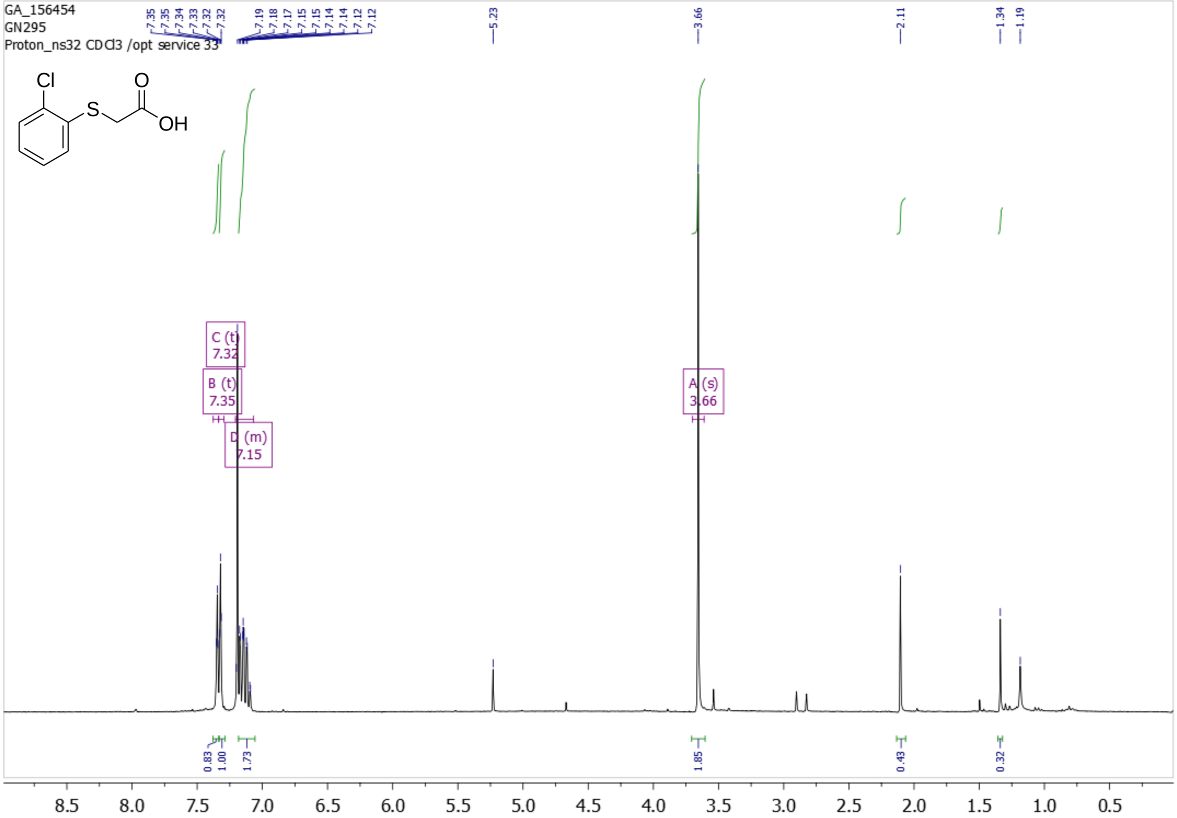




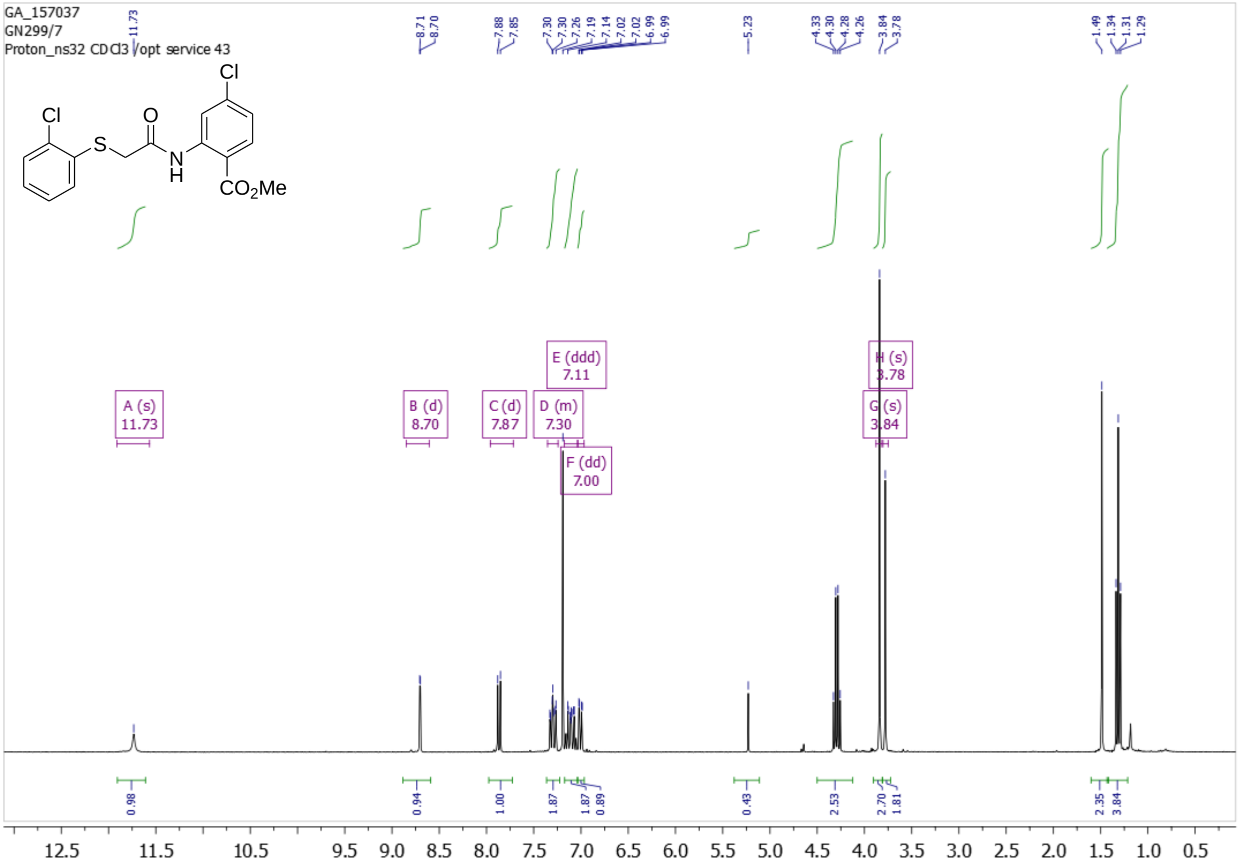
***tert*-Butyl 2-((2-chlorophenyl)thio)acetate** (**106**):

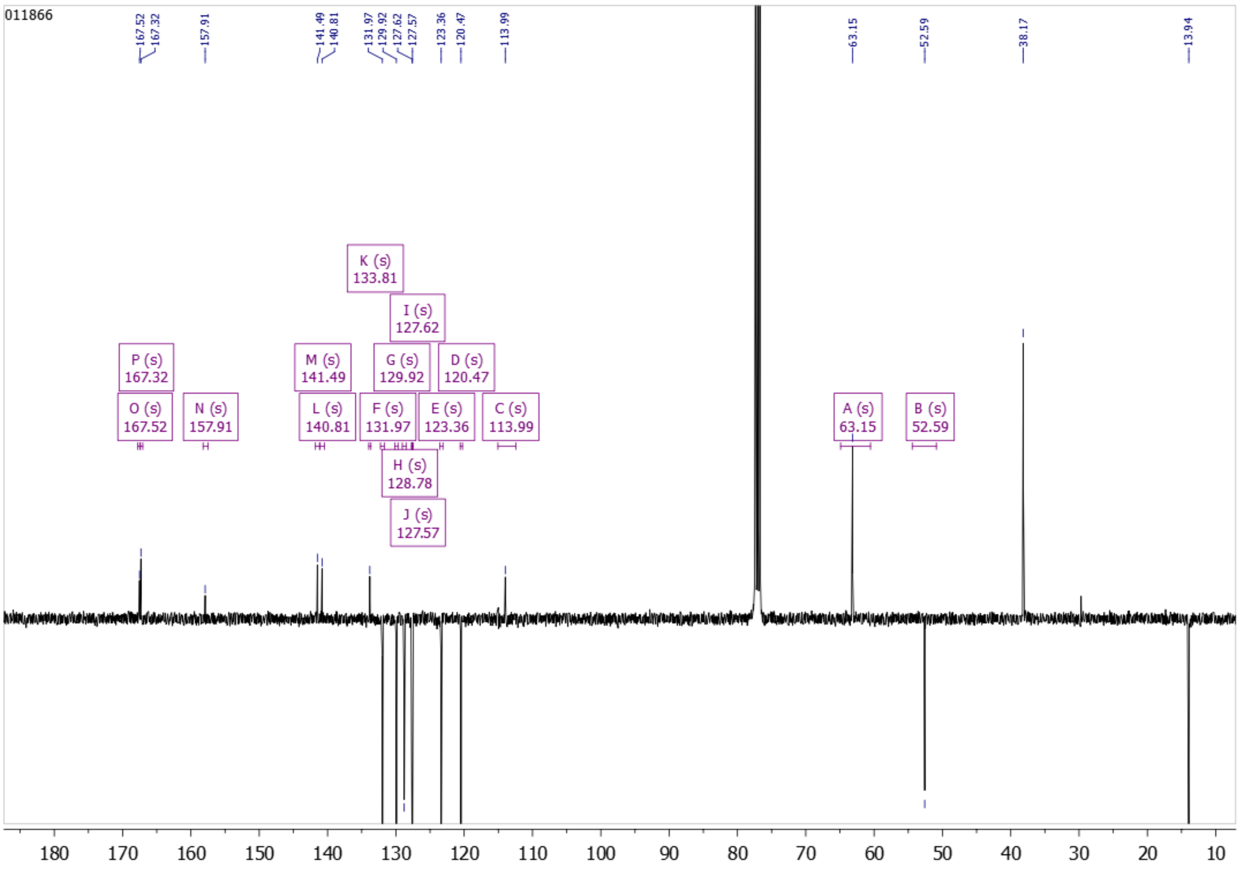


2-((2-Chlorophenyl)thio)acetic acid (**107**):

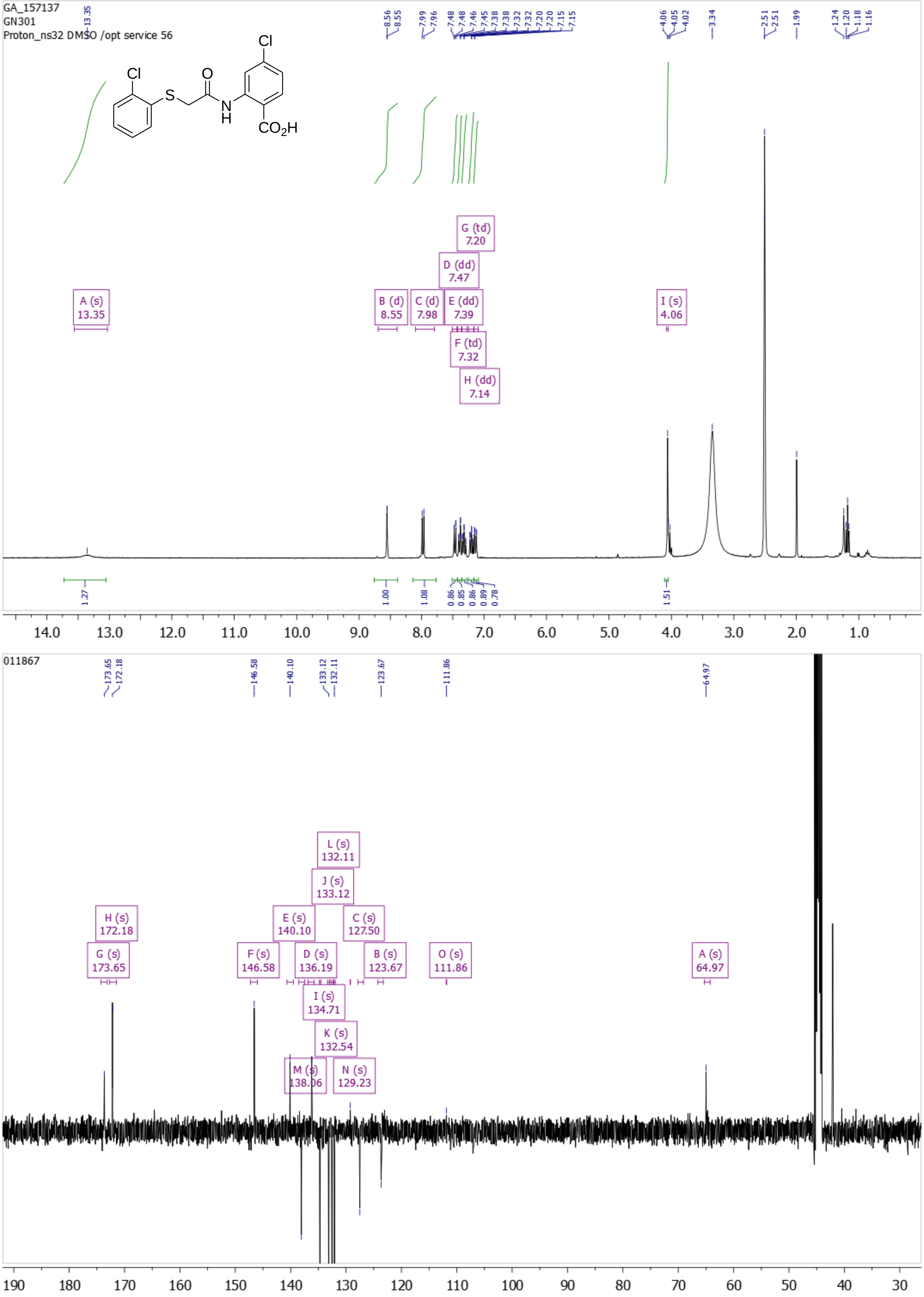


Methyl 4-chloro-2-(2-((2-chlorophenyl)thio)acetamido)benzoate (**109**):

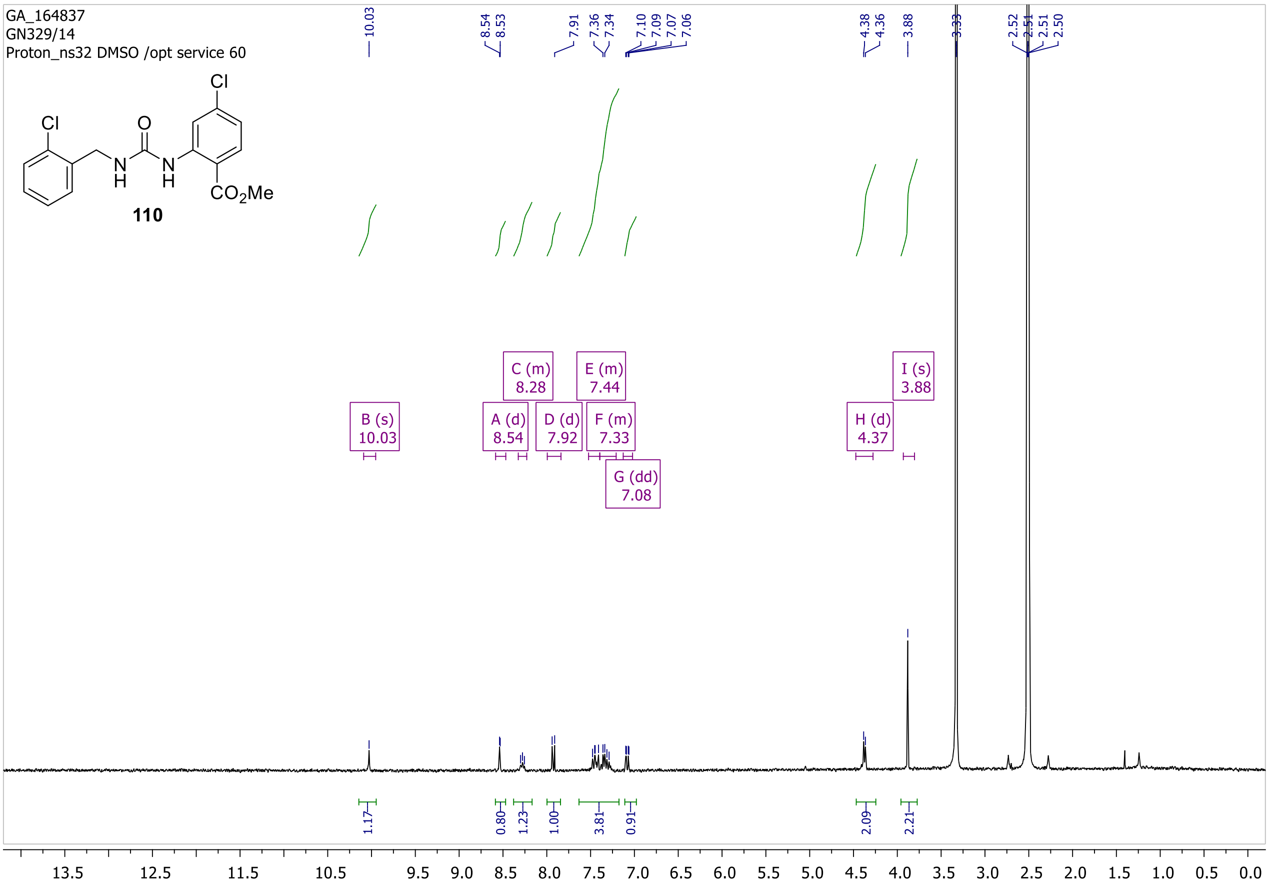




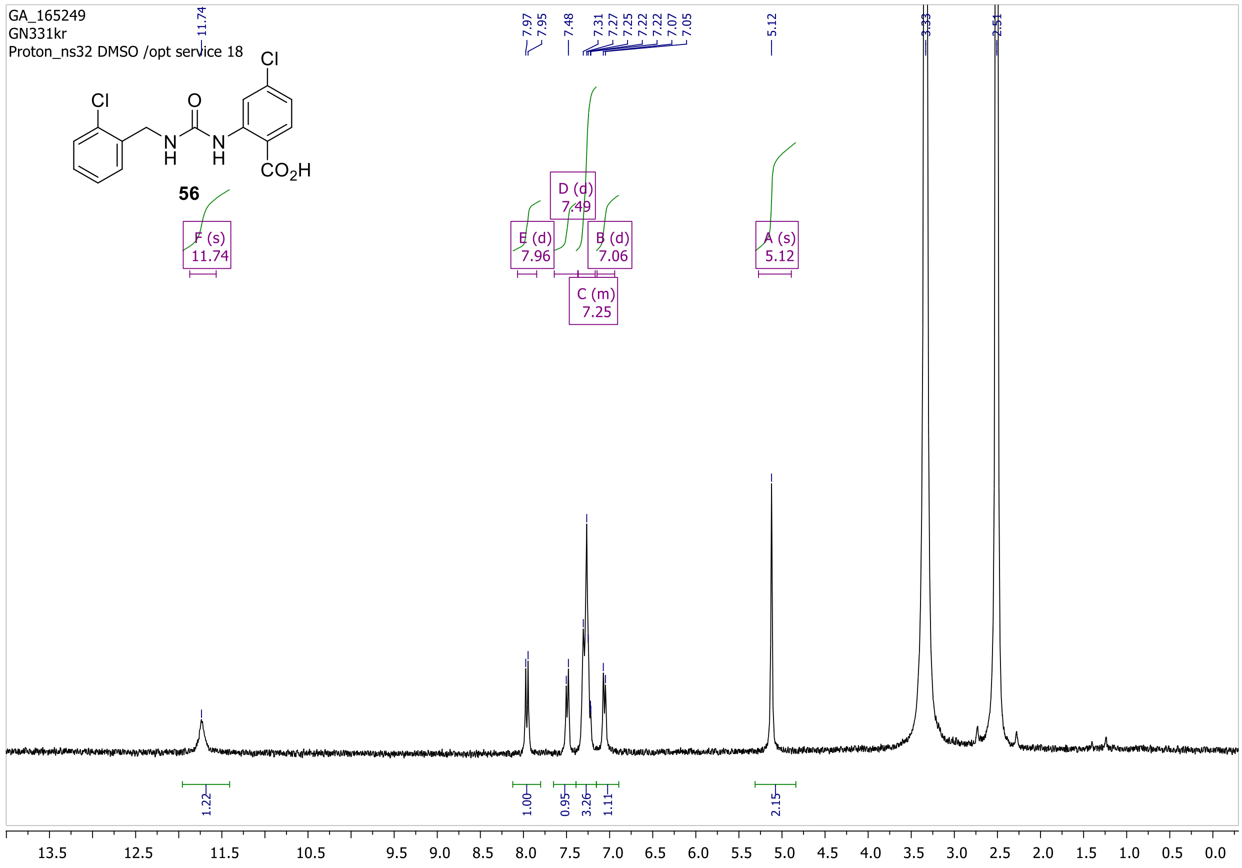
4-Chloro-2-(2-((2-chlorophenyl)thio)acetamido)benzoic acid (55):

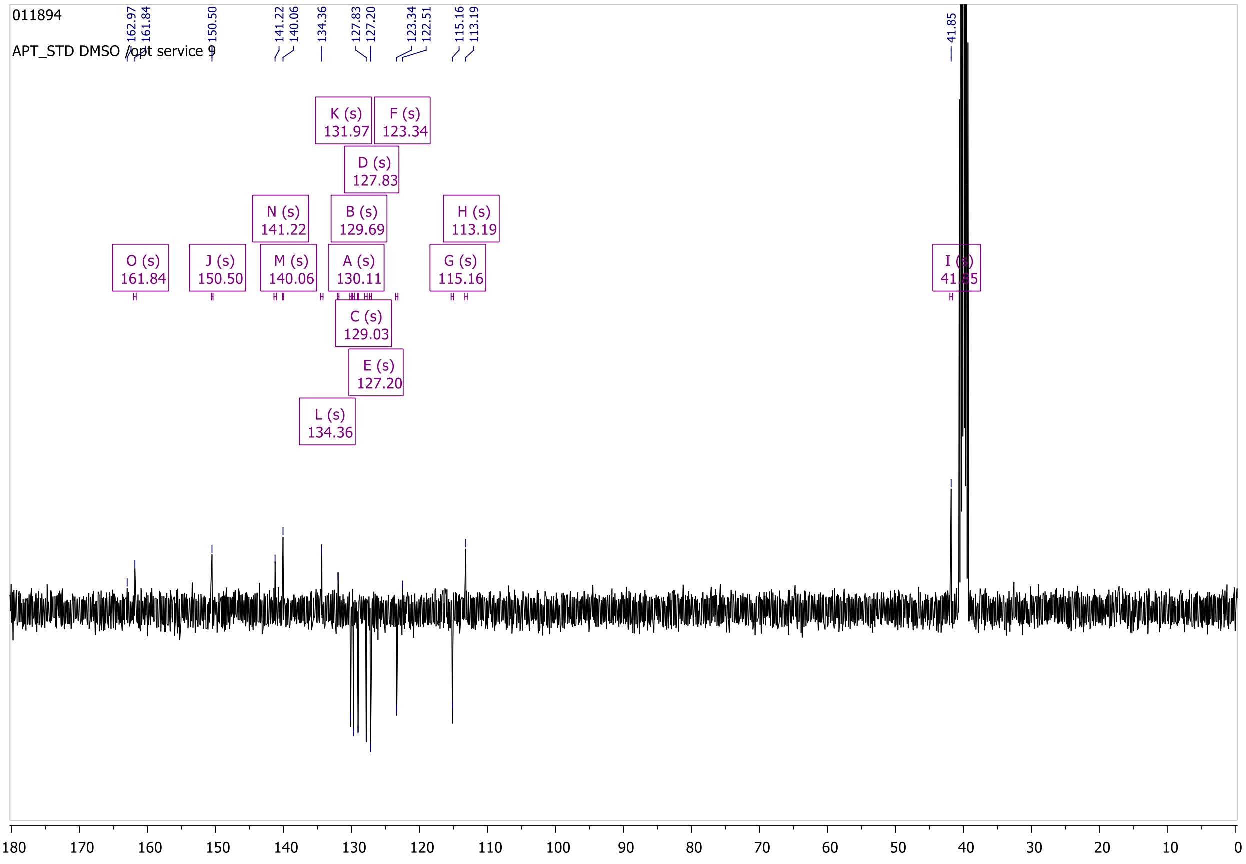


Methyl 4-chloro-2-(3-(2-chlorobenzyl)ureido)benzoate (110):

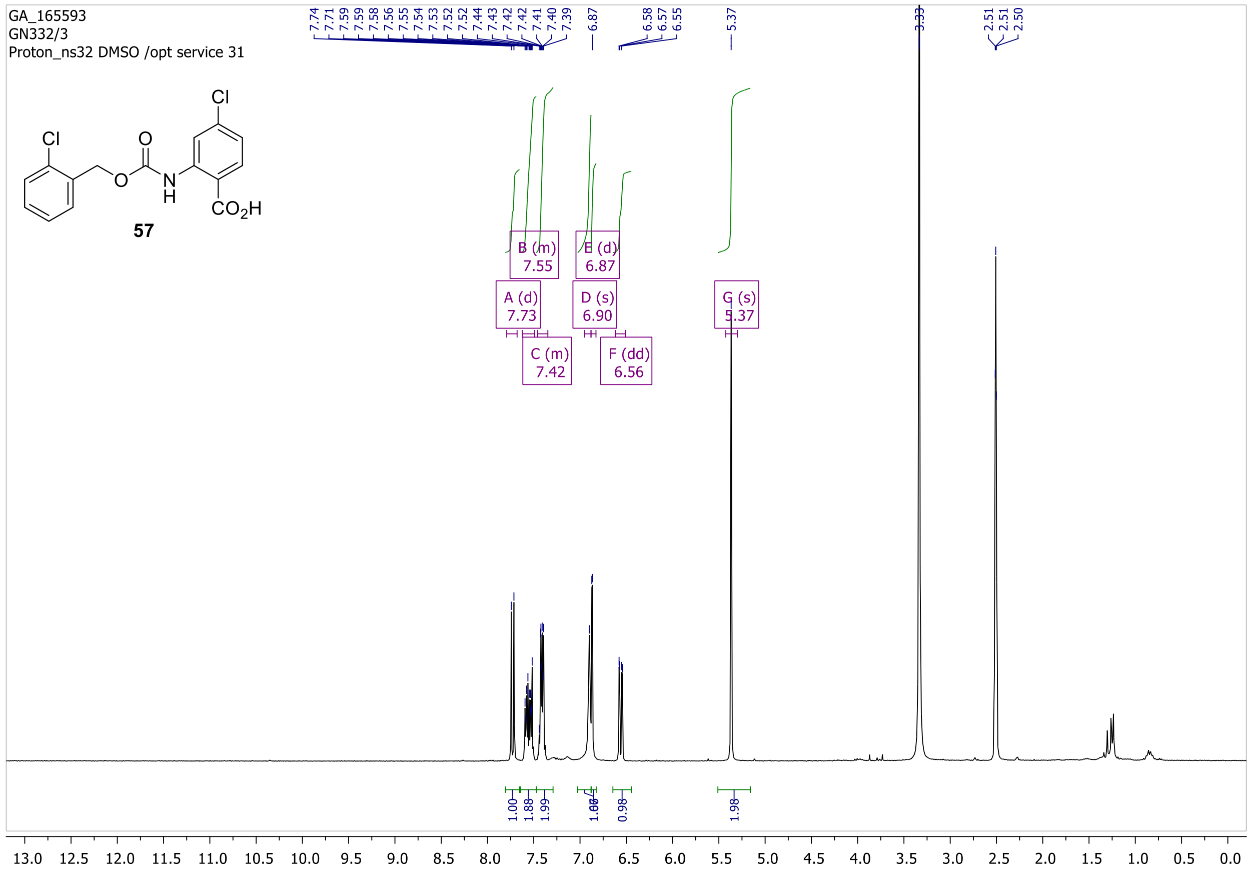


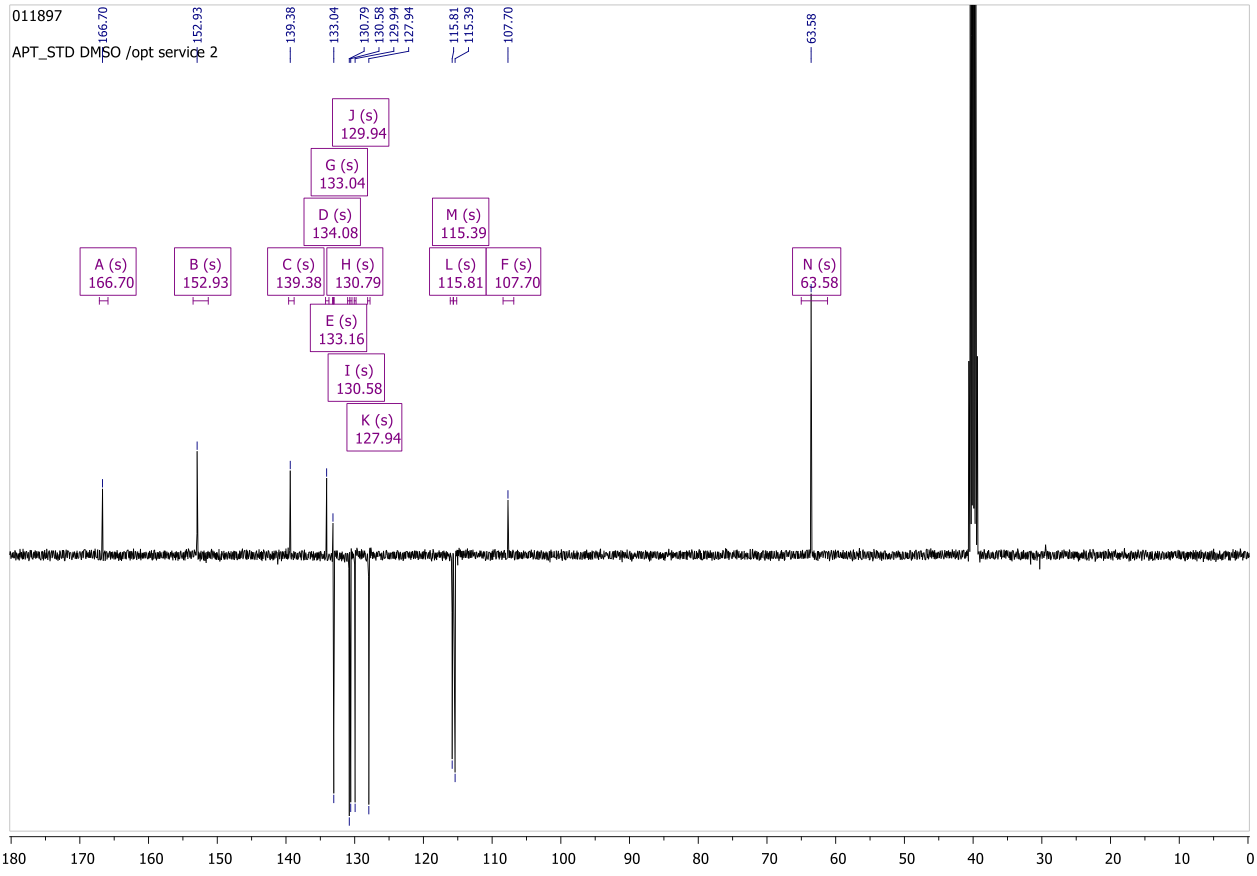
4-Chloro-2-(3-(2-chlorobenzyl)ureido)benzoic (56):



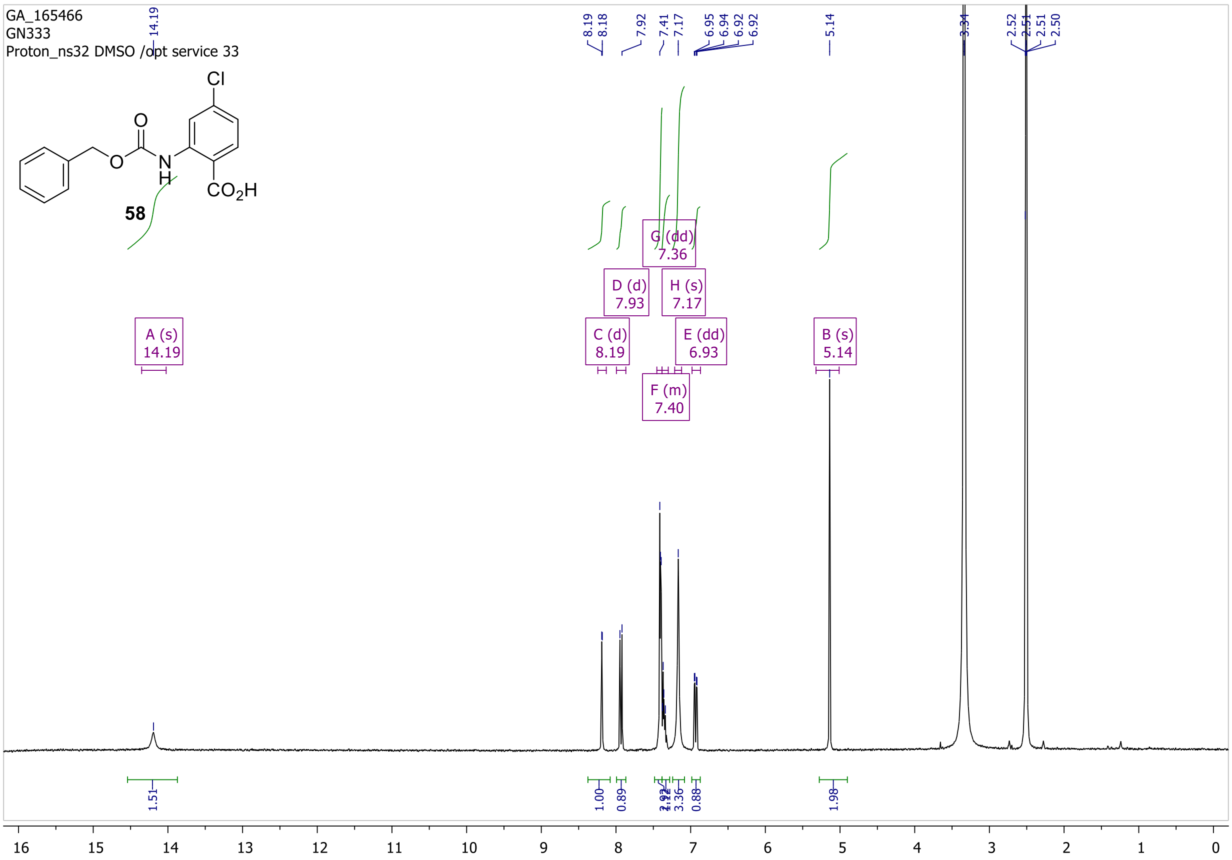


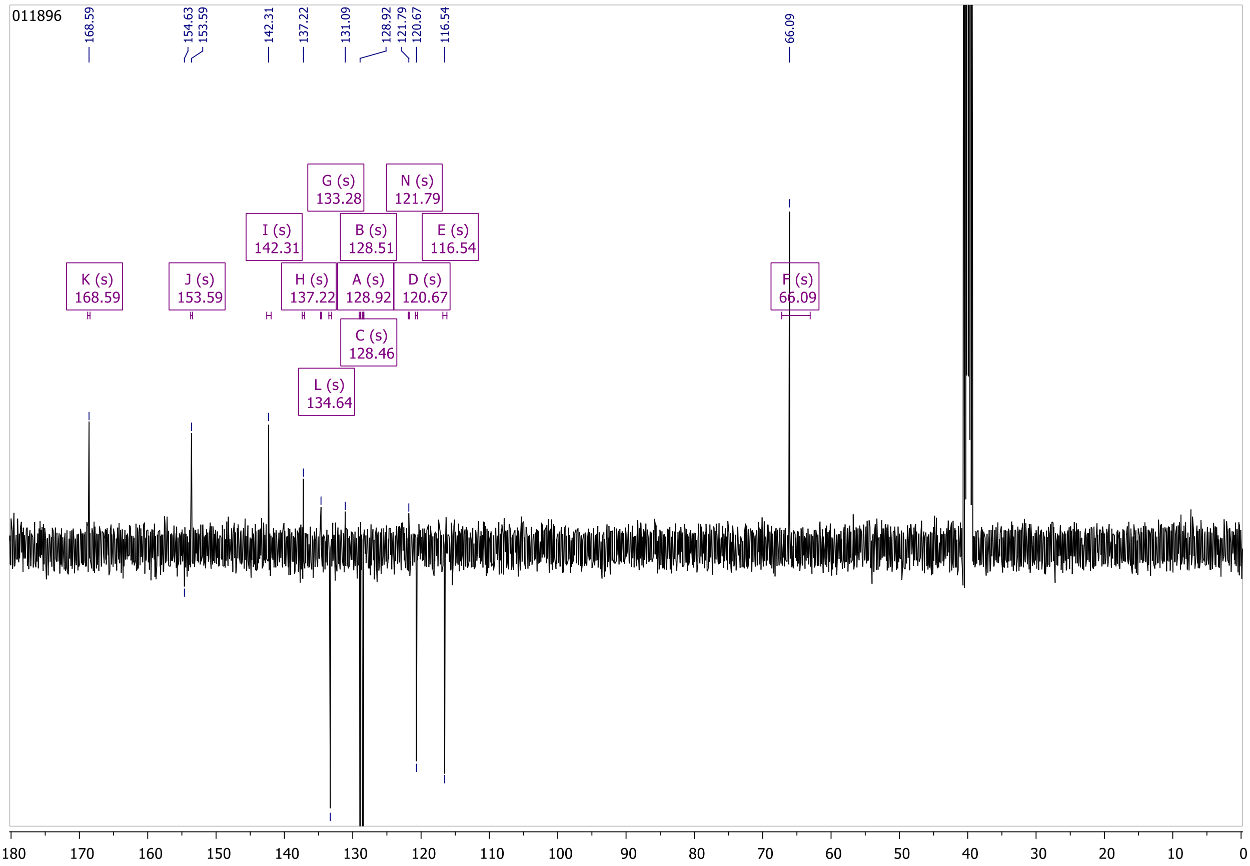
4-Chloro-2-((((2-chlorobenzyl)oxy)carbonyl)amino)benzoic acid (57):





2-(((Benzyloxy)carbonyl)amino)-4-chlorobenzoic acid (58):





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