Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Solvent-Free *N*-Boc Deprotection by *Ex Situ* Generation of Hydrogen Chloride Gas

Rik H. Verschueren, Philippe Gilles, Seger Van Mileghem and Wim M. De Borggraeve*

KU Leuven, Department of Chemistry, Molecular Design and Synthesis, Celestijnenlaan 200F - box 2404, B-3001 Leuven, Belgium

*E-mail: wim.deborggraeve@kuleuven.be

Supporting Information

Contents

1. General Information

^{1}H NMR spectra

^{1}H NMR spectra were recorded on Bruker Avance III HD 400 (working at 400 MHz, console with a Bruker Ascend™ 400 magnet, equipped with a 5 mm PABBO BB/19F-1H/D probe with z-gradients and ATM accessory for Automatic Tuning and Matching) and Bruker Avance II^{+} 600 (600 MHz) spectrometers. Samples were dissolved in $CDCl_3$ or DMSO-d_6 and tetramethylsilane was used as an internal standard. The δ-values are expressed in ppm. The following abbreviations are used in reporting NMR data: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and as combinations thereof, with "br" indicating a broadened peak(s) and "app" indicating apparent.

^{13}C NMR spectra

^{13}C-NMR spectra were recorded on Bruker Avance III HD 400 (working at 100 MHz) and Bruker Avance II^{+} 600 (working at 151 MHz) spectrometers. The deuterated solvents were used as internal standard ($CDCl_3$: 77.16 ppm, triplet; DMSO-d_6: 39.52 ppm, septet). The δ-values are expressed in ppm.

^{19}F NMR spectra

^{19}F NMR spectra were recorded on a Bruker Avance III HD 400 (working at 376 MHz) spectrometer. Samples were dissolved in $CDCl_3$ or DMSO-d_6. The δ-values are expressed in ppm and referenced to $CFCl_3$.

Elemental analysis

CHN (carbon, hydrogen, nitrogen) elemental analyses were obtained using a Thermo Scientific Interscience Flash 2000 Elemental analyser.

HR-MS spectra

HR-MS spectra were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA). Samples were dissolved in a mixture of 1:1 (v/v) acetonitrile:water and infused at 5 µL/min. Spectra were obtained in positive ionization mode with a resolution of 15000 (fwhm) using leucine enkephalin as lock mass.

Chiral HPLC

The enantiomeric purities were determined by HPLC analysis employing an InfinityLab Poroshell 120 Chiral-T (4.6x100mm, 2.7 µm) chiral stationary phase column by comparing the samples with the appropriate racemic mixtures. Conditions are specified in the individual experiments.

Polarimeter

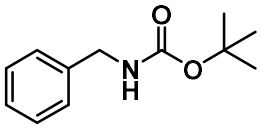
Specific optical rotations were obtained using a Propol Automatic Polarimeter with an optical path length of 0.7 dm and sample holder volume of 5 mL.

Materials

All reagents were obtained from commercially available sources and were used as purchased without further purification. Concentrated sulfuric acid was used as purchased with a minimum concentration of 95%. Other *N*-Boc starting materials were synthesized as reported in this SI. All moisture-sensitive reactions were carried out under argon atmosphere and in flame-dried glassware. Yields refer to isolated compounds after quantitative conversion or after chromatography.

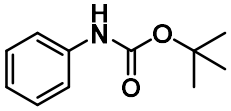
2. Synthesis of *N*-Boc starting materials

***tert*-butyl benzylcarbam6'ate (compound 1')**



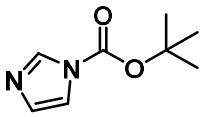
This is an adapted literature procedure.[1] To a 100 mL flask was added subsequently di-*tert*-butyl dicarbonate (21.825 g, 0.100 mol, 1.0 equiv.) and benzylamine (10.9 mL, 0.100 mol, 1.0 equiv.). Under solvent-free conditions, the mixture was heated to 80 °C under vacuum using a rotary evaporator. The pressure was gradually lowered. After full conversion, as monitored via TLC (typically after 15 minutes), the vacuum was increased to fully evaporate the remaining volatiles (*t*BuOH and CO_2). The crude product was recrystallized from heptane to afford *tert*-butyl benzylcarbamate (18.719 g, 0.090 mol, 90%) as transparent crystals. We reused the mother liquor fraction in a second crystallization which significantly increased the product yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.21 (m, 5H), 4.88 (br s, 1H), 4.29 (d, *J* = 5.6 Hz, 2H), 1.46 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.9, 139.0, 128.6, 127.5, 127.3, 79.5, 44.7, 28.4.
These data are in agreement with literature data.[2]

***tert*-butyl phenylcarbamate (compound 6')**



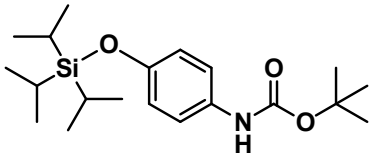
This is an adapted literature procedure.[1] To a 25 mL flask was added subsequently di-*tert*-butyl dicarbonate (4.365 g, 20 mmol, 1.0 equiv.) and aniline (1.8 mL, 20 mmol, 1.0 equiv.). Under solvent-free conditions, the mixture was heated to 80 °C under vacuum using a rotary evaporator. The pressure was gradually lowered. After full conversion, as monitored via TLC, the vacuum was increased to fully evaporate the remaining volatiles (*t*BuOH and CO_2). The crude product was recrystallized from heptane to afford *tert*-butyl phenylcarbamate (3.389 g, 88%) as transparent needles. We reused the mother liquor fraction in a second crystallization which significantly increased the product yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.9 Hz, 2H), 7.26 (t, *J* = 7.9 Hz, 2H), 7.01 (t, *J* = 7.3 Hz, 1H), 6.61 (br s, 1H), 1.51 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.9, 138.4, 129.0, 123.0, 118.6, 80.5, 28.4.
These data are in agreement with literature data.[3]

***tert*-butyl 1*H*-imidazole-1-carboxylate (compound 8')**



This is an adapted literature procedure.[1] To a 25 mL flask was added subsequently di-*tert*-butyl dicarbonate (2.182 g, 10 mmol, 1.0 equiv.) and imidazole (0.681 g, 10 mmol, 1.0 equiv.). The substrates started reaction immediately upon being added to the flask (beware exothermic). Under solvent-free conditions, the mixture was further heated to 80 °C under vacuum using a rotary evaporator. The pressure was gradually lowered. After full conversion, as monitored via TLC (less than 15 minutes), the vacuum was increased to fully evaporate the remaining volatiles (*t*BuOH and CO_2). The crude product was recrystallized from heptane to afford *tert*-butyl 1*H*-imidazole-1-carboxylate (1.543 g, 92%) as transparent crystals. We reused the mother liquor fraction in a second crystallization which significantly increased the product yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (t, *J* = 1.0 Hz, 1H), 7.39 – 7.36 (m, 1H), 7.04 (dd, J_1 = 0.9 Hz, J_2 = 1.6 Hz, 1H), 1.63 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 147.1, 137.0, 130.2, 117.1, 85.5, 27.8.
These data are in agreement with literature data.[2]

***tert*-butyl (4-((triisopropylsilyl)oxy)phenyl)carbamate (compound 23')**



This is a modification of three literature procedures.[4-6] To a solution of *tert*-butyl (4-hydroxyphenyl)carbamate (1.05 g, 5 mmol, 1.0 equiv.) and imidazole (0.681 g, 10 mmol, 2.0 equiv.) in anhydrous THF (10 mL) was slowly added TIPS-Cl (1.377 mL, 6.5 mmol, 1.3 equiv.) via a syringe. The reaction mixture is stirred for 3 hours at room temperature. The reaction mixture is transferred to a separatory funnel along with 10 mL of MTBE and 20 mL of a saturated aq. $NaHCO_3$ solution. After mixing and settling, the aq. layer is removed and the organic layer is washed with brine (20 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography (SiO_2, heptane/Et_2O 9:1). The retrieved oil was crystallized from ethanol (heated for dissolution and supersaturation). After additon of a few drops of water (anti-solvent), the crystallization took place overnight at -26 °C to give colorless needles (1.12 g, 61%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 6.78 – 6.72 (m, 2H), 1.46 (s, 9H), 1.20 (septet, *J* = 7.4 Hz, 3H), 1.05 (d, *J* = 7.3 Hz, 18H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 153.3, 150.7, 133.6, 120.0, 119.8, 79.1, 28.6, 18.2, 12.5.
These data are in agreement with the literature data.[4-6]

3. *N*-Boc Deprotection of *tert*-Butyl Carbamates

3.1. Two-chamber reactors

For this procedure we used two-chamber reactors. You can use a regular two-chamber reactor (Figure S3). However, because this procedure obviates the need for purification and work-up steps, a variant was devised having a detachable chamber allowing direct product isolation. With a classical two-chamber reactor, the product still needs to be retrieved from chamber B, which sometimes can be inconvenient. Furthermore, this transfer step can cause product loss, especially for small-scale reactions. In addition, chamber A still holds sulfuric acid which comes with the accompanied risks.
Regular two-chamber reactors are commercially available or can simply be made by means of glassblowing. Detachable two-chamber reactors can be made by glassblowing using the following parts:

- GL 18 (open) screw caps (1)
- PTFE disk with hole (recyclable) (2)
- Silicone/PTFE septum (3)
- GL 18 screwthread tubes (4)
- A connection joint:
  - Cone with rim (5)
  - Threaded socket (6)
  - Loosening ring (7)
  - Open screw cap (8)
  - O-ring (9)

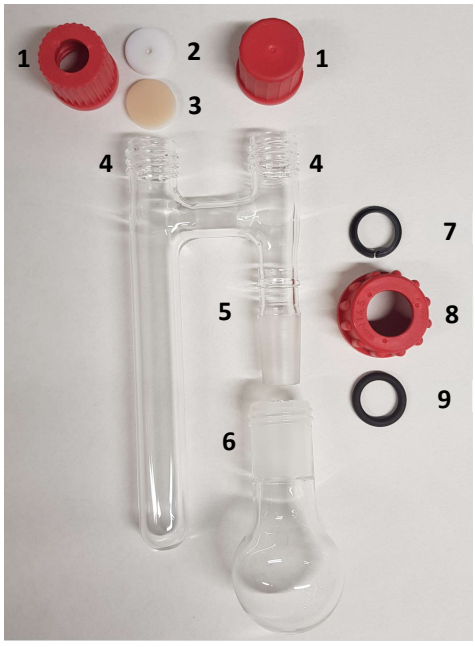


Figure S1: Components to make a detachable two-chamber reactor.

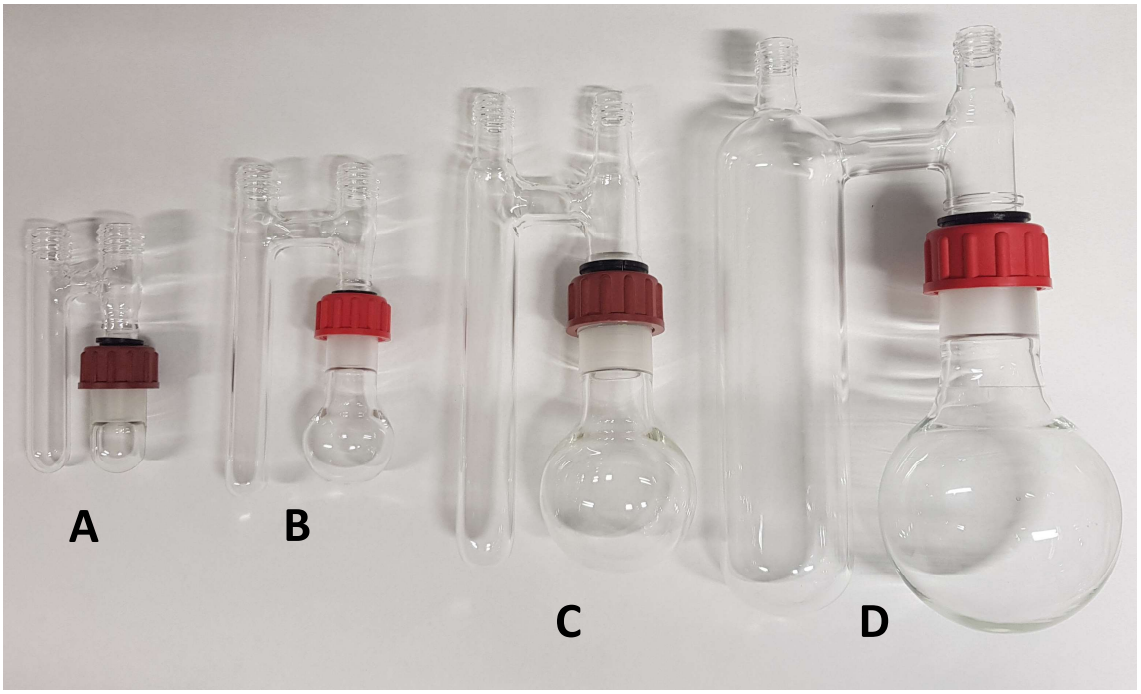


Figure S2: Detachable two-chamber reactors of different sizes: small (**A**, B14 joint, V = 23 mL); small (**B**, B14 joint, V = 46 mL); medium (**C**, B24 joint, V = 170 mL); large (**D**, B29 joint, V = 620 mL).

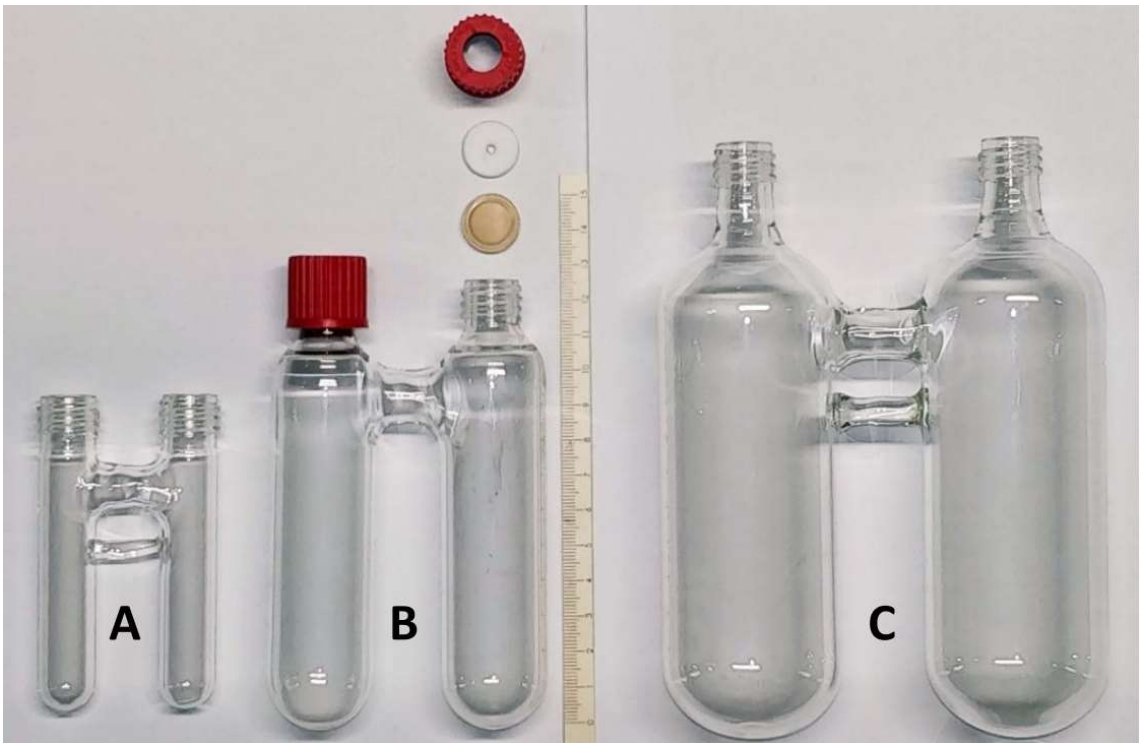
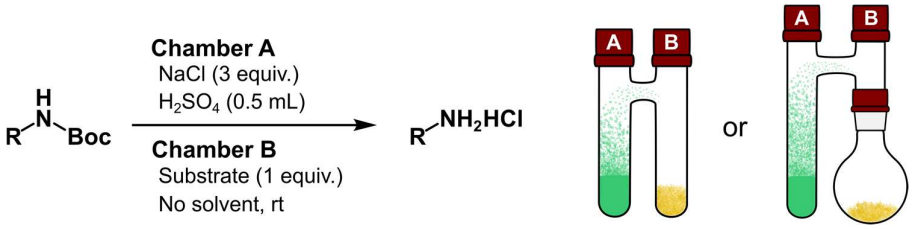


Figure S3: Regular two-chamber reactors of different sizes: small (**A**, V = 22 mL); medium (**B**, V = 120 mL); large (**D**, V = 400 mL). Invented by the Skrydstrup group.[7, 8]

3.2. General Procedures



Procedure A

Chamber A of a flame-dried small two-chamber reactor (Figure S2-S3) was charged with a stirring bar and sodium chloride (88 mg, 1.5 mmol, 3.0 equiv.). Next, the *N*-Boc protected substrate is finely ground with a pestle and mortar and the powder (0.5 mmol, 1.0 equiv.) is transferred to (detachable) chamber B. Finally, the reactor was capped and 0.5 mL of concentrated sulfuric acid (H_2SO_4, >95%) was added by injection through the septum in chamber A and instant gas formation was observed.

After 1 to 20 hours at room temperature, depending on the substrate, one of the caps was carefully removed to release the residual pressure. The reaction was stirred for another few minutes to ensure that all hydrogen chloride gas was extracted out of the fume hood.

Next, chamber B was detached to isolate the hydrochloric acid salt in quantitative yield. After homogenization, a sample of the product was taken and submitted to ^{1}H NMR to confirm the substrate was fully deprotected and no side reactions had occurred.

Procedure B

In case when acid labile functionalities are present. Identical to procedure A, except after closing the system the air is replaced with nitrogen or argon gas to eliminate moisture.

An instructional video is available online in the *Supplementary Information* section: N-Boc_Instructional_Video.mp4

Caution !

1) Hydrogen chloride gas is highly corrosive. Residual HCl gas can be evacuated by carefully unscrewing the caps in a fumehood. Even safer, before unscrewing, release the pressure by venting the system with a needle of which the outlet passes through an alkaline solution (e.g. NaOH) to quench the HCl gas.
2) Our lab typically employs a maximum pressure in a two-chamber vessel of 5 bar. In order not to exceed this pressure, the molar amount of generated gas needs to be limited depending on the size of the reactor. For our smallest reactor, the amount of generated gas was limited to 3.7 mmol at room temperature. This was calculated using the ideal gas law based on an inner volume of 23 mL. For the large detachable two-chamber reactor (inner volume of 610 mL), the amount of generated gas was limited to 100 mmol at room temperature.

Large scale deprotection of N-Boc benzylamine

Chamber A of a flame-dried medium-sized detachable two-chamber reactor (Figure S2) was charged with a stirring bar and sodium chloride (NaCl, 877 mg, 15 mmol, 3.0 equiv.). Next, *N*-Boc benzylamine is finely ground with a pestle and mortar and the powder (1.036 g, 5 mmol, 1.0 equiv.) is transferred to (detachable) chamber B. Then, chamber B was attached and the reactor capped. At these larger scales it is advised to cool chamber A to slow down the gas generation rate. We cooled chamber A with acetone/dry ice and added 4 mL of concentrated sulfuric acid (H_2SO_4, >95%) by injection through the septum. Instant gas formation was observed, yet at a slower pace due to cooling. After 4 hours of reaction time, full conversion was achieved and the pressure was released by venting the system by introducing a needle through the septum. The needle outlet was passed through an alkaline solution (NaOH) to quench the excess HCl gas. Then, one of the caps was removed and chamber A was stirred for another few minutes to ensure that all HCl gas was extracted out of the fume hood. Passing

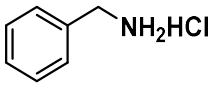
pressurized air or nitrogen gas through the reactor can help in the process. Finally, chamber B was detached to isolate benzylamine hydrochloride in quantitative yield as a white powder (721 mg, 5 mmol, >99%).

Large scale deprotection of Boc-L-pyroglutamate

Chamber A of a flame-dried large detachable two-chamber reactor (Figure S2) was charged with a stirring bar and sodium chloride (2.4 g, 41.10 mmol, 2.0 equiv.). Next, Boc-*L*-pyroglutamate is finely ground with a pestle and mortar and the powder (5.0 g, 20.55 mmol, 1.0 equiv.) is transferred to (detachable) chamber B. Then, chamber B was attached and the reactor capped. At these larger scales it is advised to cool chamber A to slow down the gas generation rate. We cooled chamber A with acetone/dry ice and added 10 mL of sulfuric acid (H_2SO_4) by injection through the septum. Instant gas formation was observed, yet at a slower pace due to cooling. After 4 hours of reaction time, full conversion was achieved and the pressure was released by introducing a needle through the septum of which the outlet was passed through an alkaline solution (NaOH) to quench the excess HCl gas. Then, one of the caps was removed and chamber A was stirred for another few minutes to ensure that all HCl gas was extracted out of the fume hood. Blowing pressurized air or nitrogen gas through the reactor can help in the process. Finally, chamber B was detached to isolate methyl *L*-pyroglutamate in quantitative yield as a slightly yellow oil (3.01 g, 20.55 mmol, >99%).

3.3. Deprotected substrates

benzylamine hydrochloride (compound 1)

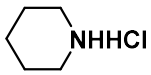


General procedure A was followed using 104 mg of *N*-Boc benzylamine (0.5 mmol, 1.0 equiv.). After 1 hour of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as a white powder (72 mg, >99%).

^{1}H NMR (400 MHz, DMSO- d_6) δ 8.50 (br s, 3H), 7.54 – 7.47 (m, 2H), 7.45 – 7.34 (m, 3H), 4.00 (s, 2H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 134.6, 129.4, 129.0, 128.8, 42.6. **Elemental analysis**: calculated for $C_7H_{10}ClN$: C, 58.54%; H, 7.02%; N, 9.75%; found: C, 58.36%; H, 7.08%; N, 9.71%.

These data are in agreement with literature data.[9]

piperidine hydrochloride (compound 2)

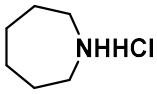


General procedure A was followed using 93 mg of *N*-Boc-piperidine (0.5 mmol, 1.0 equiv.). After 1 hour of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as an off-white solid (61 mg, >99%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (br s, 2H), 3.01 – 2.91 (m, 4H), 1.72 – 1.63 (m, 4H), 1.59 -1.50 (m, 2H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 43.9, 22.5, 22.2.

These data are in agreement with literature data.[10, 11]

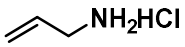
azepane hydrochloride (compound 3)



General procedure A was followed using 100 mg of *N*-Boc-hexamethyleneimine (0.5 mmol, 1.0 equiv.). After 1 hour of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as an off-white solid (68 mg, >99%).

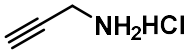
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (br s, 2H), 3.07 – 3.01 (m, 4H), 1.80 – 1.71 (m, 4H), 1.63 - 1.54 (m, 4H). **^{13}C NMR** (75 MHz, DMSO-d_6) δ 44.8, 26.1, 24.4. **Elemental analysis**: calculated for $C_6H_{14}ClN$: C, 53.13%; H, 10.40%; N, 10.33%; found: C, 52.89%; H, 10.45%; N, 9.96%.

allylamine hydrochloride (compound 4)



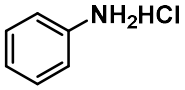
General procedure A was followed using of 79 mg *N*-Boc allylamine (0.5 mmol, 1.0 equiv.). After 1 hour of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as a white solid (47 mg, >99%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (br s, 3H), 5.97 – 5.84 (m, 1H), 5.43 – 4.34 (m, 1H), 5.33 – 5.26 (m, 1H), 3.48 – 3.36 (m, 2H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 136.2, 125.0, 46.0.
These data are in agreement with literature data.[12]

propargylamine hydrochloride (compound 5)



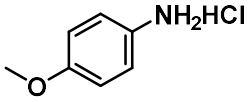
General procedure A was followed using 78 mg of *N*-Boc-propargylamine (0.5 mmol, 1.0 equiv.). After 1 hour of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as an off-white solid (slight tan) (46 mg, >99%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (br s, 3H), 3.71 (*J* = d, 2.6 Hz, 2H), 3.59 (t, *J* = 2.6 Hz, 1H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 78.3, 77.4, 28.5. **Elemental analysis**: calculated for C_3H_6ClN: C, 39.36%; H, 6.61%; N, 15.30%; found: C, 38.96%; H, 6.67%; N, 14.75%.

aniline hydrochloride (compound 6)



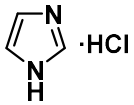
General procedure A was followed using 97 mg of *N*-Boc aniline (0.5 mmol, 1.0 equiv.). After 1 hour of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as a white powder (65 mg, >99%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (br s, between 2H & 3H), 7.50 – 7.42 (m, 2H), 7.37 – 7.26 (m, 3H).
^{13}C NMR (100 MHz, DMSO-d_6) δ 132.8, 130.2, 128.2, 123.5.
These data are in agreement with literature data.[13]

4-methoxyaniline hydrochloride (compound 7)



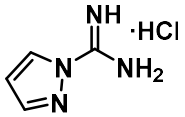
General procedure A was followed using 112 mg of *N*-Boc-4-methoxyaniline (0.5 mmol, 1.0 equiv.). After 3 hours of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as a yellow powder (78 mg, >99%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (br s, 3H), 7.33 – 7.26 (m, 2H), 7.07 – 7.00 (m, 2H), 3.78 (s, 3H).
^{13}C NMR (100 MHz, DMSO-d_6) δ 159.1, 124.9, 124.7, 115.3, 55.9.
These data are in agreement with literature data.[14]

imidazole hydrochloride (compound 8)



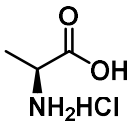
General procedure A was followed using 84 mg of Boc-imidazole (0.5 mmol, 1.0 equiv.). After 1 hour of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as a white powder (52 mg, >99%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 17.71 (br s, 2H), 9.14 (t, J = 1.3 Hz, 1H), 7.69 (d, J = 1.3 Hz, 2H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 134.4, 119.6. **Elemental analysis**: calculated for $C_3H_5ClN_2$: C, 34.47%; H, 4.82%; N, 26.80; found: C, 34.23%; H, 4.91%; N, 26.43%.

1*H*-pyrazole-1-carboxamidine hydrochloride (compound 9)



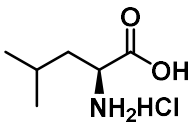
General procedure A was followed using 105 mg of *tert*-butyl (imino(1*H*-pyrazol-1-yl)methyl)carbamate (0.5 mmol, 1.0 equiv.). After 3 hours of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as a white powder (73 mg, >99%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.69 (br s, 2H), 9.44 (br s, 2H), 8.85 (d, J = 2.9 Hz, 1H), 8.10 (d, J = 1.5 Hz, 1H), 6.81 (dd, J_1 = 1.6 Hz, J_2 = 2.9 Hz, 1H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 152.5, 146.1, 131.7, 112.0. **Elemental analysis**: calculated for $C_4H_7ClN_4$: C, 32.78%; H, 4.81%; N, 38.22%; found: C, 31.75%; H, 4.94%; N, 9.71%.
These data are in agreement with literature data.[15]

***L*-alanine hydrochloride (compound 10)**



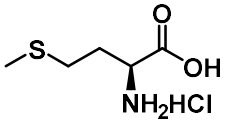
General procedure A was followed using 95 mg of Boc-*L*-alanine (0.5 mmol, 1.0 equiv.). After 1 hour of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as a white powder (63 mg, >99%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.68 (br s, 1H), 8.41 (br s, 3H), 3.91 (q, J = 7.2 Hz, 1H), 1.4 (d, J = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 171.4, 47.7, 15.7. **Elemental analysis**: calculated for $C_3H_8ClNO_2$: C, 28.70%; H, 6.42%; N, 11.16%; found: C, 28.59%; H, 6.41%; N, 10.94%. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = + 14.57° (c = 2 g/dL, 6N HCl). These data are in agreement with literature data.[16]

***L*-leucine hydrochloride (compound 11)**



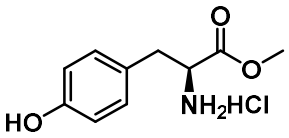
General procedure A was followed using 116 mg of Boc-*L*-leucine (0.5 mmol, 1.0 equiv.). After 3 hours of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as a white powder (84 mg, >99%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.78 (br s, 1H), 8.30 (br s, 3H), 3.82 (t, J = 7.0 Hz, 1H), 1.78 (septet, J = 6.6 Hz, 1H), 1.69 – 1.55 (m, 2H), 0.90 (m, J_1 = 2.7 Hz, J_2 = 6.5 Hz, 6H). **^{13}C NMR** (100 MHz, DMSO-d_6) **Elemental analysis**: calculated for $C_6H_{14}ClNO_2$: C, 42.99%; H, 8.42%; N, 8.36%; found: C, 42.81%; H, 8.42%; N, 8.17%. **Chiral HPLC**: H_2O/H_3PO_4 1 wt.%, 0.1 mL/min, 30 °C, 210 nm, RT = 7.03 min.
These data are in agreement with literature data.[17]

_L_-methionine hydrochloride (compound 12)



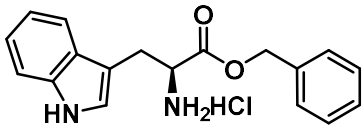
General procedure A was followed using 125 mg of Boc-*L*-methionine (0.5 mmol, 1.0 equiv.). After 1 hour of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as a white powder (93 mg, >99%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.89 (br s, 1H), 8.38 (br s, 3H), 3.97 (t, *J* = 6.2 Hz, 1H), 2.69 – 2.52 (m, 2H), 2.13 –1.96 (m, 5H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 170.5, 50.8, 29.4, 28.5, 14.2. $[\alpha]_D^{25}$ = + 23.14° (c = 2 g/dL, 6N HCl). **Chiral HPLC**: H_2O/H_3PO_4 1 wt.%, 0.2 mL/min, 30 °C, 210 nm, RT = 4.17 min.
These data are in agreement with literature data.[16]

methyl _L_-tyrosinate hydrochloride (compound 13)



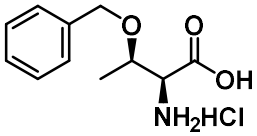
General procedure A was followed using 148 mg of Boc-*L*-tyrosine methyl ester (0.5 mmol, 1.0 equiv.). After 14 hours of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as a white powder (116 mg, >99%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.45 (s, 1H), 8.54 (br s, 3H), 7.04 – 6.97 (m, 2H), 6.75 – 6.69 (m, 2H), 4.16 (t, *J* = 6.4 Hz, 1H), 3.67 (s, 3H), 3.09 – 2.94 (m, 2H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 169.4, 156.7, 130.3, 124.3, 115.4, 53.4, 52.5, 35.0.
These data are in agreement with literature data.[18]

benzyl _L_-tryptophanate hydrochloride (compound 14)



General procedure B was followed using 197 mg of *N*α-Boc-*L*-tryptophan benzyl ester (0.5 mmol, 1.0 equiv.) and by generating 2.5 mmol of HCl gas (146 mg NaCl, 0.5 mL H_2SO_4). After 14 hours of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as a white powder (165 mg, >99%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1H), 8.51 (br s, 3H), 7.52 (app d, *J* = 7.8 Hz, 1H), 7.4 (app d, *J* = 8.1 Hz, 1H), 7.37 – 7.31 (m, 3H), 7.25 –7.18 (m, 3H), 7.15 – 7.08 (m, 1H), 7.05 – 6.98 (m, 1H), 5.20 – 5.04 (m, 2H), 4.32 (t, *J* = 6.4 Hz, 1H), 3.37 – 3.24 (m, 2H, partial overlap with H_2O peak). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 169.8, 136.7, 135.4, 128.9, 128.7, 128.5, 127.4, 125.4, 121.6, 119.1, 118.5, 112.0, 106.9, 67.5, 53.2, 26.8. **Elemental analysis**: calculated for $C_{18}H_{19}ClN_2O_2$: 65.35%; H, 5.79%; N, 8.47%; found: C, 64.73%; H, 5.79%; N, 8.03%.
These data are in agreement with literature data.[19]

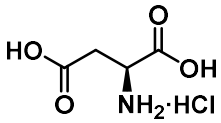
***O*-benzyl-*L*-threonine hydrochloride (compound 15)**



General procedure B was followed using 155 mg of Boc-*L*-Thr(Bzl)-OH (0.5 mmol, 1.0 equiv.). After 5 hours of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as a white powder (123 mg, >99%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.91 (s, 1H), 8.37 (br s, 3H), 7.40 – 7.25 (m, 5H), 4.54 (ABq, J = 11.9 Hz, 2H), 4.16 – 4.08 (m, 1H), 4.02 (d, J = 3.2 Hz, 1H), 1.29 (d, J = 6.5 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 169.8, 138.4, 128.6, 128.1, 128.0, 73.1, 70.7, 57.0, 16.6. **Elemental analysis**: calculated for $C_{11}H_{16}ClNO_3$: C, 53.77%; H, 6.56%; N, 5.70%; found: C, 53.60%; H, 6.55%; N, 5.62%.

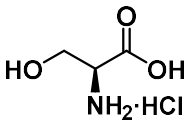
***L*-aspartic acid hydrochloride (compound 16)**



General procedure B was followed using 145 mg of Boc-Asp(O*t*Bu)-OH (0.5 mmol, 1.0 equiv.). After 16 hours of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as a white powder (85 mg, >99%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 14.3 – 12.6 (br s, 2H), 8.36 (br s, 2H), 4.15 (t, J = 5.3 Hz, 1H), 2.86 (d, J = 5.4 Hz, 2H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 171.4, 170.3, 48.9, 34.7. **Elemental analysis**: calculated for $C_4H_8ClNO_4$: C, 28.33%; H, 4.76%; N, 8.26%; found: C, 28.29%; H, 4.76%; N, 8.18%. **Chiral HPLC**: H_2O/H_3PO_4 1 wt.%, 0.1 mL/min, column cooled on ice, 210 nm, RT = 12.58 min.

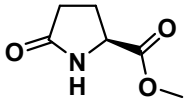
***L*-serine hydrochloride (compound 17)**



General procedure B was followed using 131 mg of Boc-Ser(*t*Bu)-OH (0.5 mmol, 1.0 equiv.). After 16 hours of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as a white powder (71 mg, >99%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 14.1 – 13.3 (br s, 1H), 8.36 (br s, 3H), 5.84 – 5.31 (m, 1H), 3.96 (s, 1H), 3.82 (m, 2H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 169.8, 59.9, 54.8. **Elemental analysis**: calculated for $C_3H_8ClNO_3$: C, 25.46%; H, 5.70%; N, 9.90%; found: C, 25.40%; H, 5.71%; N, 9.77%.

methyl *L*-pyroglutamate (compound 18)

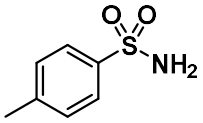


General procedure B was followed using 122 mg of methyl Boc-*L*-pyroglutamate (0.5 mmol, 1.0 equiv.). After 2 hours of reaction time, full conversion was achieved and methyl *L*-pyroglutamate was readily obtained as a slightly yellow oil (73 mg, >99%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.0 (br s, 1H), 4.18 (dd, J_1 = 3.8 Hz, J_2 = 9.1 Hz, 1H), 3.67 (s, 3H), 2.40 – 2.27 (m, 1H), 2.21 – 2.06 (m, 2H), 2.04 – 1.93 (m, 1H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 177.5, 173.8, 55.1, 52.5, 29.3, 24.9.

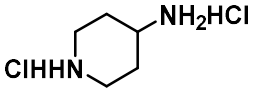
These data are in agreement with literature data.[20]

4-methylbenzenesulfonamide (compound 19)



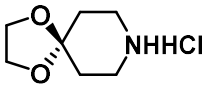
General procedure A was followed using 136 mg of *N*-Boc-sulfonamide (0.5 mmol, 1.0 equiv.). After 4 hours of reaction time, full conversion was achieved and *p*-toluenesulfonamide was readily obtained as a white powder (86 mg, >99%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (d, *J* = 8.3, 2H), 7.36 (d, 2H), 7.26 (br s, 2H), 2.37 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 142.3, 141.9, 129.8, 126.1, 21.4. **Elemental analysis**: calculated for $C_7H_9NO_2S$: C, 49.11%; H, 5.30%; N, 8.18%; found: C, 48.76%; H, 5.30%; N, 7.69%.
These data are in agreement with literature data.[21]

4-aminopiperidine dihydrochloride (compound 20)



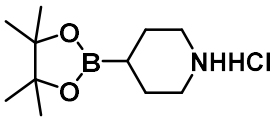
General procedure A was followed using 100.1 mg of 4-(*N*-Boc-amino)piperidine (0.5 mmol, 1.0 equiv.). Due to the extra amine functionality, 2.5 mmol of HCl gas was generated (146 mg NaCl, 0.5 mL H_2SO_4). After 5 hours of reaction time, full conversion was achieved and the bis hydrochloride product was readily obtained as a white powder (87 mg, >99%).
^{1}H NMR (100 MHz, DMSO-d_6) δ 9.02 (app d, *J* = 64.1 Hz, 2H, $^{+}NH_2$), 8.36 (br s, 3H, $^{+}NH_3$), 3.36-3.24 (m, 3H), 2.94 (q, *J* = 11.8 Hz, 2H), 2.06 (d, *J* = 11.5 Hz, 2H), 1.85-1.70 (m, 2H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 45.5, 41.6, 26.8. **Elemental analysis**: calculated for $C_5H_{14}Cl_2N_2$: C, 34.70%; H, 8.15%; N, 16.19%; found: C, 33.51%; H, 8.26%; N, 14.87%.

1,4-dioxa-8-azaspiro[4.5]decane hydrochloride (compound 21)



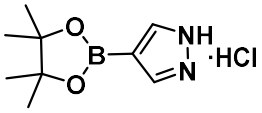
General procedure B was followed using 122 mg of *tert*-butyl 1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (0.5 mmol, 1.0 equiv.). After 4 hours of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as a white powder (90 mg, >99%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (br s, 2H), 3.93 (s, 4H), 3.13 – 3.07 (m, 4H), 1.84 (app t, *J* = 6.1 Hz, 4H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 104.6, 64.5, 42.5, 31.9. **Elemental analysis**: calculated for $C_7H_{14}ClNO_2$: C, 46.80%; H, 7.85%; N, 7.80%; found: C, 46.63%; H, 7.95%; N, 7.14%.
These data are in agreement with literature data.[22]

4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine hydrochloride (compound 22)



General procedure B was followed using 156 mg of *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine-1-carboxylate (0.5 mmol, 1.0 equiv.). After 4 hours of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as a white powder (124 mg, >99%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 1H), 8.87 (s, 1H), 3.09 – 2.98 (m, 2H), 2.90 – 2.77 (m, 2H), 1.78 – 1.69 (m, 2H), 1.66 – 1.53 (m, 2H), 1.19 (s, 12H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 83.6, 44.0, 25.0, 23.8. (^{13}C signal of carbon with "C-B" bond not visible due to quadrupole relaxation)[23] **Elemental analysis**: calculated for $C_{11}H_{23}BClNO_2$: C, 53.37%; H, 9.36%; N, 5.66%; found: C, 42.95%; H, 9.31%; N, 5.31%.

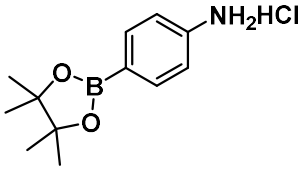
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole hydrochloride (compound 23)



General procedure B was followed using 147 mg of *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole-1-carboxylate (0.5 mmol, 1.0 equiv.). After 2 hours of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as a white powder (115 mg, >99%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (s, 2H), 1.25 (s, 12H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 140.0, 83.5, 25.1. (^{13}C signal of carbon with "C-B" bond not visible due to quadrupole relaxation)[23] **Elemental analysis**: calculated for $C_9H_{16}BClN_2O_2$: C, 46.90%; H, 7.00%; N, 12.15%; found: C, 47.03%; H, 7.00%; N, 11.97%.

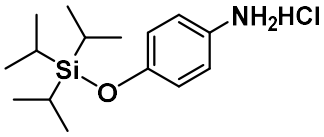
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline hydrochloride (compound 24)



General procedure B was followed using 160 mg of *tert*-butyl (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamate (0.5 mmol, 1.0 equiv.) but 2.5 mmol of HCl gas (5 equiv.) was generated (146 mg NaCl, 0.5 mL H_2SO_4). After 14 hours of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as a white powder (128 mg, >99%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (app d, *J* = 7.8 Hz, 2H), 6.99 (app d, *J* = 7.8 Hz, 2H), 1.28 (s, 12H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 136.3, 120.5, 84.1, 25.1. (^{13}C signal of carbon with "C-B" bond not visible due to quadrupole relaxation)[23] **Elemental analysis**: calculated for $C_{12}H_{19}BClNO_2$: C, 56.40%; H, 7.49%; N, 5.48%; found: C, 55.81%; H, 7.55%; N, 4.83%.

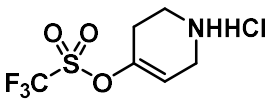
4-((triisopropylsilyl)oxy)aniline hydrochloride (compound 25)



General procedure B was followed using 183 mg of *tert*-butyl (4-((triisopropylsilyl)oxy)phenyl)carbamate (0.5 mmol, 1.0 equiv.) but 2.5 mmol of HCl gas (5 equiv.) were generated (146 mg NaCl, 0.5 mL H_2SO_4). After 14 hours of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as a white powder (151 mg, >99%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (br s, 3H), 7.31 – 7.24 (m, 2H), 7.00 – 6.93 (m, 2H), 1.26 (septet, *J* = 7.4 Hz, 3H), 1.06 (d, *J* = 7.4 Hz, 18H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 155.4, 125.6, 124.9, 121.0, 18.2, 12.4. **Elemental analysis**: calculated for $C_{15}H_{28}ClNOSi$: C, 59.67%; H, 9.35%; N, 4.64; found: C, 58.93%; H, 9.22%; N, 4.25%.

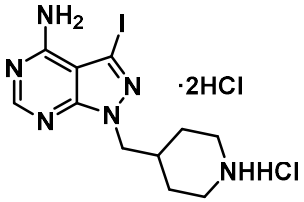
1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate hydrochloride (compound 26)



General procedure B was followed using 166 mg of *N*-Boc-4-trifluoromethanesulfonyloxy-3,6-dihydro-2*H*-pyridine (0.5 mmol, 1.0 equiv.). After 2 hours of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as an off-white solid (134 mg, >99%).

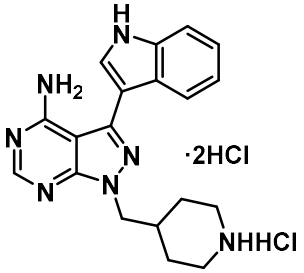
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.55 (br s, 2H), 6.11 – 6.07 (m, 1H), 3.78 (app d, *J* = 2.9 Hz, 2H), 3.32 (t, *J* = 6.0 Hz, 2H), 2.70 – 2.62 (m, 2H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 145.9, 118.4 (q, *J* = 320.5 Hz, 1C, CF_3), 114.3, 40.4, 40.3, 24.6. **^{19}F NMR** (377 MHz, DMSO-d_6) δ -73.6. **Elemental analysis**: calculated for $C_6H_9ClF_3NO_3S$: C, 26.93%; H, 3.39%; N, 5.23%; found: C, 27.33%; H, 3.43%; N, 4.73%.

3-iodo-1-(piperidin-4-ylmethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine trihydrochloride (compound 27)



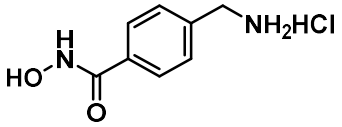
General procedure B was followed using 92 mg of *tert*-butyl 4-((4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl)piperidine-1-carboxylate (0.2 mmol, 1.0 equiv.) but 2.0 mmol of HCl gas (10 equiv.) were generated (117 mg NaCl, 0.5 mL H_2SO_4). After 20 hours of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as an off-white (yellow) powder (93 mg, >99%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (d, *J* = 10.2 Hz, 1H, $^{+}NH_2$), 8.60 (d, *J* = 10.8 Hz, 1H, $^{+}NH_2$), 8.37 (s, 1H), 4.24 (d, *J* = 7.0 Hz, 2H), 3.22 (d, *J* = 12.5 Hz, 2H), 2.81 (q, *J* = 11.6 Hz, 2H), 2.24 – 2.11 (m, 1H), 1.64 (d, *J* = 12.6 Hz, 2H), 1.48 -1.33 (m, 2H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 153.2, 152.3, 148.7, 103.1, 93.6, 52.2, 42.8, 34.3, 26.2. **Elemental analysis** calculated for $C_{11}H_{18}Cl_3IN_6$: C, 28.26%; H, 3.88%; N, 17.97%; found: C, 27.80%; H, 4.13%; N, 17.16%.

3-(1*H*-indol-3-yl)-1-(piperidin-4-ylmethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine trihydrochloride (compound 28)



General procedure B was followed using 10 mg of *tert*-butyl 4-((4-amino-3-(1*H*-indol-3-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl)piperidine-1-carboxylate. Due to the "high value" of this compound and therefore ensure good conversion, a large excess of HCl gas was generated (88 mg NaCl, 0.5 mL H_2SO_4). After 20 hours of reaction time, near full conversion was achieved (3% starting material left) and the hydrochloride product was readily obtained as a yellow powder (10 mg, >97%).
^{1}H NMR (600 MHz, DMSO-d_6) δ 11.71 (s, 1H, NH), 8.95 (app d, *J* = 9.2 Hz, 1H, $^{+}NH_2$), 8.72 (app d, *J* = 10.2 Hz, 1H, $^{+}NH_2$), 8.53 (s, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.78 (d, *J* = 2.7 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.27 – 7.20 (m, 1H), 7.18 – 7.11 (m, 1H), 4.37 (d, *J* = 7.0 Hz, 2H), 3.26 (d, *J* = 12.1 Hz, 2H), 2.86 (q, *J* = 11.8 Hz, 2H), 2.38 – 2.25 (m, 1H), 1.75 (d, *J* = 12.4 Hz, 2H), 1.59 – 1.45 (m, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 154.3, 152.5, 149.5, 142.1, 137.0, 127.0, 126.0, 122.8, 120.5, 120.5, 112.5, 106.5, 97.3, 51.7, 43.0, 34.3, 26.4.
These data are in agreement with literature data.[24]

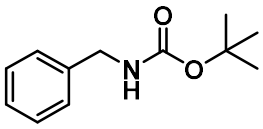
4-(aminomethyl)-*N*-hydroxybenzamide hydrochloride (compound 29)

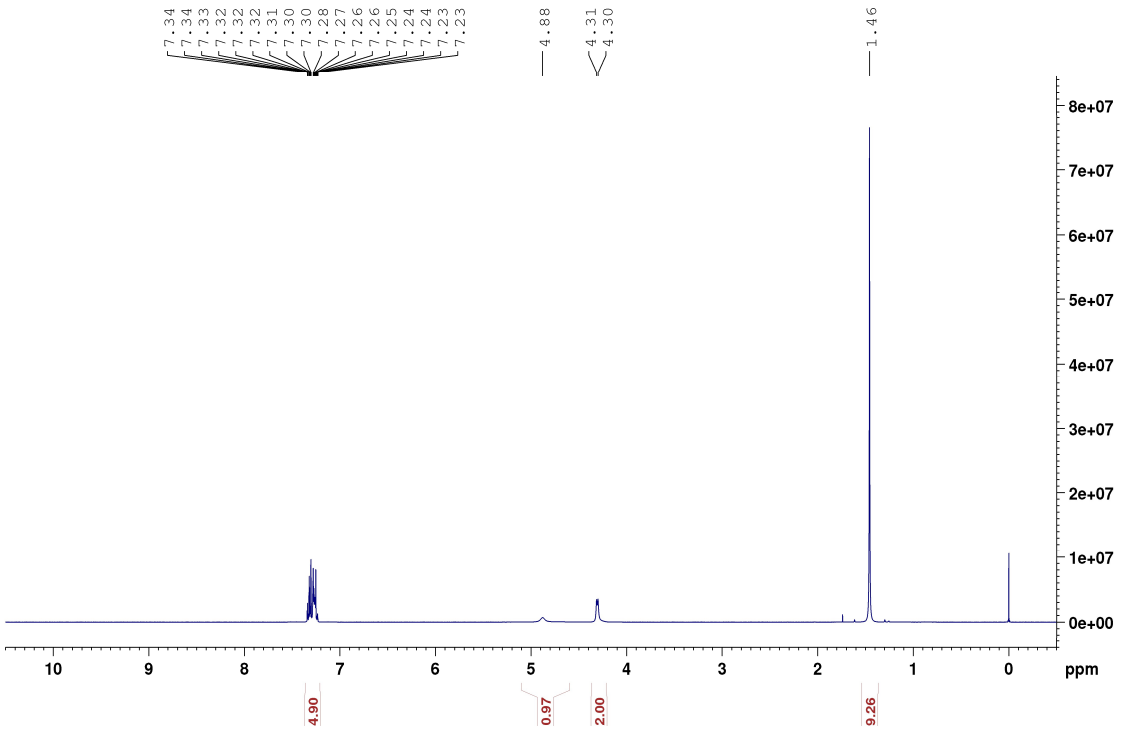


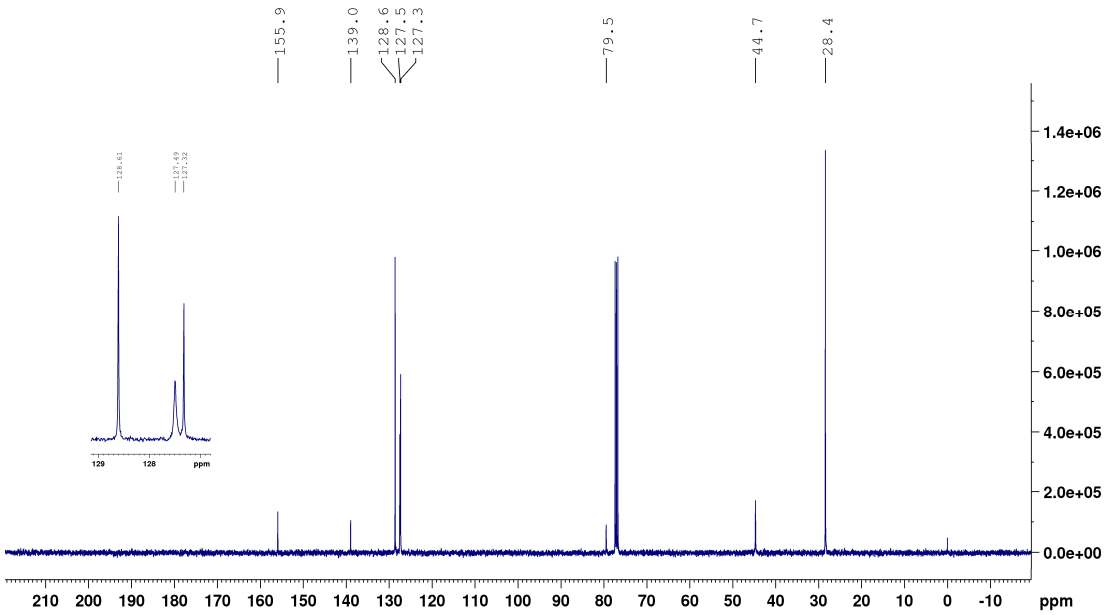
General procedure B was followed using 53.3 mg of *tert*-butyl (4-(hydroxycarbamoyl)benzyl)carbamate (0.2 mmol, 1.0 equiv.). To ensure ensure full conversion, an excess of HCl gas was generated (10 equiv., 117 mg NaCl, 0.5 mL H_2SO_4). After 20 hours of reaction time, full conversion was achieved and the hydrochloride product was readily obtained as an off-white powder (40.5 mg, >99%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.28 (br s, 1H), 8.47 (br s, 3H), 7.82 – 7.77 (m, 2H), 7.59 – 7.54 (m, 2H), 4.08 (q, *J* = 5.8 Hz, 2H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 164.0, 137.5, 133.2, 129.3, 127.5, 42.3.
HR-MS (ESI) calculated for $C_8H_{11}N_2O_2^+$ $[M+H]^+$ 167.0815; found 167.0821.

4. NMR Spectra

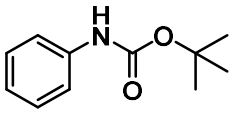
***tert*-butyl benzylcarbamate (compound 1')**

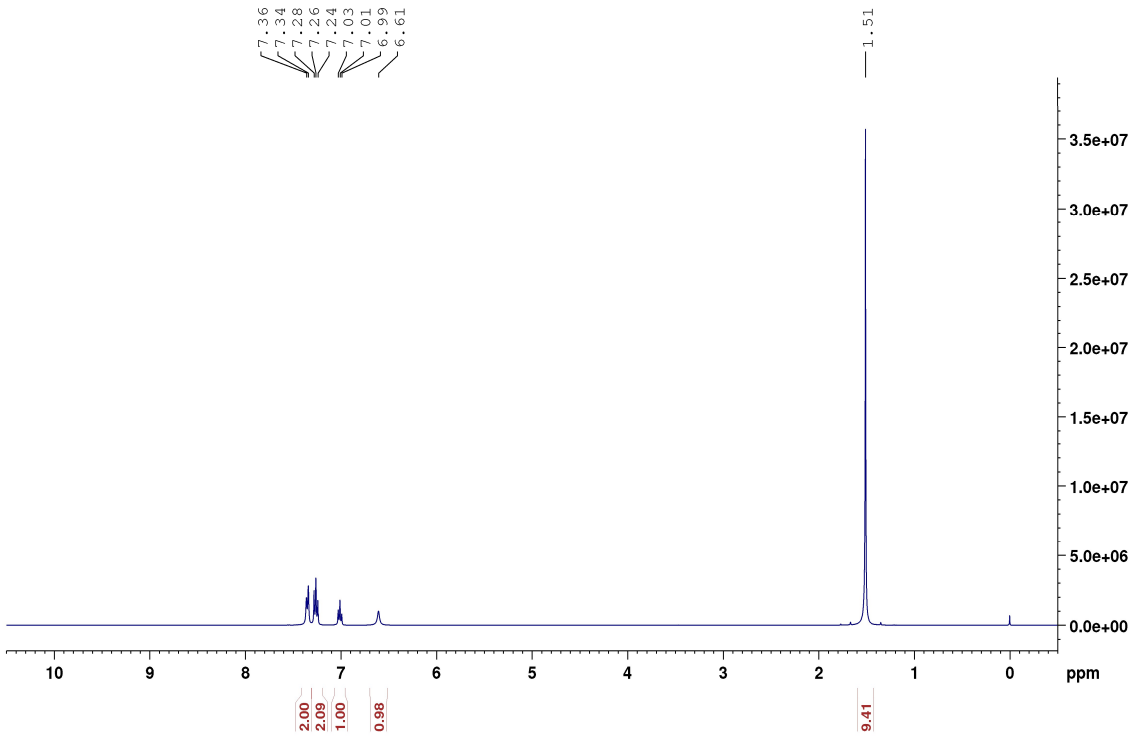


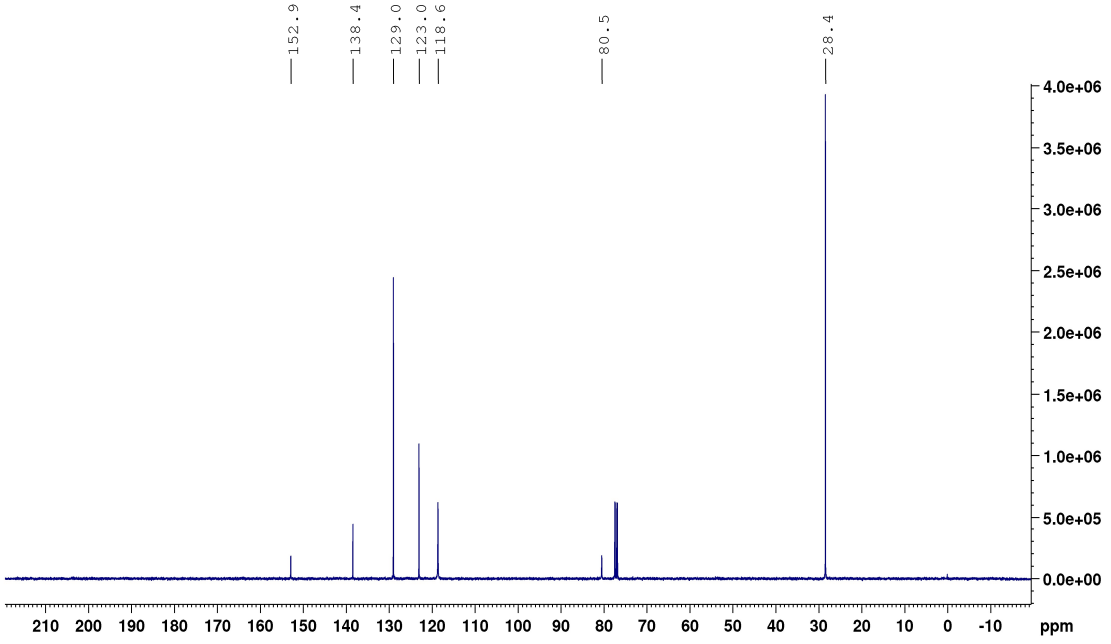




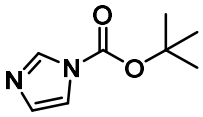
***tert*-butyl phenylcarbamate (compound 6')**

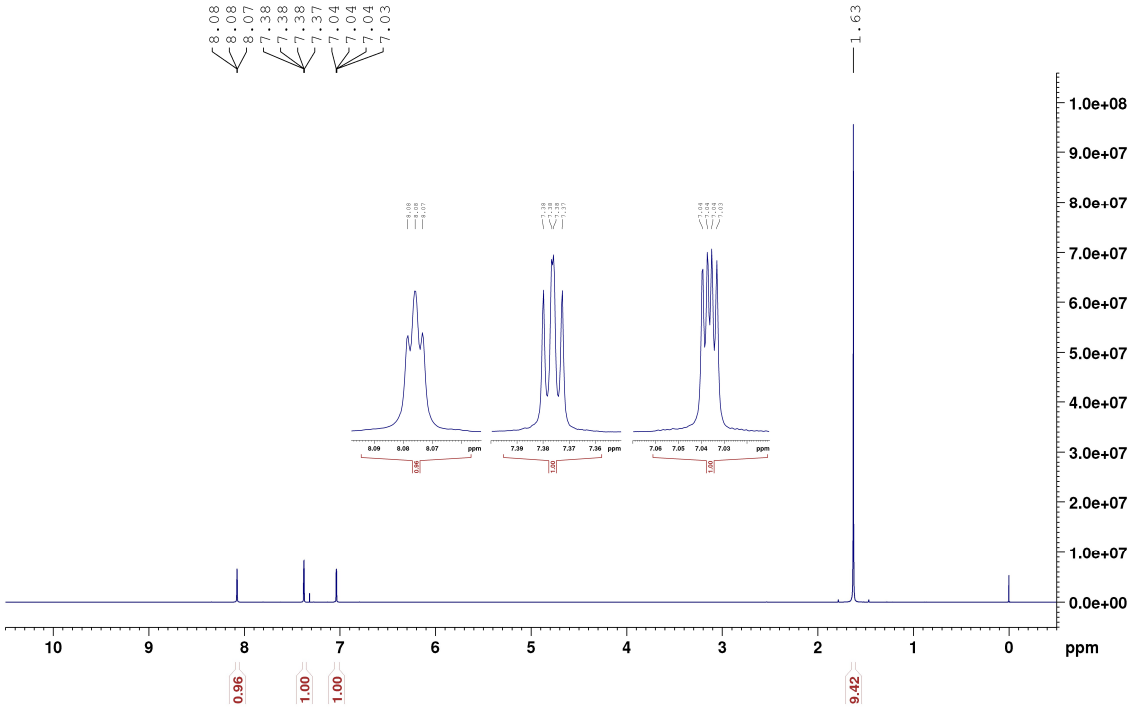


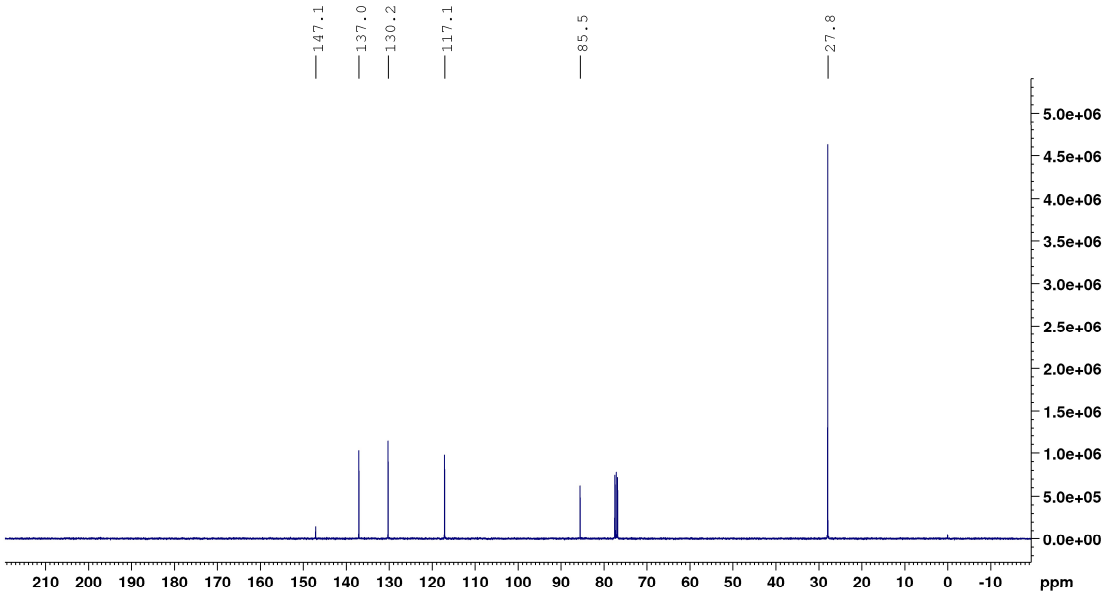




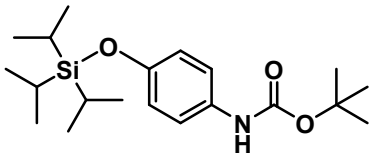
***tert*-butyl 1*H*-imidazole-1-carboxylate (compound 8')**

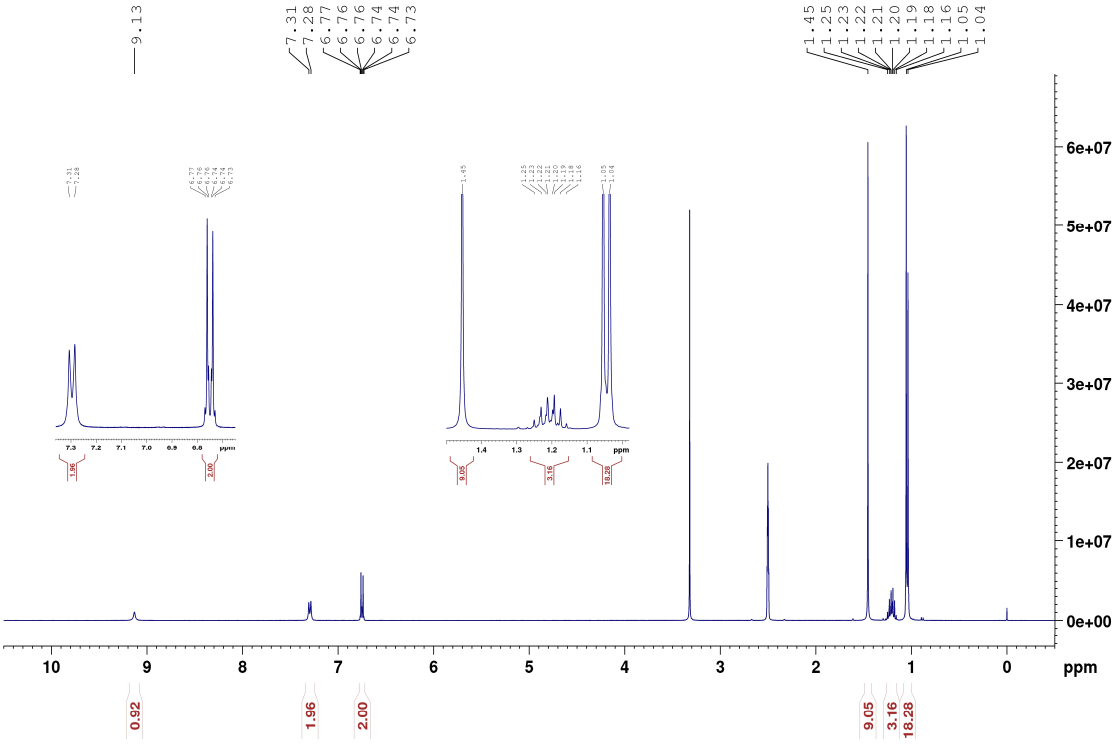


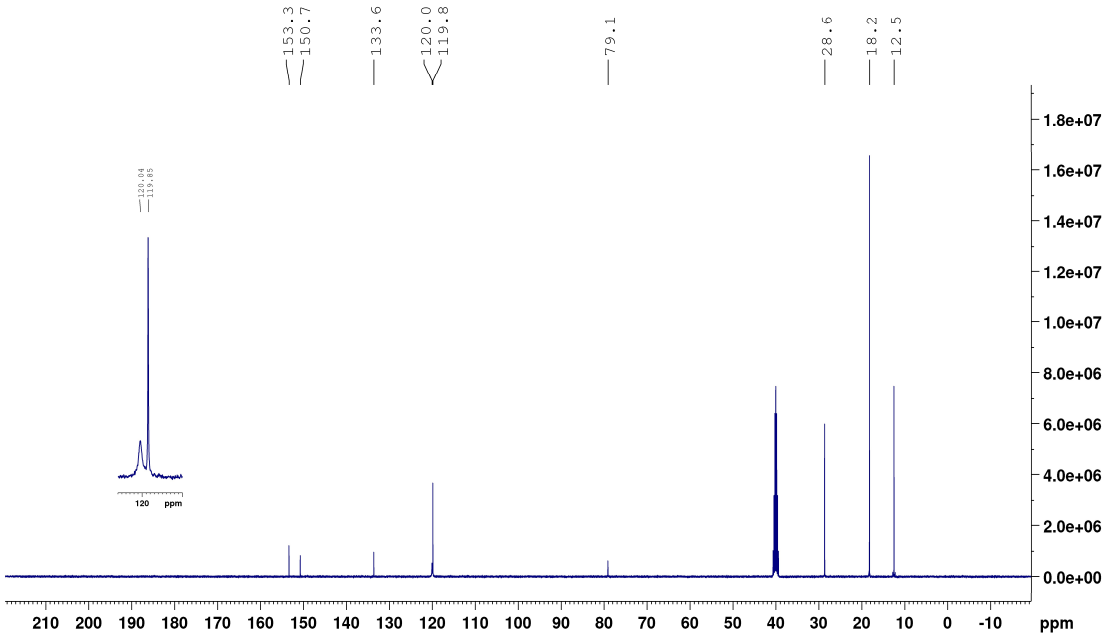




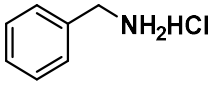
***tert*-butyl (4-((triisopropylsilyl)oxy)phenyl)carbamate (compound 23')**

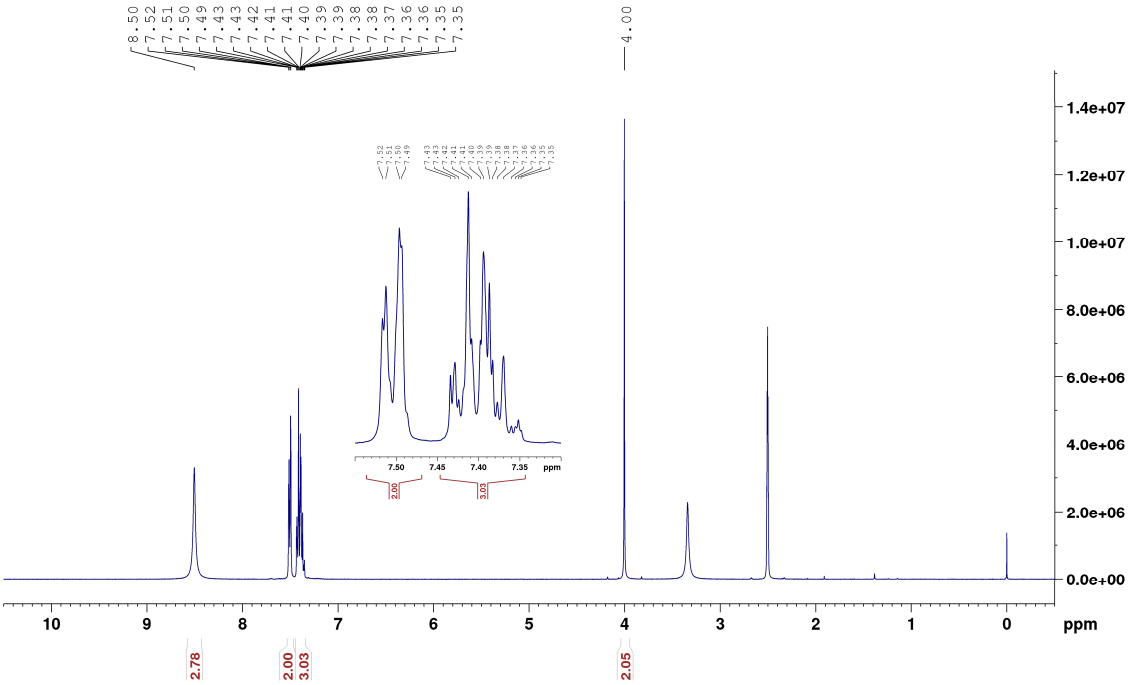


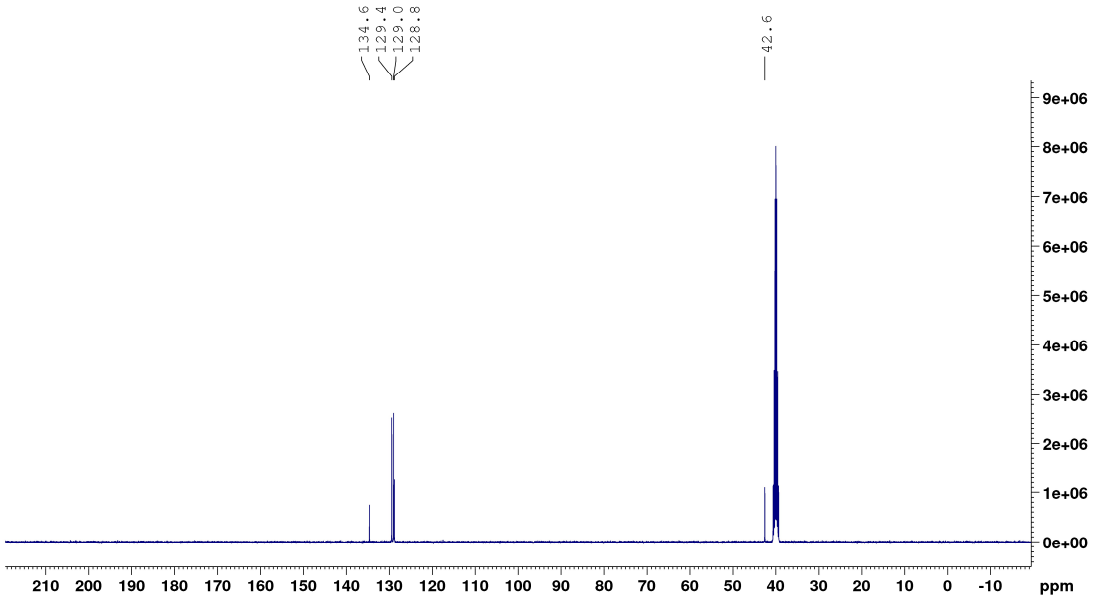




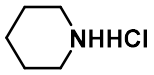
benzylamine hydrochloride (compound 1)

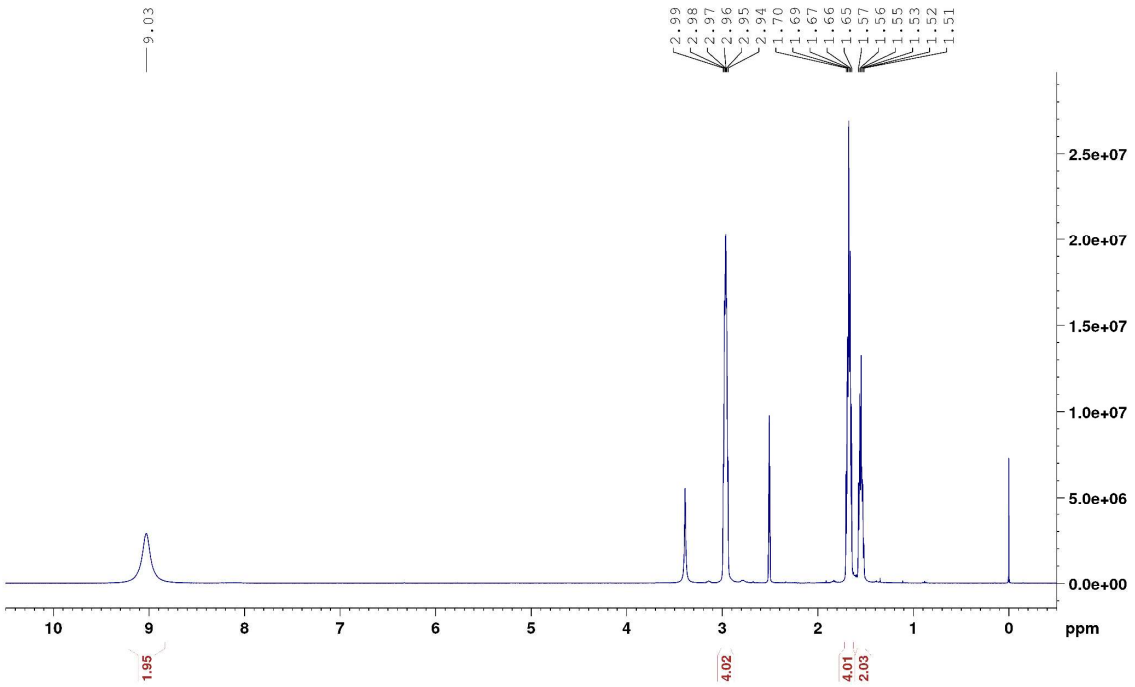


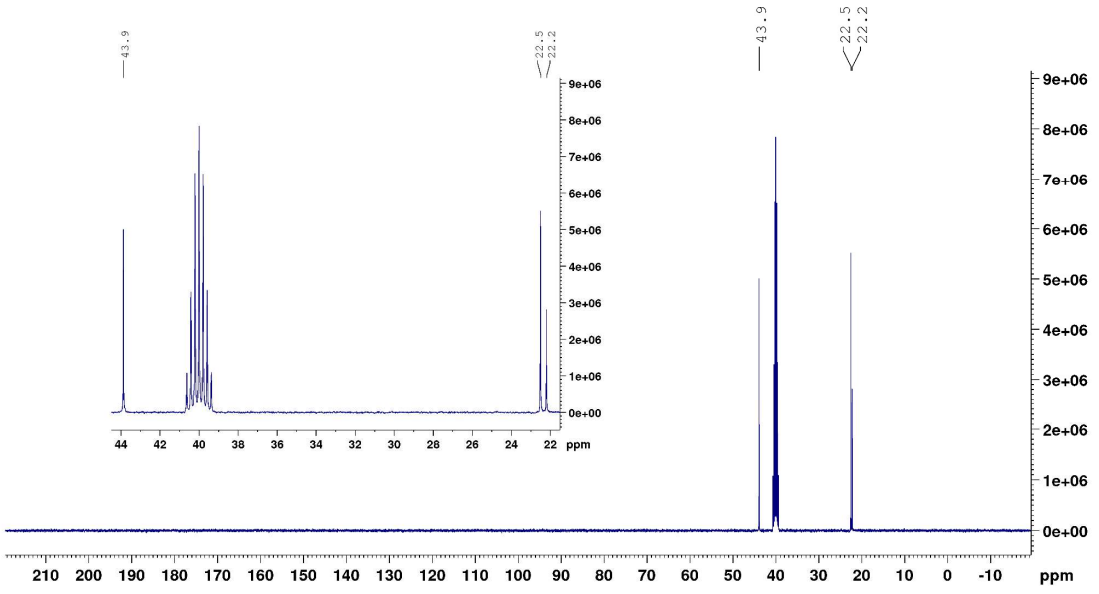




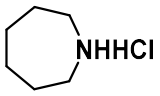
piperidine hydrochloride (compound 2)

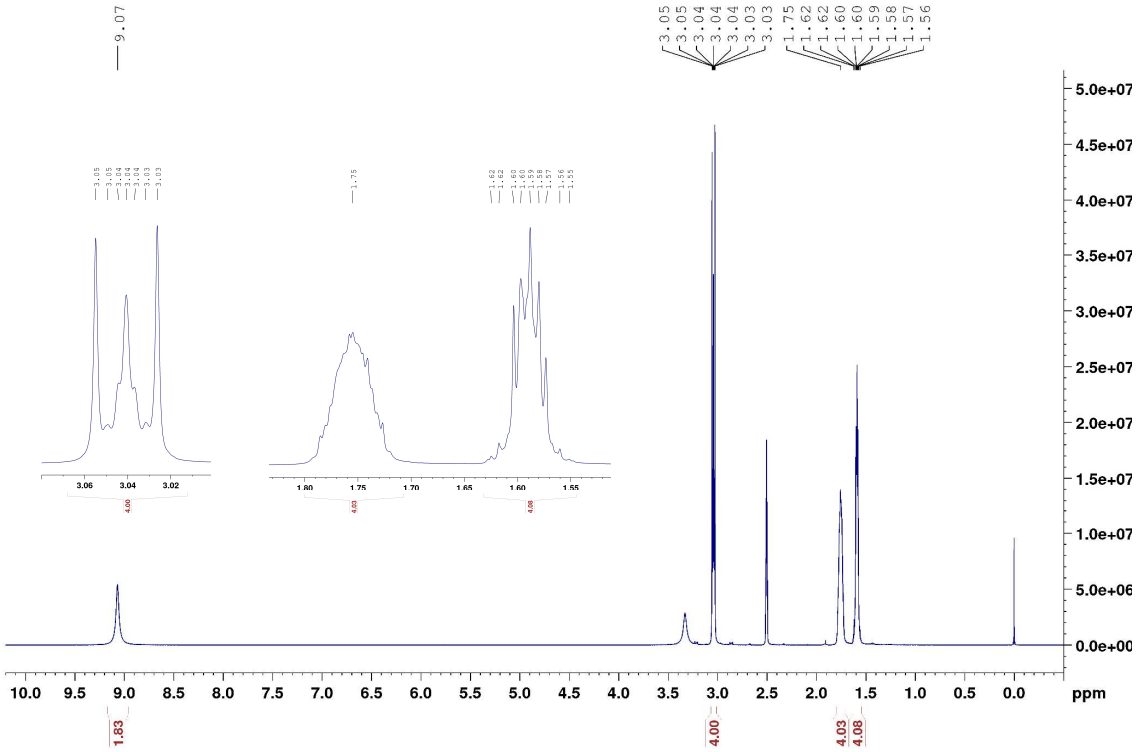


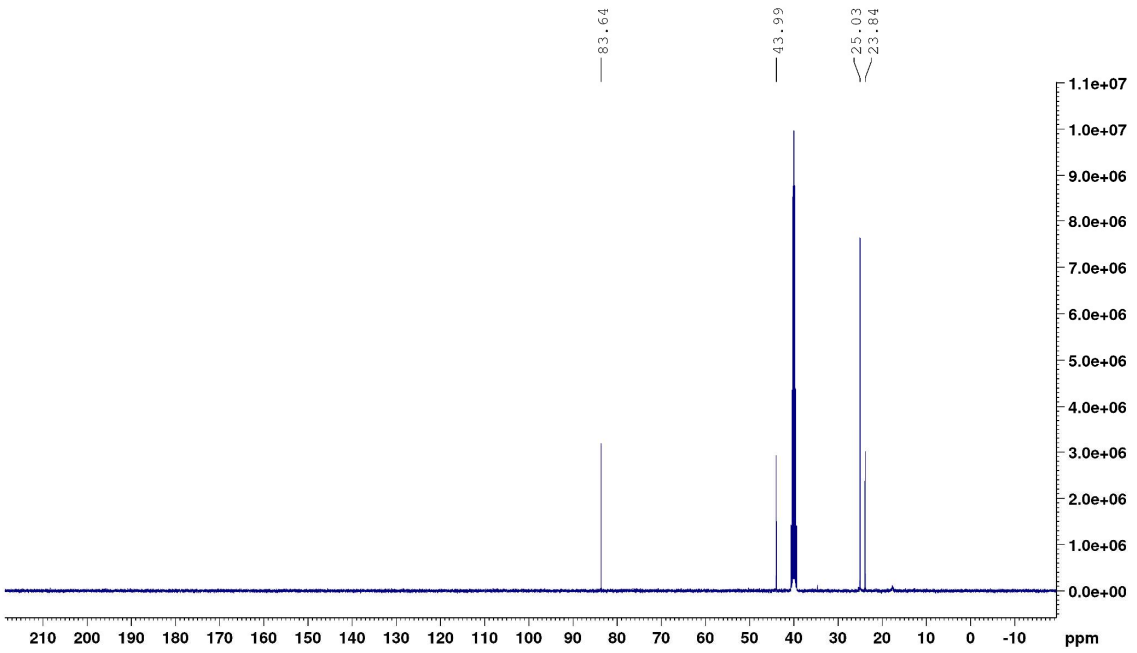




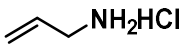
azepane hydrochloride (compound 3)

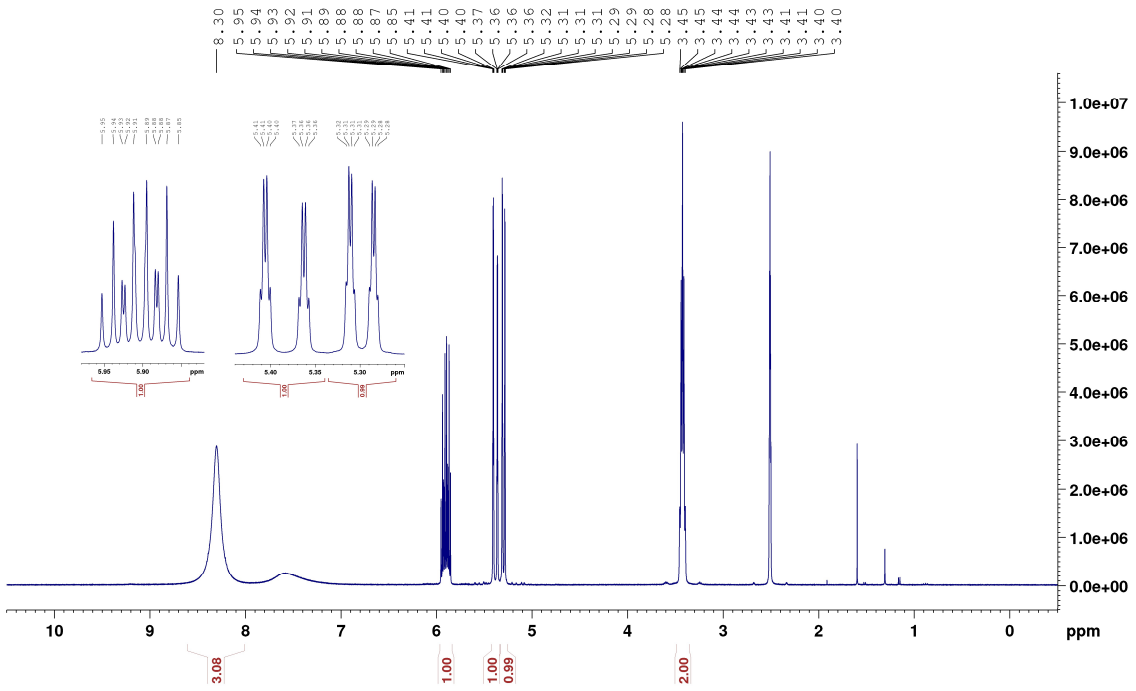


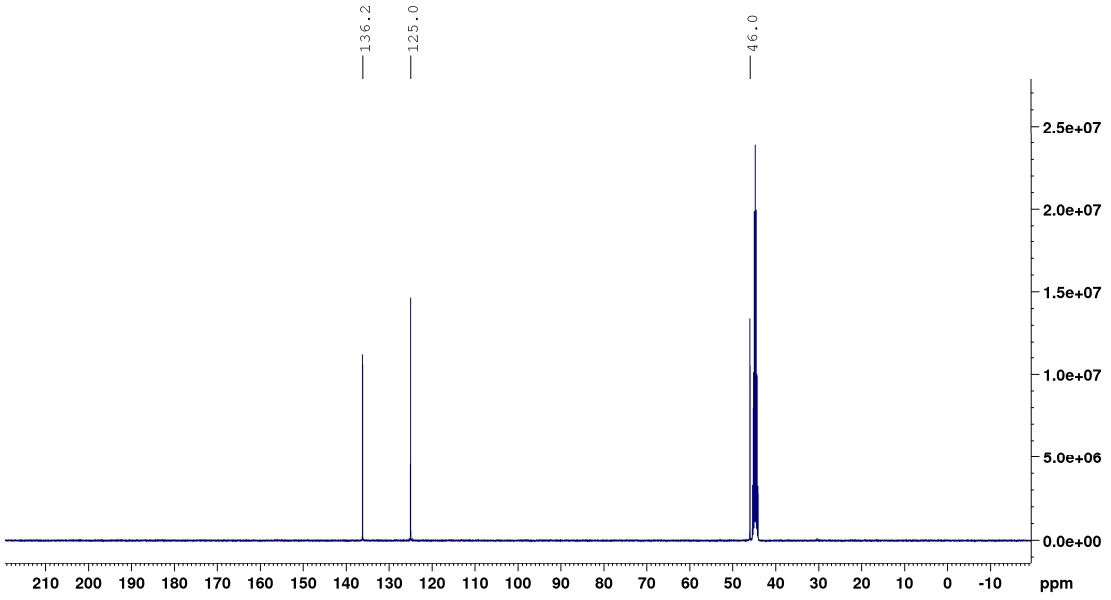




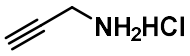
allylamine hydrochloride (compound 4)

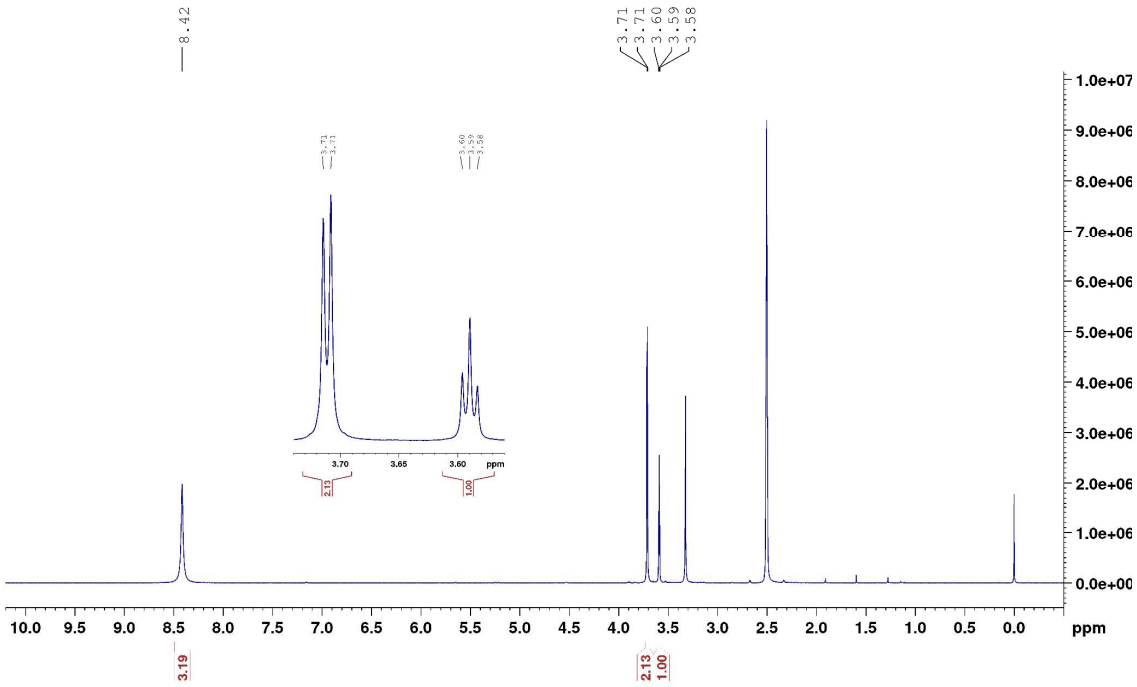


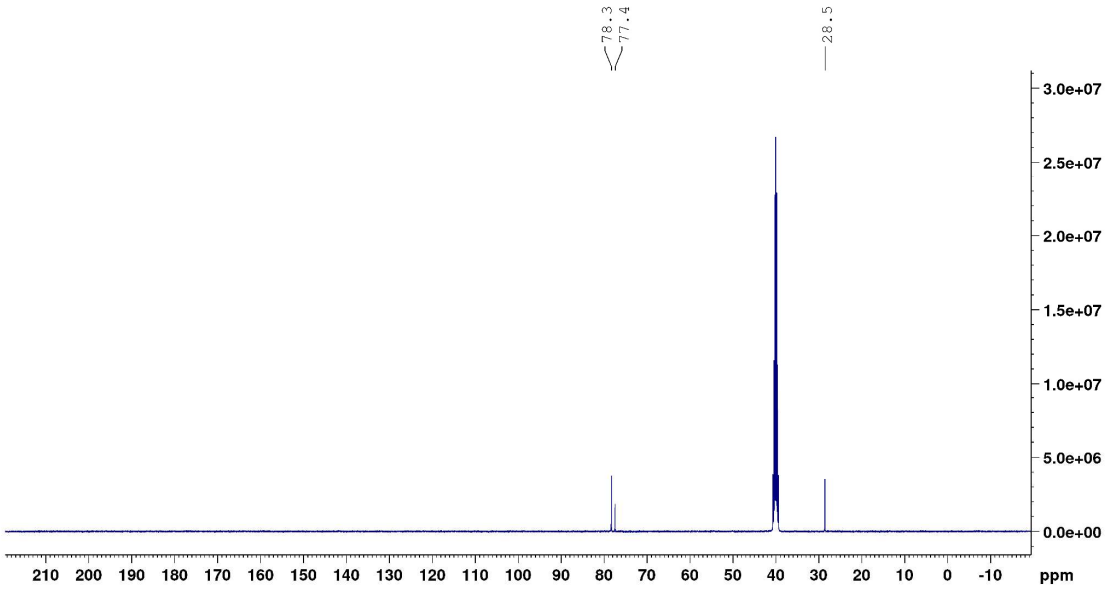




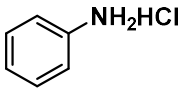
propargylamine hydrochloride (compound 5)

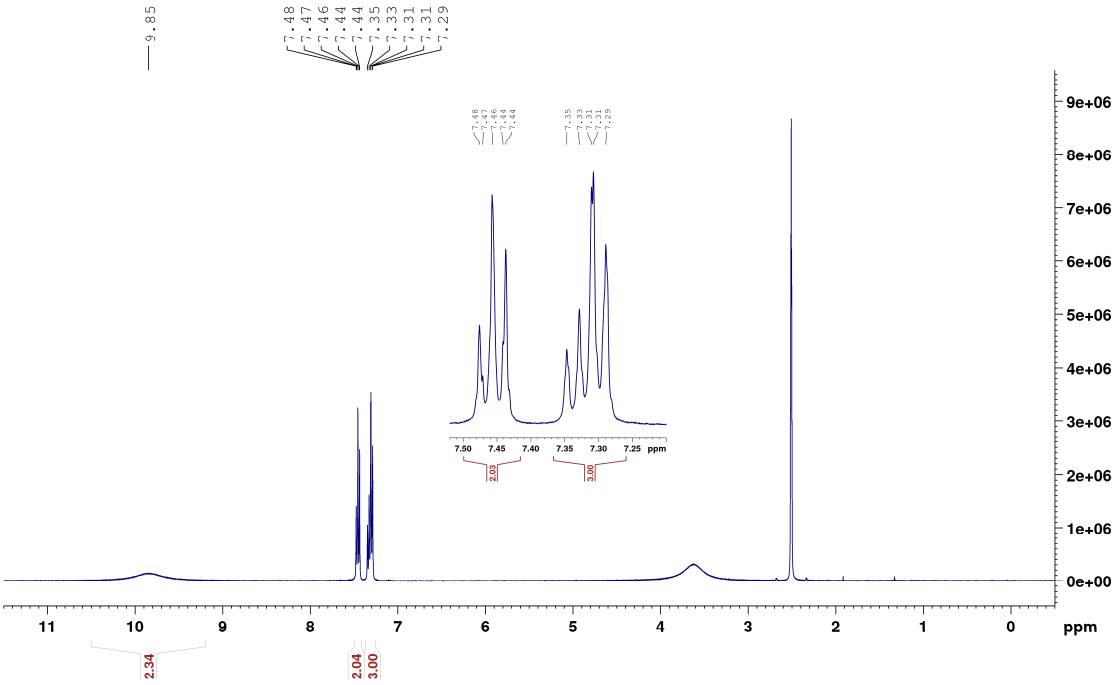


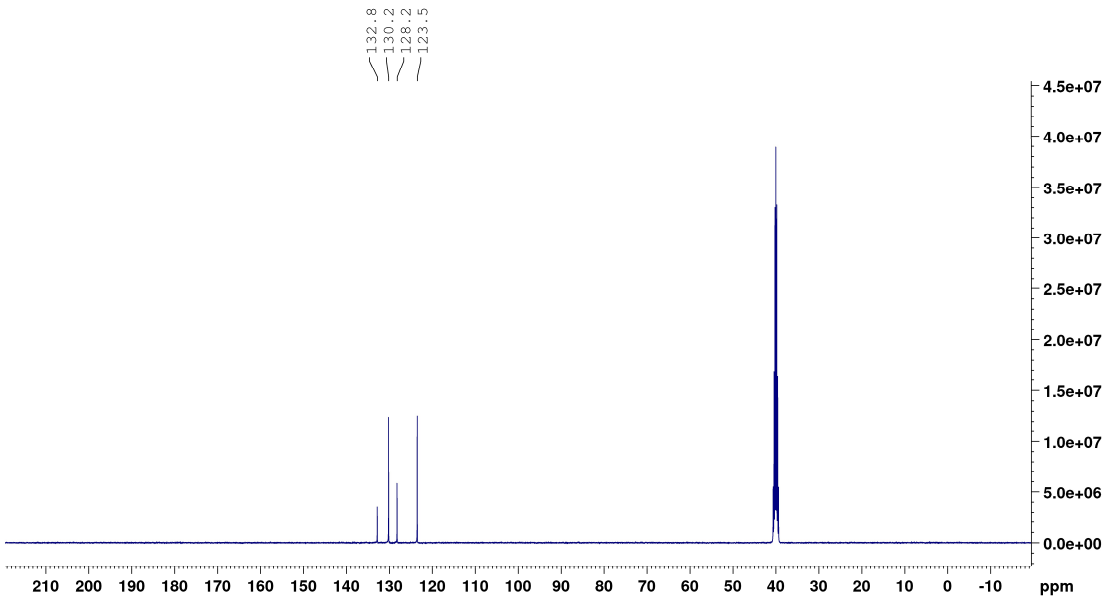




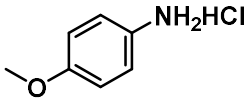
aniline hydrochloride (compound 6)

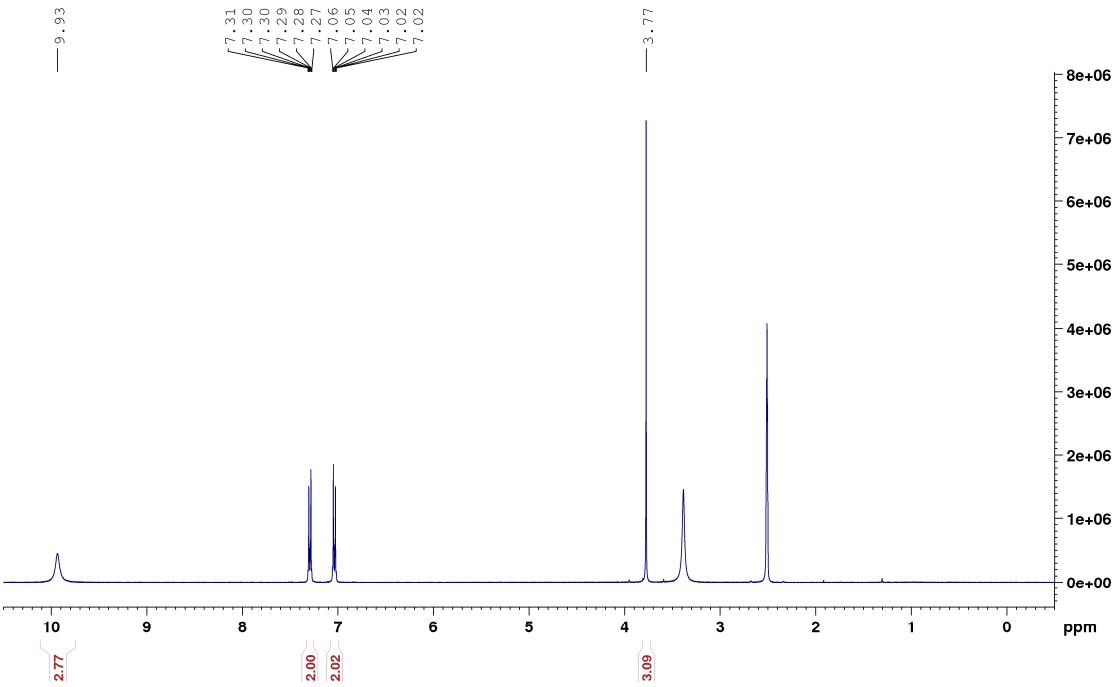


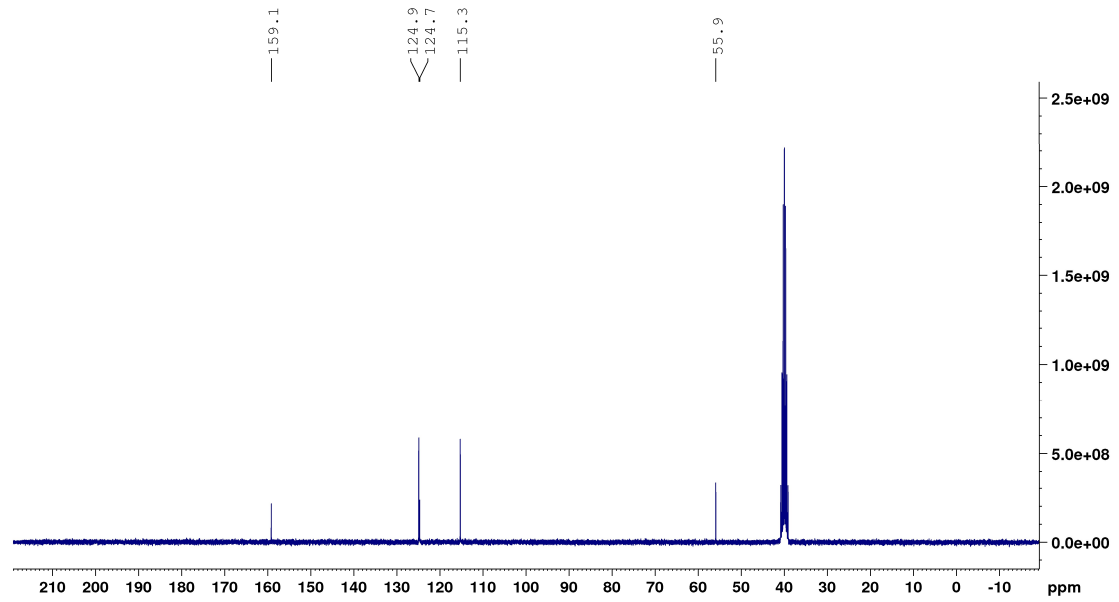




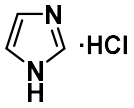
4-methoxyaniline hydrochloride (compound 7)

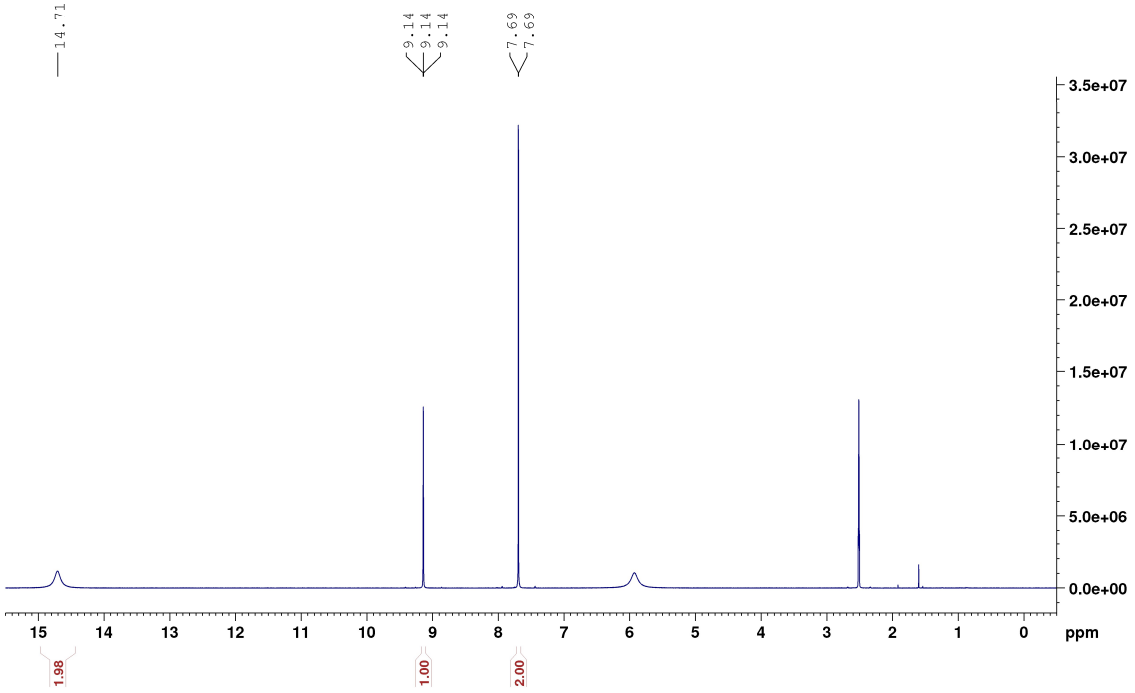


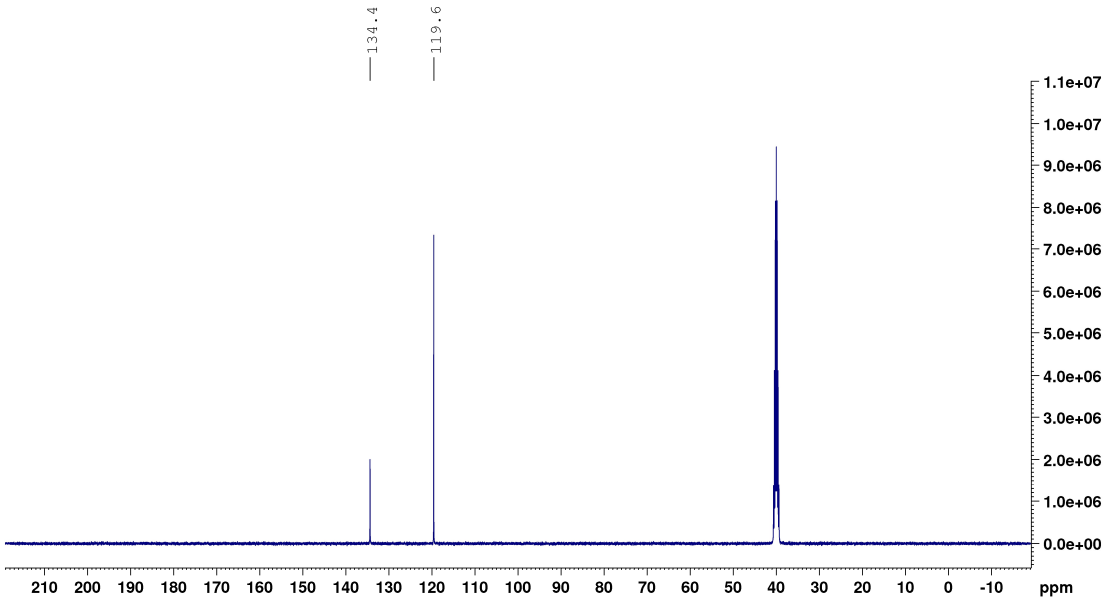




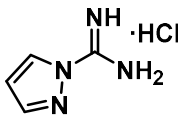
imidazole hydrochloride (compound 8)

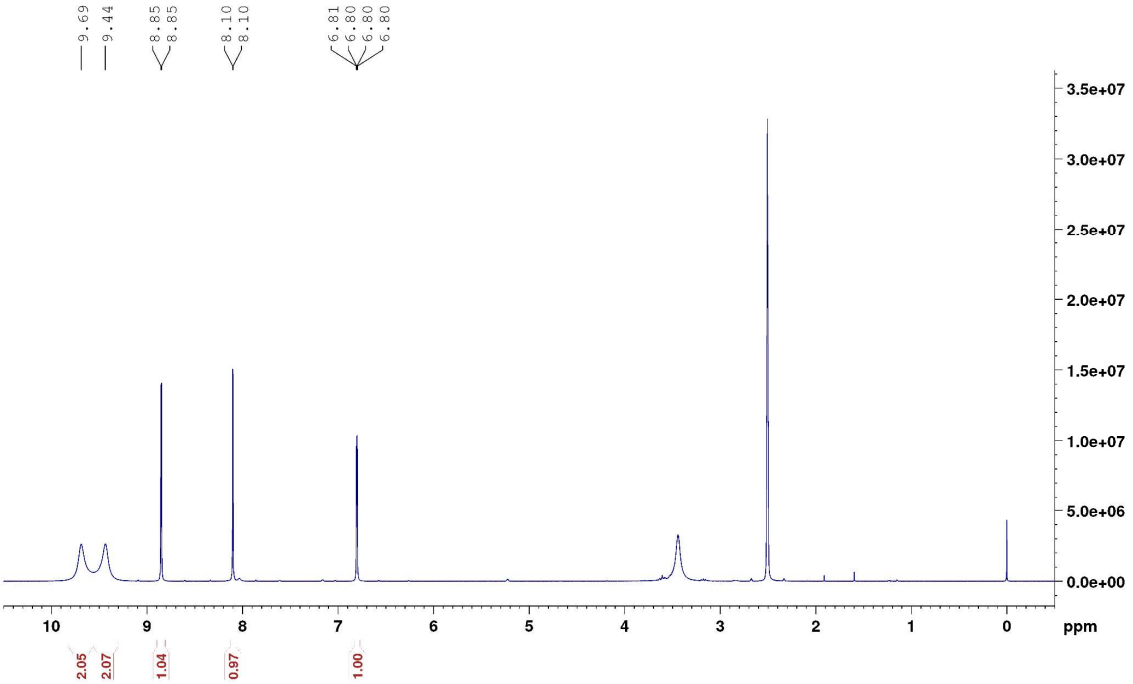


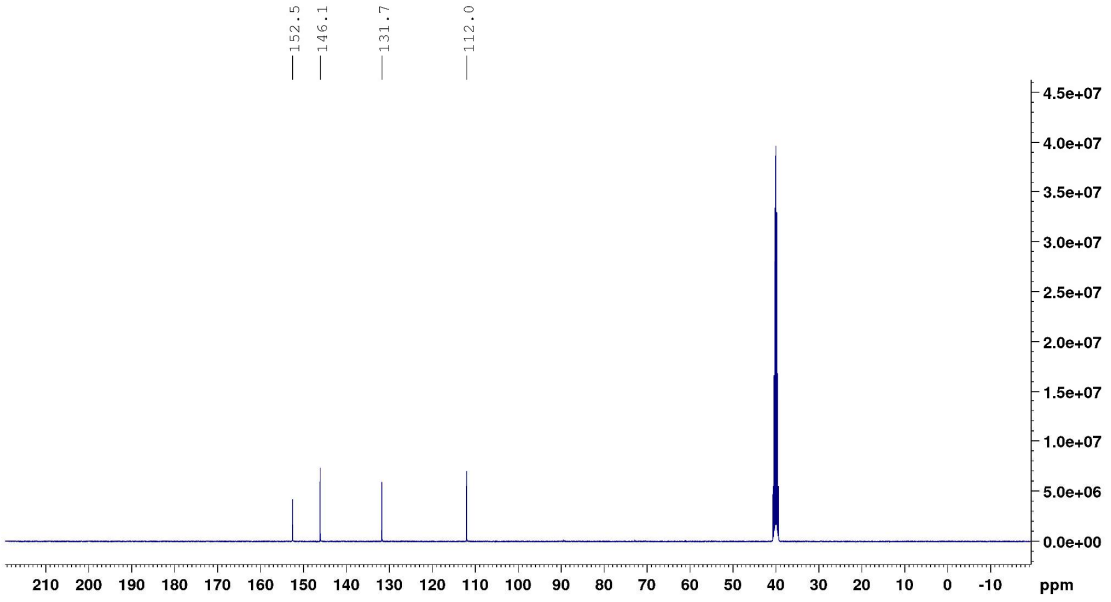




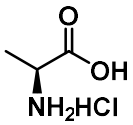
1*H*-pyrazole-1-carboximidamide hydrochloride (compound 9)

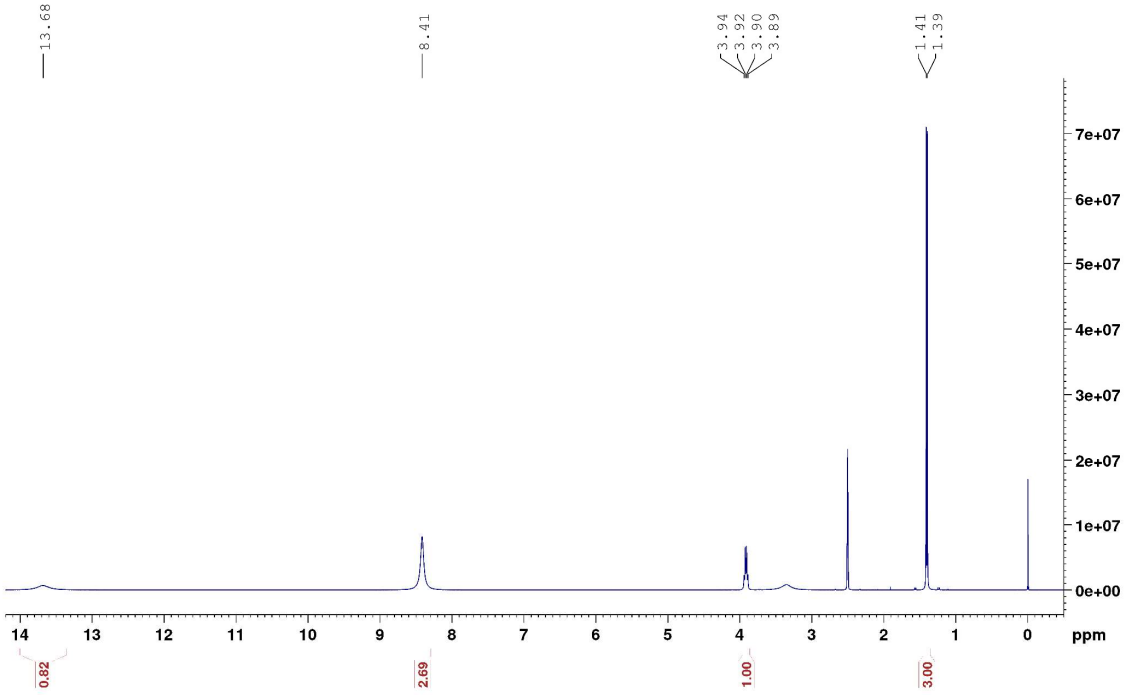


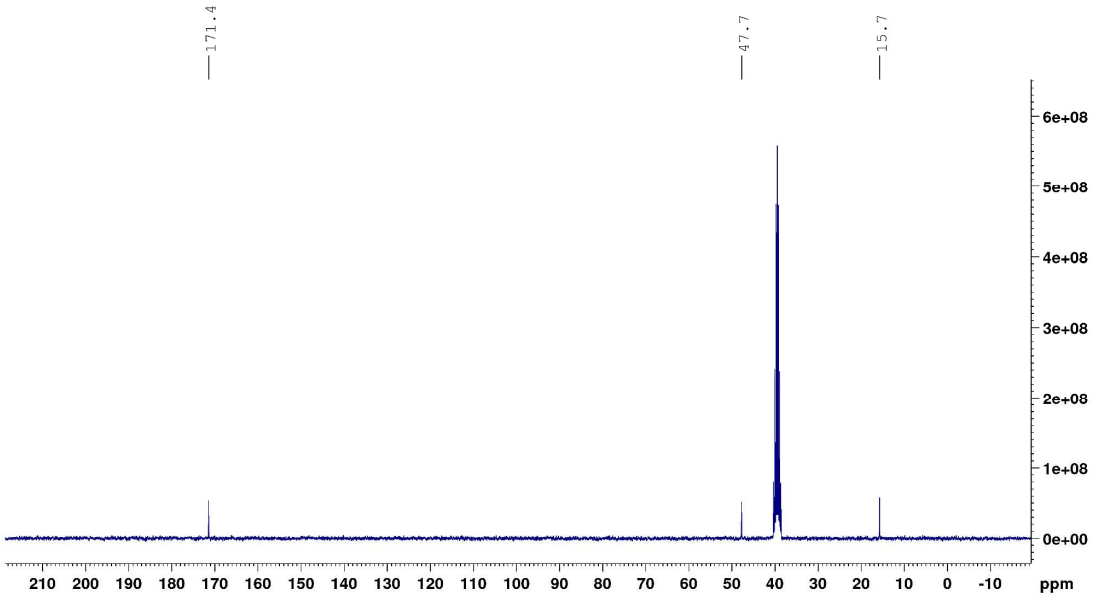




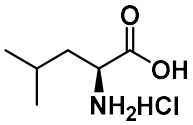
***L*-alanine hydrochloride (compound 10)**

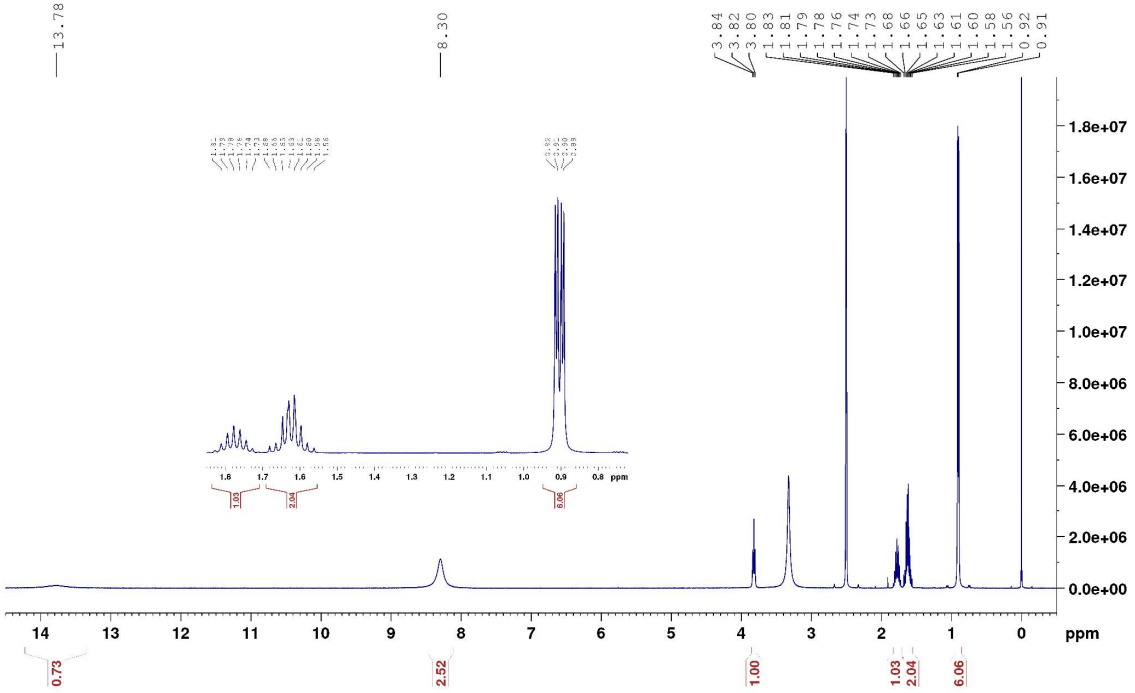


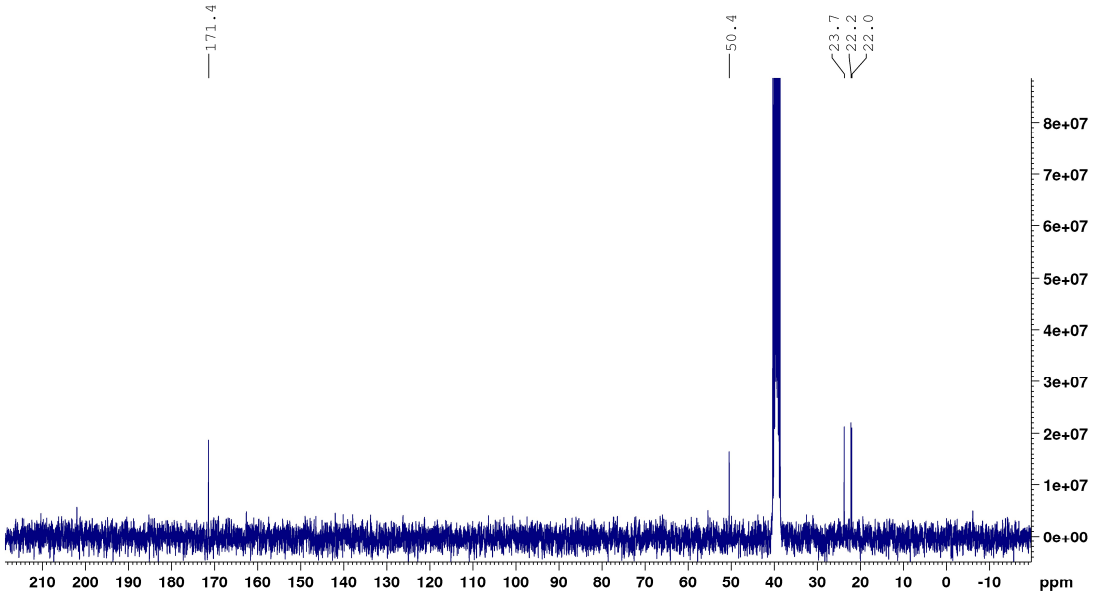




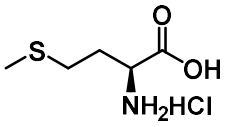
***L*-leucine hydrochloride (compound 11)**

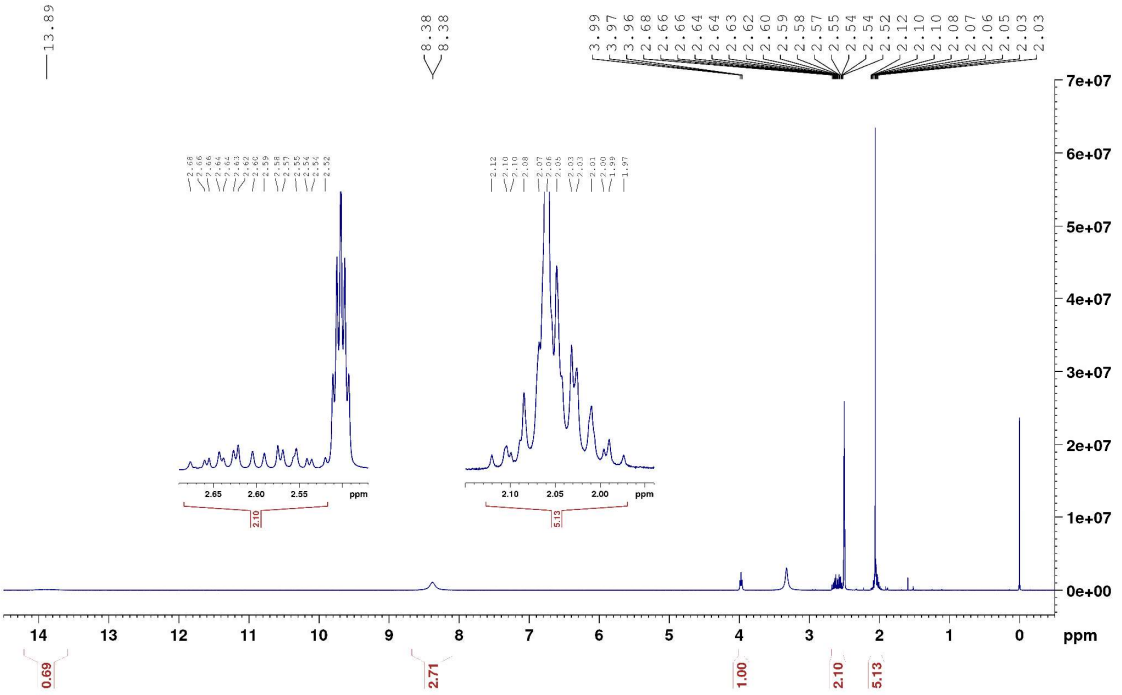


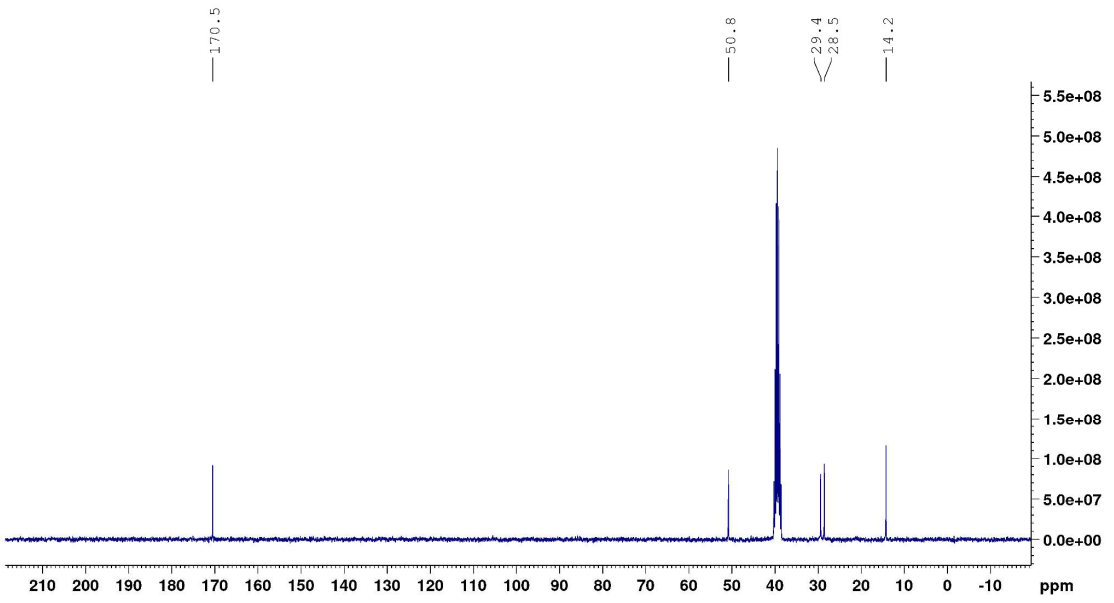




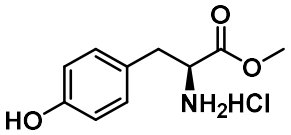
***L*-methionine hydrochloride (compound 12)**

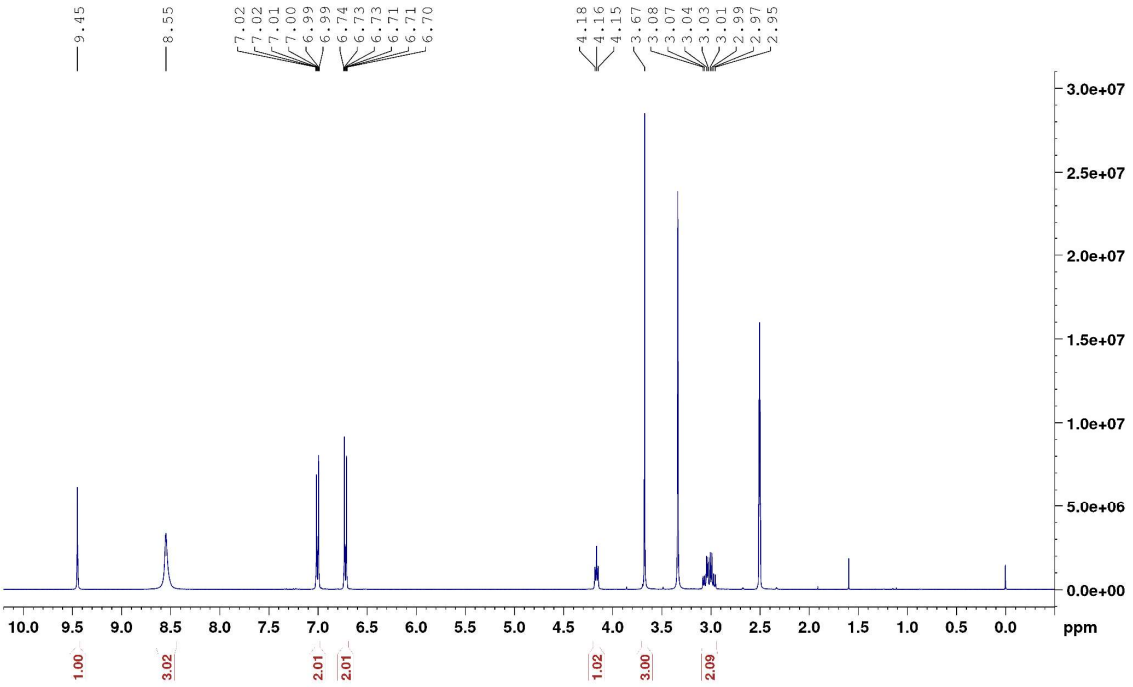


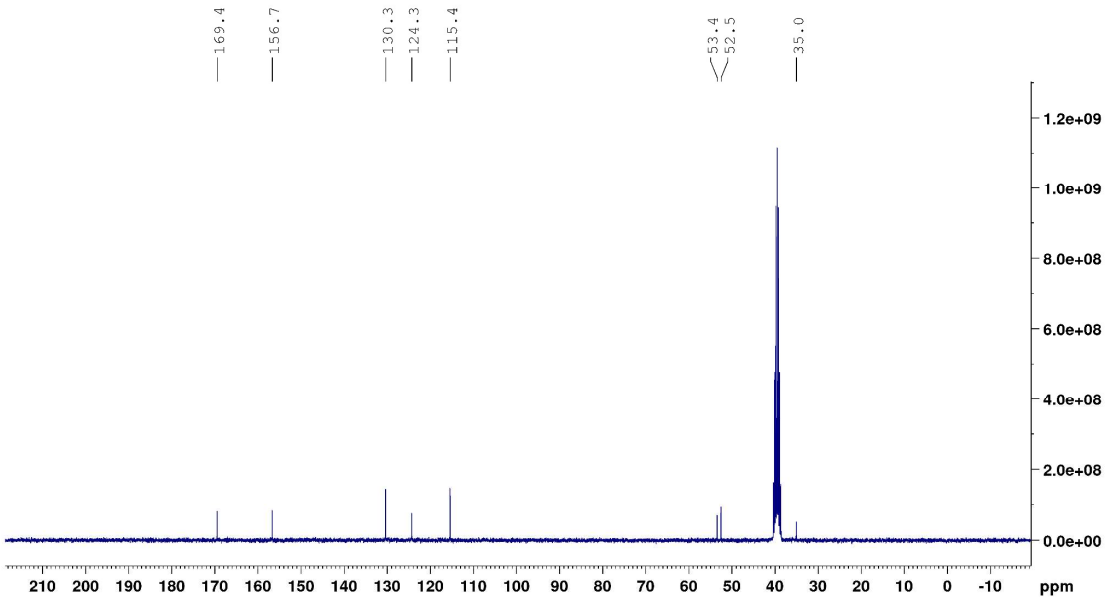




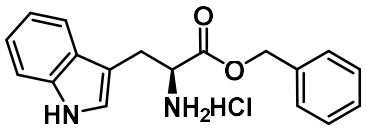
methyl *L*-tyrosinate hydrochloride (compound 13)

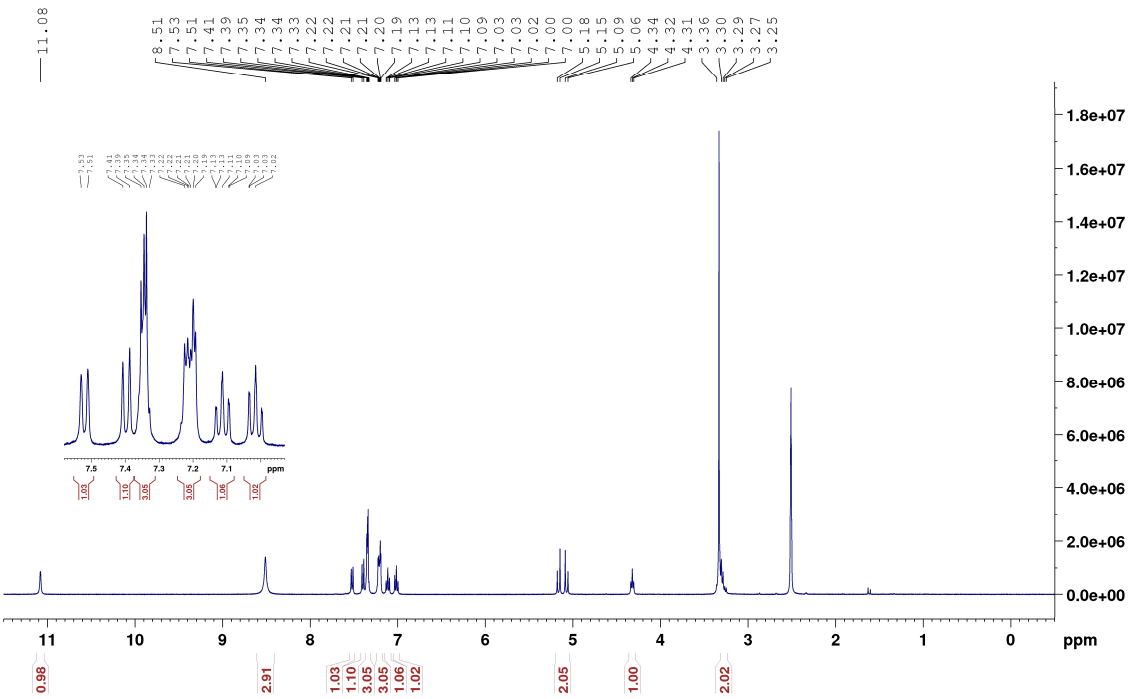


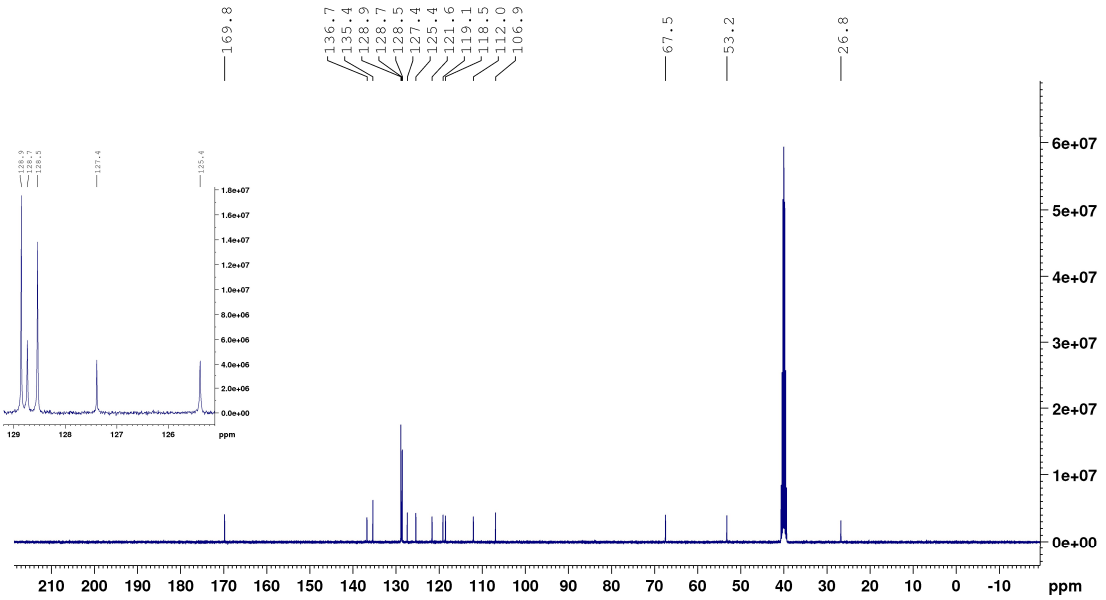




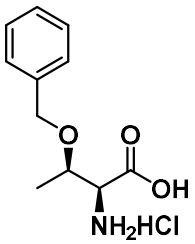
benzyl *L*-tryptophanate hydrochloride (compound 14)

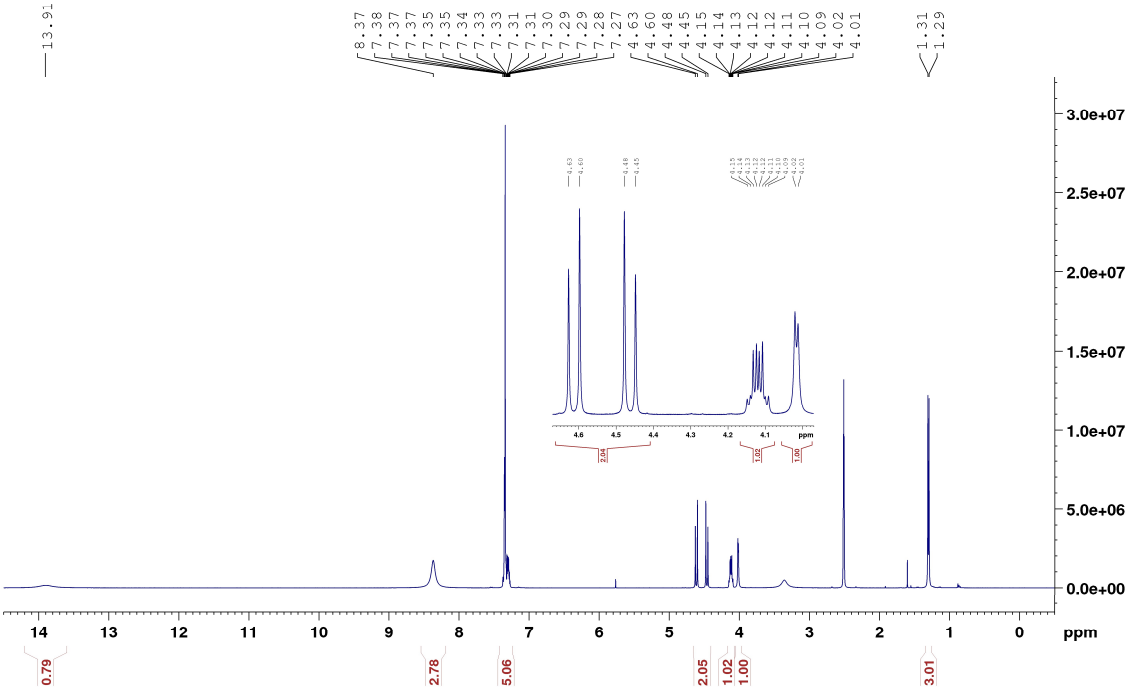


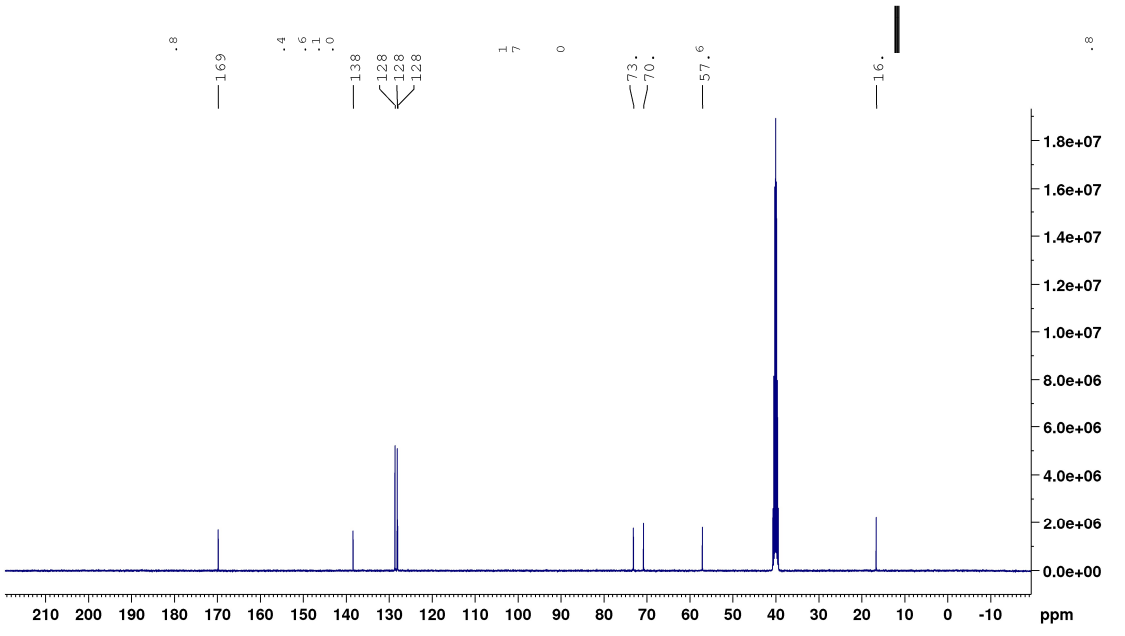




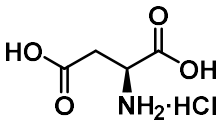
***O*-benzyl-*L*-threonine hydrochloride (compound 15)**

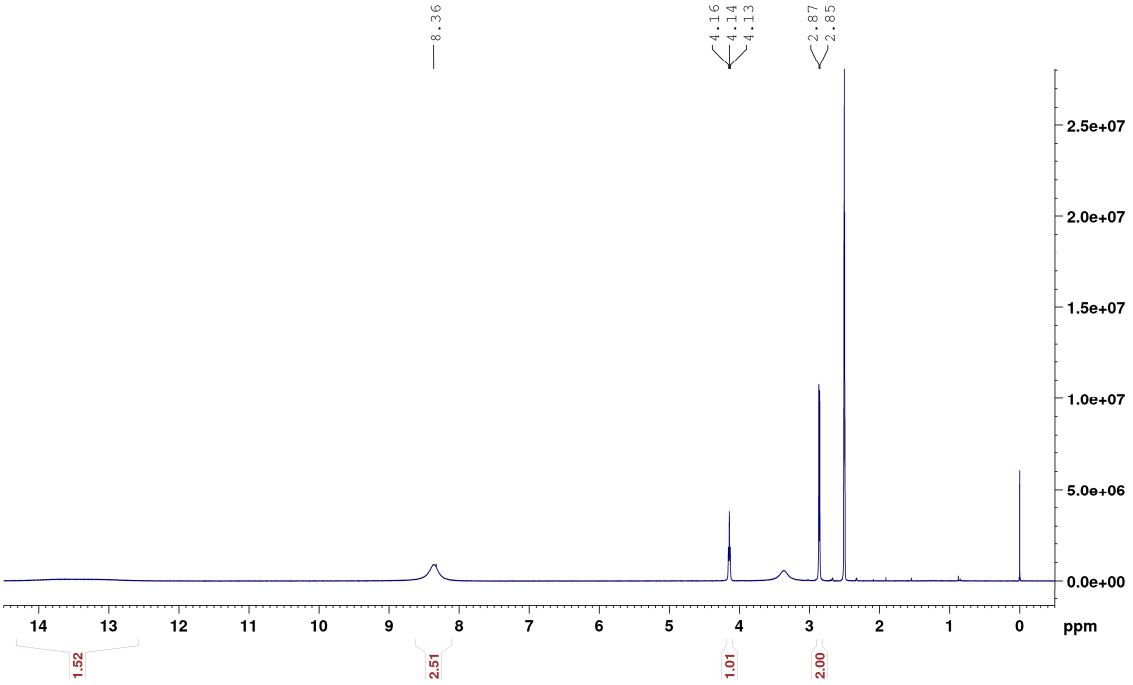


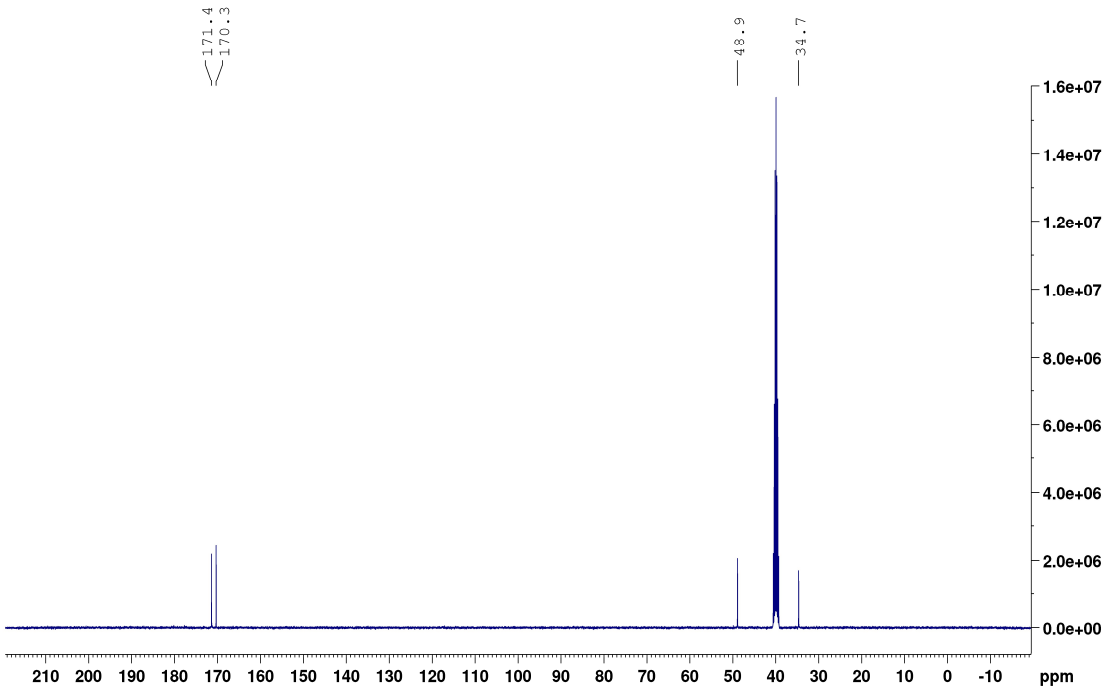




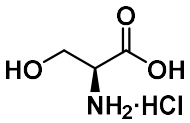
***L*-aspartic acid hydrochloride (compound 16)**

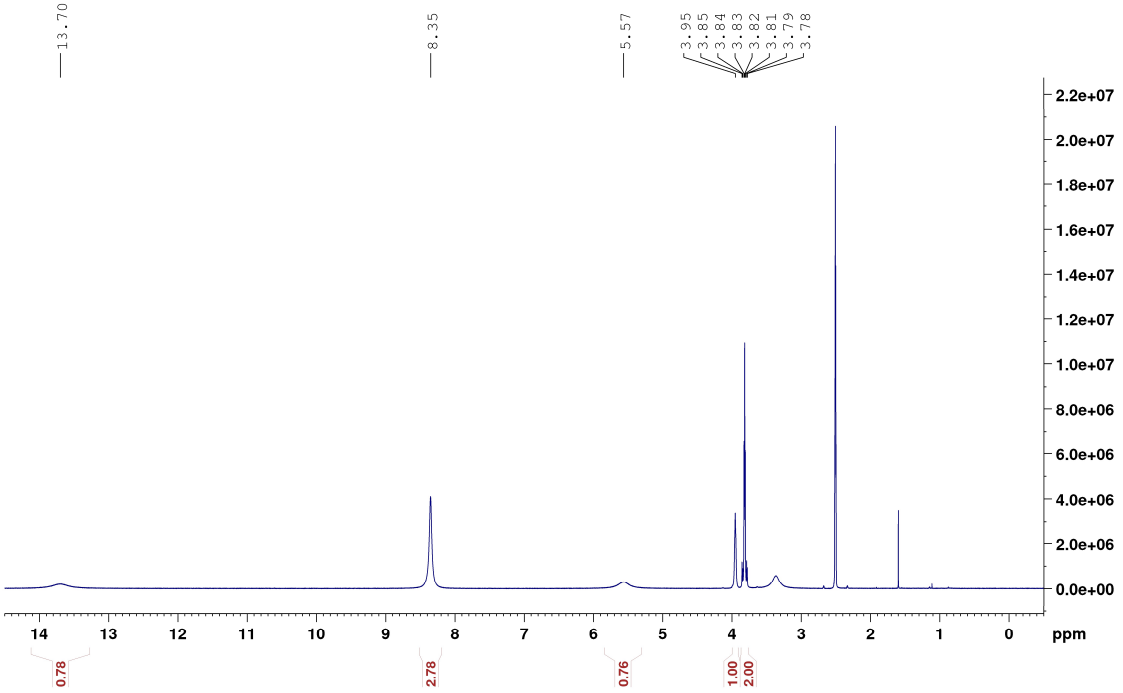


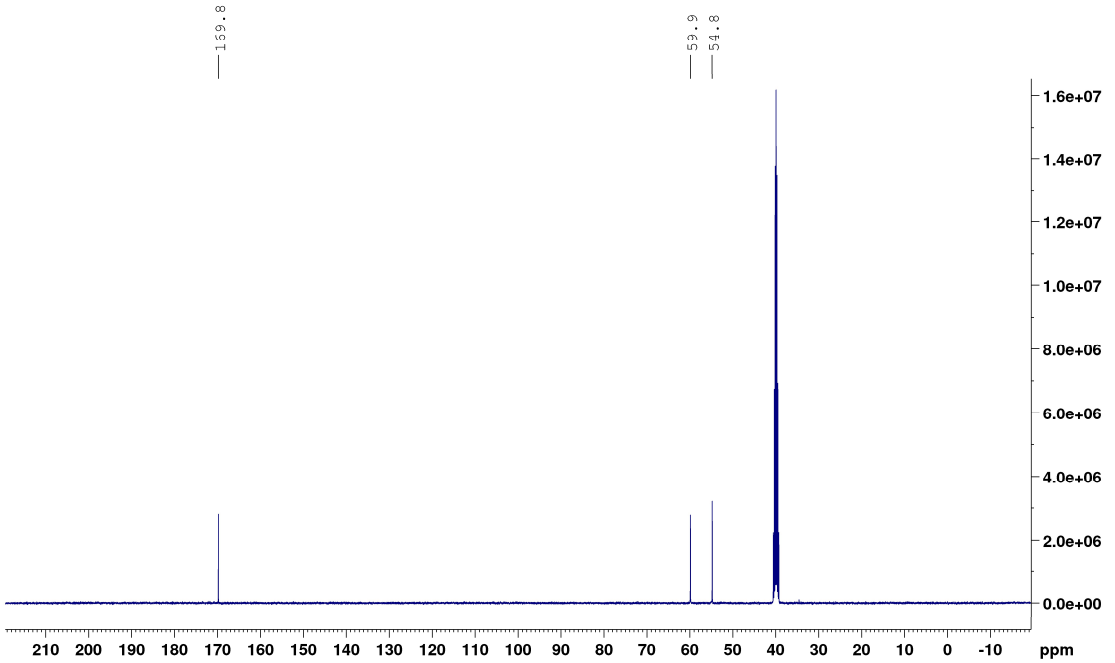




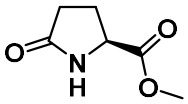
***L*-serine hydrochloride (compound 17)**

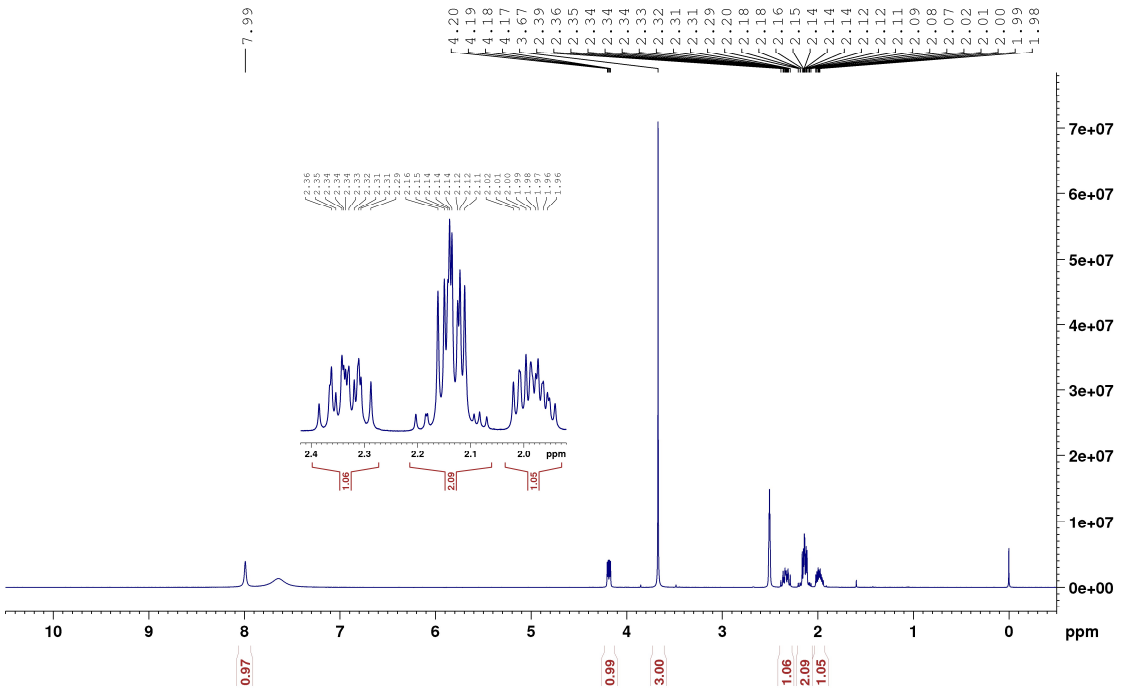


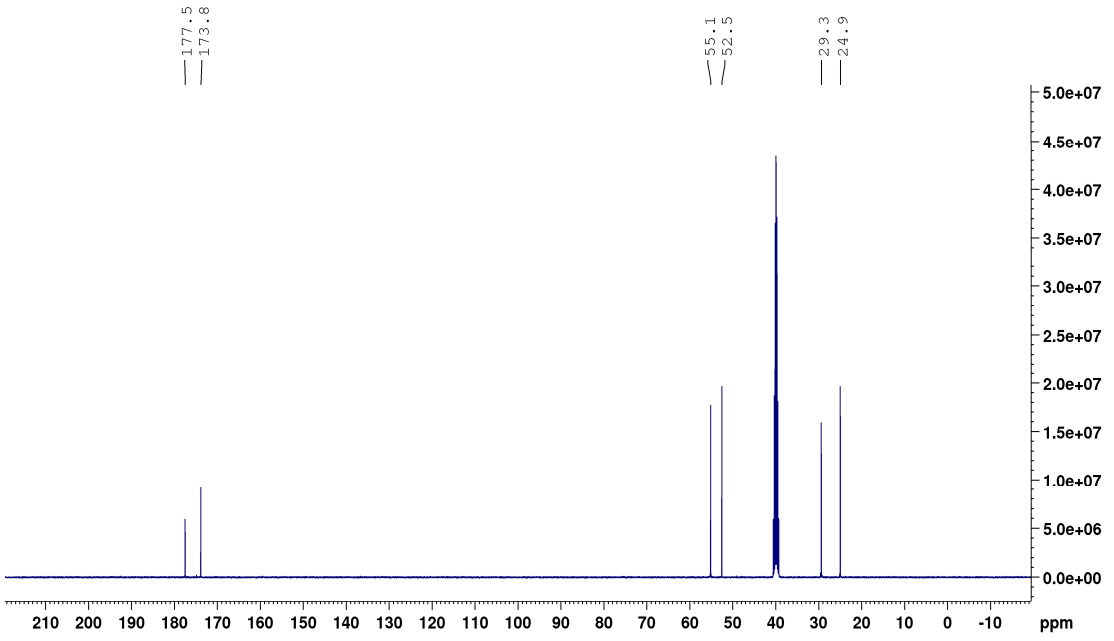




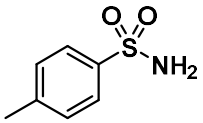
methyl *L*-pyroglutamate (compound 18)

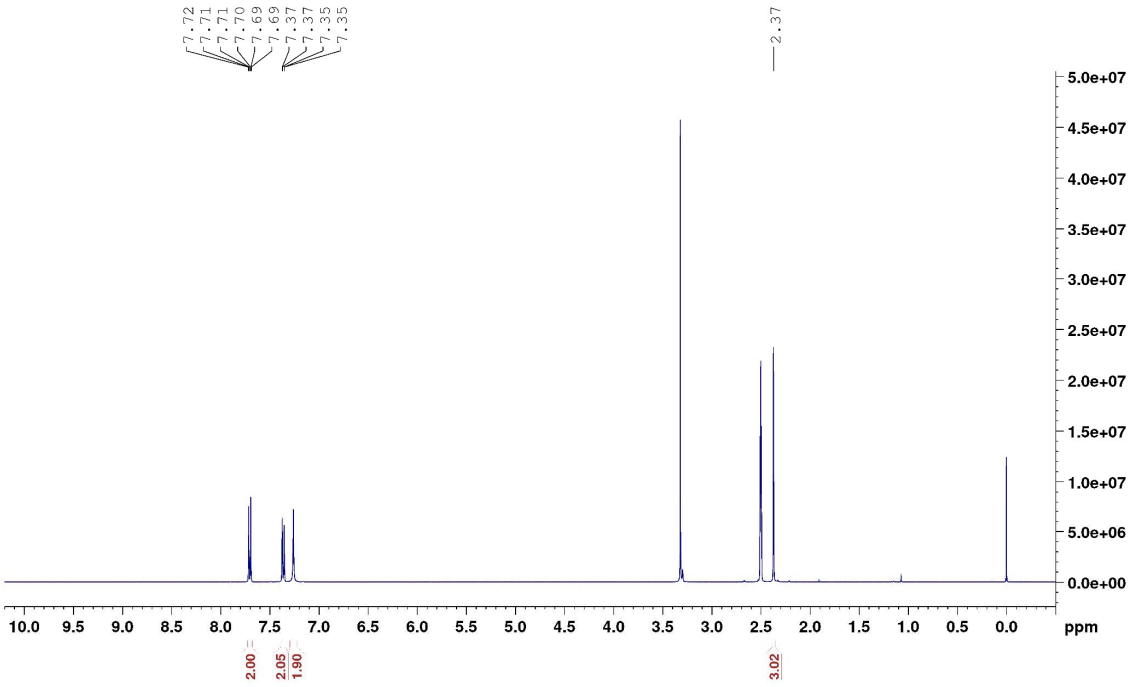


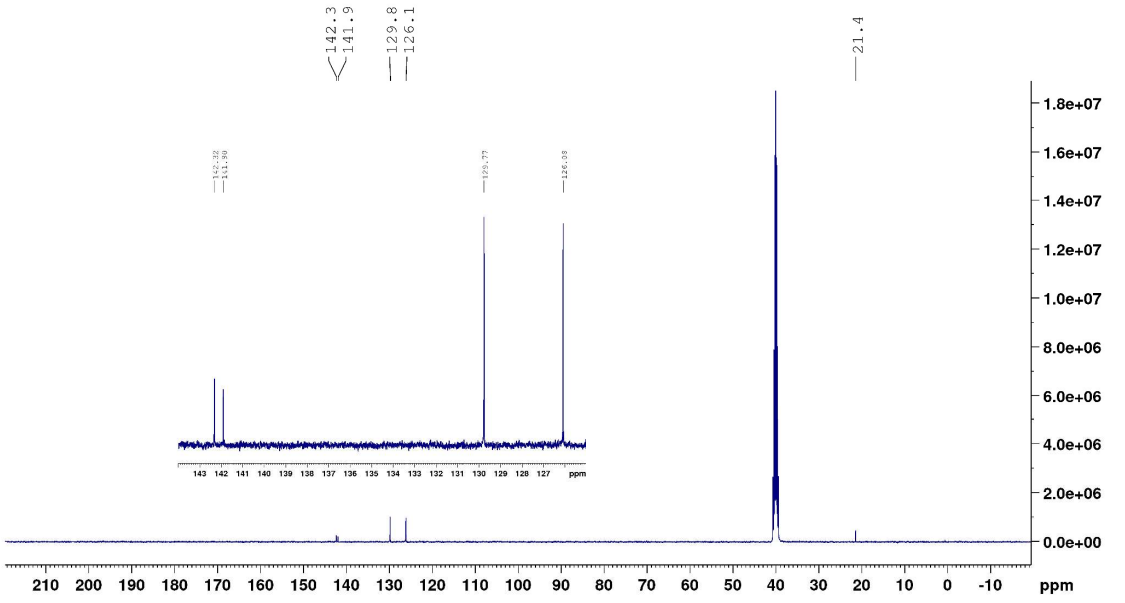




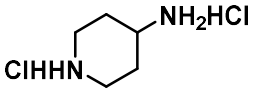
4-methylbenzenesulfonamide (compound 19)

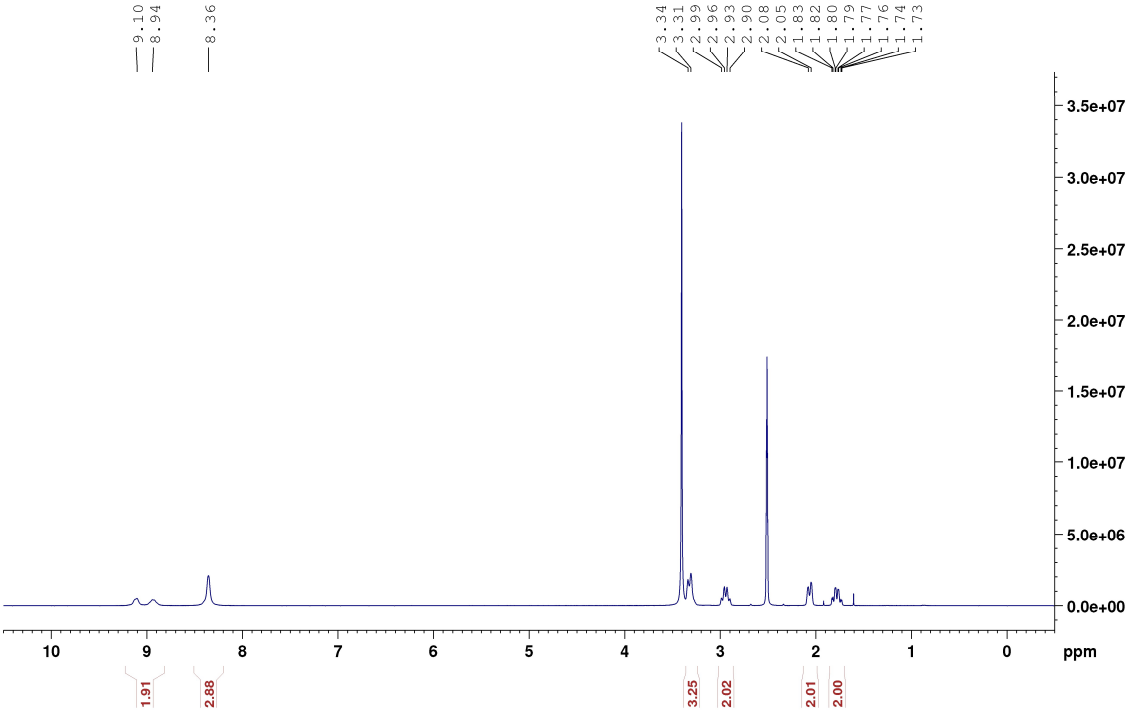


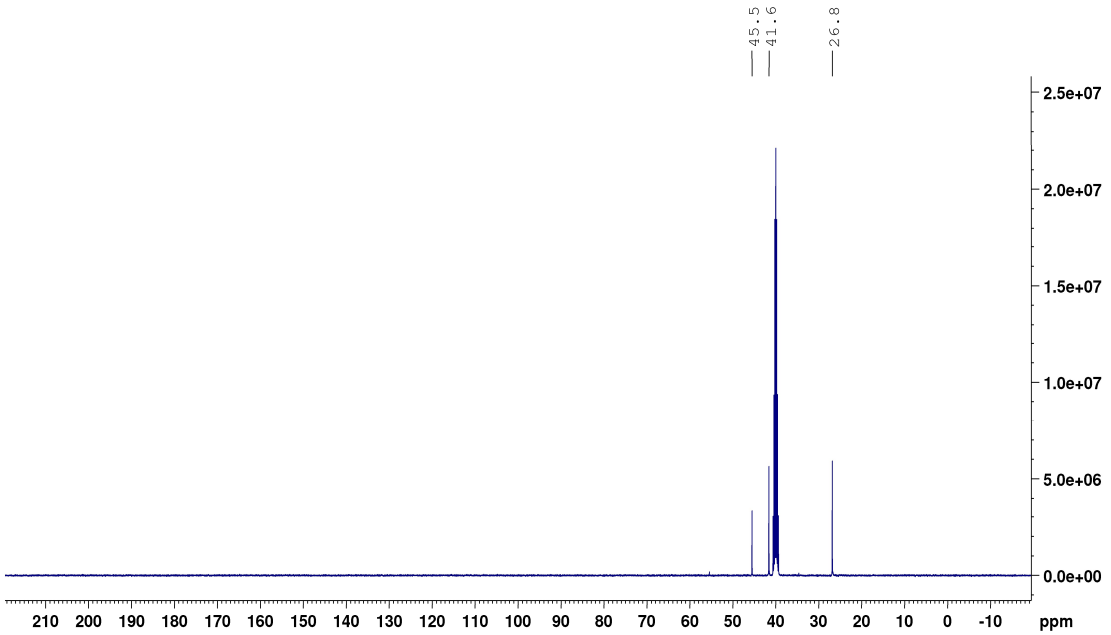




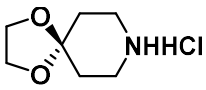
4-aminopiperidine dihydrochloride (compound 20)

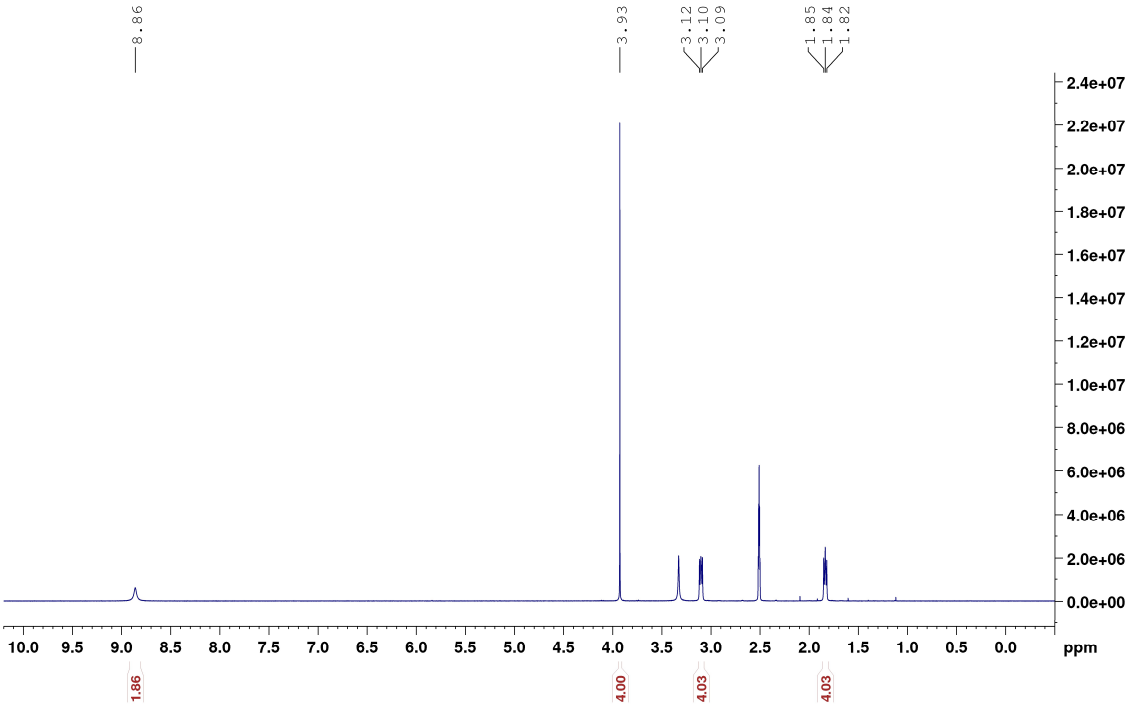


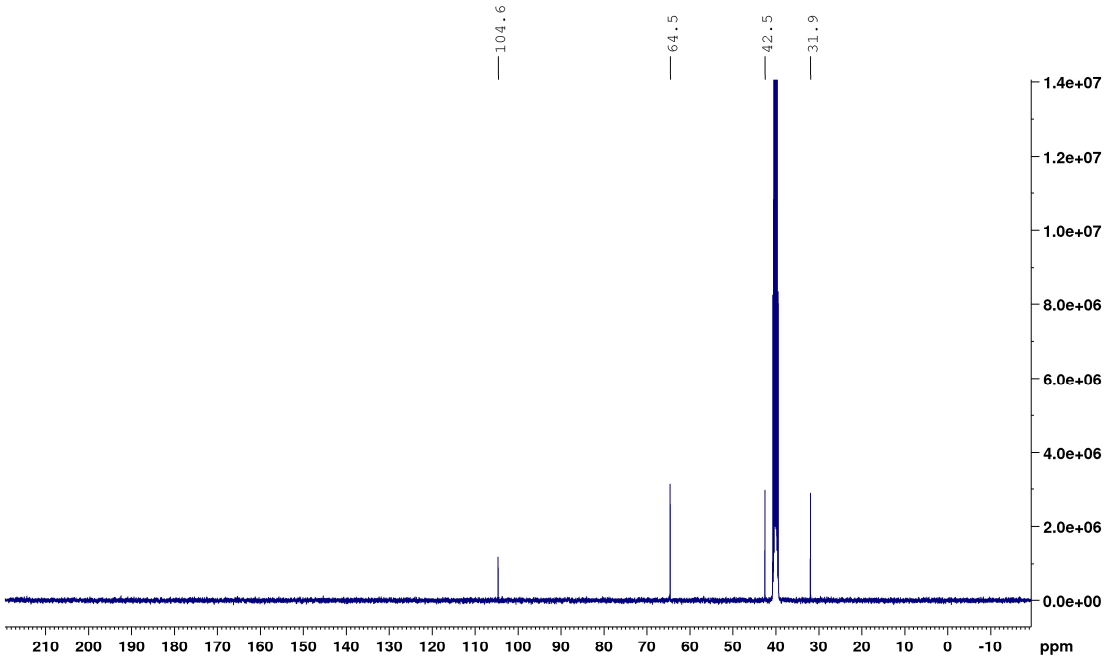




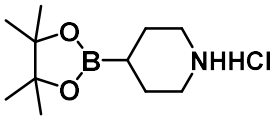
1,4-dioxa-8-azaspiro[4.5]decane hydrochloride (compound 21)

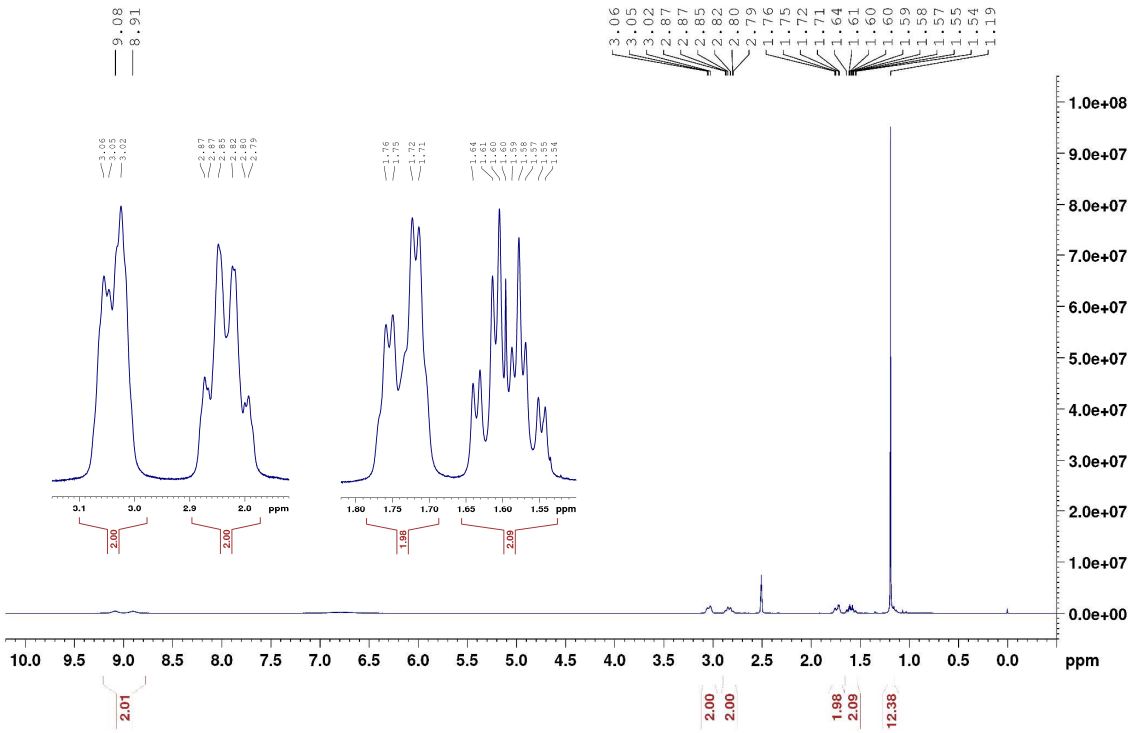


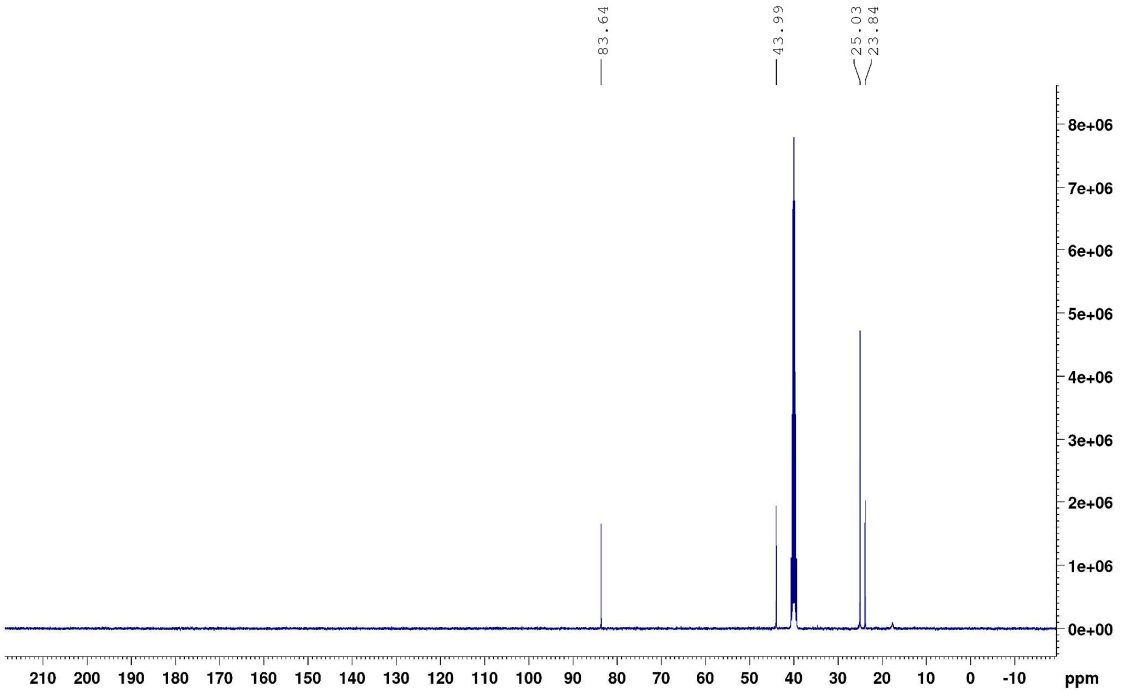




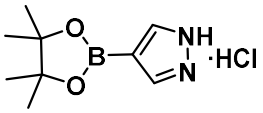
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine hydrochloride (compound 22)

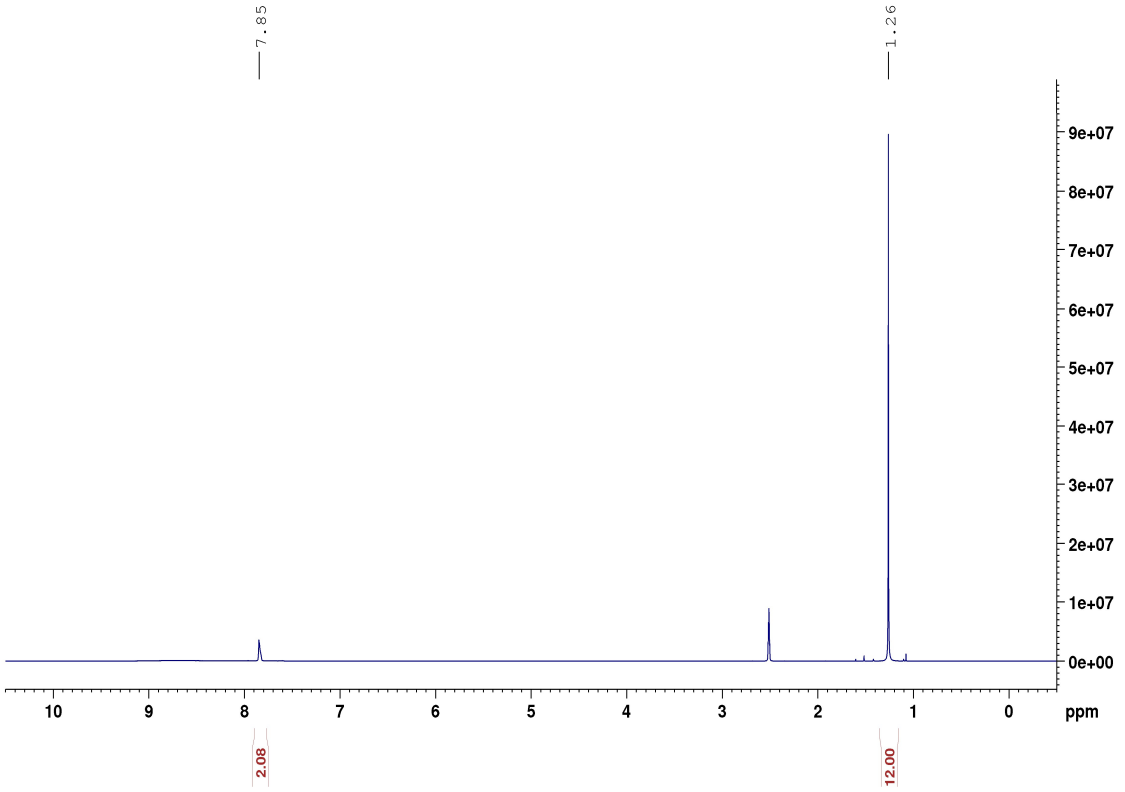


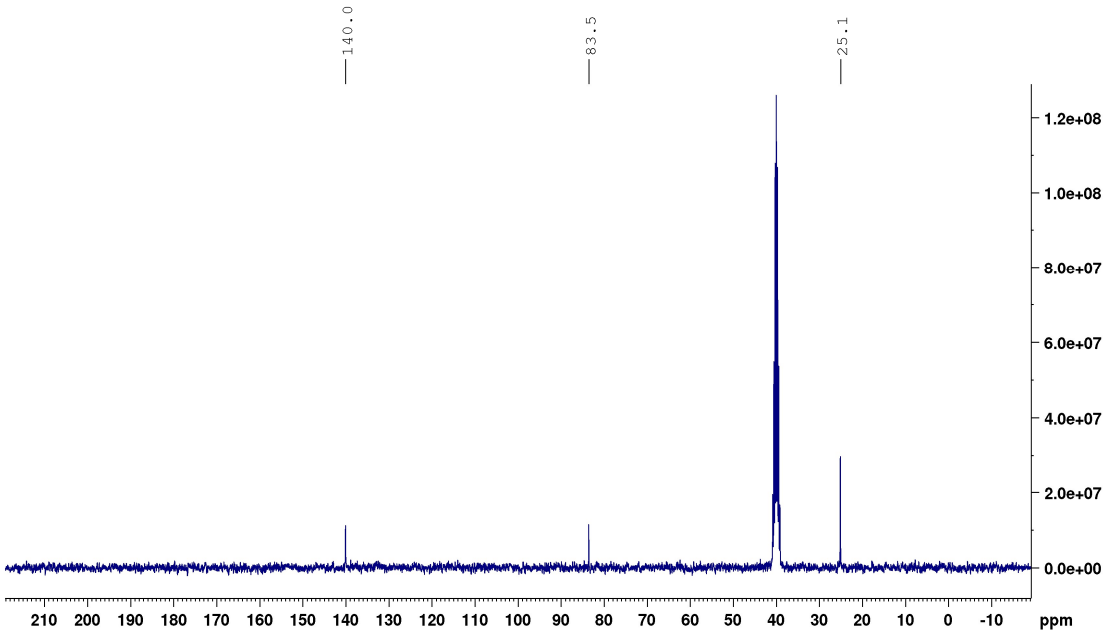




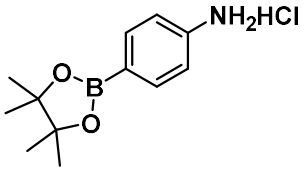
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole hydrochloride (compound 23)

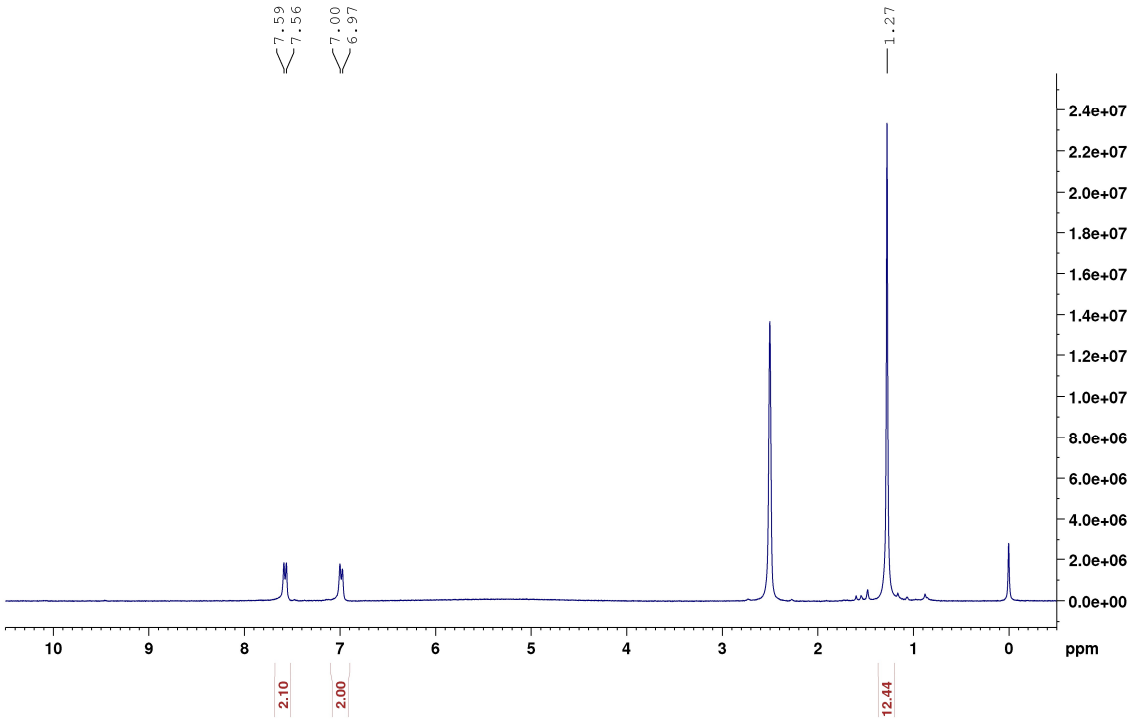


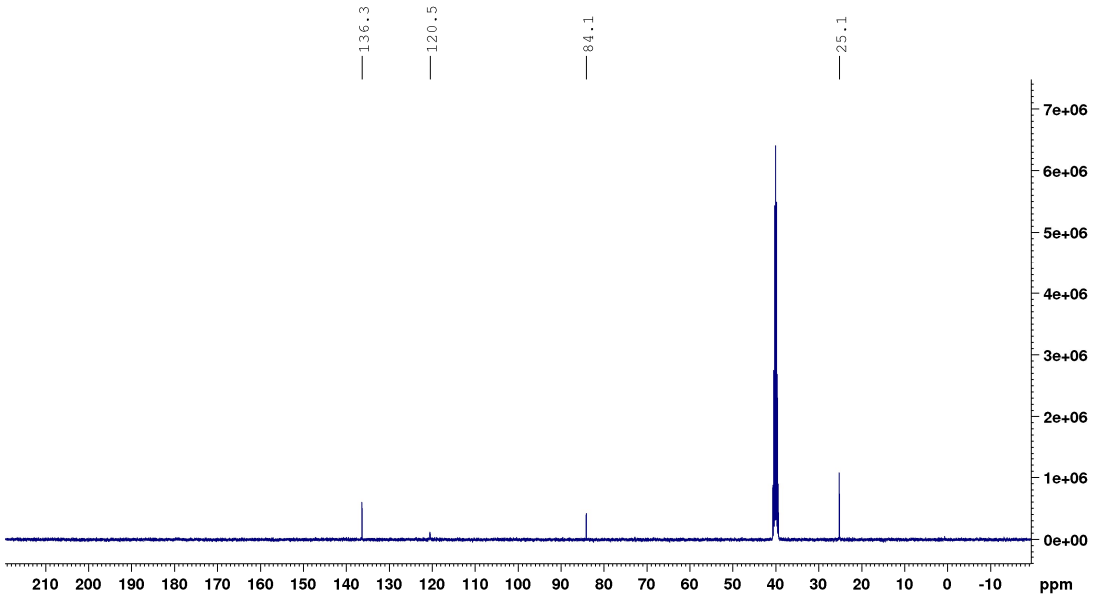




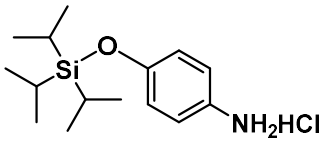
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline hydrochloride (compound 24)

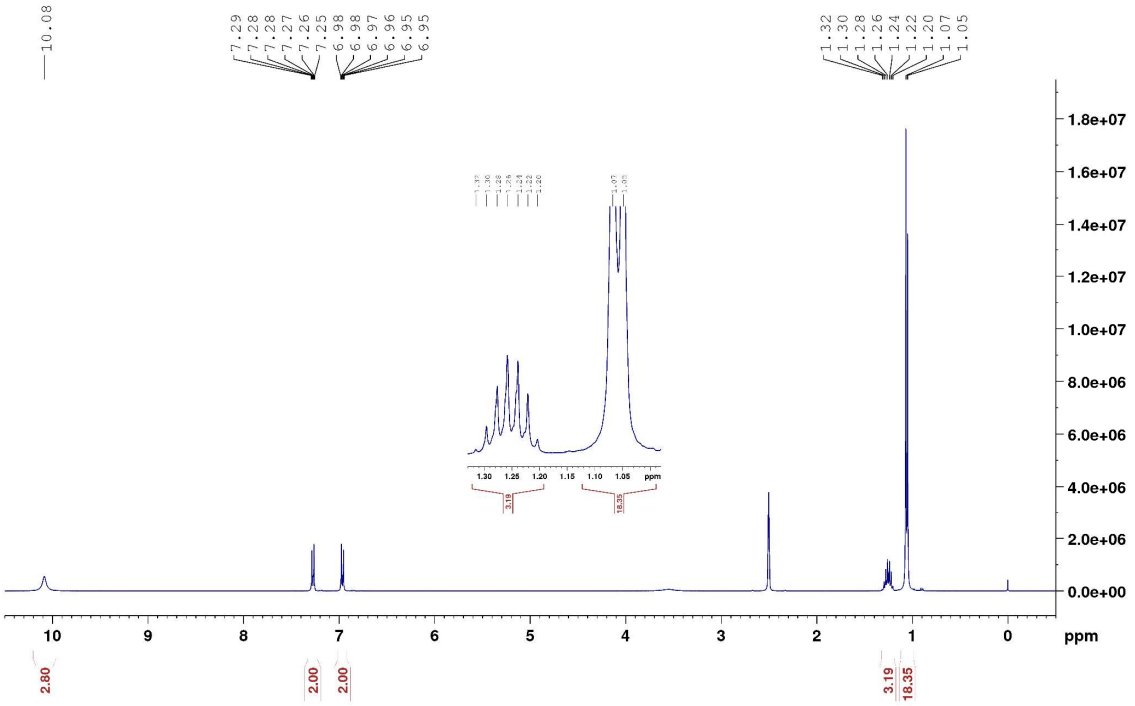


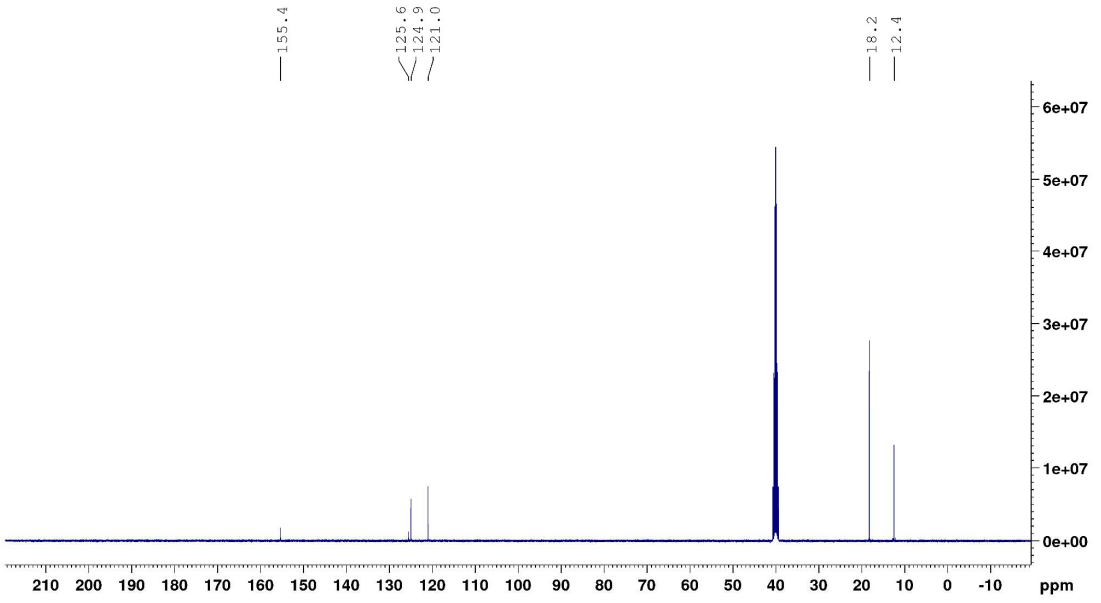




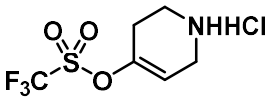
4-((triisopropylsilyl)oxy)aniline hydrochloride (compound 25)

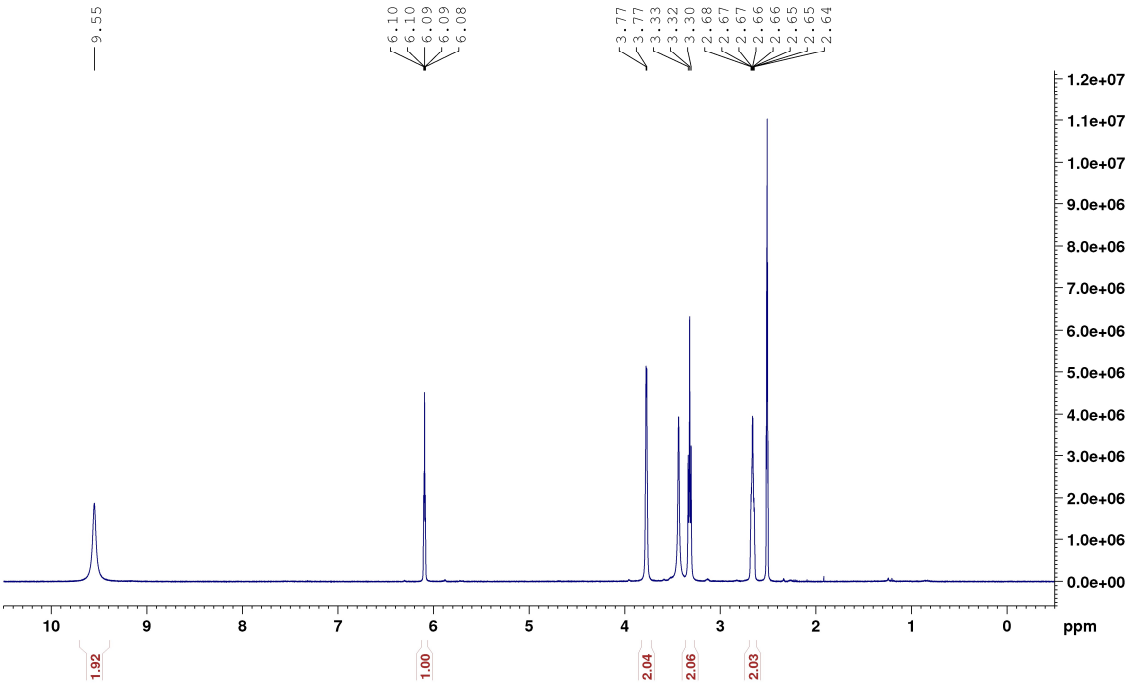


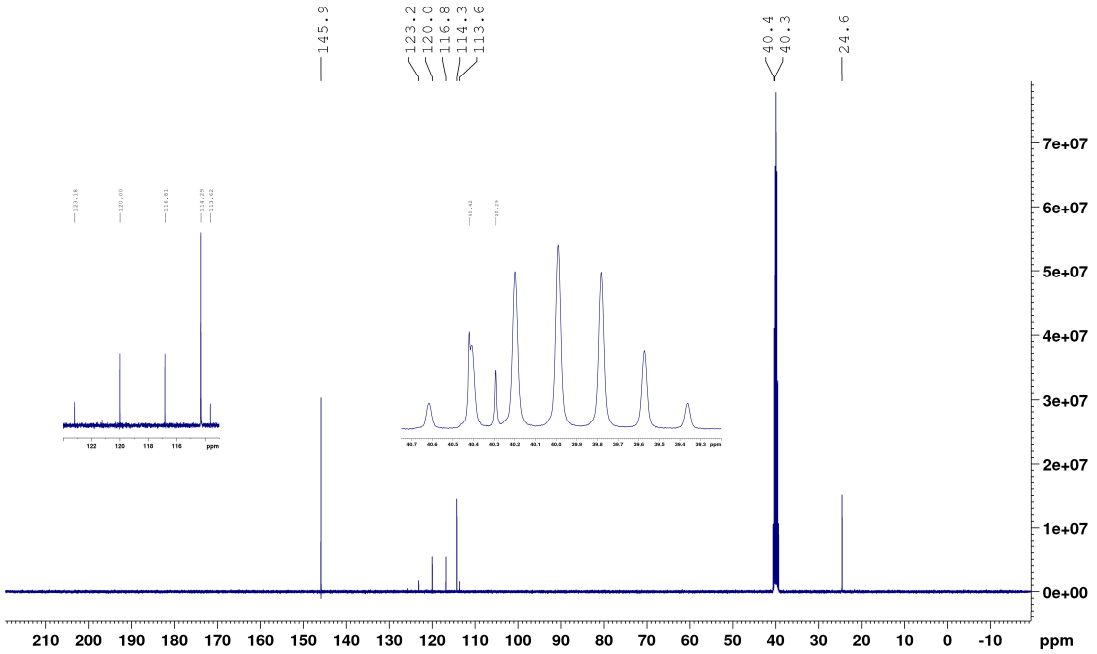


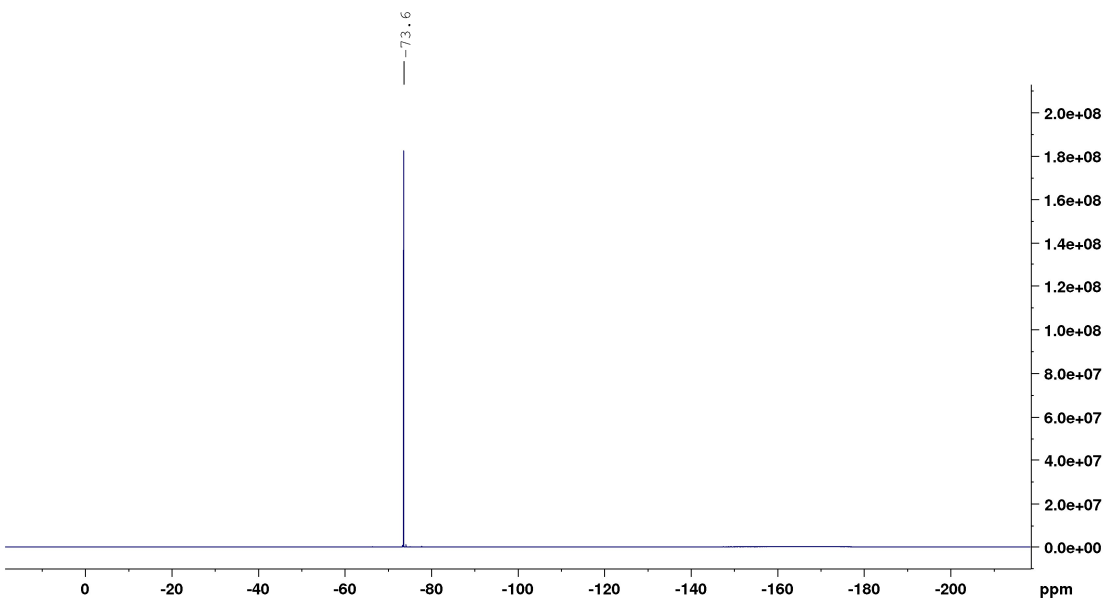


1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate hydrochloride (compound 26)

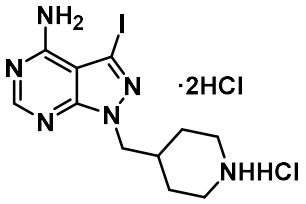


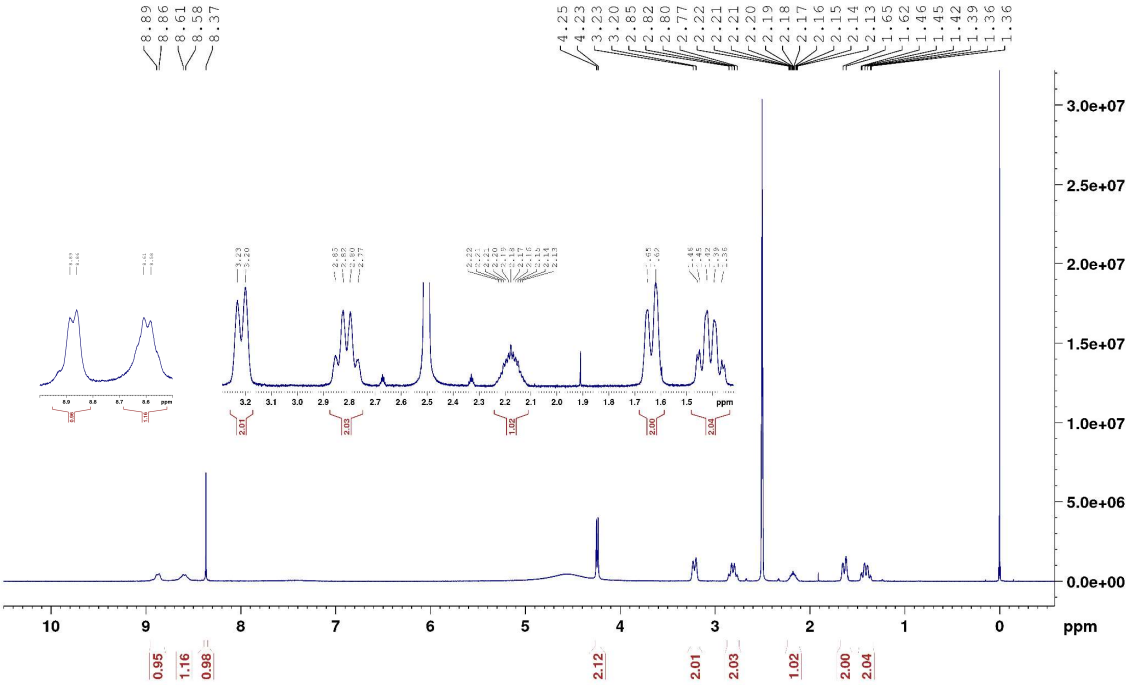


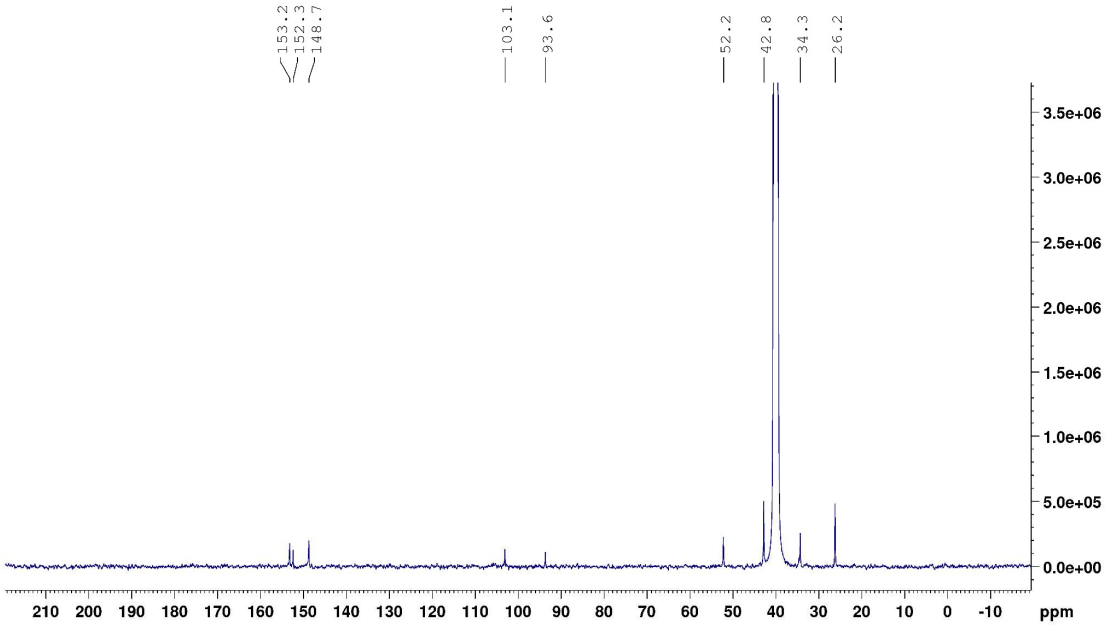



-73.6
2.0e+08
1.8e+08
1.6e+08
1.4e+08
1.2e+08
1.0e+08
8.0e+07
6.0e+07
4.0e+07
2.0e+07
0.0e+00
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm

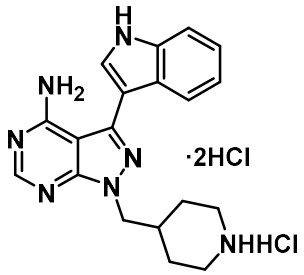
3-iodo-1-(piperidin-4-ylmethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine trihydrochloride (compound 27)

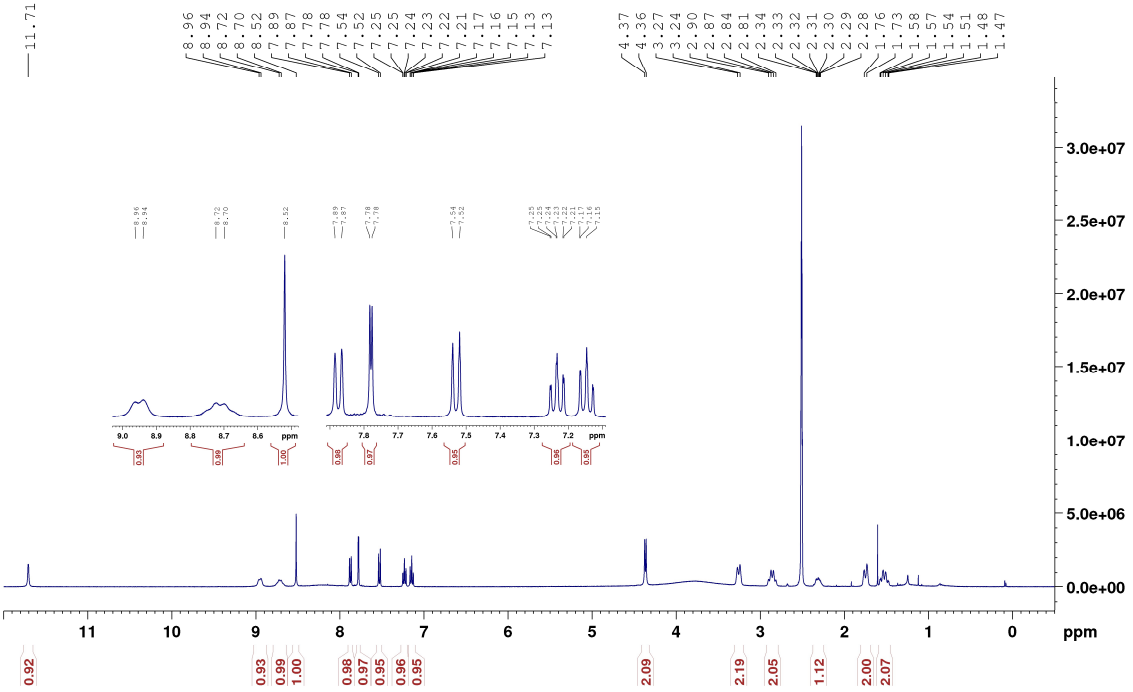


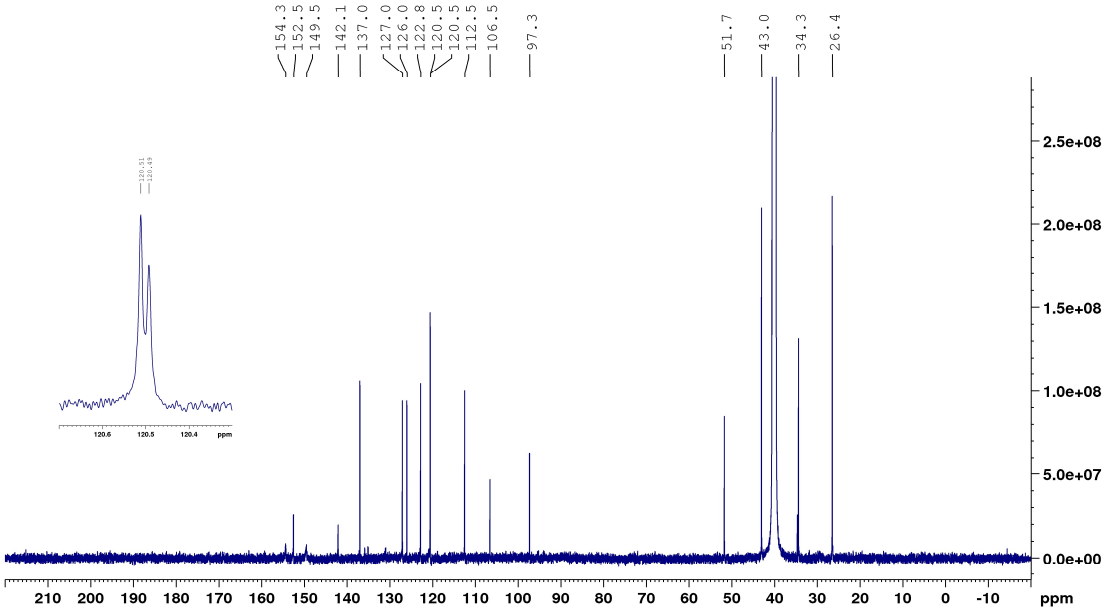




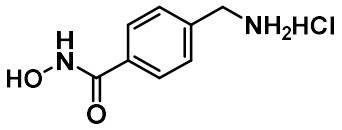
3-(1*H*-indol-3-yl)-1-(piperidin-4-ylmethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine trihydrochloride (compound 28)

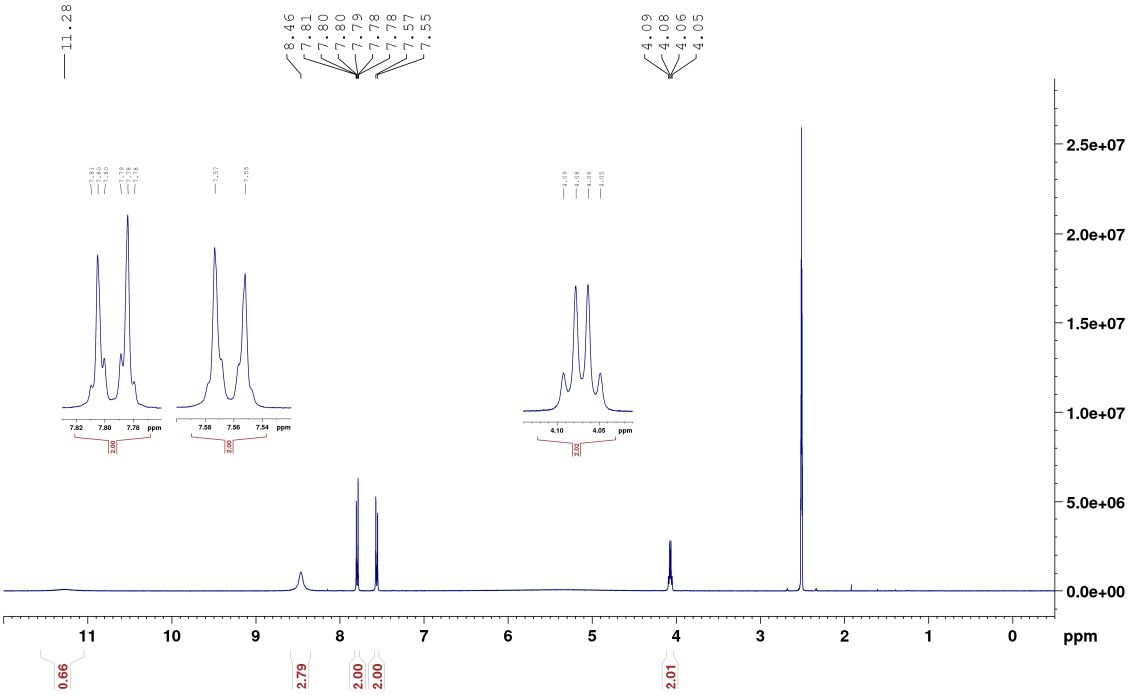


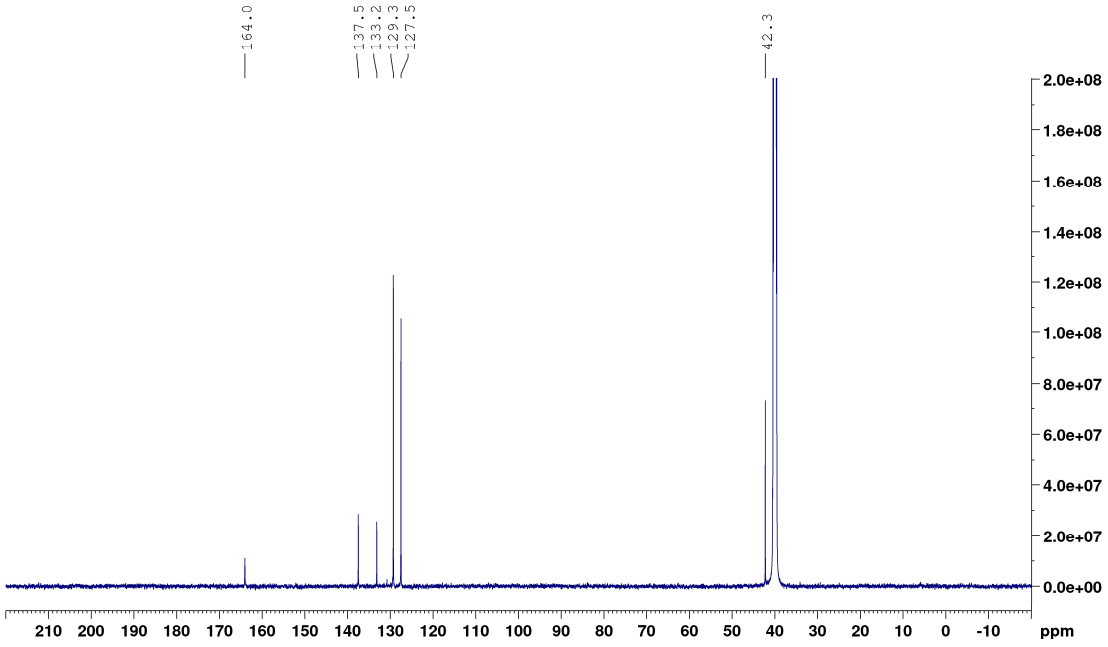




4-(aminomethyl)-*N*-hydroxybenzamide hydrochloride (compound 29)

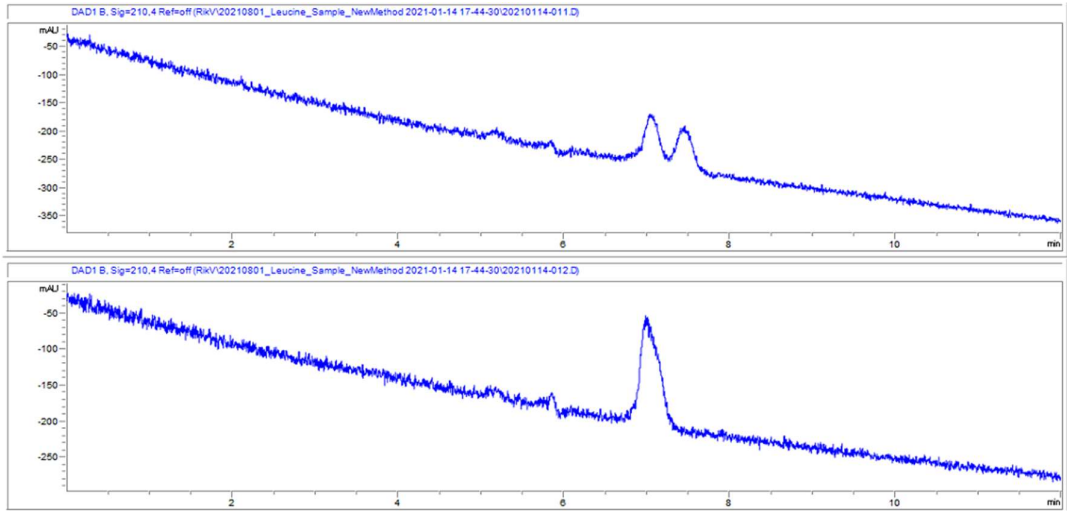




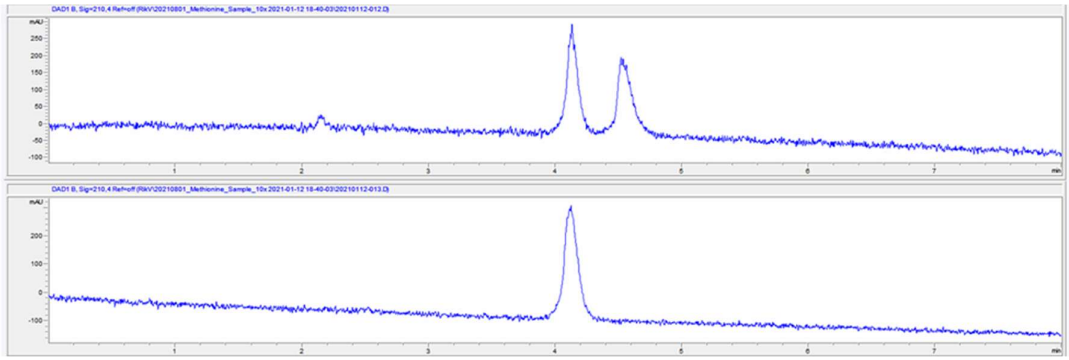


5. HPLC print-outs

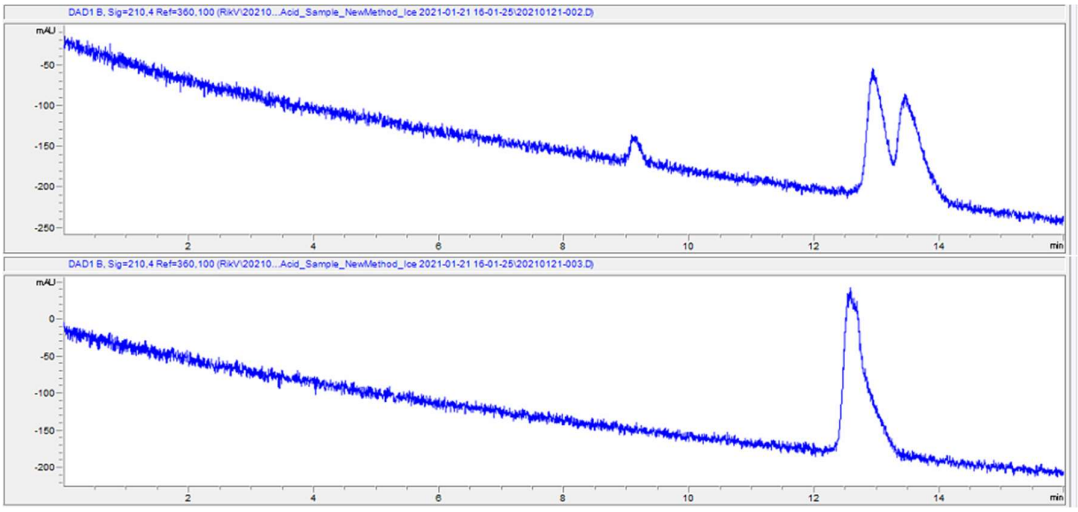
***L*-leucine hydrochloride (compound 11)**



***L*-methionine hydrochloride (compound 12)**



***L*-aspartic acid hydrochloride (compound 16)**



6. References

1. B. Viswanadham, A. S. Mahomed, H. B. Friedrich and S. Singh, Efficient and expeditious chemoselective BOC protection of amines in catalyst and solvent-free media, *Research on Chemical Intermediates*, 2017, **43**, 1355-1363.
2. R. Varala, S. Nuvula and S. R. Adapa, Molecular Iodine-Catalyzed Facile Procedure for N-Boc Protection of Amines, *J. Org. Chem.*, 2006, **71**, 8283-8286.
3. S. V. Chankeshwara and A. K. Chakraborti, Catalyst-Free Chemoselective N-tert-Butyloxycarbonylation of Amines in Water, *Org. Lett.*, 2006, **8**, 3259-3262.
4. Y. Kondo, S. Kojima and T. Sakamoto, General and Facile Synthesis of Indoles with Oxygen-Bearing Substituents at the Benzene Moiety, *J. Org. Chem.*, 1997, **62**, 6507-6511.
5. B. Wang, H.-X. Sun, B. Chen and Z.-H. Sun, Practical, environment-benign and atom economic KOAc-catalysed deprotection of aryl TIPS ethers under mild fluoride-free conditions, *Green Chem.*, 2009, **11**, 1112-1114.
6. X. Cheng, K.-H. Merz, S. Vatter, J. Zeller, S. Muehlbeyer, A. Thommet, J. Christ, S. Wölfl and G. Eisenbrand, Identification of a Water-Soluble Indirubin Derivative as Potent Inhibitor of Insulin-like Growth Factor 1 Receptor through Structural Modification of the Parent Natural Molecule, *J. Med. Chem.*, 2017, **60**, 4949-4962.
7. P. Hermange, A. T. Lindhardt, R. H. Taaning, K. Bjerglund, D. Lupp and T. Skrydstrup, Ex Situ Generation of Stoichiometric and Substoichiometric 12CO and 13CO and Its Efficient Incorporation in Palladium Catalyzed Aminocarbonylations, *J. Am. Chem. Soc.*, 2011, **133**, 6061-6071.
8. S. D. Friis, A. T. Lindhardt and T. Skrydstrup, The Development and Application of Two-Chamber Reactors and Carbon Monoxide Precursors for Safe Carbonylation Reactions, *Acc. Chem. Res.*, 2016, **49**, 594-605.
9. S. G. Koenig, C. P. Vandenbossche, H. Zhao, P. Mousaw, S. P. Singh and R. P. Bakale, A Facile Deprotection of Secondary Acetamides, *Org. Lett.*, 2009, **11**, 433-436.
10. X. Wang, Y. Dong, J. Sun, X. Xu, R. Li and Y. Hu, Nonracemic Betti Base as a New Chiral Auxiliary: Application to Total Syntheses of Enantiopure (2S,6R)-Dihydropinidine and (2S,6R)-Isosolenopsins, *J. Org. Chem.*, 2005, **70**, 1897-1900.
11. C. Cheng, J. Sun, L. Xing, J. Xu, X. Wang and Y. Hu, Highly Chemoselective Pd−C Catalytic Hydrodechlorination Leading to the Highly Efficient N-Debenzylation of Benzylamines, *J. Org. Chem.*, 2009, **74**, 5671-5674.
12. C. Chazalette, M. Rivière-Baudet, C. T. Supuran and A. Scozzafava, Carbonic Anhydrase Inhibitors: Allylsulfonamide, Styrene Sulfonamide, N -allyl Sulfonamides and Some of Their Si, Ge, and B Derivatives, *Journal of Enzyme Inhibition*, 2001, **16**, 475-489.
13. M. Kitamura, T. Suga, S. Chiba and K. Narasaka, Synthesis of Primary Amines by the Electrophilic Amination of Grignard Reagents with 1,3-Dioxolan-2-one O-Sulfonyloxime, *Org. Lett.*, 2004, **6**, 4619-4621.
14. D. C. Lenstra, P. E. Lenting and J. Mecinović, Sustainable organophosphorus-catalysed Staudinger reduction, *Green Chem.*, 2018, **20**, 4418-4422.
15. A. Porcheddu, G. Giacomelli, A. Chighine and S. Masala, New Cellulose-Supported Reagent: A Sustainable Approach to Guanidines, *Org. Lett.*, 2004, **6**, 4925-4927.

16. K. Hayashi, Y. Fujii, R. Saito, H. Kanao and T. Hino, The Influence of Measurement Parameters on the Specific Rotation of Amino Acids, *Agricultural and Biological Chemistry*, 1966, **30**, 1221-1237.
17. S. D. Bull, S. G. Davies, A. C. Garner and M. D. O'Shea, Conjugate additions of organocuprates to a 3-methylene-6-isopropyldiketopiperazine acceptor for the asymmetric synthesis of homochiral α-amino acids, *J. Chem. Soc., Perkin Trans. 1*, 2001, DOI: 10.1039/B108621A, 3281-3287.
18. A. Proteau-Gagné, V. Bournival, K. Rochon, Y. L. Dory and L. Gendron, Exploring the Backbone of Enkephalins To Adjust Their Pharmacological Profile for the δ-Opioid Receptor, *ACS Chemical Neuroscience*, 2010, **1**, 757-769.
19. C. Bolchi, F. Bavo, L. Regazzoni and M. Pallavicini, Preparation of enantiopure methionine, arginine, tryptophan, and proline benzyl esters in green ethers by Fischer–Speier reaction, *Amino Acids*, 2018, **50**, 1261-1268.
20. V. K. Aggarwal, C. J. Astle, H. Iding, B. Wirz and M. Rogers-Evans, Separation of pyrrolidine allylation products by diastereoselective enzymatic ester hydrolysis, *Tetrahedron Lett.*, 2005, **46**, 945-947.
21. D. C. Johnson and T. S. Widlanski, A reversible safety-catch method for the hydrogenolysis of N-benzyl moieties, *Tetrahedron Lett.*, 2004, **45**, 8483-8487.
22. See page 12: http://studia.ubbcluj.ro/download/pdf/411.pdf
23. B. Wrackmeyer, Carbon-13 NMR spectroscopy of boron compounds, *Progress in Nuclear Magnetic Resonance Spectroscopy*, 1979, **12**, 227-259.
24. P. Gilles, R. S. Kashyap, M. J. Freitas, S. Ceusters, K. Van Asch, A. Janssens, S. De Jonghe, L. Persoons, M. Cobbaut, D. Daelemans, J. Van Lint, A. R. D. Voet and W. M. De Borggraeve, Design, synthesis and biological evaluation of pyrazolo[3,4-d]pyrimidine-based protein kinase D inhibitors, *Eur. J. Med. Chem.*, 2020, **205**, 112638.