Supplement

Efficient Synthesis of Pharmaceutically Relevant Prochiral Heterocyclic Aminoketones

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General

All chemicals were purchased from Acros Organics (Queluz, Portugal), Aldrich (St. Louis, Missouri, United States), Alfa Aesar (Haverhill, Massachusetts, United States), Merck (Darmstadt, Germany) and Eurisotop (Saint-Aubin, France) and were used as received.

All reactions were monitored by TLC and the precoated TLC plates (Silica gel 60 F_{254}) were visualized by exposure to ultraviolet light and/or ninhydrin stain.

General procedures

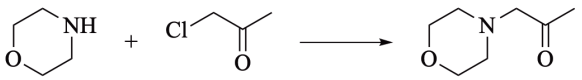
To a solution of morpholine (1000 µL, 11.6 mmol) in MTBE (10 mL) was added chloroacetone (0.5 equiv.) at room temperature. The reaction was stirred for 48 hours, then filtered and solvent was removed under reduced pressure. The residue was treated with MTBE and the precipitate was filtered, then the solvent was removed under reduced pressure to afford the crude mixture as a yellow liquid (Scheme S1).

To a solution of **4a-i** (1000 µL) in MTBE (10 mL) was added potassium carbonate (1.5 equiv.) and chloroacetone (1.1 equiv.) at room temperature. The reaction was refluxed until completion (followed by TLC DCM:MeOH 9:1+0.1 % NH_4OH), then filtered and the solvent and excess of chloroacetone removed under reduced pressure (10 mbar) by keeping the water bath at 70 °C. The residue was treated with MTBE and the precipitate was removed by filtration. The solvent was removed under reduced pressure to afford **6a-i** (Scheme S2).

To a solution of **4a-i** (1000 µL) in MTBE (10 mL) was added chloroacetone (0.6 equiv.) at room temperature. The reaction was refluxed until completion (followed by TLC DCM:MeOH 9:1+0.1 % NH_4OH), then filtered and the solvent and excess of chloroacetone removed under reduced pressure (10 mbar) by keeping the water bath at 70 °C. The residue was treated with MTBE and the precipitate was removed by filtration. The solvent was removed under reduced pressure to afford **6a-i** (Scheme S3).

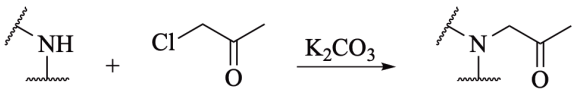
Piperazine (1000 mg, 11.6 mmol) was dissolved in MTBE (10 mL) at reflux temperature, then chloroacetone (0.5 equiv.) was added and the reaction was refluxed until completion (followed by TLC DCM:MeOH 9:1+0.1 % NH_4OH).The precipitation was filtered off, and the solvent evaporated to yield a yellow oil that was treated with MTBE. After filtration the solvent was evaporated to yield the crude mixture of **6j** and **4j** (Scheme S4).

Piperazine (1000 mg, 11.6 mmol) was dissolved in MTBE (10 mL) at reflux temperature, then potassium carbonate (3 equiv.) and chloroacetone (2.1 equiv.) was added and the reaction was refluxed until completion (followed by TLC DCM:MeOH 9:1+0.1 % NH_4OH). The mixture was filtered and



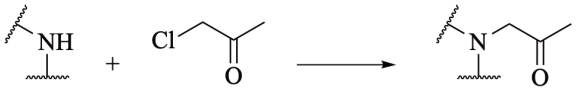
4a **5** **6a**

Scheme S1 Alkylation of morpholine (**4a**) at room temperature



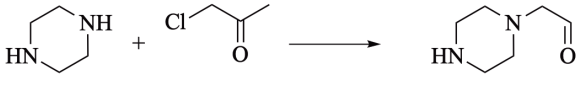
4a-i **5** **6a-i**

Scheme S2 General procedure for alkylation of amine heterocycles (**4a-i**) with external base K_2CO_3



4a-i **5** **6a-i**

Scheme S3 General procedure for alkylation of amine heterocycles (**4a-i**) without external base



4j **5** **6j**

Scheme S4 Monoalkylation of piperazine (**4j**)

the solvent and excess chloroacetone removed under reduced pressure (10 mbar) by keeping the water bath at 70 °C to yield **6k** (Scheme S5).

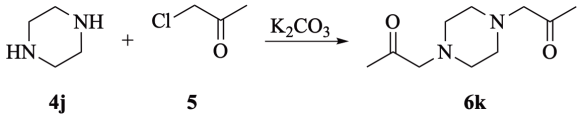
The solution of **6a-g** in MTBE was treated with 4N HCl in dioxane (1.05 equiv.) under nitrogen atmosphere. The forming crystals were triturated and filtered under N_2 atm. to afford **7a-g**. If the hydrochloride was not forming properly, the MTBE was evaporated and the residue was taken up in EtOH, then the hydrochloride was recrystallized by addition of MTBE (Scheme S6).

The solution of **6h,i,k** in MTBE was treated with 4N HCl in dioxane (2.05 equiv.) under nitrogen atmosphere. The forming crystals were triturated and filtered under N_2 atm to afford **7h,i,k** (Scheme S7).

The solution of **6j** in MTBE was treated with 4N HCl in dioxane (1.05 equiv.) under nitrogen atmosphere. The forming crystals were triturated and filtered under N_2 atm. to afford **7j** (Scheme S8).

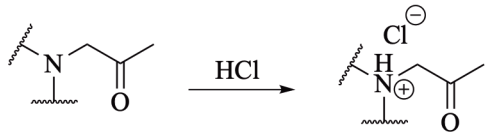
Regeneration of 4i

The filter cake of the respective preparation of **6i** with external base was dissolved in aqueous 1N NaOH solution (20 mL, pH > 10) and extracted with ethyl acetate. The organic phases were combined and dried on sodium sulfate. The solvent was evaporated to yield **4i** as a colorless liquid.



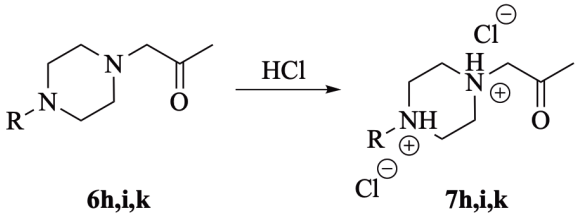
4j **5** **6k**

Scheme S5 Dialkylation of piperazine (**4j**)



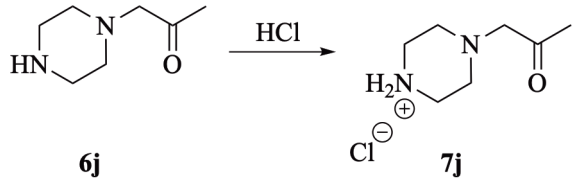
6a-i **7a-g**

Scheme S6 General procedure for the hydrochloric salt formation of **6a-g**



6h,i,k **7h,i,k**

Scheme S7 General procedure for the hydrochloric salt formation of N,N-dialkylated piperazine derivatives **6h**,**i**,**k**



6j **7j**

Scheme S8 Hydrochloric salt formation of N-monoalkylated piperazine derivative **6j**

Characterization of compounds

All melting points (mp) were determined on TA Instruments DSC250 calorimeter and are uncorrected. NMR spectra (Fig. S1–Fig. S36) were obtained with a Bruker Fourier 300 spectrometer, or a Magritec Spinsolve Benchtop NMR spectrometer at room temperature. Proton NMR spectra were recorded at 43 or 300 MHz, ^{13}C NMR spectra were recorded at 75 MHz. Chemical shifts are given in ppm units, (^1H NMR in DMSO-d_6: δ 2.50 ppm, or D_2O: δ = 4.79; ^{13}C NMR in DMSO-d_6: δ = 39.5). Splitting patterns are designated as *s*, singlet; *d*, doublet; *t*, triplet; *q*, quartet; *m*, multiplet; *br*, broad. Spin-spin coupling constants (*J*) were given in Hz units. Infrared spectra (IR) of solid samples were recorded on a Nicolet Avatar 360 Fourier Transform Infrared spectrometer, of oils spectra were recorded on a Shimadzu IRAffinity-1 FTIR spectrometer. High-resolution mass spectra (HRMS) were recorded on an AB Sciex TripleTOF® 6600 System mass spectrometer.

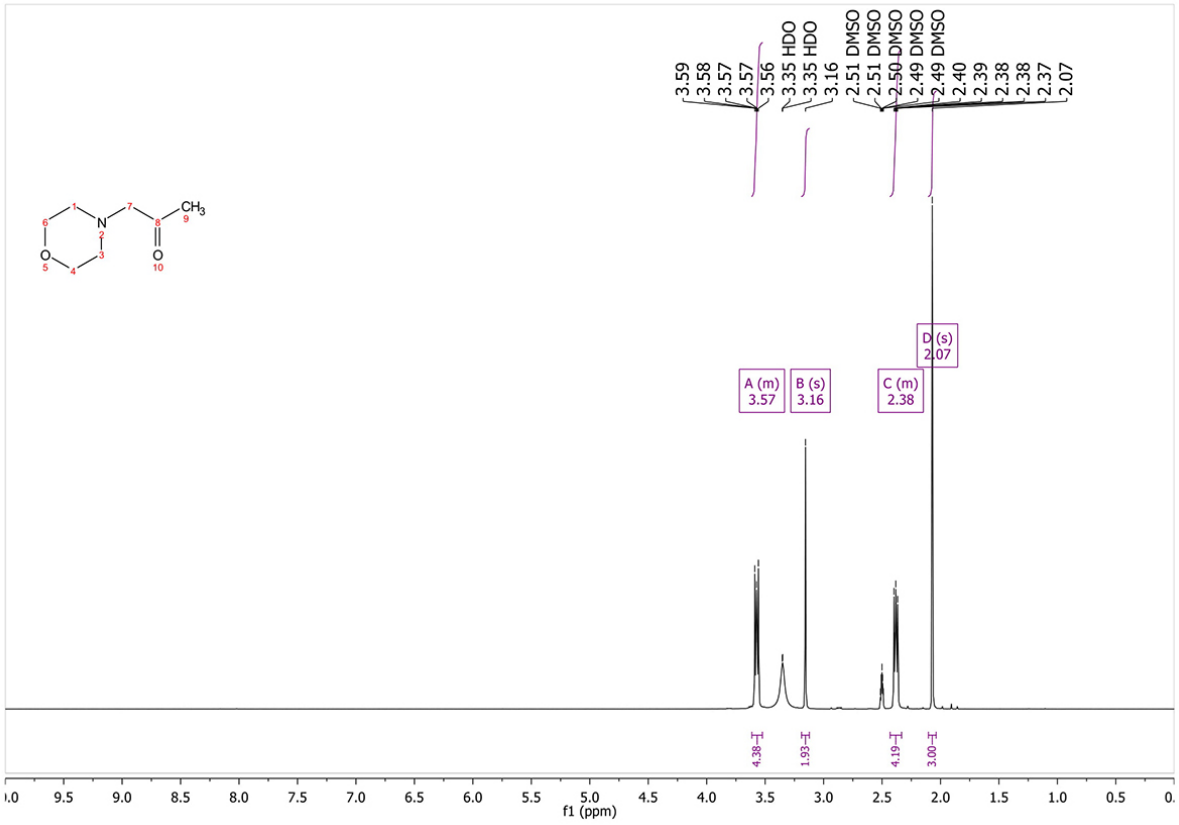


Fig. S1 [1]H NMR of 1-morpholinopropan-2-one (**6a**)

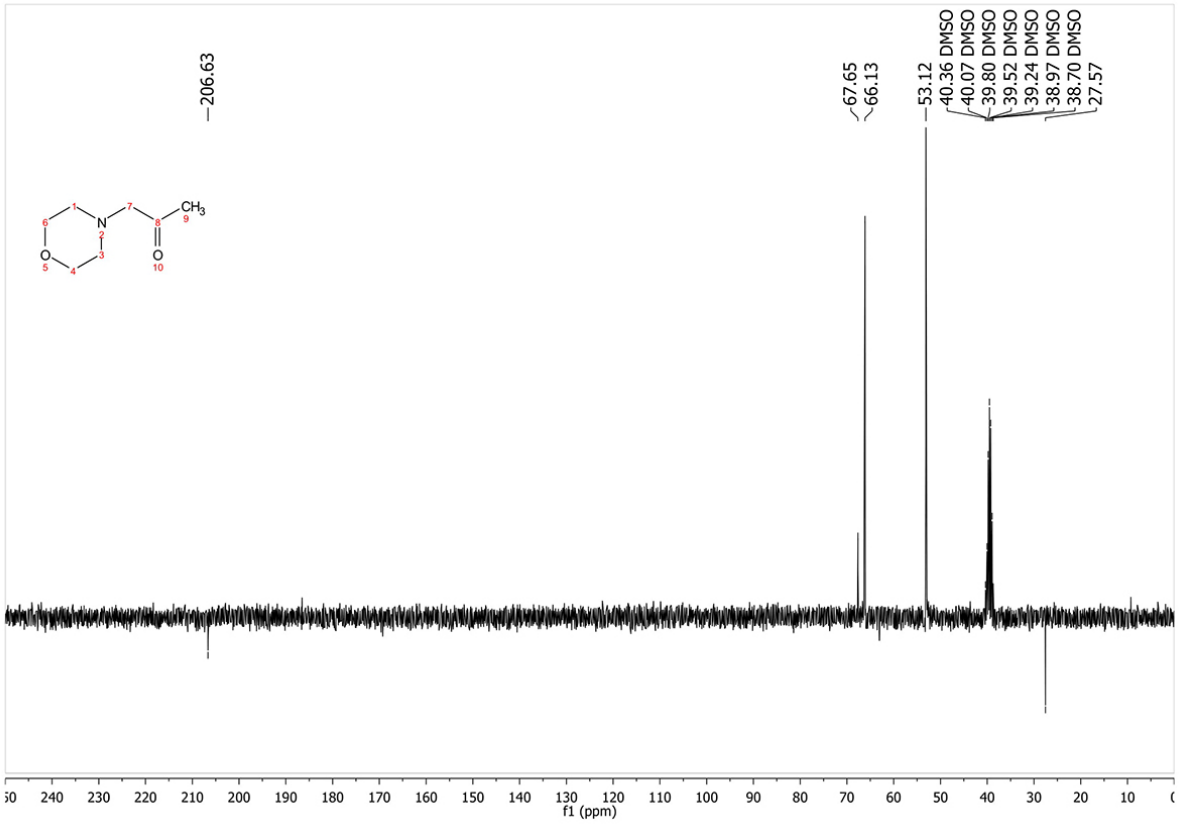


Fig. S2 [13]C NMR of 1-morpholinopropan-2-one (**6a**)

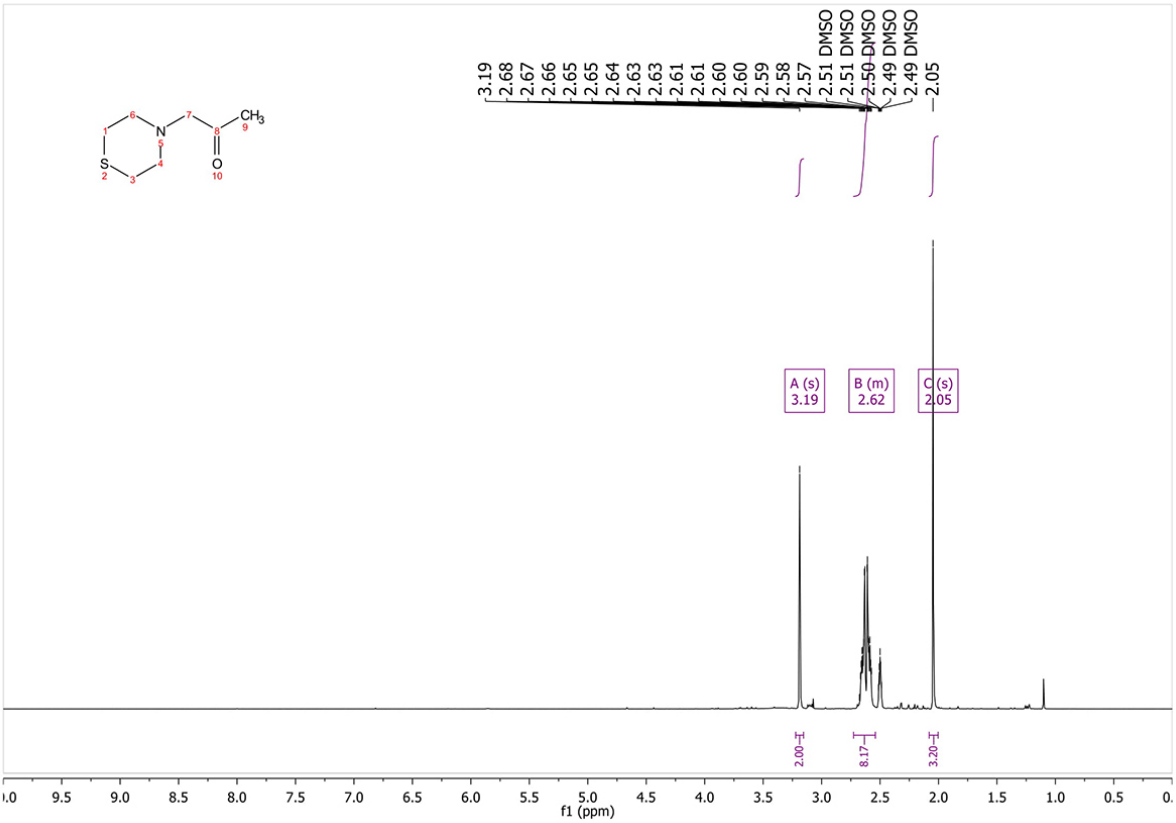


Fig. S3 [1]H NMR of 1-thiomorpholinopropan-2-one (**6b**)

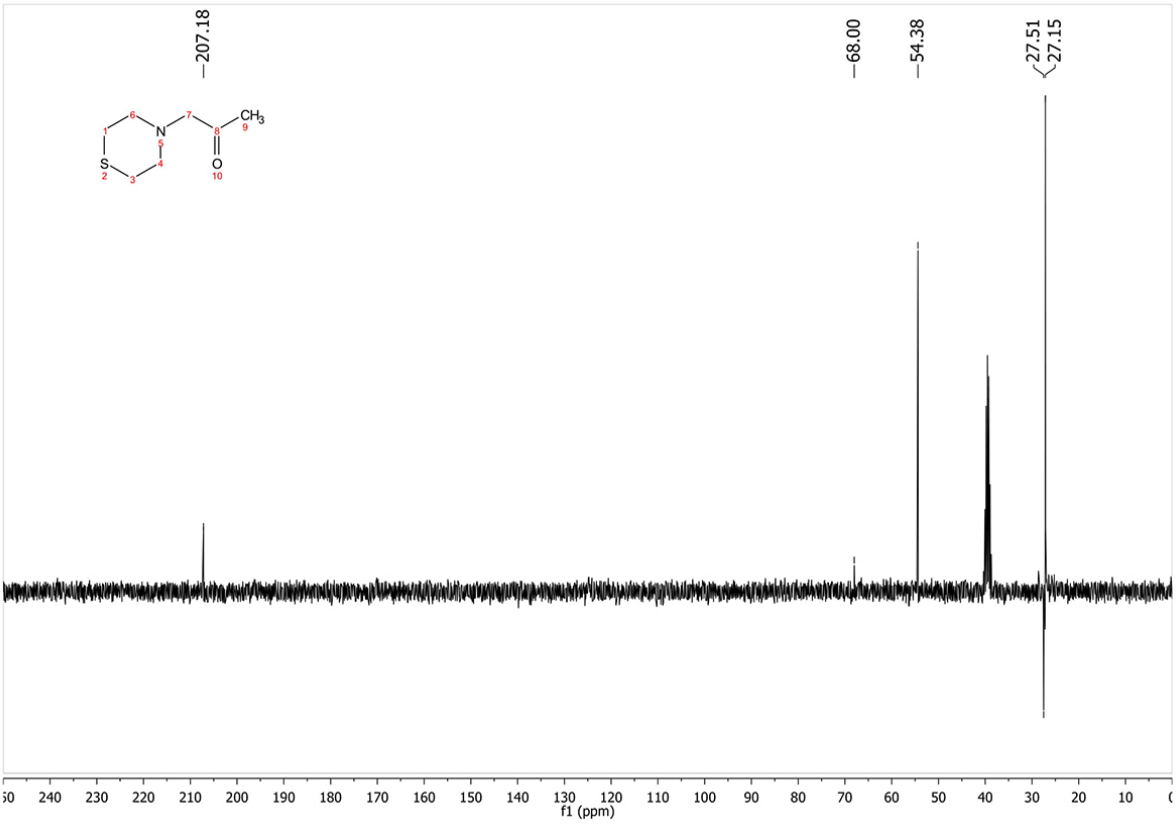


Fig. S4 [13]C NMR of 1-thiomorpholinopropan-2-one (**6b**)

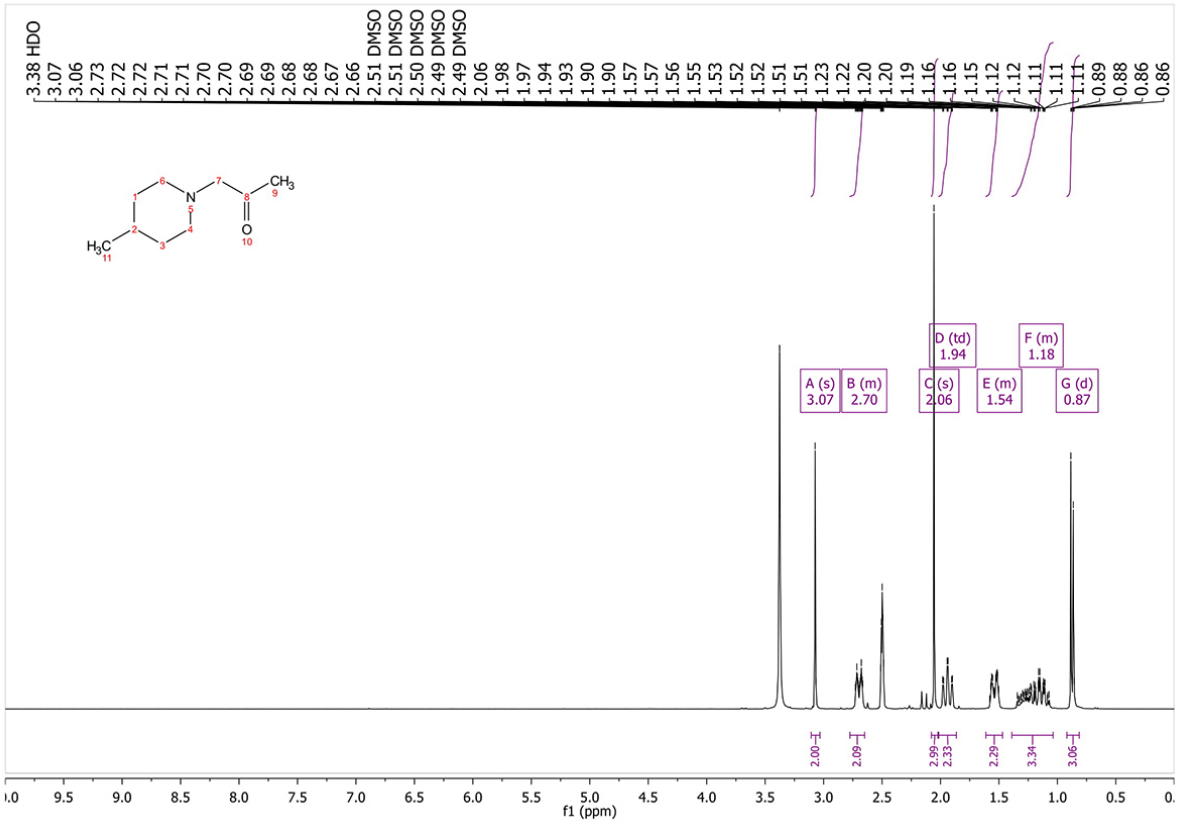


Fig. S5 [1]H NMR of 1-(4-methylpiperidin-1-yl)propan-2-one (**6c**)

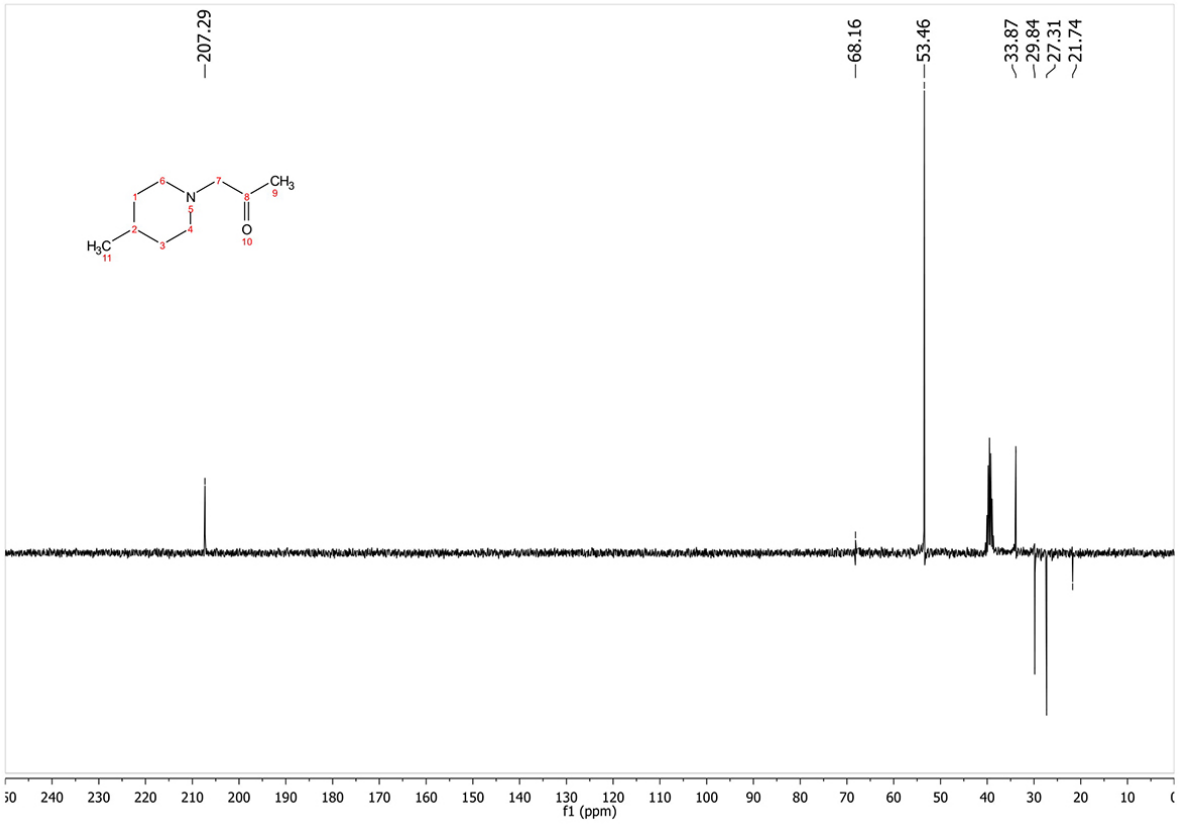


Fig. S6 [13]C NMR of 1-(4-methylpiperidin-1-yl)propan-2-one (**6c**)

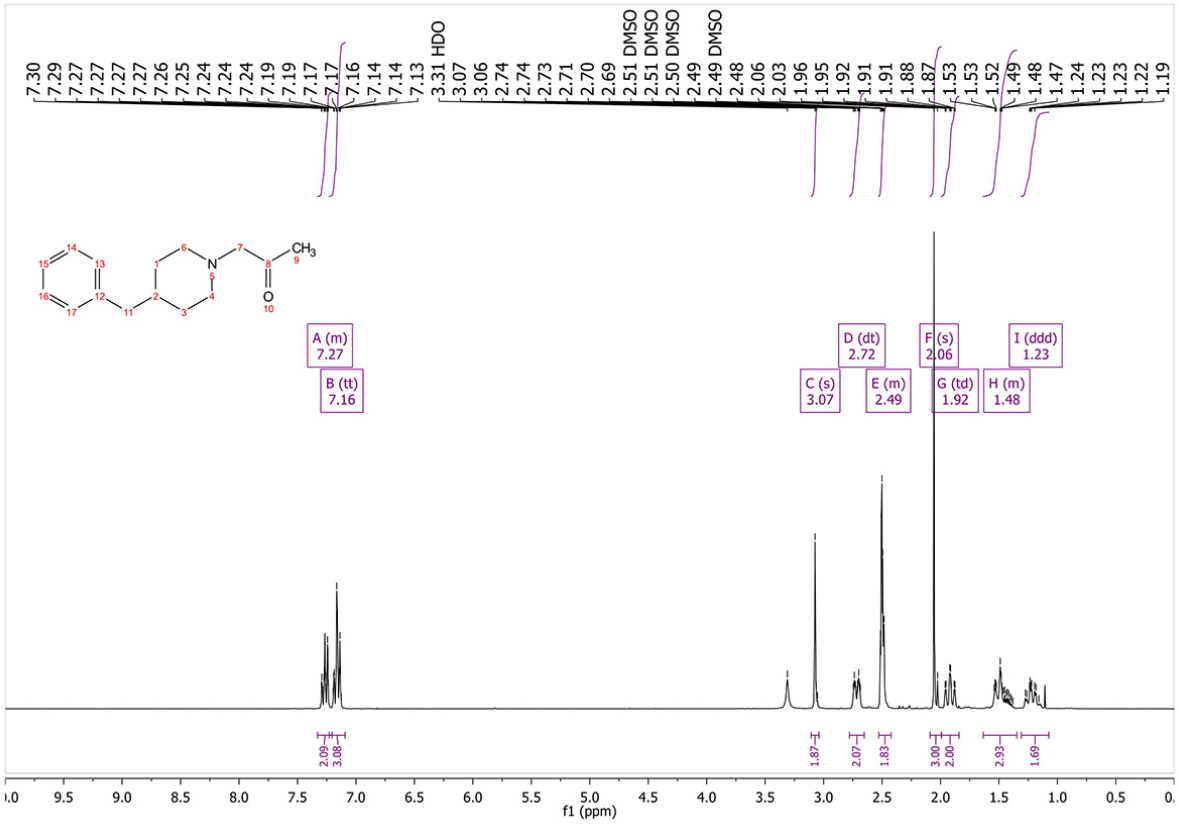


Fig. S7 [1]H NMR of 1-(4-benzylpiperidin-1-yl)propan-2-one (**6d**)

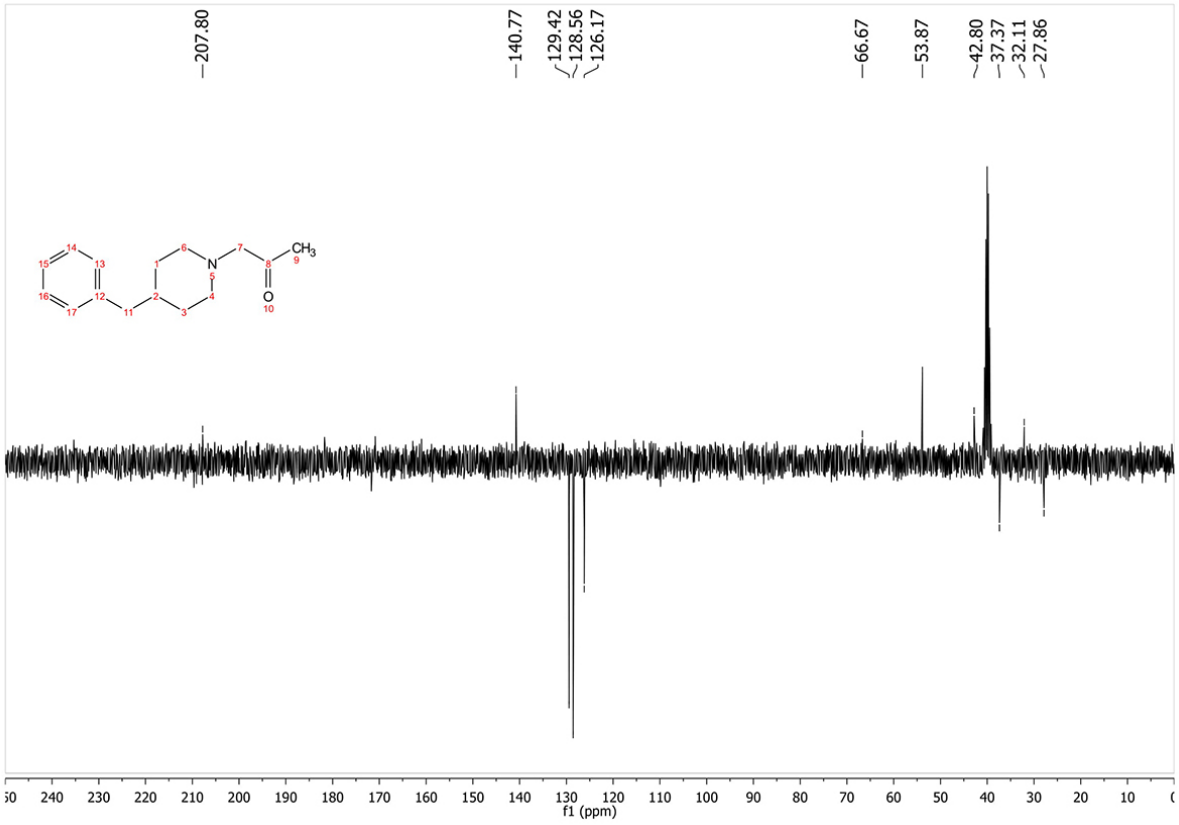


Fig. S8 [13]C NMR of 1-(4-benzylpiperidin-1-yl)propan-2-one (**6d**)

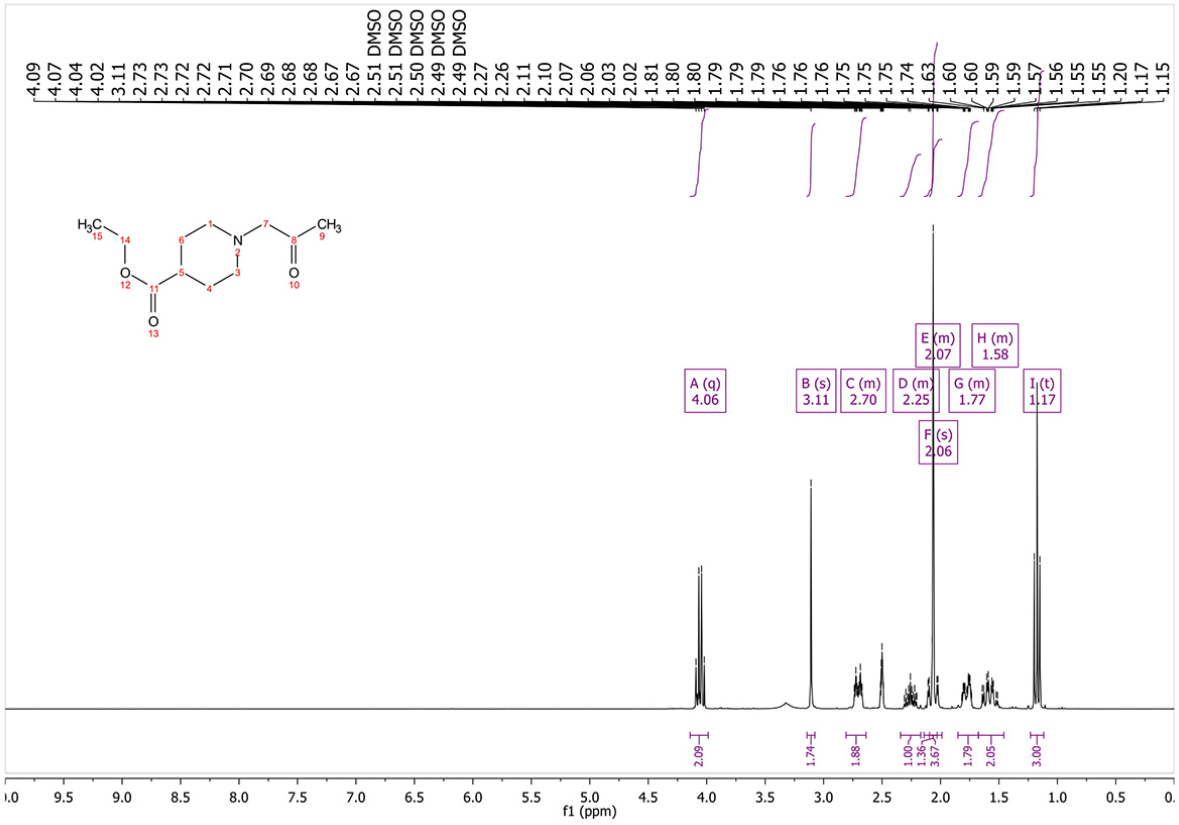


Fig. S9 [1]H NMR of 1-(2-oxopropyl)piperidine-4-carboxylate (**6e**)

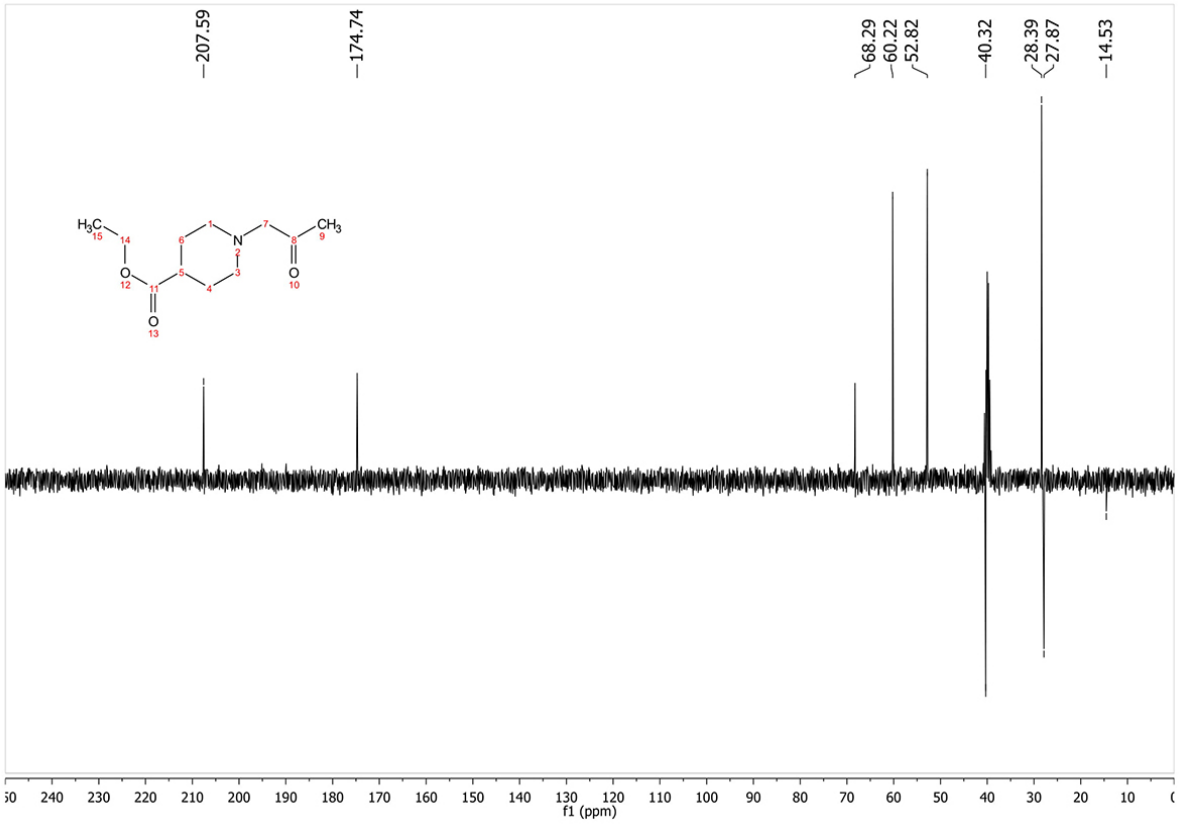


Fig. S10 [13]C NMR of 1-(2-oxopropyl)piperidine-4-carboxylate (**6e**)

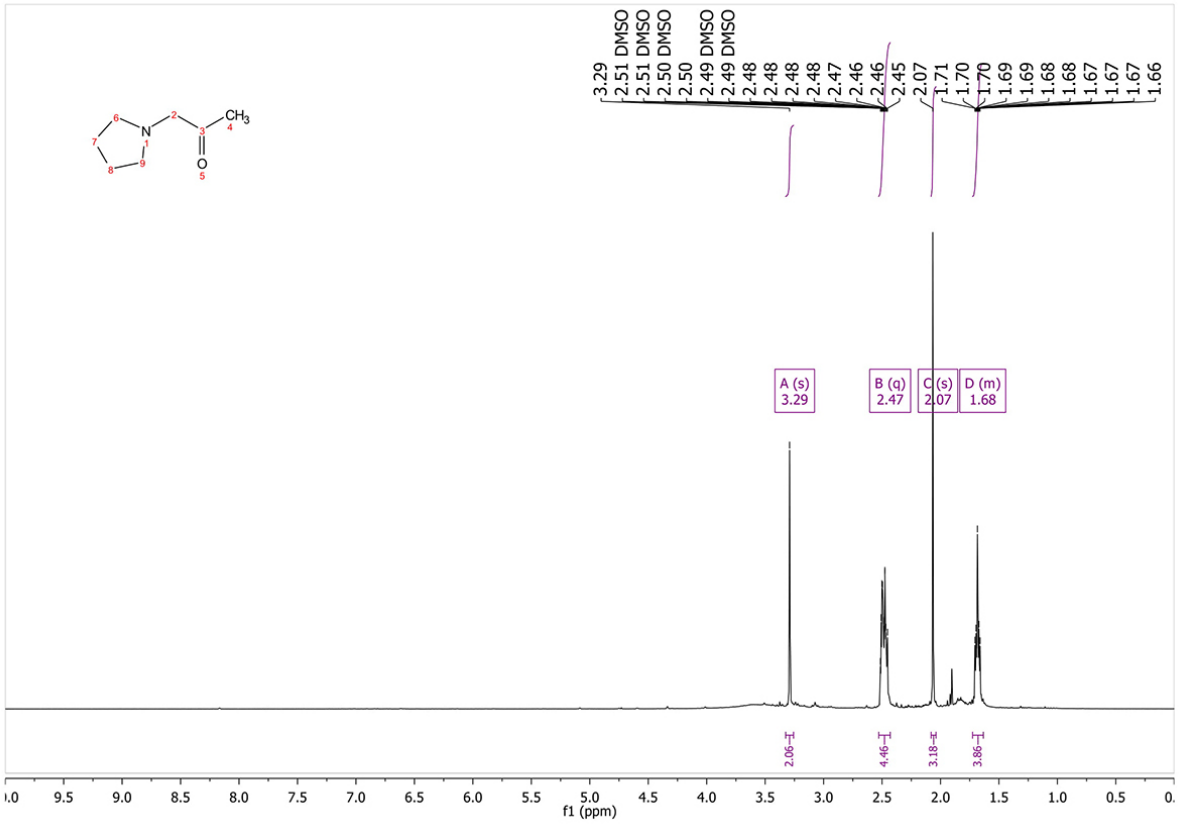


Fig. S11 [1]H NMR of 1-(pyrrolidin-1-yl)propan-2-one (**6f**)

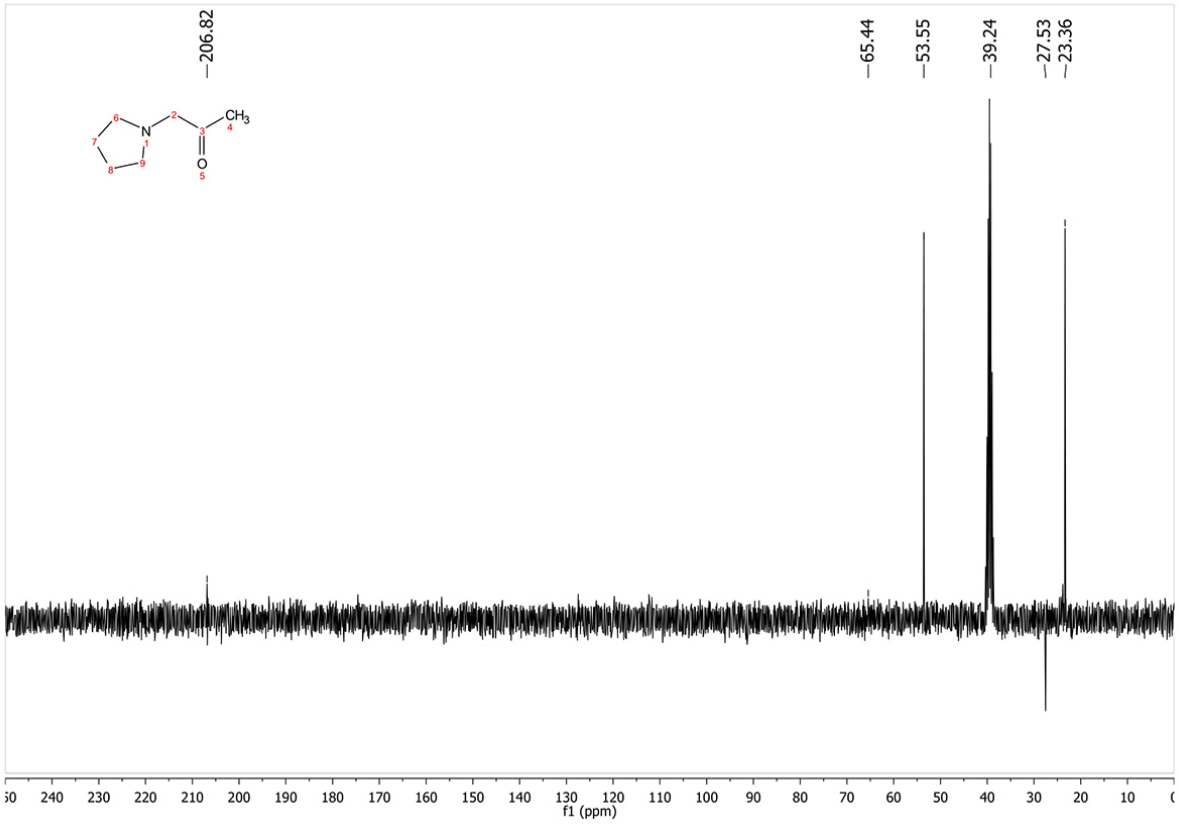


Fig. S12 [13]C NMR of 1-(pyrrolidin-1-yl)propan-2-one (**6f**)

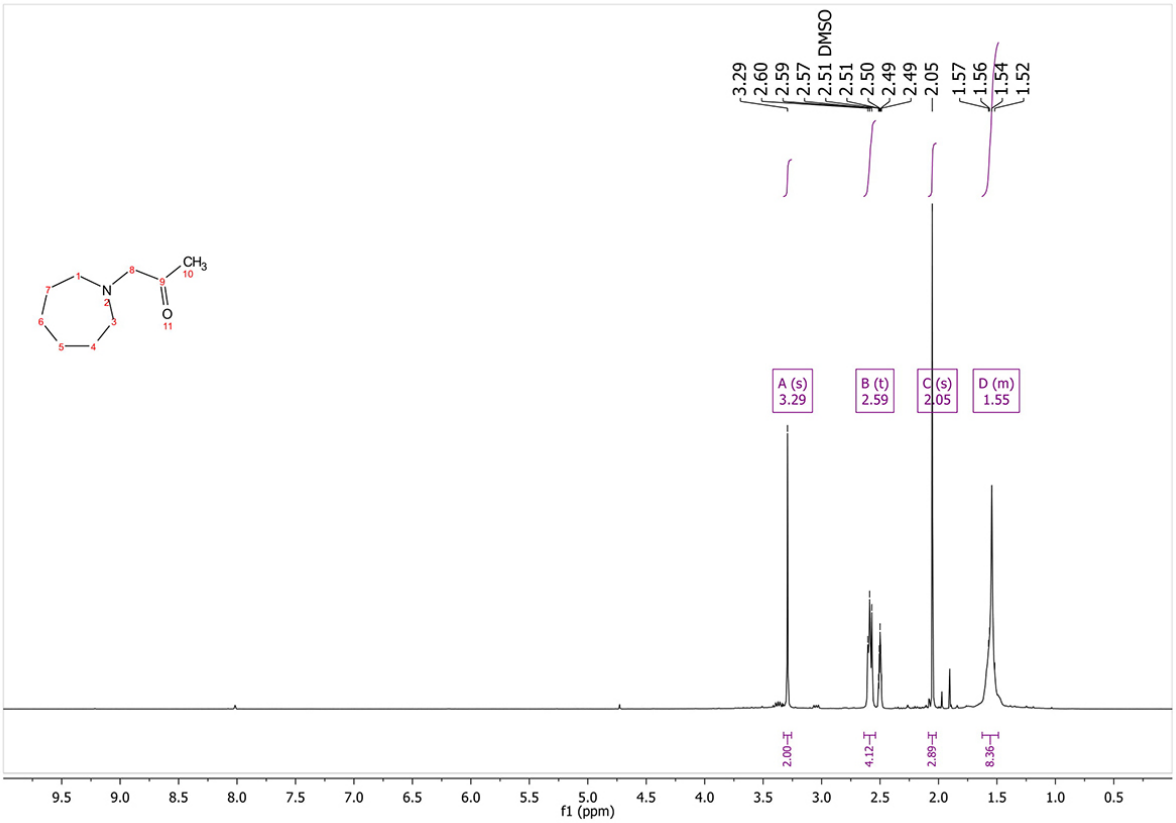


Fig. S13 [1]H NMR of 1-(azepan-1-yl)propan-2-one (**6g**)

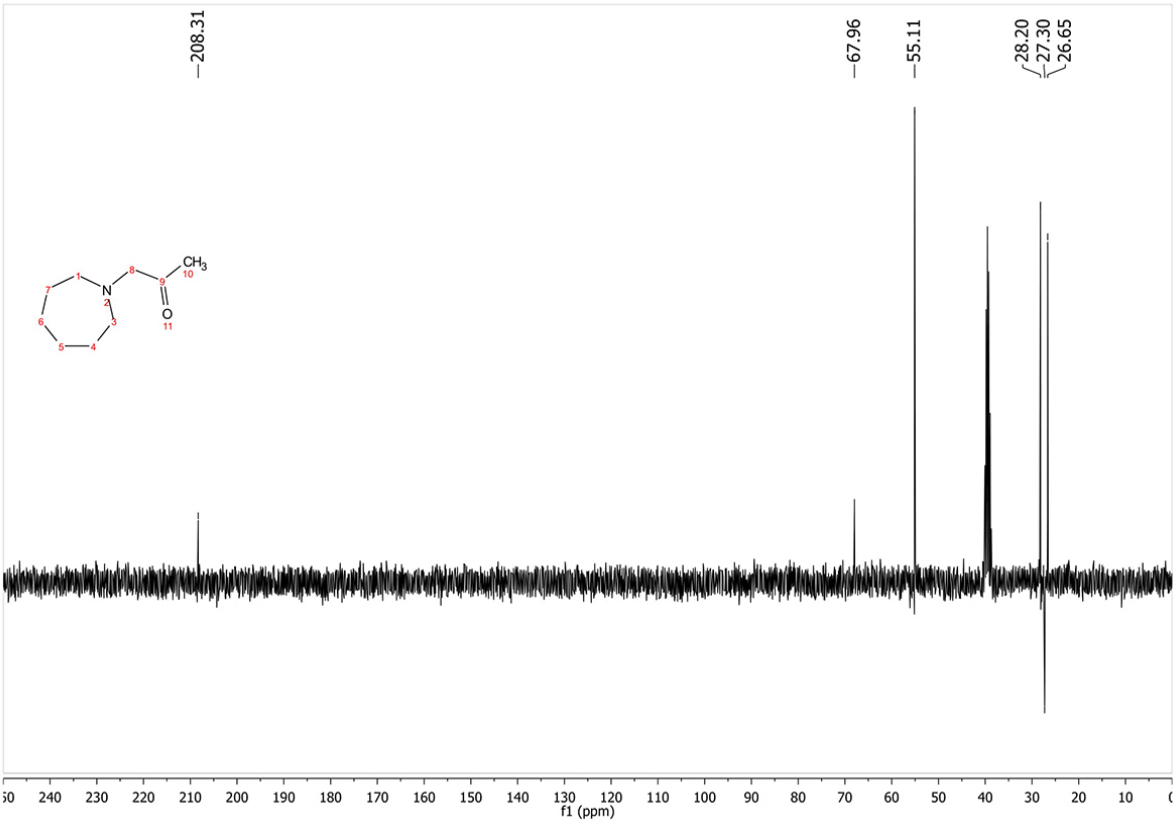


Fig. S14 [13]C NMR of 1-(azepan-1-yl)propan-2-one (**6g**)

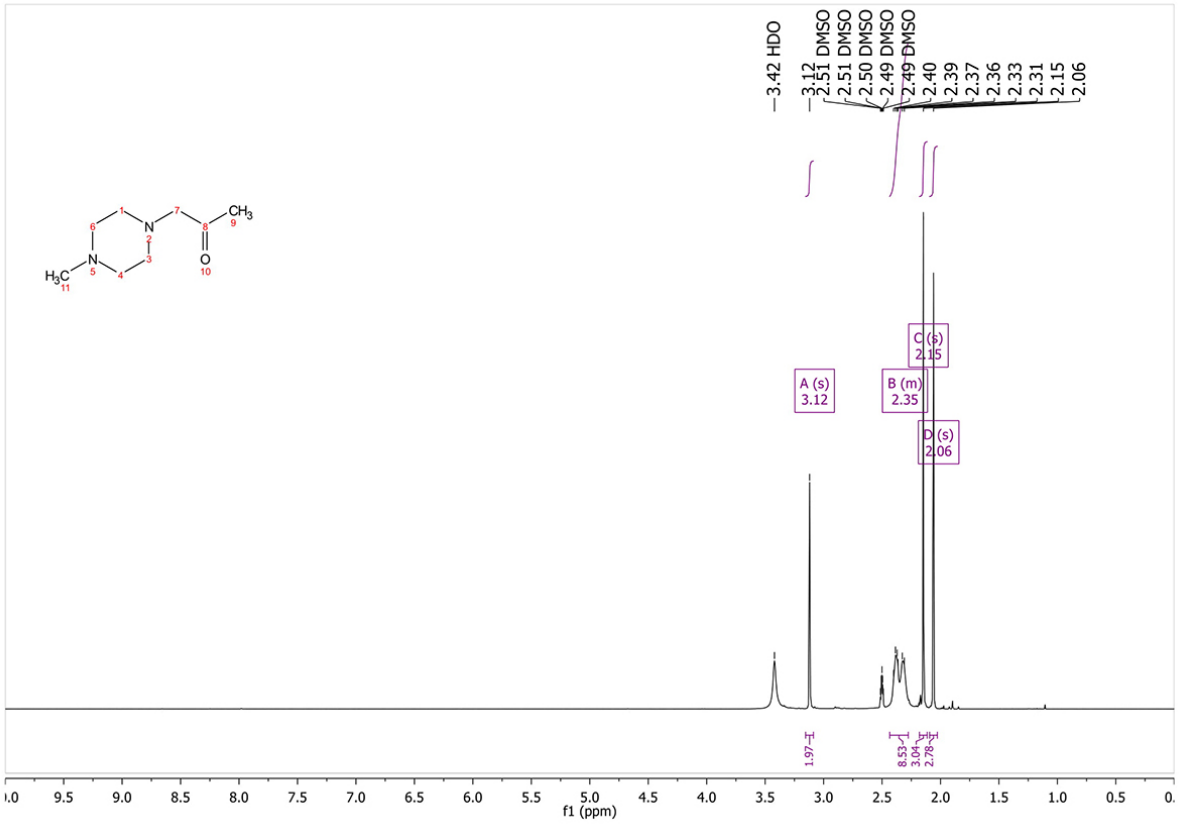


Fig. S15 [1]H NMR of 1-(4-methylpiperazin-1-yl)propan-2-one (**6h**)

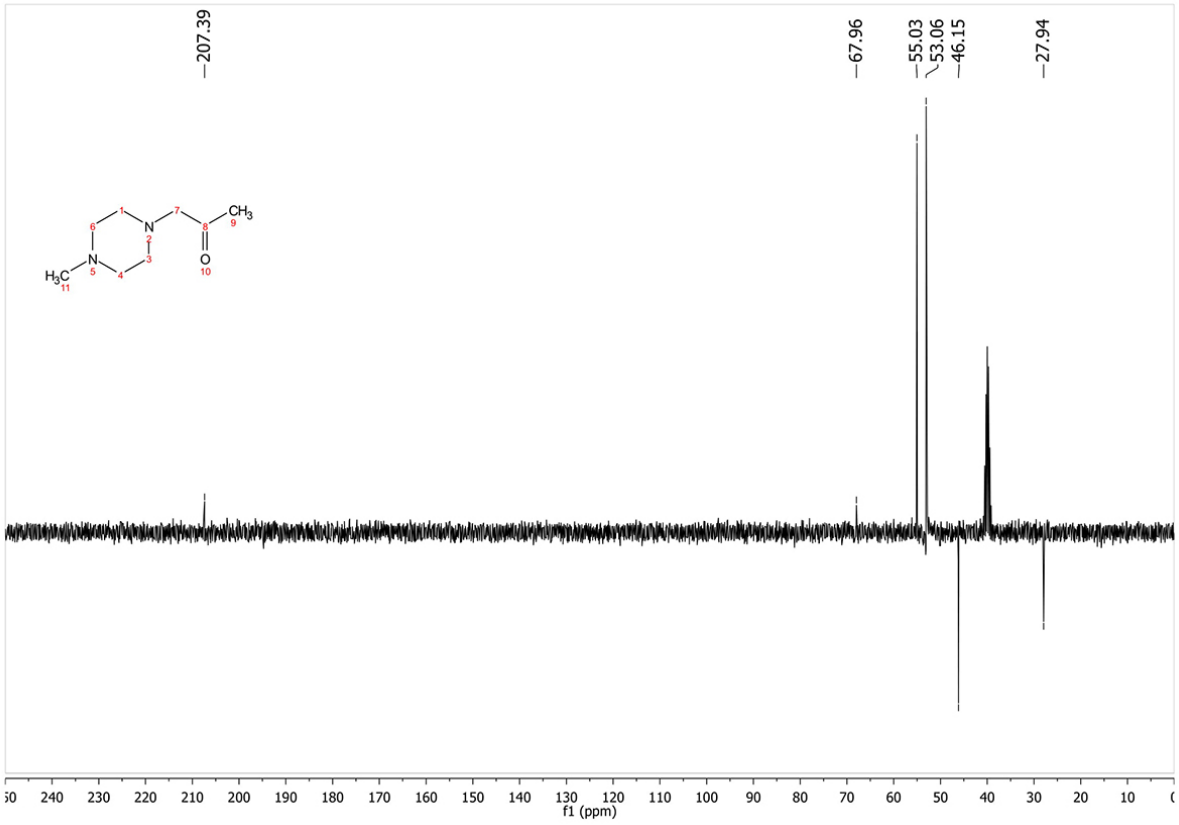


Fig. S16 [13]C NMR of 1-(4-methylpiperazin-1-yl)propan-2-one (**6h**)

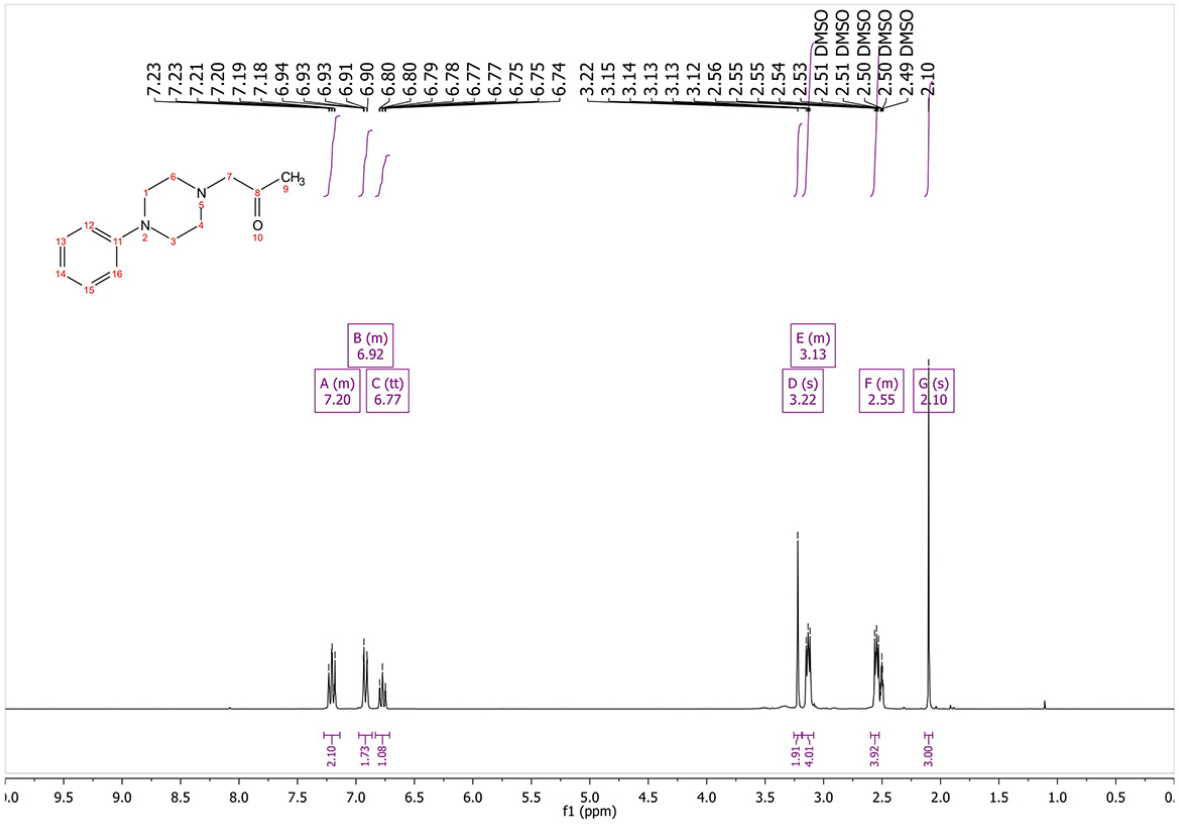


Fig. S17 [1]H NMR of 1-(4-phenylpiperazin-1-yl)propan-2-one (**6i**)

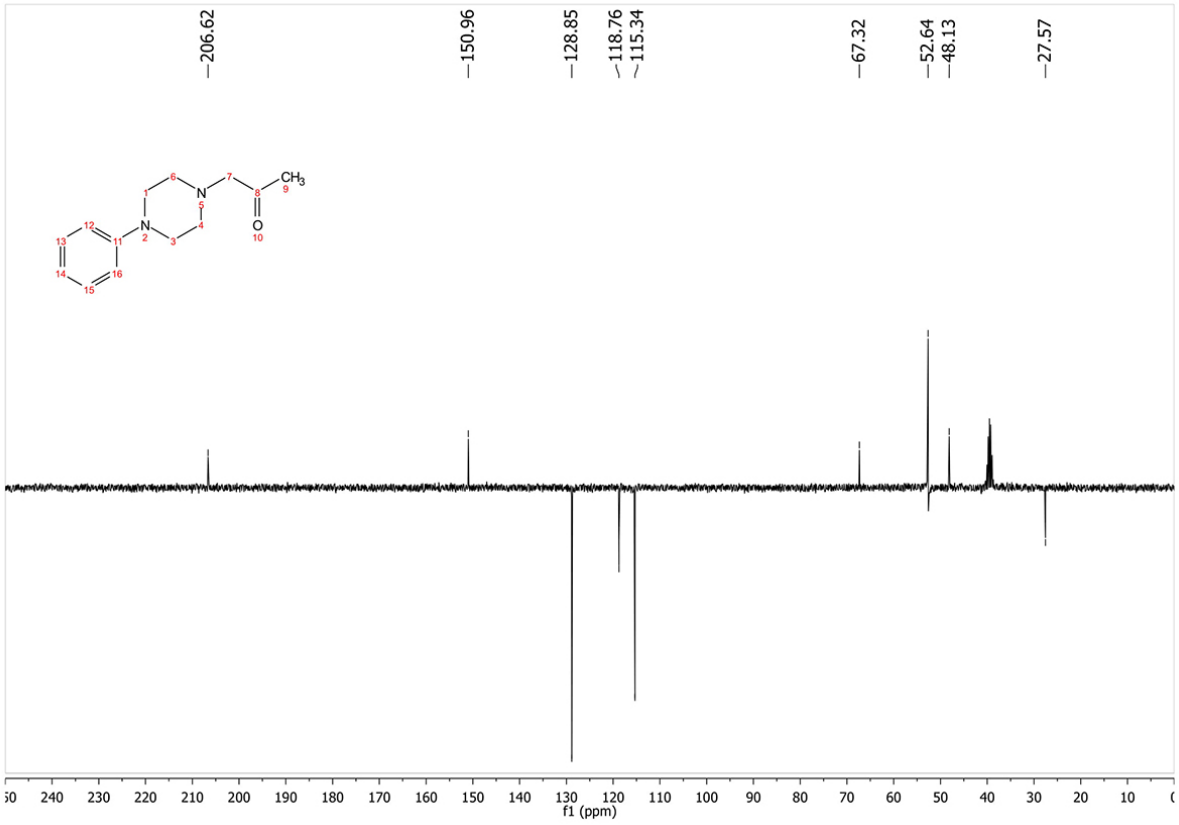


Fig. S18 [13]C NMR of 1-(4-phenylpiperazin-1-yl)propan-2-one (**6i**)

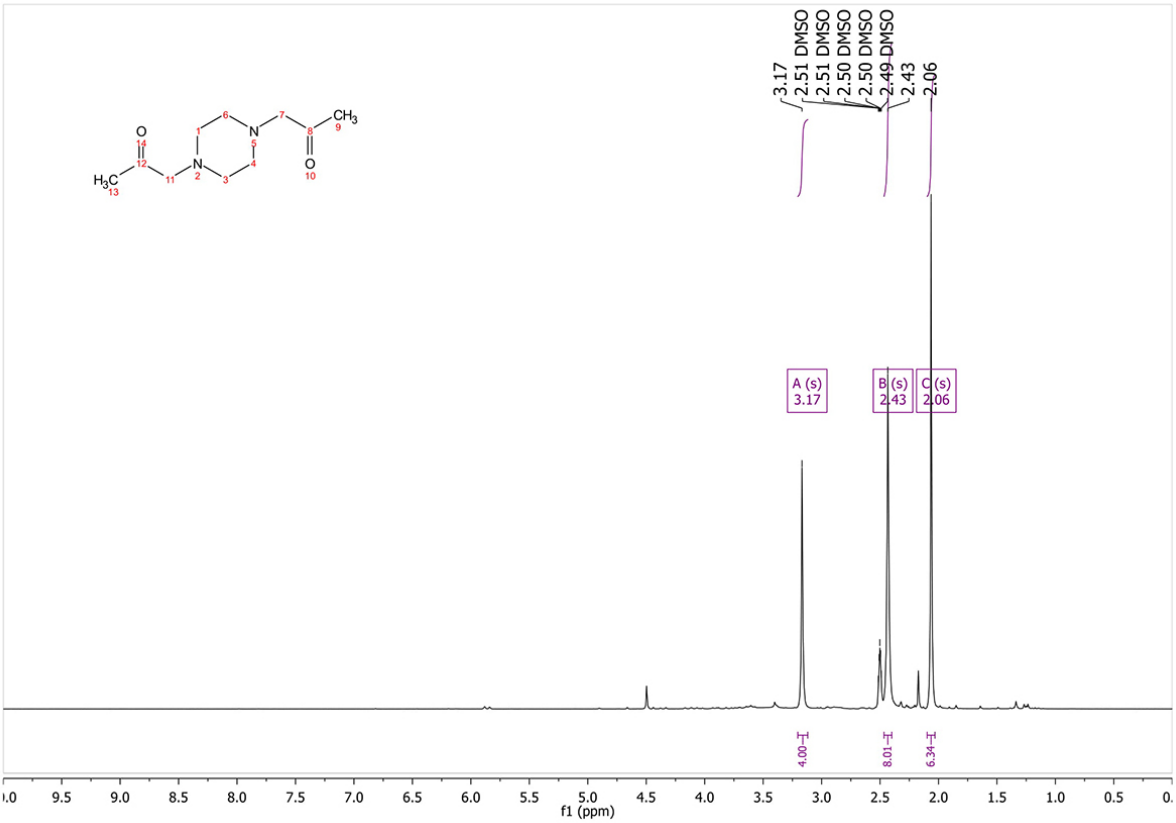


Fig. S19 1H NMR of 1,1'-(piperazine-1,4-diyl)bis(propan-2-one) (**6k**)

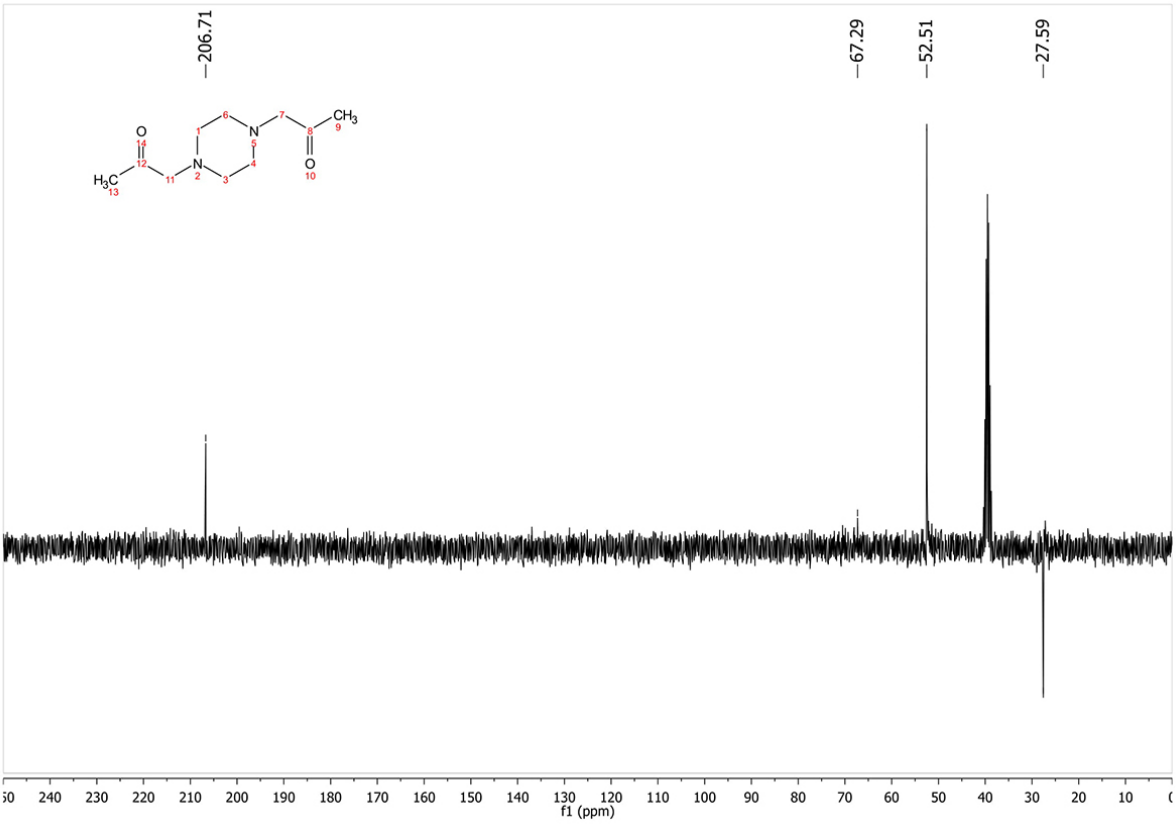


Fig. S20 ^{13}C NMR of 1,1'-(piperazine-1,4-diyl)bis(propan-2-one) (**6k**)

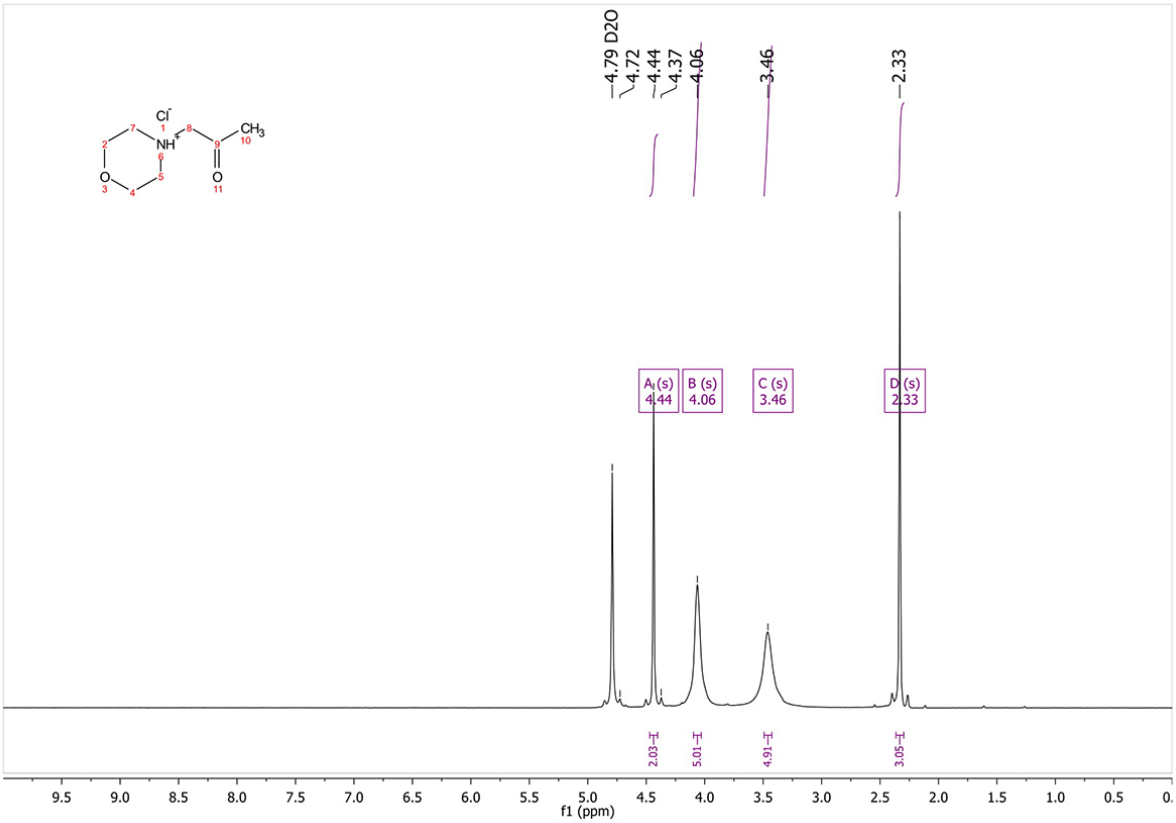


Fig. S21 [1]H NMR of 1-morpholinopropan-2-one hydrochloride (**7a**)

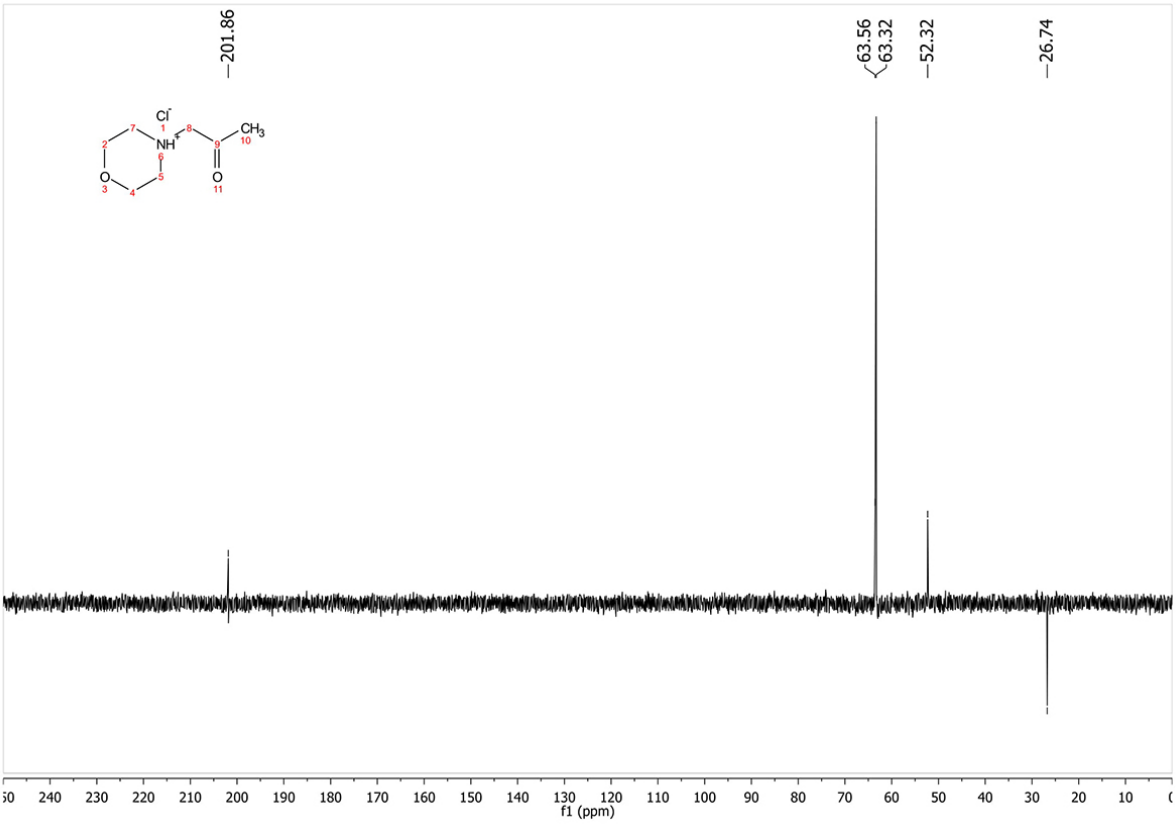


Fig. S22 [13]C NMR of 1-morpholinopropan-2-one hydrochloride (**7a**)

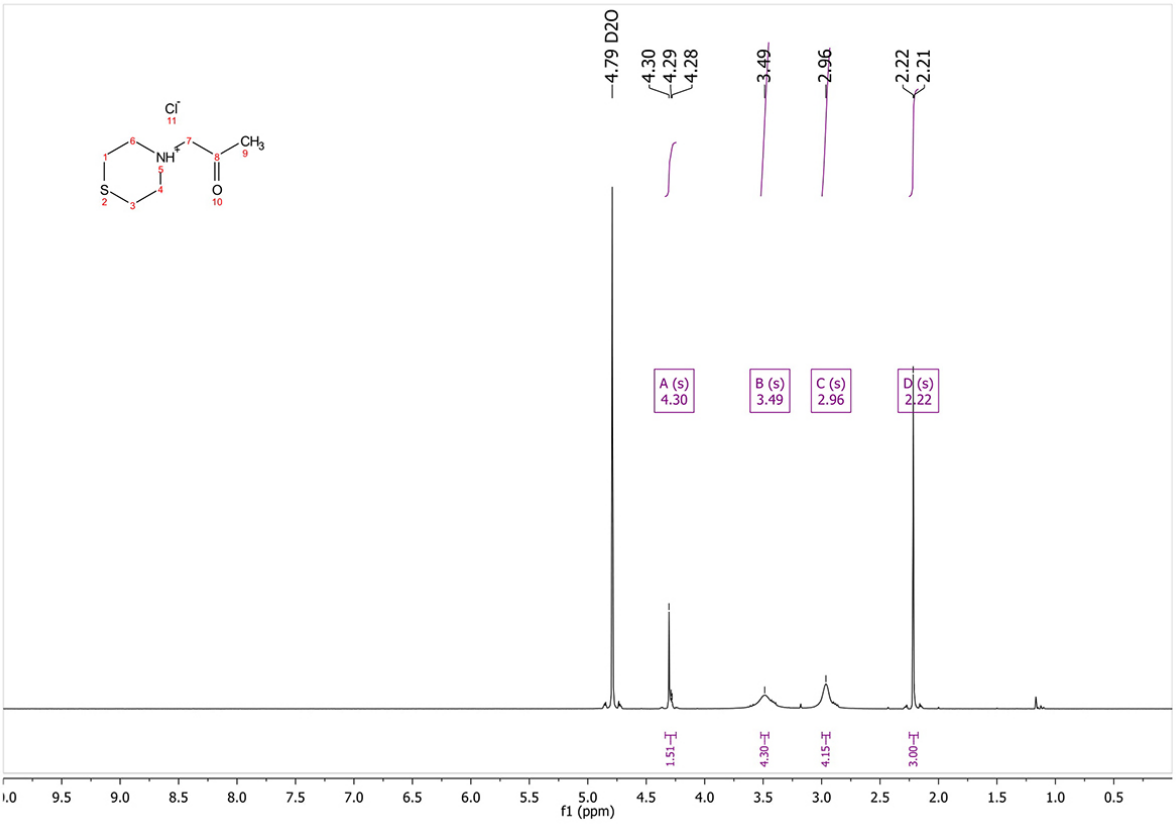


Fig. S23 [1]H NMR of 1-thiomorpholinopropan-2-one hydrochloride (**7b**)

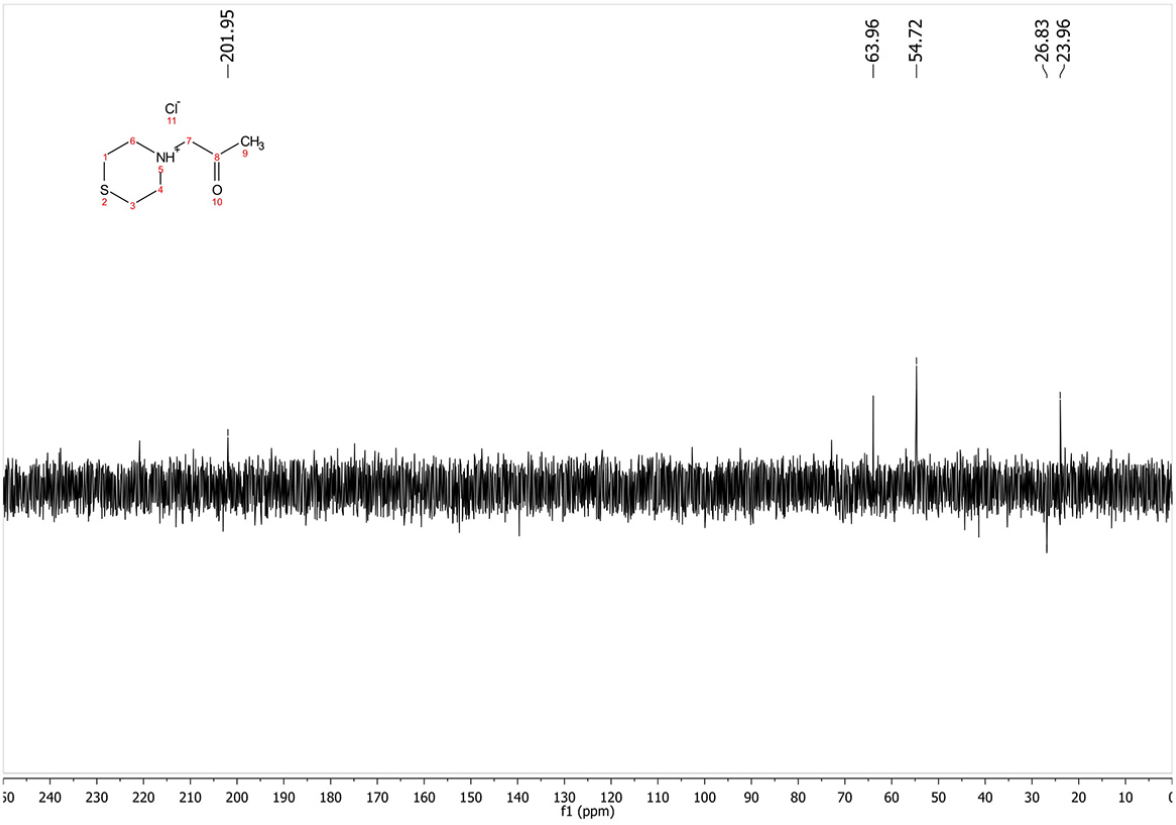


Fig. S24 [13]C NMR of 1-thiomorpholinopropan-2-one hydrochloride (**7b**)

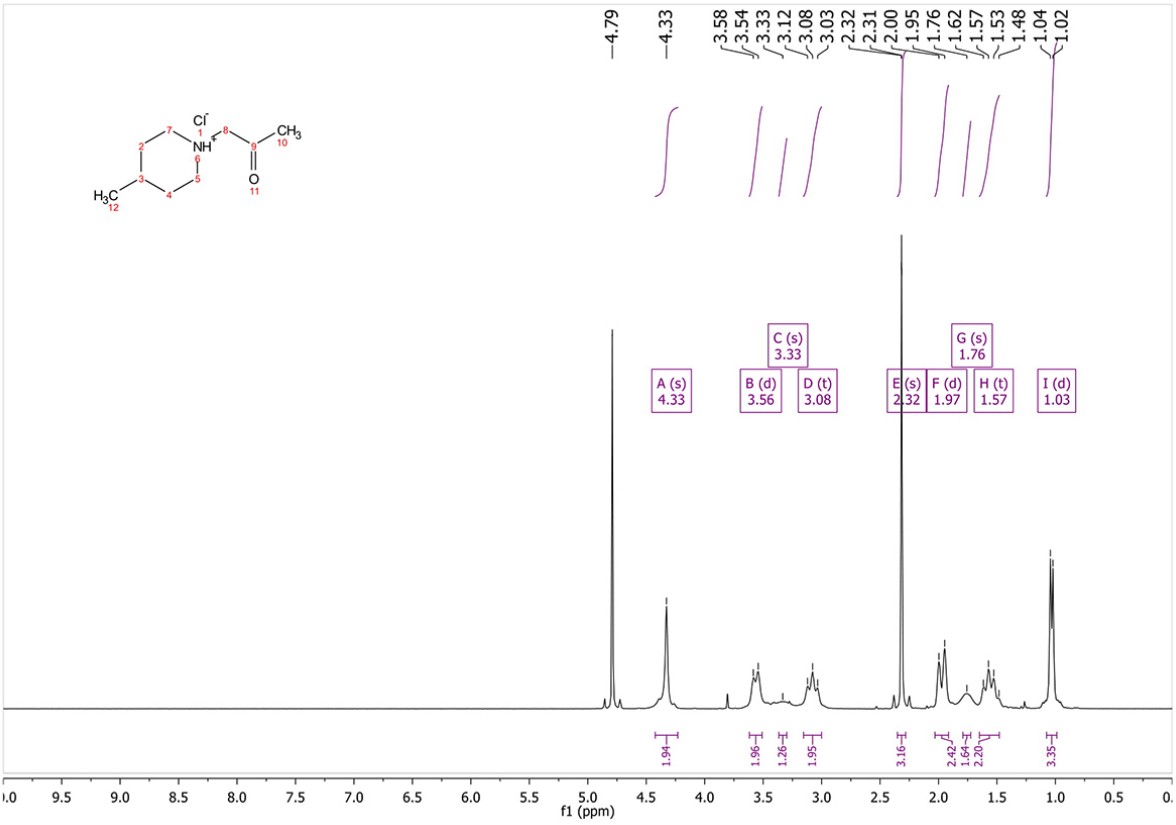


Fig. S25 [1]H NMR of 1-(4-methylpiperidin-1-yl)propan-2-one hydrochloride (**7c**)

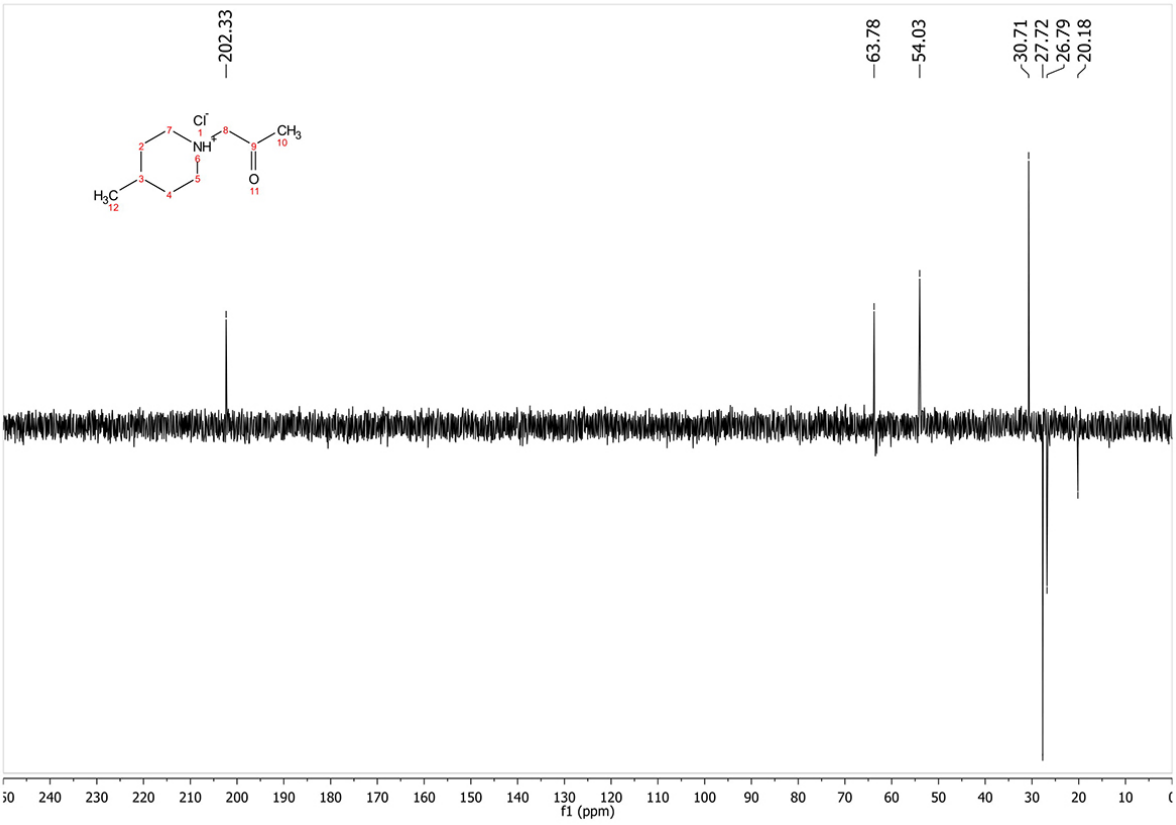


Fig. S26 [13]C NMR of 1-(4-methylpiperidin-1-yl)propan-2-one hydrochloride (**7c**)

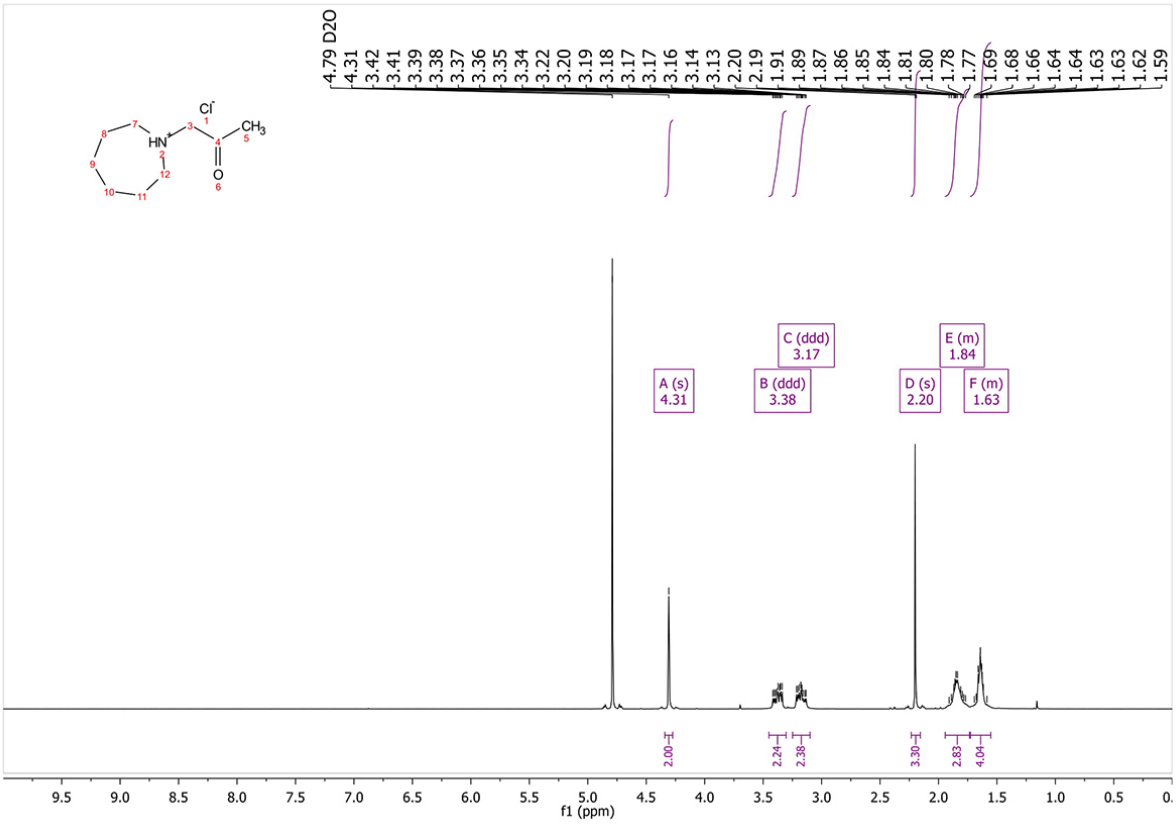


Fig. S27 ^{1}H NMR of 1-(azepan-1-yl)propan-2-one hydrochloride (**7g**)

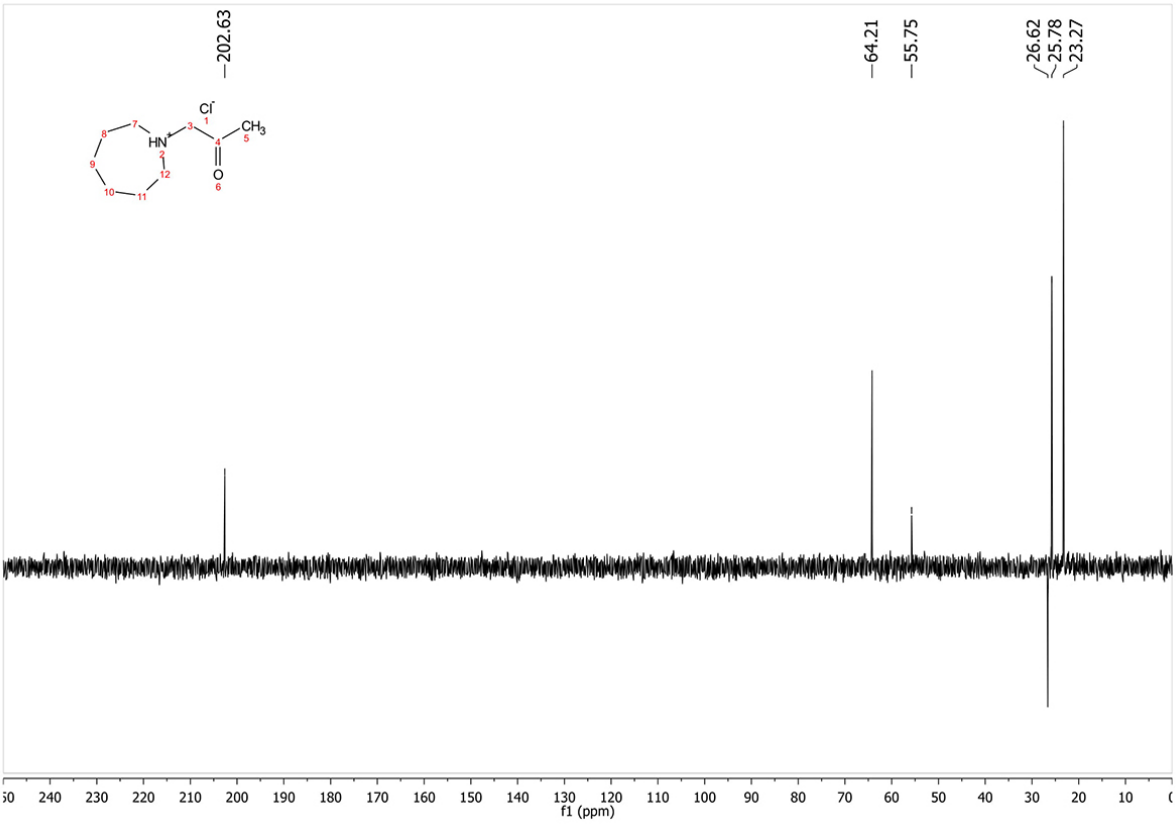


Fig. S28 ^{13}C NMR of 1-(azepan-1-yl)propan-2-one hydrochloride (**7g**)

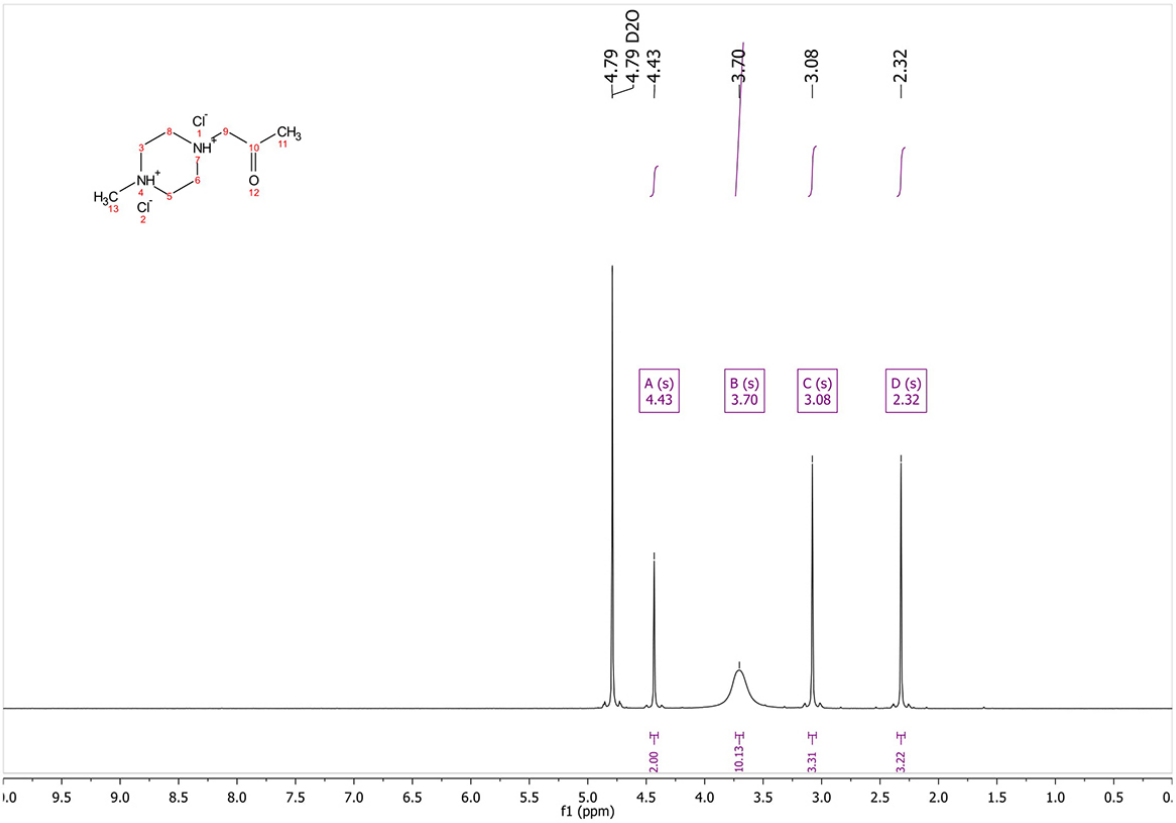


Fig. S29 [1]H NMR of 1-(4-methylpiperazin-1-yl)propan-2-one hydrochloride (**7h**)

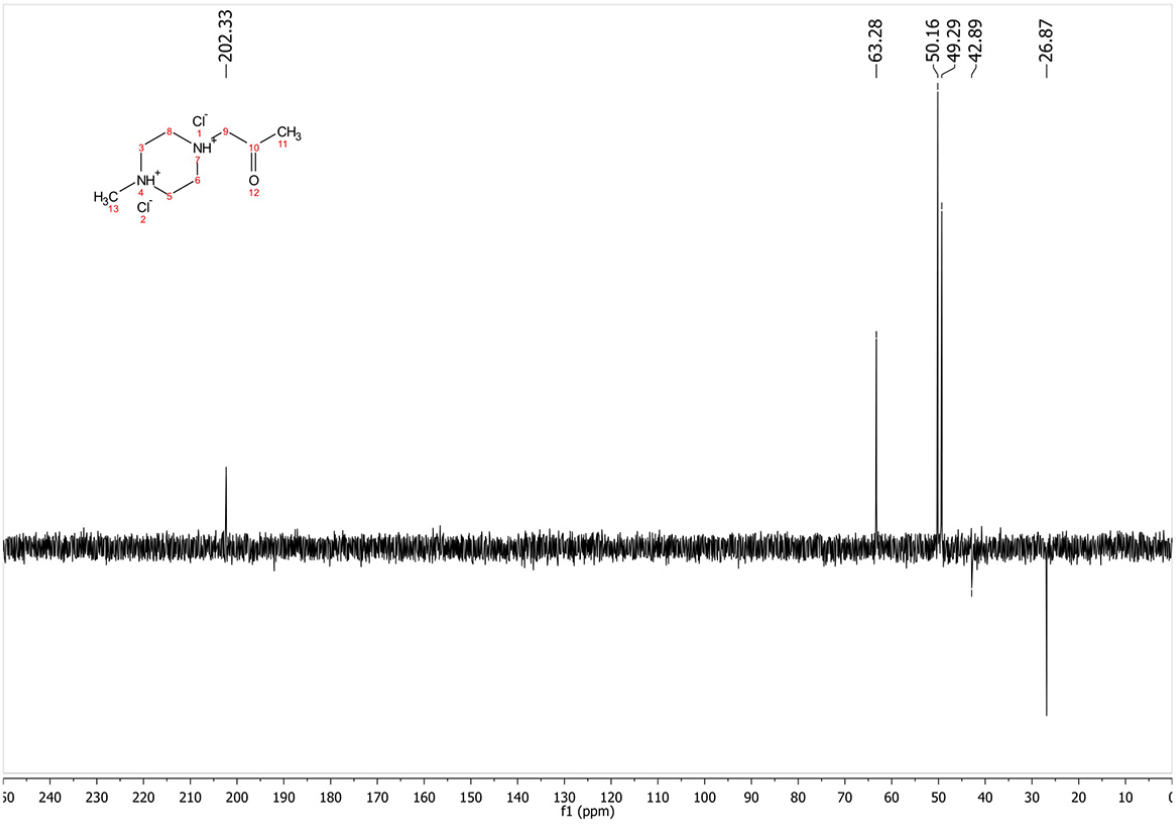


Fig. S30 [13]C NMR of 1-(4-methylpiperazin-1-yl)propan-2-one hydrochloride (**7h**)

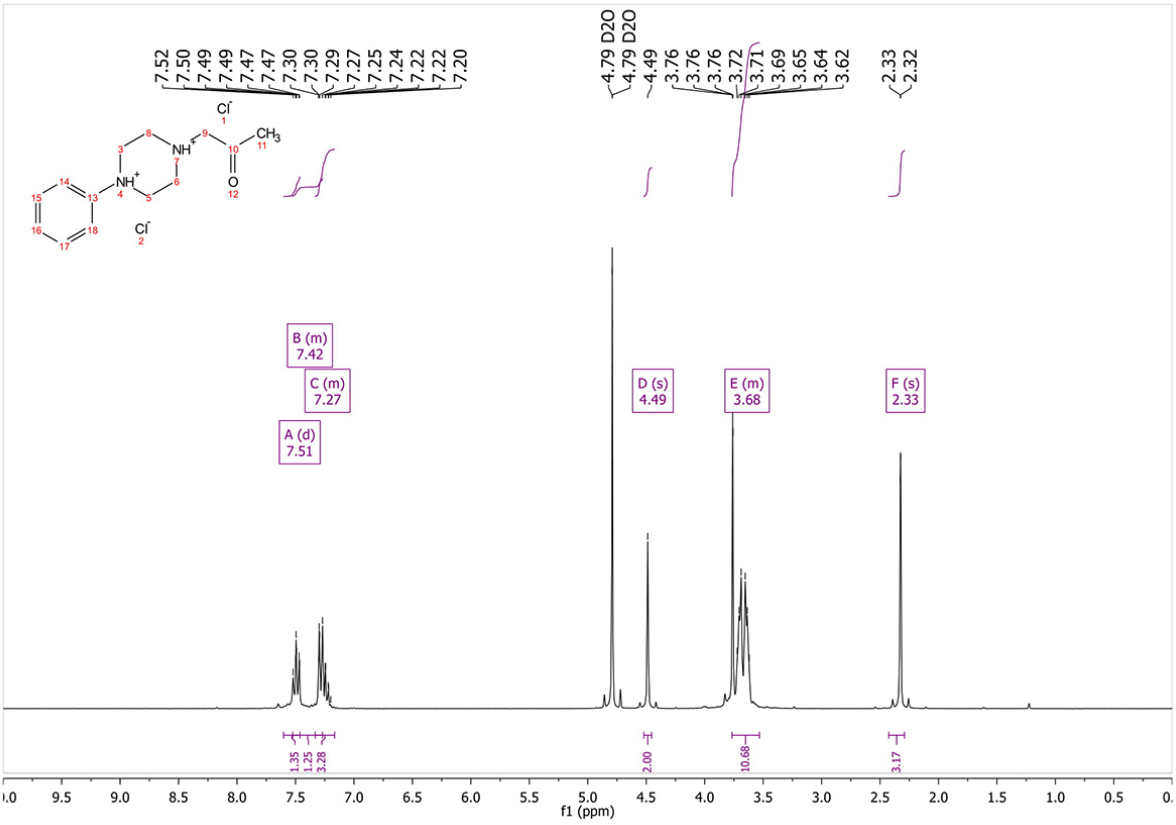


Fig. S31 [1]H NMR of 1-(4-phenylpiperazin-1-yl)propan-2-one hydrochloride (**7i**)

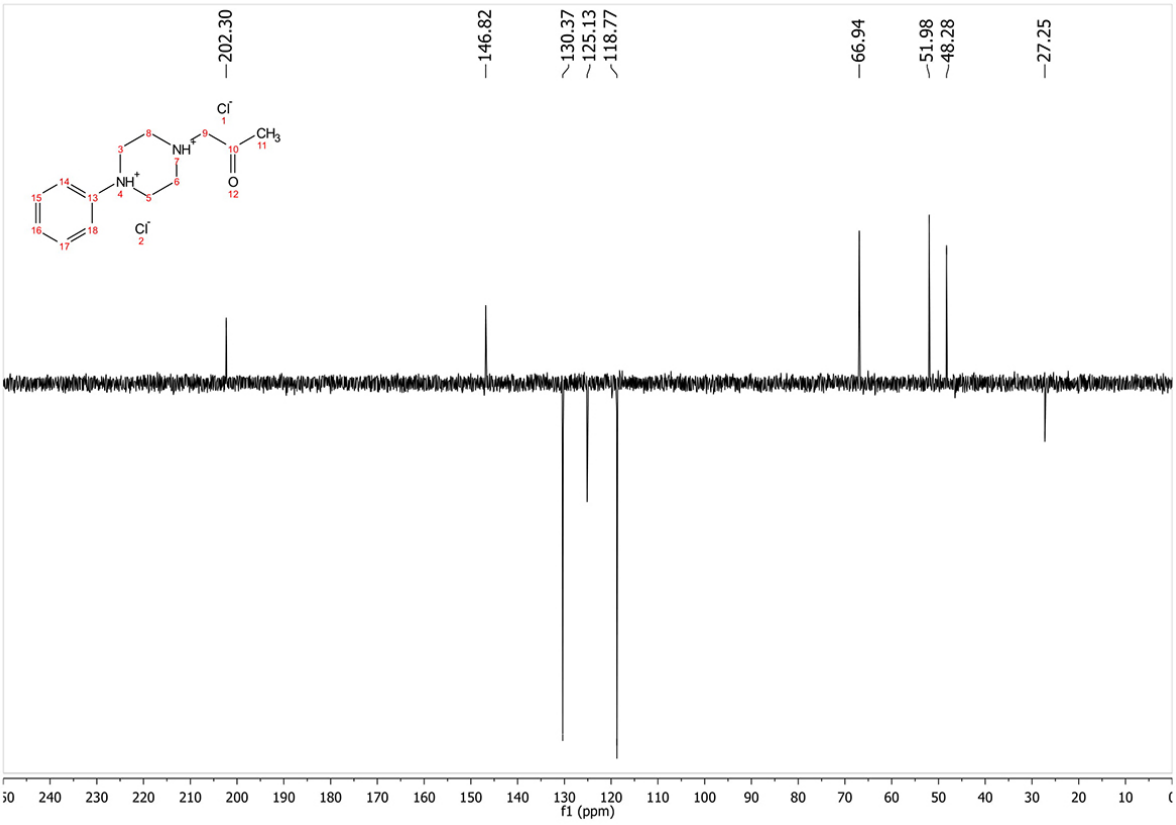


Fig. S32 [13]C NMR of 1-(4-phenylpiperazin-1-yl)propan-2-one hydrochloride (**7i**)

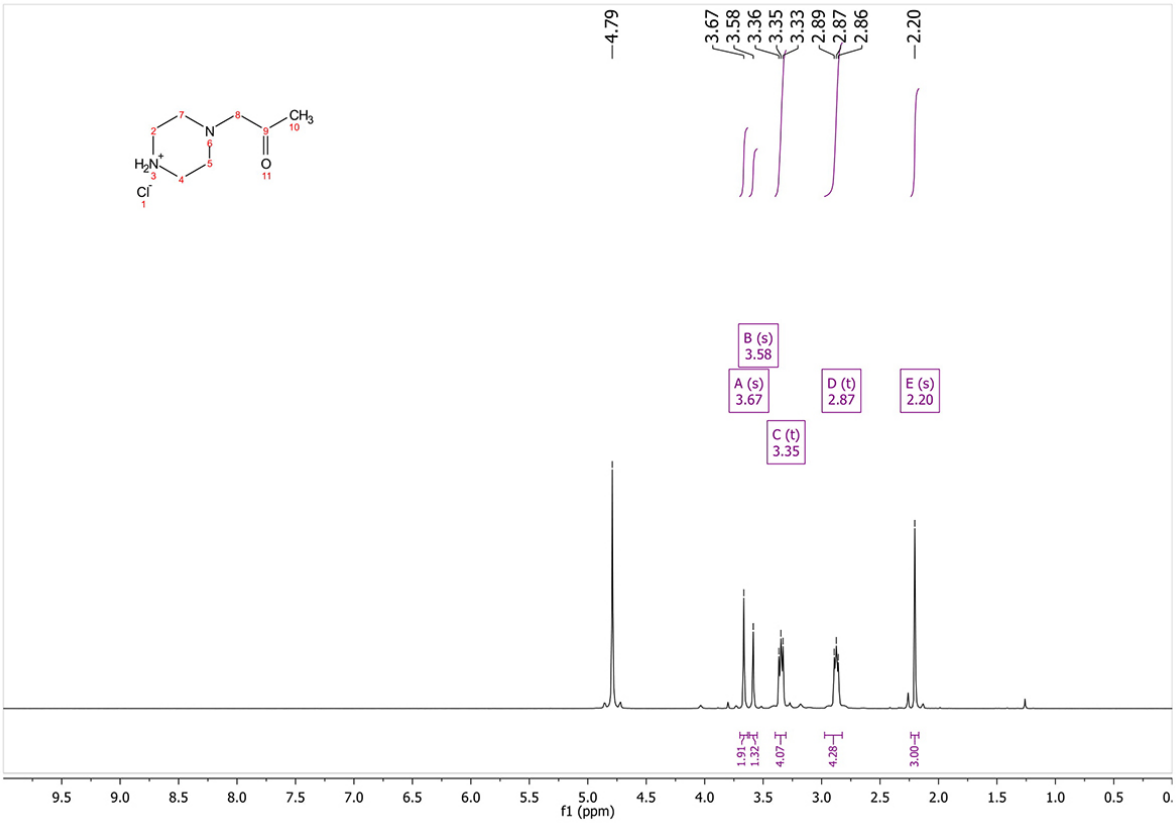


Fig. S33 [1]H NMR of 4-(2-oxopropyl)piperazin-1-ium hydrochloride (**7j**)

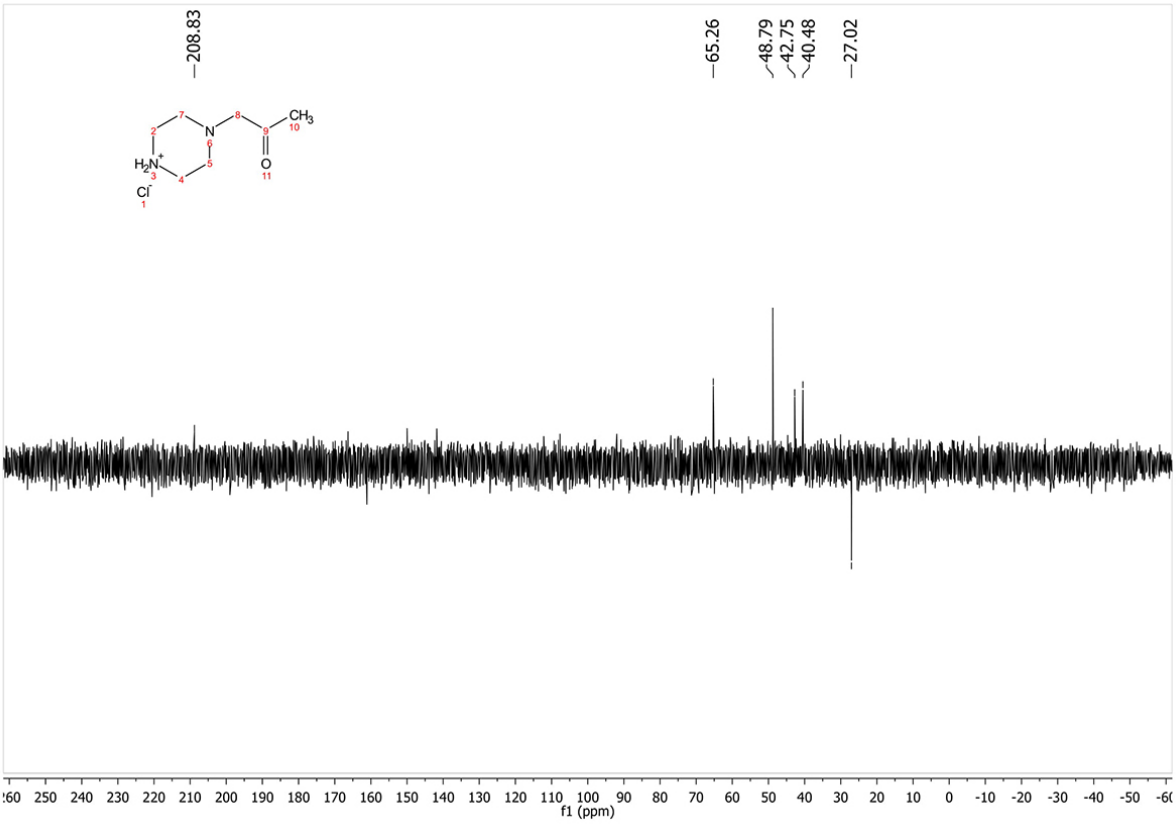


Fig. S34 [13]C NMR of 4-(2-oxopropyl)piperazin-1-ium hydrochloride (**7j**)

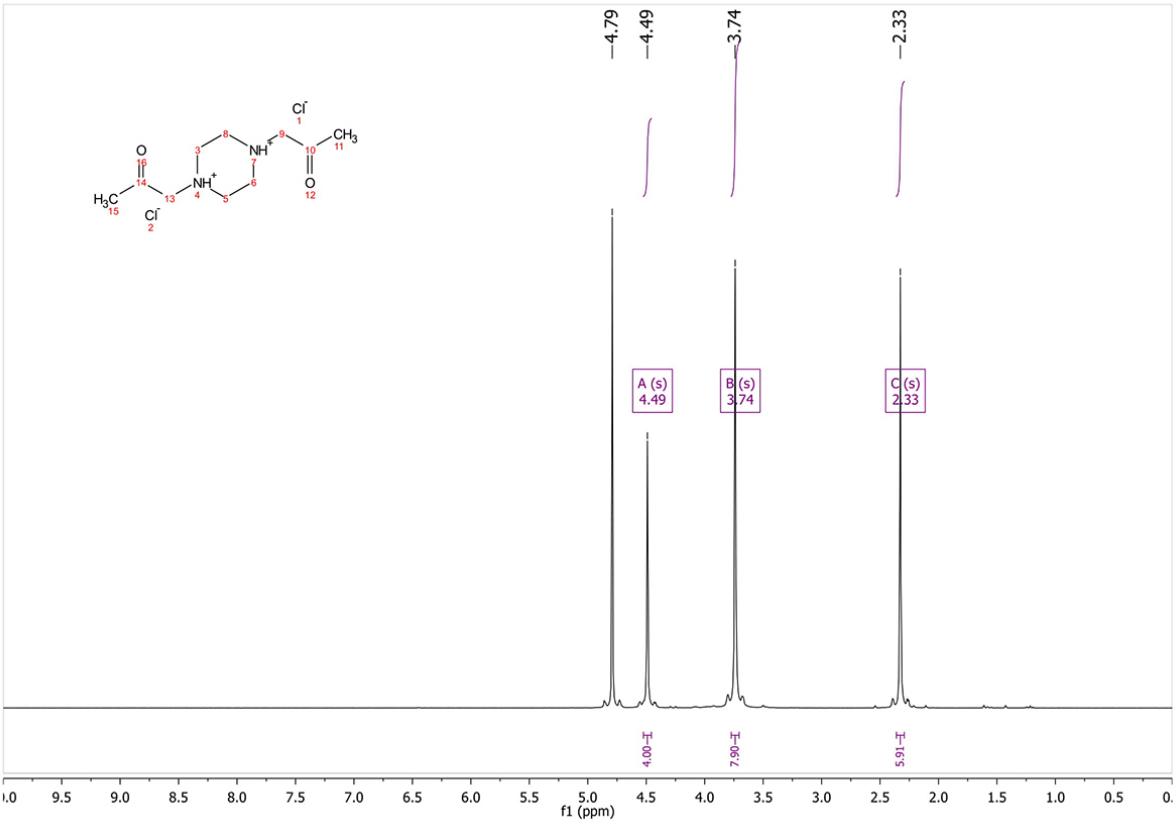


Fig. S35 [1]H NMR of 1,1'-(piperazine-1,4-diyl)bis(propan-2-one) hydrochloride (**7k**)

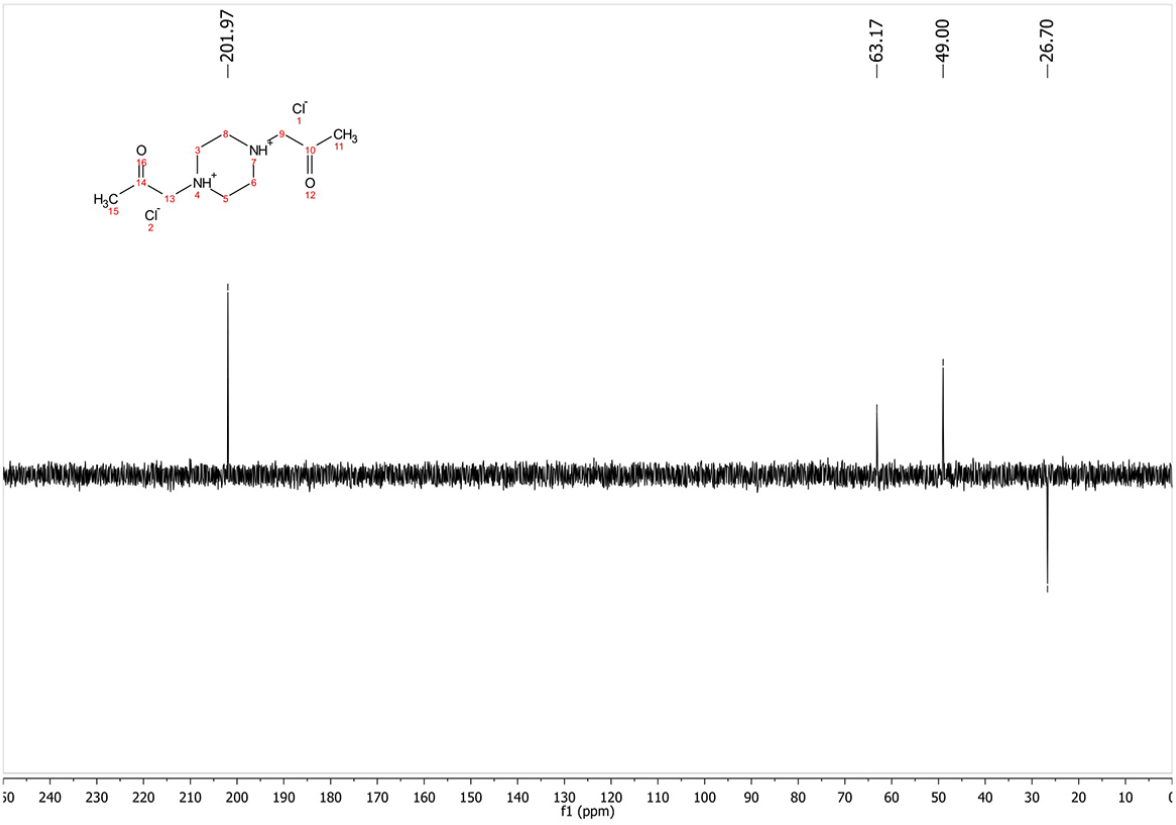


Fig. S36 [13]C NMR of 1,1'-(piperazine-1,4-diyl)bis(propan-2-one) hydrochloride (**7k**)

Yellow oil. **TLC** (R_f) 0.69 (DCM:MeOH 9:1+0.1 % NH_4OH); **^{1}H NMR** (δ, 300 MHz, *DMSO*-d_6) 3.61 – 3.52 (m, 4H), 3.16 (s, 2H), 2.43 – 2.33 (m, 4H), 2.07 (s, 3H); **^{13}C NMR** (75 MHz, *DMSO*-d_6) δ 207.08, 68.10, 66.57, 53.56, 28.01; **IR** (cm^{-1}): 3441, 2965, 2920, 2858, 2816, 1722, 1714, 1651, 1456, 1356, 1298, 1244, 1152, 1115, 1070, 1015, 869; **HRMS** (*ESI*+) [*M*+*H*] $C_7H_{14}NO_2$ calcd. 144.1025, found: 144.1027 (Scheme S9).

Yellow oil. **TLC** (R_f) 0.78 (DCM:MeOH 9:1+0.1 % NH_4OH); **^{1}H NMR** (δ, 300 MHz, *DMSO*-d_6) 3.19 (s, 2H), 2.73 – 2.54 (m, 8H), 2.05 (s, 3H); **^{13}C NMR** (δ, 75 MHz, *DMSO*-d_6) 207.18, 68.00, 54.38, 27.51, 27.15; **IR** (cm^{-1}): 3417, 2913, 2810, 1726, 1714, 1645, 1454, 1418, 1387, 1290, 1227, 1179, 1138, 1015, 959; **HRMS** (*ESI*+) [*M*+*H*] $C_7H_{14}NOS$ calcd. 160.0796, found: 160.0799 (Scheme S10).

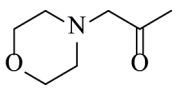
Yellow oil. **TLC** (R_f) 0.74 (DCM:MeOH 9:1+0.1 % NH_4OH); **^{1}H NMR** (δ, 300 MHz, *DMSO*-d_6) 3.07 (s, 2H), 2.77 – 2.65 (m, 2H), 2.06 (s, 3H), 1.94 (td, J = 11.4, 2.4 Hz, 2H), 1.61 – 1.47 (m, 2H), 1.39 – 1.04 (m, 3H), 0.87 (d, J = 6.3 Hz, 3H); **^{13}C NMR** (δ, 75 MHz, *DMSO*-d_6) 207.29, 68.16, 53.46, 33.87, 29.84, 27.31, 21.74; **IR** (cm^{-1}): 2924, 2805, 1728, 1715, 1645, 1454, 1391, 1354, 1283, 1234, 1159, 1134, 980; **HRMS** (*ESI*+) [*M*+*H*] $C_9H_{17}NO$ calcd. 156.1388, found: 156.1384 (Scheme S11).

Yellow oil. **TLC** (R_f) 0.72 (DCM:MeOH 9:1+0.1 % NH_4OH); **^{1}H NMR** (δ, 300 MHz, *DMSO*-d_6) 7.33 – 7.20 (m, 2H), 7.16 (tt, J = 7.7, 1.4 Hz, 3H), 3.07 (s, 2H), 2.72 (dt, J = 12.2, 3.2 Hz, 2H), 2.53 – 2.42 (m, 2H), 2.06 (s, 3H), 1.92 (td, J = 11.6, 2.3 Hz, 2H), 1.63 – 1.35 (m, 3H), 1.23 (ddd, J = 13.3, 11.3, 3.8 Hz, 2H); **^{13}C NMR** (δ, 75 MHz, *DMSO*-d_6) 207.80, 140.77, 129.42, 128.56, 126.17, 66.67, 53.87, 42.80, 37.37, 32.11, 27.86; **IR** (cm^{-1}): 3026, 2918, 2847, 2805, 1728, 1713, 1603, 1495, 1389, 1354, 1275, 1231, 1142, 1111, 1078, 974, 781, 746, 700; **HRMS** (*ESI*+) [*M*+*H*] $C_{15}H_{22}NO$ calcd. 232.1701, found: 232.1730 (Scheme S12).

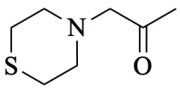
Orange oil. **TLC** (R_f) 0.67 (DCM:MeOH 9:1+0.1 % NH_4OH); **^{1}H NMR** (δ, 300 MHz, *DMSO*-d_6) 4.06 (q, J = 7.1 Hz, 2H), 3.11 (s, 2H), 2.81 – 2.64 (m, 2H), 2.34 – 2.17 (m, 1H), 2.14 – 1.99 (m, 2H), 2.06 (s, 3H), 1.85 – 1.68 (m, 2H), 1.67 – 1.46 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (δ, 75 MHz, *DMSO*-d_6) 207.59, 174.74, 68.29, 60.22, 52.82, 40.32, 28.39, 27.87, 14.53; **IR** (cm^{-1}): 2943, 2806, 1732, 1715, 1645, 1447, 1393, 1356, 1287, 1260, 1182, 1115, 1049, 1028, 868; **HRMS** (*ESI*+) [*M*+*H*] $C_{11}H_{20}NO_3$ calcd. 214.1443, found: 214.1462 (Scheme S13).

Brown oil. **TLC** (R_f) 0.58 (DCM:MeOH 9:1+0.1 % NH_4OH); **^{1}H NMR** (δ, 300 MHz, *DMSO*-d_6) 3.29 (s, 2H), 2.47 (t, J = 2.6 Hz, 4H), 2.07 (s, 3H), 1.72 – 1.63 (m, 4H); **^{13}C NMR** (δ, 75 MHz, *DMSO*-d_6) 206.82, 65.44, 53.55, 27.53, 23.36; **IR** (cm^{-1}): 3478, 2967, 2803, 1722, 1715, 1651, 1607, 1549, 1524, 1504, 1462, 1352, 1150; **HRMS** (*ESI*+) [*M*+*H*] $C_7H_{14}NO$ calcd. 128.1075, found: 128.1080 (Scheme S14).

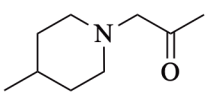
Orange oil. **TLC** (R_f) 0.80 (DCM:MeOH 9:1+0.1 % NH_4OH); **^{1}H NMR** (δ, 300 MHz, *DMSO*-d_6) 3.29 (s, 2H), 2.59 (t, J = 5.2 Hz, 4H), 2.05 (s, 3H), 1.63 – 1.49 (m, 8H); **^{13}C NMR** (δ, 75 MHz, *DMSO*-d_6) 208.31, 67.96, 55.11, 28.20, 27.30, 26.65; **IR** (cm^{-1}): 2926, 2853, 1721, 1713, 1672, 1454, 1352, 1238, 1180, 1138, 1092, 964; **HRMS** (*ESI*+) [*M*+*H*] $C_9H_{18}NO$ calcd. 156.1388, found: 156.1408 (Scheme S15).



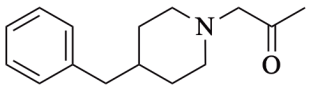
Scheme S9 1-morpholinopropan-2-one (**6a**)



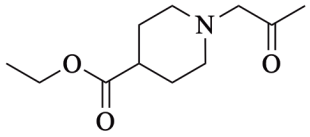
Scheme S10 1-thiomorpholinopropan-2-one (**6b**)



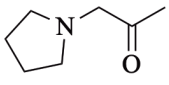
Scheme S11 1-(4-methylpiperidin-1-yl)propan-2-one (**6c**)



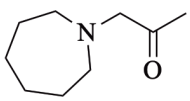
Scheme S12 1-(4-benzylpiperidin-1-yl)propan-2-one (**6d**)



Scheme S13 1-(2-oxopropyl)piperidine-4-carboxylate (**6e**)



Scheme S14 1-(pyrrolidin-1-yl)propan-2-one (**6f**)



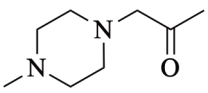
Scheme S15 1-(azepan-1-yl)propan-2-one (**6g**)

Orange oil. **TLC** (R_f) 0.56 (DCM:MeOH 9:1+0.1 % NH_4OH); **^{1}H NMR** (δ, 300 MHz, *DMSO-d_6*) 3.12 (s, 2H), 2.43 – 2.28 (m, 8H), 2.15 (s, 3H), 2.06 (s, 3H); **^{13}C NMR** (δ, 75 MHz, *DMSO-d_6*) 207.39, 67.96, 55.03, 53.06, 46.15, 27.94; **IR** (cm^{-1}): 3374, 2945, 2812, 1722, 1715, 1651, 1462, 1456, 1377, 1356, 1296, 1287, 1167, 1152, 1011; **HRMS** (*ESI+*) [*M+H*] $C_8H_{17}N_2O$ calcd. 157.1341, found: 157.1341 (Scheme S16).

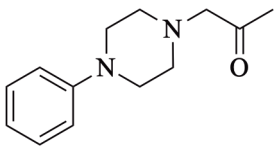
Orange oil. **TLC** (R_f) 0.76 (DCM:MeOH 9:1+0.1 % NH_4OH); **^{1}H NMR** (δ, 300 MHz, *DMSO-d_6*) 7.27 – 7.14 (m, 2H), 6.98 – 6.86 (m, 2H), 6.77 (tt, *J* = 7.3, 1.1 Hz, 1H), 3.22 (s, 2H), 3.18 – 3.09 (m, 4H), 2.60 – 2.52 (m, 4H), 2.10 (s, 3H); **^{13}C NMR** (δ, 75 MHz, *DMSO-d_6*) 206.62, 150.96, 128.85, 118.76, 115.34, 67.32, 52.64, 48.13, 27.57; **IR** (cm^{-1}): 3421, 3024, 2940, 2909, 2818, 1728, 1713, 1599, 1504, 1454, 1385, 1352, 1234, 1146, 1015, 926, 760, 692; **HRMS** (*ESI+*) [*M+H*] $C_{13}H_{19}N_2O$ calcd. 219.1497, found: 219.1564 (Scheme S17).

Yellow oil. **TLC** (R_f) 0.62 (DCM:MeOH 9:1+0.1 % NH_4OH); **^{1}H NMR** (δ, 300 MHz, *DMSO-d_6*) 3.17 (s, 4H), 2.43 (s, 8H), 2.06 (s, 6H); **^{13}C NMR** (δ, 75 MHz, *DMSO-d_6*) 206.71, 67.29, 52.51, 27.59; **IR** (cm^{-1}): 3418, 2938, 2816, 1722, 1715, 1697, 1651, 1462, 1427, 1385, 1360, 1296, 1238, 1161, 1016, 978, 825; **HRMS** (*ESI+*) [*M+H*] $C_{10}H_{19}N_2O_2$ calcd. 199.1447, found: 199.1470 (Scheme S18).

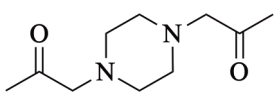
Faint-yellow solid. **Mp**: 191 °C; **^{1}H NMR** (δ, 300 MHz, *Deuterium Oxide*) 4.44 (s, 2H), 4.06 (br, 4H), 3.46 (br, 4H), 2.33 (s, 3H); **^{13}C NMR** (δ, 75 MHz, *Deuterium Oxide*) 201.86, 63.56, 63.32, 52.32, 26.74; **IR** (cm^{-1}): 3418, 2923, 2640, 1728, 1630, 1449, 1400, 1360, 1270, 1128, 1037, 879; **HRMS** (*ESI+*) [*M+H*] $C_7H_{14}NO_2$ calcd. 144.1025, found: 144.1017 (Scheme S19).



Scheme S16 1-(4-methylpiperazin-1-yl)propan-2-one (**6h**)



Scheme S17 1-(4-phenylpiperazin-1-yl)propan-2-one (**6i**)

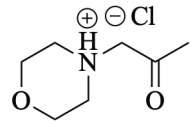


Scheme S18 1,1'-(piperazine-1,4-diyl)bis(propan-2-one) (**6k**)

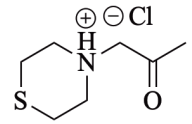
White solid. **Mp**: 185 °C; **^{1}H NMR** (δ, 300 MHz, *Deuterium Oxide*) 4.30 (s, 2H), 3.49 (s, 4H), 2.96 (s, 4H), 2.22 (s, 3H); **^{13}C NMR** (δ, 75 MHz, *Deuterium Oxide*) 201.95, 63.96, 54.72, 26.83, 23.96; **IR** (cm^{-1}): 3428, 2946, 2848, 2645, 2539, 1725, 1395, 1340, 1188, 933, 625; **HRMS** (*ESI+*) [*M+H*] $C_7H_{14}NOS$ calcd. 160.0796, found: 160.0785 (Scheme S20).

White solid. **Mp**: 167 °C; **^{1}H NMR** (δ, 300 MHz, *Deuterium Oxide*) 4.33 (s, 2H), 3.56 (d, *J* = 12.5 Hz, 2H), 3.33 (br, 1H), 3.08 (t, *J* = 13.1 Hz, 2H), 2.32 (s, 3H), 1.97 (d, *J* = 14.8 Hz, 2H), 1.76 (br, 1H), 1.57 (t, *J* = 13.3 Hz, 2H), 1.03 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (δ, 75 MHz, *Deuterium Oxide*) 202.33, 63.78, 54.03, 30.71, 27.72, 26.79, 20.18; **IR** (cm^{-1}): 3446, 2957, 2663, 1729, 1639, 1456, 1394, 1365, 1188, 1064, 952; **HRMS** (*ESI+*) [*M+H*] $C_9H_{17}NO$ calcd. 156.1388, found: 156.1384 (Scheme S21).

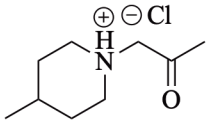
Yellow solid. **Mp**: 137 °C; **^{1}H NMR** (δ, 300 MHz, *Deuterium Oxide*) 4.31 (s, 2H), 3.38 (ddd, *J* = 13.5, 6.8, 3.7 Hz, 2H), 3.17 (ddd, *J* = 13.5, 7.7, 3.7 Hz, 2H), 2.20 (s, 3H), 1.94 – 1.73 (m, 4H), 1.73 – 1.55 (m, 4H); **^{13}C NMR** (δ, 75 MHz, *Deuterium Oxide*) 202.63, 64.21, 55.75, 26.62, 25.78, 23.27; **IR** (cm^{-1}): 3420, 2940, 2600, 1737, 1631, 1473, 1362, 1344, 1173, 1064, 1013; **HRMS** (*ESI+*) [*M+H*] $C_9H_{18}NO$ calcd. 156.1388, found: 156.1384 (Scheme S22).



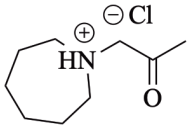
Scheme S19 1-morpholinopropan-2-one hydrochloride (**7a**)



Scheme S20 1-thiomorpholinopropan-2-one hydrochloride (**7b**)



Scheme S21 1-(4-methylpiperidin-1-yl)propan-2-one hydrochloride (**7c**)



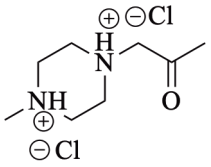
Scheme S22 1-(azepan-1-yl)propan-2-one hydrochloride (**7g**)

Faint-yellow solid. **Mp**: 197 °C; **^{1}H NMR** (δ, 300 MHz, *Deuterium Oxide*) 4.43 (s, 2H), 3.70 (br, 10H), 3.08 (s, 3H), 2.32 (s, 3H); **^{13}C NMR** (δ, 75 MHz, *Deuterium Oxide*) 202.33, 63.28, 50.16, 49.29, 42.89, 26.87; **IR** (cm^{-1}): 3446, 2992, 2806, 2694, 2610, 2430, 1731, 1635, 1474, 1436, 1410, 1371, 1336, 1288, 1188, 1034, 985, 656, 591; **HRMS** (*ESI*+) [*M*+*H*] $C_8H_{17}N_2O$ calcd. 157.1341, found: 157.1328 (Scheme S23).

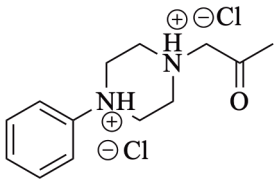
Faint-yellow solid. **Mp**: 198 °C; **^{1}H NMR** (δ, 300 MHz, *Deuterium Oxide*) 7.51 (d, J = 7.7 Hz, 1H), 7.52 – 7.27 (m, 1H), 7.33 – 7.17 (m, 3H), 4.49 (s, 2H), 3.77 – 3.53 (m, 11H), 2.33 (s, 3H); **^{13}C NMR** (δ, 75 MHz, *Deuterium Oxide*) 202.30, 146.82, 130.37, 125.13, 118.77, 66.94, 51.98, 48.28, 27.25; **IR** (cm^{-1}): 3429, 3015, 2966, 2849, 2360, 2332, 1733, 1597, 1495, 1446, 1231, 1364, 1271, 1186, 762, 695, 540; **HRMS** (*ESI*+) [*M*+*H*] $C_{13}H_{19}N_2O$ calcd. 219.1497, found: 219.1497 (Scheme S24).

Faint-yellow solid. **Mp**: 116 °C; **^{1}H NMR** (δ, 300 MHz, *Deuterium Oxide*) 3.67 (s, 2H), 3.35 (t, J = 5.3 Hz, 4H), 2.87 (t, J = 5.3 Hz, 4H), 2.20 (s, 3H); **^{13}C NMR** (δ, 75 MHz, *Deuterium Oxide*) 208.83, 65.26, 48.79, 42.75, 27.02; **HRMS** (*ESI*+) [*M*+*H*] $C_7H_{15}N_2O$ calcd. 143.1184, found: 143.1167 (Scheme S25).

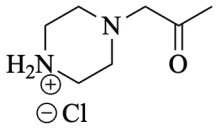
Faint-yellow solid. **Mp**: 232 °C; **^{1}H NMR** (δ, 300 MHz, *Deuterium Oxide*) 4.49 (s, 4H), 3.74 (s, 8H), 2.33 (s, 6H); **^{13}C NMR** (δ, 75 MHz, *Deuterium Oxide*) 201.97, 63.17, 49.00, 26.70; **IR** (cm^{-1}): 3444, 3026, 2917, 2394, 1732, 1490, 1458, 1436, 1367, 1345, 1184, 1110, 1006, 545; **HRMS** (*ESI*+) [*M*+*H*] $C_{10}H_{19}N_2O_2$ calcd. 199.1447, found: 199.1426 (Scheme S26).



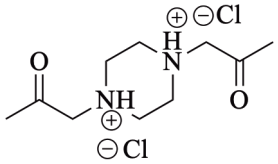
Scheme S23 1-(4-methylpiperazin-1-yl)propan-2-one hydrochloride (**7h**)



Scheme S24 1-(4-phenylpiperazin-1-yl)propan-2-one hydrochloride (**7i**)



Scheme S25 4-(2-oxopropyl)piperazin-1-ium hydrochloride (**7j**)



Scheme S26 1,1'-(piperazine-1,4-diyl)bis(propan-2-one) hydrochloride (**7k**)