Supporting Information

Green, fast and simple continuous-flow protocol for the N-alkylation of amines in a biphasic solvent system

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Table of Contents

1. General information

Solvents were purified according to standard procedures, whenever necessary.[1] The starting materials, Michael acceptors, potassium hydroxide and tetrabutylammonium bromide were purchased from Sigma-Aldrich and used as received. Unless stated, the reported yields refer to isolated products.

Chromatography

The reactions were monitored by TLC on Merck silica gel (TLC silica gel 60 F_{254}) by using UV light as a visualizing agent. Solvent mixtures for TLC are reported in percentages. Sigma-Aldrich silica gel (particle size 0.040-0.063 nm) was used for flash chromatography, when necessary. Gas chromatography studies were conducted using a Shimadzu GC-2010plus chromatograph fitted with a capillary column (Restek, DB17MS - 1, 30 m × 0.25 mm) and a flame ionization detector (FID). Nitrogen was used as the mobile phase.

NMR spectra

NMR spectra were recorded on Bruker DRX 400 and 500 instruments (400 and 500 MHz for ^{1}H; 101 and 125 for ^{13}C, respectively). Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent peak as the internal reference: $CDCl_3$ (δ = 7.26 ppm for ^{1}H and δ = 77.16 ppm for ^{13}C) or TMS (δ = 0.00 ppm for ^{1}H and for ^{13}C). Coupling constants (*J*) are given in Hz and multiplicities of the signals are abbreviated as follows: s = singlet; bs = broad singlet; d = doublet; t = triplet; m = multiplet; dd = doublet of doublets and td = triplet of doublets and app = apparent.

Mass spectra

Mass spectra (MS) were acquired on a Shimadzu GCMS-QP 2010 equipped with DB-5 MS column and the ionization method was electron impact mode (EI, 70 eV). Helium was used as the mobile phase. High resolution mass spectra (HRMS) were recorded in an electron-spray ionization/time-of-flight (ESI-TOF) Bruker timsTOF flex.

Melting point

Melting points (MP) were measured on a BÜCHI M-560 Type, Labortechnik AG 9230.

Equipment and experiment setup

The microwave reactions were conducted in an Anton-Paar Monowave 300 reactor with standard power of 850 W, adjusting the temperature and time. The experiments in continuous-flow system were run in Syrris pump, model Asia or a Vapourtec peristaltic pump, model SF-10. The heating

module used was a model Asia, purchased from Syrris, with a stainless-steel coil with a volume of 4 mL. PTFE tubing and connections (1/16" O.D. dimension), T-mixer, BPR, 6-port manual switching injection valves were purchased from Idex Health and Science. The equipment and setup for the experiments can be seen in figure S1.

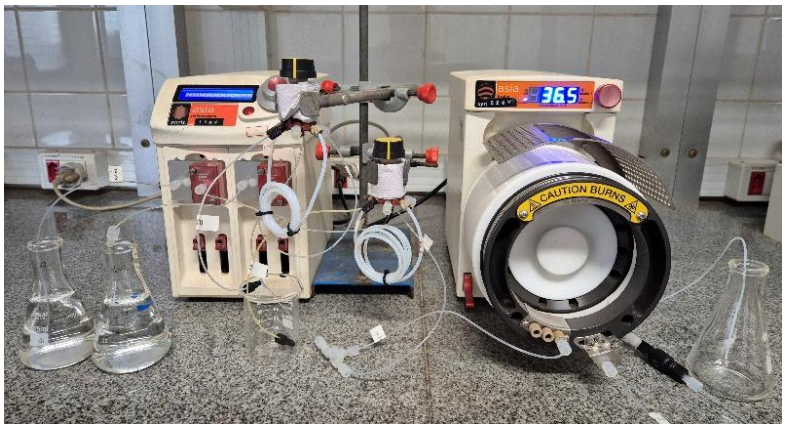


Figure S1. Setup for the continuous-flow experiments

2. Green chemistry metrics

For quantitative and qualitative analysis of green metrics, the toolkit available in the work of McElroy, Clark and colleagues[2] were employed with addition of the classic E factor and the complete calculation form (cE-Factor) metric, which includes water as residue, as defined by Sheldon.[3] The figure S2 resumes the formulas used for metrics' calculation.

$$AE = \frac{product\ molar\ mass}{\sum(reagent\ molar\ mass)} \times 100$$

$$E - Factor = \frac{\sum(all\ residue\ mass)}{product\ mass}$$

complete $E - Factor\ (cE - Factor)$
includes water mass as residue

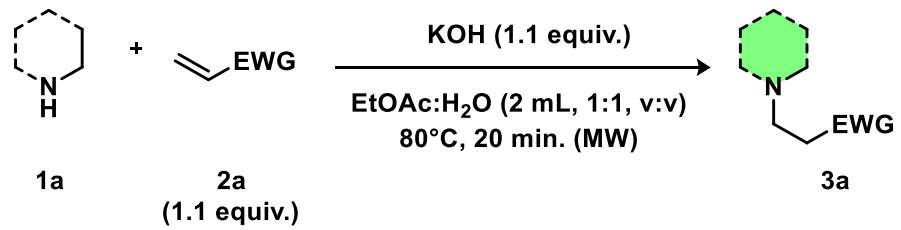
$$RME = \frac{isolated\ product\ mass}{\sum(reagent\ mass)} \times 100$$

$$PMI = \frac{\sum(mass\ of\ all\ components)}{product\ mass} \times 100$$

Figure S2. Green chemistry metrics' formulas employed.

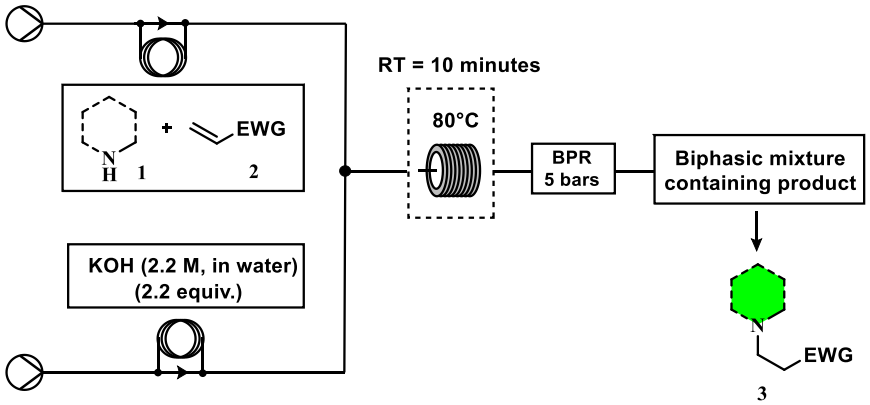
3. Experimental Procedures

3.1 General Procedure for N-alkylation of amines in microwave reactor (GP1)



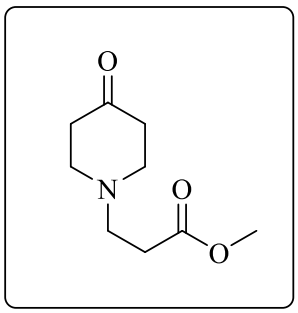
A vial for microwave reactor, under magnetic stirring, was charged with the amine of choice (1 equiv., 1 mmol), followed by the addition of 1 mL of ethyl acetate, Michael acceptor (1.1 equiv., 1.1 mmol) and KOH (1.1 equiv., 1.1 mmol) dissolved in 1 mL of water. A stock solution of 1.1 M of the base can be used instead. The vial was capped and placed at the microwave reactor. The temperature was set to 80°C for 20 minutes. After the reaction time, the biphasic mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 x 5mL). The combined organic phase was dried over $MgSO_4$ and evaporated under reduced pressure.

3.2 General Procedure for N-alkylation of amines in continuous-flow system (GP2)



A 1 mL loop connected to a 6-port manual switching injection valve was charged with a ~~stock~~ freshly prepared solution of the amine of choice (1 equiv., 1 mmol), Michael acceptor (1.1 equiv., 1.1 mmol) and 1 mL of ethyl acetate. A second 1 mL loop connected to a 6-port manual switching injection valve was charged with a stock solution of KOH (2.2 M, 2.2 equiv., 2.2 mmol) in water. Water-soluble amines can be mixed in the stock solution of base, prior to injection. Each solution stream was pumped at a flow rate of 200 µL/min, after opening the injection valves. The combined streams remained in the heating unit for a residence time of 10 min or 60 min for imidazole and benzimidazole, at a temperature of 80 ºC. The biphasic effluent was collected and diluted with water (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford the desired product.

Methyl 3-(4-oxopiperidin-1-yl)propanoate (3a)



Prepared according to **GP2** from piperidin-4-one monohydrate hydrochloride (1 mmol, 153.6 mg) and methyl acrylate (1.1 mmol). Isolated as a colorless oil (142.5 mg, 77%).

CAS Nº: 190515-96-9.

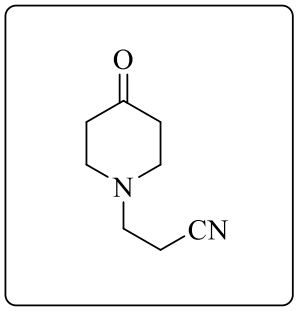
^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.04 (t, *J* = 6.2 Hz, 4H), 2.50 (t, *J* = 7.1 Hz, 2H), 2.73 (t, *J* = 6.1 Hz, 4H), 2.78 (t, *J* = 7.2 Hz, 2H), 3.66 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 32.6, 41.1 (2C), 51.7, 52.5, 52.8 (2C), 127.7, 208.9.

GC-MS (EI, 70 eV) (*m/z*, relative abundance %): 112 (100), 42 (55), 84 (26), 56 (26), 98 (18), 185 (12).

R_f = 0.45 (Hexanes /EtOAc, 50:50).

3-(4-oxopiperidin-1-yl)propanenitrile (3b)



Prepared according to **GP2** from piperidin-4-one monohydrate hydrochloride (1 mmol, 153.6 mg) and methyl acrylate (1.1 mmol). Isolated as an orange oil (126.3 mg, 83%).

CAS Nº: 1225599-16-5

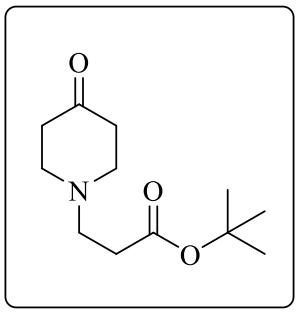
^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.45 (t, *J* = 6 Hz, 4H), 2.55 (t, *J* = 6.8 Hz, 2H), 2.80 (dt, *J* = 6.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 16.6, 41.0 (2C), 52.4, 52.6 (2C), 118.6, 208.2.

GC-MS (EI, 70 eV) (*m/z*, relative abundance %): 112 (100), 42 (68), 84 (20), 152 (2).

R_f = 0.42 (Hexanes/EtOAc, 50:50).

***Tert*-butyl 3-(4-oxopiperidin-1-yl)propanoate (3c)**



Prepared according to **GP2** from piperidin-4-one monohydrate hydrochloride (1 mmol, 153.6 mg) and *tert*-butyl acrylate (1.1 mmol). Isolated as a colorless oil (70.4 mg, 31%).

CAS Nº: 181943-44-2.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.46 (s, 9H), 2.43 – 2.47 (m, 6H), 2.78 (q app, *J* = 5.2, 6.9 Hz, 6H).

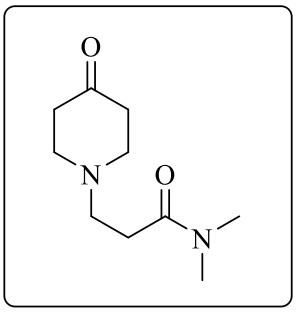
^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 28.1, 34.1, 41.2, 52.7, 52.8, 80.5, 171.7, 209.1.

GC-MS (EI, 70 eV) (*m/z*, relative abundance %): 112 (100), 42 (22), 170 (21), 56 (15), 128 (14), 227 (4).

MP: 48.5 – 52.3°C

R_f = 0.52 (Hexanes/EtOAc, 35:65).

***N,N*-dimethyl-3-(4-oxopiperidin-1-yl)propanamide (3d)**



Prepared according to **GP2** from piperidin-4-one monohydrate hydrochloride (1 mmol, 153,6 mg) and *N,N*-dimethylacrylamide (1.1 mmol). Isolated as a light-yellow solid (43.6 mg, 22%).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.40 (t, *J* = 6.2 Hz, 4H), 2.51 (t, *J* = 7.2 Hz, 2H), 2.74 (t, *J* = 6.2 Hz, 4H), 2.40 (t, *J* = 7.1 Hz, 2H), 2.90 (s, 3H), 2.98 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 31.5, 35.4, 37.2, 41.1 (2C), 52.8, 53.2 (2C), 171.3, 208.9.

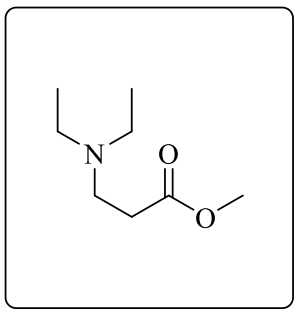
HRMS (**ESI**, *m/z*)**:** $[M+H]^+$ calculated for $C_{10}H_{19}N_2O_2$, 198.1441; found: 199.1438.

GC-MS (EI, 70 eV) (*m/z*, relative abundance %): 112 (100), 98 (96), 42 (62), 56 (43), 72 (27), 198 (3).

MP: 78.4 – 80.7°C

R_f = 0.47 (Methanol/ EtOAc, 50:50).

Methyl 3-(diethylamino)propanoate (3e)



Prepared according to **GP2** from diethylamine (1 mmol, 73.1 mg) and methyl acrylate (1.1 mmol). Isolated as a colorless oil (68.4 mg, 43%).

CAS Nº: 5351-01-9

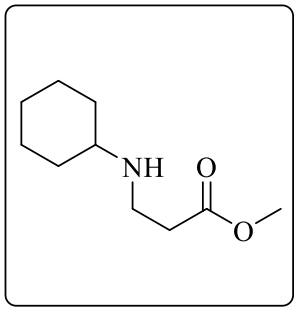
^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.02 (t, *J* = 7.2 Hz, 6H), 2.47 (t, *J* = 7.1 Hz, 2H), 2.53 (q, *J* = 7.2 Hz, 4H), 2.80 (t, *J* = 7.1 Hz, 2H), 3.65 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 11.6 (2C), 31.9, 46.8 (2C), 47.9, 51.6, 173.2.

GC-MS (EI, 70 eV) (*m/z*, relative abundance %): 86 (100), 144 (19), 42 (17), 58 (16), 102 (12), 72 (8),

R_f = 0.75 (Hexanes/AcOEt, 50:50).

Methyl 3-(cyclohexylamino)propanoate (3f)



Prepared according to **GP2** from cyclohexilamine (1 mmol, 99.2 mg) and methyl acrylate (1.1 mmol). Isolated as a colorless oil (85.3 mg, 86%).

CAS Nº: 22870-26-4

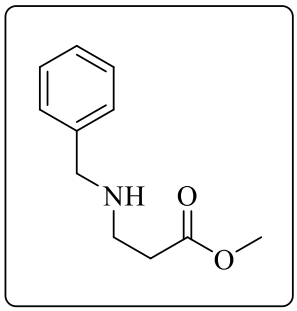
^{1}H NMR (400 MHz, CD_3OD, ppm): δ 1.05 (q, J = 11.7 Hz, 2H), 1.13 – 1.19 (m, 1H), 1.25 (q, *J* = 12.3 Hz, 2H), 1.62 (d app, *J* = 11.4 Hz, 1H), 1.72 (d app, *J* = 12.9 Hz, 2H), 1.88 (d app, *J* = 11.8 Hz, 2H), 2.37 – 2.43 (m, 1H), 2.49 (t, *J* = 6.8 Hz, 2H), 2.82 (t, *J* = 6.7 Hz, 2H), 3.31 (s, 3H).

^{13}C NMR (101 MHz, CD_3OD, ppm): δ 26.1 (2C), 27.2, 33.9 (2C), 34.8, 42.8, 49.9, 57.7, 174.6.

GC-MS (EI, 70 eV) (*m/z*, relative abundance %): 142 (100), 68 (36), 110 (34), 55 (20), 41 (15), 185 (14), 70 (10).

R_f = 0.62 (Hexanes/ EtOAc, 50:50).

Methyl 3-(benzylamino)propanoate (3g)



Prepared according to **GP2** from benzylamine (1 mmol, 107.1 mg) and methyl acrylate (1.1 mmol). Isolated as a light-yellow oil (85.0 mg, 44%).

CAS Nº: 23574-01-8

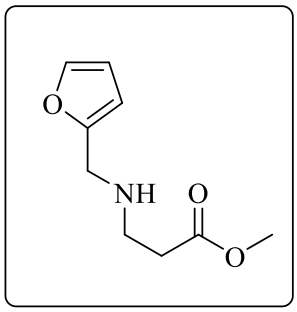
^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.54 (t, *J* = 6.5 Hz, 2H), 2.90 (t, *J* = 6.5 Hz, 2H), 7.22 – 7.27 (m, 1H), 7.31 – 7.32 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 34.6, 44.5, 51.6, 53.8, 127.0, 128.1 (2C), 128.4 (2C), 140.1, 173.3.

GC-MS (EI, 70 eV) (*m/z*, relative abundance %): 91 (100), 106 (57), 120 (25), 65 (12), 42 (8).

R_f = 0.65 (Hexanes/ EtOAc, 50:50).

Methyl 3-[(furan-2-ylmethyl)amino]propanoate (3h)



Prepared according to **GP2** from furfurylamine (1 mmol, 99.1 mg) and methyl acrylate (1.1 mmol). Isolated as a yellow oil (151.9 mg, 83%).

CAS Nº: 4063-31-4

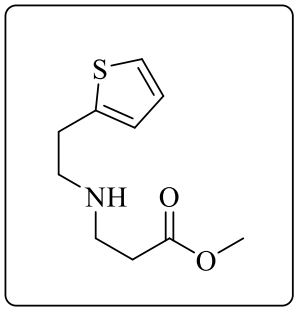
^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.53 (t, *J* = 6.5 Hz, 2H), 2.89 (t, *J* = 6.5 Hz, 2H), 3.68 (s, 3H), 3.79 (s, 2H), 6.18 (dd app, *J* = 0.7, 3.1 Hz, 1H), 6.31 (dd, *J* = 1.9, 3.1 Hz, 1H), 7.36 (dd, *J* = 0.8, 1.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 34.4, 44.2, 46.1, 51.6, 107.0, 110.1, 141.9, 153.6, 173.1.

GC-MS (EI, 70 eV) (*m/z*, relative abundance %): 81 (100), 96 (79), 110 (20), 53 (18), 108 (8).

R_f = 0.75 (Hexanes/ EtOAc, 35:65).

Methyl 3-[(2-(thiophen-2-yl)ethyl)amino]propanoate (3i)



Prepared according to **GP2** from 2-(thiophen-2-yl)ethan-1-amine (1 mmol, 127.2 mg) and methyl acrylate (1.1 mmol). Isolated as a yellow oil (189.5 mg, 89%).

CAS Nº: 1099658-96-4

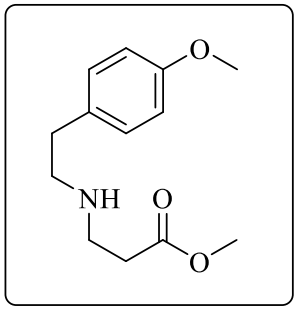
^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.51 (t, *J* = 6.5 Hz, 2H), 2.92 (t app, *J* = 6.6 Hz, 4H), 3.01 (t app, *J* = 7.0 Hz, 4H), 3.66 (s, 3H), 6.84 (dd app, *J* = 1.0, 3.4 Hz, 1H), 6.93 (dd, *J* = 3.4, 5.1 Hz, 1H), 7.14 (dd, *J* = 1.2, 5.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 30.4, 34.6, 44.8, 51.0, 51.6, 123.6, 125.0, 126.8, 142.4, 173.1.

GC-MS (EI, 70 eV) (*m/z*, relative abundance %): 116 (100), 84 (92), 42 (55), 111 (16), 140 (16).

R_f = 0.72 (Methanol/ EtOAc 50:50).

Methyl 3-[(4-methoxyphenethyl)amino]propanoate (3j)



Prepared according to **GP2** from 2-(4-methoxiphenyl)ethan-1-amine (1 mmol, 151 mg) and methyl acrylate (1.1 mmol). Isolated as a yellow oil (220 mg, 93%).

CAS Nº: 88655-07-6

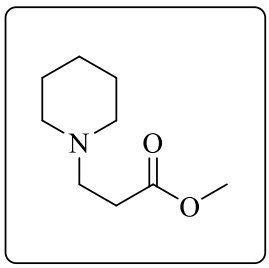
^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.51 (t, *J* = 6.6 Hz, 2H), 2.75 (t app, *J* = 6.8 Hz, 2H), 2.83 (t app, *J* = 6.5 Hz, 2H), 2.51 (t, *J* = 6.6 Hz, 2H), 3.65 (s, 3H), 3.78 (s, 3H), 6.84 (d, *J* = 8.6 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 34.5, 35.4, 44.9, 51.2, 51.6, 55.3, 113.9, 129.6, 131.9, 158.0, 173.1.

GC-MS (EI, 70 eV) (*m/z*, relative abundance %): 116 (100), 84 (72), 42 (32), 164 (11), 121 (10), 135 (10).

R_f = 0.67 (Methanol/ EtOAc, 50:50).

Methyl 3-(piperidin-1-yl)propanoate (3k)



Prepared according to **GP2** from piperidine (1 mmol, 85.1 mg) and methyl acrylate (1.1 mmol). Isolated as a colorless oil (118.1 mg, 69%).

CAS Nº: 23753-93-5

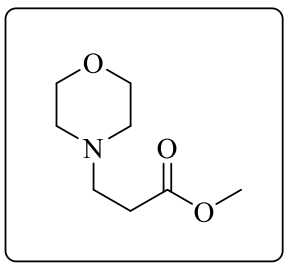
^{1}H NMR (400 MHz, CD_3OD, ppm): δ 1.38 (p, Hz, 2H), 1.53 (p, *J* = 5.5Hz, 4H), 2.36 (t, *J* = 4.5 Hz, 4H), 2.48 (t, *J* = 7.9 Hz, 2H), 2.63 (t, *J* = 7.9 Hz, 2H), 3.63 (s, 3H).

^{13}C NMR (101 MHz, CD_3OD, ppm): δ 24.20, 25.85 (2C), 31.93, 51.59, 54.20, 54.22, 173.13.

GC-MS (EI, 70 eV) (*m/z*, relative abundance %): 98 (100), 42 (41), 41 (27), 55 (19), 70 (9), 96 (8).

R_f = 0.70 (Hexanes/ EtOAc, 50:50).

Methyl 3-morpholinopropanoate (3l)



Prepared according to **GP2** from morpholine (1 mmol, 86.1 mg) and methyl acrylate (1.1 mmol). Isolated as a colorless oil (107.4 mg, 62%)

CAS Nº: 33611-43-7

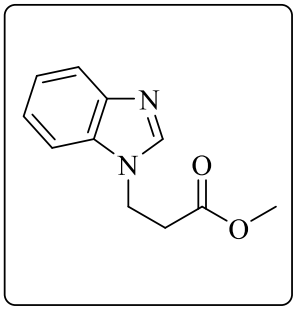
^{1}H NMR (400 MHz, CD_3OD, ppm): δ 2.47 (t, *J* = 4.7 Hz, 4H), 2.54 (t, *J* = 7.1 Hz, 2H), 2.67 (t, *J* = 7.1 Hz, 2H), 3.66 – 3.68 (m, 7H).

^{13}C NMR (101 MHz, CD_3OD, ppm): δ 32.4, 52.2, 54.5 (2C), 55.0, 67.7 (2C), 174.4.

GC-MS (EI, 70 eV) (*m/z*, relative abundance %): 173 (8), 100 (100), 56 (39), 42 (22).

R_f = 0.65 (Hexanes/ EtOAc, 50:50).

Methyl 3-(1H-benzo[d]imidazol-1-yl)propanoate (3m)



Prepared according to **GP2**, with RT of 60 min., from benzymidazole (1 mmol, 118.1 mg) and methyl acrylate (1.1 mmol). Isolated as light-yellow oil (124.6 mg, 61%).

CAS Nº: 144186-69-0

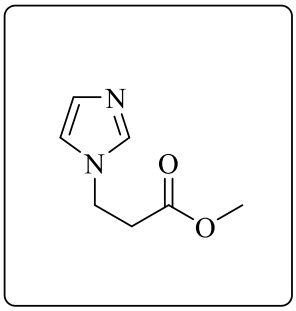
^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.87 (t, *J* = 6.5 Hz, 2H), 3.66 (s, 3H), 4.49 (t, *J* = 6.5 Hz, 2H), 7.28 – 7.34 (m, 2H), 7.40 (d app, *J* = 2.18, 6.9 Hz, 1H), 7.81 (d app, J = 1.58, 6.22 Hz, 1H), 7.98 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 34.1, 40.3, 52.2, 109.3, 120.5, 122.3, 123.1, 133.3, 143.4, 143.7, 171.1.

GC-MS (EI, 70 eV) (*m/z*, relative abundance %): 131 (100), 204 (44), 104 (18), 77 (16), 90 (11), 145 (8), 118 (6).

R_f = 0.32 (Hexanes/EtOAc, 50:50).

Methyl 3-(1H-imidazol-1-yl)propanoate (3n)



Prepared according to **GP2,** with RT of 60 min., from imidazole (1 mmol, 68.1 mg) and methyl acrylate (1.1 mmol). Isolated as a colorless oil (84.8 mg, 55%).

CAS Nº: 18999-46-7

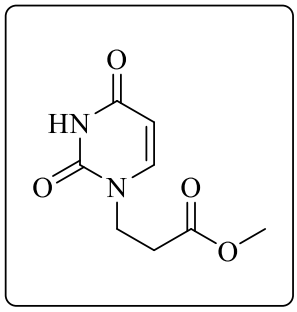
^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.77 (t, *J* = 6.6 Hz, 2H), 3.68 (s, 3H), 4.26 (t, *J* = 6.6 Hz, 2H), 6,92 (d, *J* = 0,6 Hz, 1H), 7.03 (d, *J* = 0.9 Hz, 1H), 7.50 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 35.6, 42.1, 52.0, 118.8, 129.3, 137.2, 170.9.

GC-MS (EI, 70 eV) (*m/z*, relative abundance %): 81 (100), 95 (60), 154 (52), 122 (52), 54 (40), 41 (25), 68 (19).

R_f = 0.30 (Hexanes/ EtOAc, 50:50).

Methyl 3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)propanoate (3o)



Prepared according to **GP2** from uracil (1 mmol, 112.0 mg) and methyl acrylate (1.1 mmol). Isolated as a white solid (49.5 mg, 25%).

CAS Nº: 90007-75-3

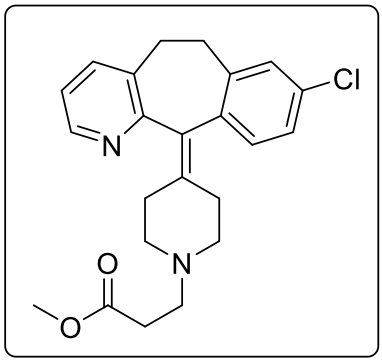
^{1}H NMR (400 MHz, CD_3OD, ppm): δ 2.75 (t, *J* = 6.4 Hz, 2H), 3.66 (s, 3H), 3.98 (t, *J* = 6.4 Hz, 2H), 5.60 (d, *J* = 7.9 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 1H).

^{13}C NMR (101 MHz, CD_3OD, ppm): δ 33.6, 46.2, 52.4, 102.0, 147.9, 152.7, 166.8, 173.2.

GC-MS (EI, 70 eV) (*m/z*, relative abundance %): 55 (100), 82 (94), 138 (87), 96 (56), 198 (37), 96 (36), 166 (31), 112 (26).

R_f = 0.80 (Methanol/EtOAc, 50:50).

Methyl 3-(4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidin-1-yl)propanoate (3q)



Prepared according to **GP2** from desloratadine (1 mmol, 310.8 mg) and methyl acrylate (1.1 mmol). Isolated as a light-pink solid (158.7 mg, 40%).

CAS Nº: 1556882-21-3

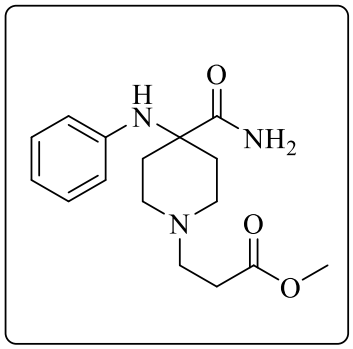
^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.11 – 2.18 (m, 2H), 2.30 – 2.41 (m, 3H), 2.37 – 2.53 (m, 3H), 2.69 (t, *J* = 7.5 Hz, 2H), 2.67 – 2.87 (m, 5H), 3.33 – 3.45 (m, 2H), 3.67 (s, 3H), 7.08 (dd, *J* = 4.8, 7.6 Hz, 1H), 7.13 – 7.15 (m, 3H), 7.44 (d app, *J* = 7,6 Hz, 1H), 8.40 (dd, *J* = 1.4, 4.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 30.70, 30.94, 31.45, 31.82, 32.20, 51.69, 53.35, 54.59, 54.62, 122.12, 126.03, 128.96, 130.85, 132.67, 132.73, 133.41, 137.29, 137.79, 138.69, 139.53.

GC-MS (EI, 70 eV) (*m/z*, relative abundance %): 142 (100), 280 (85), 266 (59), 396 (58), 168 (49), 282 (42), 116 (33).

R_f = 0.66 (Methanol /EtOAc, 50:50).

Methyl 3-(4-carbamoyl-4-(phenylamino)piperidin-1-yl)propanoate (3p)



Prepared according to **GP2** from 4-(phenylamino)piperidine-4-carboxamide (1 mmol, 219.3 mg) and methyl acrylate (1.1 mmol). Isolated as a white solid (189.3 mg, 62%).

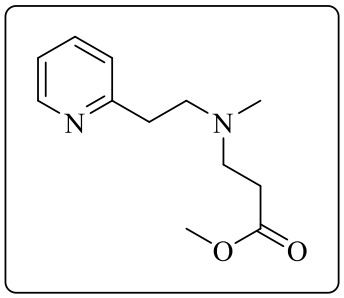
^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.93 (d app, *J* = 12.8 Hz, 2H), 2.13 (td, *J* = 1.9, 11.9 Hz, 2H), 2.29 (td, *J* = 4.0, 12.9 Hz, 2H), 2.48 (t, *J* = 7.2 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 2.74 (dt, *J* = 3.0, 12.0 Hz, 2H), 5.77 (d, *J* = 2.9 Hz, 1H), 6.63 (d app, *J* = 7.6 Hz, 2H), 6.81 (t app, *J* = 7.3 Hz, 2H), 6.90 (d, *J* = 2.8 Hz, 1H), 7.18 (t app, *J* = 7.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 31.3, 32.3 (2C), 48.6 (2C), 51.7, 53.5, 58.1, 116.1 (2C), 119.2, 129.2 (2C), 143.6, 173.0, 178.5.

GC-MS (EI, 70 eV) (*m/z*, relative abundance %): 168 (100), 116 (94), 42 (87), 146 (87), 261 (53), 77 (50), 212 (48), 232 (28), 305 (8)

R_f = 0.65 (Methanol/ EtOAc, 50:50).

Methyl 3-(methyl(2-(pyridin-2-yl)ethyl)amino)propanoate (3r)



Prepared according to **GP2** from betahistine dihydrochloride (1 mmol, 209.1 mg) and methyl acrylate (1.1 mmol). Isolated as a colorless oil (161 mg, 73%).

CAS Nº: 1040073-99-1

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.33 (s, 3H), 2.49 (t, *J* = 7.3 Hz, 2H), 2.77 – 2.82 (m, 4H), 2.94 – 2.98 (m, 2H), 3.66 (s, 3H), 7.11 (dd, *J* = 4.9, 7.4 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.59 (td, *J* = 1,8, 7,6 Hz, 1H), 8.53 (d app, *J* = 4.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 32.4, 35.9, 41.9, 51.6, 52.6, 57.2, 121.2, 123.3, 136.3, 149.2 (2C), 160.4, 173.1.

GC-MS (EI, 70 eV) (*m/z*, relative abundance %): 130 (100), 88 (31), 106 (25), 149 (16), 42 (11), 222 (1).

R_f = 0.52 (Methanol/EtOAc, 50:50).

4. NMR Spectra

Figure S3. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(4-oxopiperidin-1-yl)propanoate (**3a**)

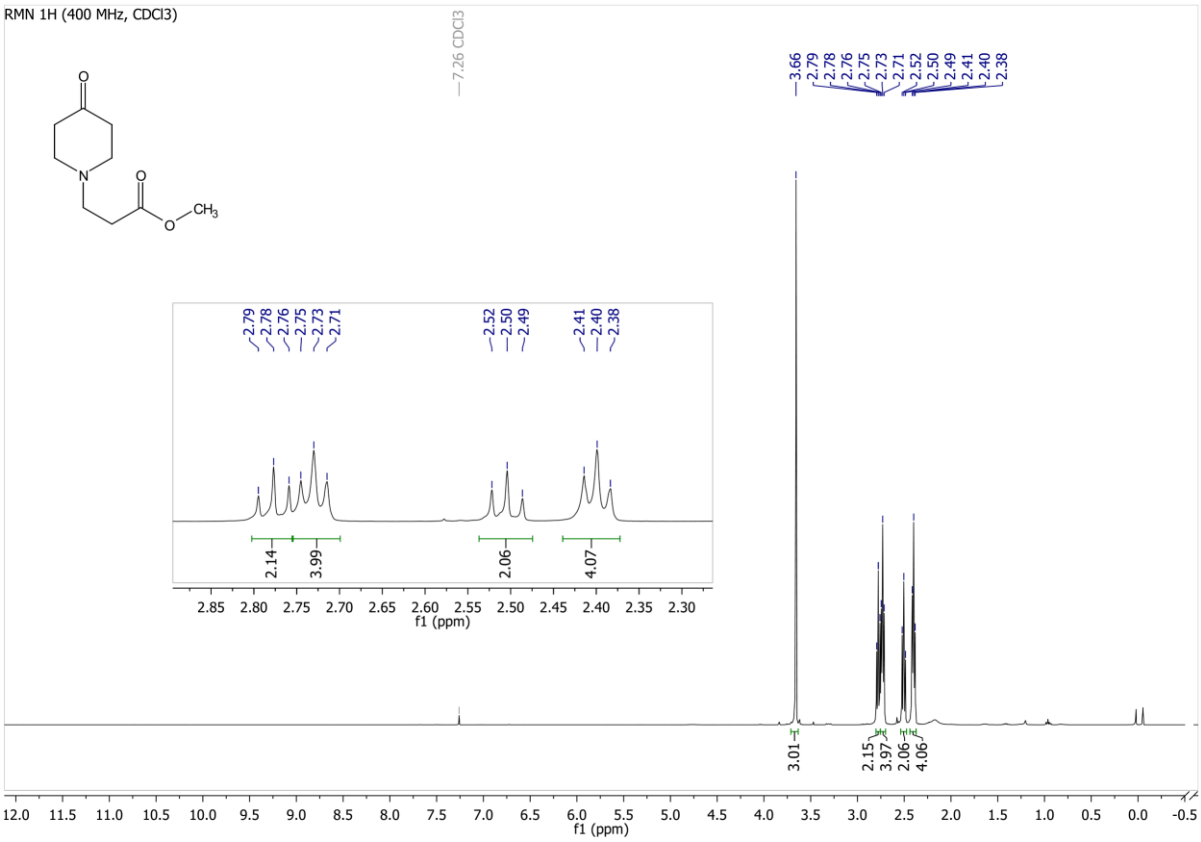


Figure S4. ^{13}C NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(4-oxopiperidin-1-yl)propanoate (**3a**)

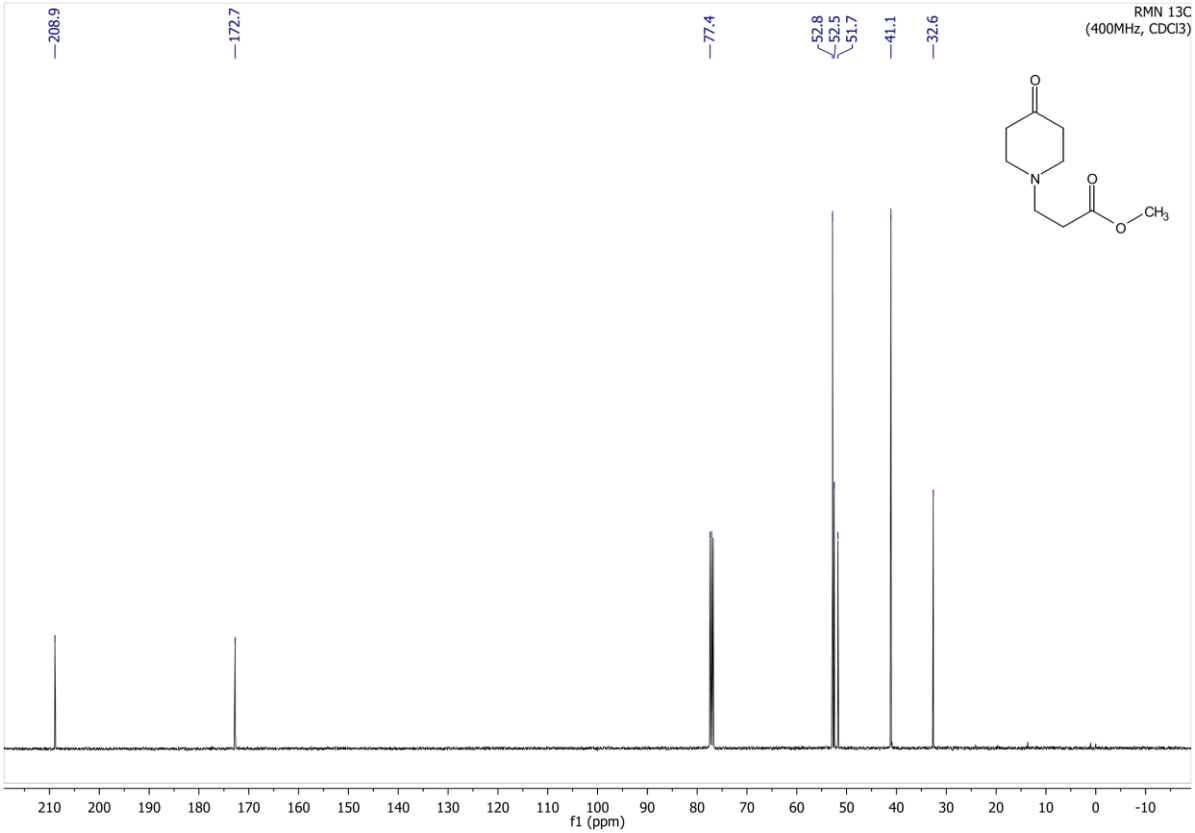


Figure S5. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) of 3-(4-oxopiperidin-1-yl)propanenitrile (**3b**)

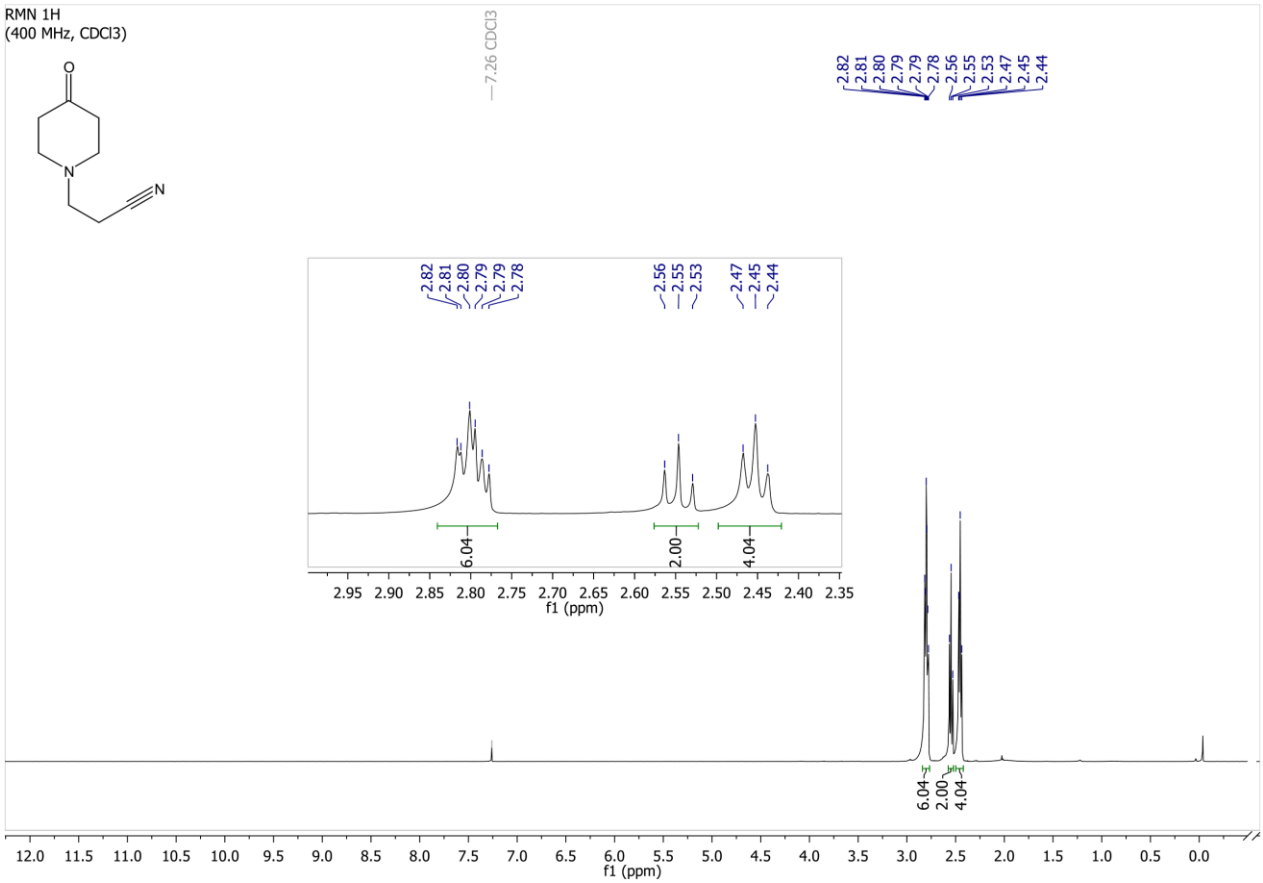


Figure S6. ^{13}C NMR (400 MHz, $CDCl_3$, ppm) of 3-(4-oxopiperidin-1-yl)propanenitrile (**3b**)

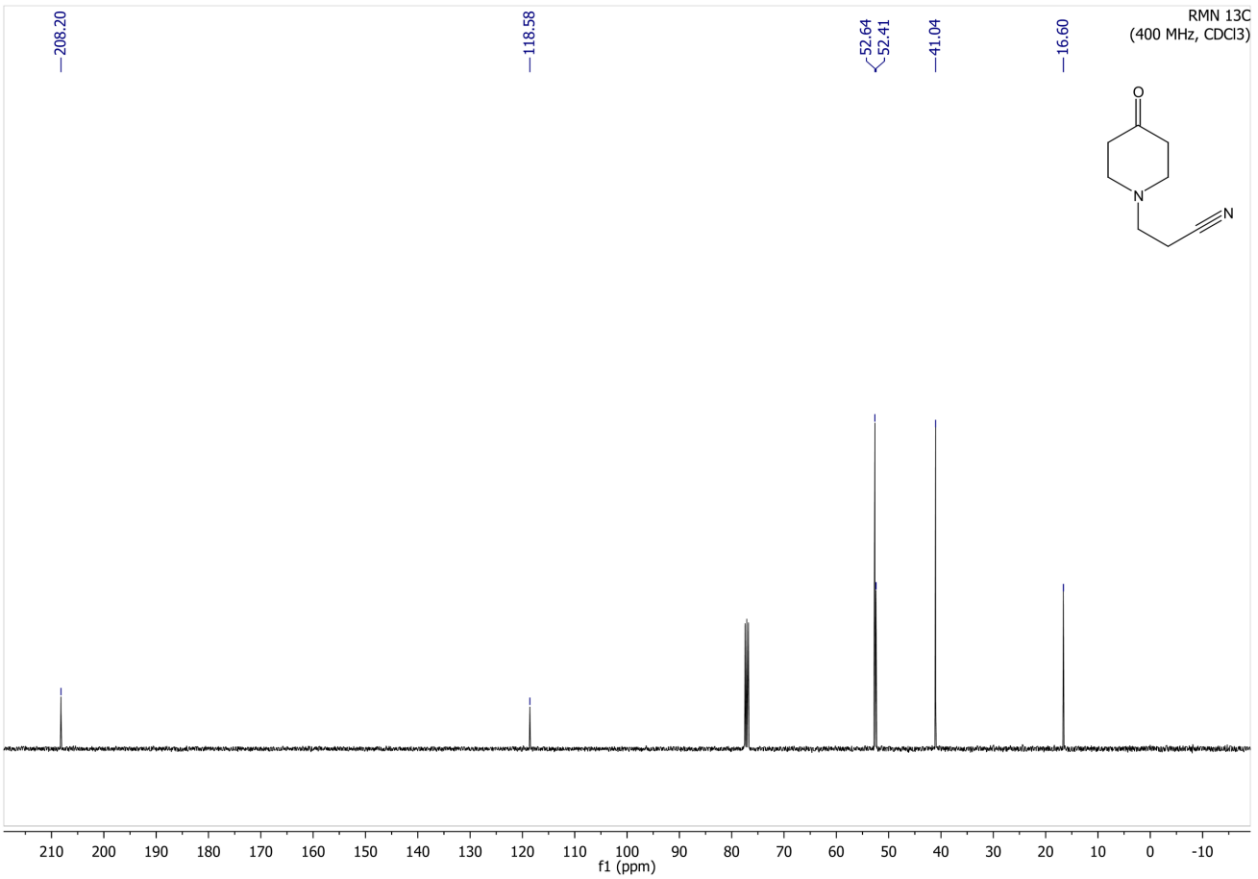


Figure S7. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) of Tert-butyl 3-(4-oxopiperidin-1-yl)propanoate (**3c**)

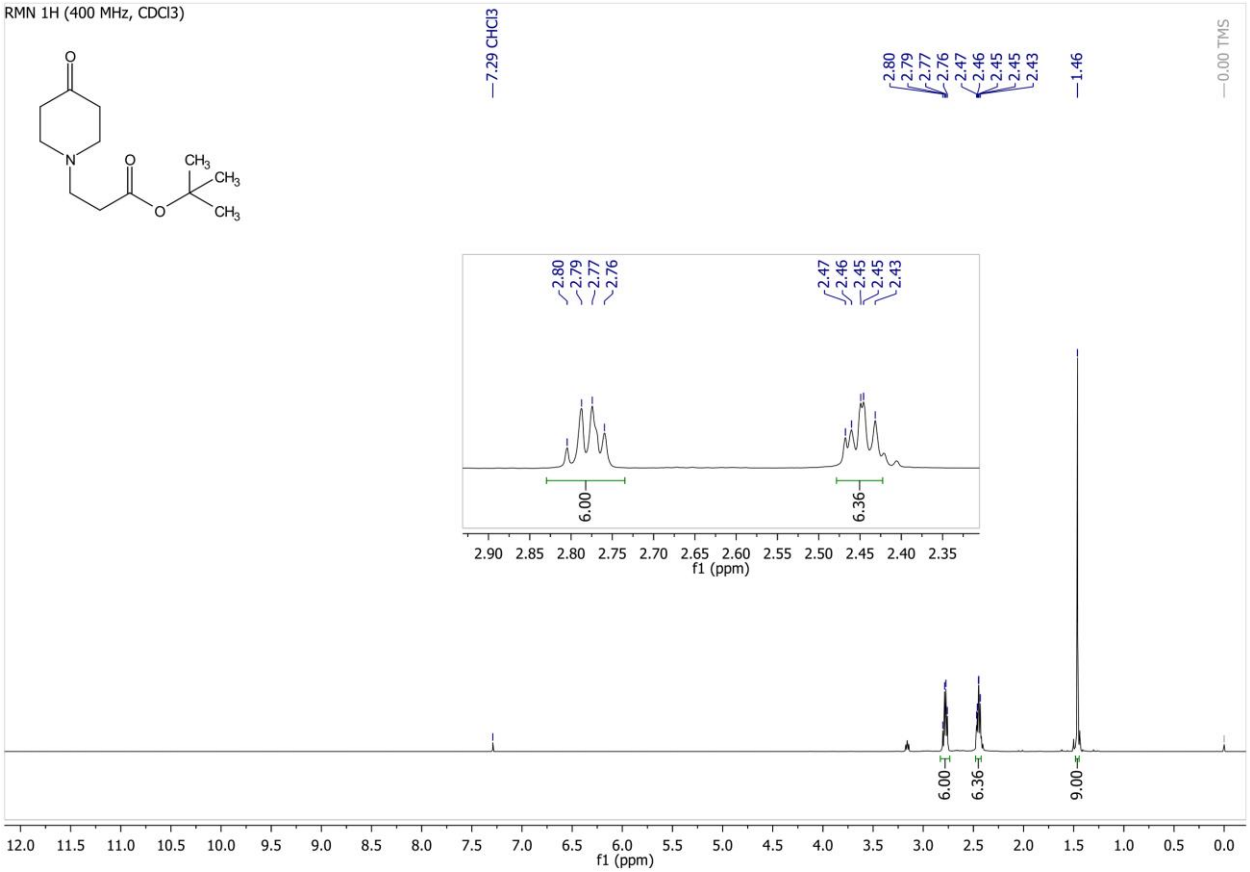


Figure S8. ^{13}C NMR (400 MHz, $CDCl_3$, ppm) of Tert-butyl 3-(4-oxopiperidin-1-yl)propanoate (**3c**)

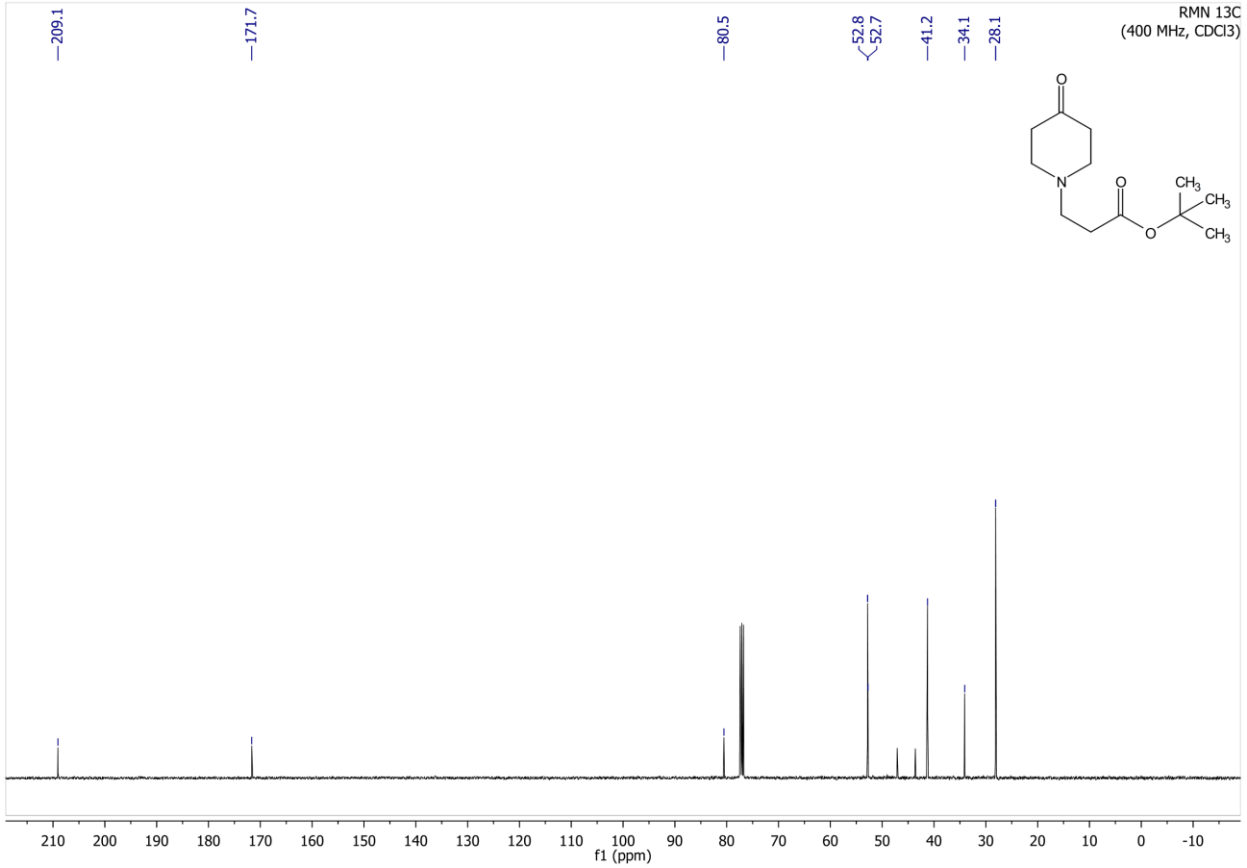


Figure S9. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) of N,N-dimethyl-3-(4-oxopiperidin-1-yl)propanamide (**3d**)

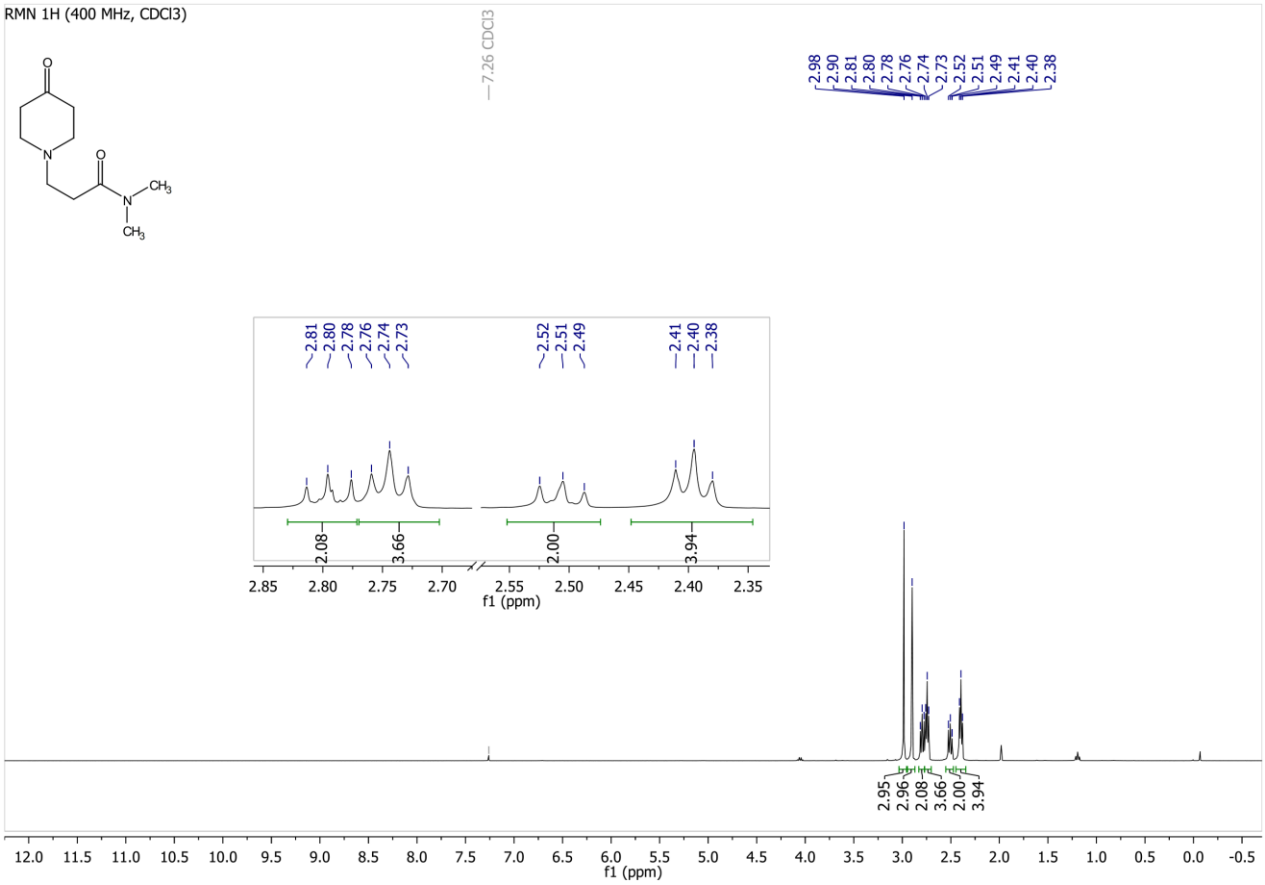


Figure S10. ^{13}C NMR (400 MHz, $CDCl_3$, ppm) of N,N-dimethyl-3-(4-oxopiperidin-1-yl)propanamide (**3d**)

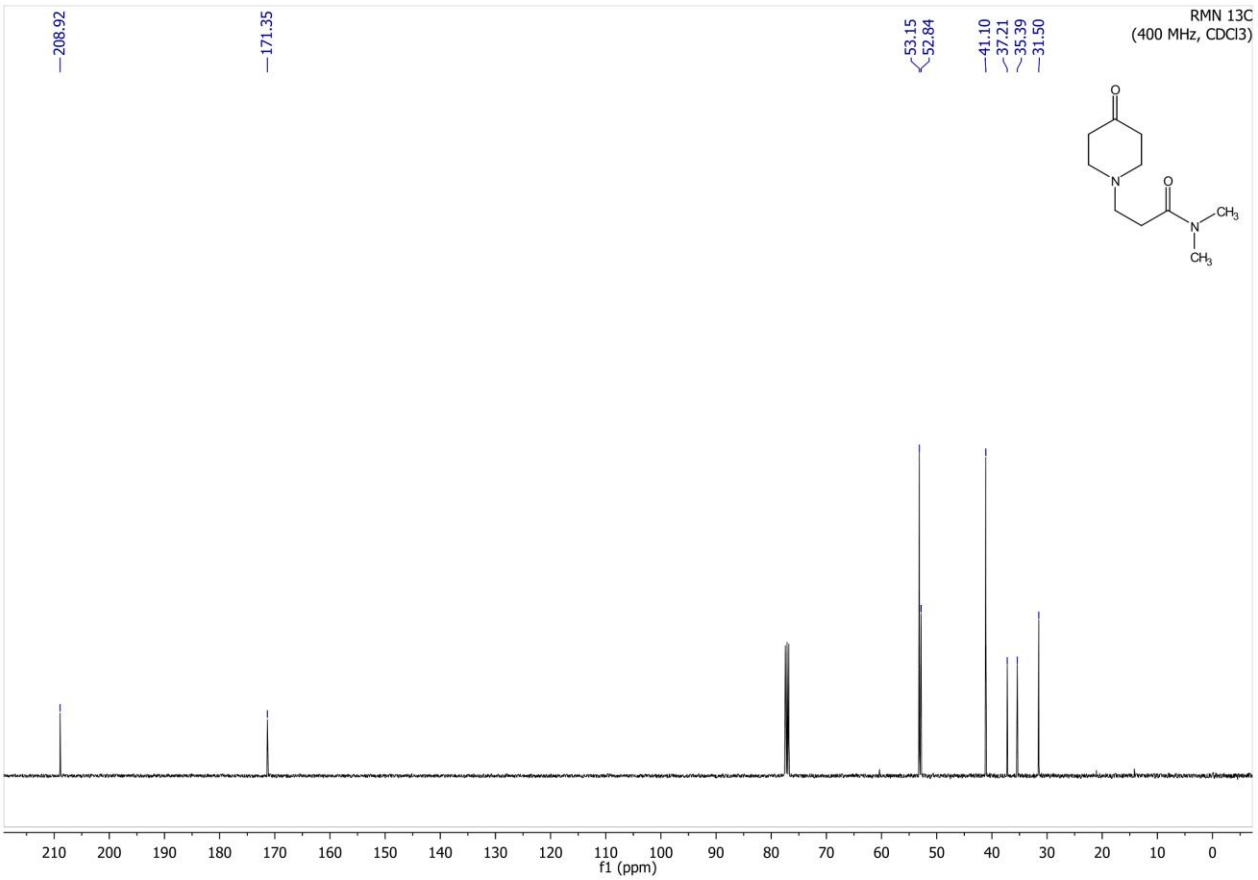


Figure S21. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(diethylamino)propanoate (**3e**)

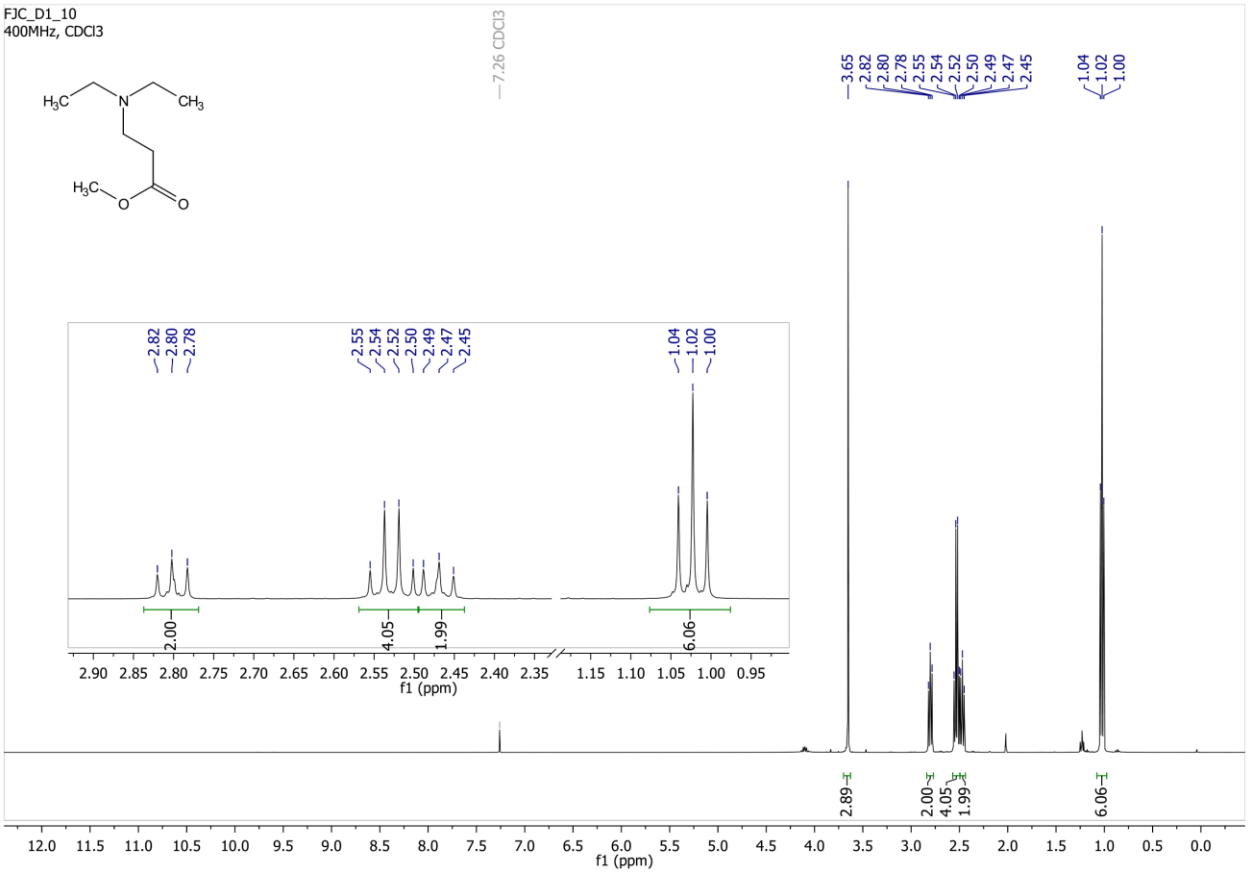


Figure S32. ^{13}C NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(diethylamino)propanoate (**3e**)

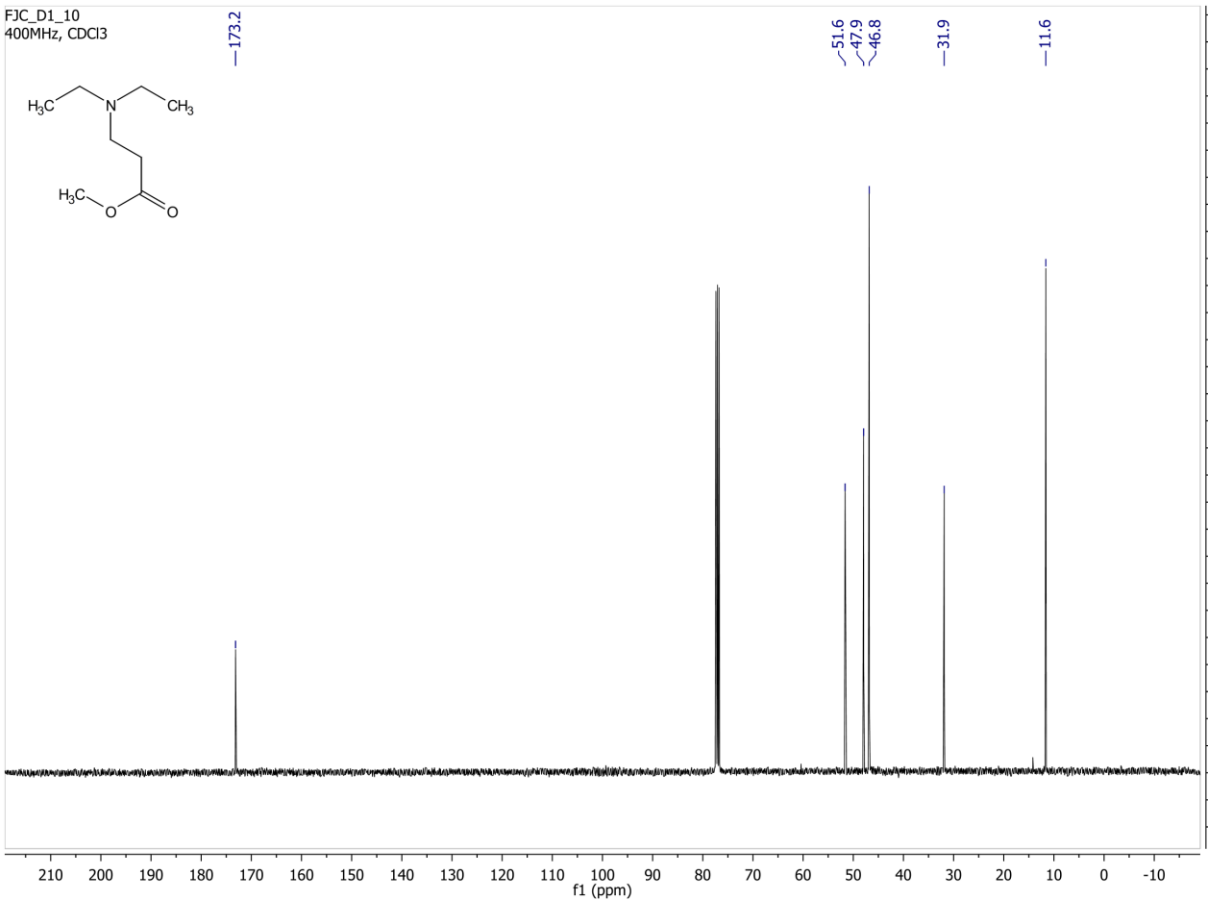


Figure S13. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(cyclohexylamino)propanoate (**3f**)

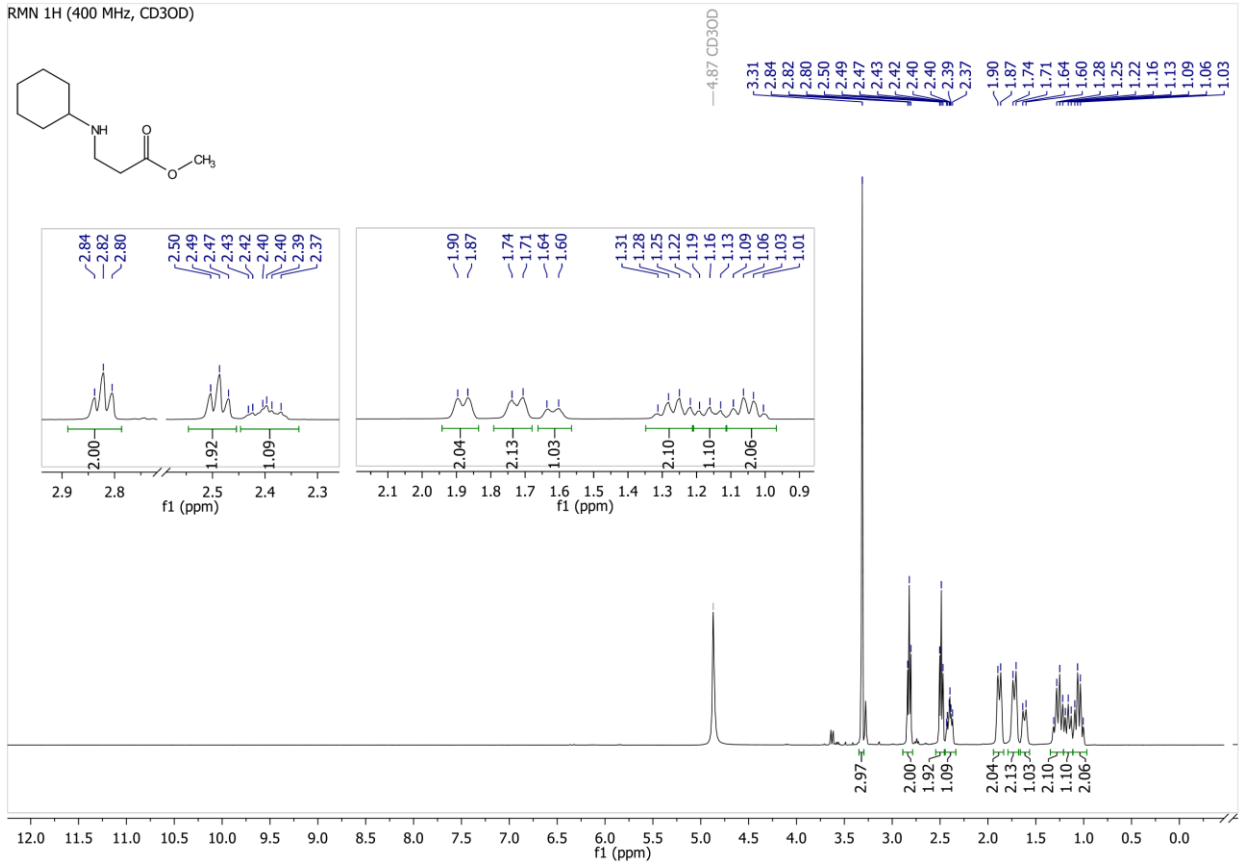


Figure S14. ^{13}C NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(cyclohexylamino)propanoate (**3f**)

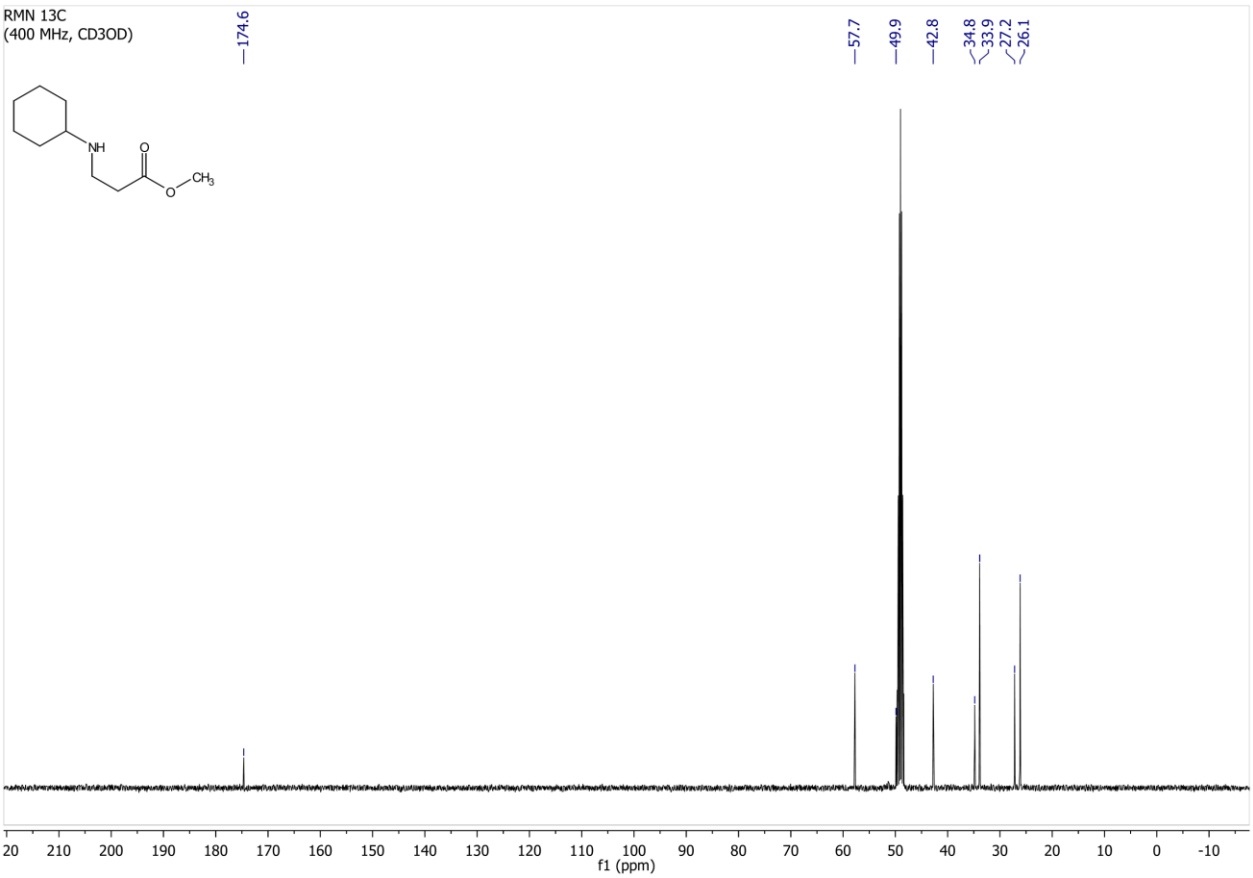


Figure S154. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(benzylamino)propanoate (**3g**)

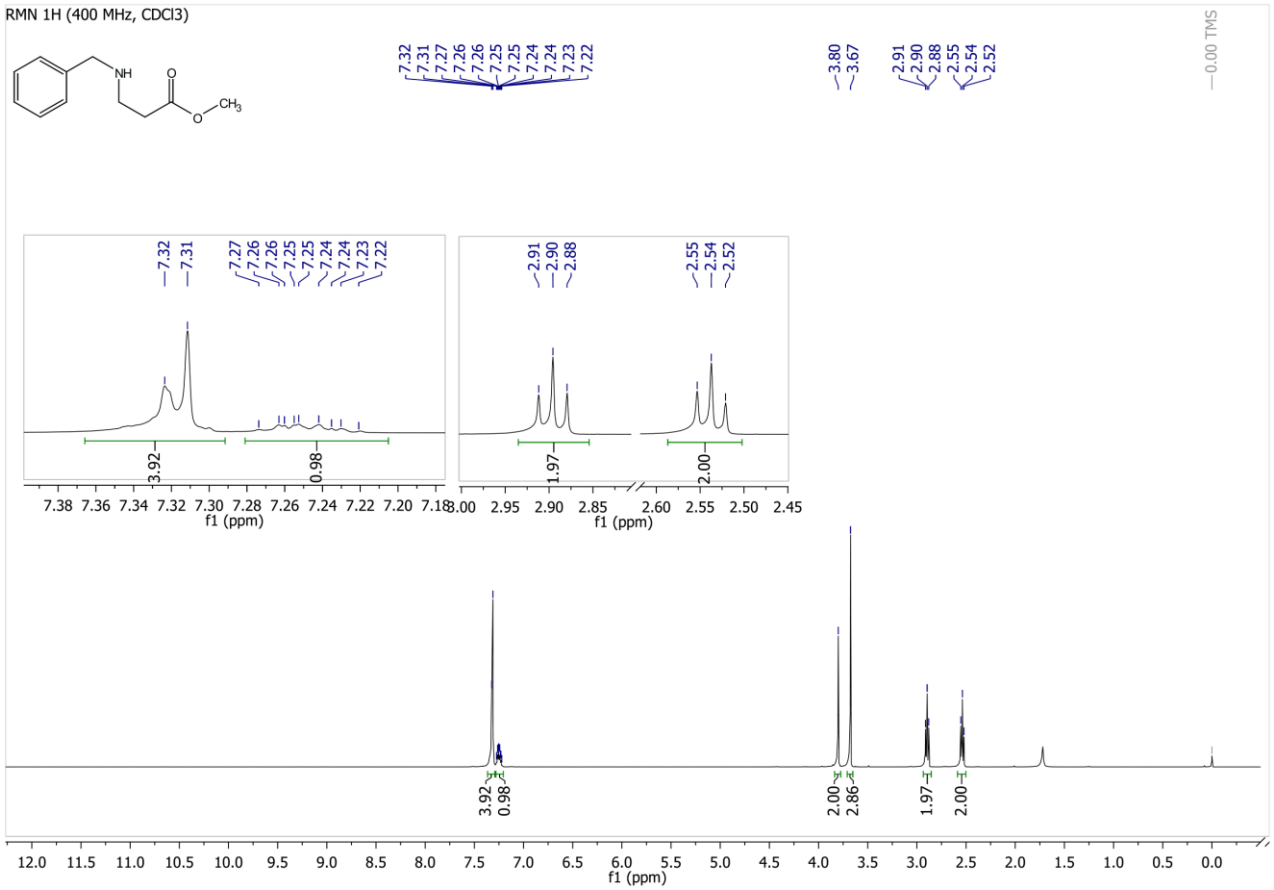


Figure S165. ^{13}C NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(benzylamino)propanoate (**3g**)

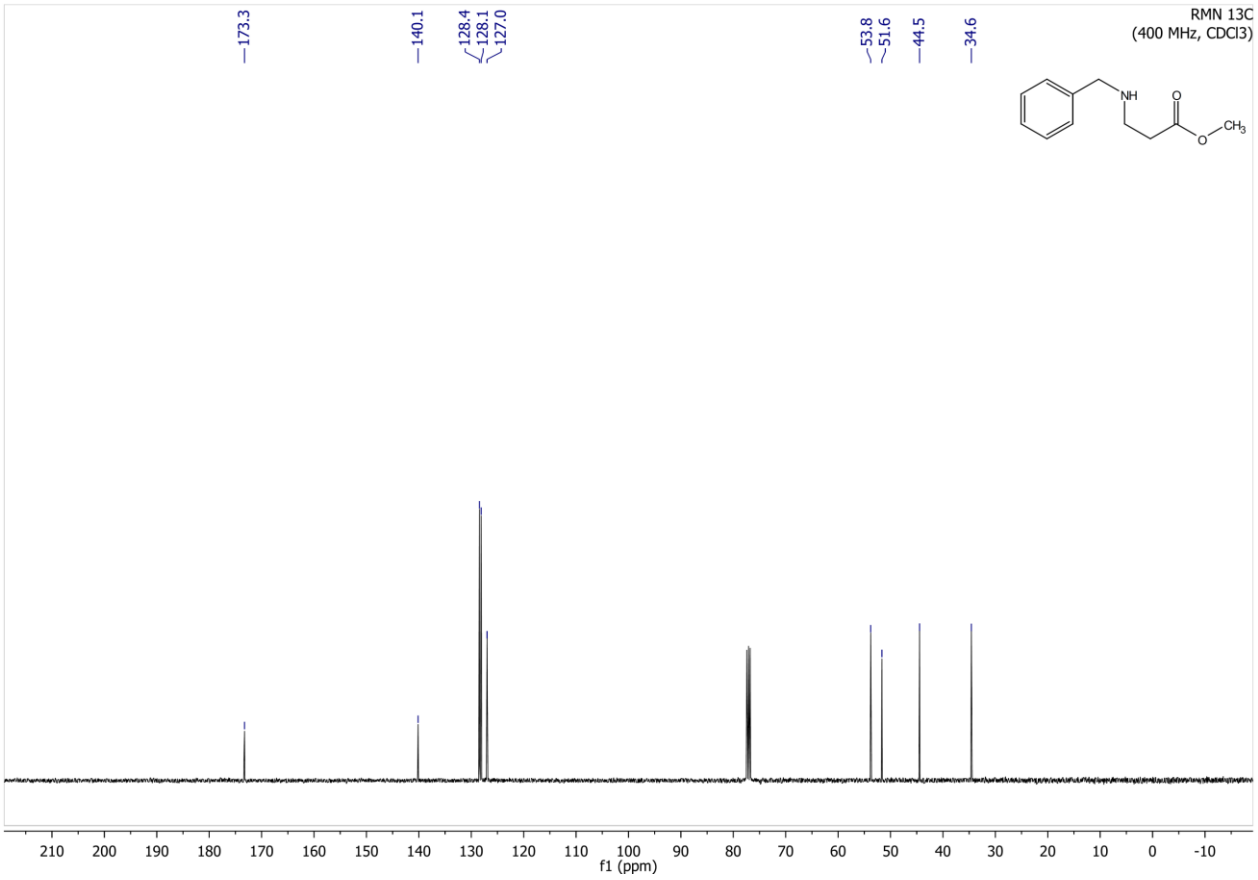


Figure S17. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-[(furan-2-ylmethyl)amino]propanoate (**3h**)

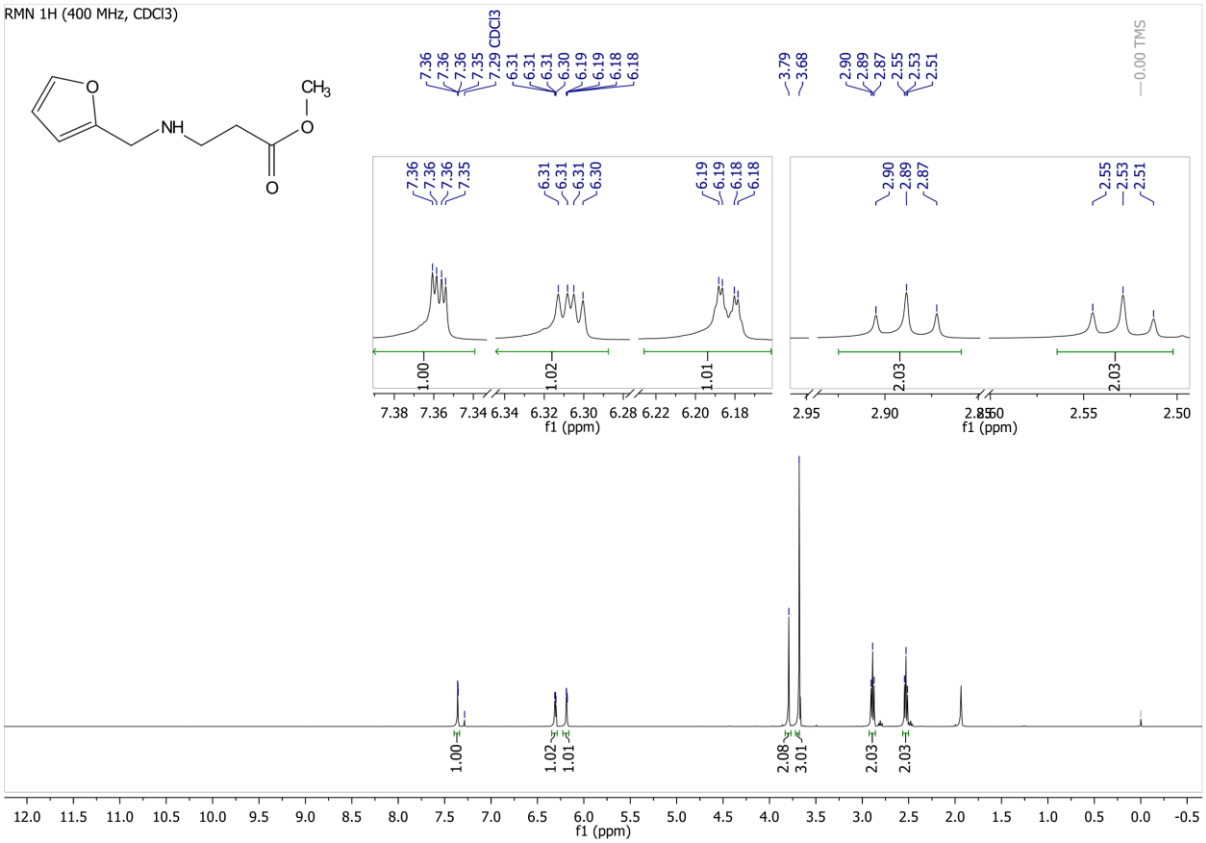


Figure S18. ^{13}C NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-[(furan-2-ylmethyl)amino]propanoate (**3h**)

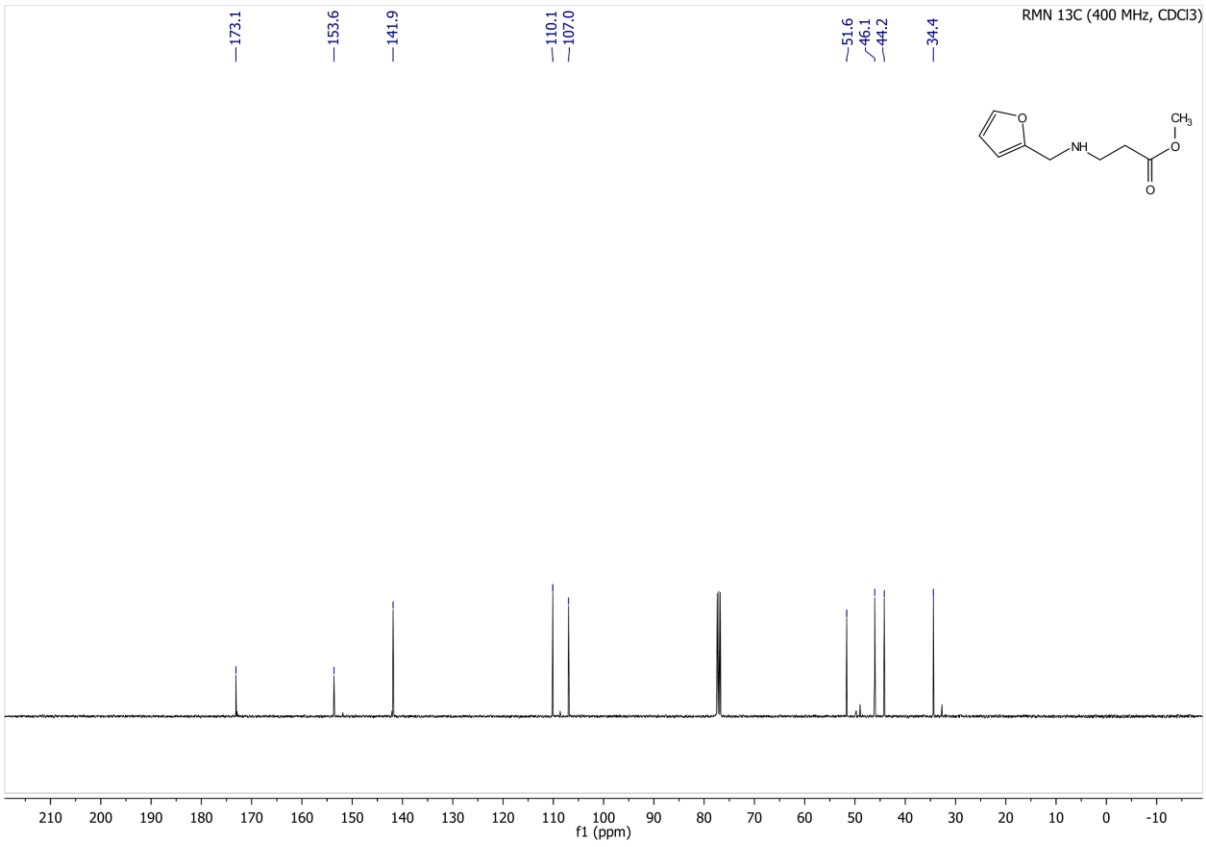


Figure S21. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-[(2-(thiophen-2-yl)ethyl)amino]propanoate (**3i**)

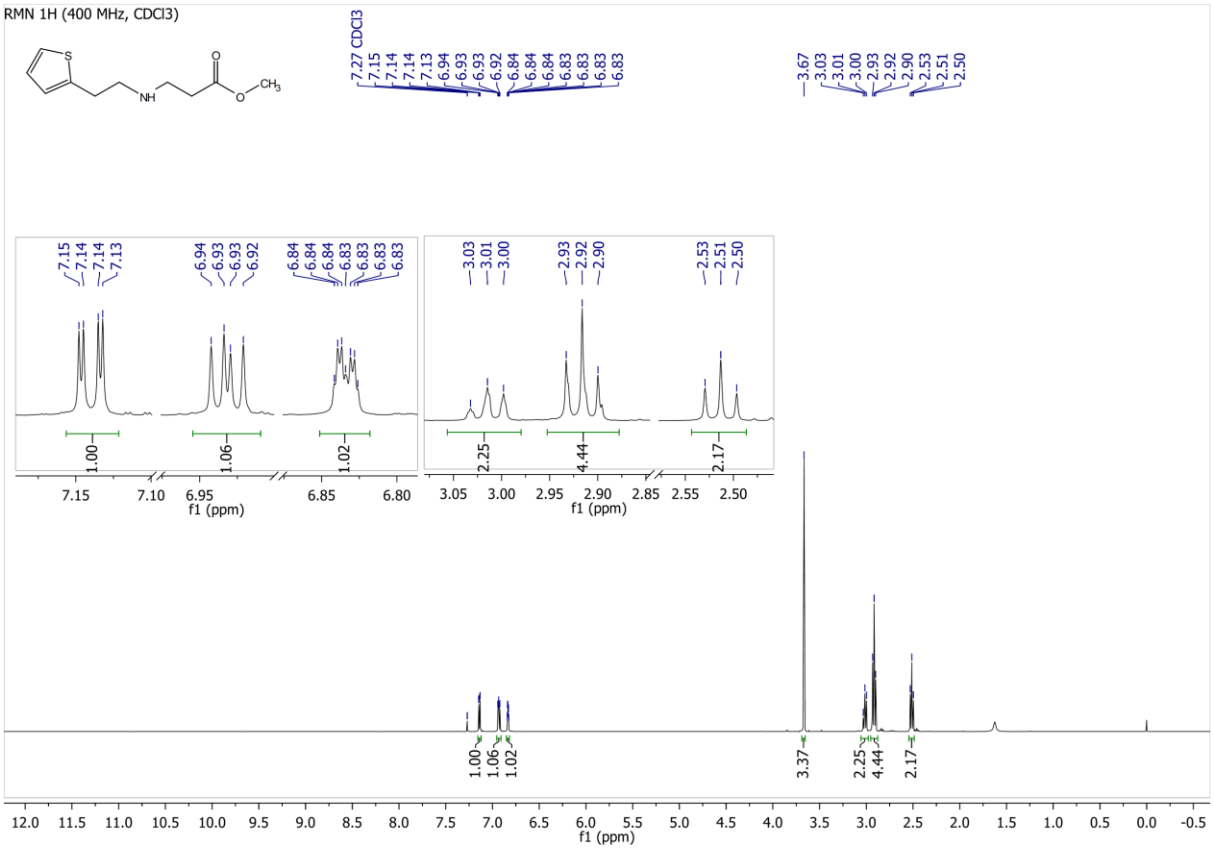


Figure S22. ^{13}C NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-[(2-(thiophen-2-yl)ethyl)amino]propanoate (**3i**)

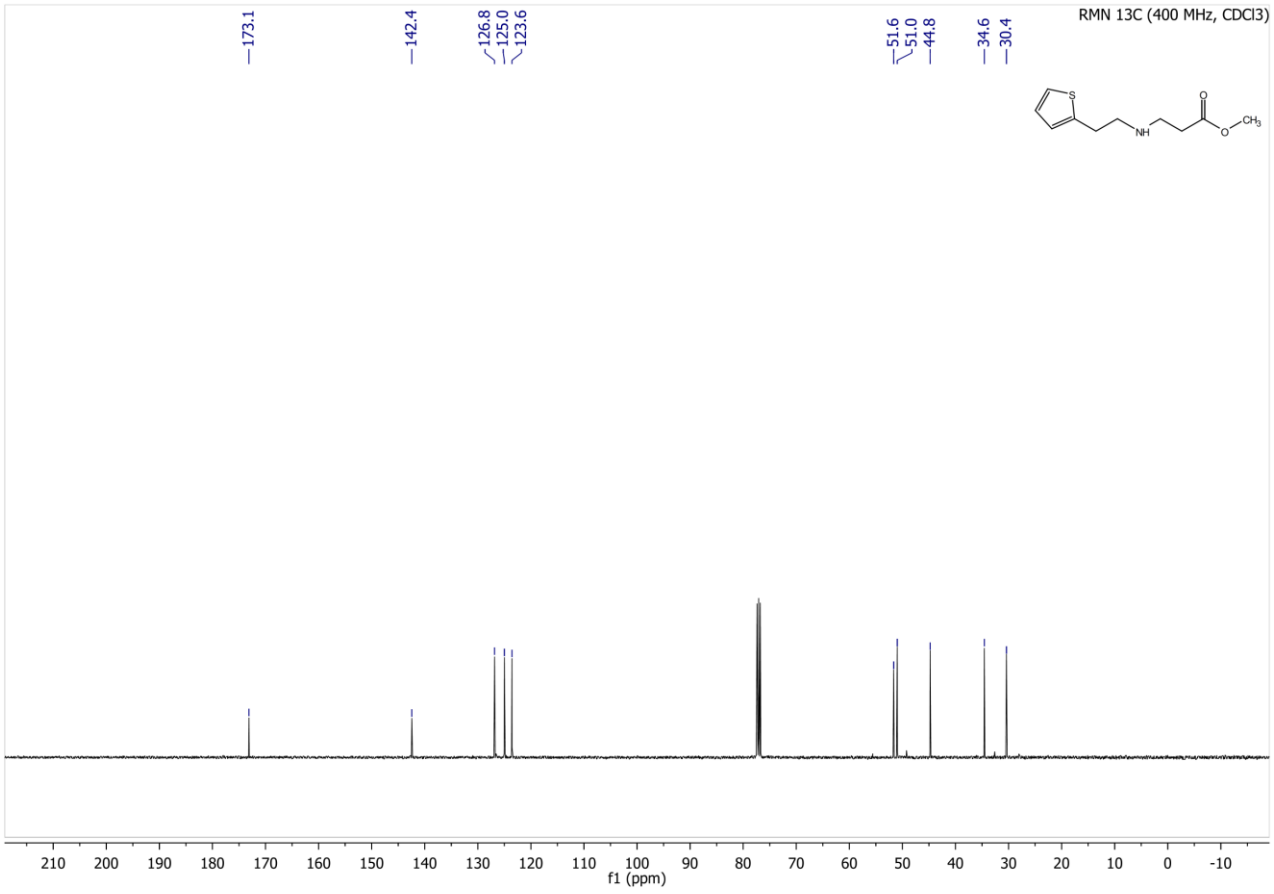


Figure S23. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-[(4-methoxyphenethyl)amino]propanoate (**3j**)

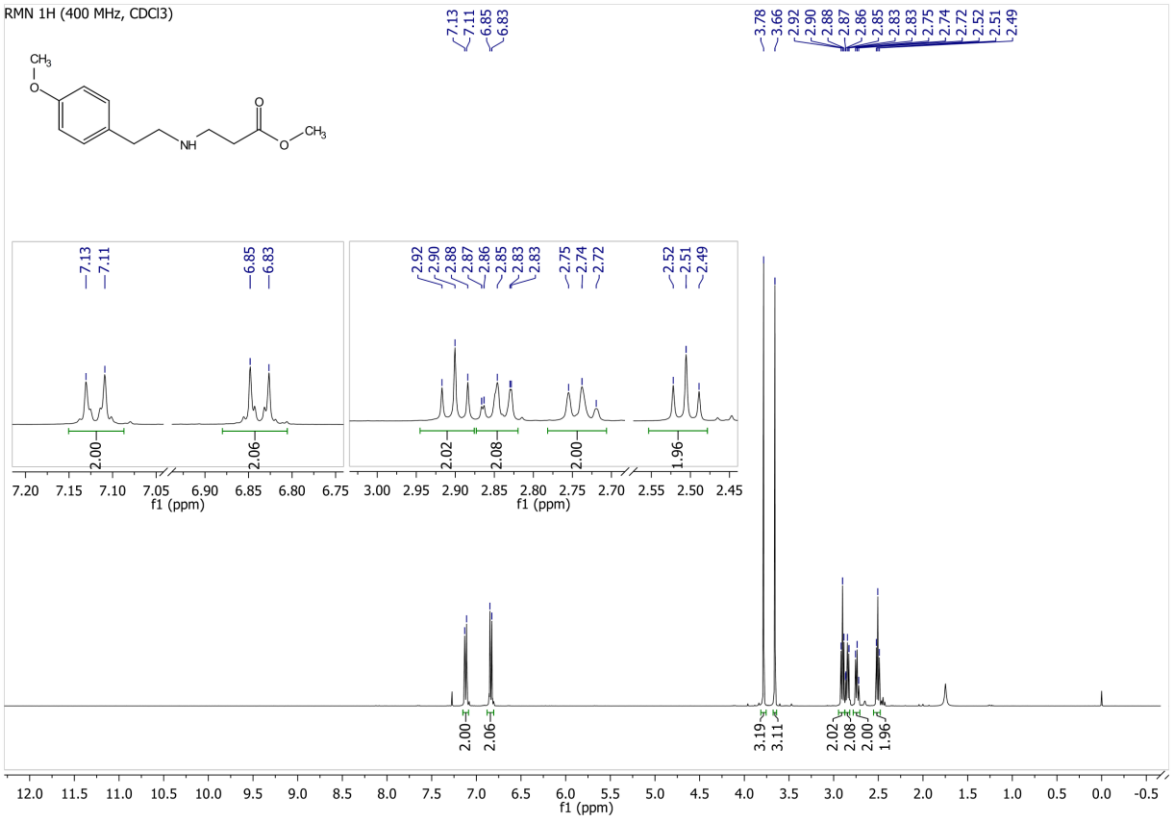


Figure S24. ^{13}C NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-[(4-methoxyphenethyl)amino]propanoate (**3j**)

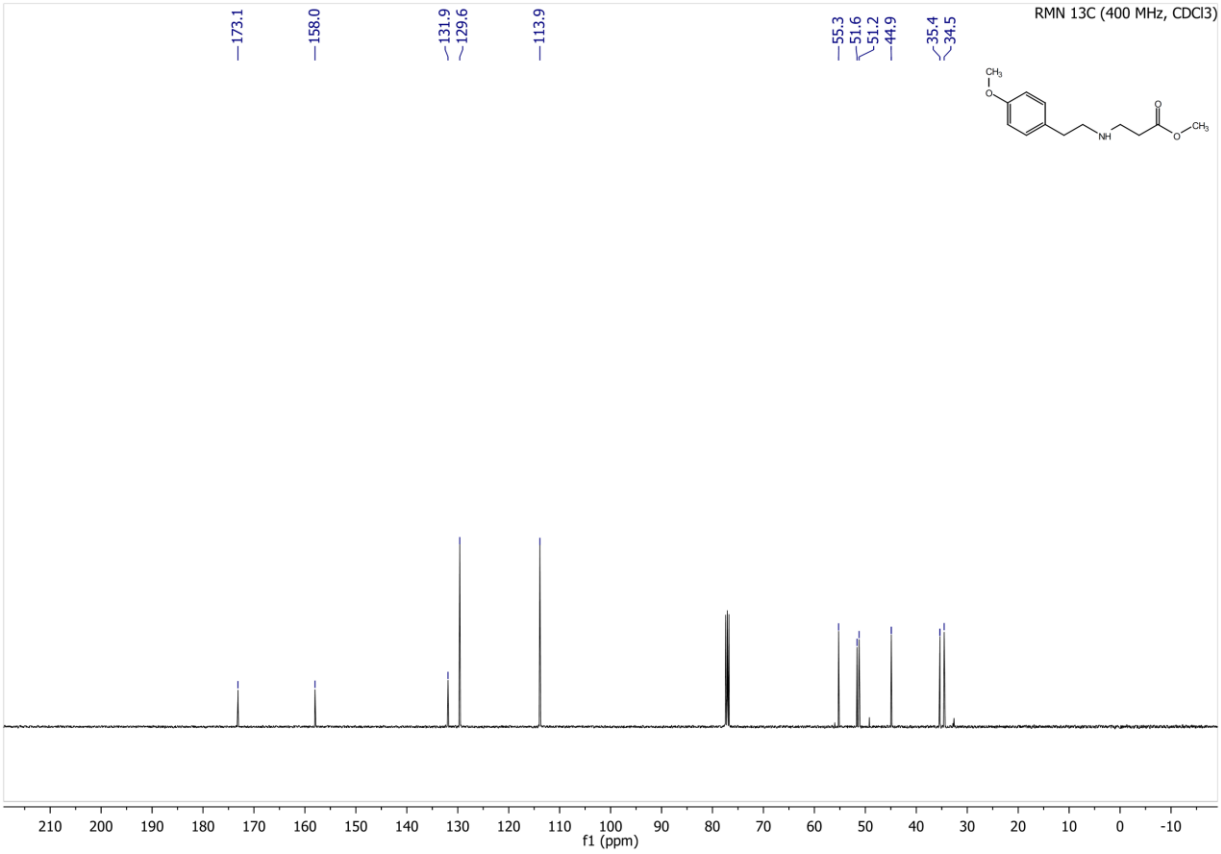


Figure S625. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(piperidin-1-yl)propanoate (**3k**)

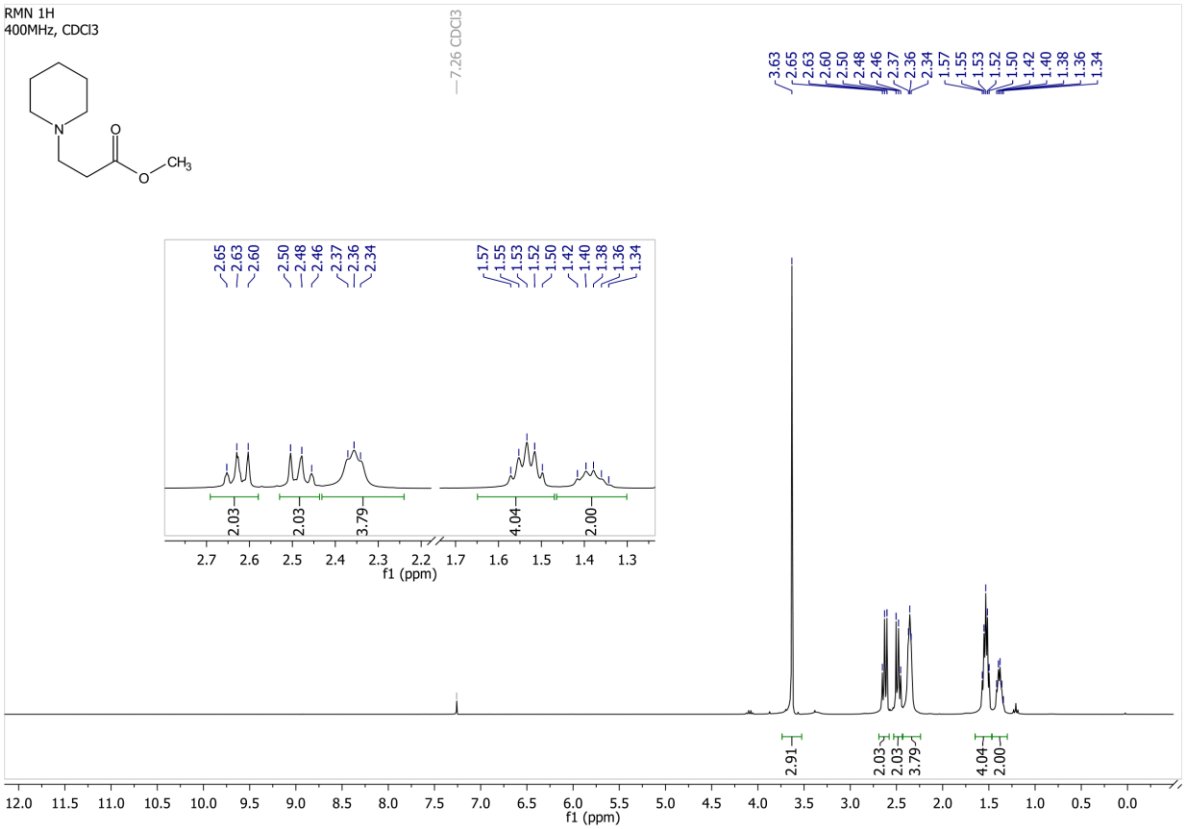


Figure S267. ^{13}C NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(piperidin-1-yl)propanoate (**3k**)

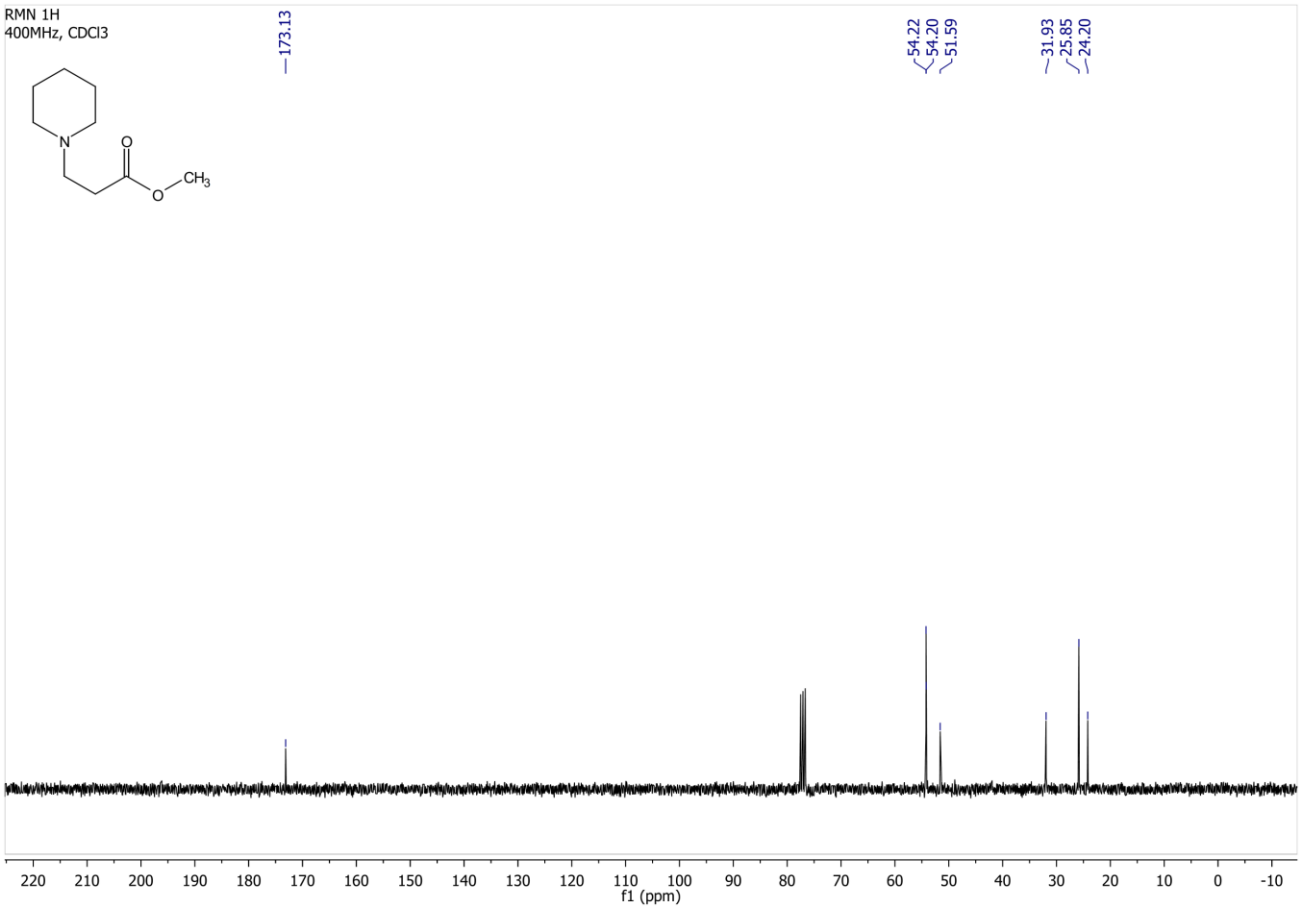


Figure S87. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-morpholinopropanoate (**3l**)

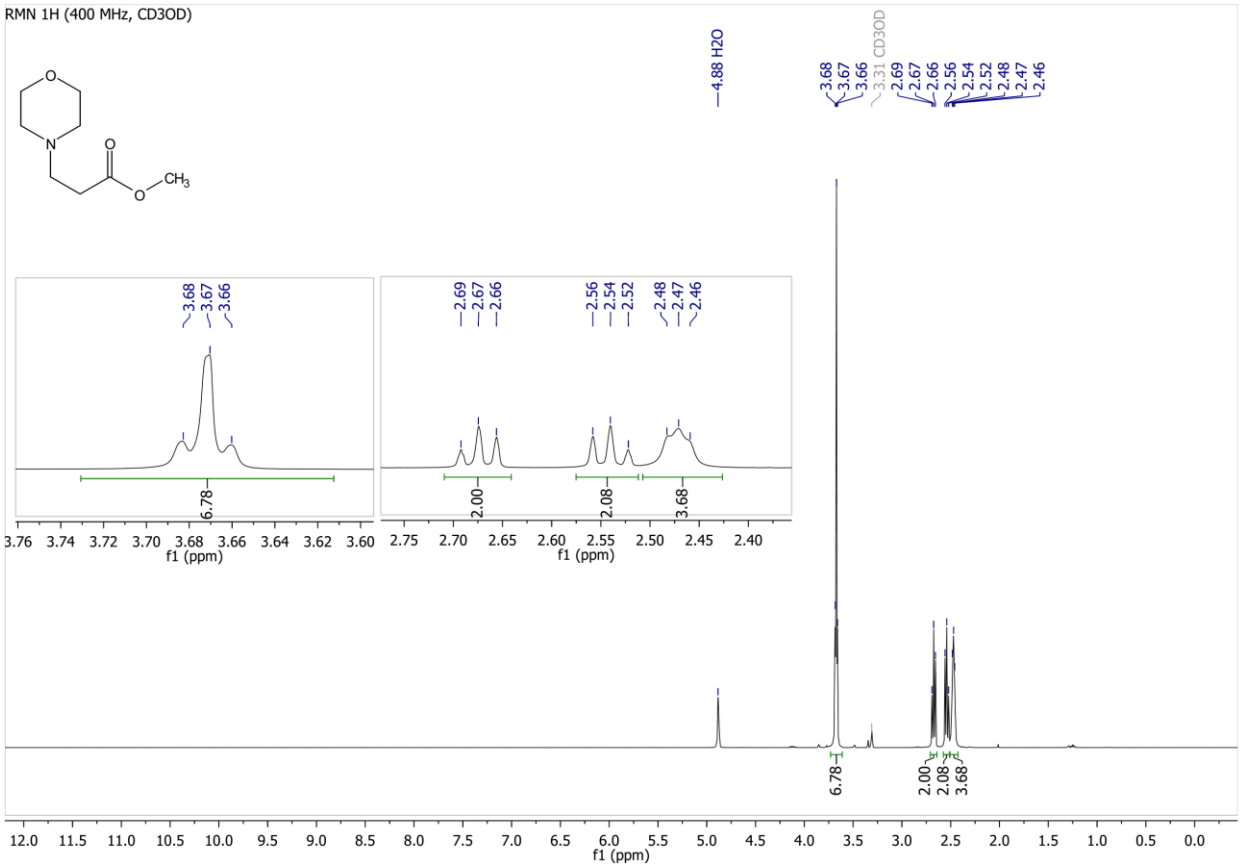


Figure S9. ^{13}C NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-morpholinopropanoate (**3l**)

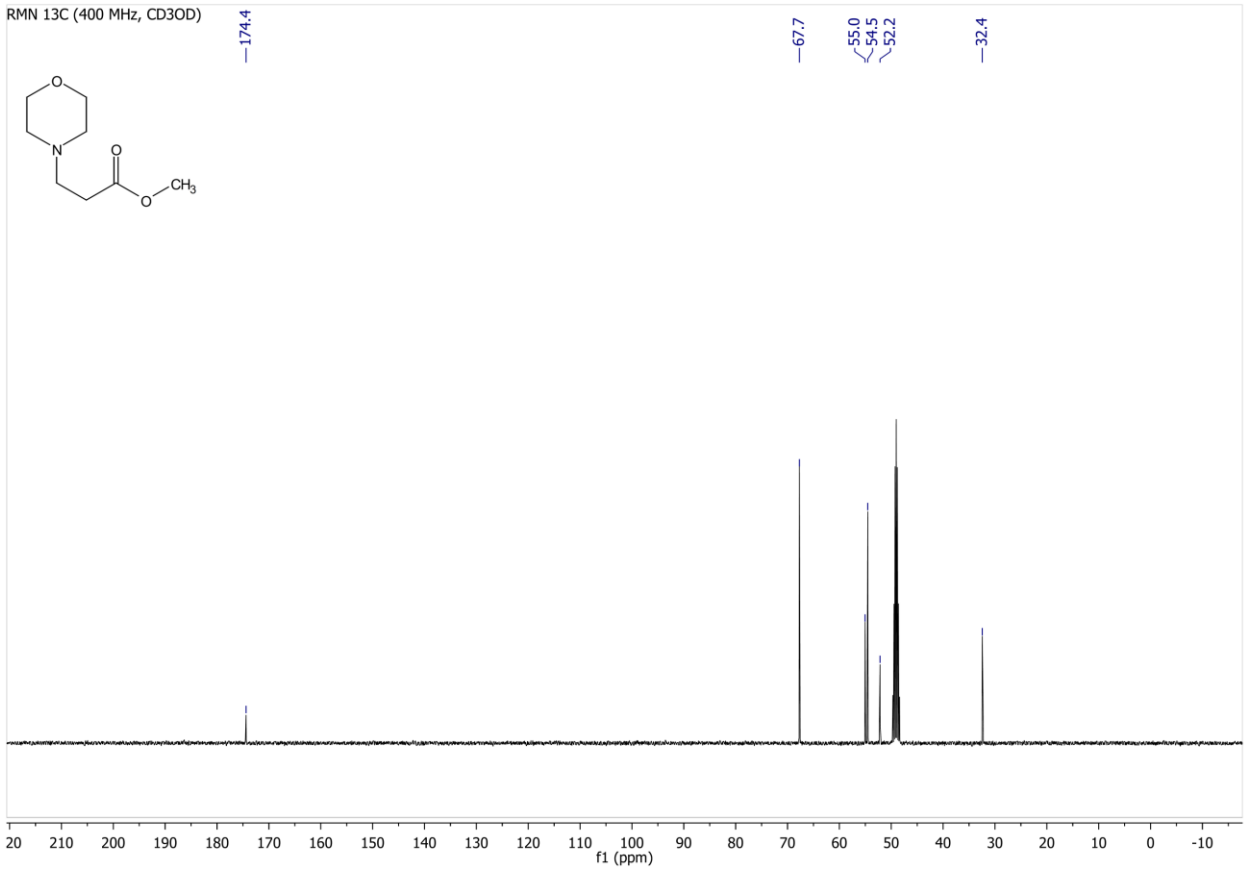


Figure S29. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(1H-benzo[d]imidazol-1-yl)propanoate (**3m**)

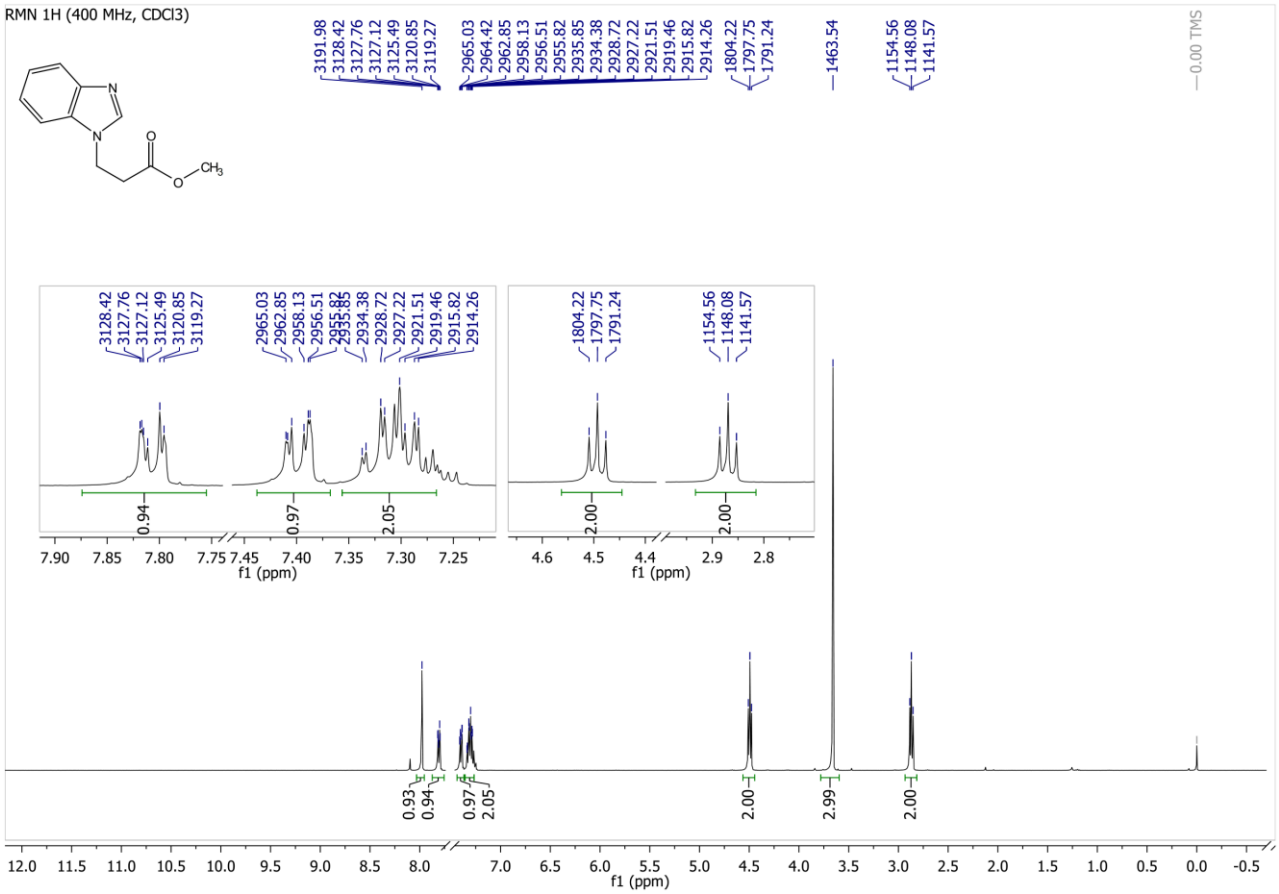


Figure S100. ^{13}C NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(1H-benzo[d]imidazol-1-yl)propanoate (**3m**)

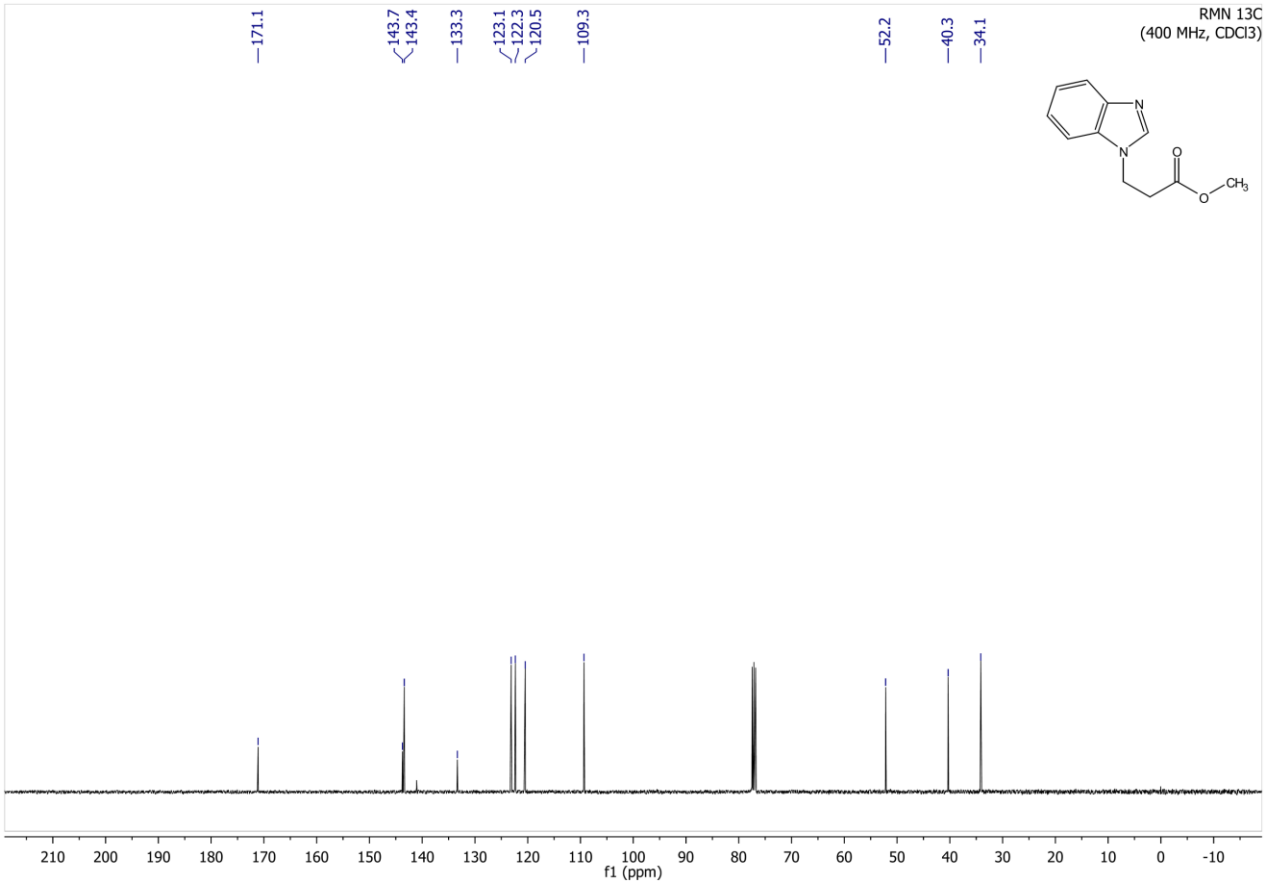


Figure S31. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(1H-imidazol-1-yl)propanoate (**3n**)

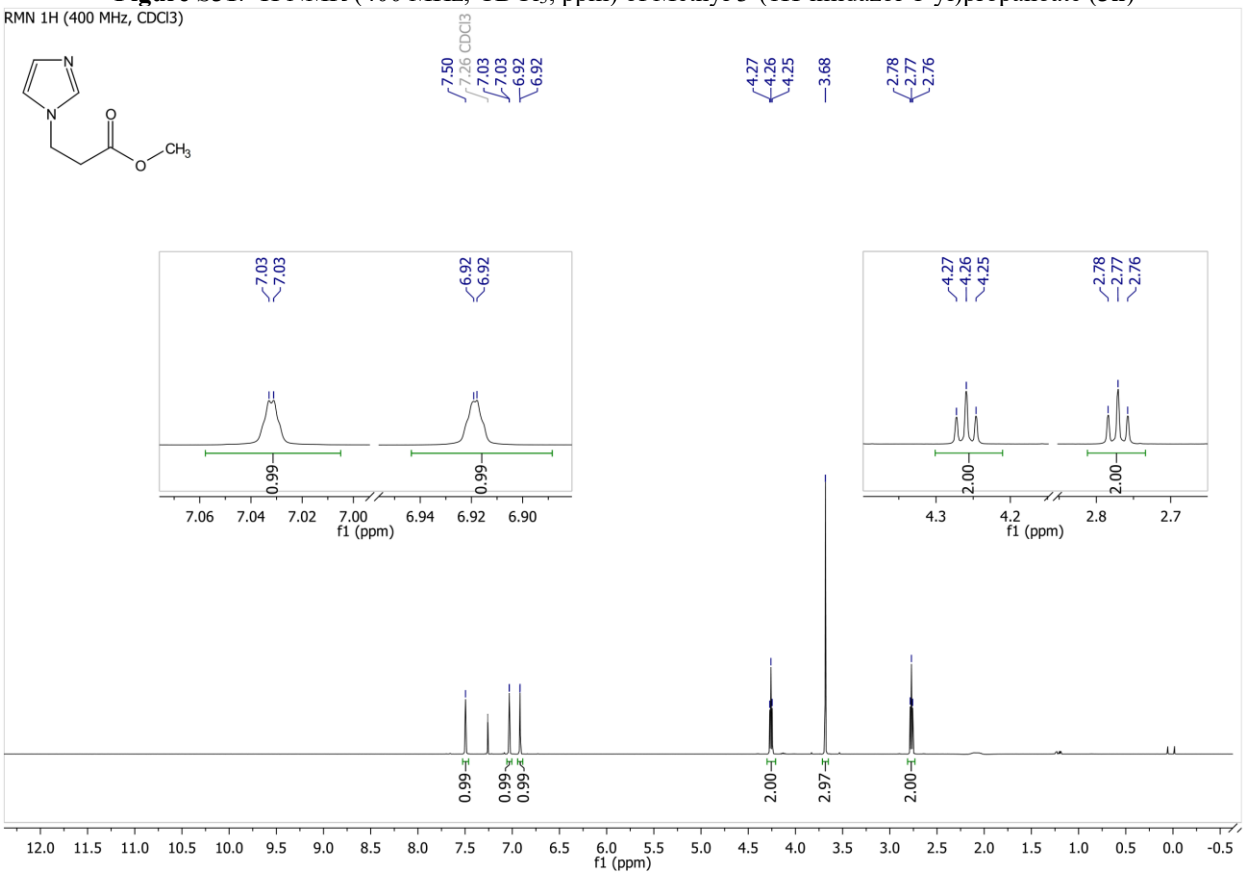


Figure S32. ^{13}C NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(1H-imidazol-1-yl)propanoate (**3n**)

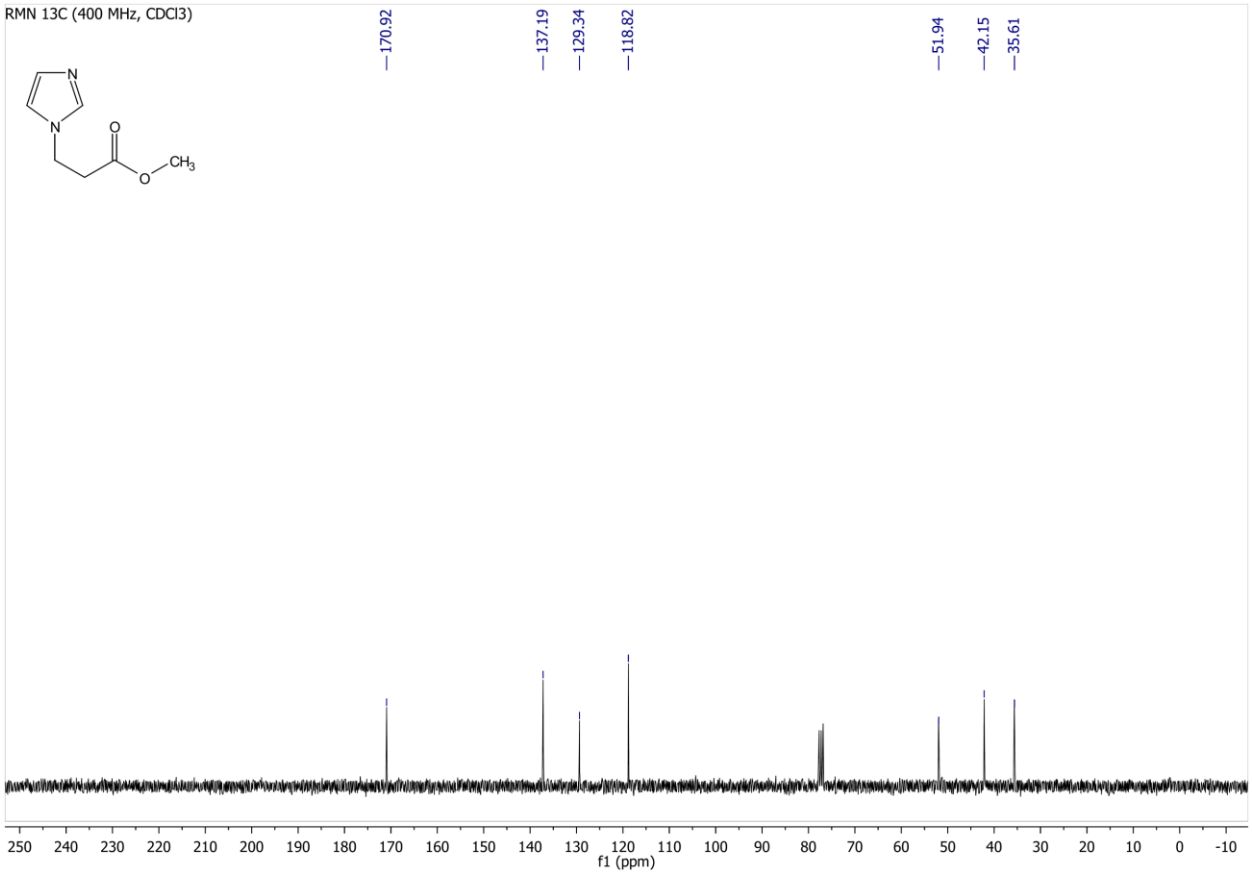


Figure S33. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)propanoate (**3o**)

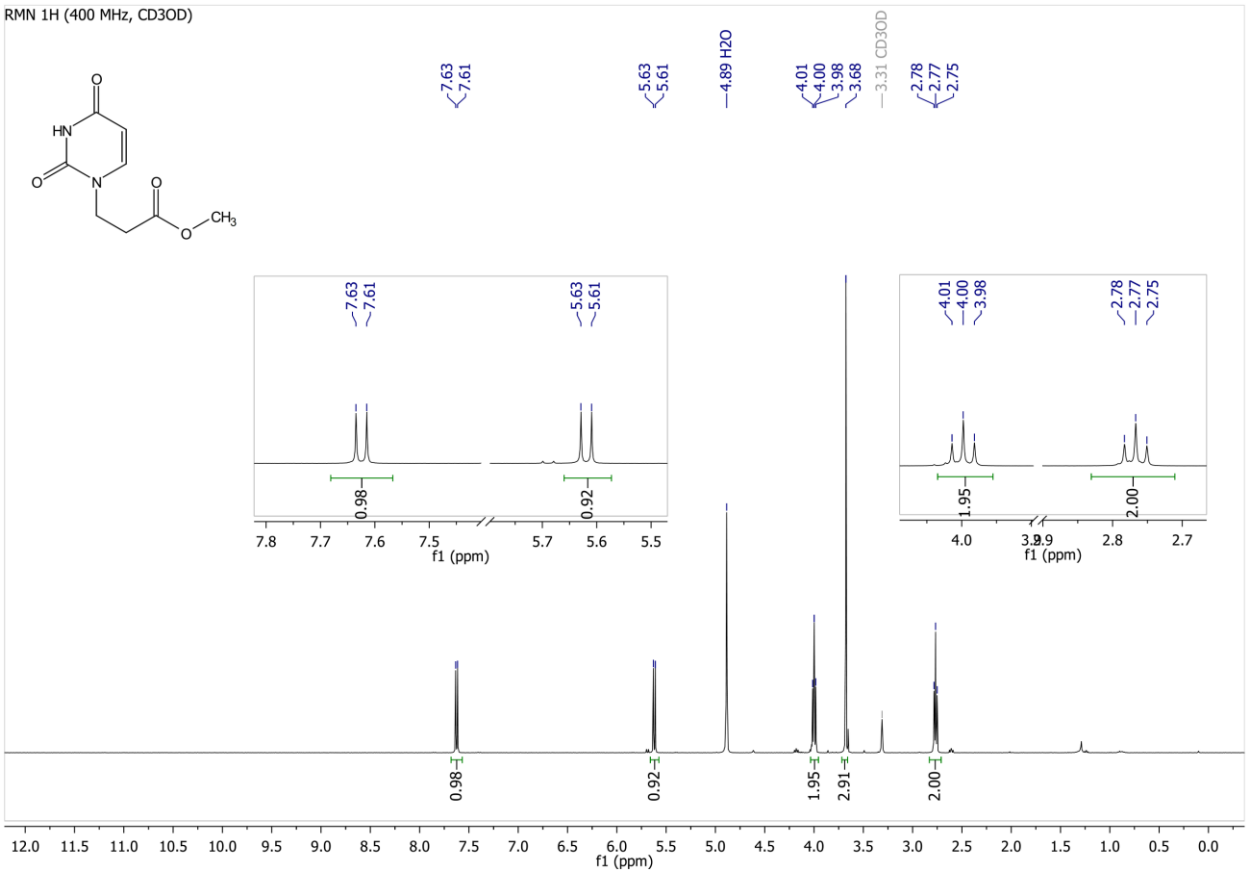


Figure S34. ^{13}C NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)propanoate (**3o**)

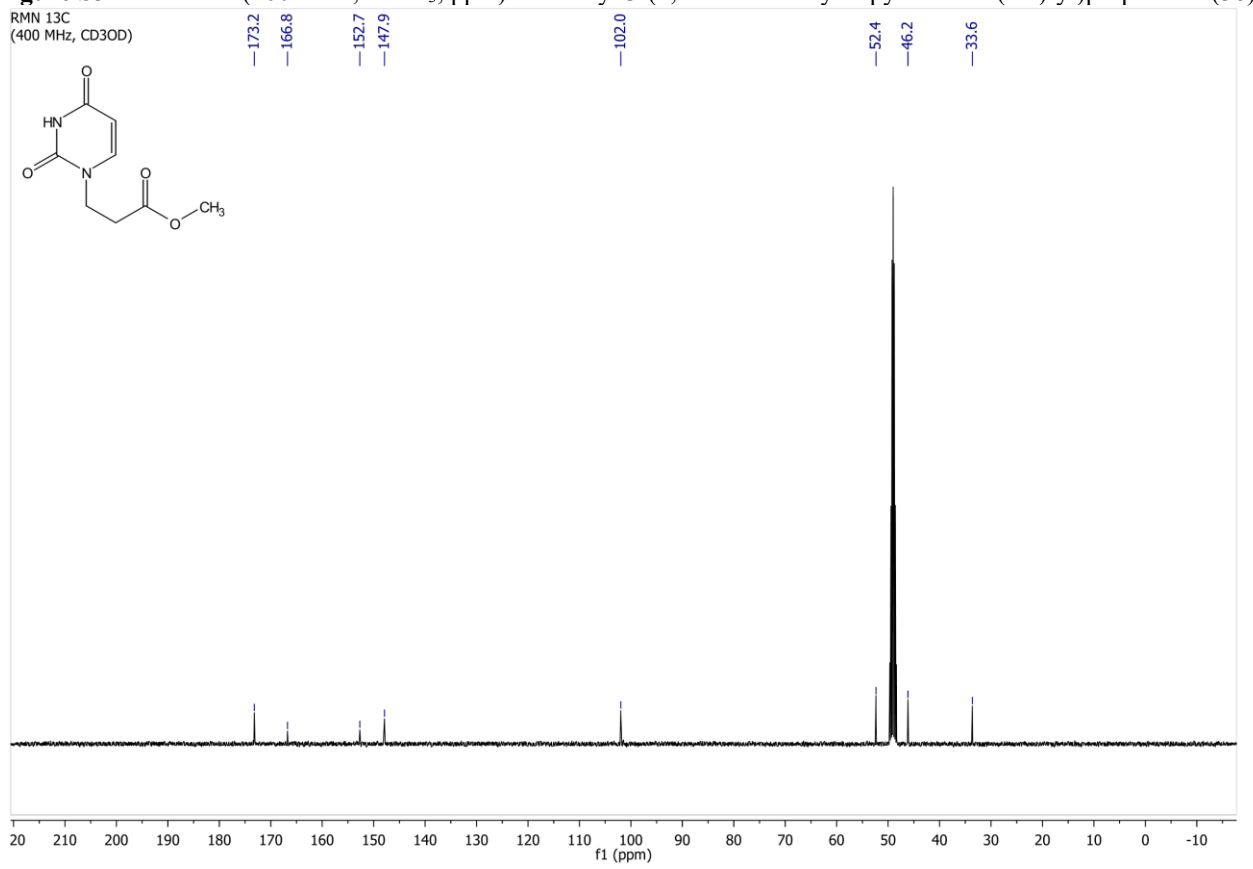


Figure S115. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(4-carbamoyl-4-(phenylamino)piperidin-1-yl)propanoate (**3p**)

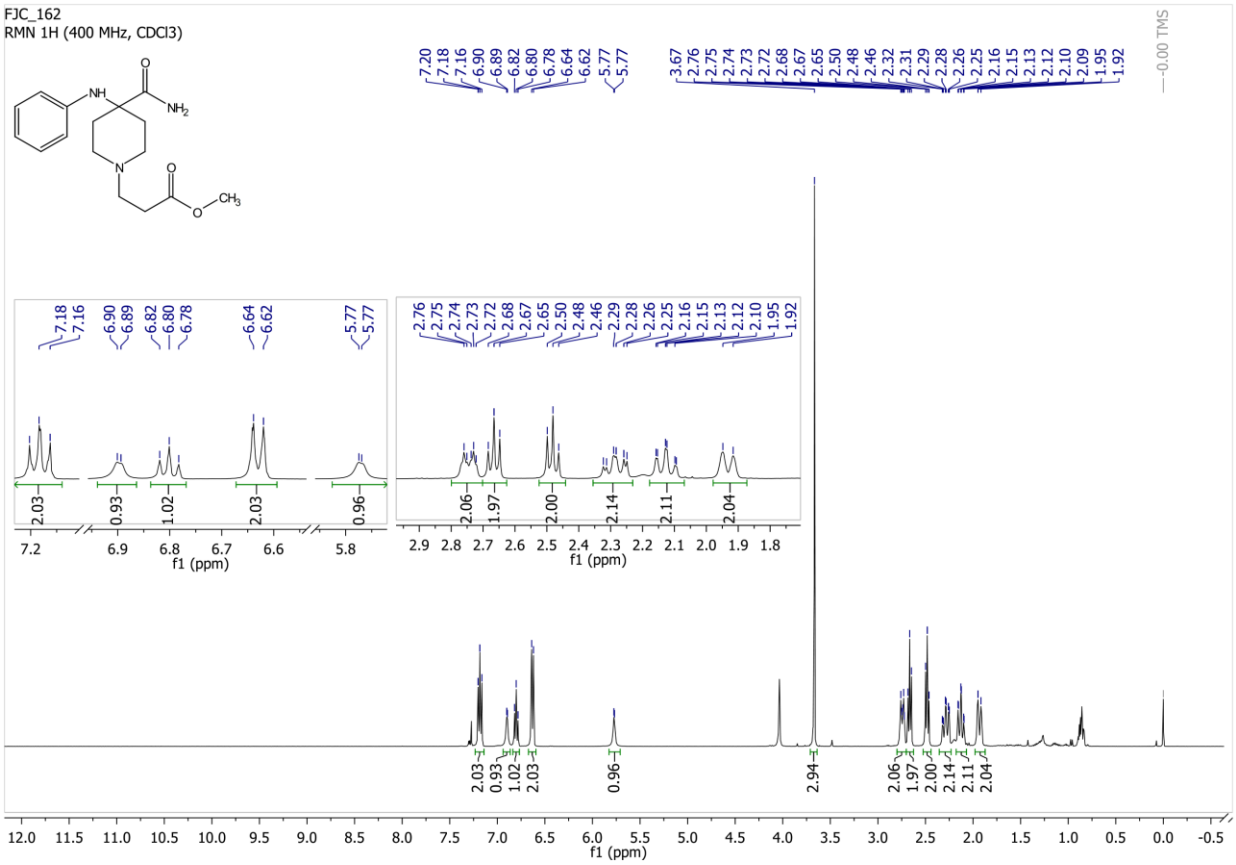


Figure S36. ^{13}C NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(4-carbamoyl-4-(phenylamino)piperidin-1-yl)propanoate (**3p**)

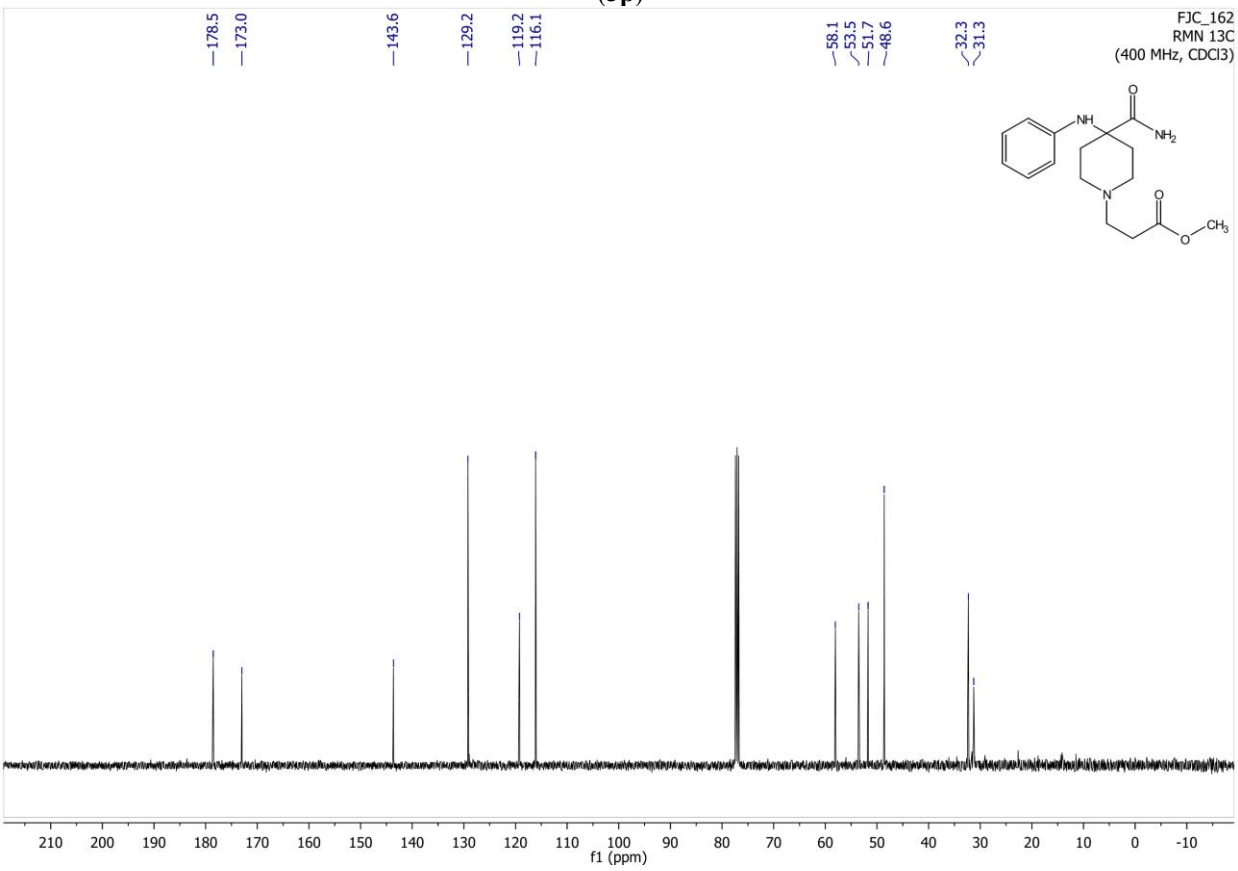


Figure S37. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidin-1-yl)propanoate (**3q**)

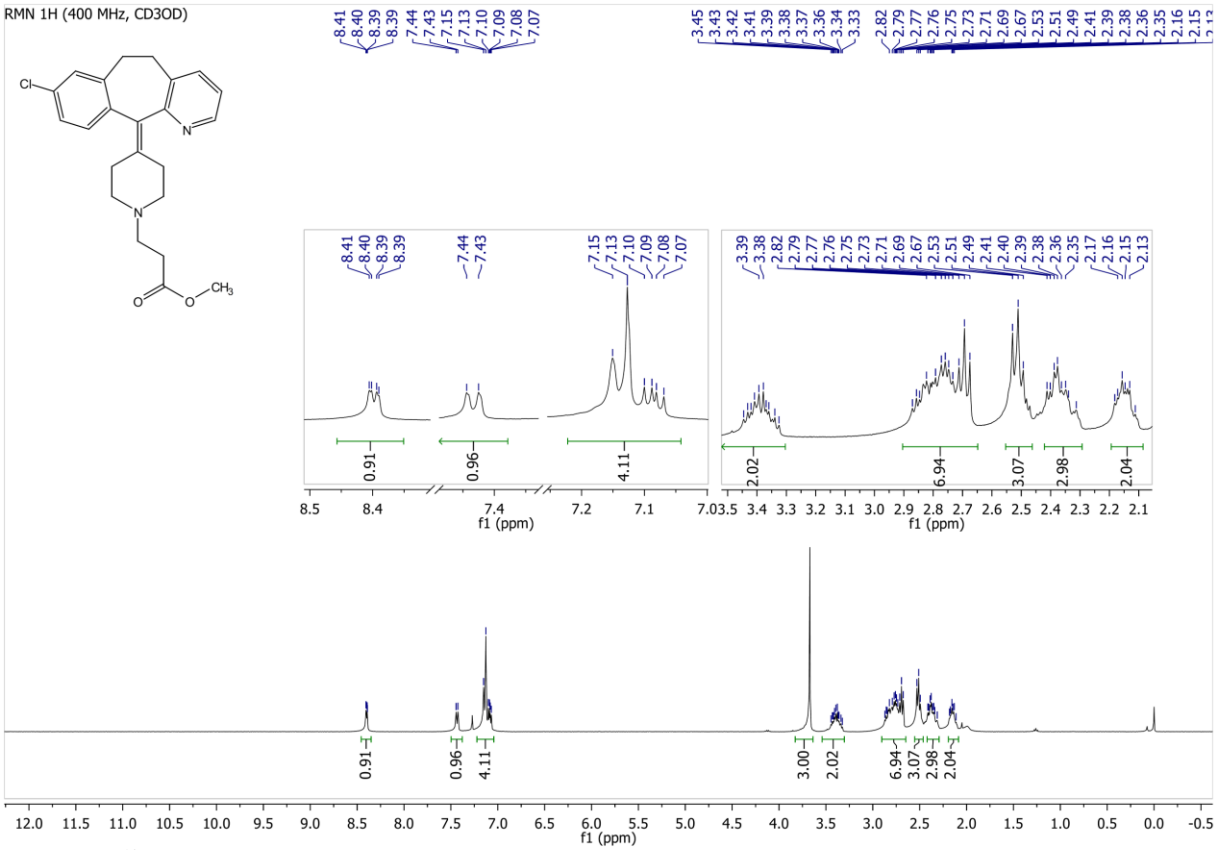


Figure S128. ^{13}C NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidin-1-yl)propanoate (**3q**)

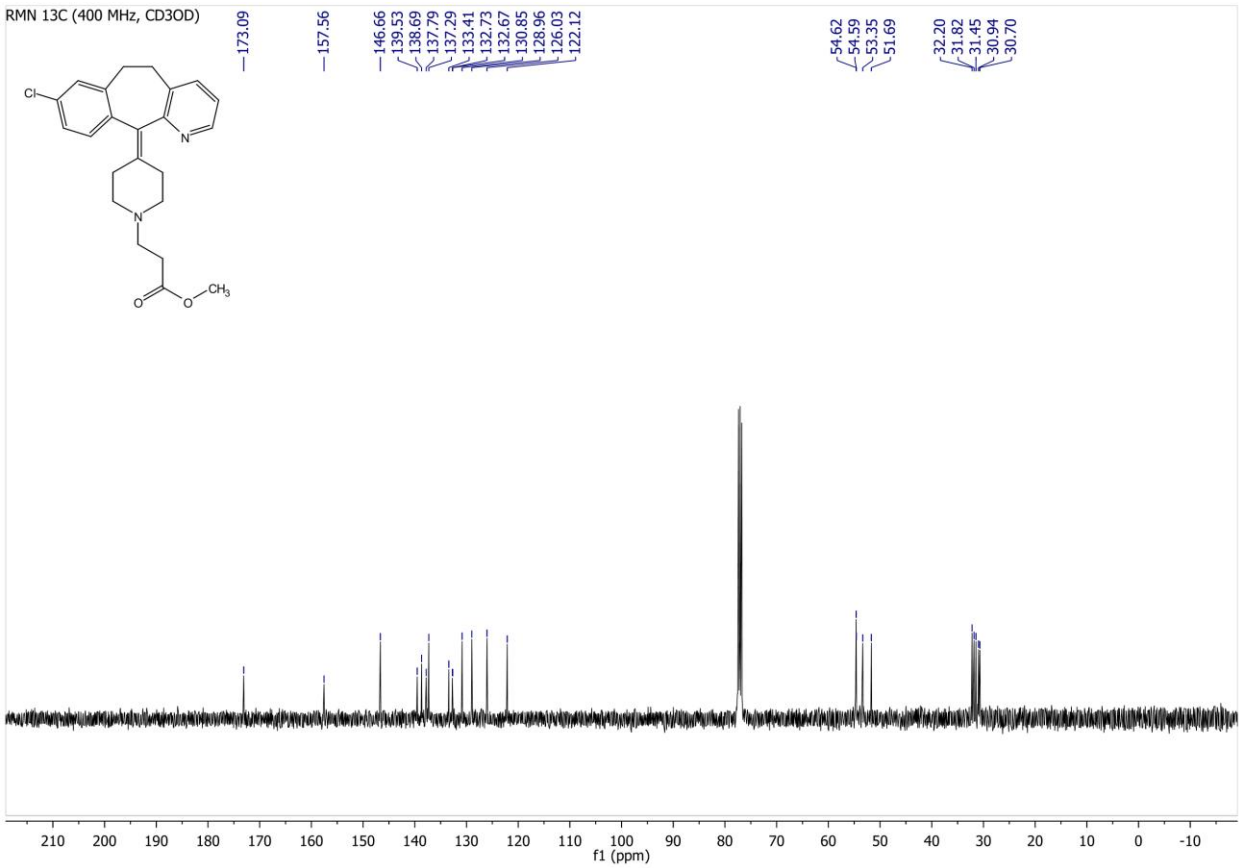


Figure S39. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(methyl(2-(pyridin-2-yl)ethyl)amino)propanoate (**3r**)

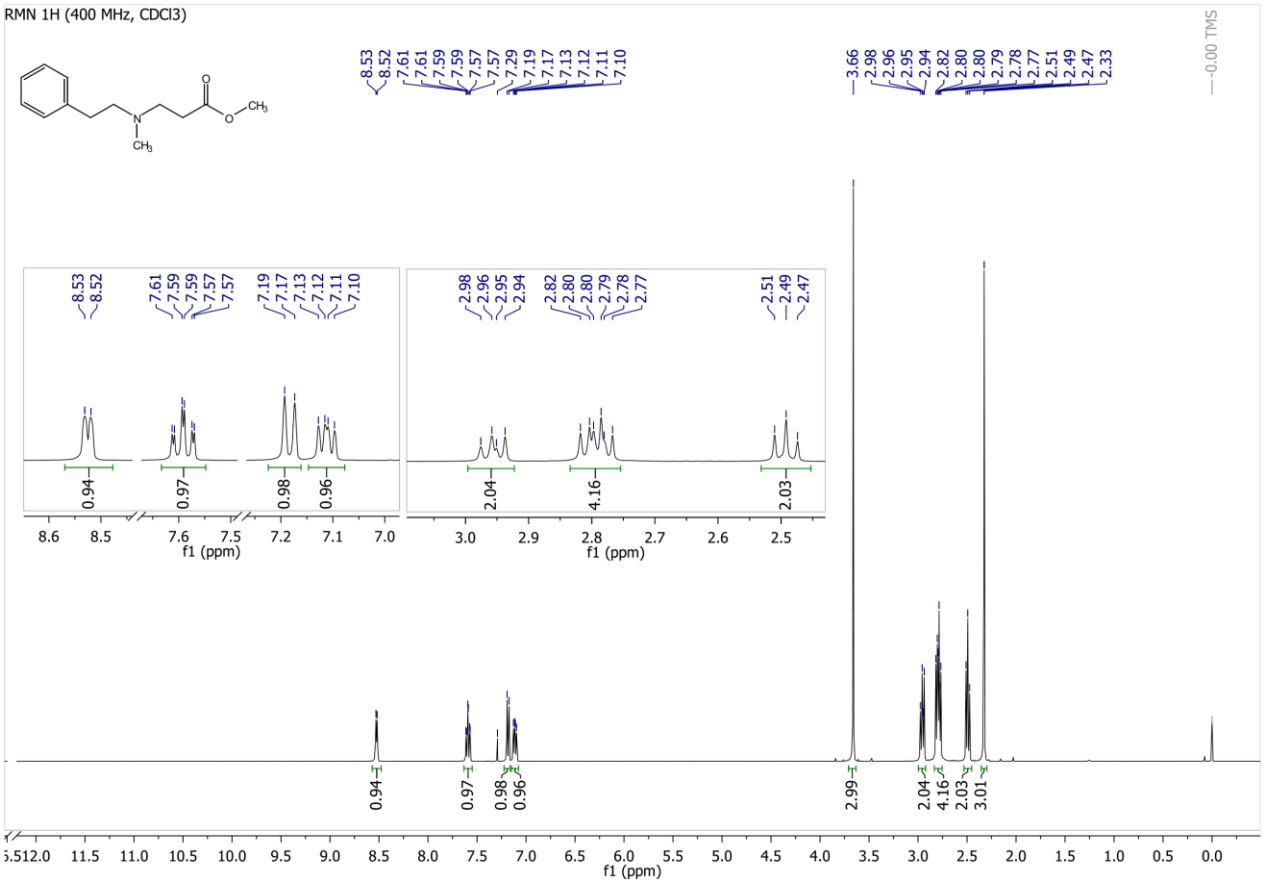
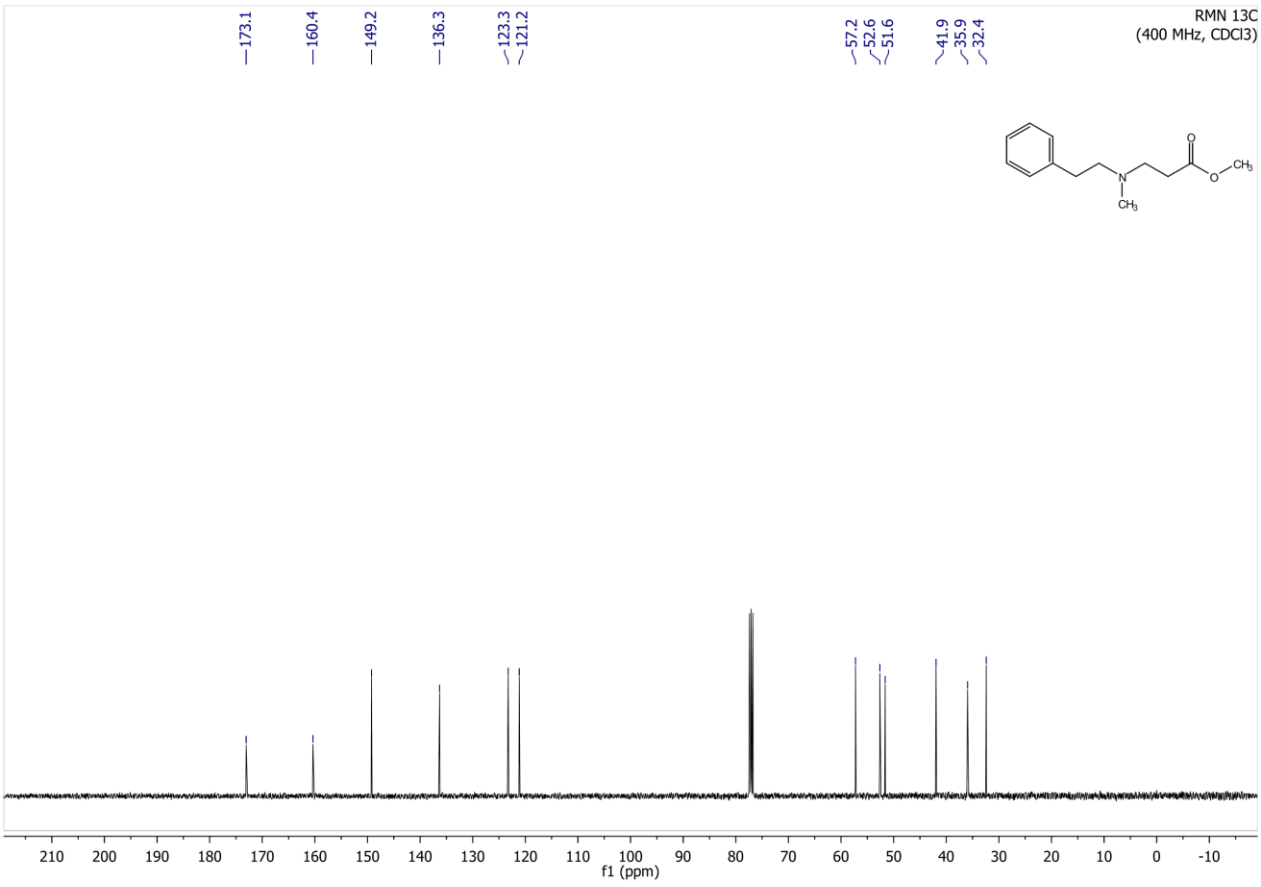


Figure S40. ^{13}C NMR (400 MHz, $CDCl_3$, ppm) of Methyl 3-(methyl(2-(pyridin-2-yl)ethyl)amino)propanoate (**3r**)



5. References

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