Supporting Information

A straightforward approach to long forgotten acetophenone-derived bis-Mannich bases: synthesis, mechanistic studies, pharmacophore potential and unique trapping of N-nucleophiles

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1. General Information

General. Unless otherwise noted, all reactions were carried out in a flame-dried Schlenk tube under an atmosphere of argon. Analytical thin-layer chromatography was performed on aluminium plates coated with 0.20 mm silica gel 60 with fluorescent indicator UV_{254} (MACHEREY-NAGEL). Visualization was accomplished by exposure to a UV lamp, and/or treatment with a solution of $KMnO_4$, a solution of vanillin or a solution of ninhydrin followed by brief heating with a heatgun. Column chromatography was performed on silica gel 60N (0.063-0.2 mm, MACHEREY-NAGEL) using standard methods.

Structural analysis. NMR spectra were measured on an Agilent DD2 NMR 400 spectrometer and chemical shifts (δ) are reported in parts per million (ppm). ^{1}H NMR spectra were recorded at 400 MHz in NMR solvents ($CDCl_3$) and referenced internally to corresponding solvent resonance, and ^{13}C NMR spectra were recorded at 101 MHz, chemical shifts were reported in ppm on the δ scale relative to $CHCl_3$ (δ = 7.26 for ^{1}H NMR, δ = 77.16 for ^{13}C NMR). Coupling constants are reported in Hz with multiplicities denoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Mass spectra were recorded using: the EI method on a GCMS - QP 2010 plus (Shimadzu); the ESI method on a LCMS-8050 (Shimadzu), the MALDI method on a time-of-flight Bruker Microflex LT mass-spectrometer, α-Cyano-4-hydroxycinnamic acid (α-CHCA) matrix. Elemental analysis was performed using an Elementar (vario MICRO cube) apparatus. X-ray diffraction data were collected on a Bruker APEX II diffractometer (λ(MoKα) = 0.71073 Å, 2θ<58.43°).

Materials. Commercial reagents were purchased from J&K, Sigma-Aldrich, Merck, Alfa Aesar, Acros Organics and used as received unless otherwise stated. THF, toluene and dioxane were purified by distillation over sodium/benzophenone and stored under argon. DMF were purchased from J&K and used directly without further purification. Zinc chloride (Sigma-Aldrich, anhydrous grade) was dried according to a known procedure[1].

2.1 Starting Material Synthesis

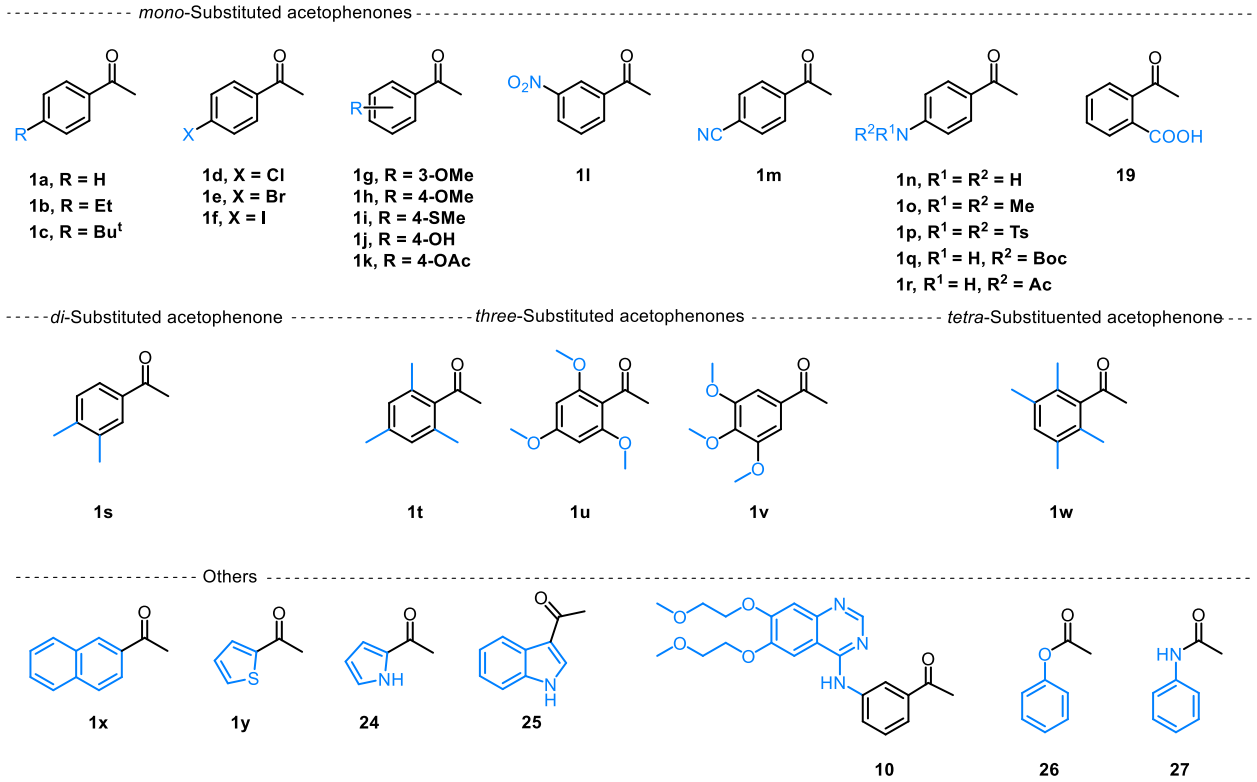
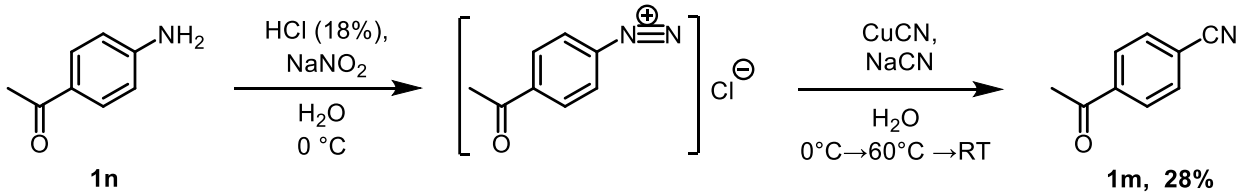


Figure S1. Substrates for synthesis of bis-Mannich bases

Compounds **1a, 1e,1g-1h, 1j, 1n, 1v, 1x, 19, 21-23** are commercially available and were used as received. **1b**[2], **1c**[3], **1d**, **1f**[4], **1i**[5], **1l**[6], **1o**[7], **1p**[8], **1q**[9], **1k**, **1r**[10], **1s**[2], **1t**[11], **1u**[12], **1w**[2], **1y**[13], **20**[14] were prepared according to the corresponding literature procedures. **1l** was prepared from **1m** according to the procedure "*Preparation of* **1m***"*. **10** was prepared from **9** according to the procedure "*Preparation of* **10***"*

*Preparation of 4-acetylbenzonitrile **1m***

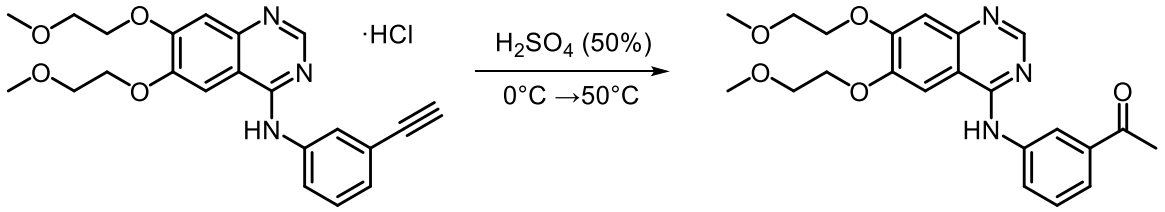


In a Schlenk flask equipped with a a Teflon-coated magnetic stir, 0.1 g (0.7 mmol) of 4`-aminoacetophenone **1n** was dissolved in 0.3 ml of 18% hydrochloric acid under argon atmosphere. The solution was stirred and was cooled to 0 °C in an ice-water bath. Then a solution of 0.05 g (0.7 mmol) of sodium nitrite in 0.11 ml of water was added dropwise to the solution. Then a solution of 0.065 g (0.7 mmol) of copper cyanide in 4.5 M aqueous sodium cyanide solution was added dropwise. The reaction mixture was heated to 60 °C and then was stirred overnight at room temperature. The reaction progress was monitored by TLC. Then the reaction mixture was extracted with MTBE/H_2O. The organic phase was dried over anhydrous Na_2SO_4. The product **1m** was isolated by column chromatography

on silica gel (eluent 25% EA – 75% PE). 0.03 g (28%) of a reddish liquid substance was isolated.

^{1}H NMR (400 MHz, Chloroform-*d*): δ = 8.04 (d, *J* = 8.6 Hz, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 2.64 (s, 2H). The spectroscopic properties were consistent with the data reported in the literature.

*Preparation of 1-(3-((6,7-bis(2-methoxyethoxy)quinazolin-4-yl)amino)phenyl)ethan-1-one **10***



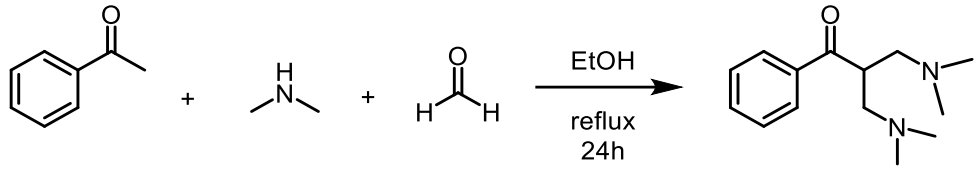
9 **10, quantitative**

Erlotinib hydrochloride (0.2 g, 0.47 mmol) was dissolved in 5 ml of 50% sulfuric acid was cooled to 0 °C in an ice-water bath, then the reaction was stirred at 50°C overnight. After completion, the reaction mixture was slowly added dropwise to 10% sodium hydroxide solution (pH = 10-11), extracted with ethyl acetate. The combined organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to obtain a product as a white solid, 0.191 g (0.47 mmol) with quantitative yield. All analytical data in agreement with literature[15]

^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 9.62 (s, 1H), 8.49 (s, 1H), 8.30 (t, *J* = 1.9 Hz, 1H), 8.22 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.90 (s, 1H), 7.73 (m, 1H), 7.55 (t, *J* = 7.9 Hz, 1H), 7.23 (s, 1H), 4.30 (m, 4H), 3.77 (m, 4H), 3.38 (s, 3H), 3.35 (s, 3H), 2.62 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d$_6$): δ = 197.79, 156.22, 153.69, 152.77, 148.14, 147.01, 139.96, 137.16, 128.79, 126.69, 123.37, 120.99, 108.92, 108.20, 103.23, 70.12, 70.05, 68.40, 68.05, 58.40, 58.34, 26.82.

2.2 Reproduction of reported method for bis-Mannich base 4a synthesis [16]



Into a 25 mL round bottom flask, equipped with a Teflon-coated magnetic stir bar, were added 0.002 mol of acetophenone, 0.006 mol of formaldehyde and 0.01 mol of *N*-methylbenzylamine were heated to boiling in EtOH for 24 h. After 24 h the solvent was distilled off and the reaction was extracted with ether. The crude product without purification was analyzed by GC-MS by using an QP 2010 plus (Shimadzu) equipped with an Rtx-5MS capillary column (length 60 m; inner diameter 0.32 mm). The injector temperature was set at 250°C, the detector temperature was 250 °C and the sample injection volume was 1 µL. Chlorobenzene was used as an internal standard.

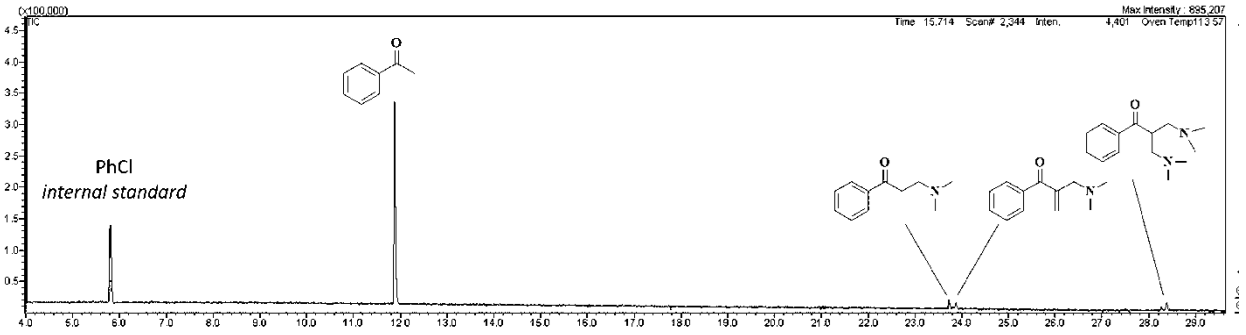


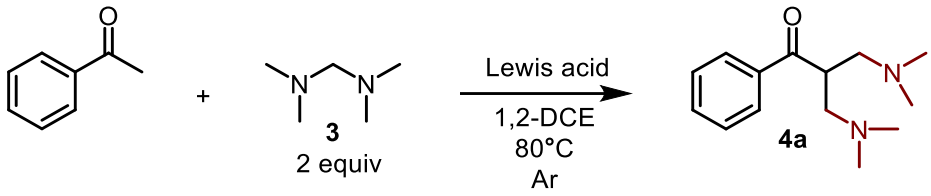
Figure S2. GC-MS chromatogram of the reaction.

2.3 Optimization Studies

All reactions were performed on 0.25 mmol scale. To an oven-dried 10 mL Schlenk tube, equipped with a Teflon-coated magnetic stir bar, and backfilled with argon were added acetophenone **1a** and *N,N,N′,N′*-tetramethylmethanediamine **3**, followed by the solvent and additive. The reaction was heated and stirred at a designated temperature for 24 h, then diluted with $CHCl_3$ and quenched with sat. Na_2CO_3. The obtained phases were separated, and the aqueous phase was extracted with $CHCl_3$ (3 × 15 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated in vacuo to obtain a crude product **4a**.

The results are compiled in Tables S1-S3.

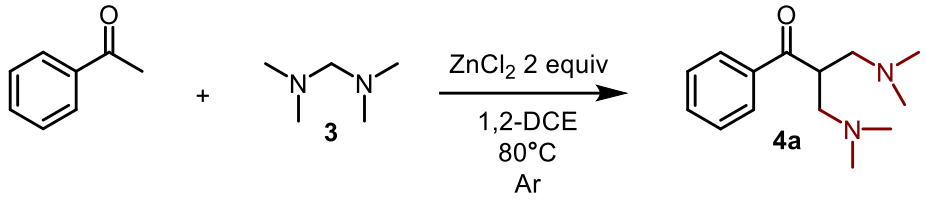
Table S1. Screening of Lewis acid



Entry	Lewis acid	LA equiv.	Yield 4a*, %
1	BF_3•Et_2O	0.1	-
2	BF_3•Et_2O	2	43
3	$Zn(OAc)_2$•$2H_2O$	0.1	39
4	$Zn(OAc)_2$•$2H_2O$	2	67
5	$InCl_3$	0.1	20
6	$InCl_3$	2	32
7	$TiCl_4$	0.1	-
8	$TiCl_4$	2	-
9	$AlCl_3$	0.1	12
10	$AlCl_3$	2	15
11	$FeCl_3$	0.1	12
12	$FeCl_3$	2	32
13	LiBr	0.1	1
14	LiBr	2	10
15	$ZnCl_2$	0.1	11
16	$ZnCl_2$	1	17
17	$ZnCl_2$	2	98[a]

* *Yields were measured by ^1H NMR using CH_2Br_2 as an internal standard*; [a] Isolated yield.

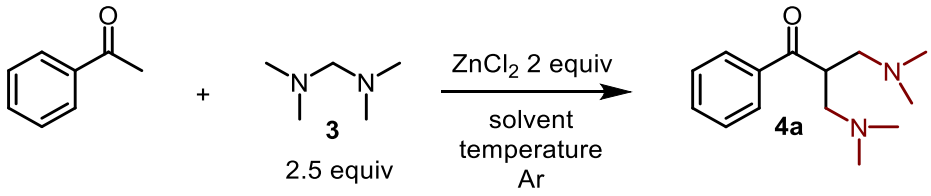
Table S2. Optimization of TMMDA equivalents for bis-Mannich base formation



Entry	TMMDA equiv.	Yield 4a*, %
1	1	3
2	2	91[a]
3	2.5	98[a]

* *Yields were measured by ^{1}H NMR using CH_2Br_2 as an internal standard*; [a] Isolated yield.

Table S3. Effect of reaction temperature on bis-Mannich base formation.



Entry	Solvent	Temperature	Yield 4a*, %
1	$CHCl_3$	rt	50
2	$CHCl_3$	50	87
3	$CHCl_3$	60	92
4	1,2-DCE	60	93
5	1,2-DCE	80	98

* Isolated yield.

2.4 Reaction monitoring by GC

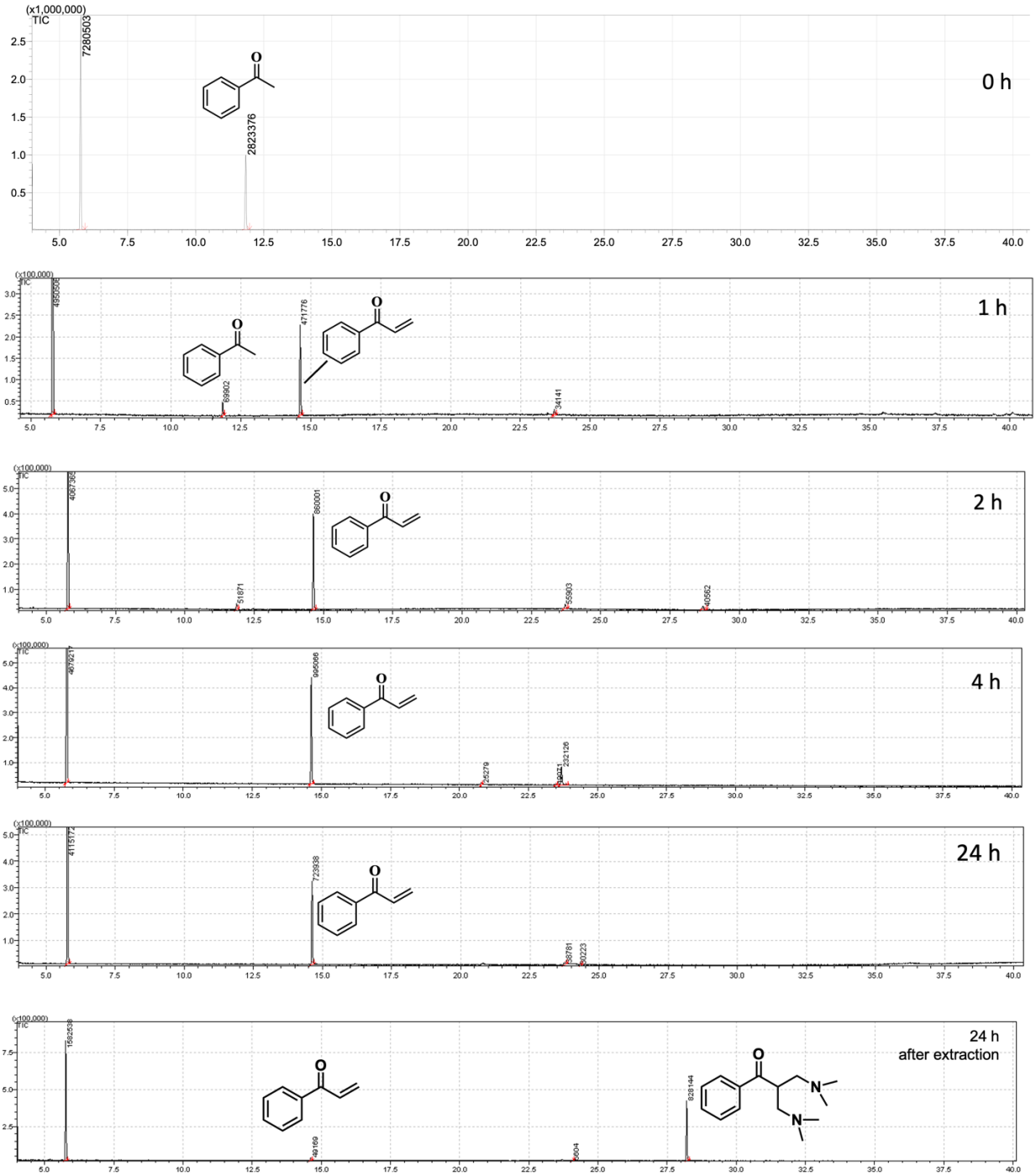
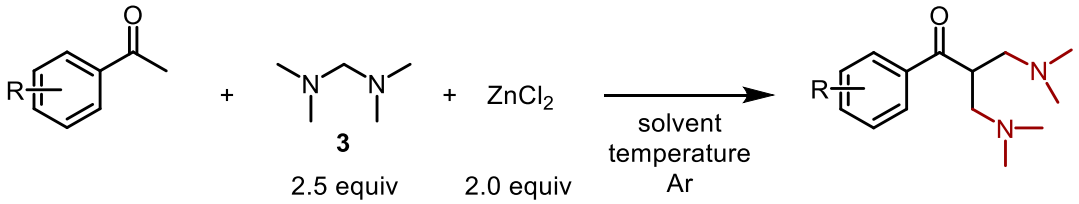


Figure S3. GC-MS chromatogram of the reaction acetophenone with TMMDA (PhCl was used as an internal standard Rt=5.78). The extraction was carried out according to the standard procedure.

2.5 Synthesis of bis-Mannich bases via aminomethylation



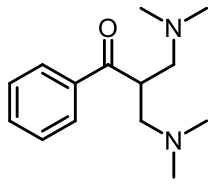
General procedure 1

Into an oven-dried 10 mL Schlenk tube, equipped with a Teflon-coated magnetic stir bar, and backfilled with argon were added acetophenone (0.25 mmol), *N,N,N`,N`*-tetramethylmethylenediamine **3** (0.09 ml, 0.63 mmol) and $ZnCl_2$ (0.068 g, 0.5 mmol) in 2 ml 1,2-dichloroethane. The reaction mixture was stirred for 24 h at 80°C. After completion (TLC control), the reaction was diluted with $CHCl_3$ and quenched with sat. Na_2CO_3. The phases were separated, and the aqueous phase was extracted with $CHCl_3$ (3 × 15 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to obtain a crude product.

General procedure 2

Into an oven-dried 10 mL Schlenk tube, equipped with a Teflon-coated magnetic stir bar, and backfilled with argon were added acetophenone (0.25 mmol), *N,N,N`,N`*-tetramethylmethylenediamine **3** (0.09 ml, 0.63 mmol) and $ZnCl_2$ (0.068 g, 0.5 mmol) in 2 ml chloroform. The reaction mixture was stirred for 24 h at 60°C. After completion (TLC control), the reaction was diluted with $CHCl_3$ and quenched with sat. Na_2CO_3. The phases were separated, and the aqueous phase was extracted with $CHCl_3$ (3 × 15 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to obtain a crude product.

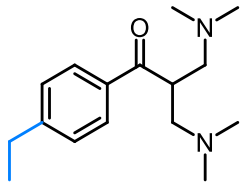
3-(dimethylamino)-2-((dimethylamino)methyl)-1-phenylpropan-1-one 4a:



Prepared according to the *General Procedure 1* in 98% yield as a white amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02-7.98 (m, 2H), 7.58-7.53 (m, 1H), 7.49-7.44 (m, 2H), 3.88 (tt, *J* = 7.9, 5.6 Hz, 1H), 2.69 (dd, *J* = 12.3, 7.9 Hz, 2H), 2.46 (dd, *J* = 12.3, 5.6 Hz, 2H), 2.20 (s, 12H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.03, 137.67, 133.00, 128.72, 128.34, 60.95, 46.07, 43.82.
Elemental analysis: calculated for $C_{14}H_{22}N_2O$: C, 71.76; H, 9.46. Found: C, 71.70; H, 9.52.
ESI-MS: calculated for $C_{14}H_{22}N_2O$ $[M+H]^+$ m/z 235.3; found m/z 235.2

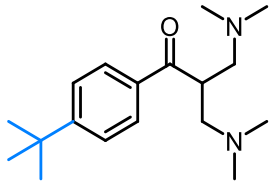
3-(dimethylamino)-2-((dimethylamino)methyl)-1-(4-ethylphenyl)propan-1-one 4b:



Prepared according to the *General Procedure 1* in 80% yield as a yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 3.87 (tt, *J* = 7.8, 5.7 Hz, 1H), 2.67 (m, 4H), 2.46 (dd, *J* = 12.3, 5.7 Hz, 2H), 2.20 (s, 12H), 1.27 (t, *J* = 7.6 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.45, 149.99, 135.23, 128.61, 128.27, 60.92, 46.06, 43.59, 29.00, 15.22.
Elemental analysis: calculated for $C_{16}H_{26}N_2O$: C, 73.24; H, 9.99. Found: C, 73.17; H, 10.08.
ESI-MS: calculated for $C_{16}H_{26}N_2O$ $[M+H]^+$ m/z 263.4; found m/z 263.1

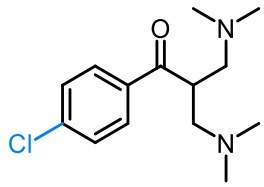
1-(4-(tert-butyl)phenyl)-3-(dimethylamino)-2-((dimethylamino)methyl)propan-1-one 4c:



Prepared according to the *General Procedure 1* in 83% yield as a yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 3.87 (tt, *J* = 7.7, 5.7 Hz, 1H), 2.68 (dd, *J* = 12.3, 7.7 Hz, 2H), 2.46 (dd, *J* = 12.3, 5.7 Hz, 2H), 2.21 (s, 12H), 1.34 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.40, 156.74, 134.86, 128.34, 125.72, 60.89, 46.07, 43.55, 35.17, 31.19.
Elemental analysis: calculated for $C_{18}H_{30}N_2O$: C, 74.44; H, 10.41. Found: C, 74.49; H, 10.46.
ESI-MS: calculated for $C_{18}H_{30}N_2O$ $[M+H]^+$ m/z 291.5; found m/z 291.2

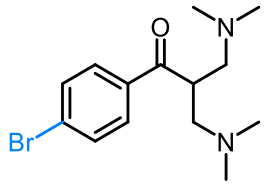
1-(4-chlorophenyl)-3-(dimethylamino)-2-((dimethylamino)methyl)propan-1-one 4d:



Prepared according to the *General Procedure 1* in 87% yield as a yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 3.80 (tt, *J* = 8.3, 5.4 Hz, 1H), 2.68 (dd, *J* = 12.4, 8.2 Hz, 2H), 2.42 (dd, *J* = 12.3, 5.4 Hz, 2H), 2.19 (s, 12H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.09, 139.40, 136.16, 129.77, 129.02, 61.04, 46.09, 43.97.
Elemental analysis: calculated for $C_{14}H_{21}ClN_2O$: C, 62.56; H, 7.88. Found: C, 62.52; H, 7.79.
ESI-MS: calculated for $C_{14}H_{21}ClN_2O$ $[M+H]^+$ m/z 269.8; found m/z 269.1

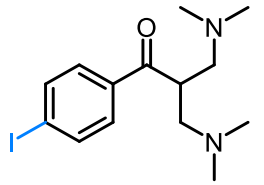
1-(4-bromophenyl)-3-(dimethylamino)-2-((dimethylamino)methyl)propan-1-one 4e:



Prepared according to the *General Procedure 1* in 88% yield as a yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.7 Hz, 2H), 7.60 (d, *J* = 8.7 Hz, 2H), 3.79 (tt, *J* = 8.2, 5.4 Hz, 1H), 2.68 (dd, *J* = 12.3, 8.2 Hz, 2H), 2.41 (dd, *J* = 12.4, 5.4 Hz, 2H), 2.18 (s, 12H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.27, 136.56, 131.98, 129.86, 128.11, 61.02, 46.07, 43.94.
Elemental analysis: calculated for $C_{14}H_{21}BrN_2O$: C, 53.68; H, 6.76. Found: C, 53.58; H, 6.81.
ESI-MS: calculated for $C_{14}H_{21}BrN_2O$ $[M+H]^+$ m/z 313.2; found m/z 313.0

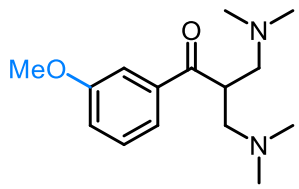
3-(dimethylamino)-2-((dimethylamino)methyl)-1-(4-iodophenyl)propan-1-one 4f:



Prepared according to the *General Procedure 1* in 78% yield as a brown amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 3.79 (tt, *J* = 8.2, 5.3 Hz, 1H), 2.69 (m, 2H), 2.46 (m, 2H), 2.18 (s, 12H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.57, 138.00, 129.76, 128.72, 128.34, 61.00, 46.07, 43.86.
Elemental analysis: calculated for $C_{14}H_{21}IN_2O$: C, 46.68; H, 5.88. Found: C, 46.72; H, 5.93.
ESI-MS: calculated for $C_{14}H_{21}IN_2O$ $[M+H]^+$ m/z 361.2; found m/z 361.0

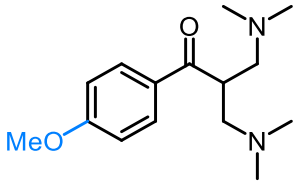
3-(dimethylamino)-2-((dimethylamino)methyl)-1-(3-methoxyphenyl)propan-1-one 4g:



Prepared according to the *General Procedure 1* in 97% yield as a white amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (m, 1H), 7.55 (m, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.10 (m, 1H), 3.86 (s, 3H), 3.82 (m, 1H), 2.69 (dd, *J* = 12.3, 8.0 Hz, 2H), 2.45 (dd, *J* = 12.3, 5.6 Hz, 2H), 2.20 (s, 12H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.77, 159.96, 139.00, 129.65, 120.84, 119.59, 112.64, 60.97, 55.45, 46.04, 43.91.
Elemental analysis: calculated for $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.15. Found: C, 68.01; H, 9.12.
ESI-MS: calculated for $C_{15}H_{24}N_2O_2$ $[M+H]^+$ m/z 265.4; found m/z 265.1

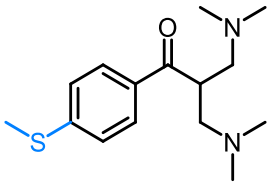
3-(dimethylamino)-2-((dimethylamino)methyl)-1-(4-methoxyphenyl)propan-1-one 4h:



Prepared according to the *General Procedure 1* in 90% yield as a white amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.9 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H), 3.82 (m, 1H), 2.67 (dd, *J* = 12.3, 7.8 Hz, 2H), 2.44 (dd, *J* = 12.3, 5.6 Hz, 2H), 2.19 (s, 12H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.22, 163.55, 130.65, 130.52, 113.89, 60.93, 55.51, 46.02, 43.30.
Elemental analysis: calculated for $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.15. Found: C, 68.04; H, 9.21.
ESI-MS: calculated for $C_{15}H_{24}N_2O_2$ $[M+H]^+$ m/z 265.4; found m/z 265.1

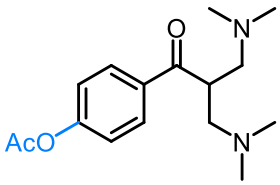
3-(dimethylamino)-2-((dimethylamino)methyl)-1-(4-(methylthio)phenyl)propan-1-one 4i:



Prepared according to the *General Procedure 1* in 99% yield as a yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.7 Hz, 2H), 3.82 (tt, *J* = 7.9, 5.5 Hz, 1H), 2.68 (dd, *J* = 12.3, 8.0 Hz, 2H), 2.52 (s, 3H), 2.44 (dd, *J* = 12.3, 5.5 Hz, 2H), 2.19 (s, 12H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.83, 145.78, 133.85, 128.76, 125.13, 60.95, 46.03, 43.48, 14.80.
Elemental analysis: calculated for $C_{15}H_{24}N_2OS$: C, 64.25; H, 8.63. Found: C, 64.31; H, 8.70.
ESI-MS: calculated for $C_{15}H_{24}N_2OS$ $[M+H]^+$ m/z 281.4; found m/z 281.0

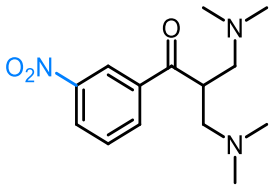
4-(3-(dimethylamino)-2-((dimethylamino)methyl)propanoyl)phenyl acetate 4k:



Prepared according to the *General Procedure 1* in 33% yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 3.81 (m, 1H), 2.66 (dd, *J* = 12.3, 7.8 Hz, 2H), 2.43 (dd, *J* = 12.3, 5.7 Hz, 2H), 2.19 (s, 12H), 2.07 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.37, 168.58, 154.06, 129.67, 121.54, 115.68, 60.51, 45.69, 43.48, 20.93.
Elemental analysis: calculated for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27. Found: C, 66.11; H, 8.64.
ESI-MS: calculated for $C_{16}H_{24}N_2O_3$ $[M]^+$ m/z 292.4; found m/z 292.1

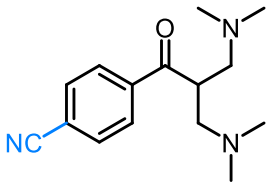
3-(dimethylamino)-2-((dimethylamino)methyl)-1-(3-nitrophenyl)propan-1-one 4l:



Prepared according to the *General Procedure 1* in 95% yield as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.83 (t, *J* = 1.9 Hz, 1H), 8.39 (m, 1H), 8.29 (m, 1H), 7.65 (t, *J* = 8.0 Hz, 1H), 3.85 (tt, *J* = 8.9, 5.0 Hz, 1H), 2.73 (dd, *J* = 12.4, 8.9 Hz, 2H), 2.40 (dd, *J* = 12.4, 5.0 Hz, 2H), 2.20 (s, 12H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.82, 148.50, 139.51, 133.82, 129.86, 127.01, 123.25, 61.11, 46.06, 44.56.
Elemental analysis: calculated for $C_{14}H_{21}N_3O_3$: C, 60.20; H, 7.58. Found: C, 60.14; H, 7.52.
ESI-MS: calculated for $C_{14}H_{21}N_3O_3$ $[M+H]^+$ m/z 280.3; found m/z 280.0

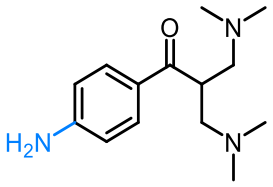
4-(3-(dimethylamino)-2-((dimethylamino)methyl)propanoyl)benzonitrile 4m:



Prepared according to the *General Procedure 1* in 85% yield as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.43 Hz, 2H), 7.76 (d, *J* = 8.40 Hz, 2H), 3.81 (tt, *J* = 8.7, 5.1 Hz, 1H), 2.70 (dd, *J* = 12.4, 8.7 Hz, 2H), 2.39 (dd, *J* = 12.3, 5.1 Hz, 2H), 2.17 (s, 12H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.76, 141.37, 132.57, 128.64, 118.21, 116.00, 61.13, 46.11, 44.70.
Elemental analysis: calculated for $C_{15}H_{21}N_3O$: C, 69.47; H, 8.16. Found: C, 69.41; H, 8.14.
ESI-MS: calculated for $C_{15}H_{21}N_3O$ $[M+H]^+$ m/z 260.3; found m/z 260.1

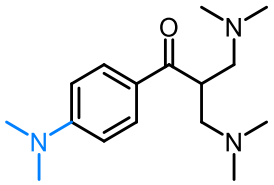
1-(4-aminophenyl)-3-(dimethylamino)-2-((dimethylamino)methyl)propan-1-one 4n:



Prepared according to the *General Procedure 1* in 35% yield as a white amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.7 Hz, 2H), 6.65 (d, *J* = 8.7 Hz, 2H), 4.13 (br s, 2H), 3.79 (tt, *J* = 7.6, 5.7 Hz, 1H), 2.65 (dd, *J* = 12.3, 7.7 Hz, 2H), 2.45 (dd, *J* = 12.3, 5.8 Hz, 2H), 2.20 (s, 12H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.60, 151.38, 130.94, 127.85, 113.99, 61.02, 46.09, 42.91.
Elemental analysis: calculated for $C_{14}H_{23}N_3O$: C, 67.43; H, 9.30. Found: C, 67.49; H, 9.38.
ESI-MS: calculated for $C_{14}H_{23}N_3O$ $[M+H]^+$ m/z 250.4; found m/z 250.1

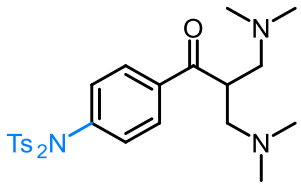
3-(dimethylamino)-2-((dimethylamino)methyl)-1-(4-(dimethylamino)phenyl)propan-1-one 4o:



Prepared according to the *General Procedure 1* in 80% yield as a yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.6 Hz, 2H), 6.64 (d, *J* = 8.5 Hz, 2H), 3.81 (m, 1H), 3.04 (s, 6H), 2.65 (dd, *J* = 12.3, 7.5 Hz, 2H), 2.46 (m, 2H), 2.20 (s, 12H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.31, 153.54, 130.66, 125.26, 110.90, 60.97, 46.07, 42.76, 40.11.
Elemental analysis: calculated for $C_{16}H_{27}N_3O$: C, 69.27; H, 9.81. Found: C, 69.17; H, 9.93.
ESI-MS: calculated for $C_{16}H_{27}N_3O$ $[M+H]^+$ m/z 278.4; found m/z 278.6

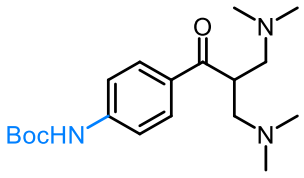
N-(4-(3-(dimethylamino)-2-((dimethylamino)methyl)propanoyl)phenyl)-4-methyl-N-tosylbenzenesulfonamide 4p:



Prepared according to the *General Procedure 1* in 68% yield as a yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.6 Hz, 2H), 7.80 (d, *J* = 8.39 Hz, 4H), 7.34 (d, *J* = 8.03 Hz, 4H), 7.12 (d, *J* = 8.54 Hz, 2H), 3.81 (tt, *J* = 8.1, 5.6 Hz, 1H), 2.70 (dd, *J* = 12.4, 8.1 Hz, 2H), 2.48 (s, 6H), 2.44 (dd, *J* = 12.4, 5.5 Hz, 2H), 2.21 (s, 12H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.40, 145.41, 138.83, 138.27, 136.51, 131.96, 129.81, 129.10, 128.72, 60.88, 46.13, 44.43, 21.86.
Elemental analysis: calculated for $C_{28}H_{35}N_3O_5S_2$: C, 60.30; H, 6.33. Found: C, 60.37, H, 6.46.
ESI-MS: calculated for $C_{28}H_{35}N_3O_5S_2$ $[M+H]^+$ m/z 558.7; found m/z 558.0

tert-butyl (4-(3-(dimethylamino)-2-((dimethylamino)methyl)propanoyl)phenyl) carbamate 4q:

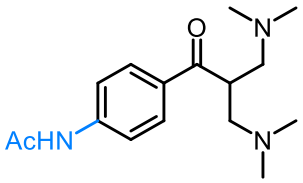


Prepared according to the *General Procedure 1* in 52% yield as a yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (dd, *J* = 23.8, 8.8 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 6.83 (br s, 1H), 3.82 (tt, *J* = 8.2, 5.6 Hz, 1H), 2.67 (dd, *J* = 12.3, 7.9 Hz, 2H), 2.44 (dd, *J* = 12.3, 5.6 Hz, 2H), 2.18 (s, 9H), 1.52 (s, 12H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.51, 152.35, 143.02, 129.96, 117.71, 117.55, 81.38, 61.03, 46.10, 43.42, 28.40.
Elemental analysis: calculated for $C_{19}H_{31}N_3O_3$: C, 65.30; H, 8.94. Found: C, 65.27; H, 9.03.

ESI-MS: calculated for $C_{19}H_{31}N_3O_3$ $[M+H]^+$ m/z 350.5; found m/z 350.1

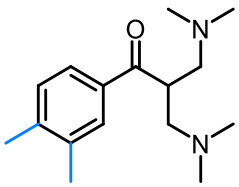
N-(4-(3-(dimethylamino)-2-((dimethylamino)methyl)propanoyl)phenyl)acetamide 4r:



Prepared according to the *General Procedure 1* in 15% yield as a white amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.8 Hz, 2H), 7.85 (br s, 1H), 7.61 (d, *J* = 8.42 Hz, 2H), 3.84 (tt, *J* = 8.0, 5.5 Hz, 1H), 2.68 (dd, *J* = 12.3, 8.03 Hz, 2H), 2.43 (dd, *J* = 12.3, 5.5 Hz, 2H), 2.19 (s, 3H), 2.18 (s, 12H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.88, 168.88, 142.48, 129.84, 129.80, 119.14, 61.05, 46.10, 43.50, 24.84.
Elemental analysis: calculated for $C_{16}H_{25}N_3O_2$: C, 65.95; H, 8.65. Found: C, 66.01; H, 8.72.
ESI-MS: calculated for $C_{16}H_{25}N_3O_2$ $[M+H]^+$ m/z 292.4; found m/z 292.0

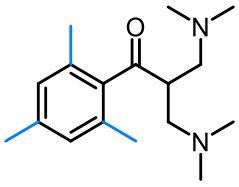
3-(dimethylamino)-2-((dimethylamino)methyl)-1-(3,4-dimethylphenyl)propan-1-one 4s:



Prepared according to the *General Procedure 1* in 77% yield as a yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 1.9 Hz, 1H), 7.75 (dd, *J* = 7.8, 2.1 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 3.86 (tt, *J* = 7.8, 5.6 Hz, 1H), 2.67 (dd, *J* = 12.3, 7.8 Hz, 2H), 2.46 (dd, *J* = 12.3, 5.6 Hz, 2H), 2.31 (s, 6H), 2.20 (s, 12H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.62, 142.63, 137.07, 135.35, 129.94, 129.54, 126.07, 60.93, 46.04, 43.53, 20.07, 19.93.
Elemental analysis: calculated for $C_{16}H_{26}N_2O$: C, 73.24; H, 9.99. Found: C, 73.17; H, 10.08.
ESI-MS: calculated for $C_{16}H_{26}N_2O$ $[M+H]^+$ m/z 263.4; found m/z 263.1

3-(dimethylamino)-2-((dimethylamino)methyl)-1-mesitylpropan-1-one 4t:

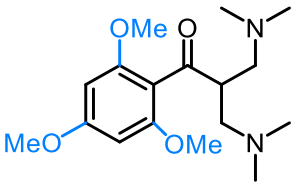


Prepared according to the *General Procedure 1* in 90% yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 (m, 2H), 3.32 (m, 1H), 2.62 (dd, *J* 12.4, 7.1 Hz, 2H), 2.46 (m, 2H), 2.28 (s, 9H), 2.15 (s, 12H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 211.96, 138.60, 134.53, 128.98, 128.29, 60.02, 49.66, 45.94, 21.19, 20.07.
Elemental analysis: calculated for $C_{17}H_{28}N_2O$: C, 73.87; H, 10.21. Found: C, 73.98; H, 10.30.

ESI-MS: calculated for $C_{17}H_{28}N_2O$ $[M+H]^+$ m/z 277.4; found m/z 277.2

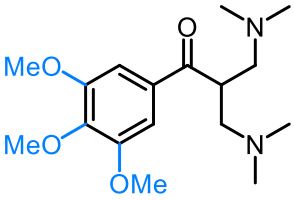
3-(dimethylamino)-2-((dimethylamino)methyl)-1-(2,4,6-trimethoxyphenyl)propan-1-one 4u:



Prepared according to the *General Procedure 1* in 98% yield as a white amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.10 (s, 2H), 3.82 (s, 3H), 3.78 (s, 6H), 3.44 (p, *J* = 6.5 Hz, 1H), 2.65 (dd, *J* = 12.4, 6.7 Hz, 2H), 2.41 (dd, *J* = 12.5, 6.3 Hz, 2H), 2.18 (s, 12H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.85, 162.18, 158.85, 129.83, 90.55, 58.94, 58.01, 55.74, 49.33, 45.52.
Elemental analysis: calculated for $C_{17}H_{28}N_2O_4$: C, 62.94; H, 8.70. Found: C, 62.81; H, 8.80.
ESI-MS: calculated for $C_{17}H_{28}N_2O_4$ $[M+H]^+$ m/z 325.4; found m/z 326.0

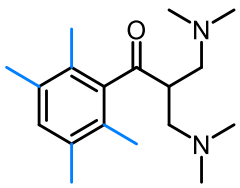
3-(dimethylamino)-2-((dimethylamino)methyl)-1-(3,4,5-trimethoxyphenyl)propan-1-one 4v:



Prepared according to the *General Procedure 2* in 90% yield as a white amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (s, 2H), 3.92 (s, 3H), 3,91 (s, 6H), 3.79 (tt, *J* = 7.9, 5.4 Hz, 1H), 2.70 (dd, *J* = 12.3, 8.0 Hz, 2H), 2.43 (dd, *J* = 12.3, 5.3 Hz, 2H), 2.22 (s, 12H)
^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.61, 153.08, 142.51, 132.77, 105.91, 61.07, 60.90, 56.24, 46.04, 43.86.
Elemental analysis: calculated for $C_{17}H_{28}N_2O_4$: C, 62.94; H, 8.70. Found: C, 63.05; H, 8.81.
ESI-MS: calculated for $C_{17}H_{28}N_2O_4$ $[M+H]^+$ m/z 325.4; found m/z 325.2

3-(dimethylamino)-2-((dimethylamino)methyl)-1-(2,3,5,6-tetramethylphenyl)propan-1-one 4w:

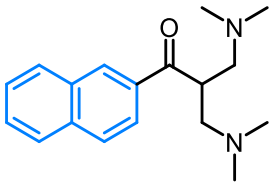


Prepared according to the *General Procedure 1* in 86% yield as a yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (s, 1H), 3.22 (p, *J* = 6.8 Hz, 1H), 2.64 (dd, *J* = 12.4, 6.9 Hz, 2H), 2.42 (dd, *J* = 12.4, 6.8 Hz, 2H), 2.20 (s, 6H), 2.15 (s, 12H), 2.11 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.43, 142.35, 134.27, 131.90, 129.68, 59.21, 50.60, 45.86, 19.74, 16.67.

Elemental analysis: calculated for $C_{18}H_{30}N_2O$: C, 74.44; H, 10.41. Found: C, 74.56; H, 10.62.
ESI-MS: calculated for $C_{18}H_{30}N_2O$ $[M+H]^+$ m/z 291.5; found m/z 291.2

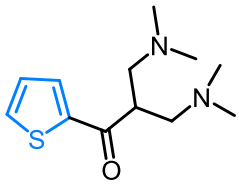
3-(dimethylamino)-2-((dimethylamino)methyl)-1-(naphthalen-2-yl)propan-1-one 4x:



Prepared according to the *General Procedure 1* in 98% yield as a yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (s, 1H), 8.50-8.47 (m, 1H), 8.09-8.07 (m, 1H), 7.96-7.91 (m, 2H), 7.53-7.49 (m, 2H), 3.82 (tt, *J* = 8.0, 5.5 Hz, 1H), 2.76 (dd, *J* = 12.3, 8.0 Hz, 2H), 2.52 (dd, *J* = 12.3, 5.5 Hz, 2H), 2.23 (s, 12H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.91, 135.62, 134.96, 132.67, 129.84, 129.76, 128.58, 128.47, 127.78, 126.74, 124.31, 61.03, 46.06, 43.94.
Elemental analysis: calculated for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51. Found: C, 75.91; H, 8.64.
ESI-MS: calculated for $C_{18}H_{24}N_2O$ $[M+H]^+$ m/z 285.4; found m/z 285.0

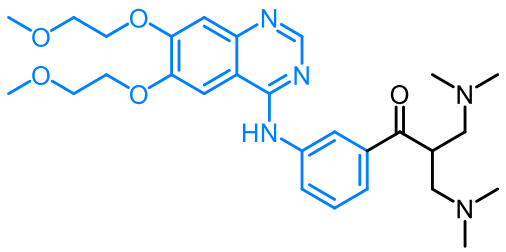
3-(dimethylamino)-2-((dimethylamino)methyl)-1-(thiophen-2-yl)propan-1-one 4y:



Prepared according to the *General Procedure 1* in 90% yield as a yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 3.7 Hz, 1H), 7.64 (d, *J* = 4.9 Hz, 1H), 7.14 (m, 1H), 3.65 (tt, *J* = 8.1, 5.6 Hz, 1H), 2.70 (dd, *J* = 12.3, 8.2 Hz, 2H), 2.44 (dd, *J* = 12.3, 5.6 Hz, 2H), 2.22 (s, 12H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.35, 145.05, 133.87, 131.76, 128.27, 60.88, 46.01, 45.99.
Elemental analysis: calculated for $C_{12}H_{20}N_2OS$: C, 59.96; H, 8.39. Found: C, 59.95; H, 8.41.
ESI-MS: calculated for $C_{12}H_{20}N_2OS$ $[M+H]^+$ m/z 241.4; found m/z 241.1

1-(3-((6,7-bis(2-methoxyethoxy)quinazolin-4-yl)amino)phenyl)-3-(dimethylamino)-2-((dimethylamino)methyl)propan-1-one 7:



Prepared according to the *General Procedure 1* in 85% yield as a white amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58 (s, 1H), 8.37 (s, 1H), 8.23 (s, 1H), 8.04 (m, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.35 (s, 1H), 7.12 (s, 1H), 4.14 (m, 4H), 3.87 (m, 1H), 3.70 (m, 4H), 3.35 (s, 3H), 3.33 (s, 3H), 2.66 (dd, *J* = 12.3, 8.0 Hz, 2H), 2.40 (dd, *J* = 12.3, 5.5 Hz, 2H), 2.15 (s, 12H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.06, 156.43, 154.44, 153.48, 148.86, 147.50, 139.72, 138.21, 129.21, 126.10, 123.47, 121.26, 109.39, 108.61, 102.54, 70.87, 70.42, 68.99, 68.29, 60.92, 59.22, 57.62, 46.00.
Elemental analysis: calculated for $C_{28}H_{39}N_5O_5$: C, 63.98; H, 7.48. Found: C, 64.12; H, 7.62.
ESI-MS: calculated for $C_{28}H_{39}N_5O_5$ $[M+H]^+$ m/z 526; found m/z 526

2.6 Limitations

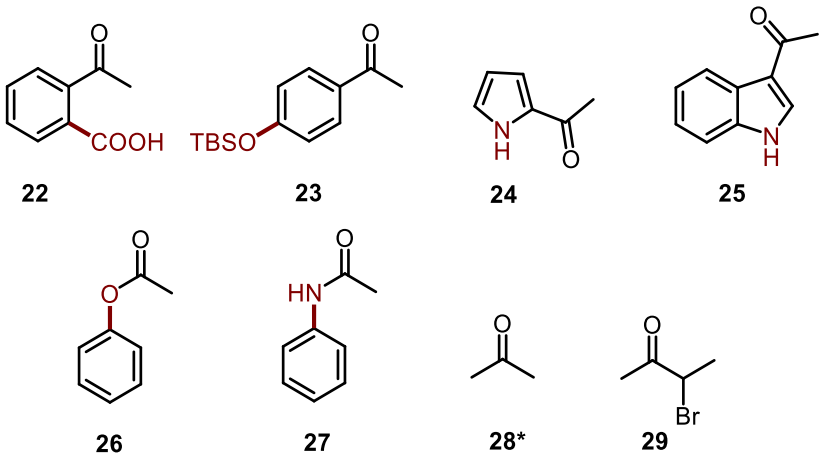
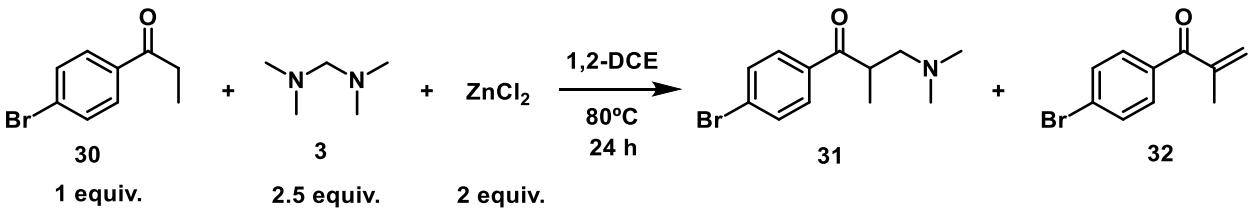


Figure S4. Substrates unreactive under standard reaction conditions. *A complex mixture with trace amounts of bis-Mannich bases is formed

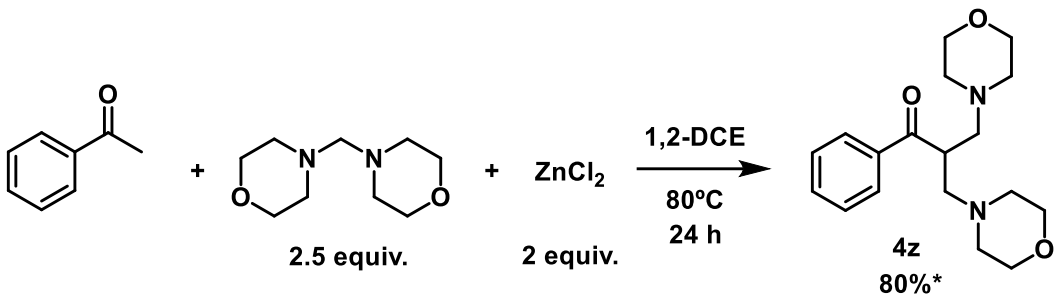
Table S4. Reactions between propiophenone **30** and TMMDA **3**.



Entry	Propiophenone **30** : TMMDA **3**: $ZnCl_2$ / mmol.	Selectivity / %		
		30	**31**	**32**
1[a]	0.2 : 0.5 : 0.4	19	42	39

[a] Yields were determined by NMR

2.7 Reaction with other methylenediamines



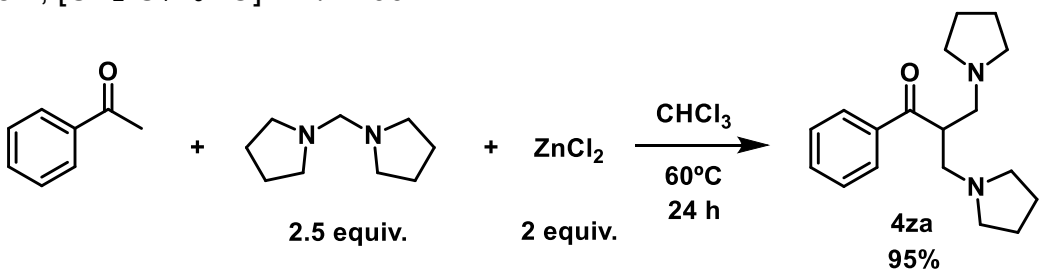
Into an oven-dried 10 mL Schlenk tube, equipped with a Teflon-coated magnetic stir bar, and backfilled with argon were added acetophenone (0.25 mmol), dimorpholinomethane (0.11 ml, 0.63 mmol) and $ZnCl_2$ (0.068 g, 0.5 mmol) in 2 ml 1,2-dichloroethane. The reaction mixture was stirred for 24 h at 80°C. After completion (TLC control), the reaction was diluted with $CHCl_3$ and quenched with sat. Na_2CO_3. The phases were separated, and the aqueous phase was extracted with $CHCl_3$ (3 × 15 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to obtain a crude product. *Yield was determined by NMR.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 6.94 Hz, 2H), 7.56 (t, *J* = 7.38 Hz, 1H), 7.47 (t, *J* = 7.73 Hz, 2H), 3.93 (m, 1H), 3.54 (m, 8H), 2.76 (dd, *J* = 12.50, 8.49 Hz, 2H), 2.52 (dd, *J* = 12.52, 5.25 Hz, 2H), 2.40 (m, 8H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.57, 138.27, 132.80, 128.59, 128.00, 66.85, 59.90, 53.98, 42.43.

Elemental analysis: calculated for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23. Found: C, 67.74; H, 8.63.

EI-MS: calculated for $C_{18}H_{26}N_2O_3$ $[M]^+$ m/z 318.2; found fragments $[M - CH_2\text{-}C_4H_9NO]^+$ m/z 218.2; $[CH_2\text{-}C_4H_9NO]^+$: m/z 100.2.



Into an oven-dried 10 mL Schlenk tube, equipped with a Teflon-coated magnetic stir bar, and backfilled with argon were added acetophenone (0.25 mmol), dipyrrolidylmethane (0.1 ml, 0.63 mmol) and $ZnCl_2$ (0.068 g, 0.5 mmol) in 2 ml chloroform. The reaction mixture was stirred for 24 h at 60°C. After completion (TLC control), the reaction was diluted with $CHCl_3$ and quenched with sat. Na_2CO_3. The phases were separated, and the aqueous phase was extracted with $CHCl_3$ (3 × 15 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to obtain a product **4za** in 95% yield as a yellow oil.

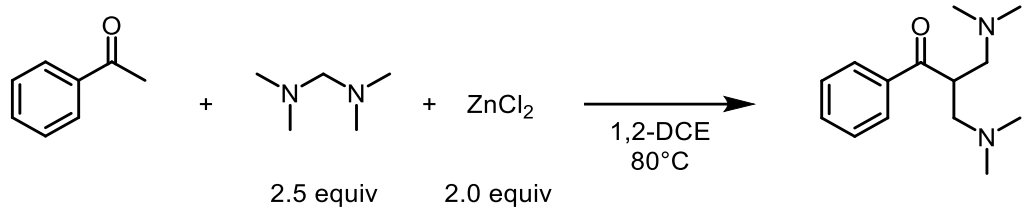
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 7.14 Hz, 2H), 7.55 (t, *J* = 7.34 Hz, 1H), 7.45 (t, *J* = 7.53 Hz, 2H), 3.92 (tt, *J* = 7.79, 5.68 Hz, 1H), 2.76 (m, 4H), 2.45 (m, 8H), 1.67 (m, 8H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.49, 137.88, 132.90, 128.66, 128.35, 57.53, 54.77, 46.45, 23.73.

Elemental analysis: calculated for $C_{18}H_{26}N_2O$: C, 75.48; H, 9.15. Found: C, 75.10; H, 9.52.

EI-MS: calculated for $C_{18}H_{26}N_2O$ $[M]^+$ m/z 286.2; found fragments $[M - CH_2\text{-}C_4H_9N]^+$ m/z 202.1; $[CH_2\text{-}C_4H_9N]^+$: m/z 84.1.

2.8 Multigram-scale synthesis of bis-Mannich base



Into a 500 mL round bottom flask, equipped with a Teflon-coated magnetic stir bar, were added acetophenone **1a** (9.7 ml, 0.083 mol), *N,N,N`,N`*-tetramethylmethylenediamine **3** (28 ml, 0.21 mol) and $ZnCl_2$ (23 g, 0.17 mol) in 200 ml 1,2-DCE. The reaction mixture was stirred for 24 h at 80°C. After completion (TLC control), the reaction was diluted with $CHCl_3$ and quenched with sat. Na_2CO_3. The phases were separated, and the aqueous phase was extracted with $CHCl_3$ (3 × 200 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to obtain a product **4a** 19.1 g (0.082 mol) in 98% yield.

Note: the reaction can be conducted in $CHCl_3$.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02-7.98 (m, 2H), 7.58-7.53 (m, 1H), 7.49-7.44 (m, 2H), 3.88 (tt, *J* = 7.9, 5.6 Hz, 1H), 2.69 (dd, *J* = 12.3, 7.9 Hz, 2H), 2.46 (dd, *J* = 12.3, 5.6 Hz, 2H), 2.20 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.03, 137.67, 133.00, 128.72, 128.34, 60.95, 46.07, 43.82.

ESI-MS: calculated for $C_{14}H_{22}N_2O$ $[M+H]^+$ m/z 235; found m/z 235

2.9 Alternative reactivity of acetophenone with TMMDA

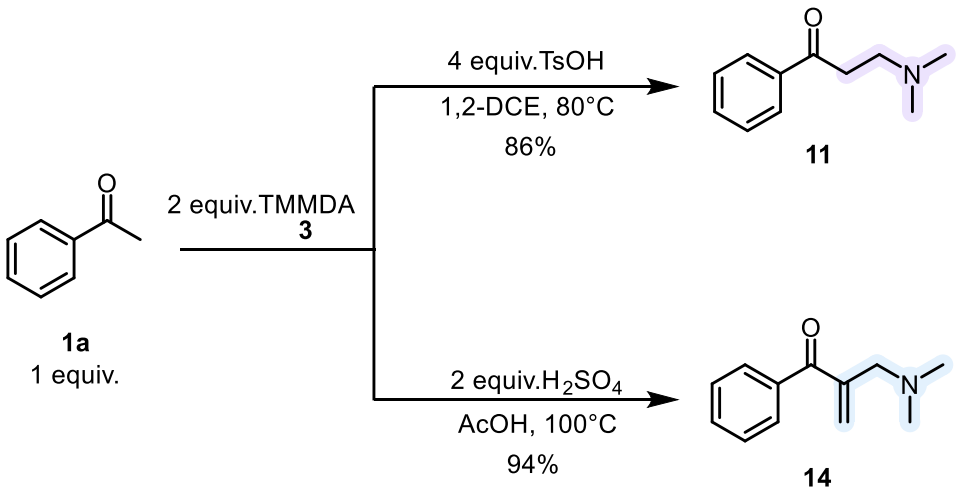


Figure S5. Reactions between acetophenone **1a** and TMMDA **3**

3-(dimethylamino)-1-phenylpropan-1-one (11)

Into an oven-dried 25 mL Schlenk tube, equipped with a Teflon-coated magnetic stir bar, and backfilled with argon were added acetophenone **1a** (0.97 ml, 0.8 mmol), *N,N,N`,N`*-tetramethylmethylenediamine **3** (0.23 ml, 1.7 mmol) and pTSA (0.63 g, 3.2 mmol) in 5 ml 1,2-DCE. The reaction mixture was stirred for 12 h at 80°C. After completion (TLC control), the reaction was diluted with DCM and quenched with sat. Na_2CO_3. The phases were separated, and the aqueous phase was extracted with DCM (3 × 50 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to obtain a 0.127 g product **11** in 86% yield as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96-7.93 (m, 2H), 7.54 (m, 1H), 7.46-7.42 (m, 2H), 3.17-3.13 (m, 2H), 2.78- 2.74 (m, 2H), 2.28 (s, 6H). All analytical data in accordance with those reported in the literature[18].

2-((dimethylamino)methyl)-1-phenylprop-2-en-1-one (14)

Into an oven-dried 25 mL Schlenk tube, equipped with a Teflon-coated magnetic stir bar, and backfilled with argon were added acetophenone **1a** (0.97 ml, 0.8 mmol), *N,N,N`,N`*-tetramethylmethylenediamine **3** (0.23 ml, 1.7 mmol) and H_2SO_4 (0.09 ml, 1.7 mmol) in 5 ml AcOH. The reaction mixture was stirred for 3 h at 100°C. After completion (TLC control), the reaction was diluted with EtOAc and quenched with sat. Na_2CO_3. The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to obtain a 0.148 g product **14** in 94% yield as a dark brown liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80-7.78 (m, 2H), 7.54-7.42 (m, 3H), 6.11 (s, 1H), 5.80 (s, 1H), 3.40 (s, 2H), 2.34 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.07, 143.51, 137.08, 132.54, 129.61, 129.14, 128.29, 59.70, 44.94. All analytical data in accordance with those reported in the literature[17].

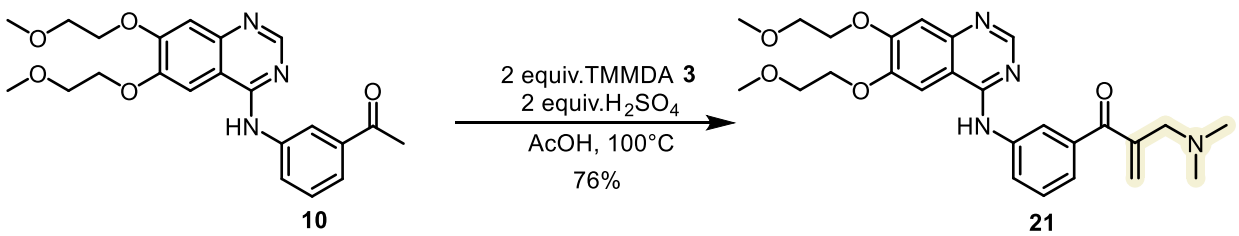


Figure S6. Reaction between acetophenone derivative **10** and TMMDA **3**

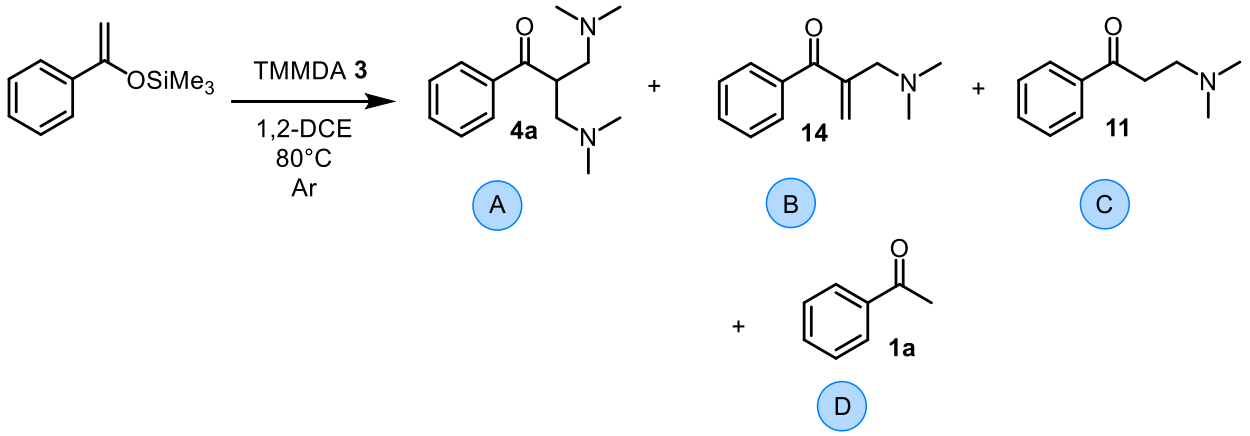
Into an oven-dried 25 mL Schlenk tube, equipped with a Teflon-coated magnetic stir bar, and backfilled with argon were added acetophenone derivative **10** (0.05 g, 0.1 mmol), *N,N,N`,N`*-tetramethylmethylenediamine **3** (0.03 ml, 0.2 mmol) and H_2SO_4 (0.02 g, 0.2 mmol) in 1 ml AcOH. The reaction mixture was stirred for 3 h at 100°C. After completion (TLC control), the reaction was diluted with EtOAc and quenched with sat. Na_2CO_3. The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to obtain a 0.036 g product **21** in 76% yield as a dark brown liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.64 (s, 1H), 8.13 – 8.09 (m, 1H), 8.08 – 8.05 (m, 1H), 7.58 – 7.54 (m, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.42 (s, 1H), 7.25 (s, 1H), 7.24 (s, 1H), 6.04 (d, *J* = 1.2 Hz, 1H), 5.85 (d, *J* = 1.1 Hz, 1H), 4.33 – 4.26 (m, 4H), 3.87 – 3.82 (m, 4H), 3.47 (d, *J* = 4.7 Hz, 6H), 3.36 (s, 2H), 2.31 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.14, 156.46, 154.63, 153.51, 149.01, 147.54, 144.44, 139.29, 137.96, 128.95, 128.39, 125.85, 125.11, 122.70, 109.42, 108.71, 102.70, 70.97, 70.53, 69.19, 68.41, 60.39, 59.33, 45.29.

2.10 Mechanistic investigation

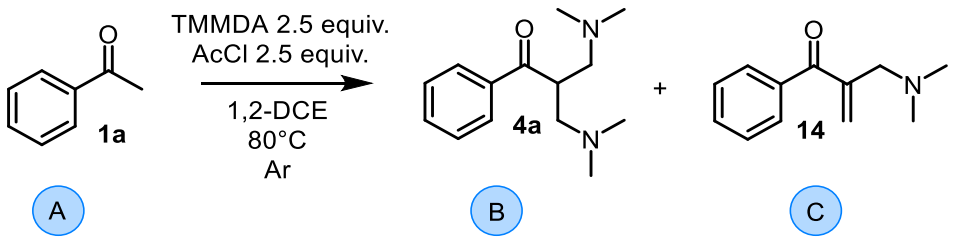
Table S5. Reaction of trimethyl((1-phenylvinyl)oxy)silane with TMMDA **3**



Entry	Enolate : TMMDA **3** : $ZnCl_2$ /equiv.	Selectivity / %			
		A	B	C	D
1[a]	1 : 2.5 : 0	33	43	6	15
2[b]	1 : 2.5 : 2	92	0	0	0

[a] Reaction conditions: 0.2 mmol enolate, 0.52 mmol TMMDA **3**, 2 ml 1,2-DCE, 80°C, Ar, 20 h [b] 0.4 mmol $ZnCl_2$; Yields were determined by NMR

Table S6. Reaction of acetophenone with TMMDA **3**



Entry	Acetophenone **1a** : TMMDA **3**: AcCl : $ZnCl_2$ / equiv.	Selectivity / %		
		A	B	C
1[a]	1 : 2.5 : 2.5 : 0	23	17	60
2[b][c]	1 : 2.5 : 2.5 : 2	7	23	18

[a] Reaction conditions: 0.2 mmol acetophenone, 0.52 mmol TMDA, 0.52 mmol AcCl, 2 ml 1,2-DCE, 80°C, Ar, 20 h [b] 0.4 mmol $ZnCl_2$; [c] 52% of DMAA – reaction product between TMMDA **3** and AcCl; Yields were determined by NMR

2.11 Complex formation of bis-Mannich product 4a with $ZnCl_2$

Experimental procedure

Into a vial, equipped with a Teflon-coated magnetic stir bar, were added 0.04 mmol of Mannich bis-base **4a** and $ZnCl_2$ (0.02, 0.04, 0.04 mmol, respectively). Experiments 1 and 2 were conducted at room temperature, experiment 3 was heated to 60 degrees for 2 hours. Then the solutions were transferred to NMR tubes and analyzed by NMR.

Complex **13** of $ZnCl_2$ and **4a**:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 – 7.87 (m, 2H), 7.72 – 7.63 (m, 1H), 7.55 (t, *J* = 7.8 Hz, 2H), 4.10 (t, *J* = 11.4 Hz, 1H), 3.39 (t, *J* = 12.3 Hz, 2H), 2.73 – 2.62 (m, 14H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.64, 134.65, 134.58, 129.52, 128.37, 62.90, 50.31, 46.27, 39.56.

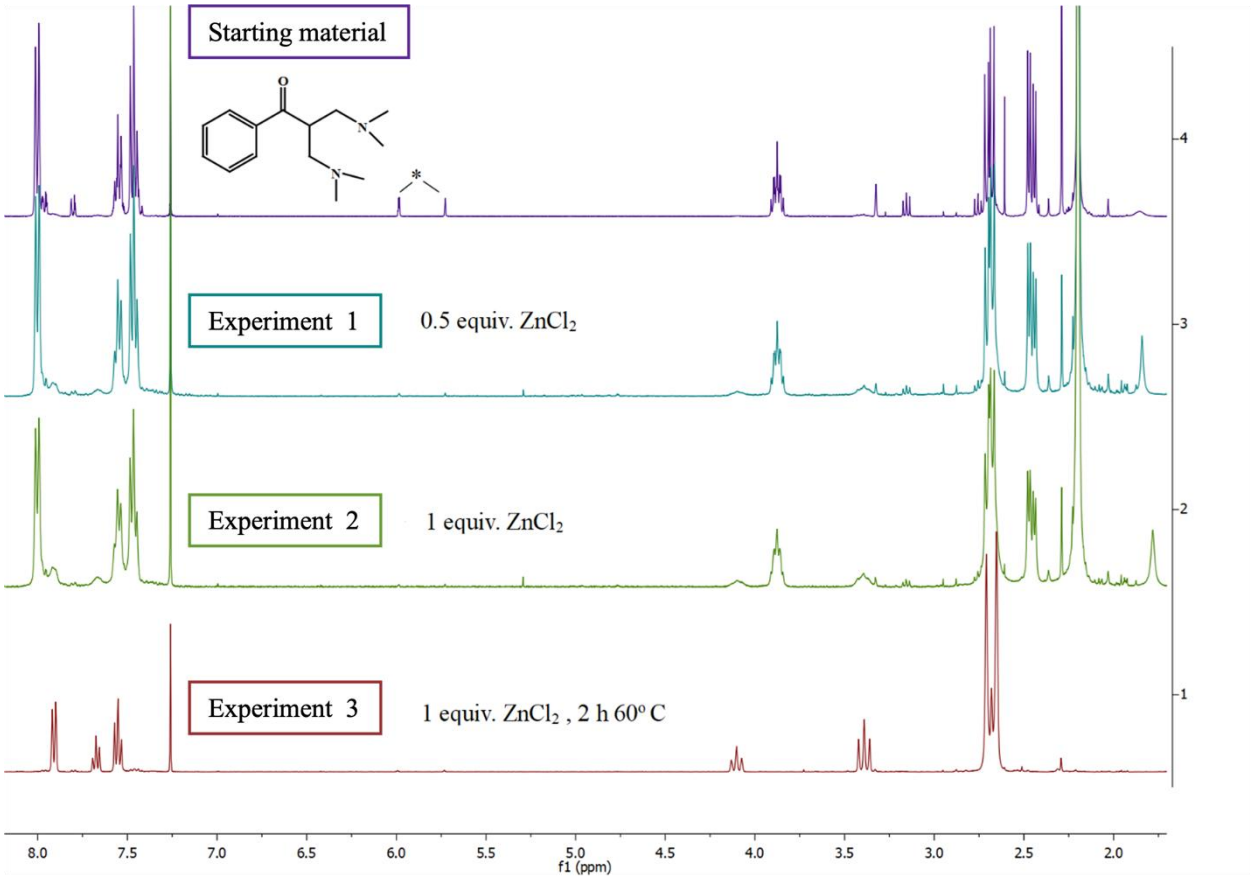


Figure S7 NMR titration experiments of bis-Mannich base **4a** (0.04 mmol) with $ZnCl_2$ in $CDCl_3$; *traces of compound **14**.

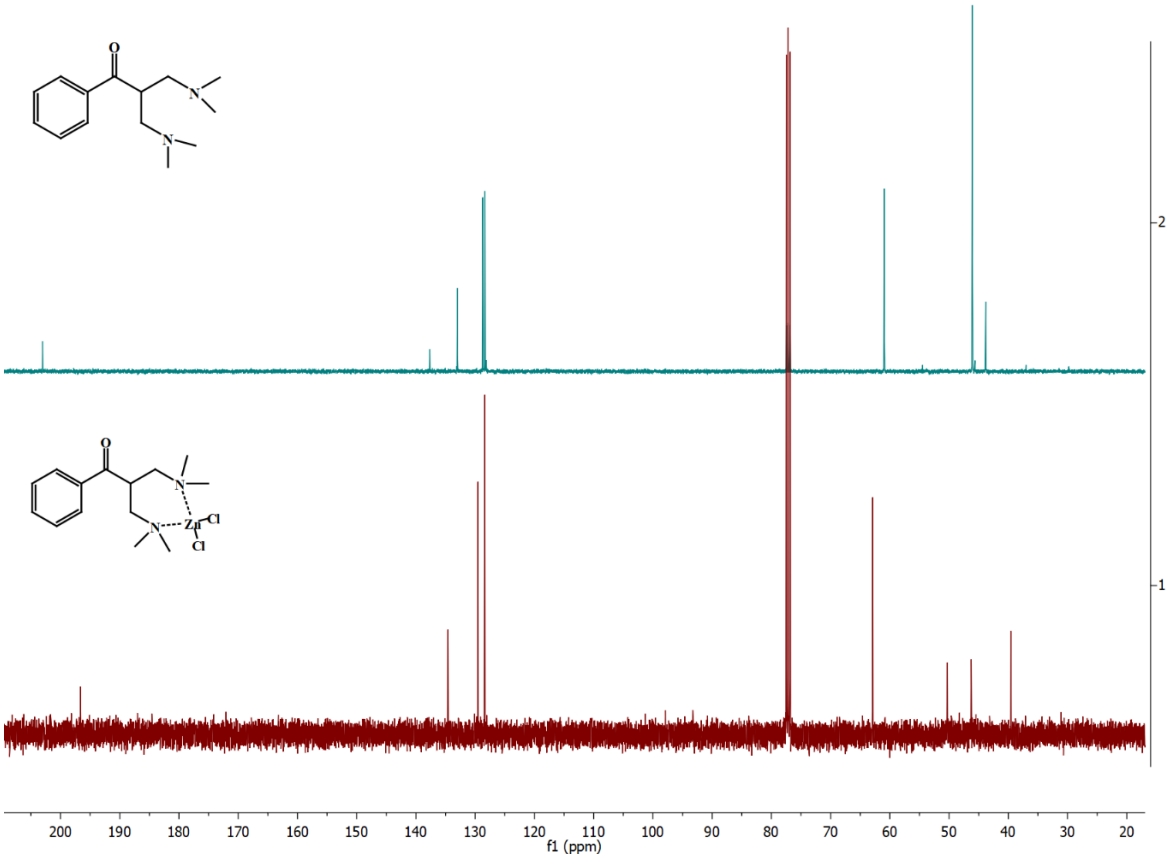


Figure S8. ^{13}C NMR spectra of bis-Mannich base **4a** and complex **13** in $CDCl_3$.

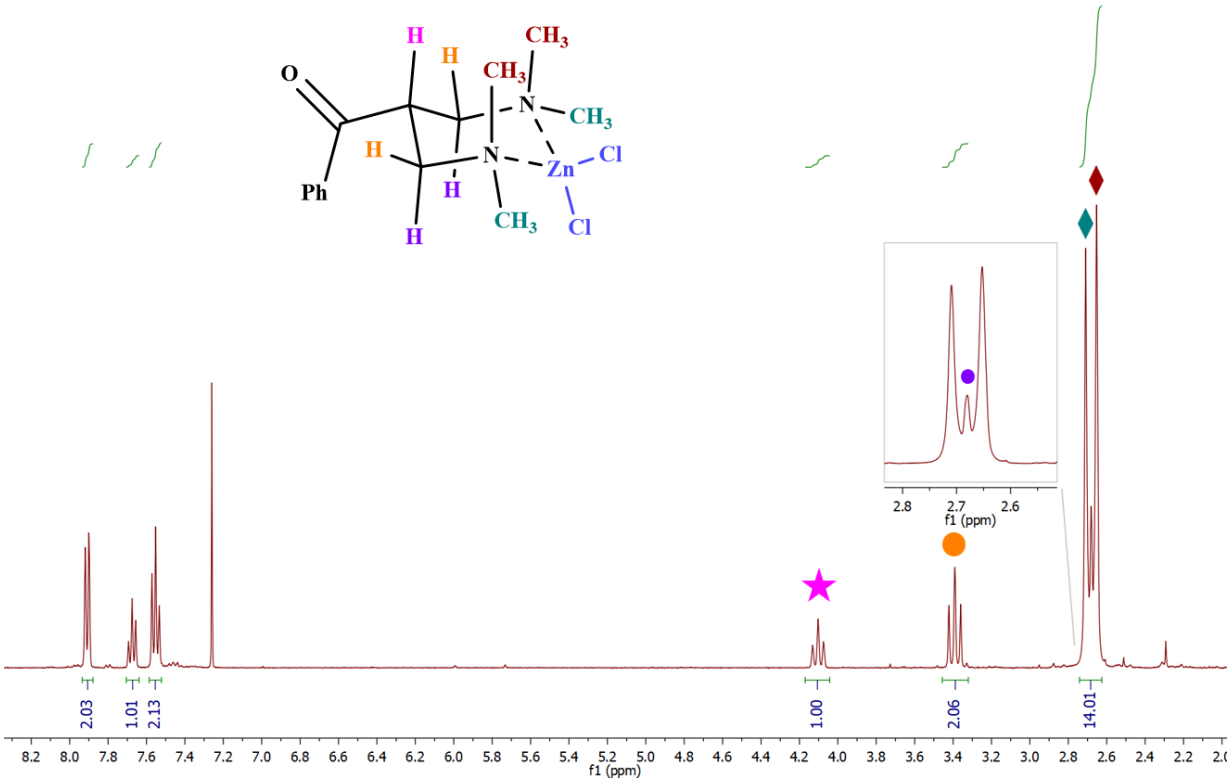


Figure S9. ^{1}H NMR complex **13**, solvent $CDCl_3$.

2.12 X-ray diffraction analysis

X-ray diffraction data for were collected on a Bruker APEX II diffractometer (λ(MoKα) = 0.71073 Å, 2θ<58.43°). Colorless crystals of $C_{14}H_{22}Cl_2N_2OZn$ at 120(2) K are monoclinic, space group $P2_1/c$, a = 13.779(2), b = 7.4635(12), c = 17.382(3) Å, β = 113.328(6)°, V = 1641.4(4) Å^3, Z = 4, d_{calc} = 1.500 g cm^{-3}. Intensities of 4406 independent reflections (R_{int} = 0.0747) out of 15020 collected were used in structure solution and refinement. The structure was solved by direct methods with SHELXT[19] program and refined by the full-matrix least-squares technique against F^2 in the anisotropic approximation with SHELXL[20] program. The positions of hydrogen atoms were calculated. Hydrogen atoms were refined in the riding model with U_{iso}(H) equal to 1.5 U_{eq}(C) and 1.2 U_{eq}(C) of the connected methyl and other carbon atoms. The refinement converged to $R1$ = 0.0444 (calculated for 2839 observed reflections with I>2σ(I)), wR2 = 0.1164 and GOF = 0.977. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Center (CCDC 2496541).

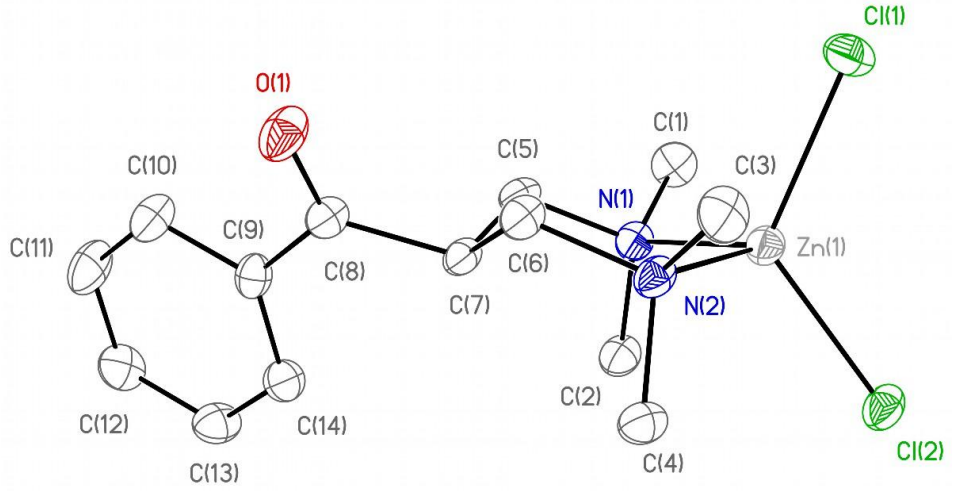
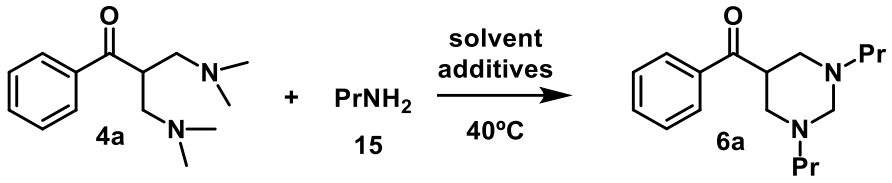


Figure S10. General view of molecule **13** in the crystal. Ellipsoids are drawn at the 50% probability level; hydrogen atoms are omitted for clarity.

3. Experimental and characterization data for the heterocyclic compounds

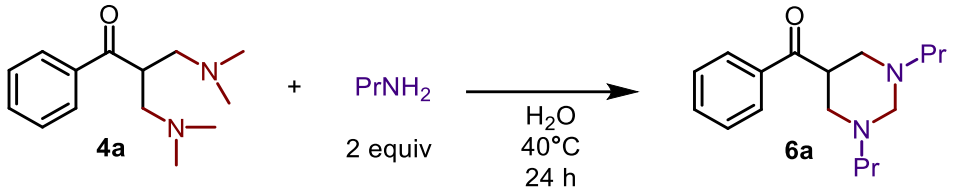
Table S7. Optimization of hexahydropyrimidine formation



Entry	Solvent	Additive	Yield 6a*, %
1	H_2O	-	51
2	H_2O	Iminium salt** 1 equiv.	39
3	H_2O	Iminium salt (*in situ*)*** 1 equiv.	9
4	MeOH	-	-
5	$CHCl_3$	-	-

* *Yields were measured by GC-MS (EI) using PhCl as an internal standard; ** N,N-dimethylmethyleneiminium bromide; *** 1 equiv. TMMDA with 1 equiv. AcCl*

(1,3-dipropylhexahydropyrimidin-5-yl)(phenyl)methanone (6a)



Into a 25 mL round bottom flask, equipped with a Teflon-coated magnetic stir bar, were added **3-(dimethylamino)-2-((dimethylamino)methyl)-1-phenylpropan-1-one 4a** (0.1 g, 0.4 mmol), *N*-propylamine (0.07 ml, 0.8 mmol) in 5 ml H_2O. The inhomogeneous reaction mixture was stirred for 24 h at 40°C. After completion (TLC control), the reaction was quenched with sat. Na_2CO_3 and was extracted with ethyl acetate (3 × 25 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The final product **6a** was obtained by silica gel column chromatography using ethyl acetate as eluent in 51% yield as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 3.93 (tt, *J* = 11.1, 3.7 Hz, 1H), 3.75 (d, *J* = 9.6 Hz, 1H), 3.18 – 3.12 (m, 2H), 2.68 (d, *J* = 9.6 Hz, 1H), 2.43 – 2.38 (m, 4H), 2.34 (t, *J* = 11.5 Hz, 2H), 1.51 (h, *J* = 7.4 Hz, 4H), 0.90 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.85, 136.28, 133.31, 128.90, 128.36, 75.36, 57.04, 55.11, 41.63, 20.60, 12.06.

EI-MS: calculated for $C_{17}H_{26}N_2O$ $[M-H]^+$ m/z 273.4; found m/z 273.2

Elemental analysis: calculated for $C_{17}H_{26}N_2O$: C, 74.41; H, 9.55. Found: C 74.36; H, 9.52.

2D NMR spectra:

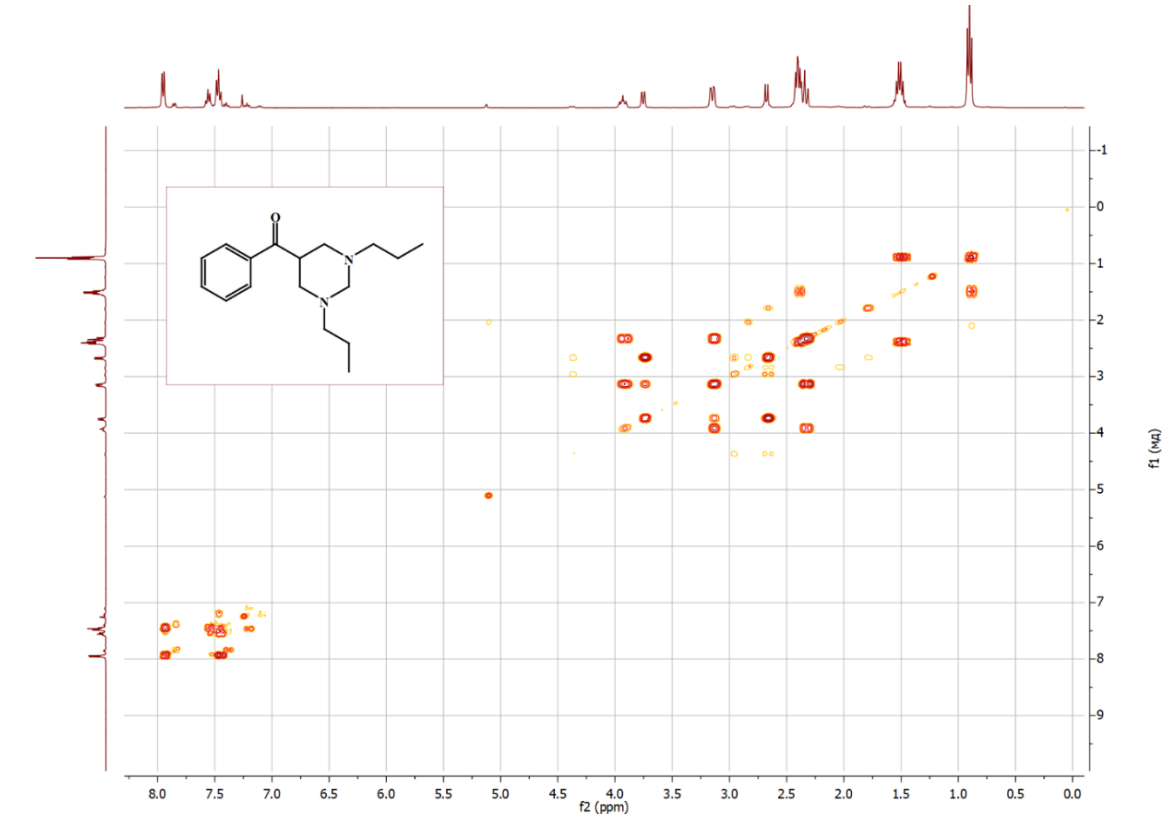


Figure S11. COSY spectrum of compound **6a**.

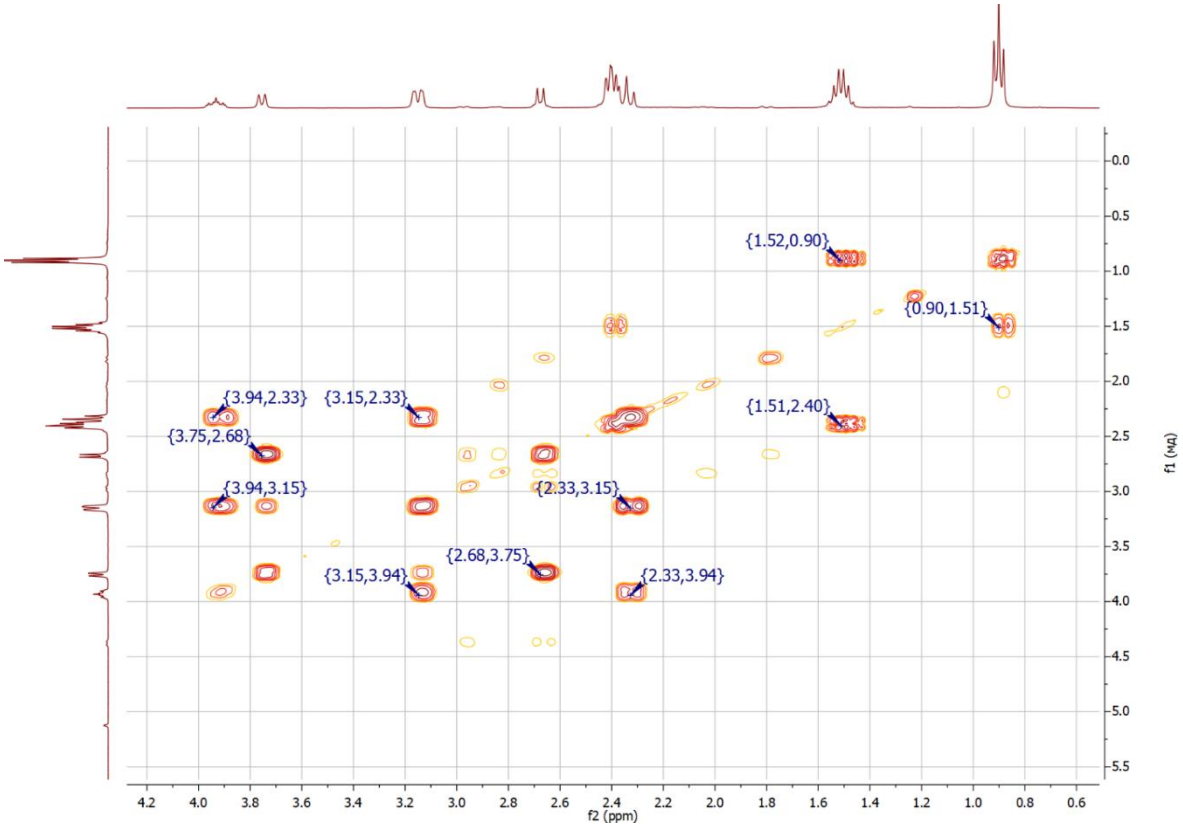


Figure S12. Zoomed-in COSY NMR spectrum of compound **6a**.

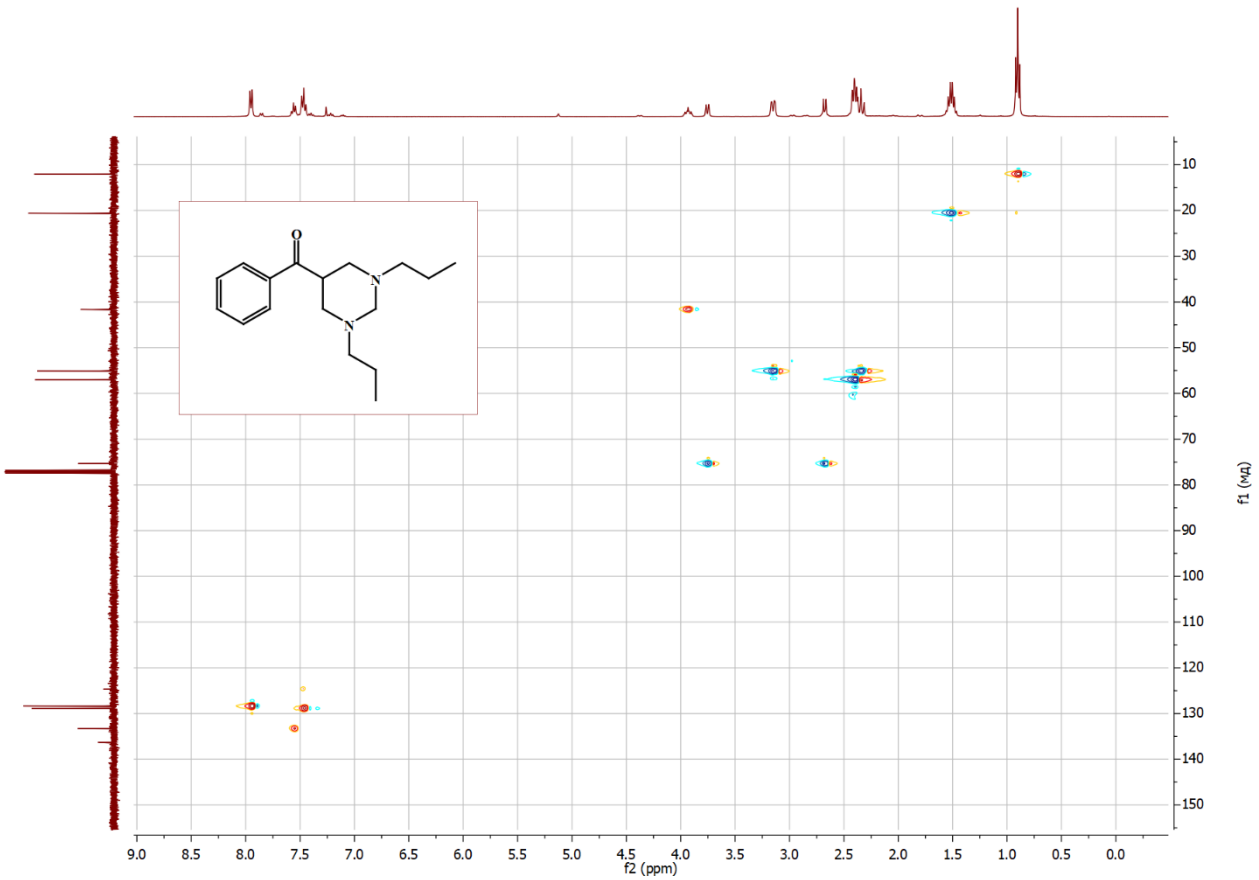


Figure S13. HSQC NMR spectrum of compound **6a**.

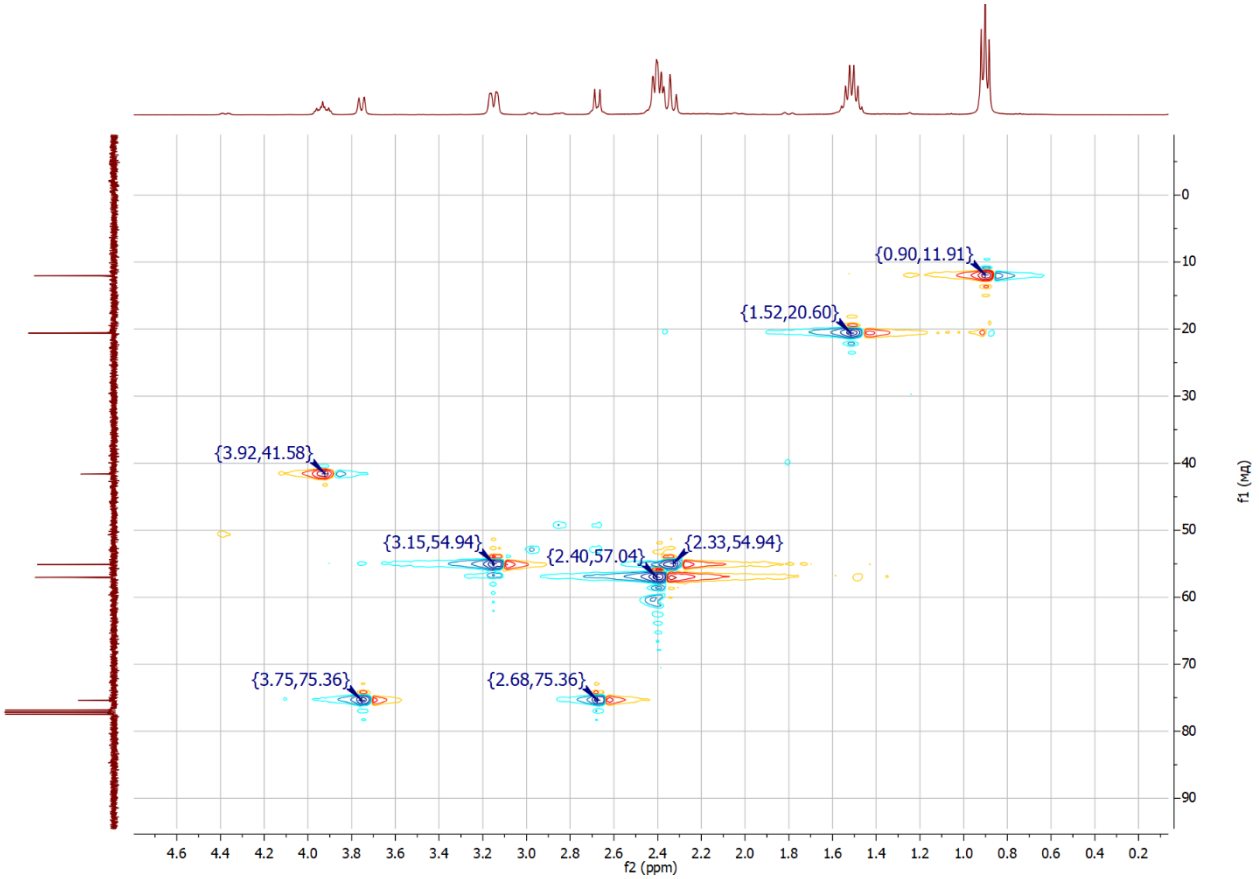
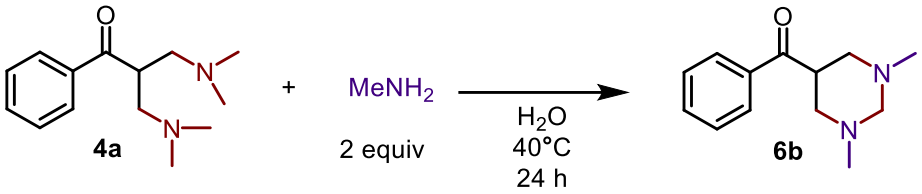


Figure S14. Zoomed-in HSQC NMR spectrum of compound **6a**.

(1,3-dimethylhexahydropyrimidin-5-yl)(phenyl)methanone (6b)



Into a 25 mL round bottom flask, equipped with a Teflon-coated magnetic stir bar, were added **3-(dimethylamino)-2-((dimethylamino)methyl)-1-phenylpropan-1-one 4a** (0.1 g, 0.4 mmol), *N*-methylamine 38% (0.114 ml, 0.8 mmol) in 5 ml H_2O. The inhomogeneous reaction mixture was stirred for 24 h at 40°C. After completion (TLC control), the reaction was quenched with sat. Na_2CO_3 and was extracted with ethyl acetate (3 × 25 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The final product **6b** was obtained by silica gel column chromatography using $CHCl_3$: TEA : MeOH (99.4 : 0.5 : 0.1) as eluent in 50% yield as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 7.4 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 3.94 (tt, *J* = 11.0, 3.7 Hz, 1H), 3.57 (d, *J* = 9.4 Hz, 1H), 3.04 (dd, *J* = 11.2, 3.6 Hz, 2H), 2.57 (d, *J* = 9.4 Hz, 1H), 2.31 (s, 6H), 2.30 – 2.23 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.41, 136.08, 133.32, 128.85, 128.32, 78.50, 56.27, 42.69, 41.52.
EI-MS: calculated for $C_{13}H_{18}N_2O$ $[M\text{-}H]^+$ m/z 217.3; found m/z 217.2
Elemental analysis: calculated for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31. Found: C, 71.43; H, 8.42.

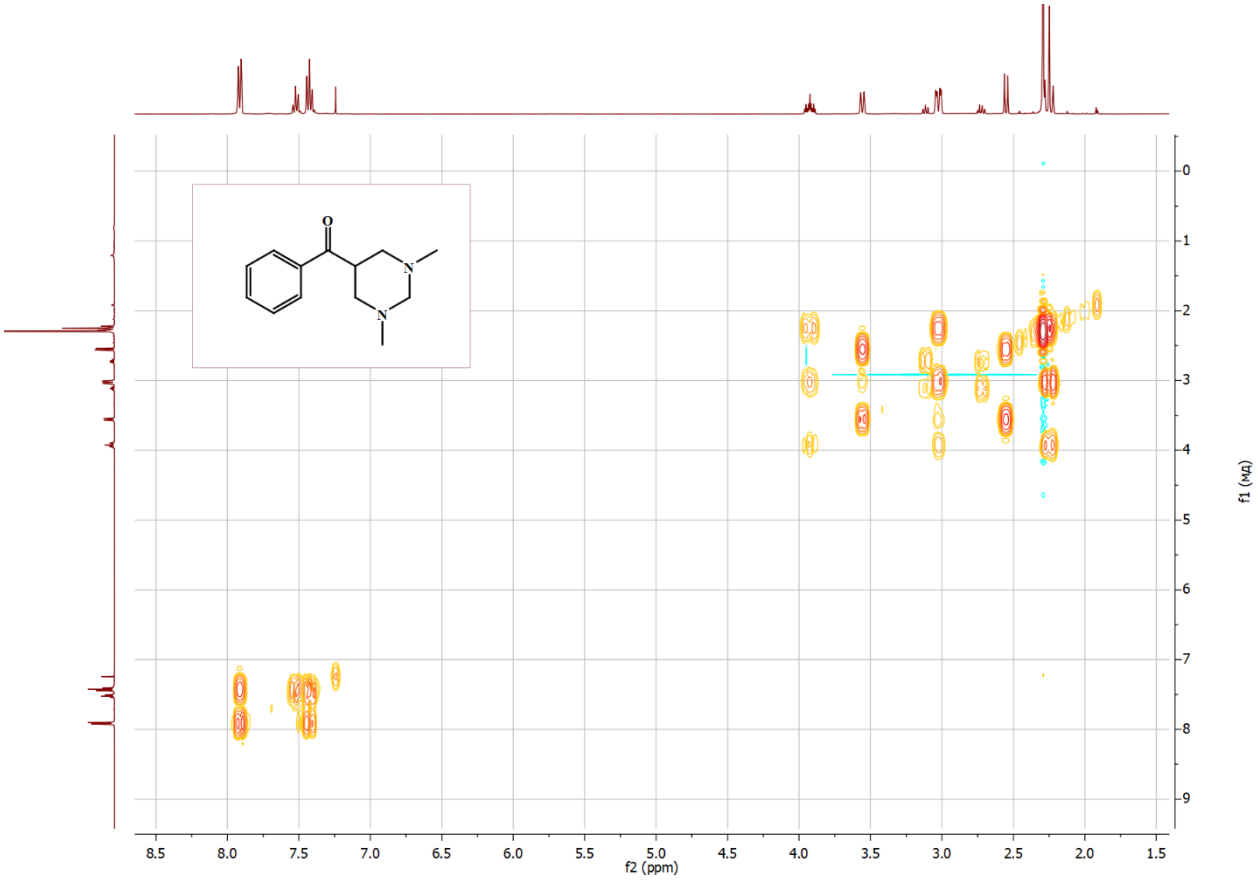


Figure S15. COSY NMR spectrum of compound **6b**.

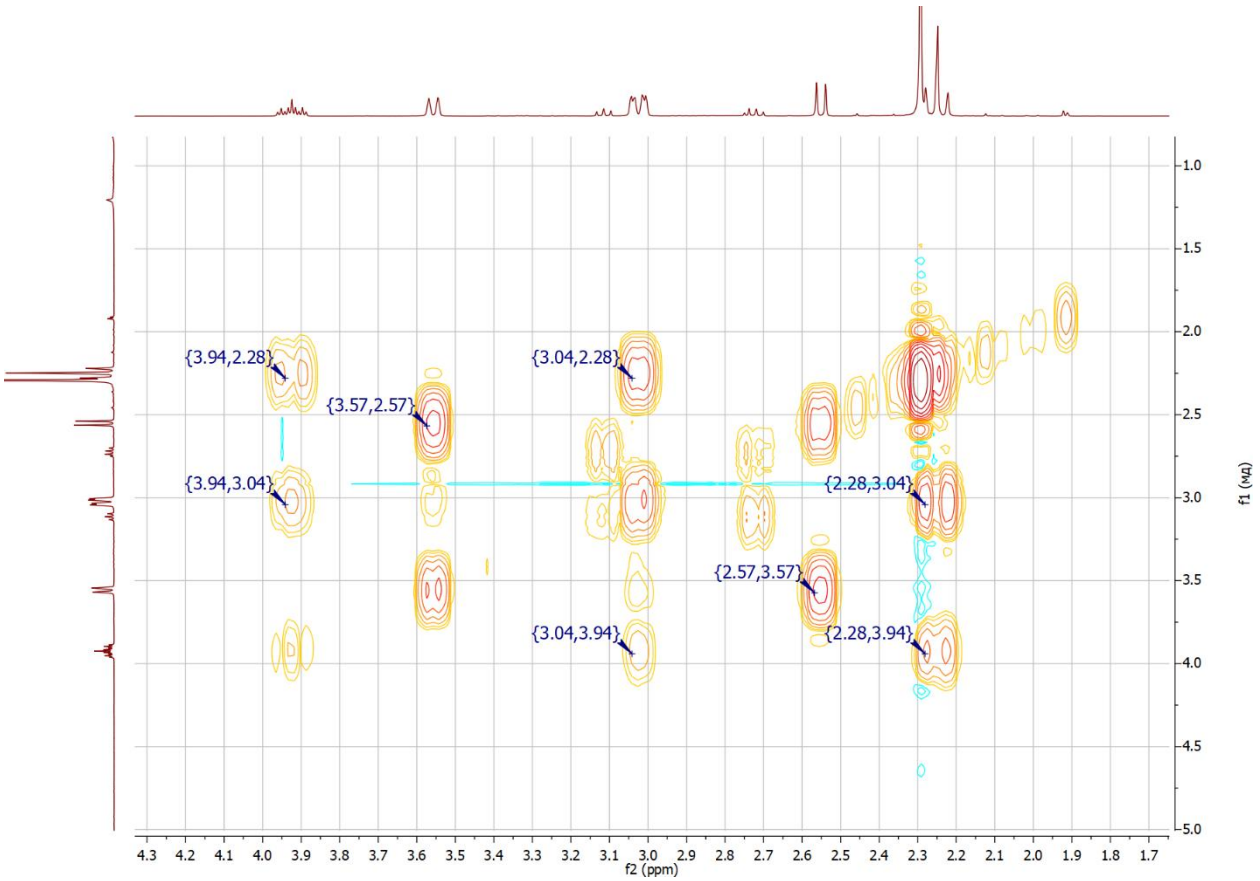


Figure S16. COSY NMR spectrum of compound **6b**.

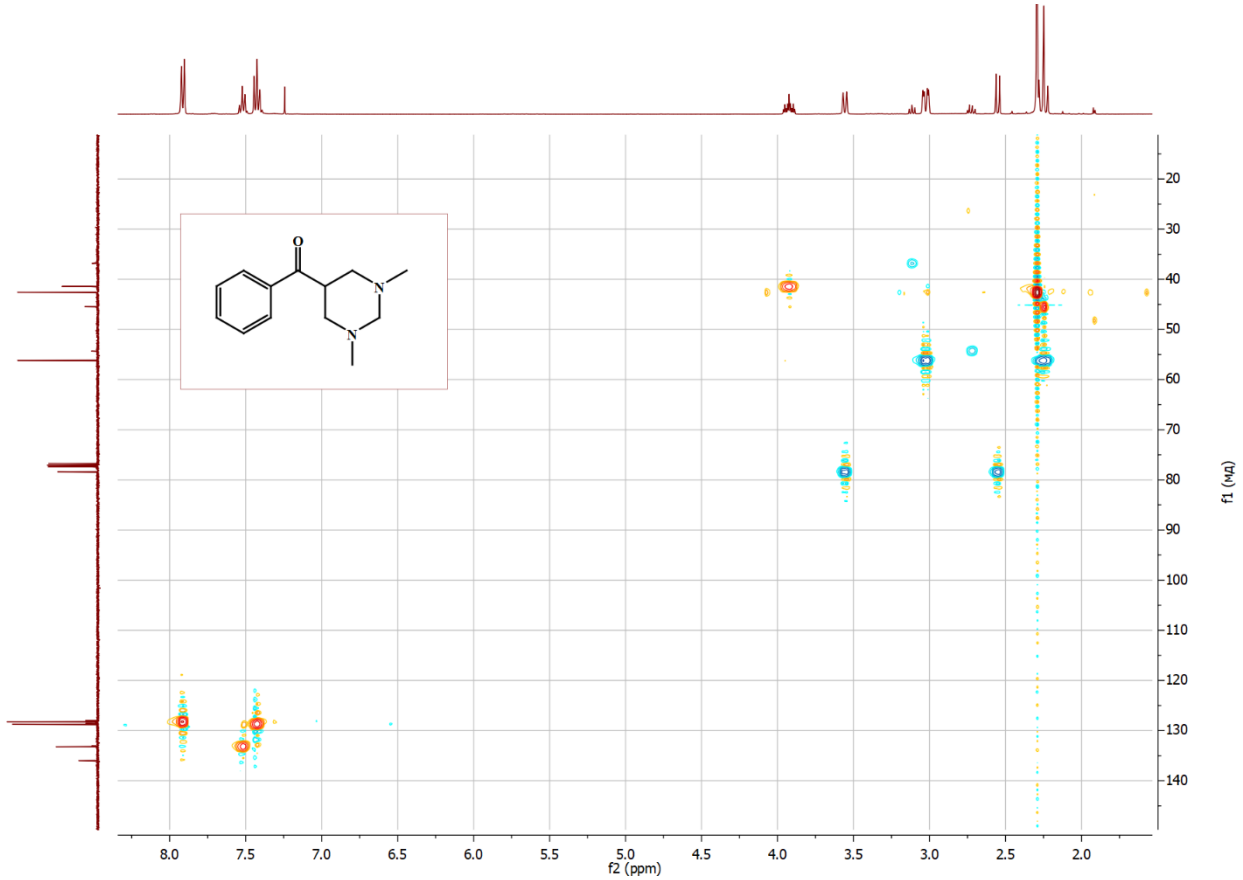


Figure S17. HSQC NMR spectrum of compound **6b**.

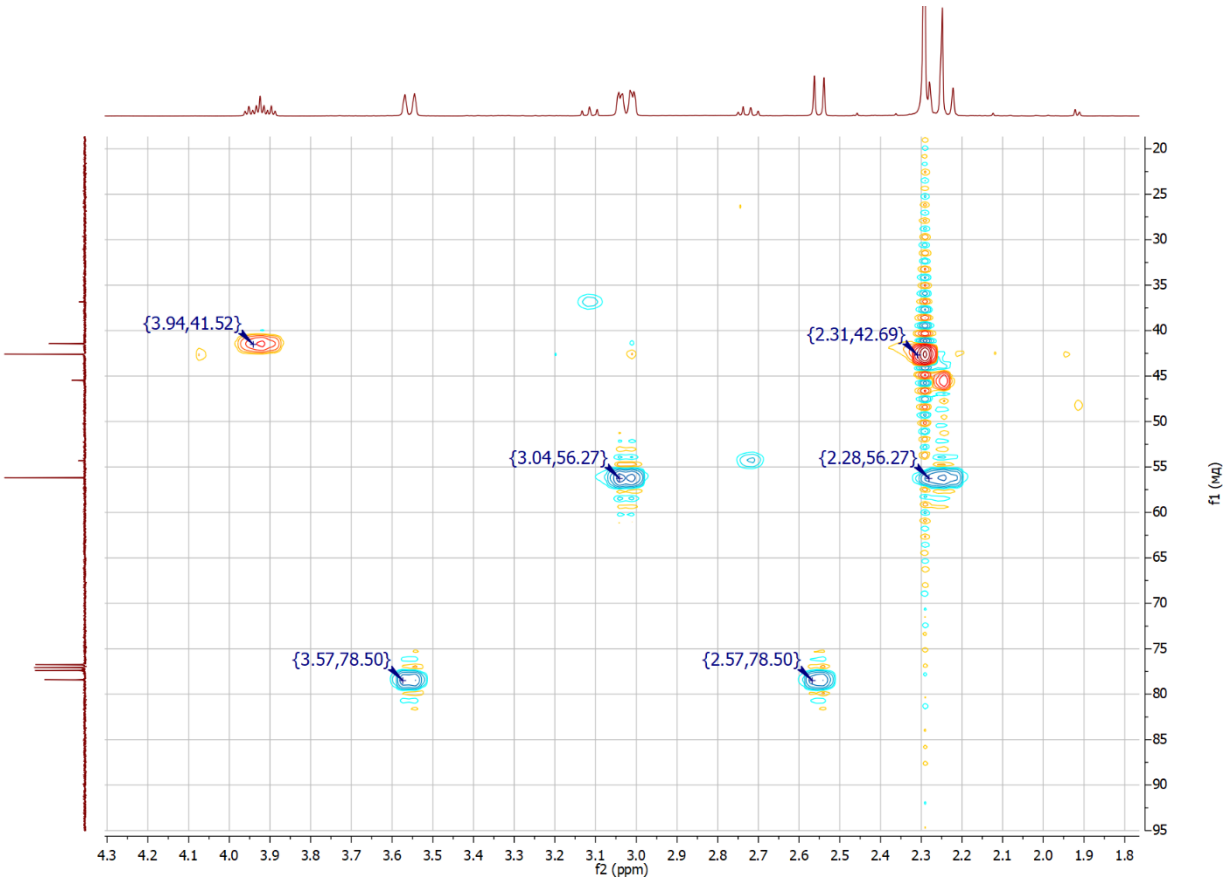
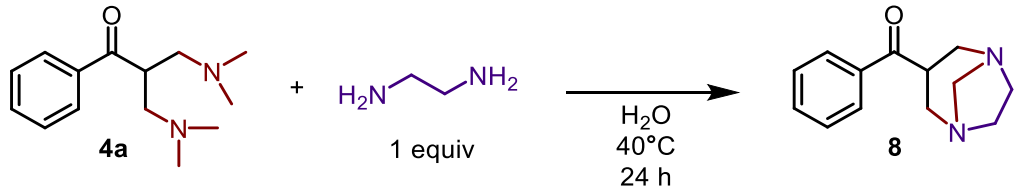


Figure S18. Zoomed-in HSQC NMR spectrum of compound **6b**.

(1,5-diazabicyclo[3.2.1]octan-3-yl)(phenyl)methanone (8)



Into a 25 mL round bottom flask, equipped with a Teflon-coated magnetic stir bar, were added **3-(dimethylamino)-2-((dimethylamino)methyl)-1-phenylpropan-1-one 4a** (0.1 g, 0.4 mmol), ethylenediamine (0.027 ml, 0.4 mmol) in 5 ml H_2O. The inhomogeneous reaction mixture was stirred for 24 h at 40°C. After completion (TLC control), the reaction was quenched with sat. Na_2CO_3 and was extracted with ethyl acetate (3 × 25 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The final product **8** was obtained by silica gel column chromatography using $CHCl_3$: TEA : MeOH (99 : 0.5 : 0.5) as eluent in 48% yield as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 4.06 (d, *J* = 10.6 Hz, 1H), 3.97 (tt, *J* = 11.4, 5.7 Hz, 1H), 3.39 – 3.28 (m, 3H), 3.16 – 3.06 (m, 4H), 3.00 – 2.94 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.29, 136.24, 133.55, 129.00, 128.22, 77.29, 56.96, 52.13, 38.32.
EI-MS: calculated for $C_{13}H_{16}N_2O$ $[M]^+$ m/z 216.3; found m/z 216.2
Elemental analysis: calculated for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46. Found: C, 72.26; H, 7.54.

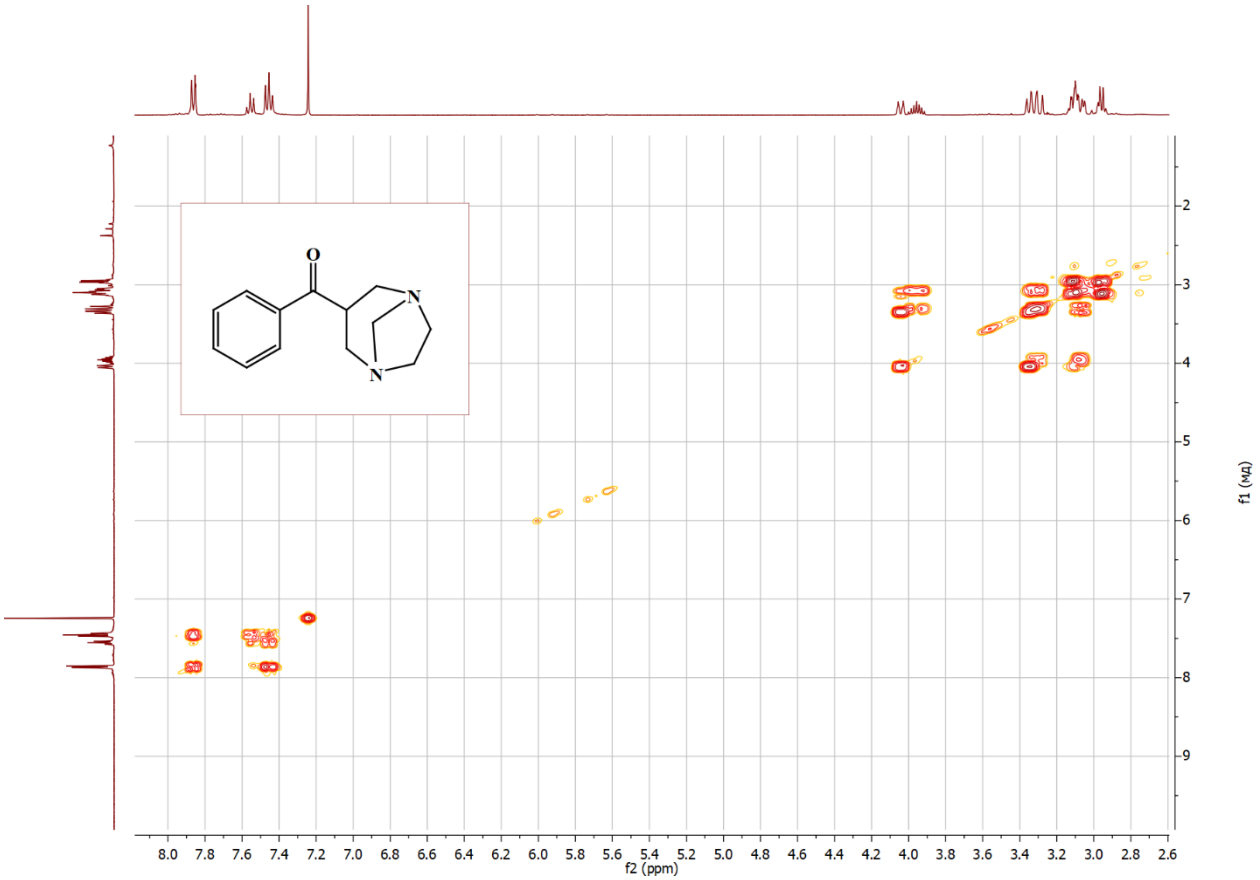


Figure S19. COSY NMR spectrum of compound **8**.

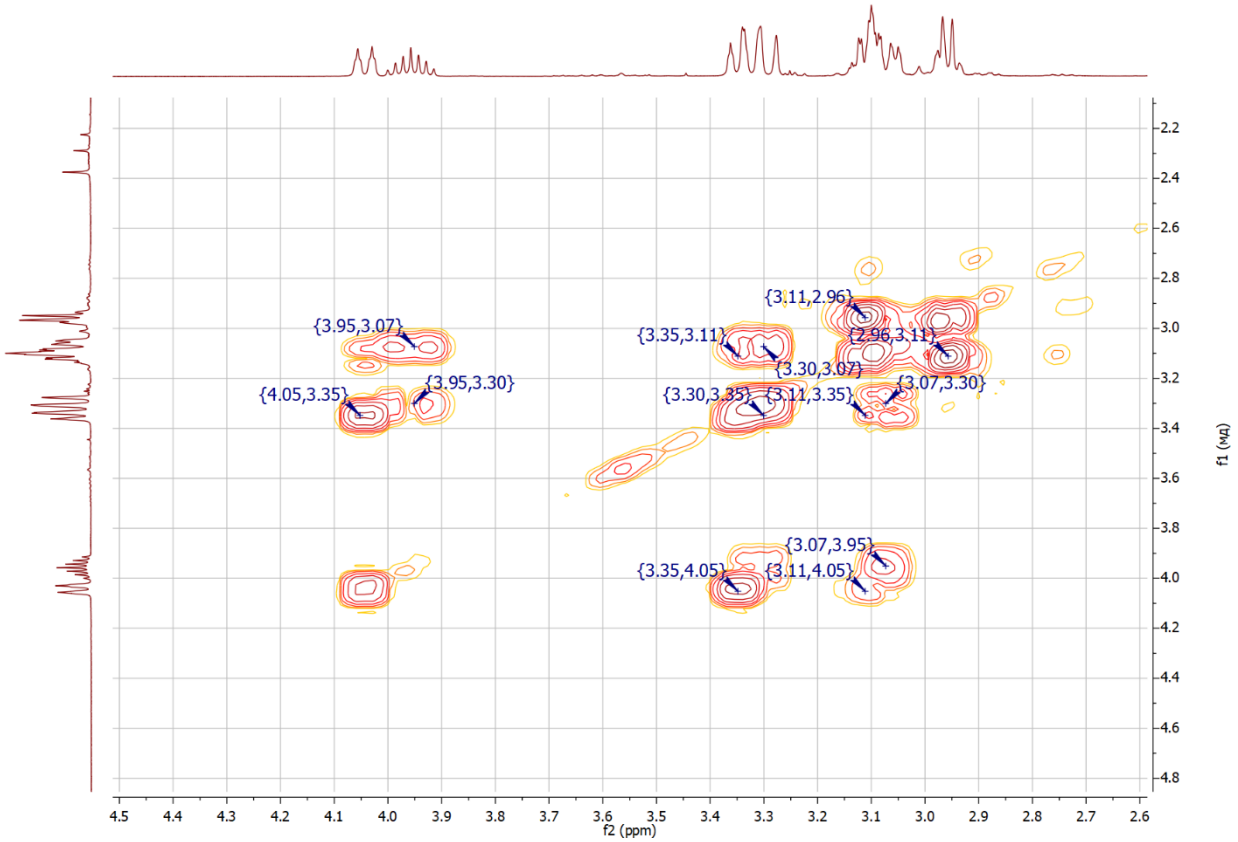


Figure S20. Zoomed-in COSY NMR spectrum of compound **8**.

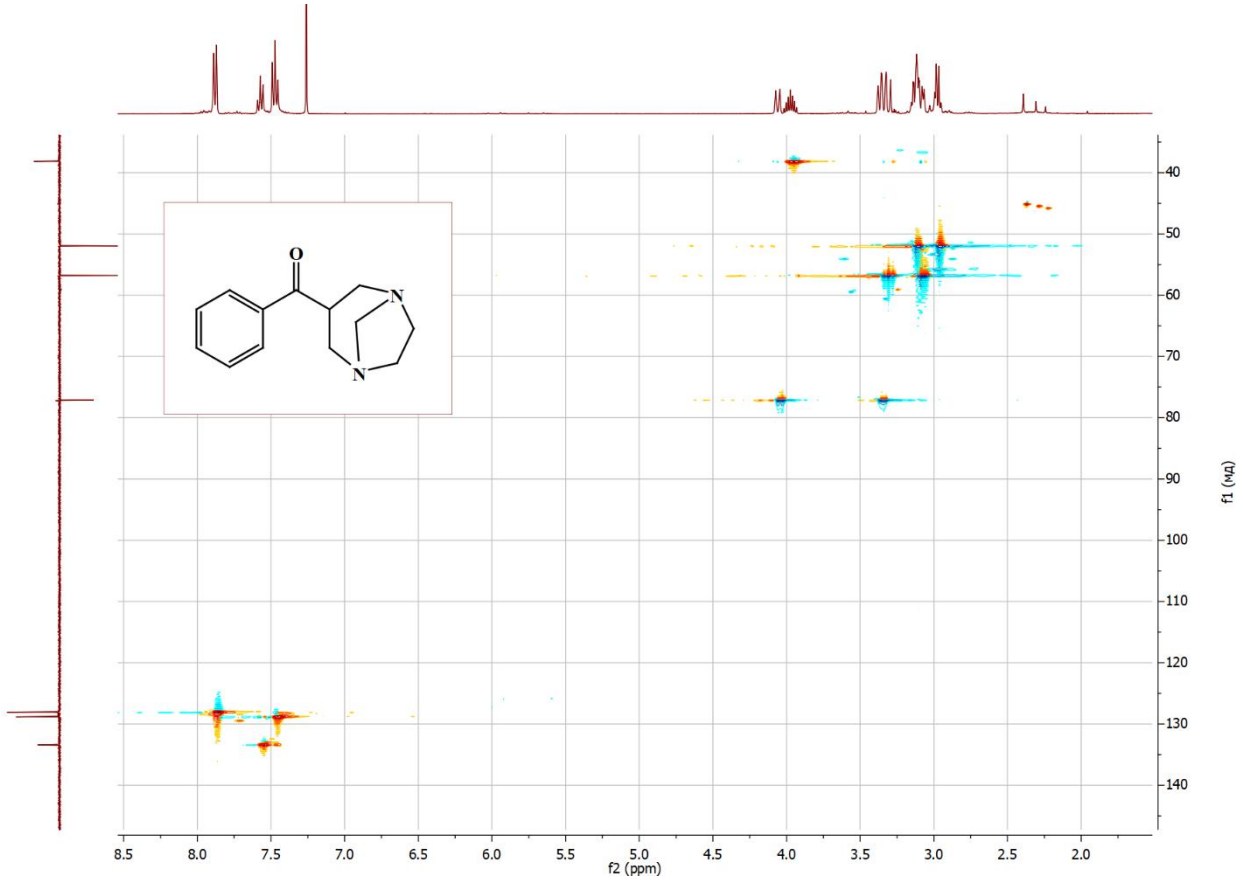


Figure S21. HSQC NMR spectrum of compound **8**.

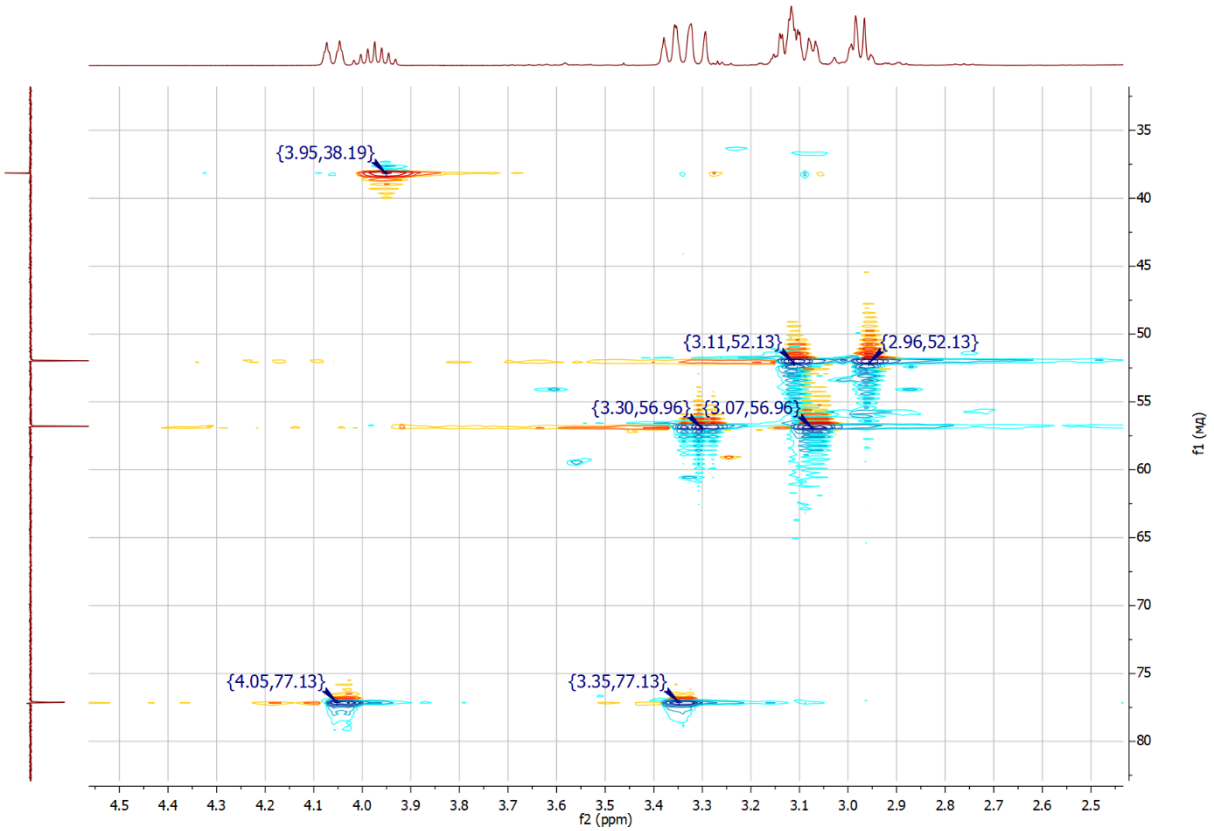
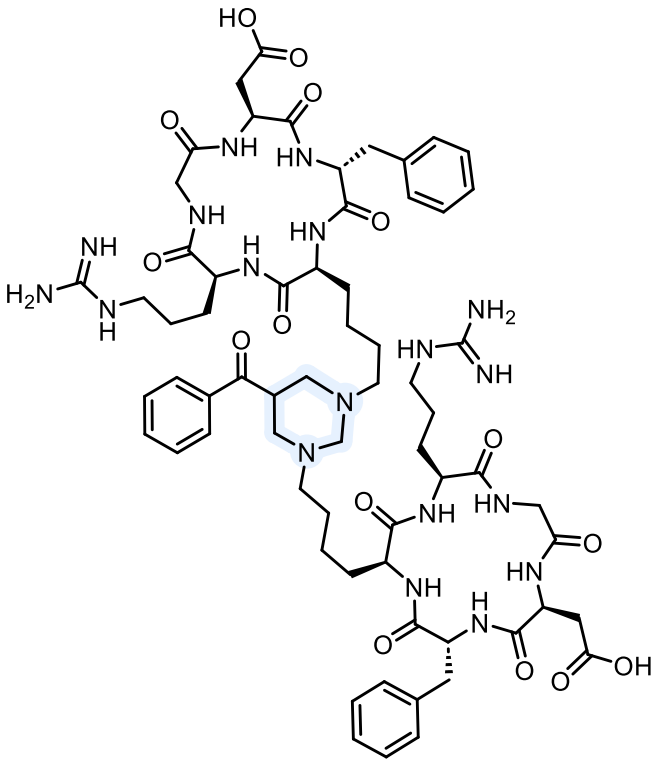


Figure S22. Zoomed-in HSQC NMR spectrum of compound **8**.

Compound 19



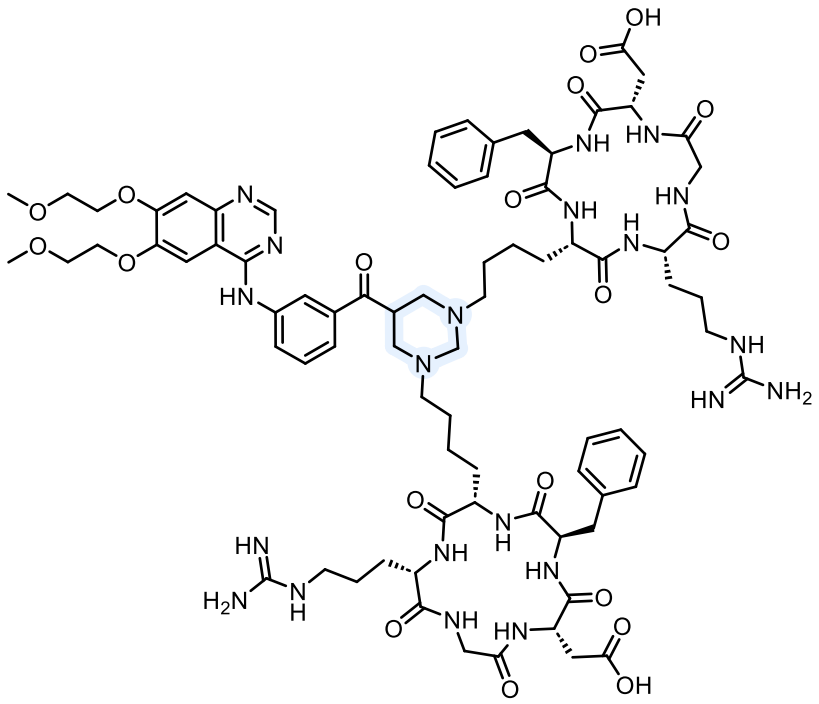
Into a 5 mL round bottom flask, equipped with a Teflon-coated magnetic stir bar, were added **3-(dimethylamino)-2-((dimethylamino)methyl)-1-phenylpropan-1-one 4a** (0.003 g, 0.013 mmol), cyclo(RGDfK) peptide (0.015 g, 0.026 mmol) in 1 ml H_2O. The inhomogeneous reaction mixture was stirred for 24 h at 40°C. After completion, the product was filtered and freeze-dried in 58% yield as a white amorphous solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 8.54 – 8.08 (m, 6H), 8.03 – 7.91 (m, 2H), 7.86 – 7.78 (m, 1H), 7.72 (t, *J* = 9.1 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.57 – 7.52 (m, 3H), 7.45 – 7.38 (m, 1H), 7.24 – 7.11 (m, 10H), 4.65 (td, *J* = 10.1, 9.6, 5.8 Hz, 1H), 4.58 – 4.45 (m, 2H), 4.36 (q, *J* = 8.5 Hz, 1H), 4.15 (p, *J* = 8.3, 7.5 Hz, 3H), 3.96 (dt, *J* = 15.6, 10.2 Hz, 1H), 3.62 (d, *J* = 10.7 Hz, 1H), 3.48 – 3.26 (m, 11H), 3.14 (t, *J* = 7.1 Hz, 1H), 3.10 – 2.98 (m, 5H), 2.79 – 2.67 (m, 3H), 2.65 – 2.57 (m, 3H), 2.54 (s, 1H), 2.37 (s, 2H), 2.33 – 2.24 (m, 2H), 2.15 (s, 2H), 2.09 (s, 2H), 2.06 – 1.99 (m, 1H), 1.89 (s, 1H), 1.84 (s, 2H), 1.80 – 1.34 (m, 13H), 1.24 (br s, 4H), 0.90 – 0.81 (m, 1H).

^{13}C NMR (101 MHz, DMSO-*d*$_6$): δ = 201.17, 199.77, 174.60, 172.43, 171.55, 171.23, 170.79, 168.03, 157.38, 138.89, 137.18, 136.33, 133.51, 129.38, 129.13, 128.41, 126.36, 75.26, 61.35, 61.03, 55.45, 54.68, 53.25, 49.02, 49.00, 46.12, 45.57, 43.35, 41.08, 37.05, 36.73, 27.74, 25.03, 22.43.

MS (MALDI): calculated for $C_{65}H_{90}N_{18}O_{15}$ $[M+H]^+$ m/z 1363.7; found m/z 1363.8

Compound 20



Into a 5 mL round bottom flask, equipped with a Teflon-coated magnetic stir bar, were added **7** (0.003 g, 0.006 mmol), cyclo(RGDfK) peptide (0.007 g, 0.011 mmol) in 1 ml H_2O. The inhomogeneous reaction mixture was stirred for 24 h at 40°C. After completion, the product was filtered and freeze-dried in 43% yield as a white amorphous solid.

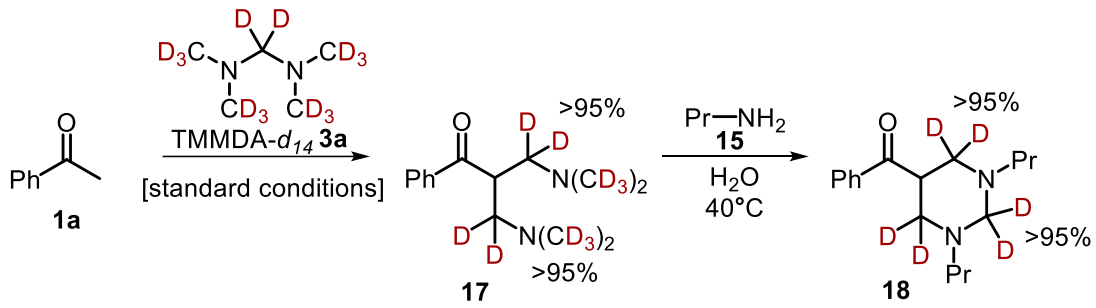
^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.57 (d, *J* = 9.2 Hz, 1H), 8.50 – 8.42 (m, 1H), 8.39 – 8.29 (m, 2H), 8.25 (d, *J* = 9.4 Hz, 3H), 8.20 – 8.03 (m, 2H), 7.98 – 7.88 (m, 1H), 7.83 – 7.65 (m, 4H), 7.61 – 7.32 (m, 4H), 7.29 – 7.06 (m, 10H), 4.64 (td, *J* = 9.3, 5.1 Hz, 2H), 4.55 – 4.44 (m, 3H), 4.43 – 4.32 (m, 3H), 4.32 – 4.21 (m, 4H), 4.20 – 4.10 (m, 5H), 3.80 – 3.72 (m, 4H), 3.42 – 3.30 (m, 8H), 3.06 (t, *J* = 6.9 Hz, 4H), 2.90 (br s, 1H), 2.71 – 2.65 (m, 5H), 2.60 (dd, *J* = 14.3, 9.5 Hz, 2H), 2.35 (s, 6H), 2.11 (d, *J* = 2.6 Hz, 2H), 2.06 (dd, *J* = 16.2, 4.6 Hz, 2H), 1.76 (s, 9H), 1.68 – 1.56 (m, 5H), 1.54 – 1.35 (m, 8H), 1.33 – 1.20 (m, 4H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 174.61, 174.12, 172.39, 171.59, 171.20, 170.79, 167.97, 157.73, 154.13, 154.01, 153.82, 153.23, 148.58, 147.46, 138.96, 129.39, 128.41, 126.38, 70.49, 68.74, 68.47, 58.81, 58.78, 55.45, 53.24, 51.23, 49.14, 46.12, 45.92, 45.56, 43.51, 43.25, 40.89, 37.07, 36.61, 32.12, 28.07, 27.90, 25.19, 23.70, 23.08.

MS (MALDI): calculated for $C_{79}H_{107}N_{21}O_{19}$ $[M+H]^+$ m/z 1655.9; found m/z 1656.1

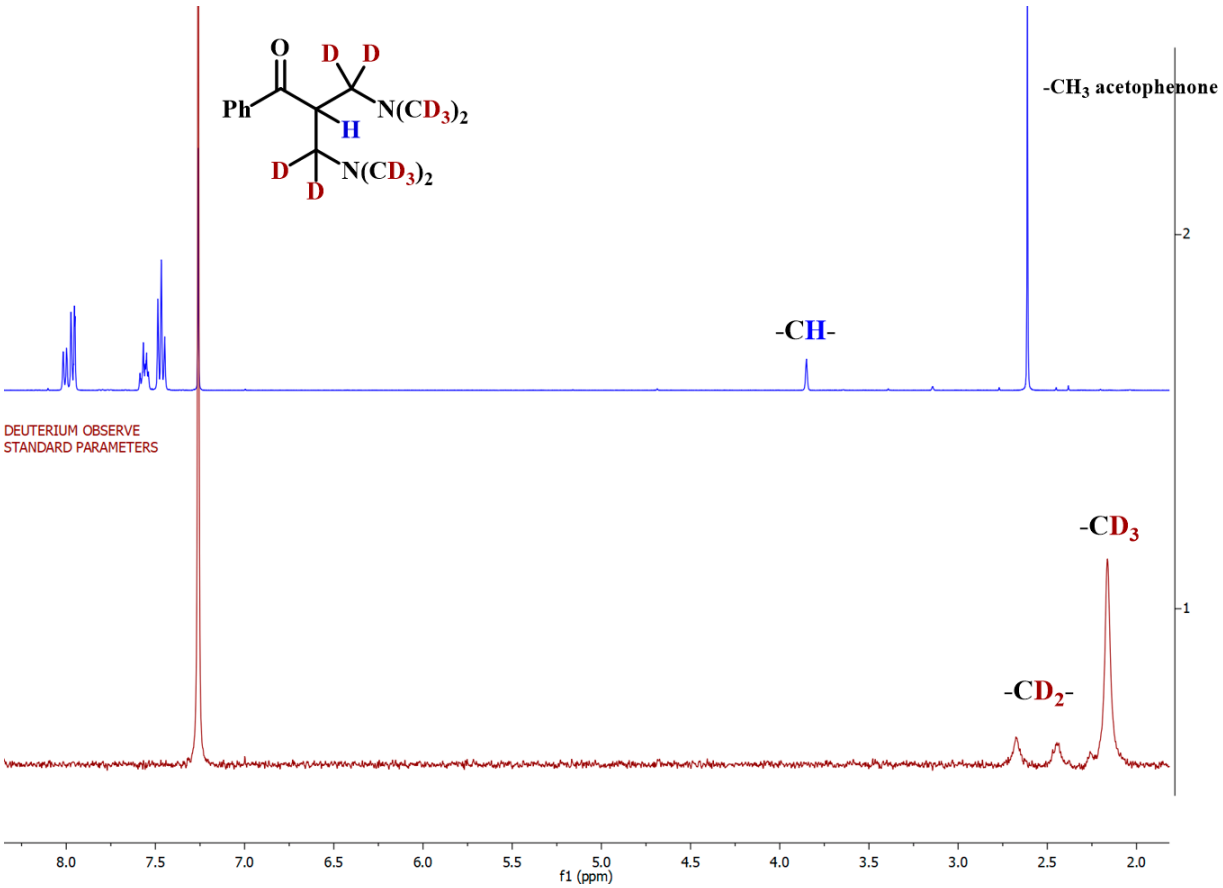
4. Deuterium Labelling Studies

Synthesis of deuterated starting material (**3a**) was previously described[21].



Following the general procedure 1, acetophenone **1a** (20 mg, 0.17 mmol) was subjected to the reaction with TMMDA-d_{14} **3a** (0.065 ml, 0.4 mmol), $ZnCl_2$ (45 mg, 0.3 mmol) in 1,2-DCE (1 ml). Product **17** was isolated by extraction with $CHCl_3$ as a colorless solid (20 mg, 0.08 mmol, 33% yield).

Into a 5 mL round bottom flask, equipped with a Teflon-coated magnetic stir bar, were added **17** (20 mg, 0.08 mmol), *N*-propylamine **15** (0.02 ml, 0.16 mmol) in 1 ml H_2O. The reaction mixture was stirred for 24 h at 40°C. After completion, the reaction was quenched with sat. Na_2CO_3 and was extracted with $CHCl_3$ (3 × 5 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to obtain a crude product **18** which was analyzed by ^1H, ^2H NMR.



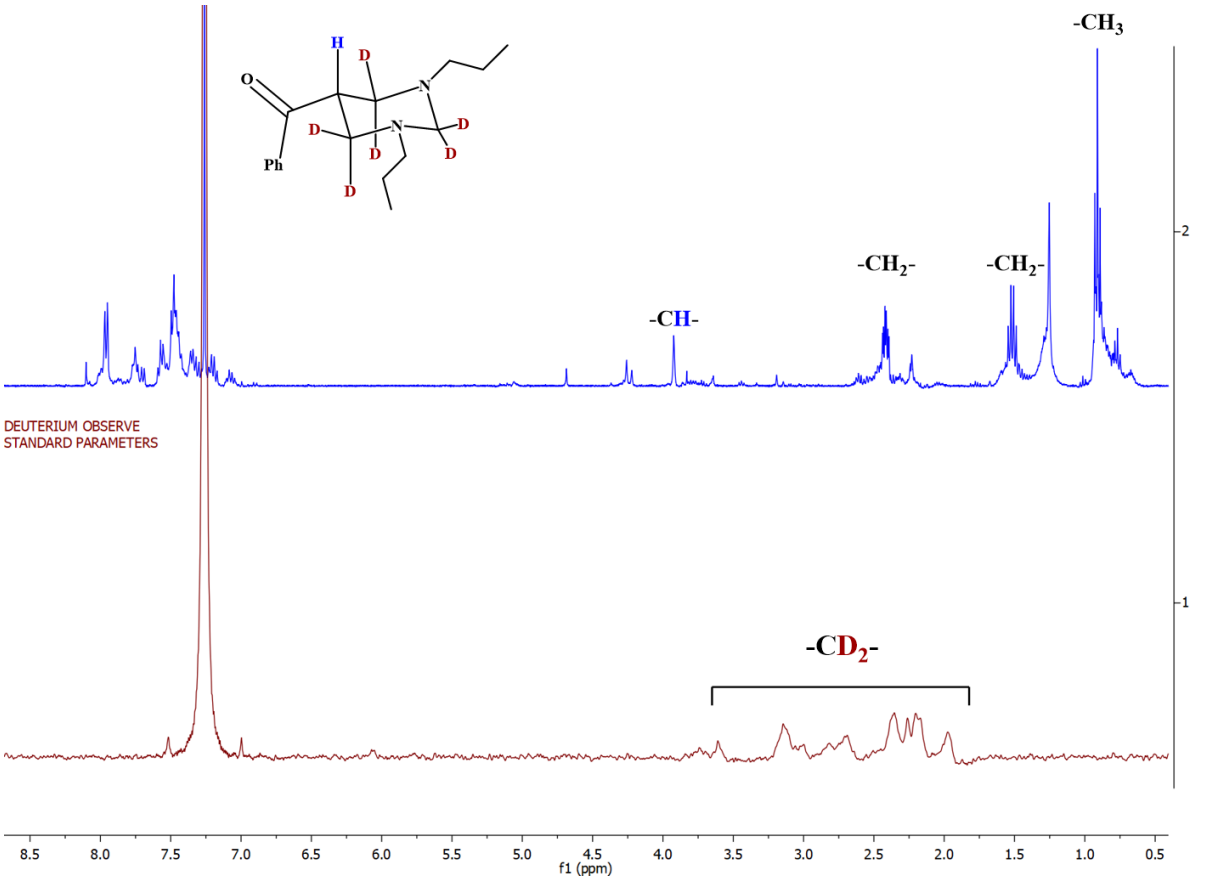


Figure S21. ^{1}H and ^{2}H NMR Spectra of Compounds **17** and **18**

5. *In vitro* cytotoxic activity

Cell Line and Culturing Conditions

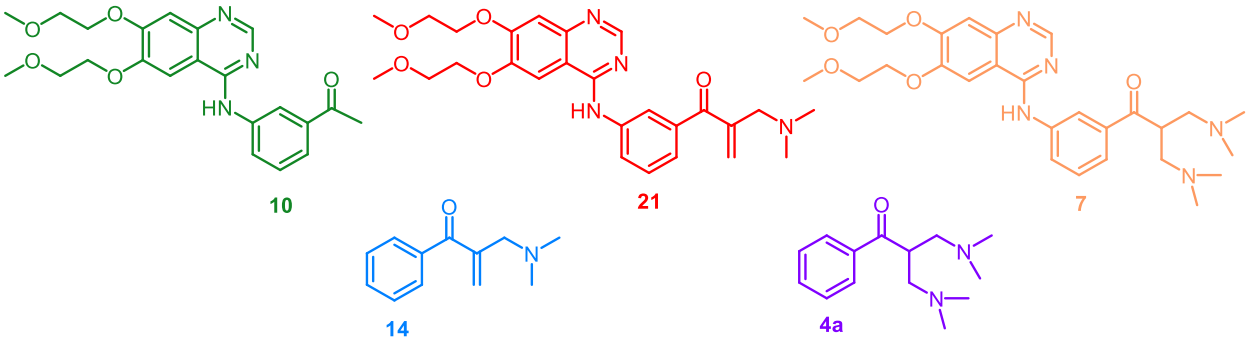
Cell lines of human epidermoid carcinoma A431 and chinese hamster ovary CHO (both lines obtained from Russian Collection of Cell Cultures of Vertebrates) were cultured in Eagle's minimum essential medium (MEM) (PanEco, Russia) with 10% (v/v) fetal calf serum (HyClone) and 2 mM L-glutamine in 5% CO_2 at 37 °C. At each passaging stage, the cells were treated with trypsin-EDTA (1:1) solution (PanEco, Russia). All cells were washed with 10 mM phosphate-buffered saline (PBS).

Cytotoxicity study

The effect of tested compounds on cell viability was estimated using the microculture tetrazoline test (MTT)[22]. Cells were seeded in 96-well plates at the density of 4×10^3 cells per well and allowed to attach overnight. The medium was then exchanged with fresh serum-free growth medium containing the tested compounds in different concentrations, which were prepared by diluting 20 mM DMSO stock solutions. The cells were incubated for 48 h before cell viability was measured. For this, the cells were incubated with serum-free medium containing 0.5 mg/mL MTT reagent [3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazole bromide, Alfa Aesar, U.K.] for 4 h. The formazan formed from the reduction of MTT by cell dehydrogenases was dissolved in DMSO, and the absorbance was measured at 570 nm with a Synergy MX plate reader.

Cell viability was expressed as the ratio of the optical density of treated and untreated cells (in percentage). Three independent experiments (all in triplicate) were performed. Data analysis and calculation of half-maximal inhibition concentration IC_{50} were performed using the GraphPad Prism 6 software and a four-parameter model for the lognormal distribution.

Table S8. *In vitro* cytotoxic activity of tested compounds.



Compound	$IC_{50\ A431}$, μM	$IC_{50\ CHO}$, μM
Erlotinib hydrochloride 9	0.03 [0.02-0.05]	21.89 [14.96-35.61]
21	1.64 [1.43-1.88]	6.82 [5.07-9.50]
7	3.55 [3.07-4.06]	4.48 [3.78-5.28]
10	7.42 [5.85-9.61]	22.37 [13.63-44.76]
14	1.26 [1.01-1.53]	1.42 [1.01-1.20]
4a	1.40 [1.19-1.65]	1.50 [1.10-2.04]

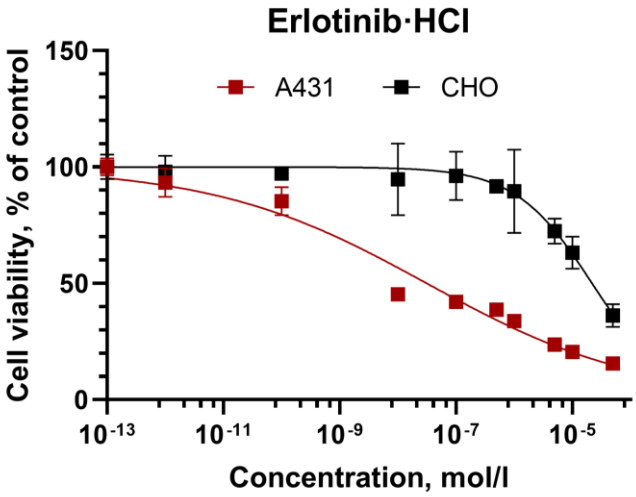


Figure S22. Relative viability of A431 and CHO cells treated with erlotinib hydrochloride **9.** Cells were incubated with the tested compound for 48 h. After that cell viability was measured by MTT-assay and expressed as the percentage to untreated cells. Means ± SD are presented; the experimental data are fitted using four parameters model.

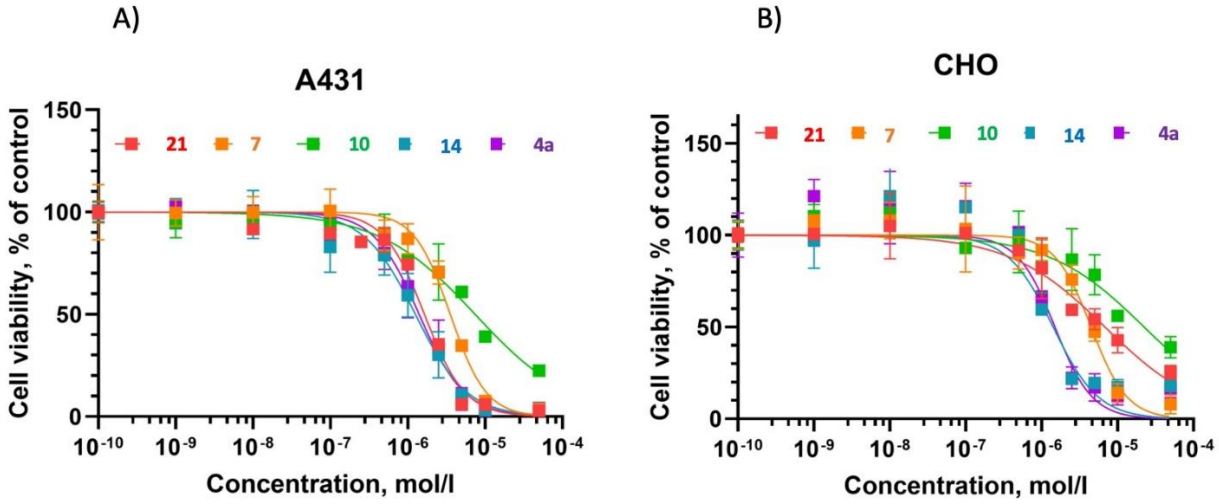
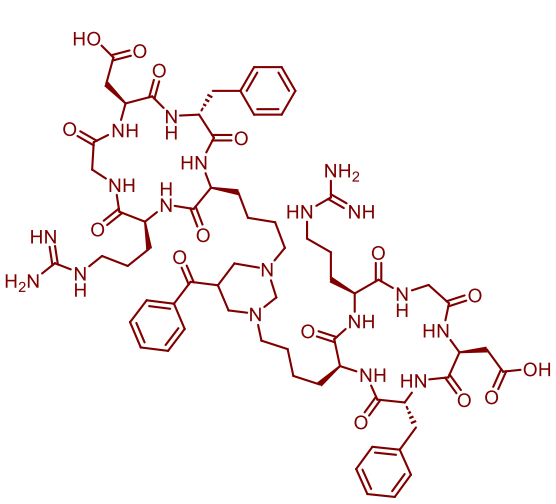
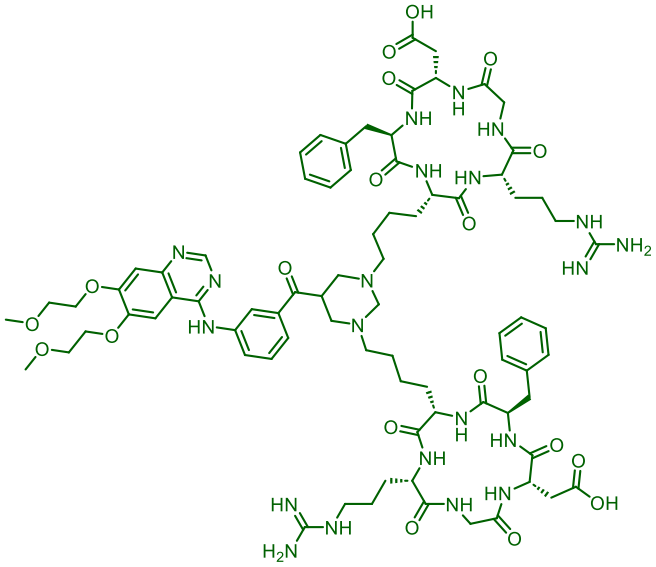


Figure 23. Relative viability of A431 (**A**) and CHO (**B**) cells treated with compounds **4a, 7, 10, 14, 21**. Cells were incubated with tested compounds for 48 h. After that cell viability was measured by MTT-assay and expressed as the percentage to untreated cells. Means ± SD are presented; the experimental data are fitted using four parameters model.

Table S9. *In vitro* cytotoxic activity of tested compounds **19,20.**



19



20

Compound	$IC_{50\ A431}$, μM	$IC_{50\ CHO}$, μM
19	2.64 [1.95-3.60]	2.72 [1.40-5.33]
20	6.07 [5.16-7.14]	6.27 [4.26-13.47]

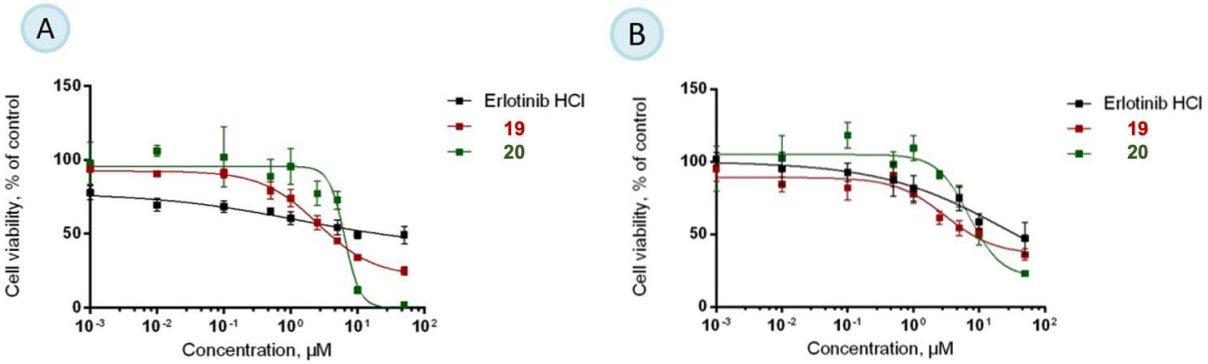


Figure 24. Relative viability of A431 (A) and CHO (B) cells treated with compounds **19,20**. Cells were incubated with tested compounds for 48 h. After that cell viability was measured by MTT-assay and expressed as the percentage to untreated cells. Means ± SD are presented; the experimental data are fitted using four parameters model.

6. Photograph of the reaction flask during the preparation of bis-Mannich base **4a**

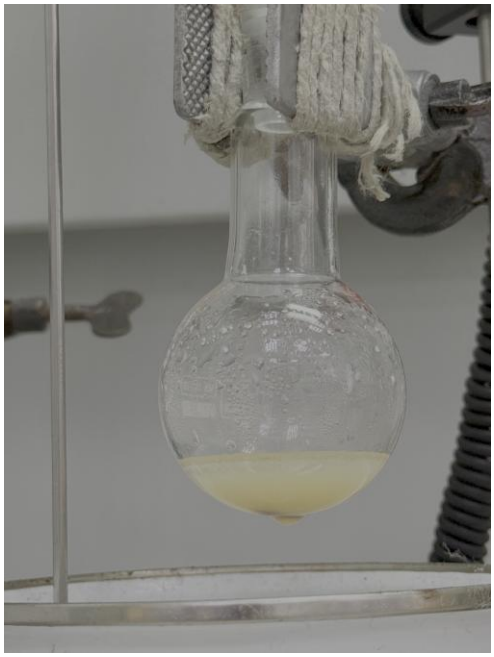
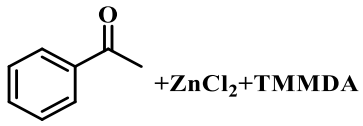


Figure S25. Photograph of the reaction flask during the preparation of bis-Mannich base **4a**.

6. Computational data

DFT calculations were carried with the ORCA 6.0 software[23-30] package using the M06-2X functional (with the GRID3 integration) with the def2-SVP basis set for all atoms. Frequency calculations were conducted for all structures, confirming either a minimum or a TS. Transition states were found using NEB-TS algorithm implemented in ORCA 6.0. All structures were optimized with the CPCM solvent model applied for DCE to evaluate solvent effects. Unless otherwise stated, all results presented are at the (CPCM= DCE)/M06-2X/def2-SVP level of theory. The Gibbs Free energy values are reported at 298 K, unless noted otherwise. Three-dimensional structures were produced with CYLView20[31] and plots for reaction coordinates were created with the mechaSVG software[32].

Cartesian coordinates



Charge: 0

Multiplicity: 1

Number of Imaginary Frequencies: 0

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C -3.24838 2.65151 0.47742

C -2.91698 1.80296 -0.58924

C -3.28683 0.74844 1.97566

C -2.98297 -0.09480 0.90481

C -2.80000 0.43159 -0.37575

H -2.77008 2.20741 -1.59172

H -2.88008 -1.16848 1.07088

H -2.56153 -0.22864 -1.21052

H -3.62443 2.76962 2.61861

H -3.40794 0.34092 2.97998

C -3.39805 4.11158 0.26343

O -4.09748 4.79292 1.01565

C -2.69147 4.76938 -0.87659

H -1.64973 4.42901 -0.94569

H -2.74813 5.85710 -0.76490

H -3.20007 4.47735 -1.80988

Zn -5.70142 4.20940 2.15764

Cl -5.38776 4.56134 4.31208

Cl -6.95589 3.13732 0.68718

N -0.49057 4.93778 3.37553

C -1.83372 4.71848 3.87418

H -1.93389 3.68479 4.23013

H -2.04440 5.40296 4.70858

H -2.60650 4.89400 3.09475

C -0.11324 3.96371 2.37668

N -0.04348 2.62165 2.91128

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H 0.86623 4.28034 1.95179

C -0.33133 6.28558 2.87298

H -0.57674 7.01017 3.66237

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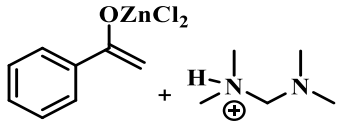
H 0.70784 6.45555 2.55672



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Multiplicity: 1

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C -4.22469 -0.72405 0.46981

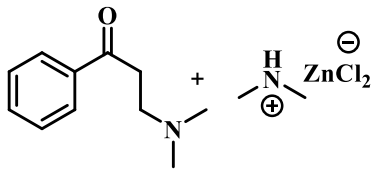
C -4.53891 -1.07060 -0.84499

C -4.06440 -0.28629 -1.89889

H -2.94119 1.46684 -2.46511
H -5.15725 -1.94639 -1.04904
H -4.31615 -0.54514 -2.92891
H -3.20435 0.67424 1.75884
H -4.59060 -1.33252 1.29876
C -2.16714 2.42090 -0.01411
O -2.47472 3.02979 1.13990
C -1.17836 2.85792 -0.81848
H -1.25093 3.46840 1.98846
H -0.63897 3.77542 -0.57382
H -0.89610 2.30381 -1.71278
Zn -4.28833 3.25506 1.78279
Cl -4.33287 3.92835 3.93786
Cl -6.05006 2.83811 0.48733
N -0.33310 5.77636 4.15701
C -1.18640 6.09199 5.29102
H -1.87880 5.26167 5.48544
H -0.56901 6.24666 6.18743
H -1.78540 7.00916 5.12369
C -1.00933 5.21546 3.03640
N -0.57840 3.79563 2.76220
C 0.82455 3.71233 2.31366
H 1.47485 4.05100 3.13079
H 0.95887 4.35262 1.43359
H 1.05433 2.67147 2.05830
C -0.83610 2.91186 3.91946
H -0.23899 3.26188 4.77046
H -1.90695 2.95694 4.15451
H -0.54939 1.88934 3.64751
H -2.09630 5.15354 3.19507
H -0.81676 5.76518 2.10234
C 0.61513 6.83357 3.85232
H 1.23370 7.03775 4.73774

H 0.11486 7.77770 3.55861

H 1.28301 6.52577 3.03672



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C -5.49816 3.48693 0.24345

C -5.61810 2.40566 1.12005

C -4.47539 1.78921 1.62879

H -2.32905 1.76793 1.68725

H -6.60692 2.04630 1.41141

H -4.56741 0.94730 2.31681

H -4.12305 4.78702 -0.80780

H -6.39162 3.97702 -0.14755

C -1.75100 3.85628 -0.07164

O -1.67812 4.57465 -1.04799

C -0.53040 3.50686 0.75065

H 0.35890 3.74379 0.14959

H -0.51896 2.42583 0.94303

Cl -4.17830 4.73484 3.61163

H -1.52938 4.51501 2.41408

H -0.08751 3.61300 2.87964

C -0.49654 4.27520 2.10305

H -3.47326 8.22914 4.33916

Zn -3.64626 6.55655 2.44999

H 0.17121 6.09999 0.05961

N -2.71703 7.89044 3.73822

H 2.08319 4.80949 1.15425

H -2.87730 9.50844 2.39473

C -0.09454 6.44158 1.08043

N 0.28957 5.49671 2.11044

H -1.18409 6.60623 1.08823

C 1.71946 5.25784 2.10262

H -2.24542 6.36485 5.10740

C -2.12746 9.04744 3.04886

C -1.73905 7.18817 4.58815

H 1.99337 4.58566 2.92815

H -1.75076 9.78846 3.77047

H 0.40652 7.40574 1.25603

H -1.28814 7.87374 5.32224

H -1.28966 8.69904 2.43074

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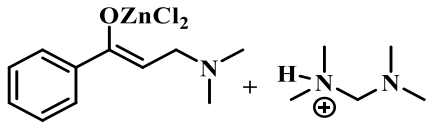

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C -4.56749 2.79575 -1.26371

C -5.54748 2.60807 -0.28896

C -5.22377 2.81185 1.05507

H -3.70450 3.37968 2.46926

H -6.55777 2.30819 -0.57246

H -5.98299 2.67422 1.82751

H -2.52021 3.32659 -1.67098

H -4.80359 2.63902 -2.31813

C -1.55222 3.87934 0.78208

O -0.93826 4.54464 -0.18481

C -1.02195 3.59125 1.99596

H -1.63668 2.96339 2.64748

H 0.05532 4.51399 3.58024

H 0.78587 3.03885 2.97771

C 0.29688 3.97306 2.64353

H 0.16718 6.26339 0.91609

H 1.26128 3.96003 -0.04185

C 0.94382 6.13089 1.69386

N 1.29357 4.75171 1.94531

H 0.58381 6.59396 2.62731

C 1.92787 4.07977 0.83171

H 2.26904 3.08302 1.15293

H 1.84148 6.68443 1.37420

H 2.81559 4.65139 0.51657

Zn -1.69031 5.86778 -1.32890

Cl -1.91996 8.02058 -0.59843

Cl -2.11818 5.42153 -3.48392

H -2.65295 9.32900 1.99997

H -1.45081 8.21279 4.14249

C -3.65980 8.99659 2.27911

C -1.75151 7.26467 4.60792

H -2.04023 7.47117 5.64818

H -4.41450 9.61040 1.77550

H -3.79583 9.03213 3.36592

H -0.87544 6.58693 4.62266

H -1.81294 7.06976 2.11604

N -2.88122 6.68927 3.89558

N -3.81941 7.59114 1.84132

C -2.77724 6.68726 2.48033

H -3.59567 7.57061 0.82987

C -3.34812 5.44736 4.48967

C -5.19374 7.08866 2.05960

H -3.57400 5.61407 5.55203

H -5.89781 7.74062 1.53147

H -2.94395 5.69455 2.03735

H -5.39529 7.10550 3.13729

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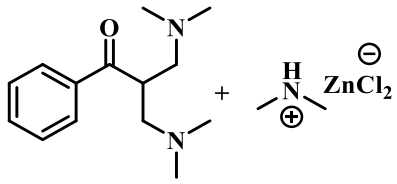
H -4.27057 5.11024 3.99751

H -5.25835 6.06374 1.67379



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C -4.25312 2.08803 -1.41050

C -5.33235 1.95180 -0.53232

C -5.21378 2.38637 0.78742

H -3.95241 3.28578 2.26996

H -6.26695 1.50728 -0.87906

H -6.05347 2.28314 1.47633

H -2.21805 2.78565 -1.64142

H -4.34365 1.75122 -2.44447

C -1.62167 3.72742 0.75298

O -0.73610 3.81880 -0.07132

C -1.46186 4.28823 2.15355

H -2.07488 3.66902 2.82559

H -0.11854 4.72076 3.73355

H 0.14889 3.14648 3.00460

C -0.03659 4.20335 2.76060

H 0.44518 5.98689 0.51542

H 1.52754 3.53029 0.30060

C 1.05602 5.98125 1.44232

N 1.13944 4.68587 2.06866

H 0.62683 6.72031 2.13420

C 1.91922 3.72883 1.31403

H 1.96339 2.77402 1.85795

H 2.06797 6.32582 1.17637

H 2.95188 4.10193 1.21292

Zn -2.80152 7.95235 0.17127

Cl -0.90380 9.04871 0.63466

Cl -3.24863 6.27889 -1.23141

H -3.30697 10.15797 2.14933

H -0.97666 7.87515 3.19310

C -3.97197 9.35288 2.48493

C -1.33384 7.19742 3.98280

H -1.77163 7.81506 4.78325

H -4.83910 9.77696 3.01354

H -3.41851 8.69074 3.16396

H -0.46242 6.66703 4.41505

H -1.50080 6.38142 1.56317

N -2.36381 6.33218 3.44465

N -4.40125 8.55426 1.32414

C -2.12110 5.69896 2.16522

H -4.92763 9.16311 0.69142

C -3.02085 5.50807 4.43205

C -5.27979 7.43841 1.71703

H -3.40376 6.14331 5.24499

H -6.20835 7.80990 2.17571

H -3.09302 5.58410 1.64895

H -4.73994 6.82148 2.44923

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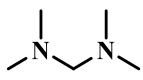

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N -1.68644 -0.09025 5.84253

C -1.63058 1.00827 4.90028

H -2.31708 1.84097 5.16535

H -1.90611 0.65587 3.89481

H -0.60976 1.41233 4.84714

C -1.13036 0.21976 7.15748

H -1.89274 0.03471 7.93384

H -0.86832 1.29074 7.20302

N 0.05223 -0.53483 7.51881

C -0.21146 -1.95624 7.62199

H -0.48888 -2.41087 6.64856

H -1.03547 -2.13389 8.32968

H 0.68294 -2.47573 7.99647

C 1.16871 -0.26567 6.63472

H 0.98284 -0.60812 5.59580

H 1.37223 0.81565 6.60714

H 2.06969 -0.77683 7.00481

$ZnCl_2$

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Multiplicity: 1

Number of Imaginary Frequencies: 0

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Cl 2.77753 -0.64520 0.00018

Cl 4.42782 3.35277 -0.00019

Charge: 0

Multiplicity: 1

Number of Imaginary Frequencies: 0

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H -8.87278 -3.39963 -0.97216

C -6.06012 -3.54424 -1.87529

C -9.04807 -3.36920 0.10074

H -6.94419 -4.74471 0.15435

H -5.73775 -4.58717 -1.95725

H -9.34578 -4.36397 0.44735

H -5.48728 -2.93454 -2.57155

H -9.85384 -2.66408 0.29743

C -6.65500 -3.74814 0.50084

Zn -6.85610 -1.18821 -0.06817

N -5.83708 -3.04315 -0.50951

N -7.83871 -2.91896 0.80668

H -6.06310 -3.84392 1.40891

C -4.40288 -3.09717 -0.18820

C -8.10347 -2.84660 2.25141

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H -8.35007 -3.83434 2.65331

H -3.85626 -2.52265 -0.93381

H -8.94395 -2.17503 2.41828

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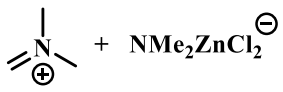

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Multiplicity: 1

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H -4.73557 -4.98838 1.08133

H -9.33451 -4.40436 0.40970

H -5.90472 -3.66202 1.32747

H -10.42159 -3.02682 0.57851

C -4.53886 -3.06754 -1.34621

Zn -7.29281 -1.30922 -0.15583

N -5.19221 -3.86262 -0.60507

N -8.35681 -2.56659 0.79235

H -4.76032 -3.02621 -2.40472

C -6.26813 -4.71283 -1.12199

C -8.31556 -2.74098 2.22202

H -6.01586 -5.74868 -0.90195

H -8.16275 -3.79784 2.50260

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H -9.24894 -2.42481 2.71643

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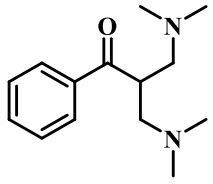

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Multiplicity: 1

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C -5.75109 2.62448 -0.28428

C -5.36985 2.85443 1.03845

H -3.75615 3.29351 2.38652

H -6.79726 2.42525 -0.52317

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H -2.69656 2.90919 -1.77207

H -5.08960 2.46848 -2.33616

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H -1.64101 3.29963 2.67754

H 0.45704 3.87495 3.27805

H 0.75313 3.03208 1.73995

C 0.32424 3.95250 2.19028

H 1.66328 4.45526 -0.16031

H 3.00570 4.32668 2.06472

C 1.14041 5.30167 0.33264

N 1.04979 5.14020 1.76963

H 0.14101 5.37755 -0.11560

C 2.36421 5.17908 2.37804

H 2.27469 5.15182 3.47367

H 1.68920 6.22751 0.10557

H 2.87943 6.10870 2.09642

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H -2.50470 7.73755 3.30916

H -1.36199 7.56644 4.67203

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N -1.57567 5.82231 3.53134

C -1.77355 5.38199 2.16174

C -2.54665 5.24583 4.43803

H -2.32544 5.55294 5.47020

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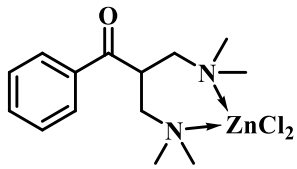

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Multiplicity: 1

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H -6.75795 2.43241 -0.63864

H -6.12847 2.72848 1.75026

H -2.65172 3.08796 -1.78513

H -5.02156 2.61492 -2.41485

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H 0.39041 3.69616 3.36300

H 0.63077 2.98177 1.75661

C 0.26334 3.87827 2.28496

H 1.54881 4.58886 -0.06471

H 2.88426 3.82121 1.78532

C 1.14585 5.40694 0.55350

N 1.14017 5.02431 1.97326

H 0.13405 5.63861 0.20491

C 2.51855 4.68224 2.37039

H 2.54611 4.44675 3.44132

H 1.76235 6.30786 0.44198

H 3.16728 5.54881 2.18332

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C -2.20977 7.44926 3.36595

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H -1.92927 8.00501 4.27052

H -1.52940 6.08013 1.28712

N -1.51161 6.15103 3.36348

C -1.85180 5.43794 2.12062

C -1.88656 5.38931 4.56198

H -1.64798 5.98839 5.44887

H -2.95044 5.35430 2.04771

H -1.31130 4.45763 4.62685

H -2.96618 5.15670 4.54788

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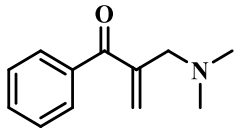
Cl 0.89375 8.53268 2.14711

Cl 1.37941 6.11785 5.35058



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Charge: 0

Multiplicity: 1

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C -5.23145 2.03061 3.18251

C -4.02462 2.37809 3.79443

H -2.24358 3.60749 3.68386

H -5.87342 1.27202 3.63440

H -3.71709 1.88547 4.71840

H -5.06157 4.07564 0.45423

H -6.56451 2.38045 1.51435

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O -2.67158 4.97808 0.09099

C -1.69442 5.71956 2.11348

H -5.48102 4.58804 3.75690

H 0.01315 4.59351 1.64496

H -0.28476 5.94132 0.53014

C -0.28353 5.65377 1.59993

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N 0.73935 6.41175 2.32500

H -0.36261 8.22184 2.37513

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H 2.17691 4.88842 2.13499

H 1.38432 8.35953 2.72921

H 2.84212 6.53357 2.30551

H 0.75137 8.63980 5.85241

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H -0.36196 8.46842 7.23321

H -1.52746 7.06580 3.76232

N -0.38661 6.88768 5.80544

C -2.16080 6.42093 3.14910

C -1.63531 6.35505 6.24577

H -1.76125 6.39041 7.35397

H -3.21449 6.33820 3.42619

H -1.74351 5.29909 5.93986

H -2.52506 6.90320 5.83975

Zn 0.78687 6.03513 4.50820

Cl 2.91960 6.92130 4.88760

Cl 0.46935 3.73153 4.33123

N -6.05551 5.08053 4.45634

C -5.24034 5.08383 5.74938

N -5.92494 5.76612 6.78240

C -5.33230 7.02528 7.20859

H -6.06156 7.58491 7.81043

H -4.42146 6.87315 7.81883

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C -6.37244 4.94315 7.89578

H -7.09664 5.50881 8.49804

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H -4.27943 5.55073 5.48278

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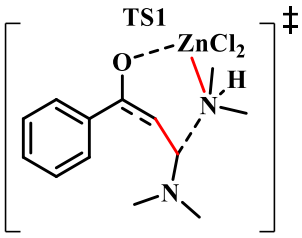
H -7.10062 3.31750 4.96082

H -7.84448 4.30560 3.65248



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Multiplicity: 1

Number of Imaginary Frequencies: 1

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C -1.23671 -1.67578 -1.53128

C -0.71962 -2.78751 -0.84949

C -3.47637 -2.55244 -1.17848

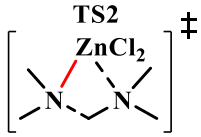
C -2.95135 -3.64922 -0.49248

C -1.56965 -3.76432 -0.33016

H 0.36125 -2.87876 -0.71642
H -3.61714 -4.41221 -0.08559
H -1.15068 -4.61705 0.20725
H -3.04489 -0.72737 -2.24058
H -4.55483 -2.46029 -1.31879
C -0.33473 -0.61041 -2.08298
O -0.73918 0.64237 -1.97463
C 0.83700 -0.95785 -2.66566
H 1.49221 -0.18765 -3.07577
H 1.11524 -2.00484 -2.78061
Cl -2.73024 0.73319 1.06716
H -0.19395 0.13530 0.49750
H 0.44546 -1.29801 1.57276
C 0.62724 -0.46757 0.88491
H -0.73188 2.18062 1.80723
Zn -2.08124 1.53272 -0.95186
H 2.87348 0.60309 -1.06201
N 0.22181 2.44334 1.56885
H 3.44334 -1.44135 0.18008
H -0.54364 3.75663 0.12266
C 2.13273 0.94252 -0.32857
N 1.82492 -0.18330 0.55542
H 1.21358 1.27603 -0.82150
C 2.97504 -0.94538 1.04038
H 0.52692 2.23047 3.67126
C 0.23019 3.73353 0.90389
C 1.09194 2.35709 2.73449
H 2.64443 -1.68416 1.77670
H 0.04792 4.58820 1.58506
H 2.55704 1.74495 0.29140
H 1.69517 3.27224 2.83974
H 1.20242 3.90254 0.41307
H 3.69021 -0.24500 1.48995

Cl -2.74937 3.53654 -1.69898

H 1.80152 1.51217 2.66447



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Multiplicity: 1

Number of Imaginary Frequencies: 1

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C 0.56456 -1.43970 -0.71322

C -2.37568 0.47683 -0.60305

H 1.56544 -0.78638 1.60791

H 0.97233 -2.22278 -1.35215

H -2.44010 -0.52400 -1.07163

H -0.22488 -0.89316 -1.22466

H -3.41399 0.76193 -0.37204

C 2.02545 -0.26342 0.78089

Zn -0.25999 1.84267 0.93981

N 1.64242 -0.49606 -0.40904

N -1.52350 0.46910 0.55700

H 2.80580 0.46217 0.96660

C 2.21064 0.19243 -1.57033

C -2.00014 -0.45286 1.55398

H 2.63676 -0.56003 -2.23303

H -2.02736 -1.49067 1.17022

H 1.40884 0.73704 -2.06557

H -3.02598 -0.23255 1.88903

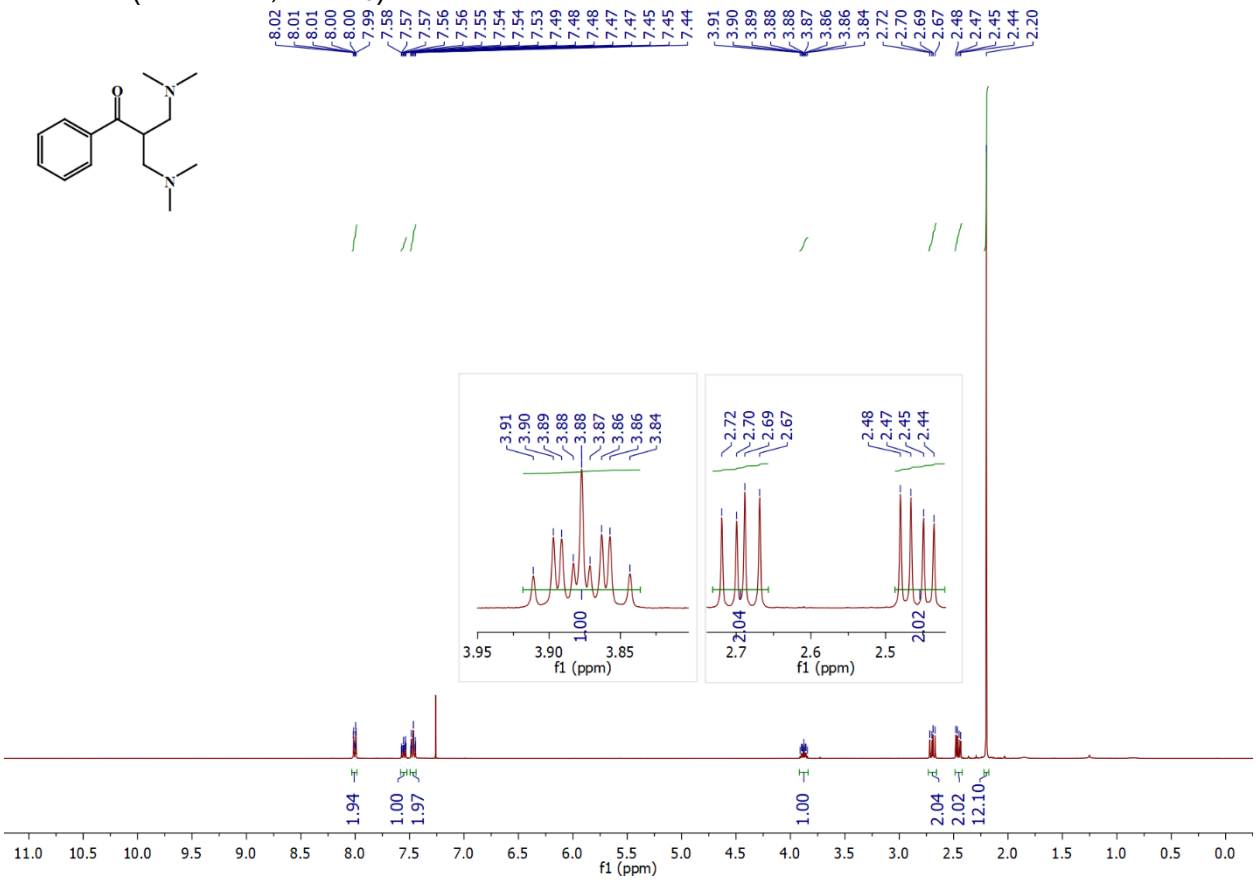
Cl 0.98372 1.62124 2.82344

H 2.96153 0.90366 -1.24237

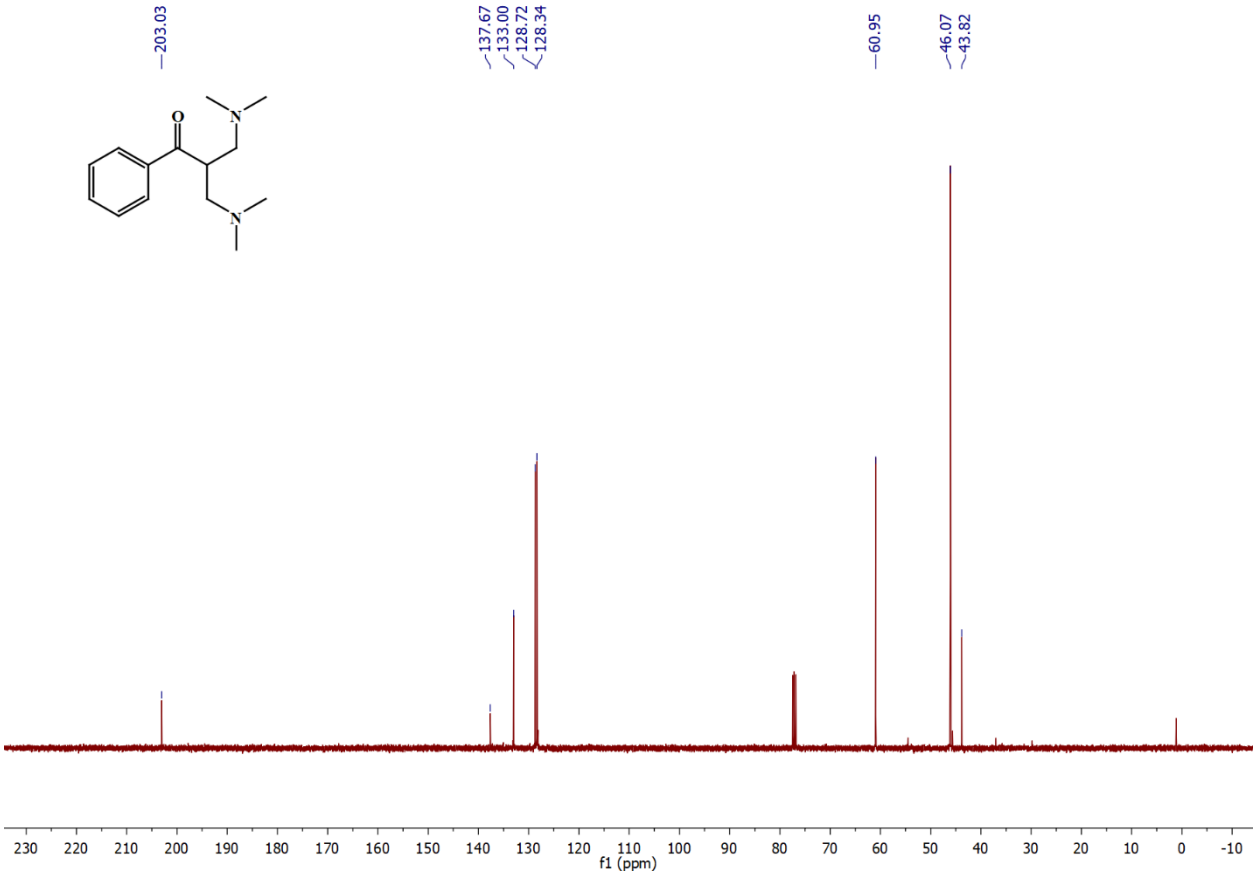
H -1.35577 -0.43669 2.43664

7.1 Copies of NMR spectra

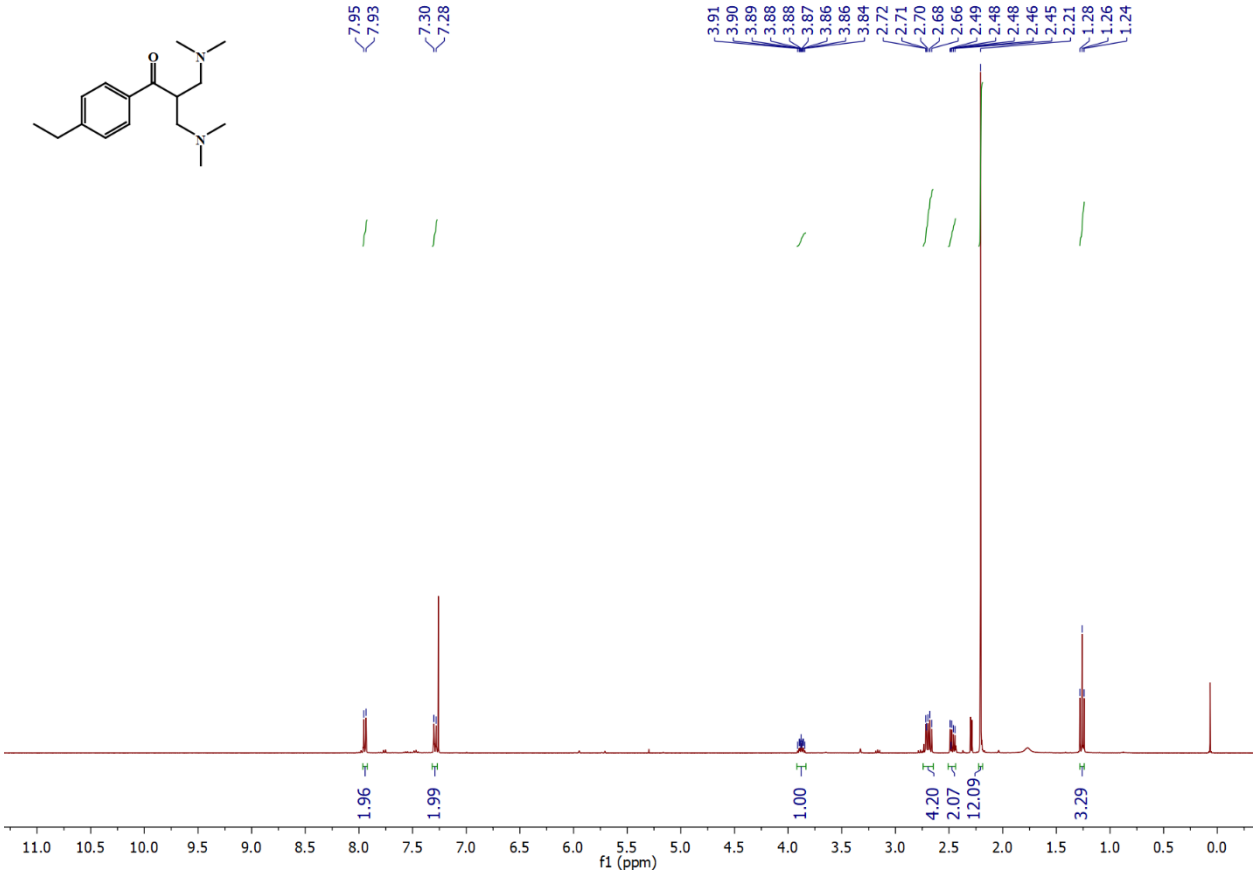
^{1}H NMR (400 MHz, $CDCl_3$) of **4a**



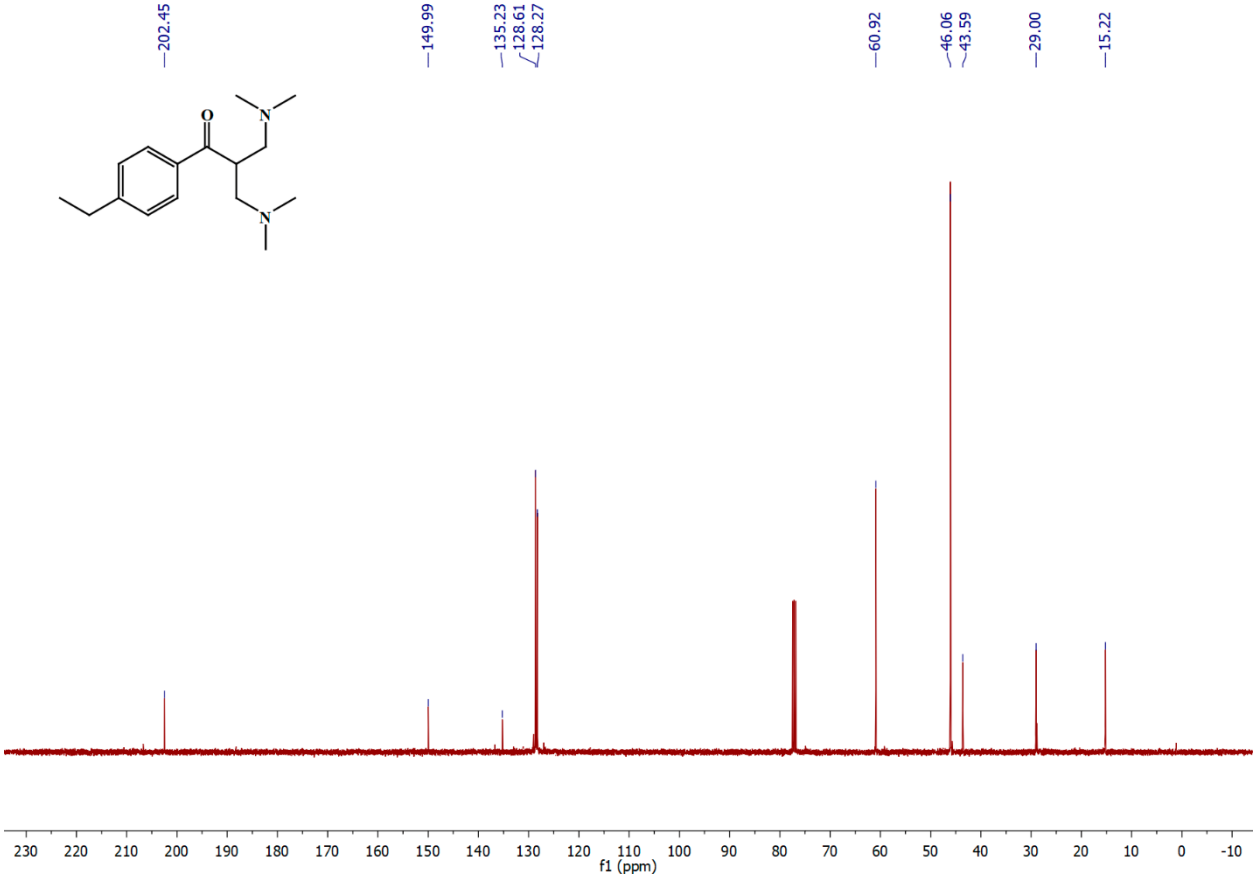
^{13}C NMR (101 MHz, $CDCl_3$) of **4a**



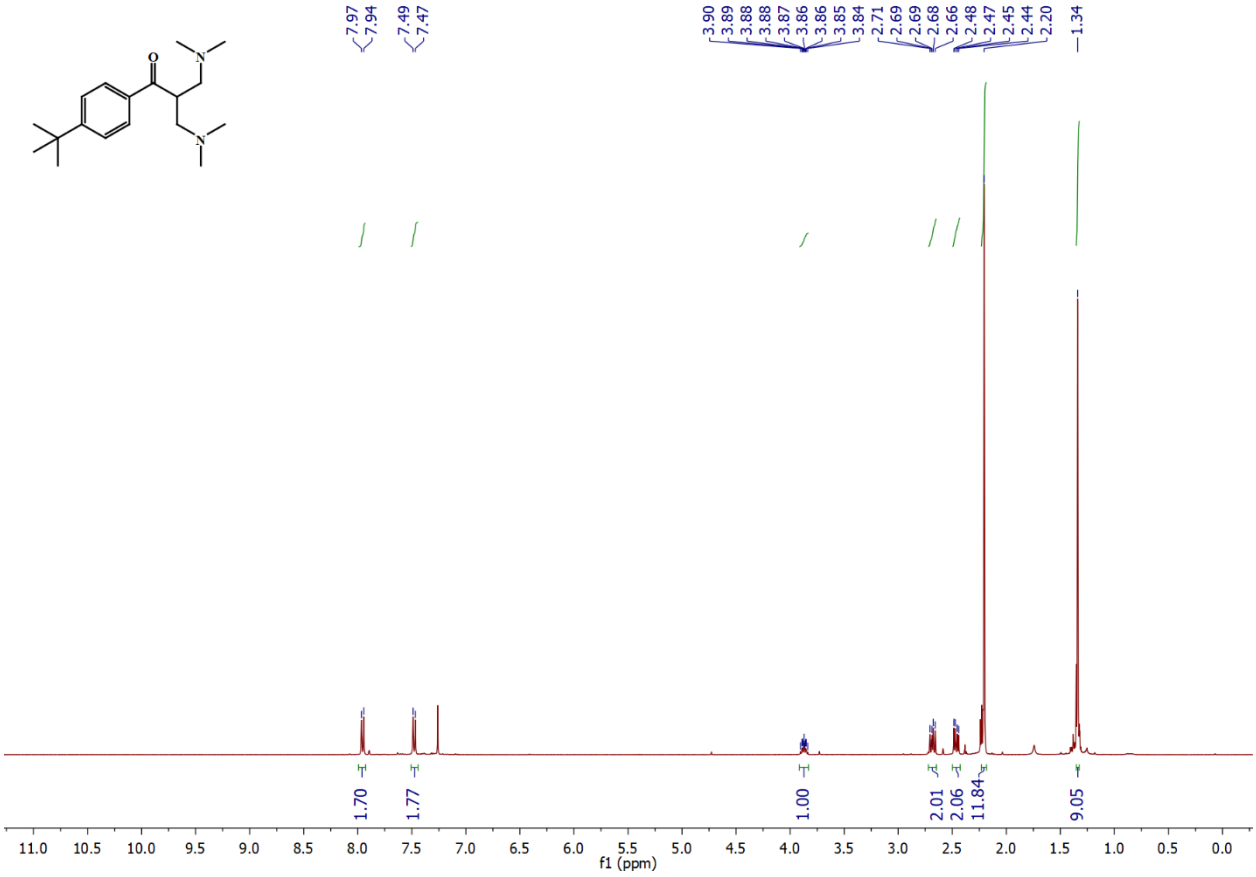
^{1}H NMR (400 MHz, $CDCl_3$) of **4b**



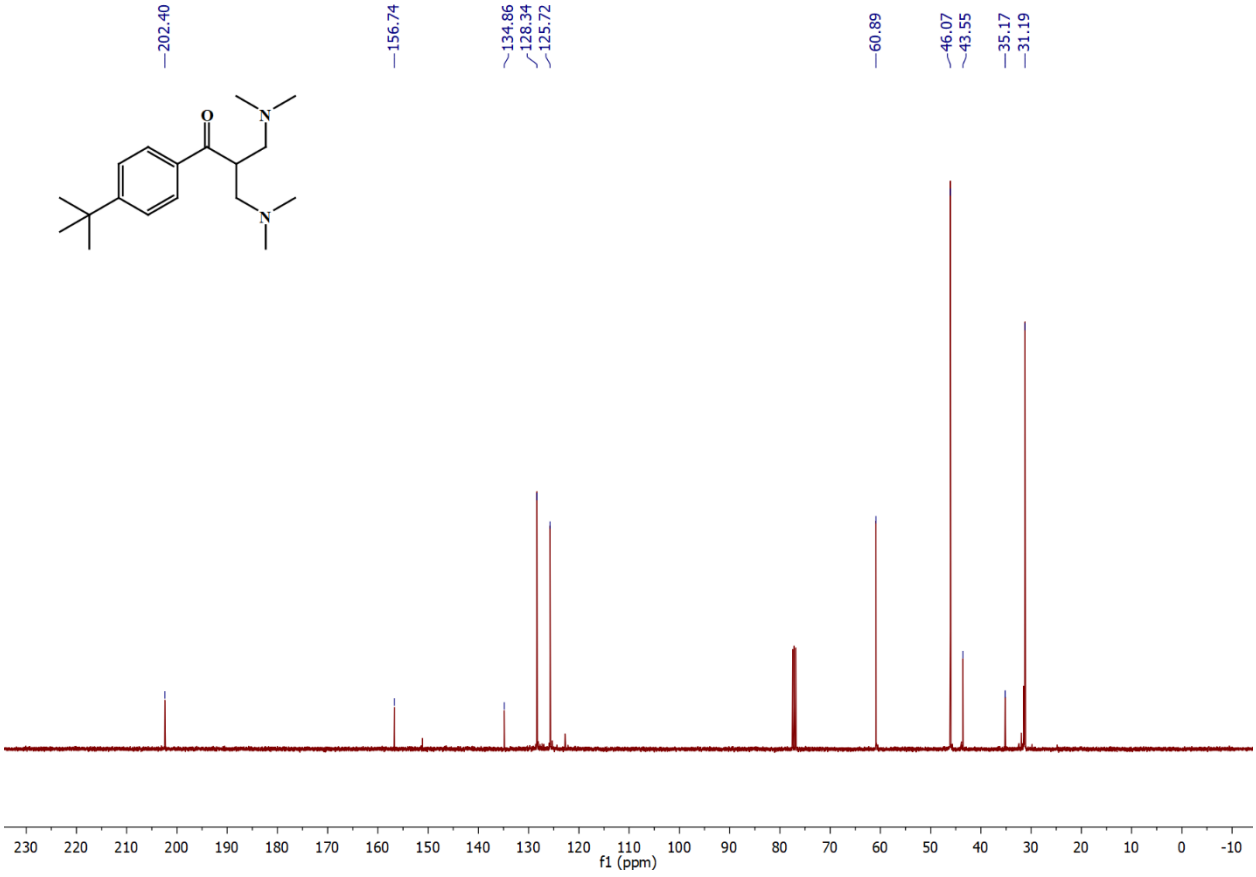
^{13}C NMR (101 MHz, $CDCl_3$) of **4b**



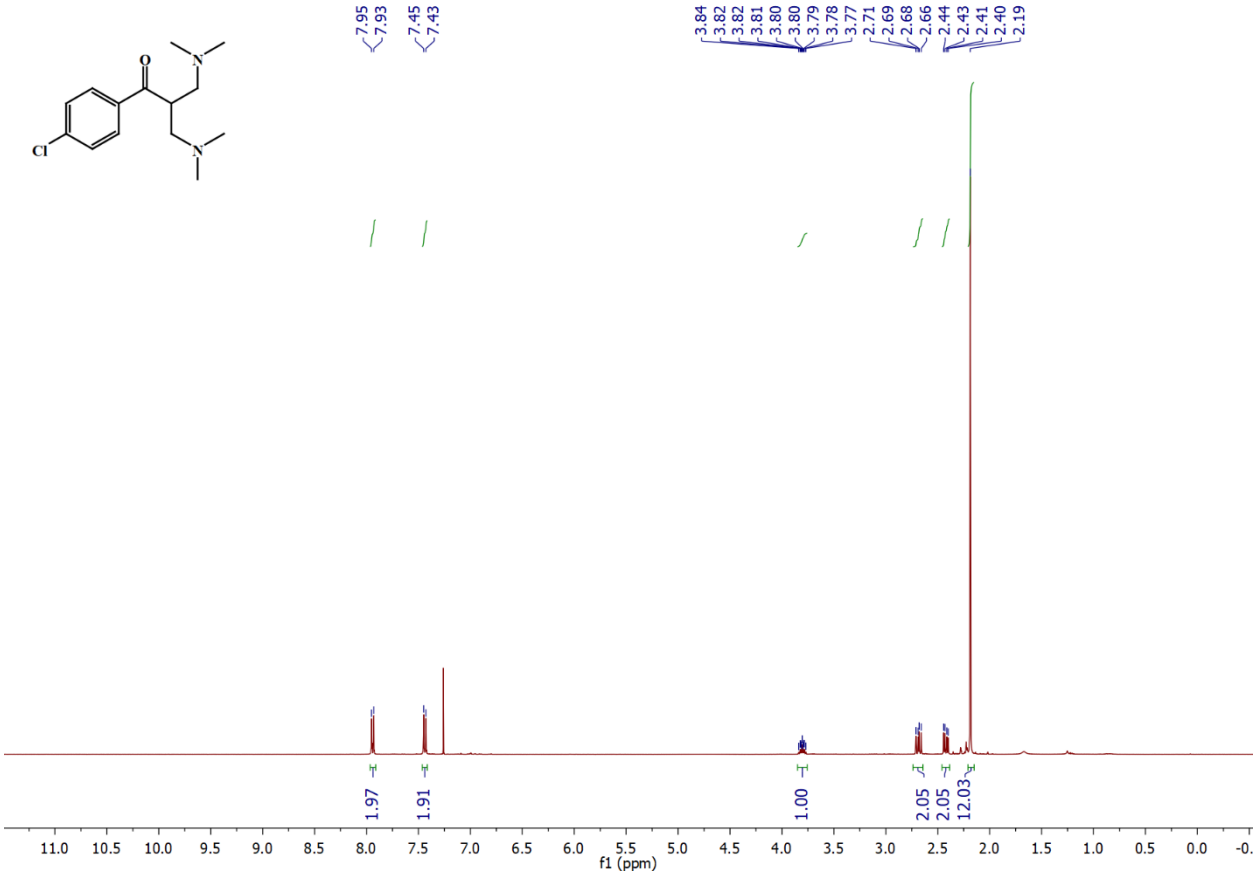
^{1}H NMR (400 MHz, $CDCl_3$) of **4c**



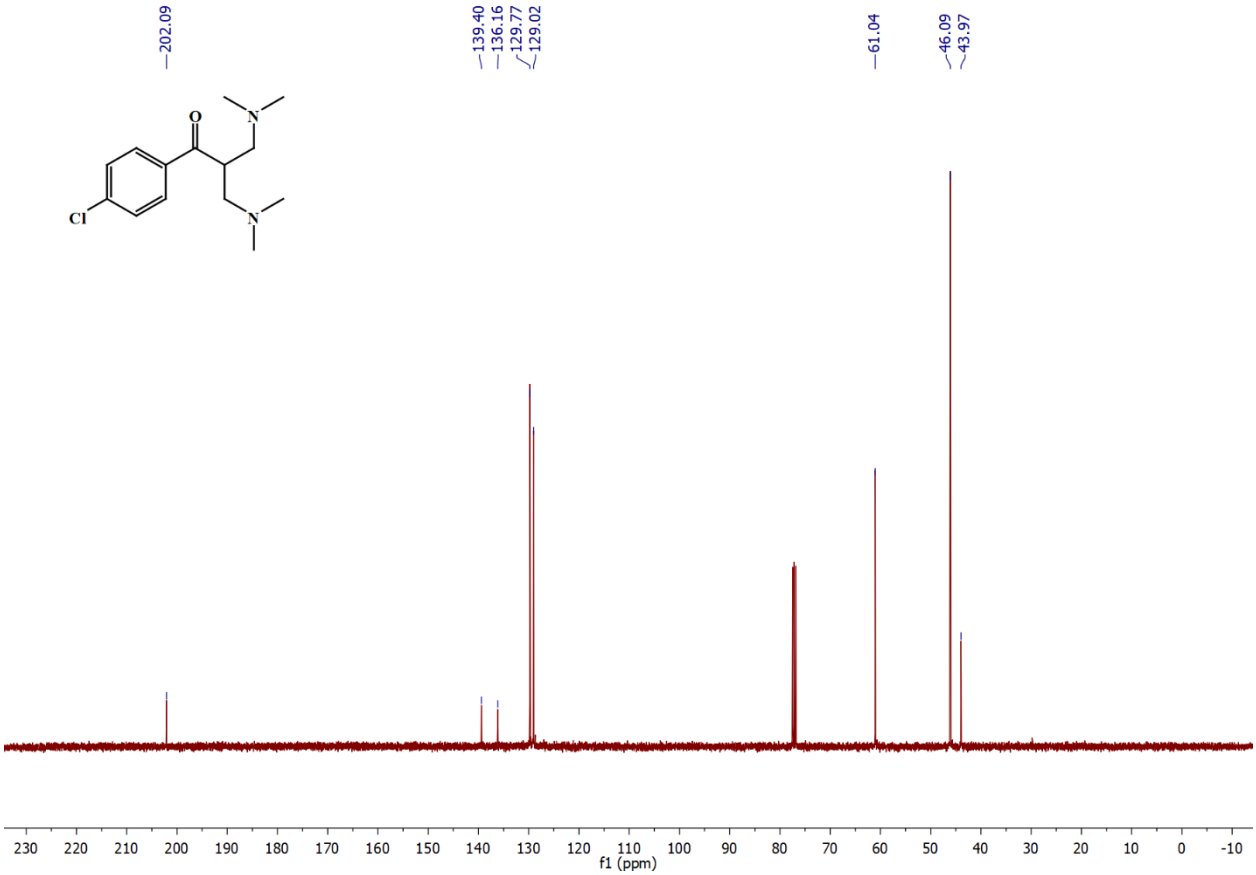
^{13}C NMR (101 MHz, $CDCl_3$) of **4c**



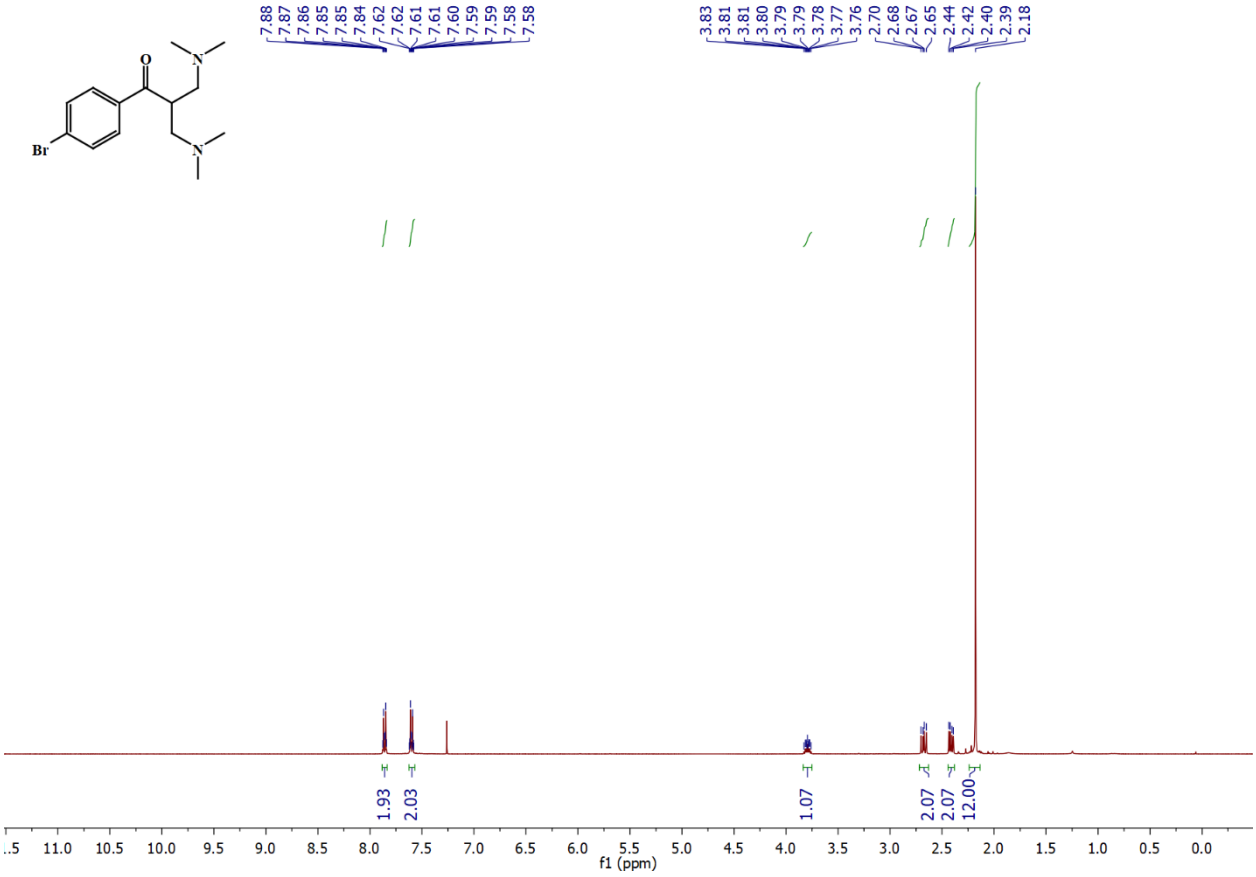
^{1}H NMR (400 MHz, $CDCl_3$) of **4d**



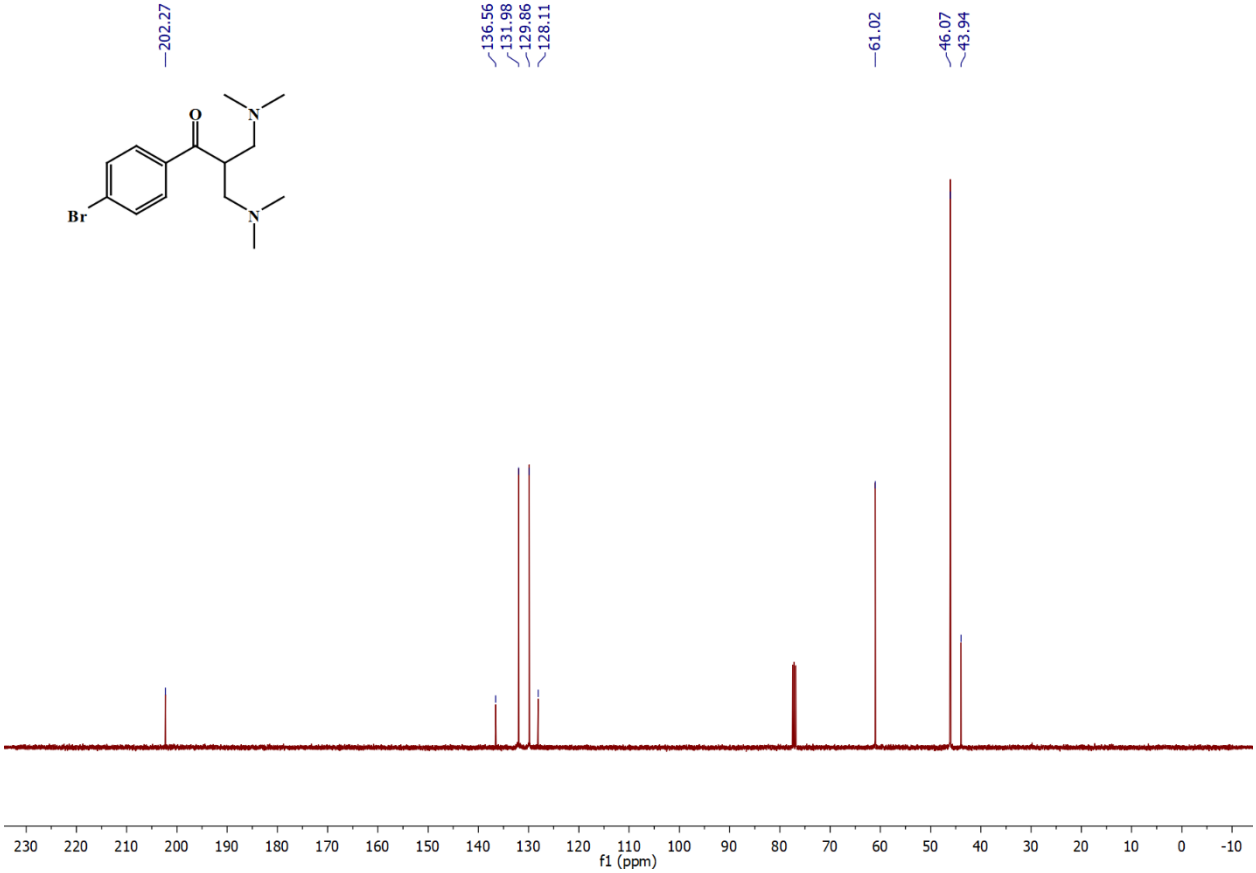
^{13}C NMR (101 MHz, $CDCl_3$) of **4c**



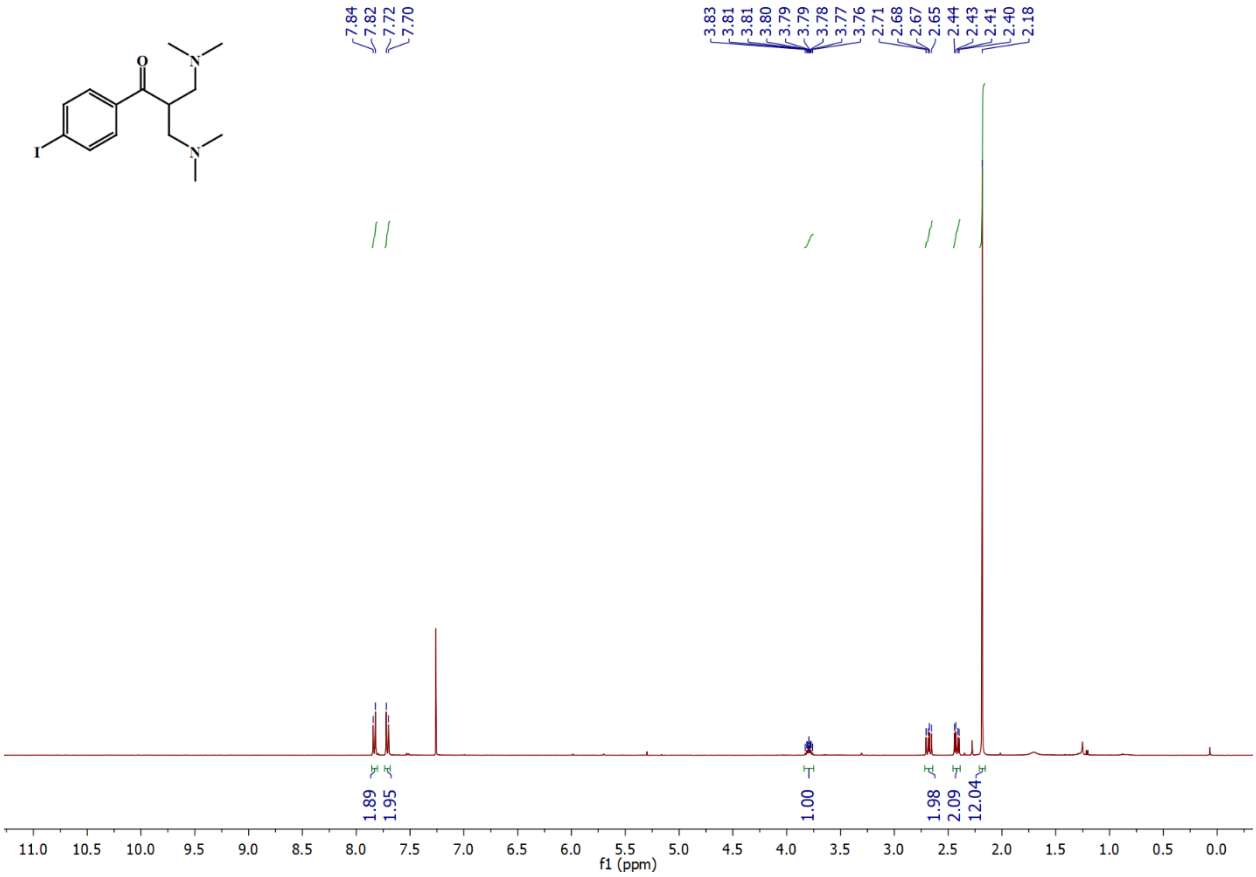
^{1}H NMR (400 MHz, $CDCl_3$) of **4e**



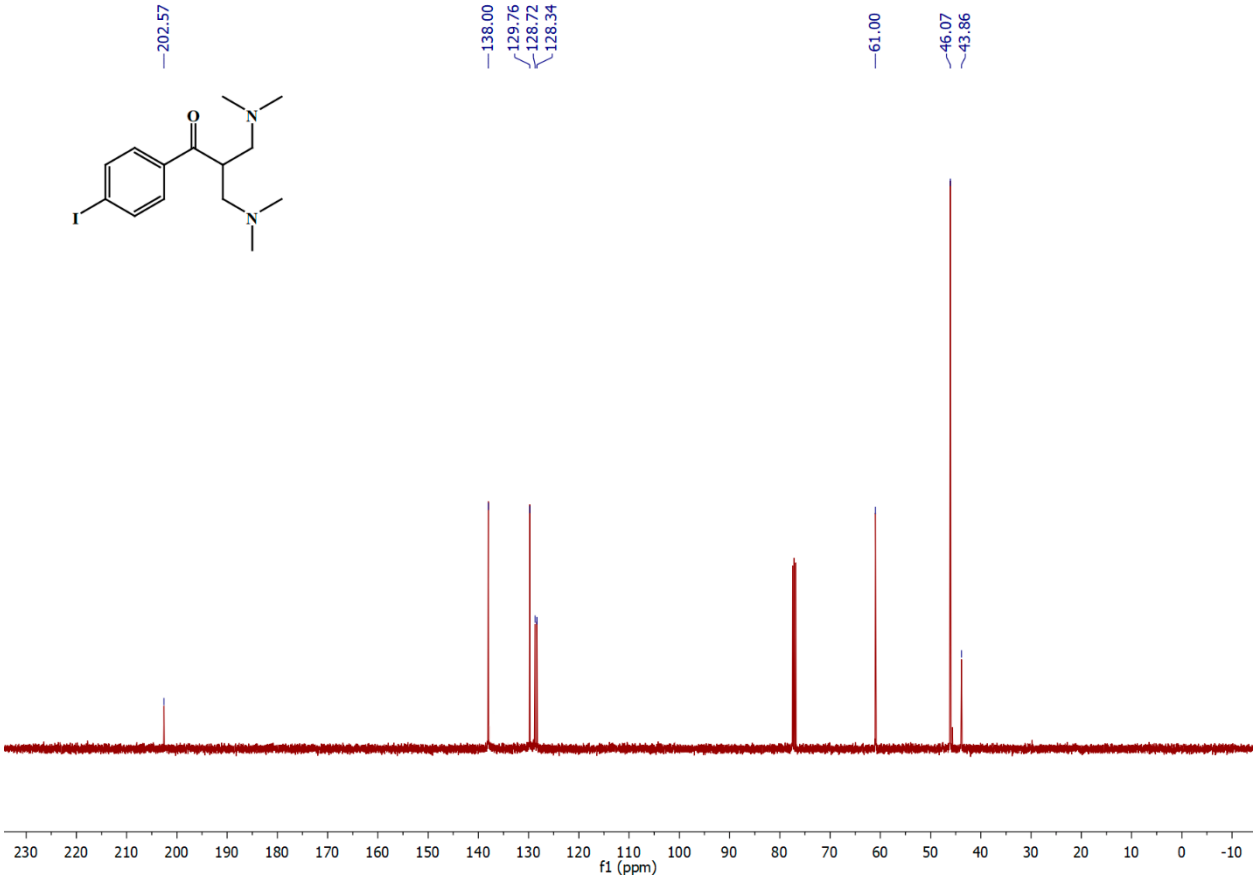
^{13}C NMR (101 MHz, $CDCl_3$) of **4e**



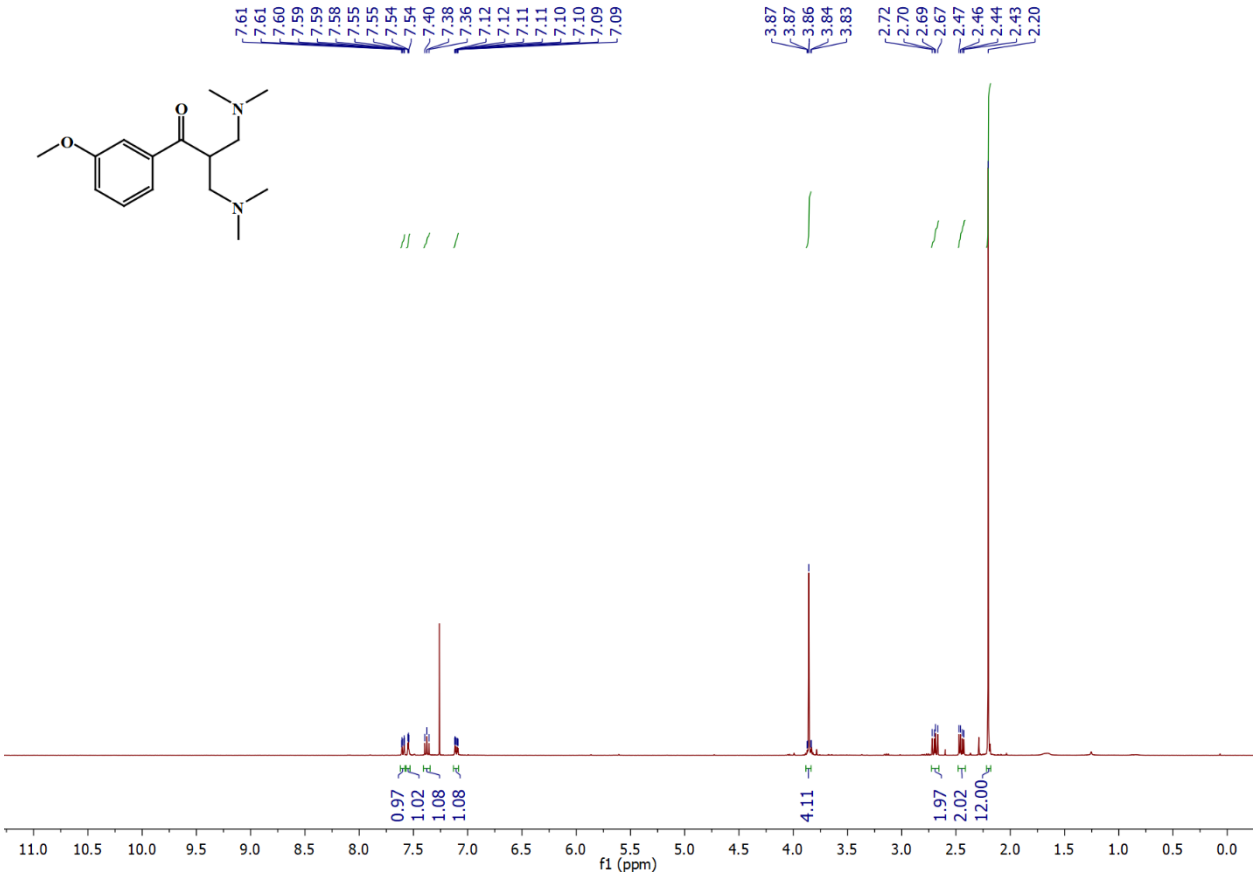
^{1}H NMR (400 MHz, $CDCl_3$) of **4f**



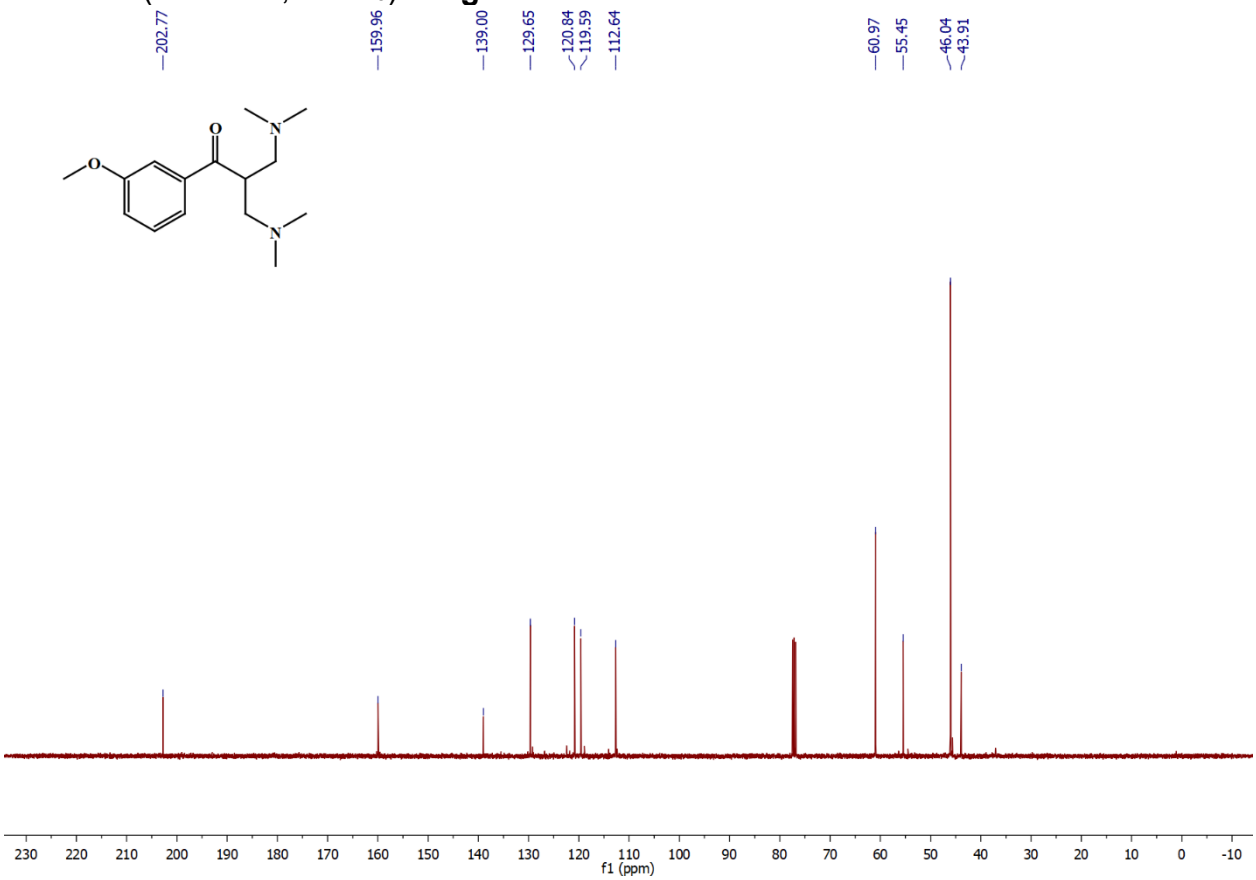
^{13}C NMR (101 MHz, $CDCl_3$) of **4f**



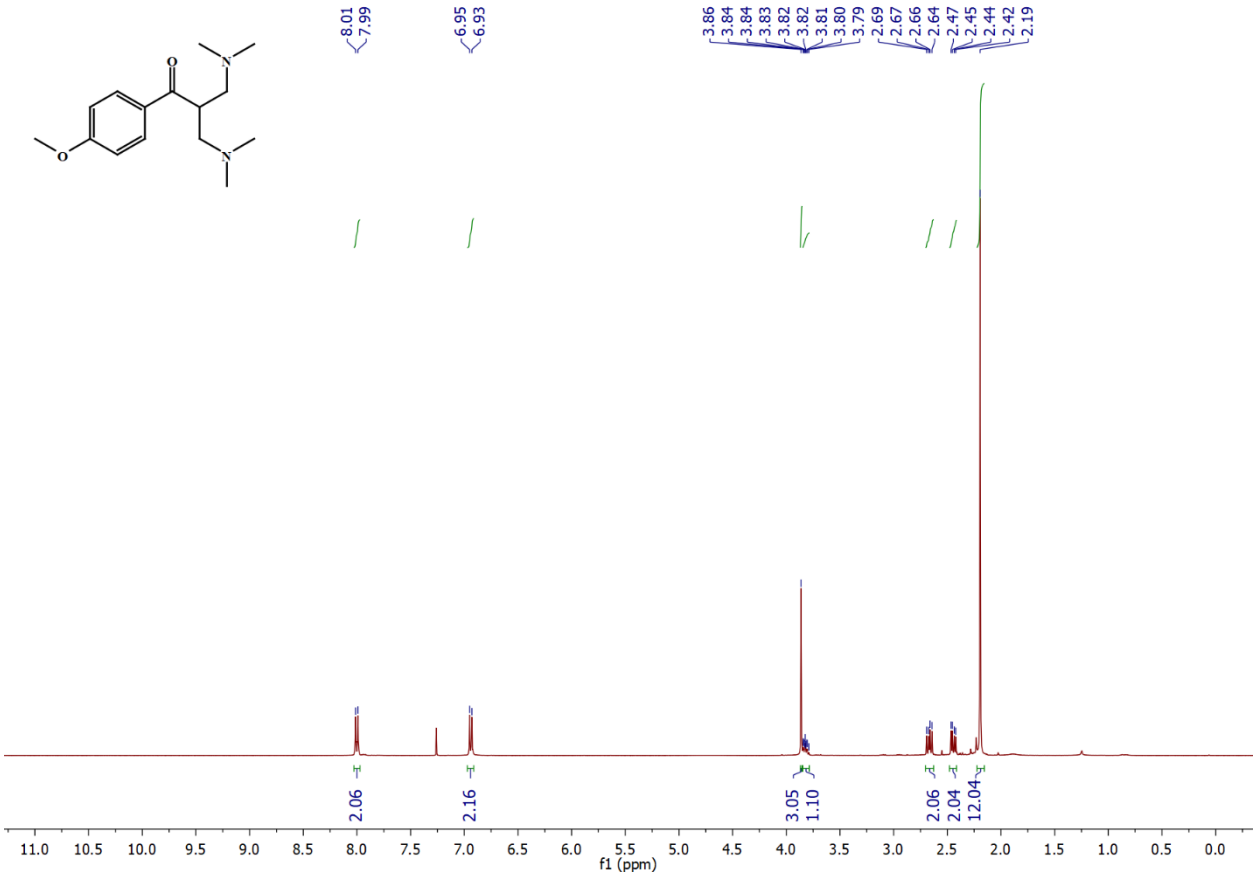
^{1}H NMR (400 MHz, $CDCl_3$) of **4g**



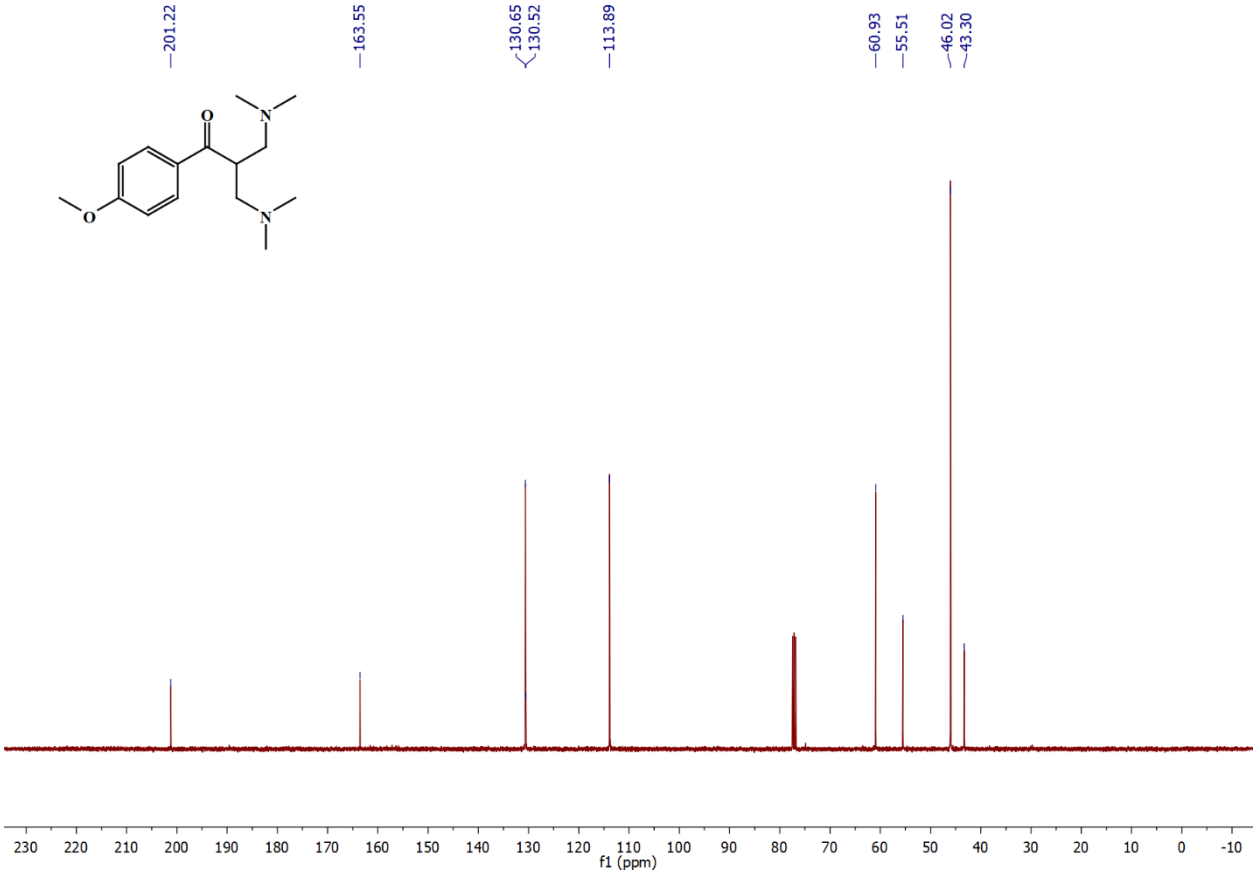
^{13}C NMR (101 MHz, $CDCl_3$) of **4g**



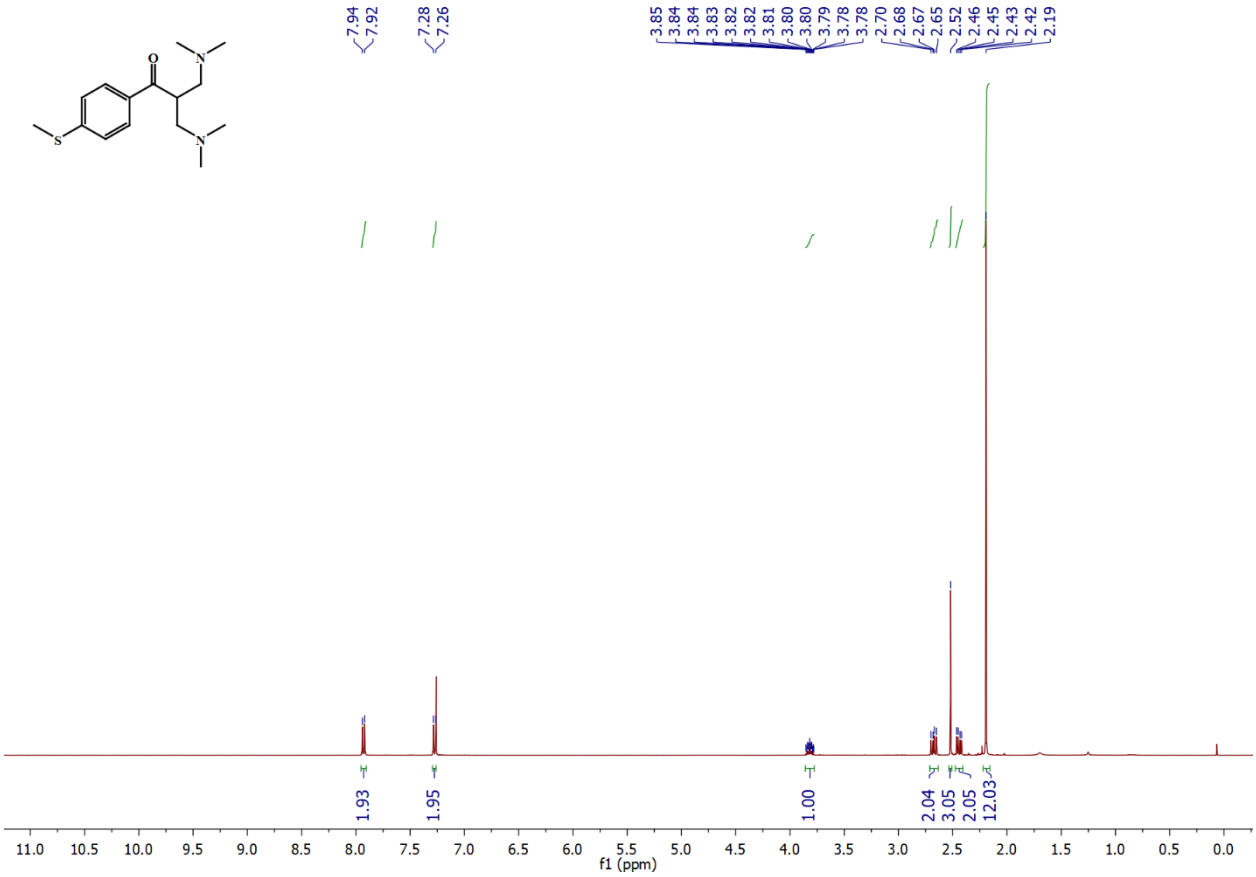
^{1}H NMR (400 MHz, $CDCl_3$) of **4h**



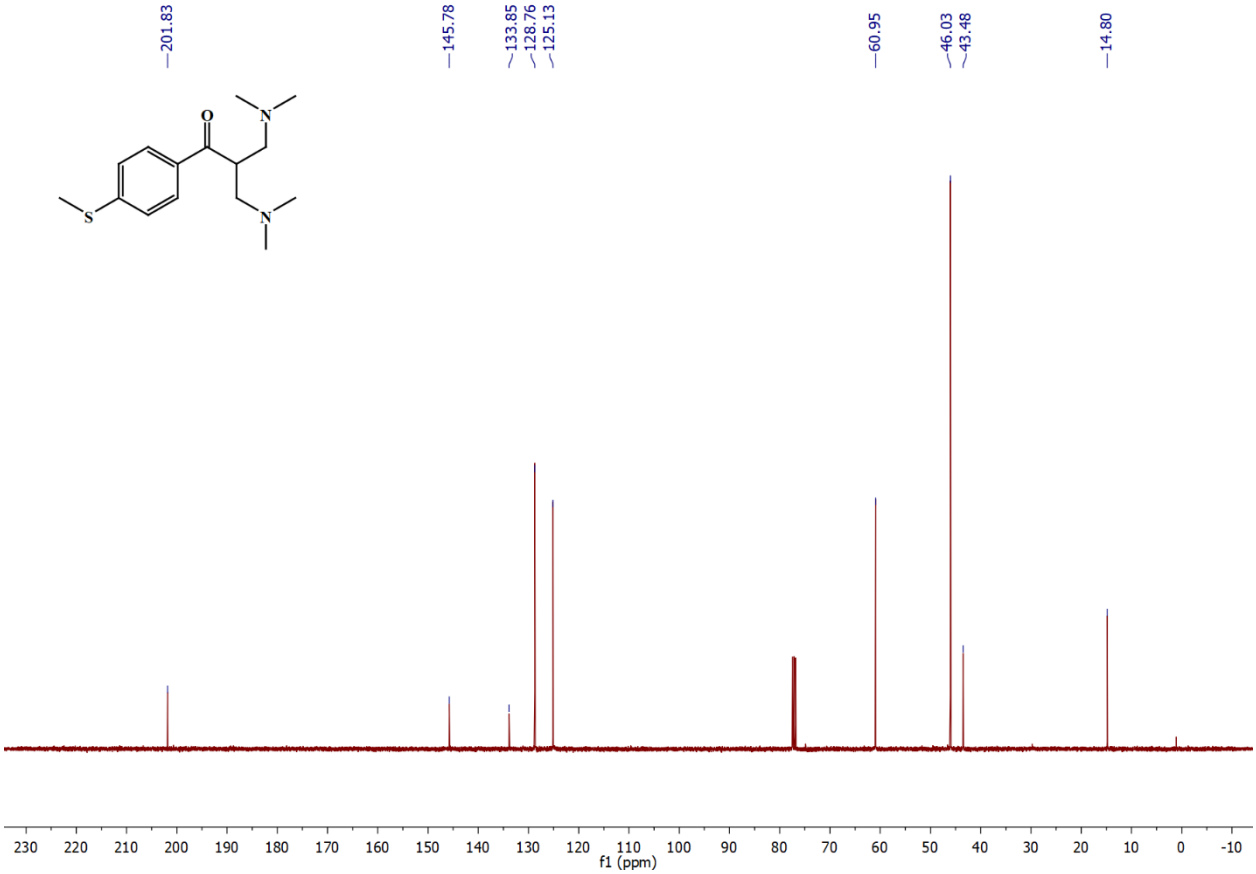
^{13}C NMR (101 MHz, $CDCl_3$) of **4h**



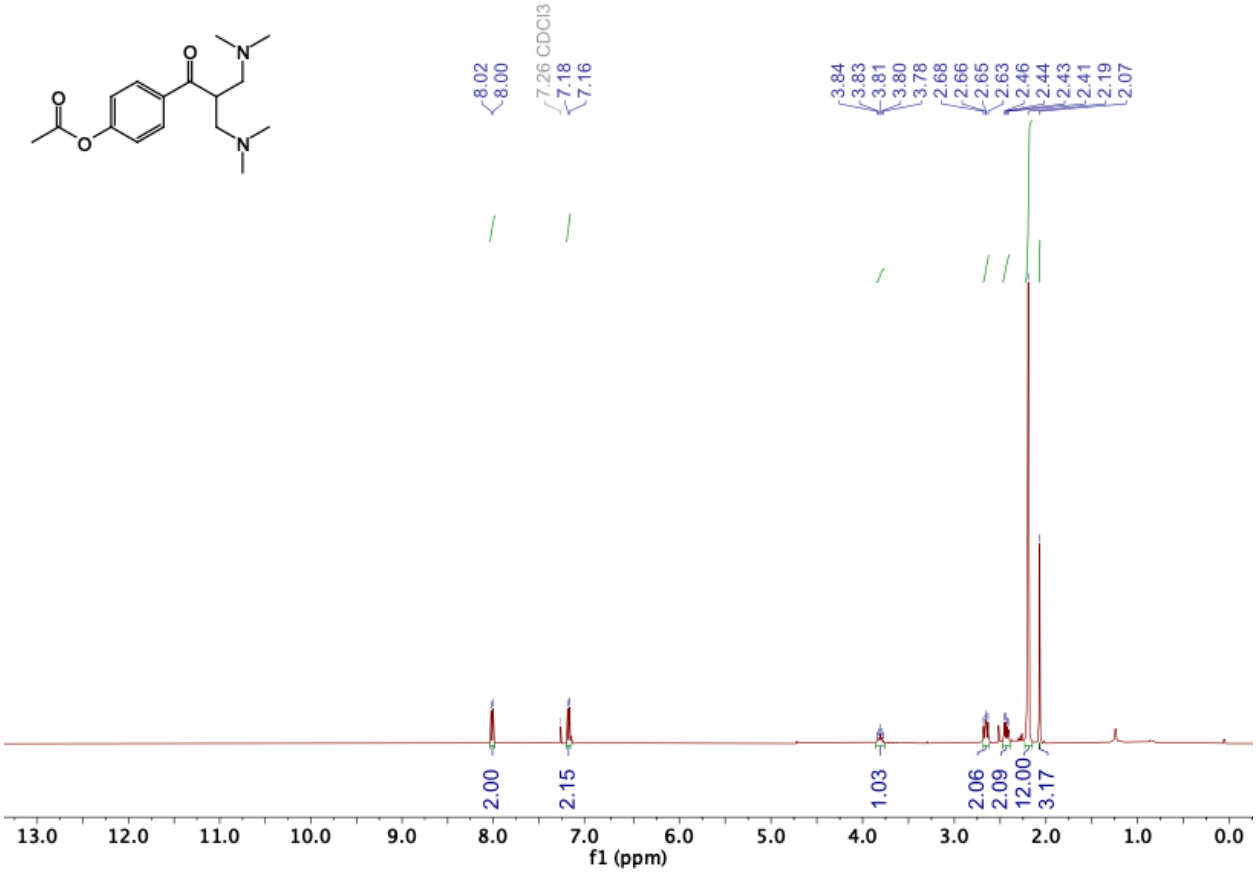
^{1}H NMR (400 MHz, $CDCl_3$) of **4i**



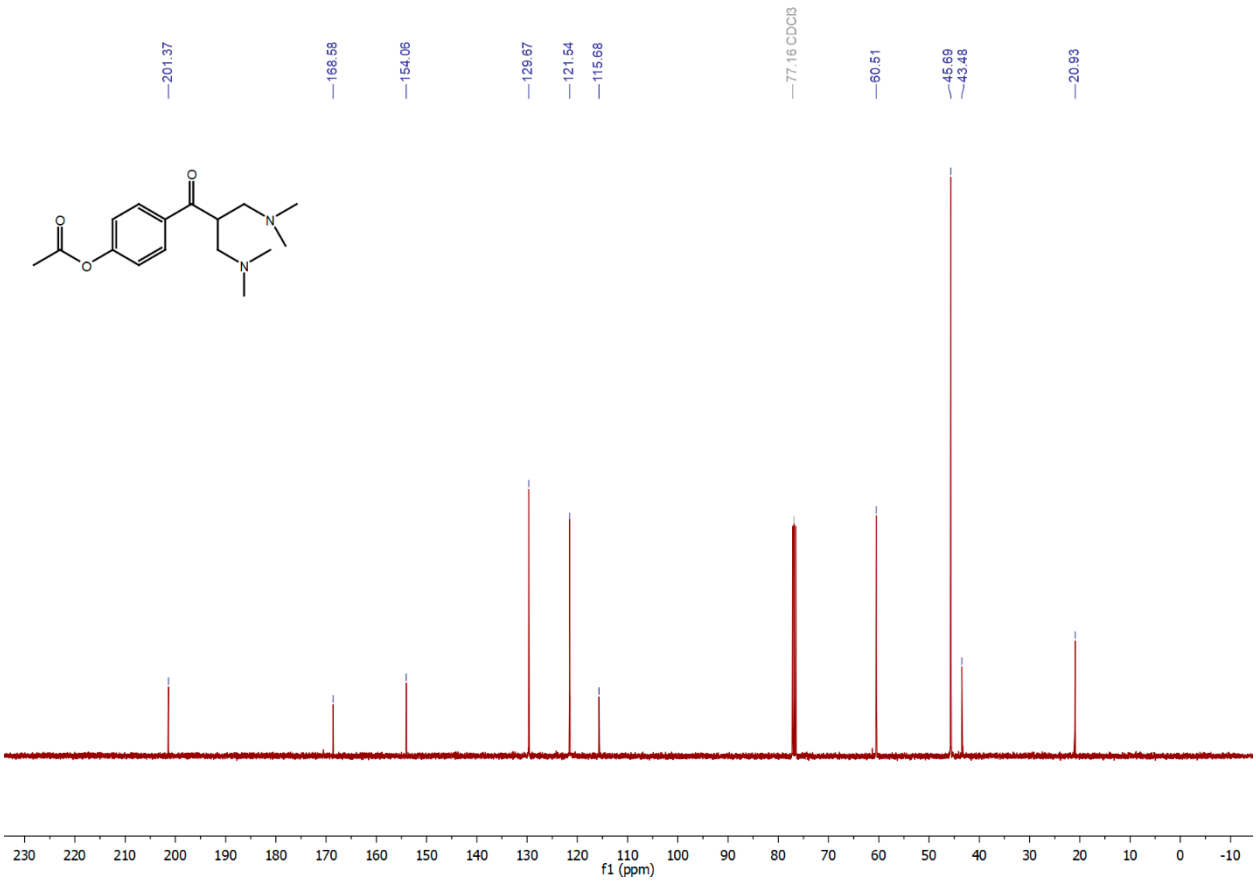
^{13}C NMR (101 MHz, $CDCl_3$) of **4i**



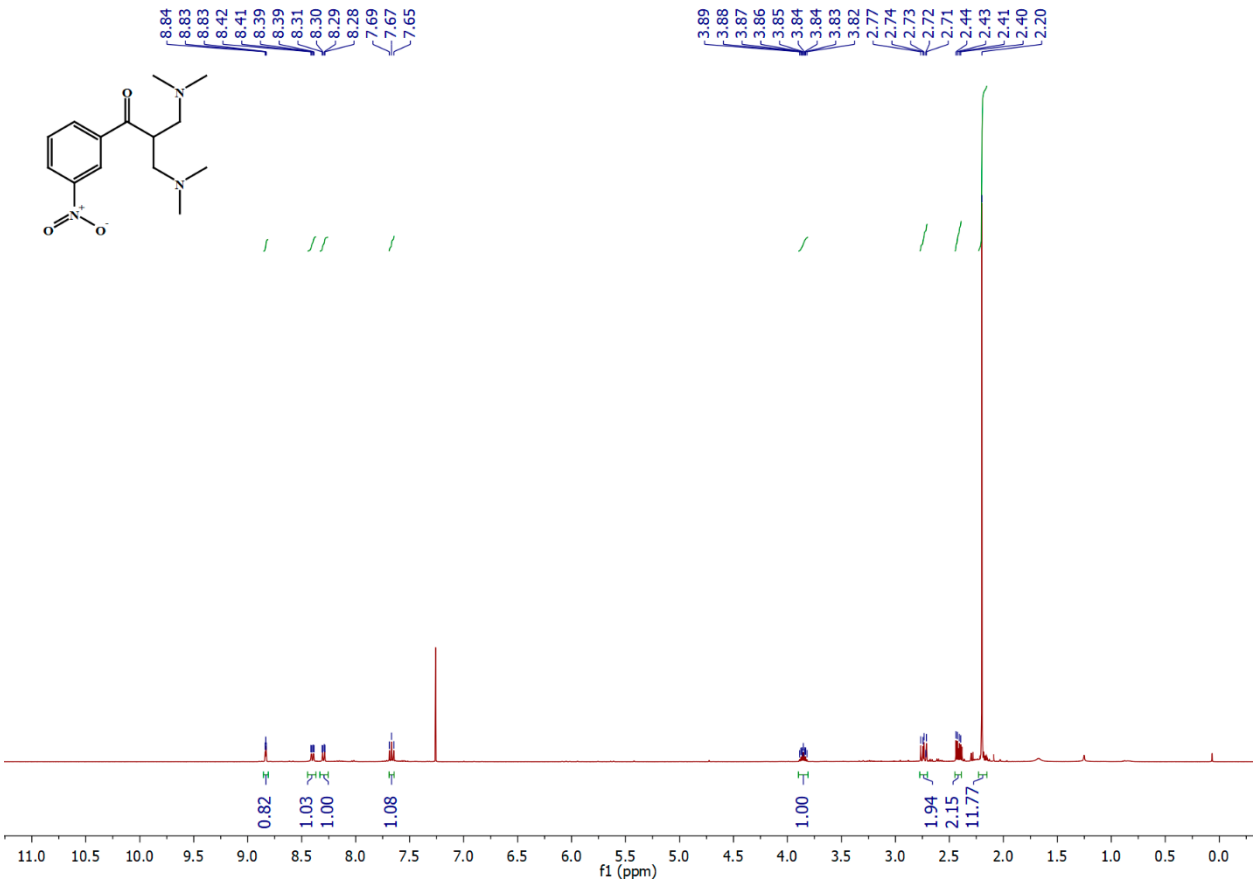
^{1}H NMR (400 MHz, $CDCl_3$) of **4k**



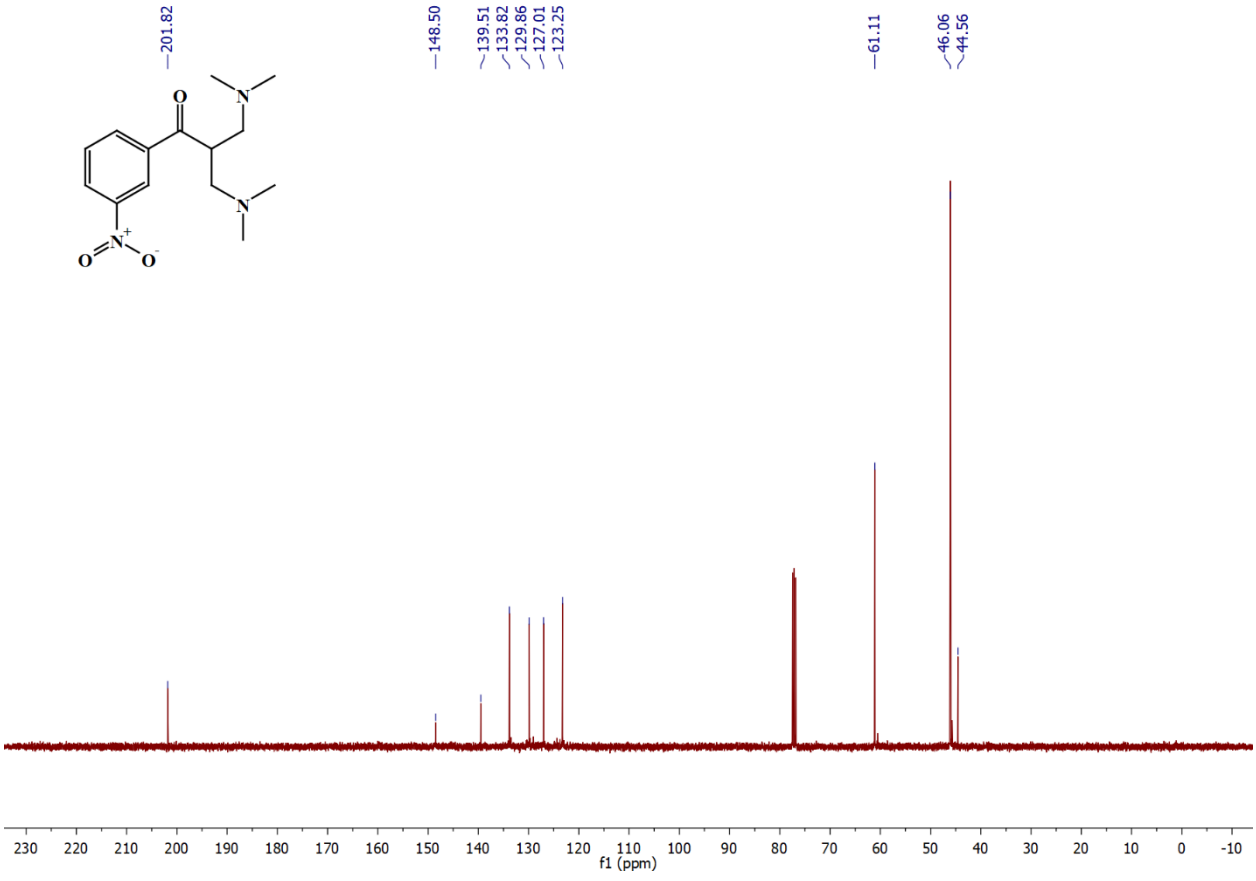
^{13}C NMR (101 MHz, $CDCl_3$) of **4k**



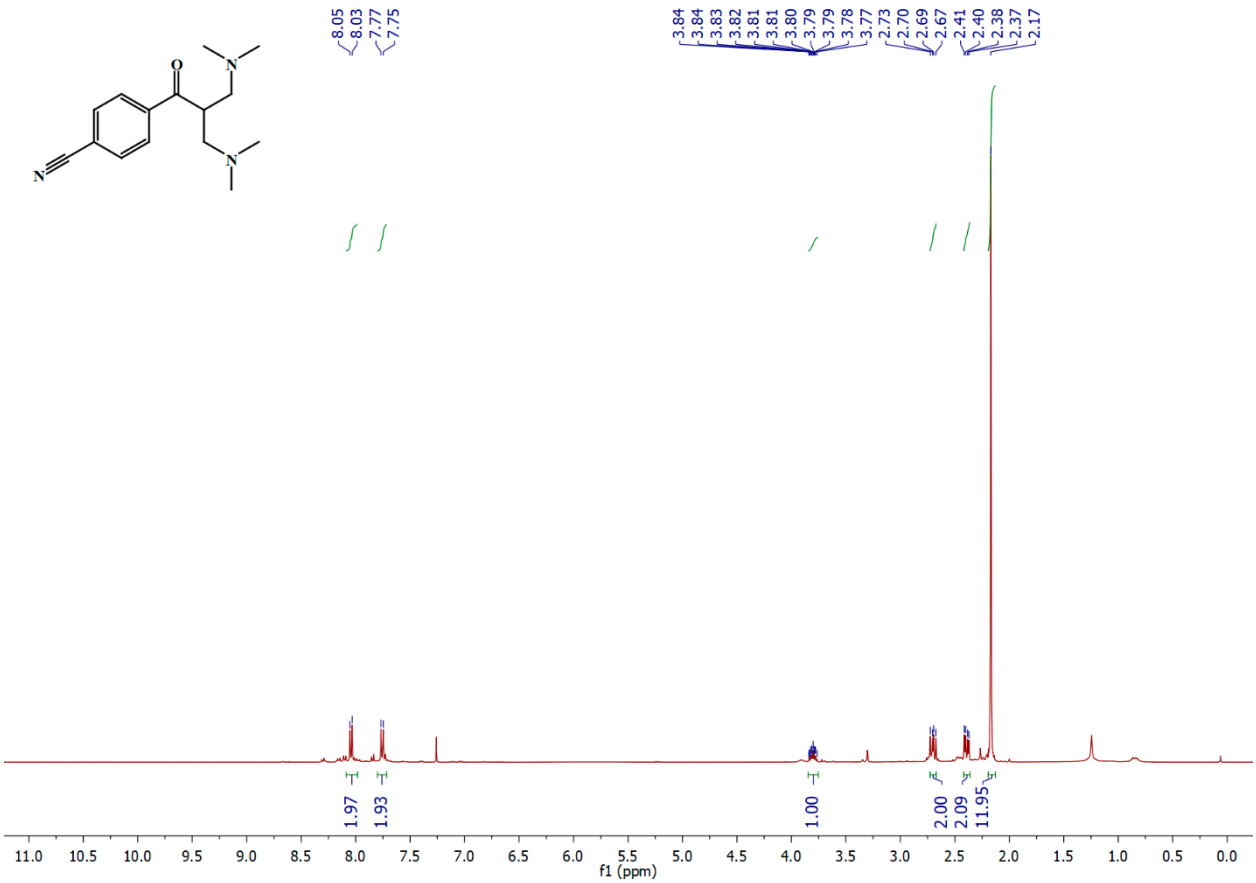
^{1}H NMR (400 MHz, $CDCl_3$) of **4l**



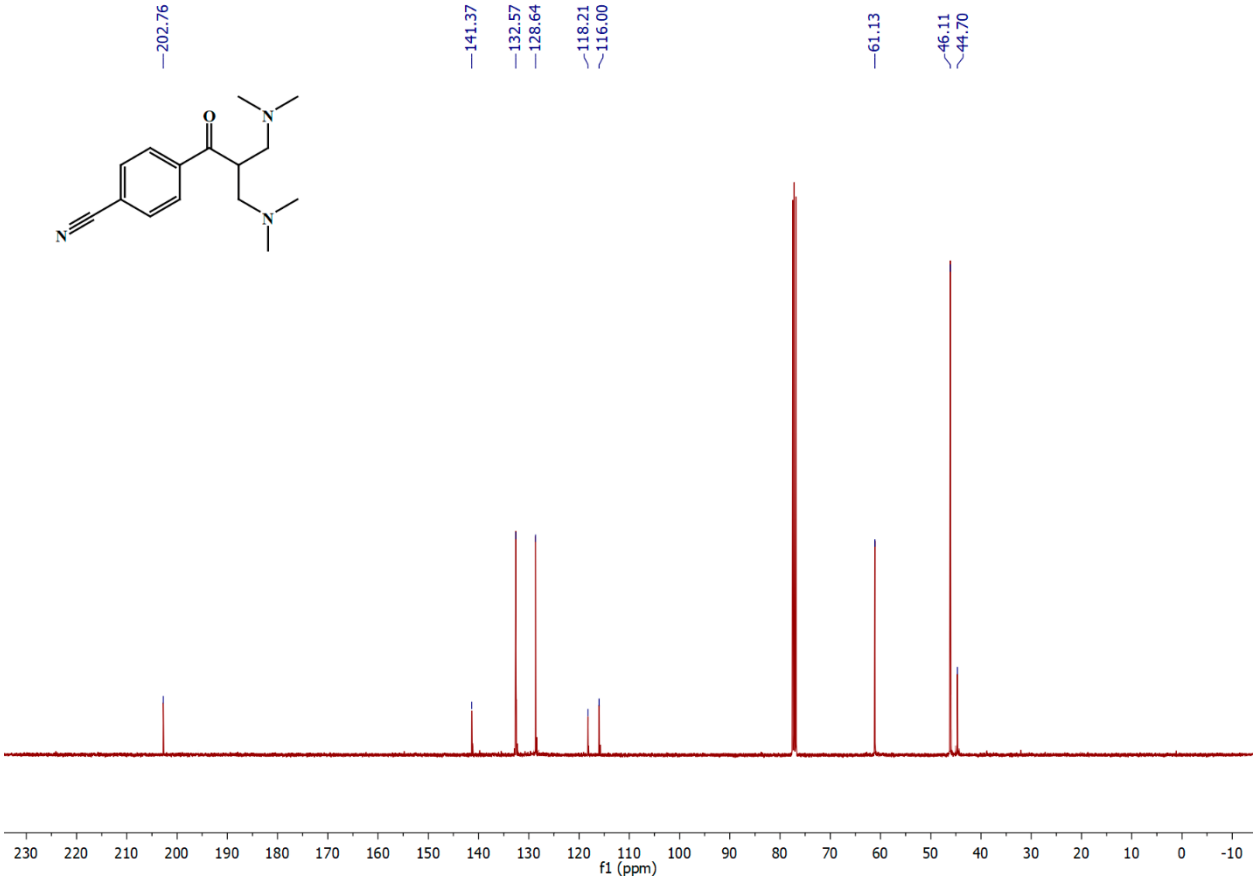
^{13}C NMR (101 MHz, $CDCl_3$) of **4l**



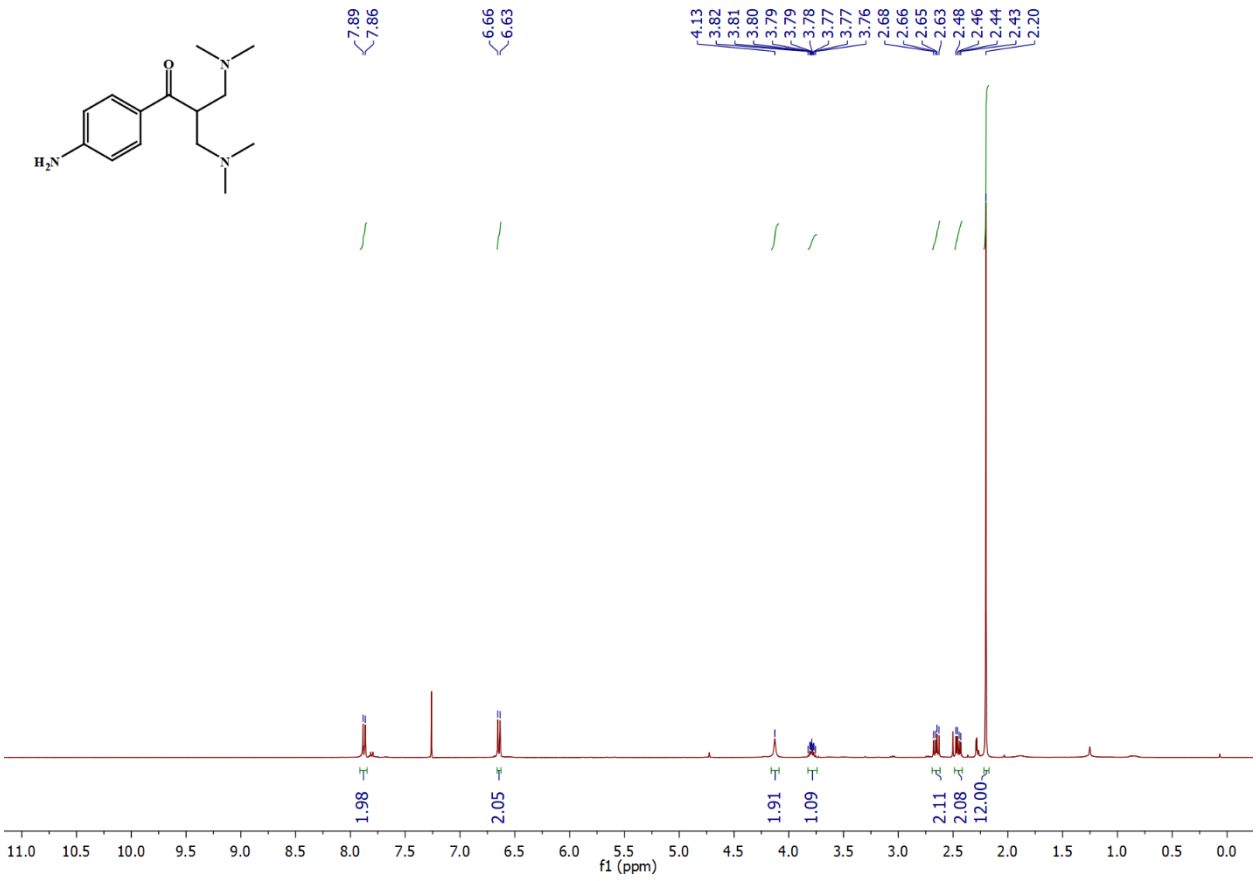
^{1}H NMR (400 MHz, $CDCl_3$) of **4m**



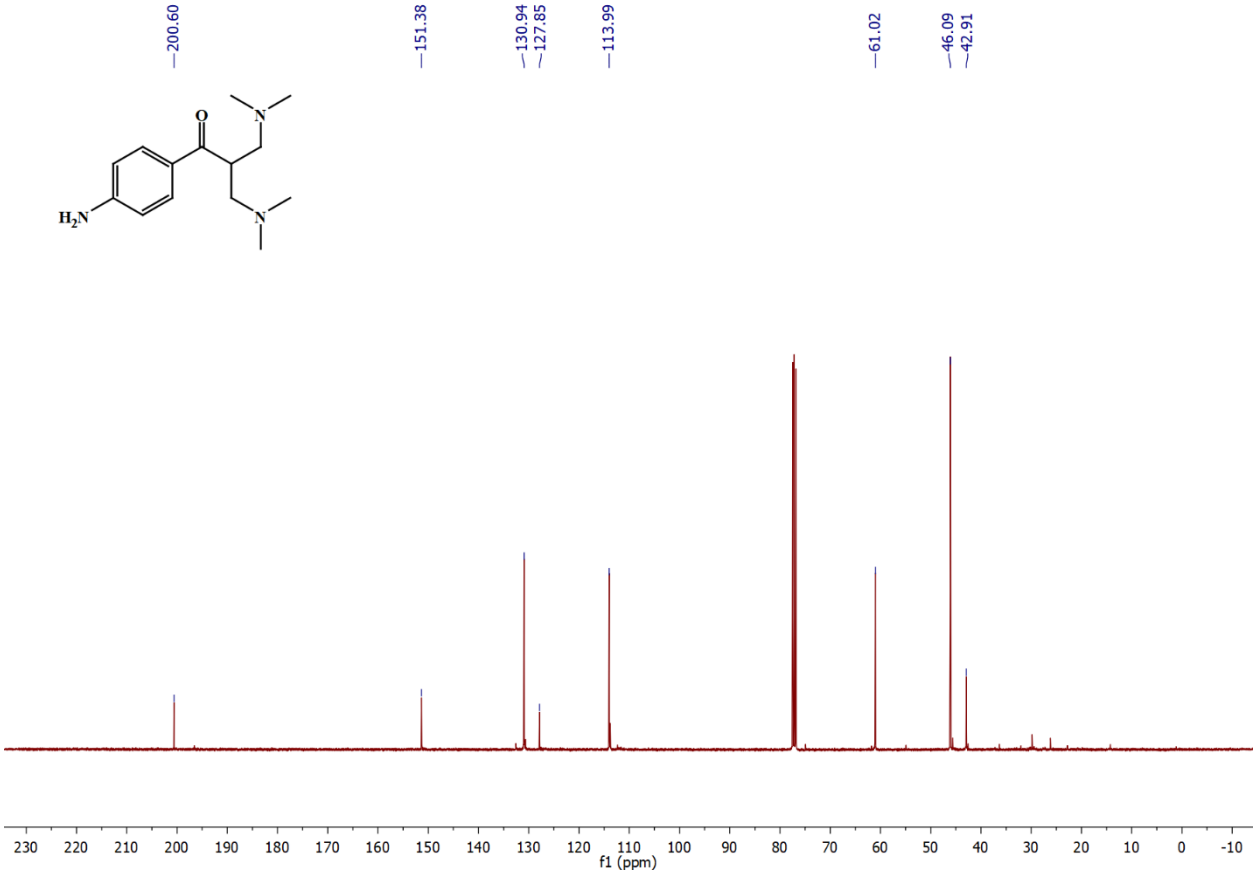
^{13}C NMR (101 MHz, $CDCl_3$) of **4m**



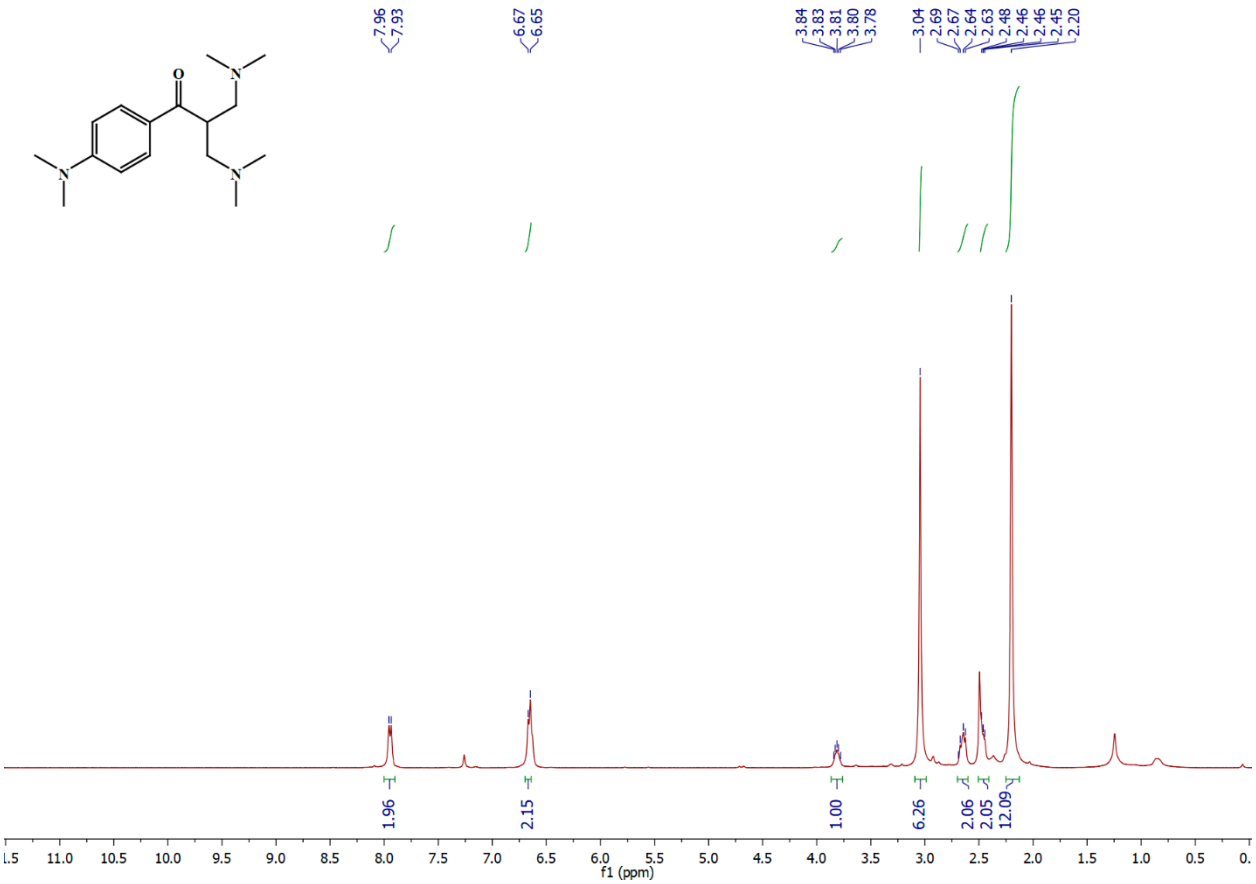
^{1}H NMR (400 MHz, $CDCl_3$) of **4n**



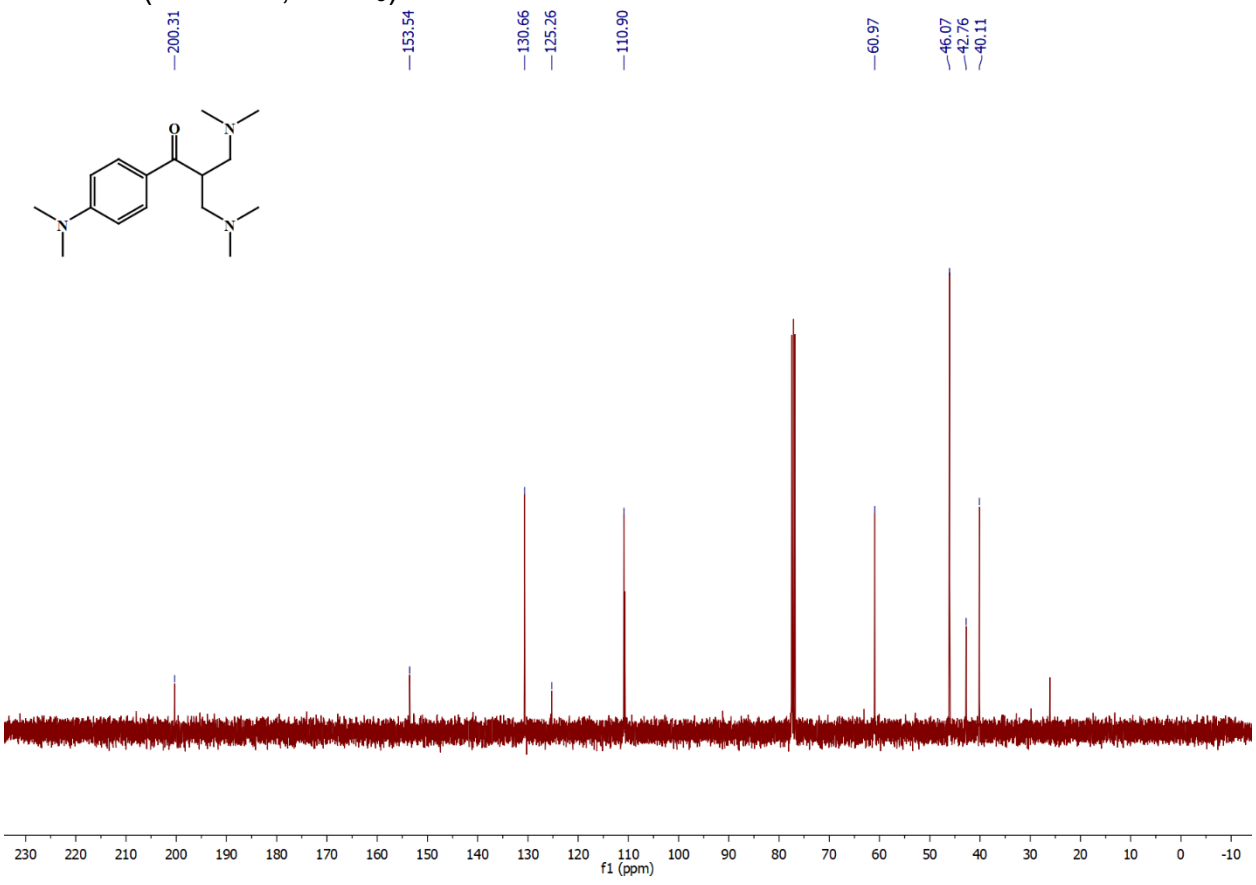
^{13}C NMR (101 MHz, $CDCl_3$) of **4n**



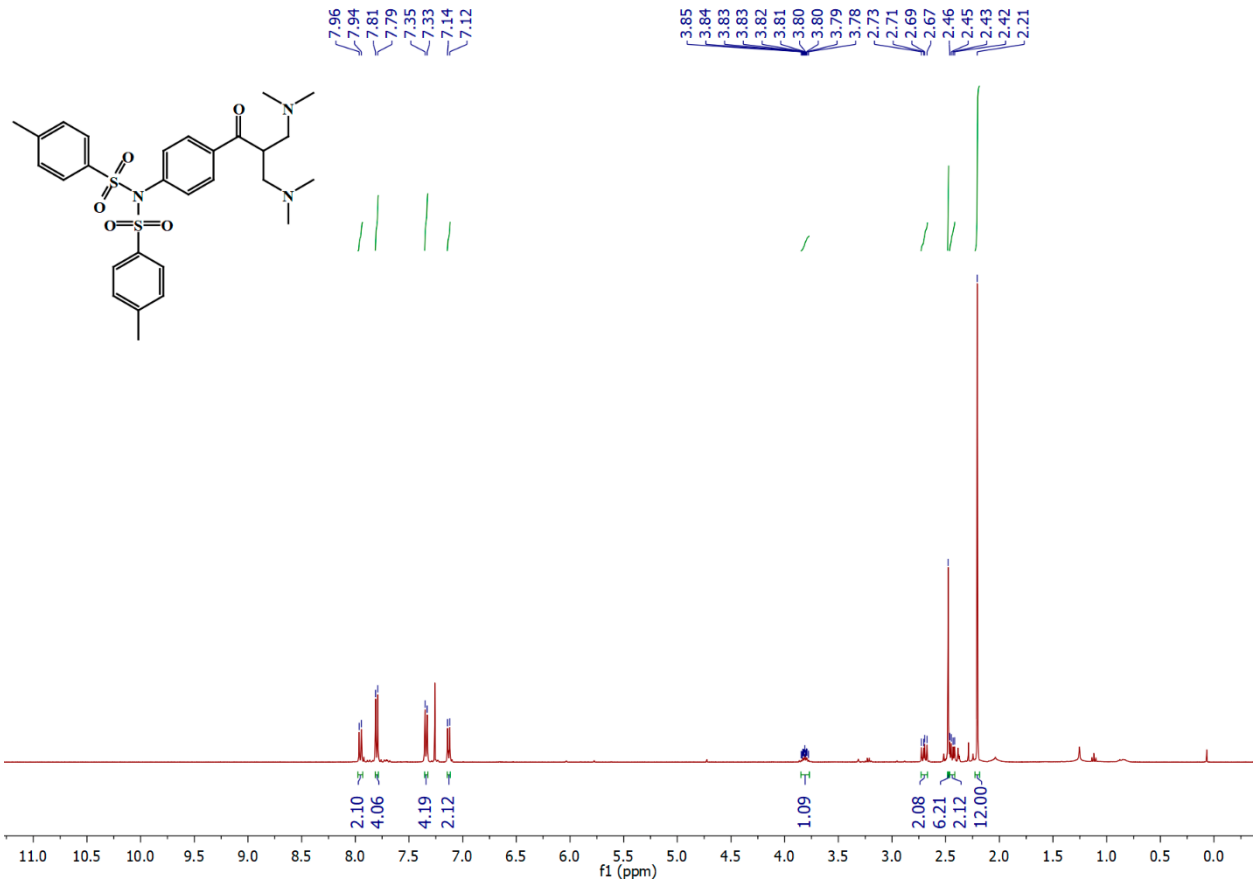
^{1}H NMR (400 MHz, $CDCl_3$) of **4o**



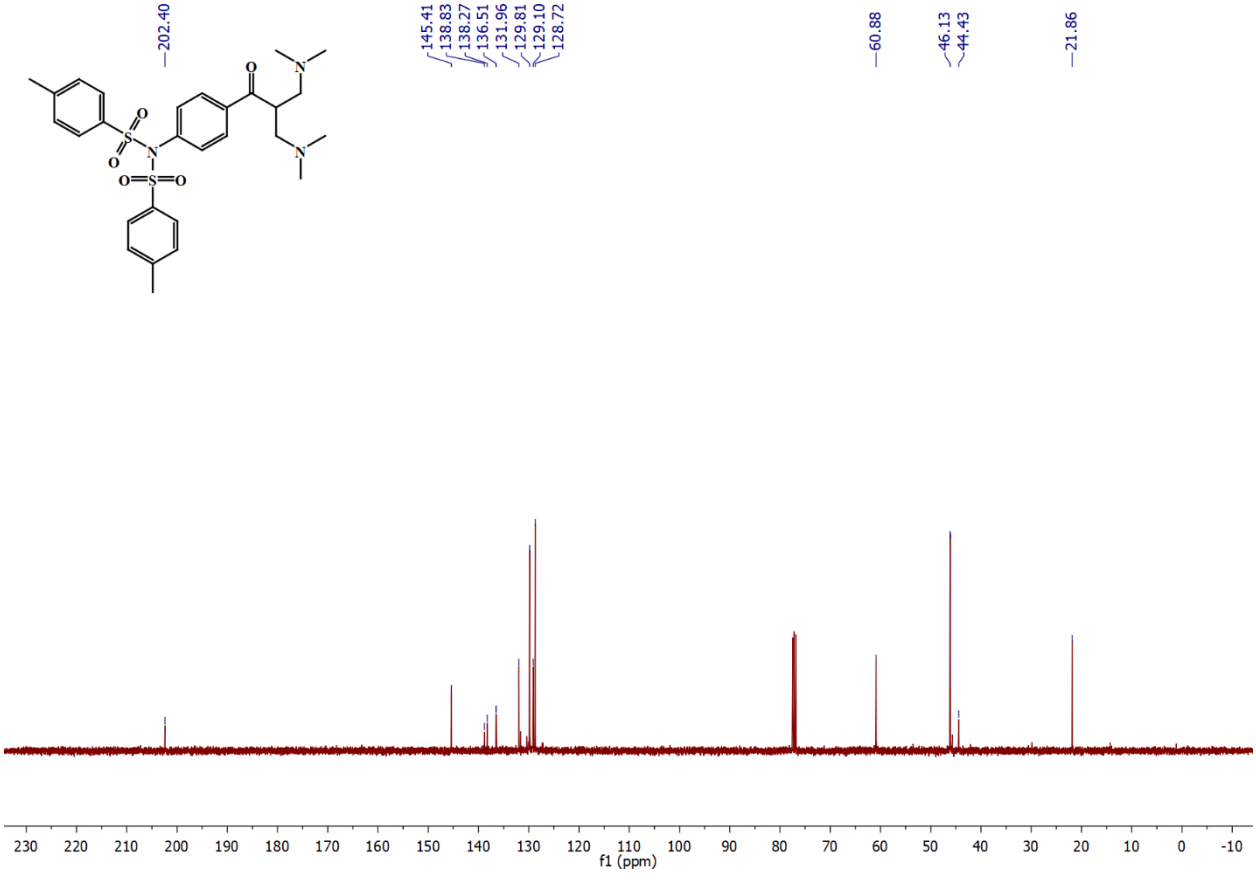
^{13}C NMR (101 MHz, $CDCl_3$) of **4o**



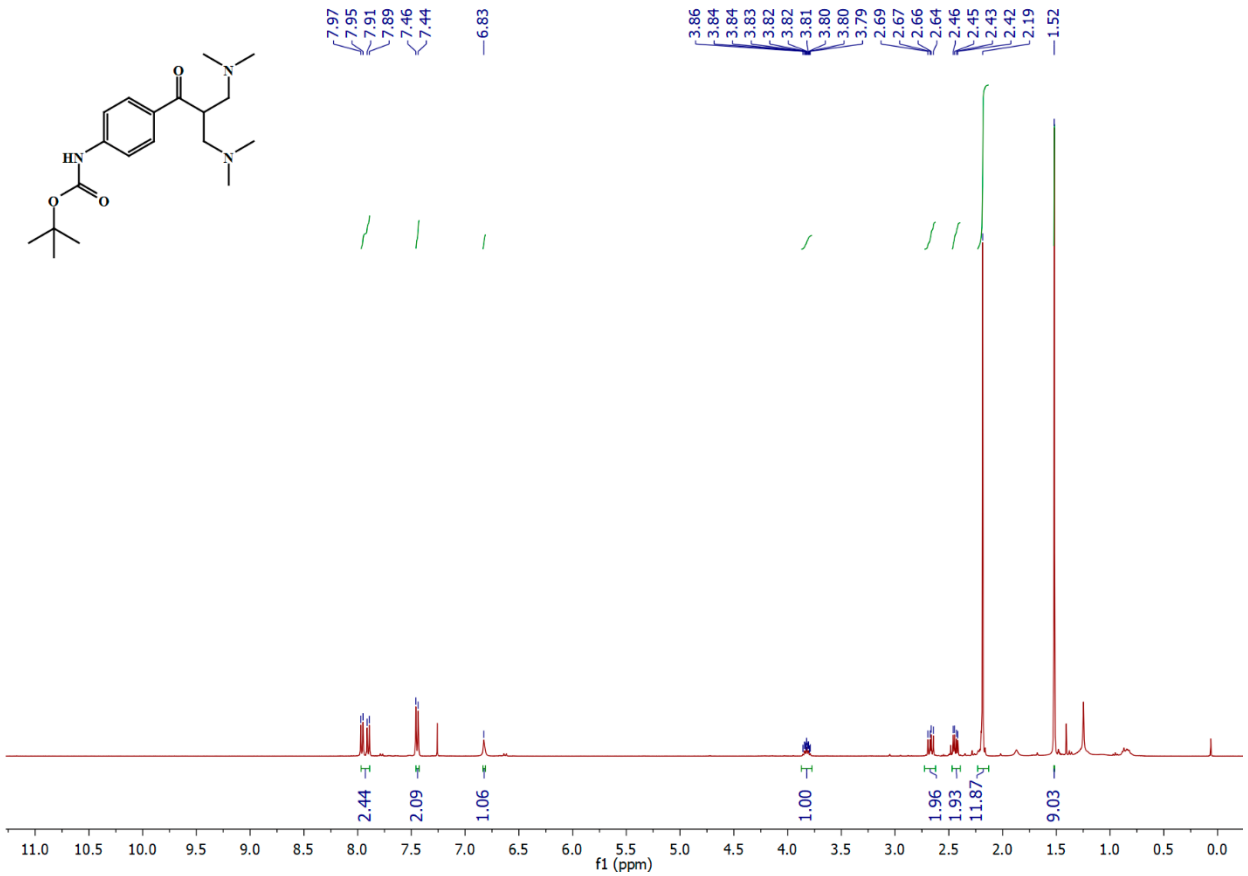
^{1}H NMR (400 MHz, $CDCl_3$) of **4p**



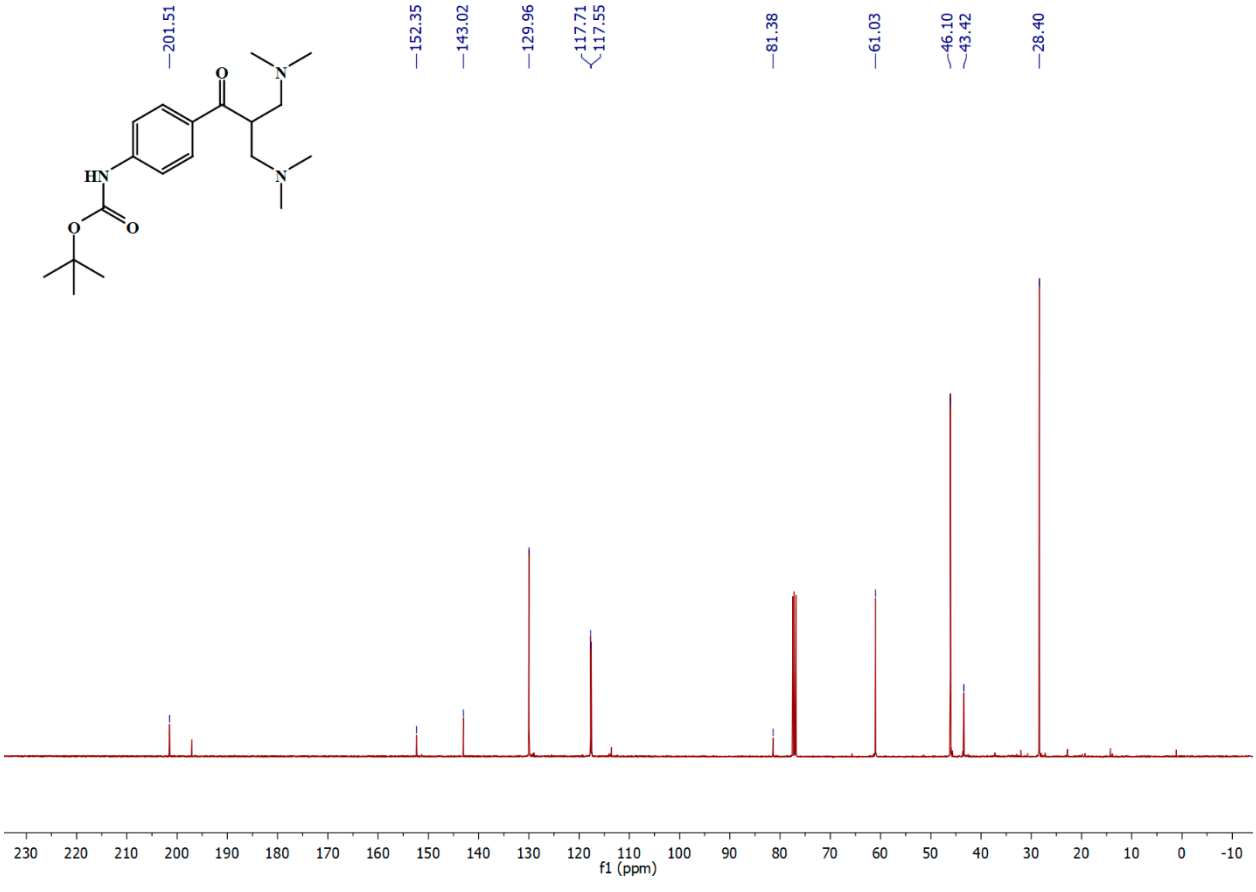
^{13}C NMR (101 MHz, $CDCl_3$) of **4p**



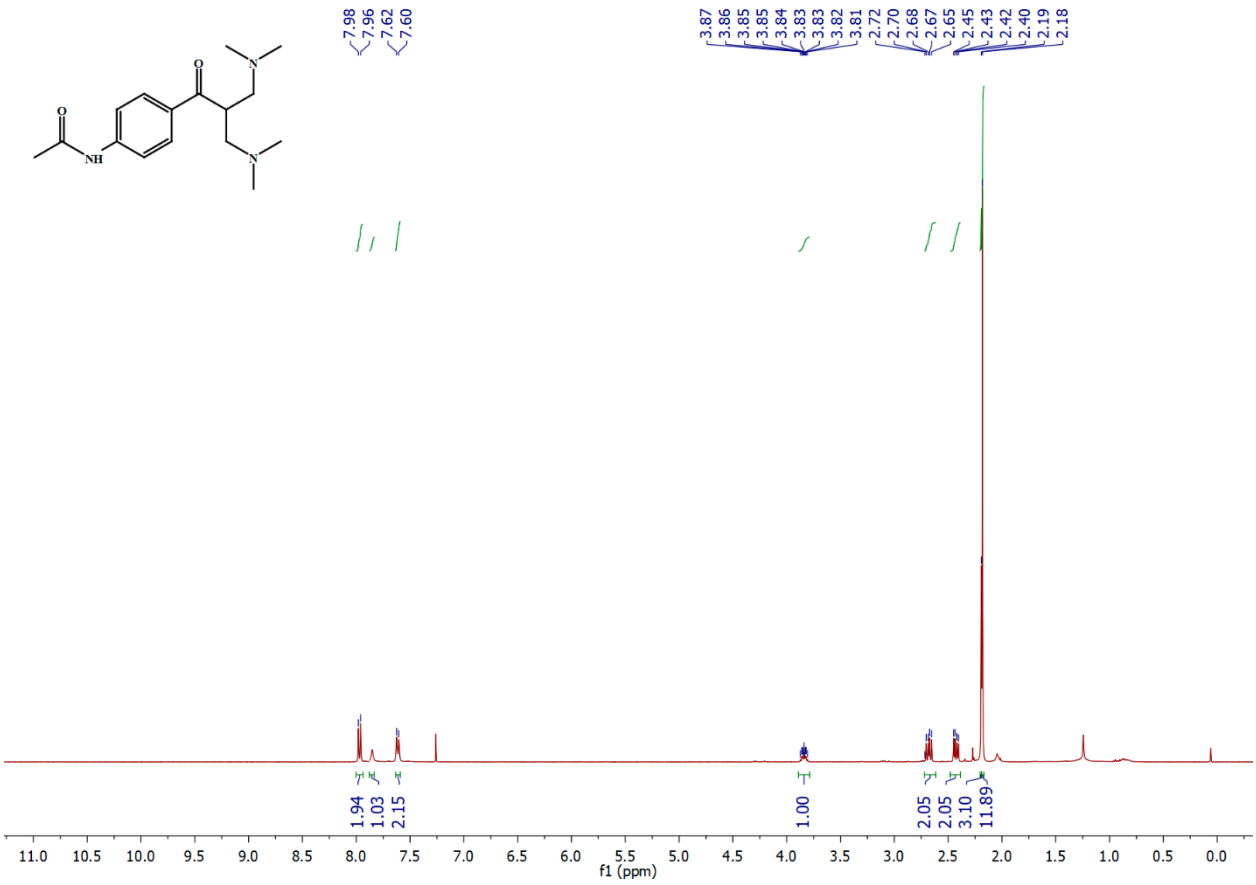
^{1}H NMR (400 MHz, $CDCl_3$) of **4q**



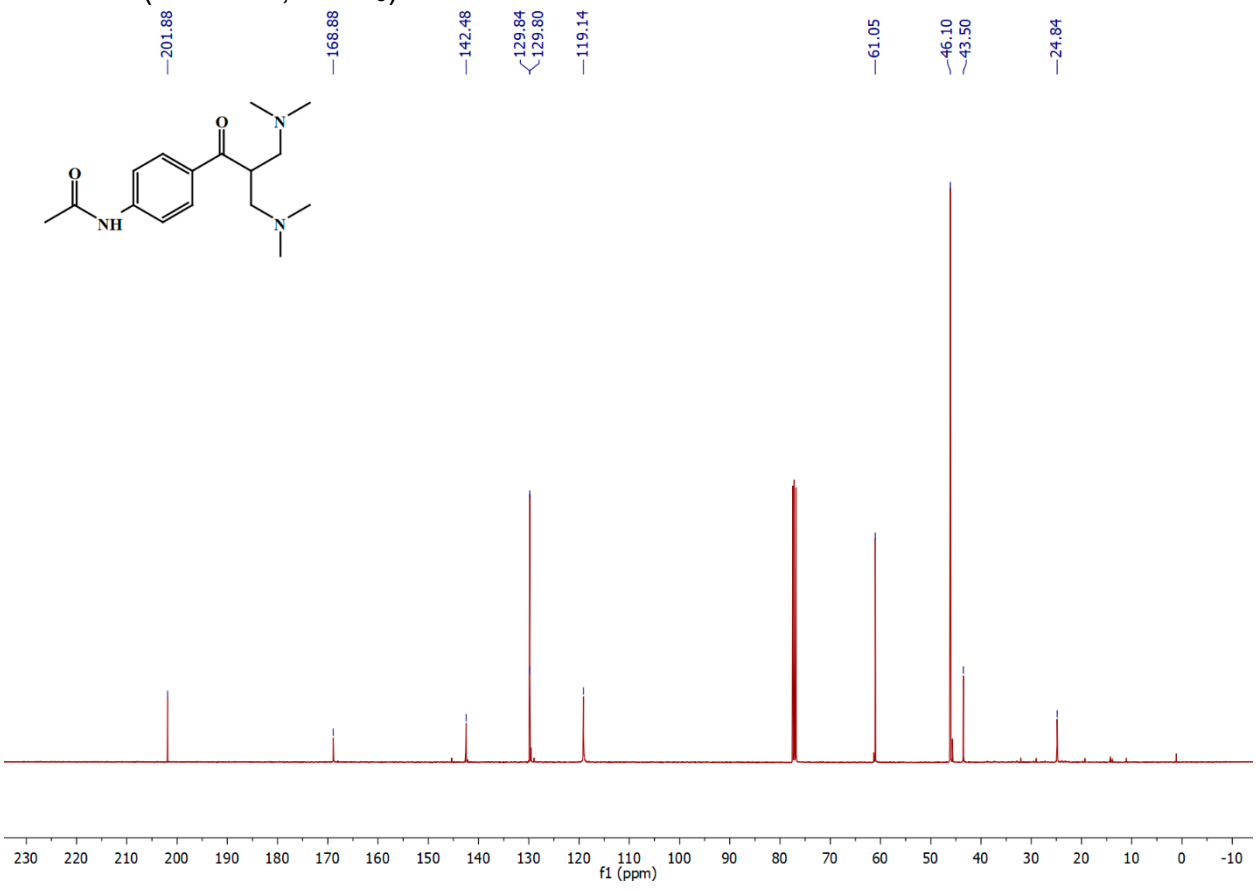
^{13}C NMR (101 MHz, $CDCl_3$) of **4q**



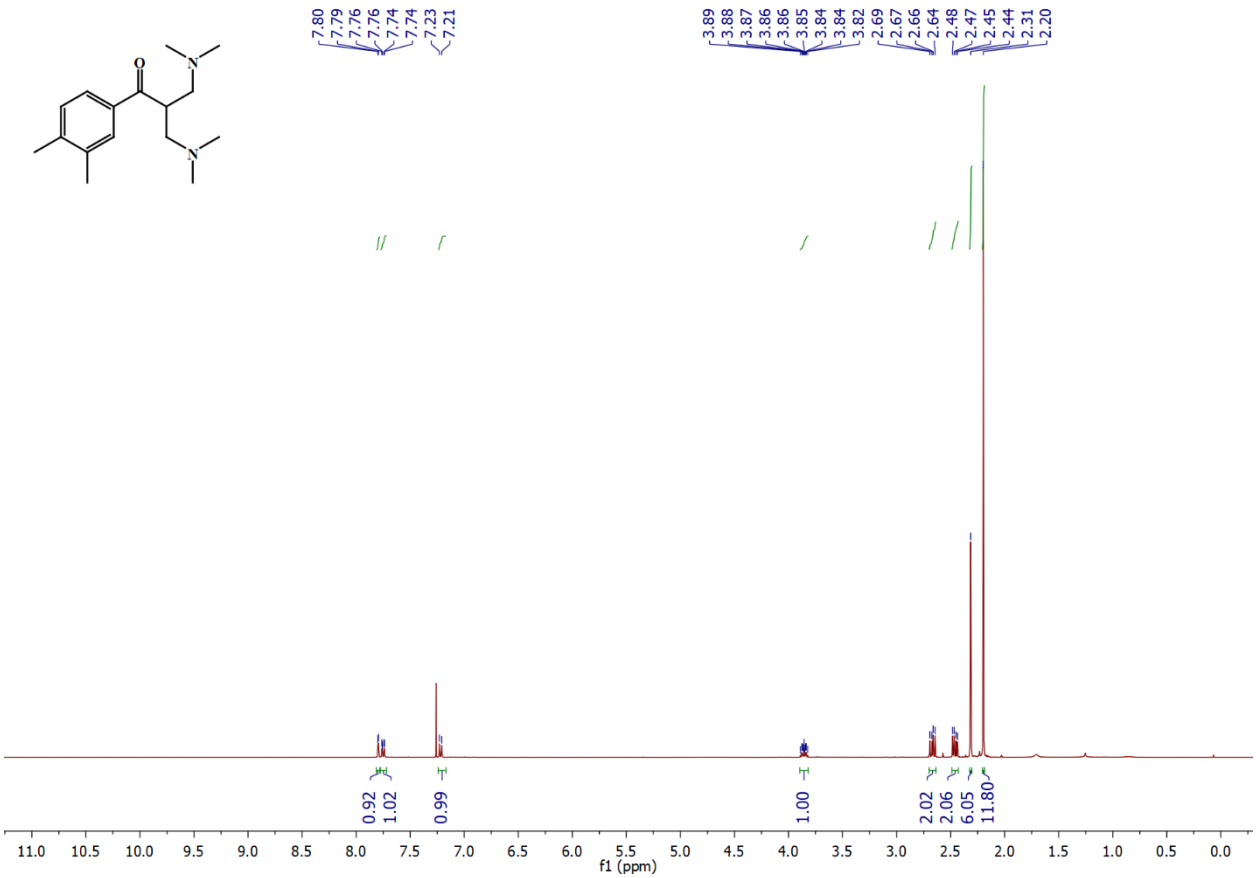
^{1}H NMR (400 MHz, $CDCl_3$) of **4r**



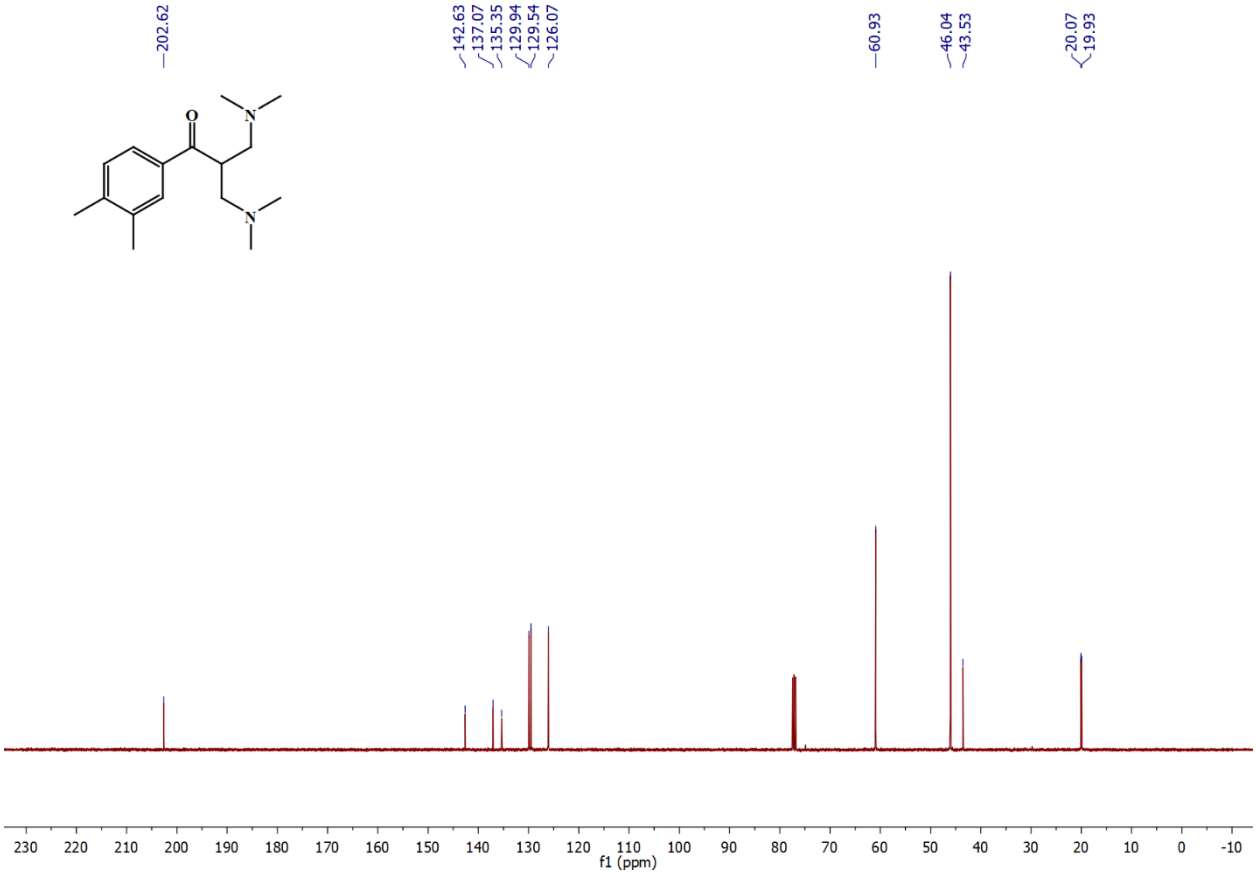
^{13}C NMR (101 MHz, $CDCl_3$) of **4r**



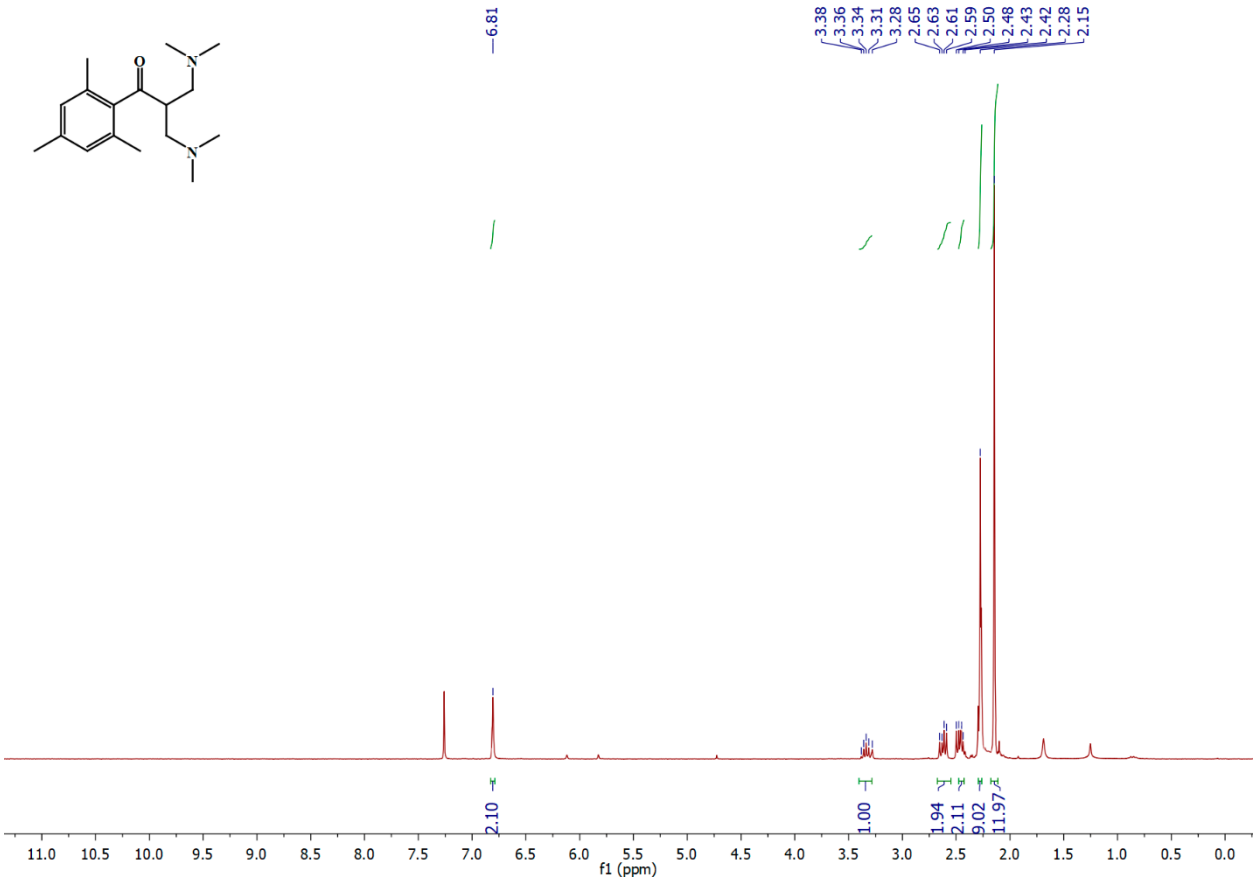
^{1}H NMR (400 MHz, $CDCl_3$) of **4s**



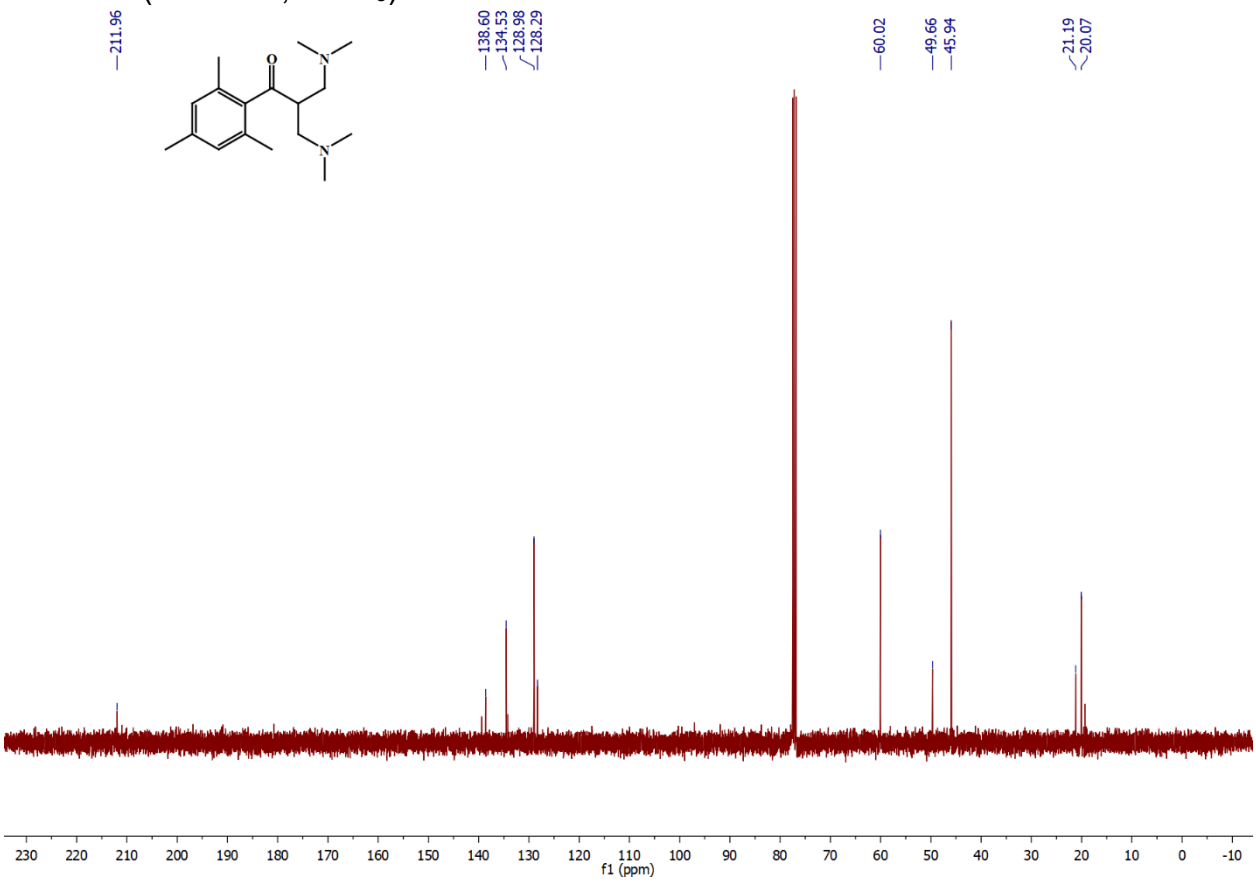
^{13}C NMR (101 MHz, $CDCl_3$) of **4s**



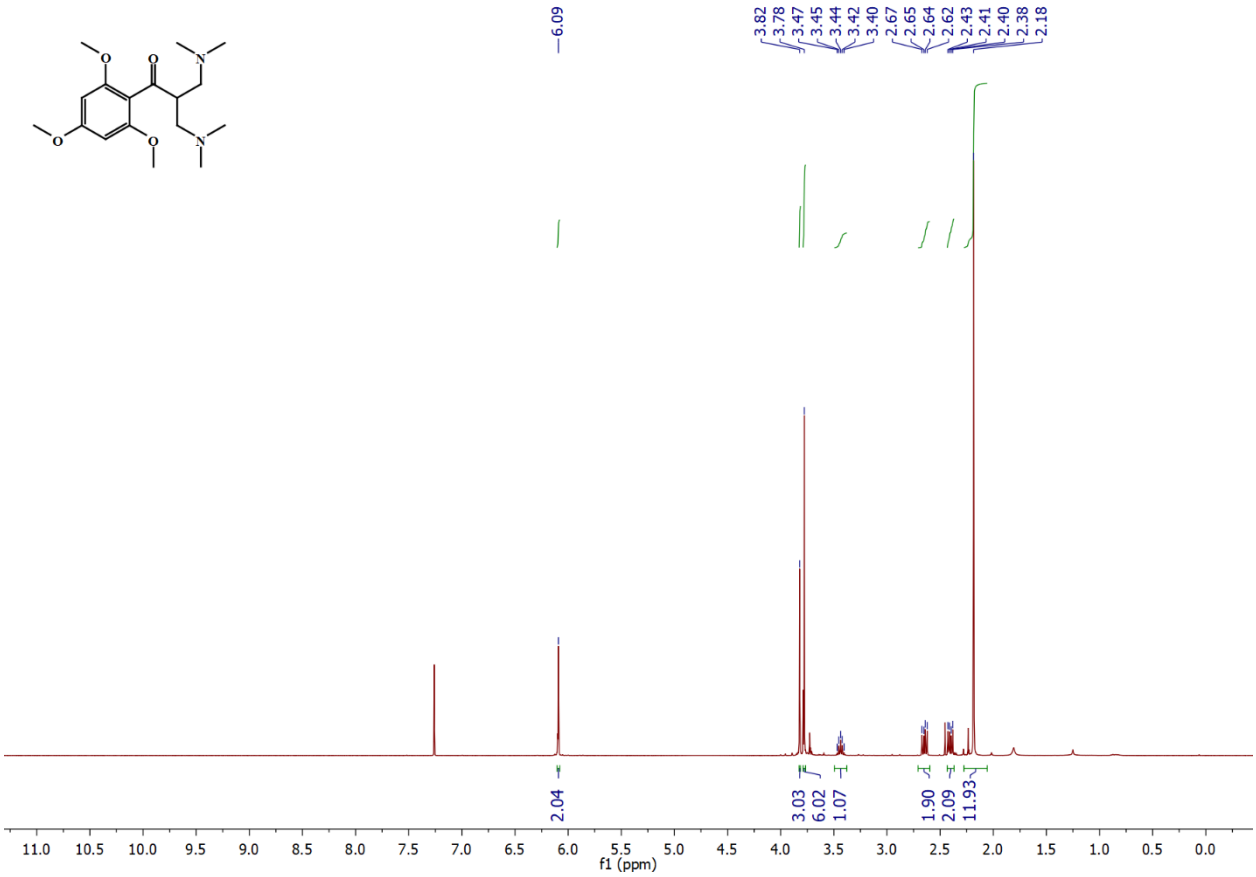
^{1}H NMR (400 MHz, $CDCl_3$) of **4t**



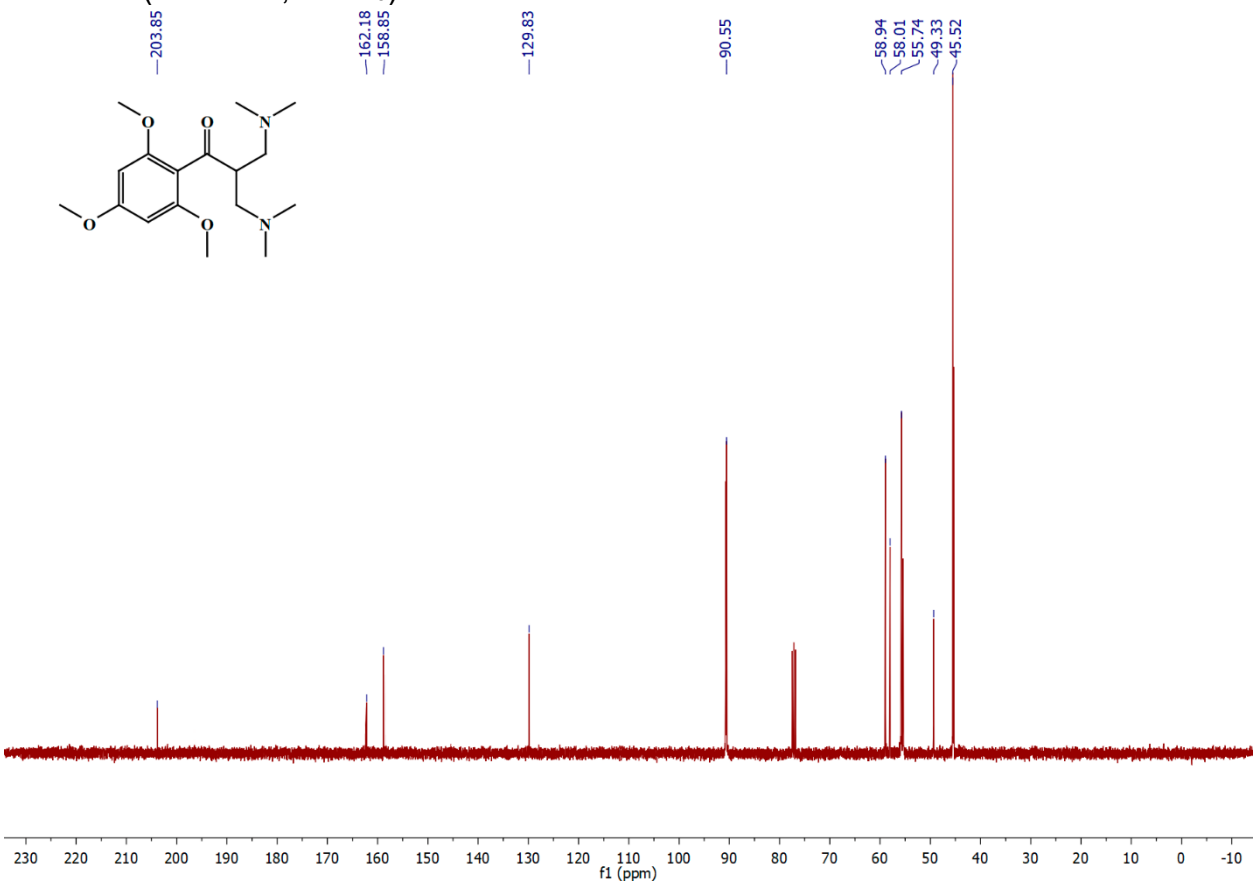
^{13}C NMR (101 MHz, $CDCl_3$) of **4t**



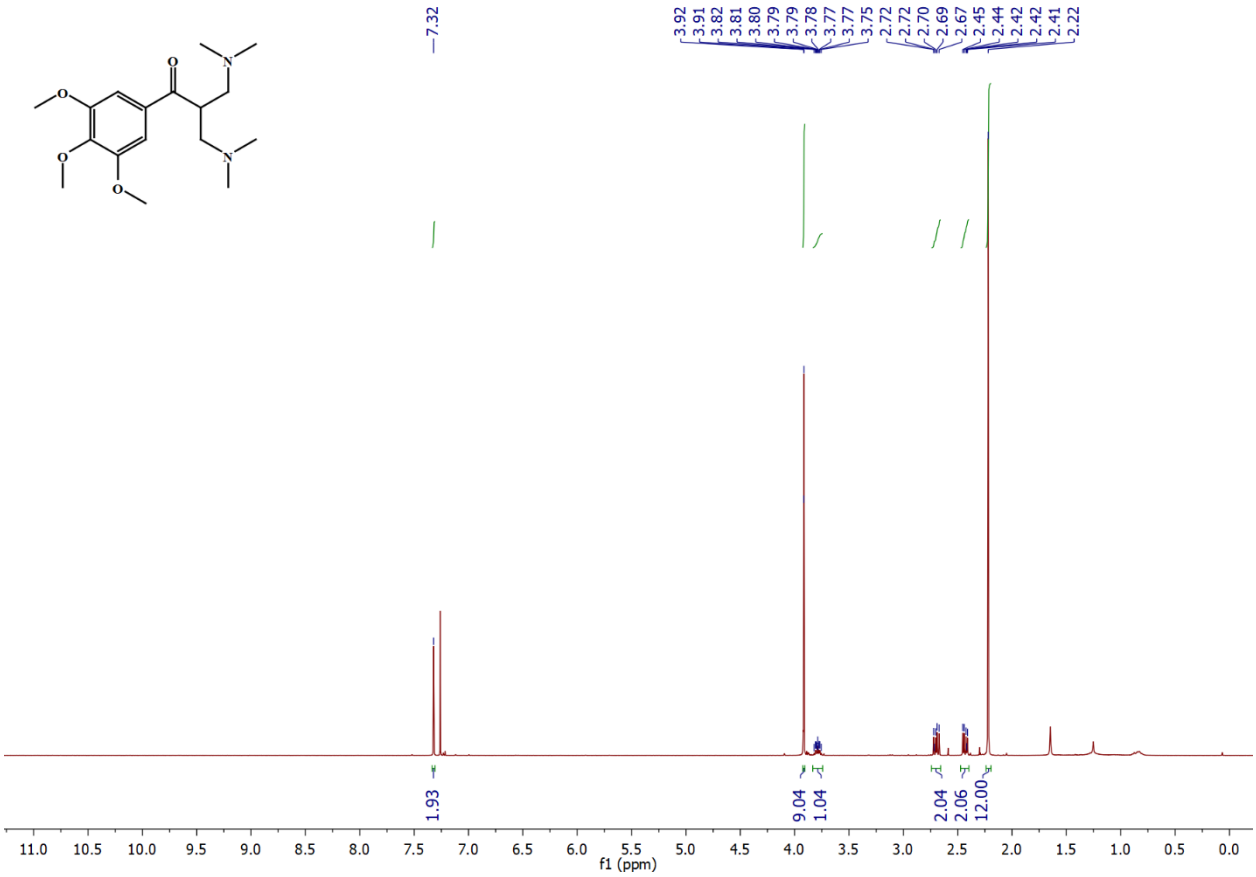
^{1}H NMR (400 MHz, $CDCl_3$) of **4u**



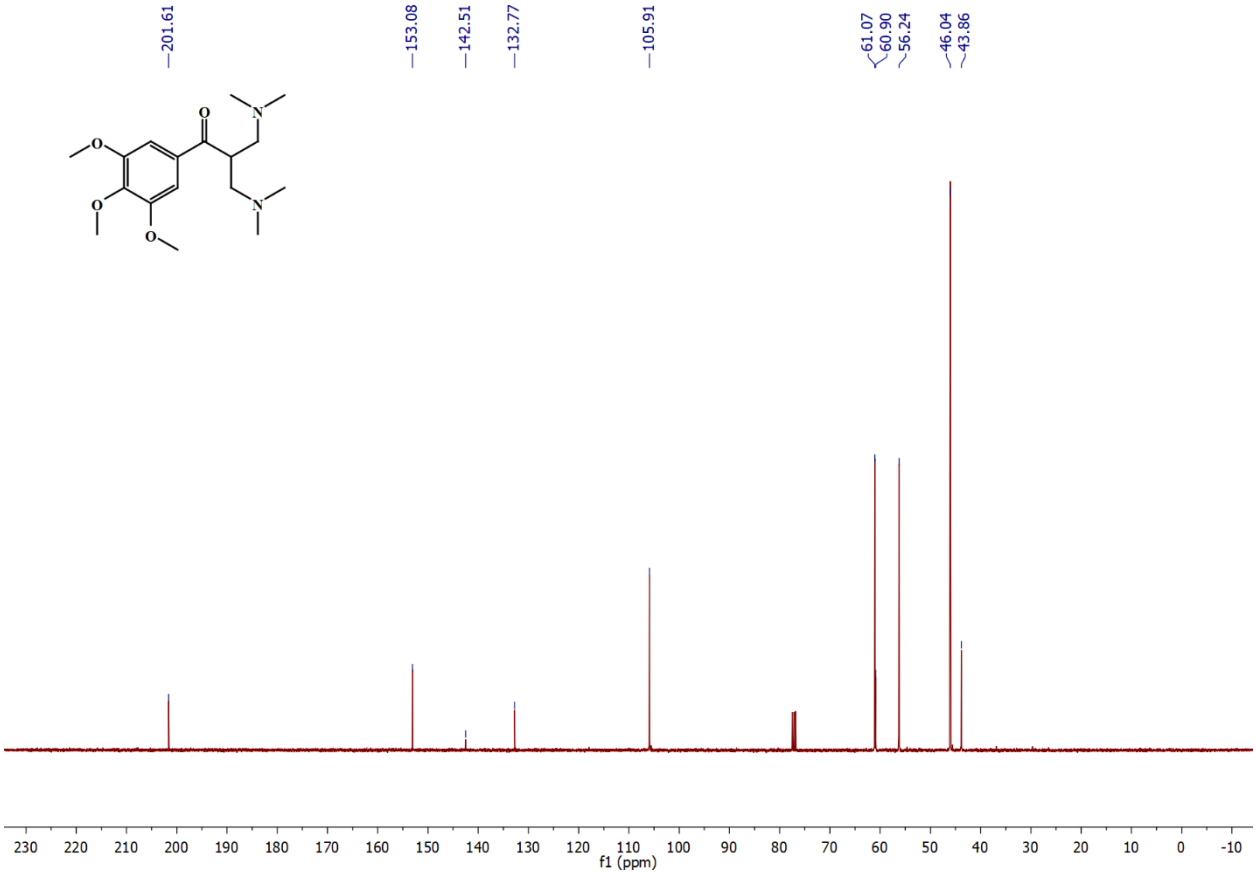
^{13}C NMR (101 MHz, $CDCl_3$) of **4u**



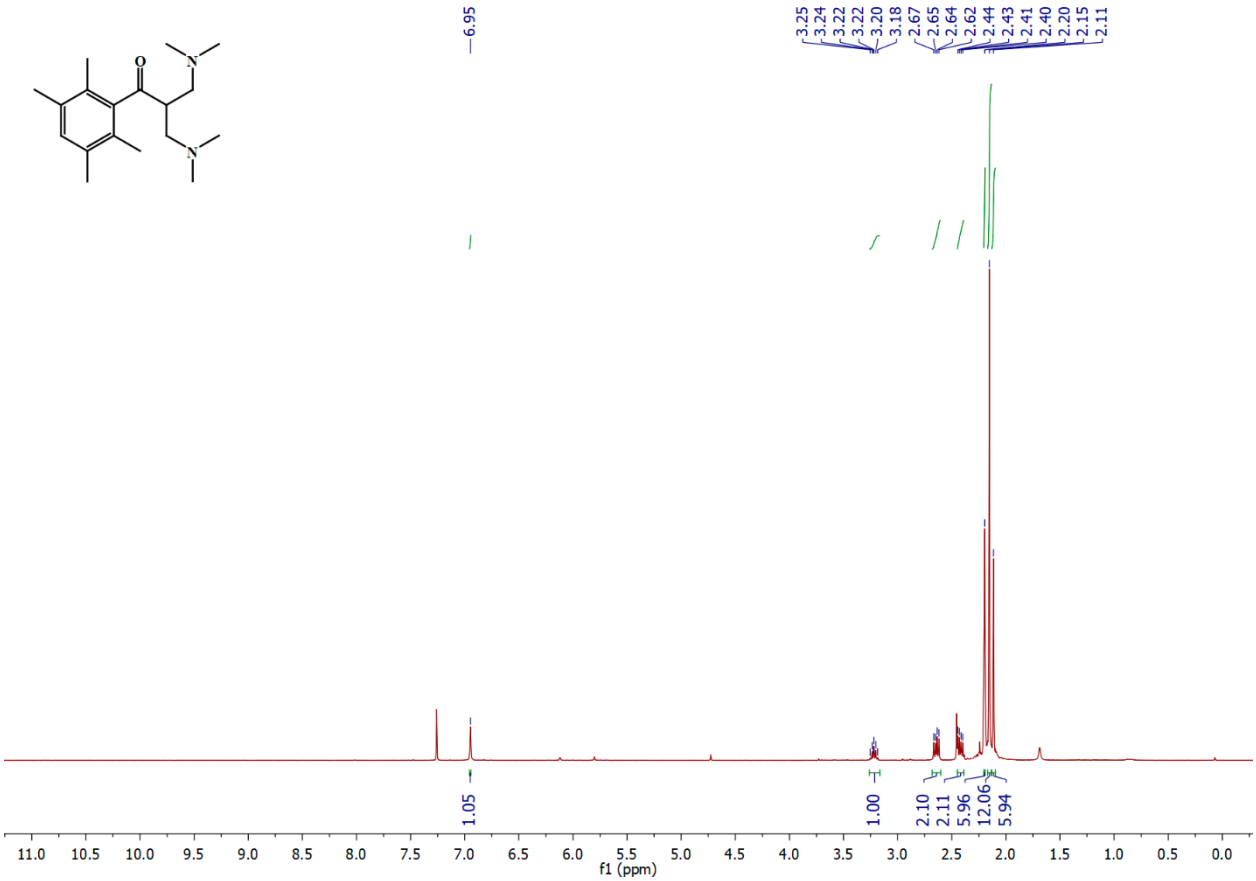
^{1}H NMR (400 MHz, $CDCl_3$) of **4v**



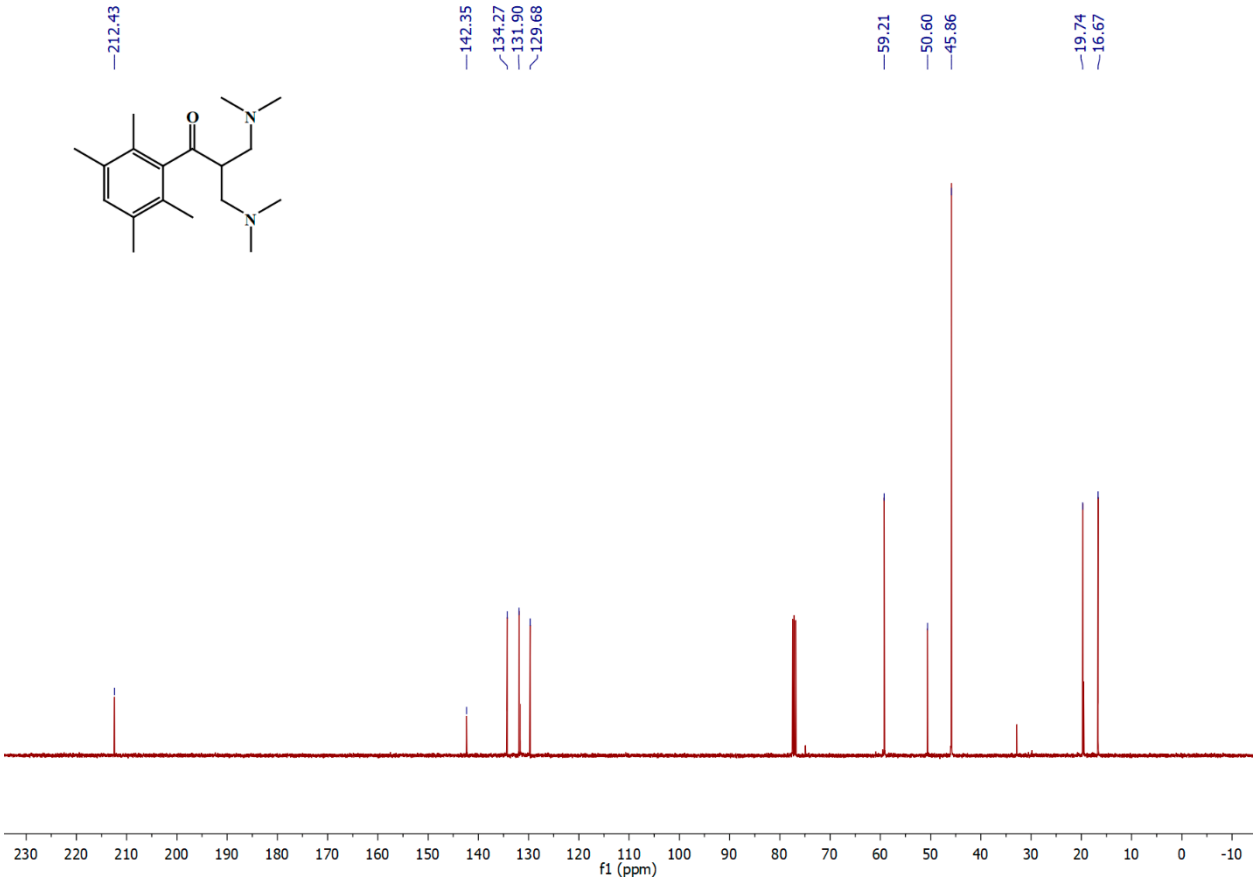
^{13}C NMR (101 MHz, $CDCl_3$) of **4v**



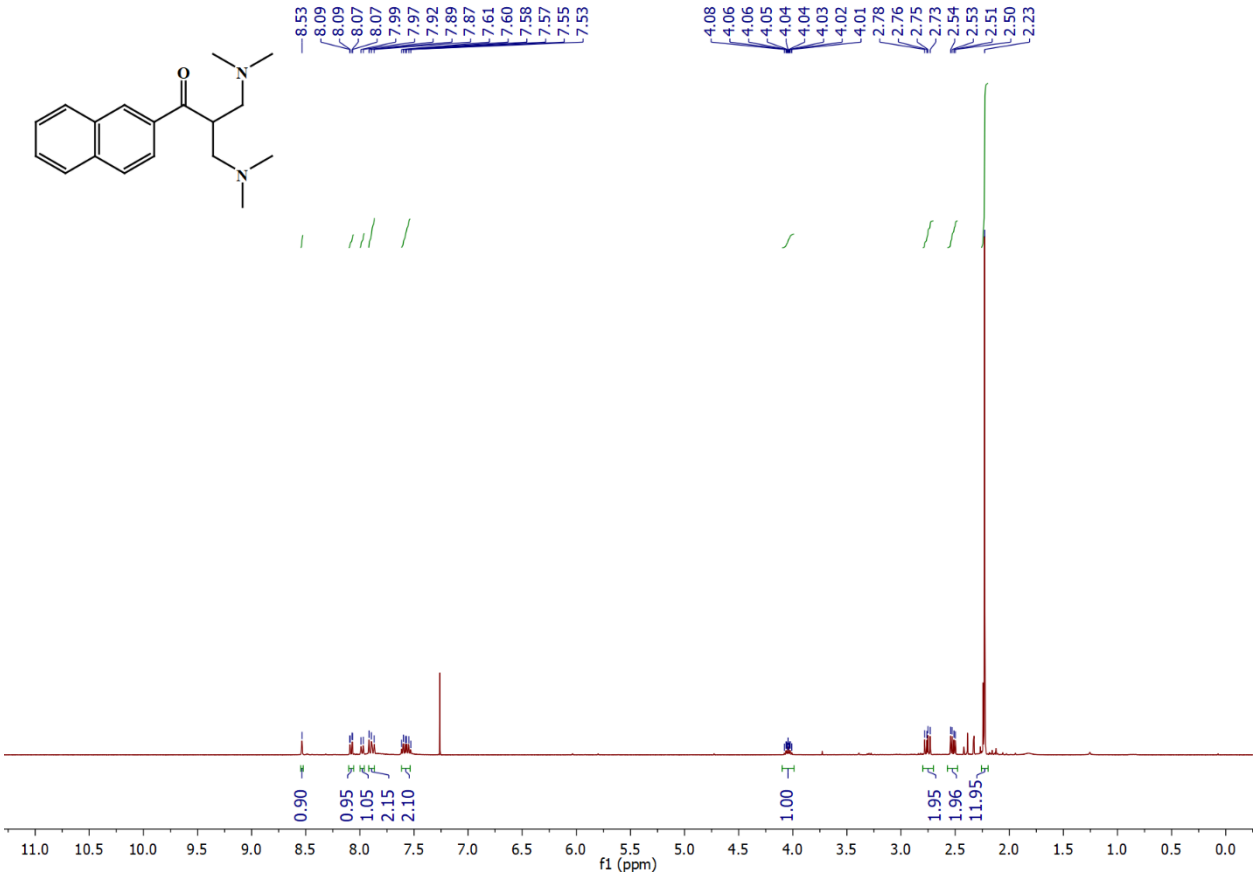
^{1}H NMR (400 MHz, $CDCl_3$) of **4w**



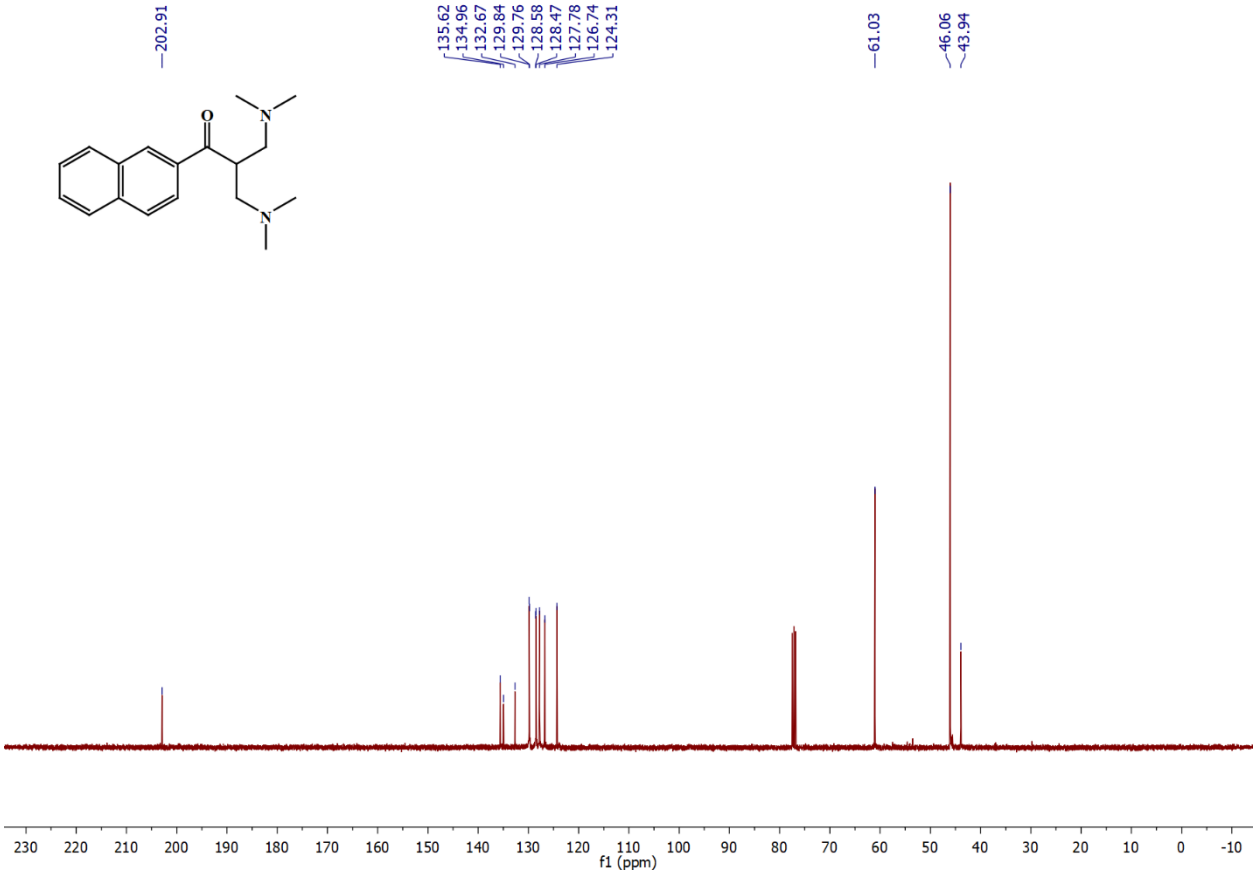
^{13}C NMR (101 MHz, $CDCl_3$) of **4w**



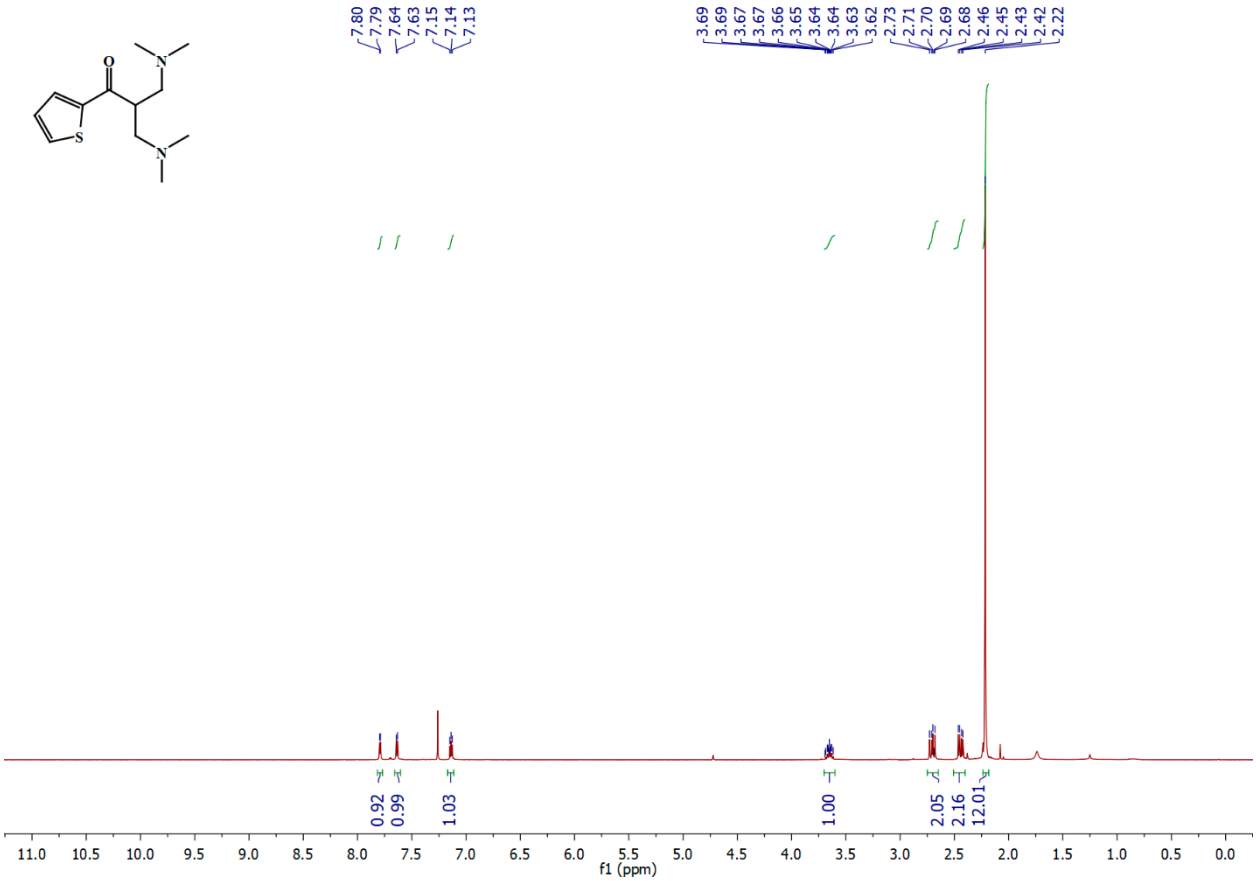
^{1}H NMR (400 MHz, $CDCl_3$) of **4x**



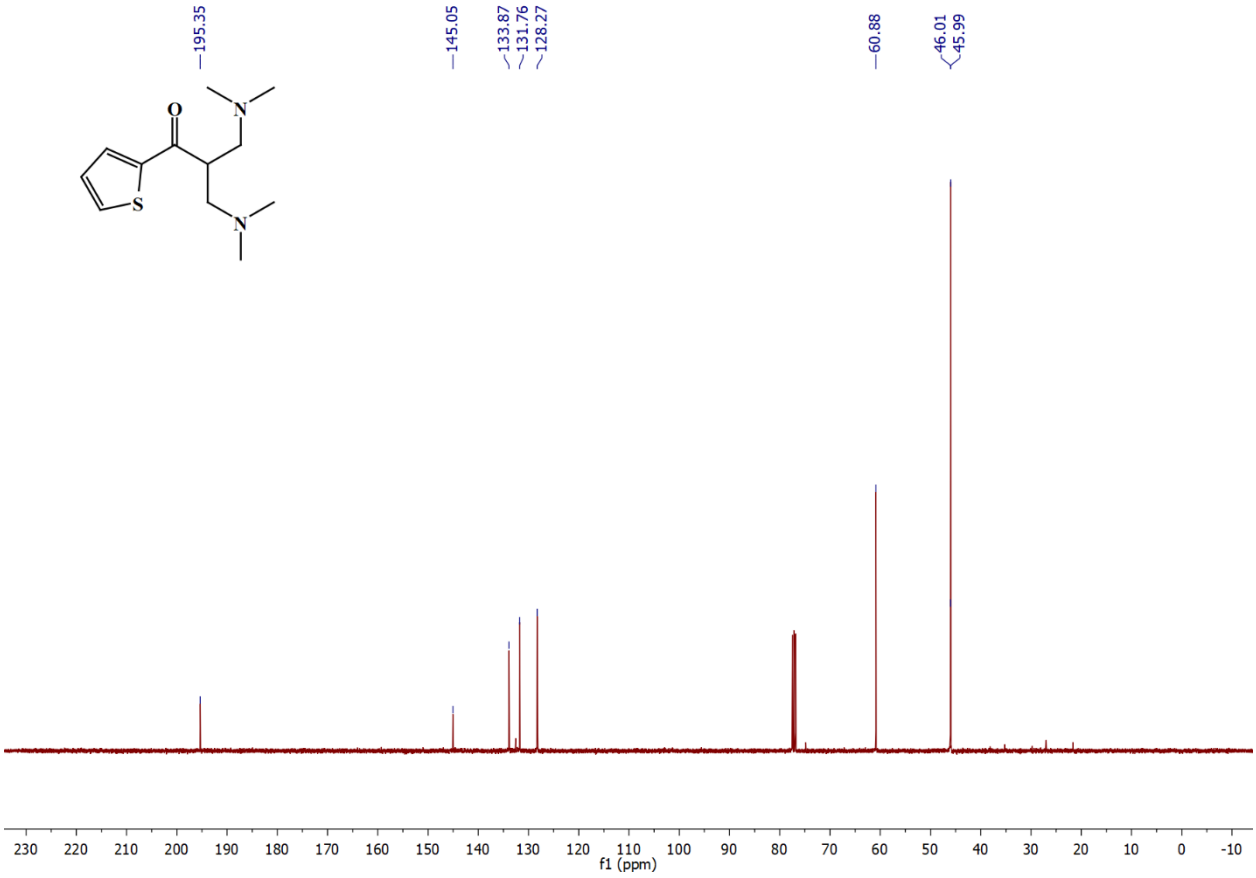
^{13}C NMR (101 MHz, $CDCl_3$) of **4x**



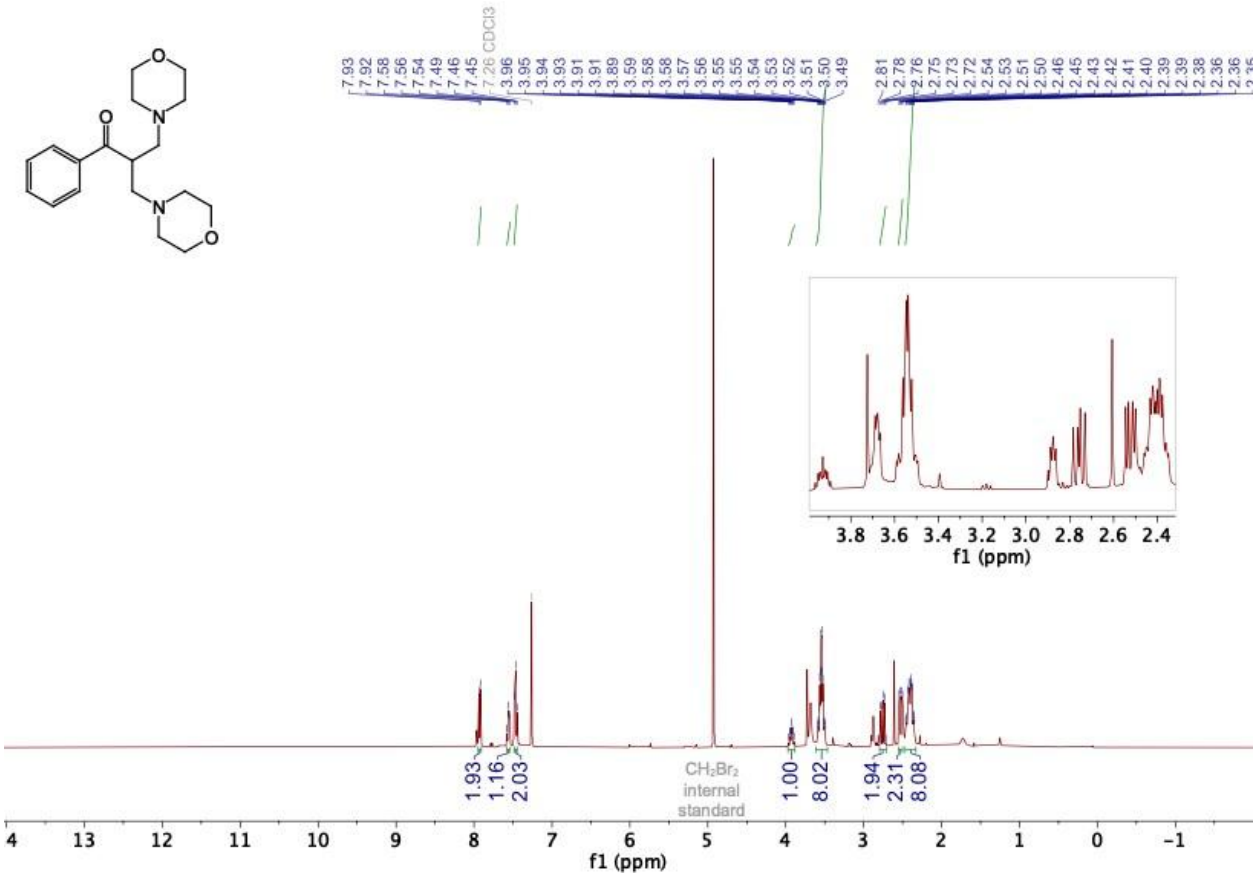
^{1}H NMR (400 MHz, $CDCl_3$) of **4y**



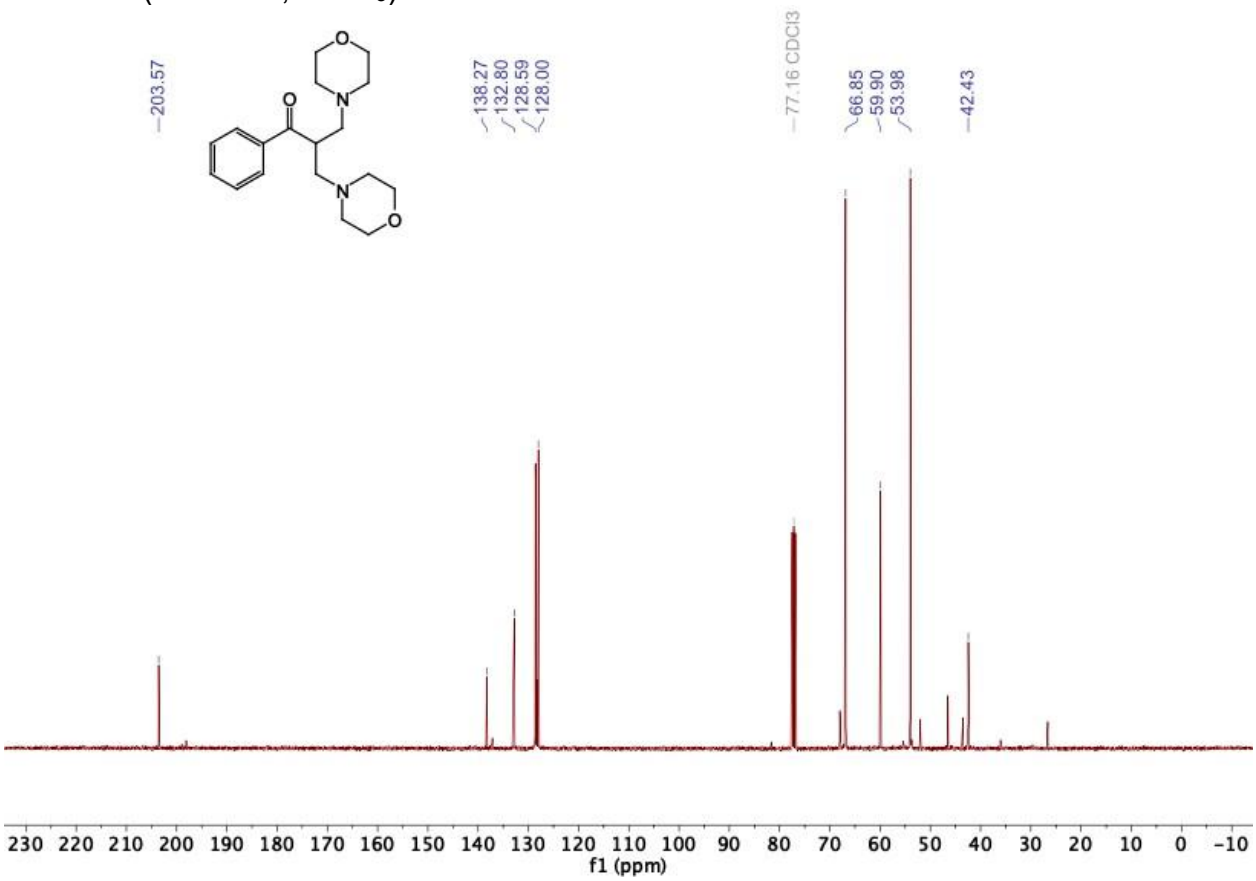
^{13}C NMR (101 MHz, $CDCl_3$) of **4y**



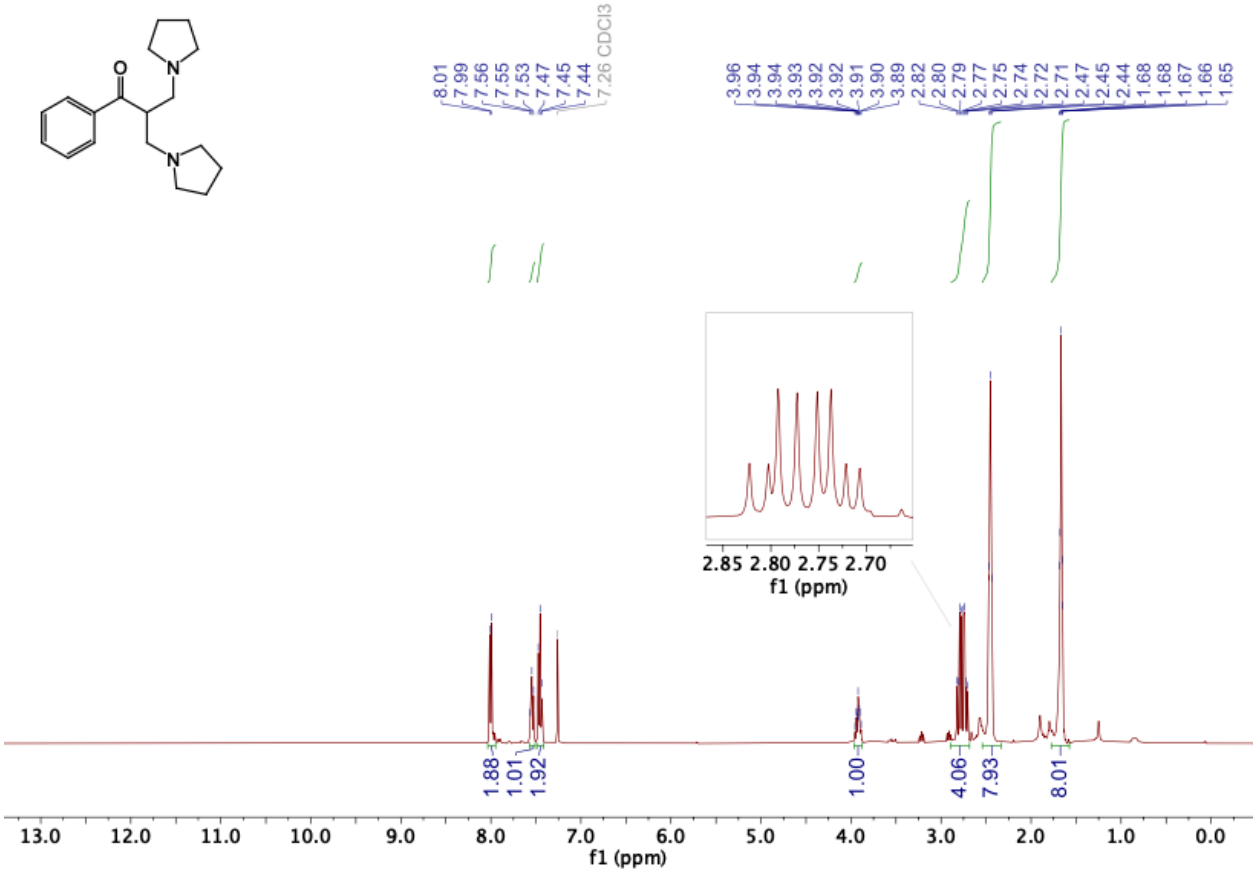
^{1}H NMR (400 MHz, $CDCl_3$) of **4z**



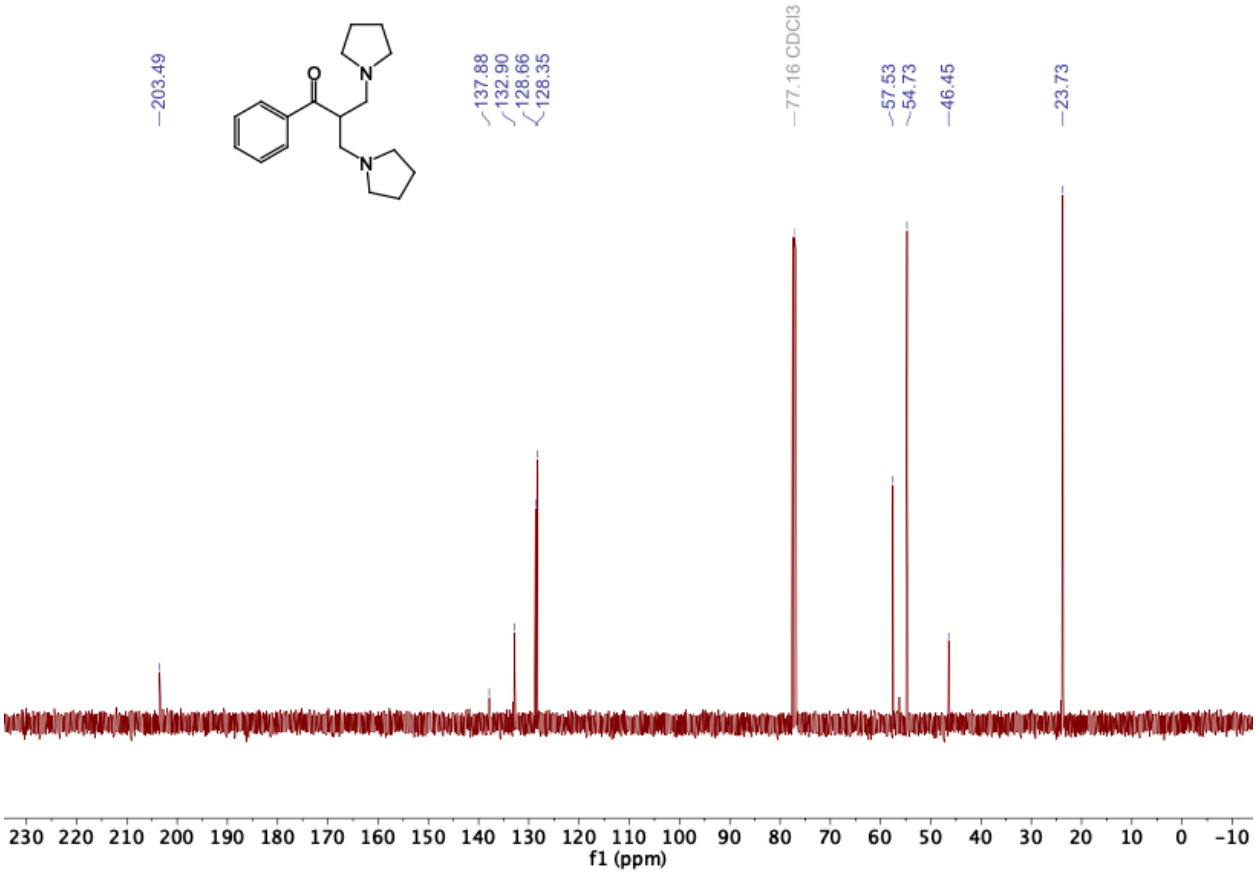
^{13}C NMR (101 MHz, $CDCl_3$) of **4z**



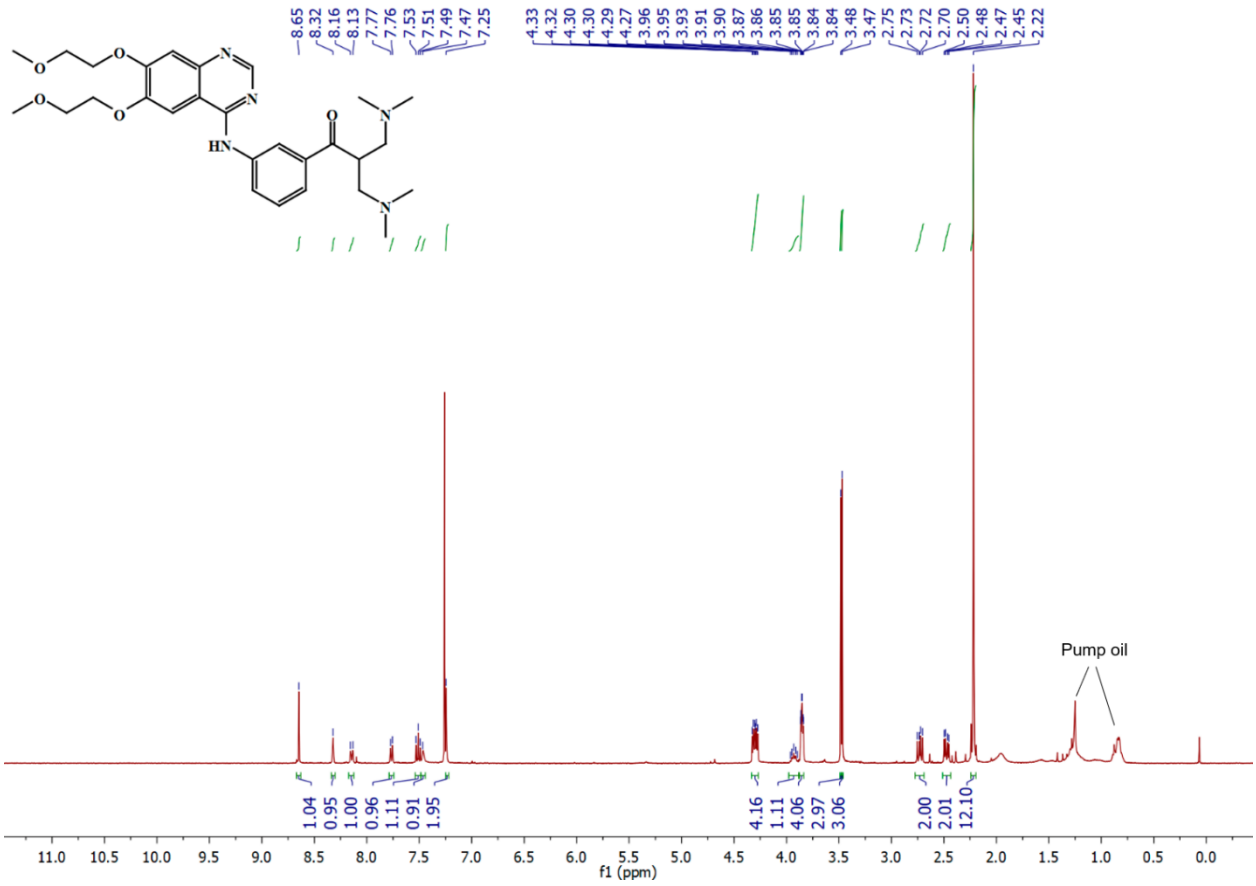
^{1}H NMR (400 MHz, $CDCl_3$) of **4za**



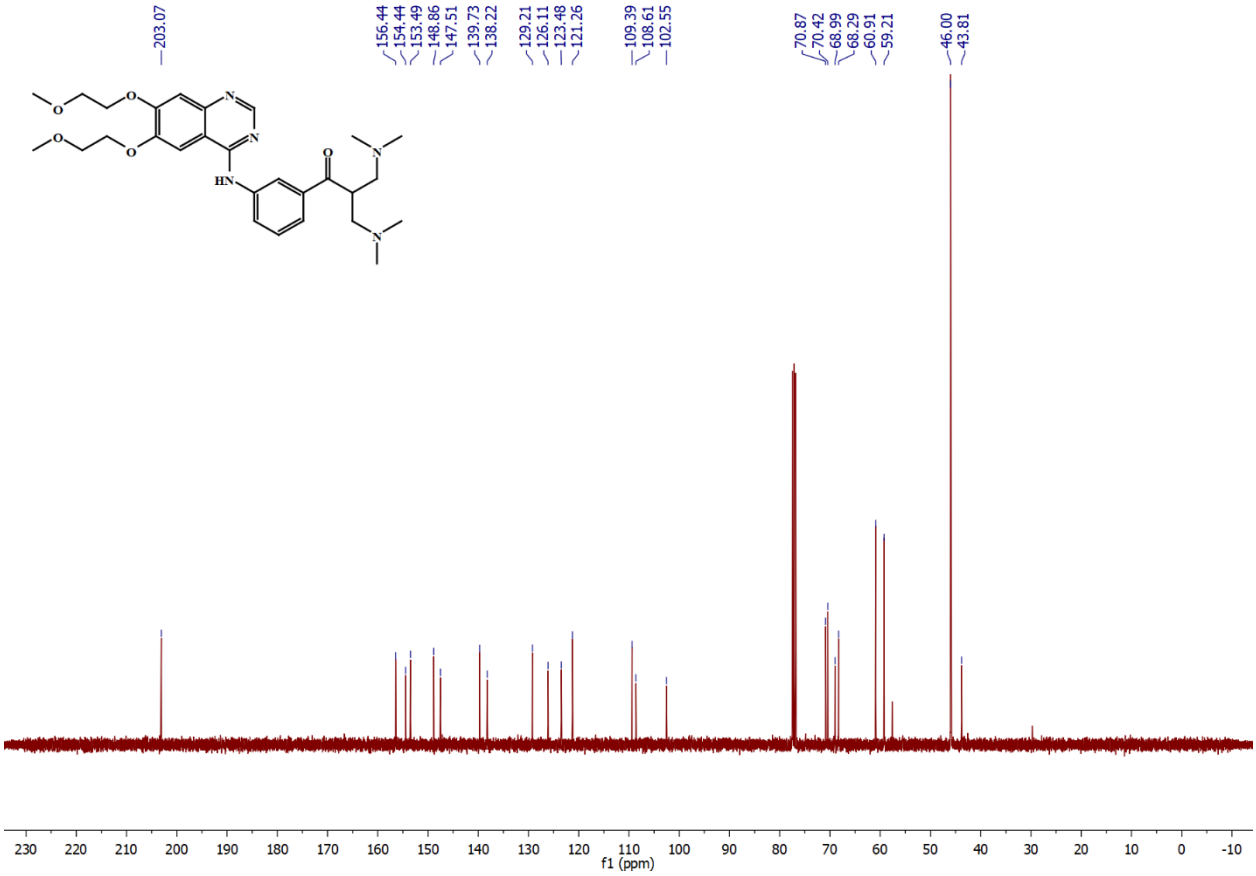
^{13}C NMR (101 MHz, $CDCl_3$) of **4za**



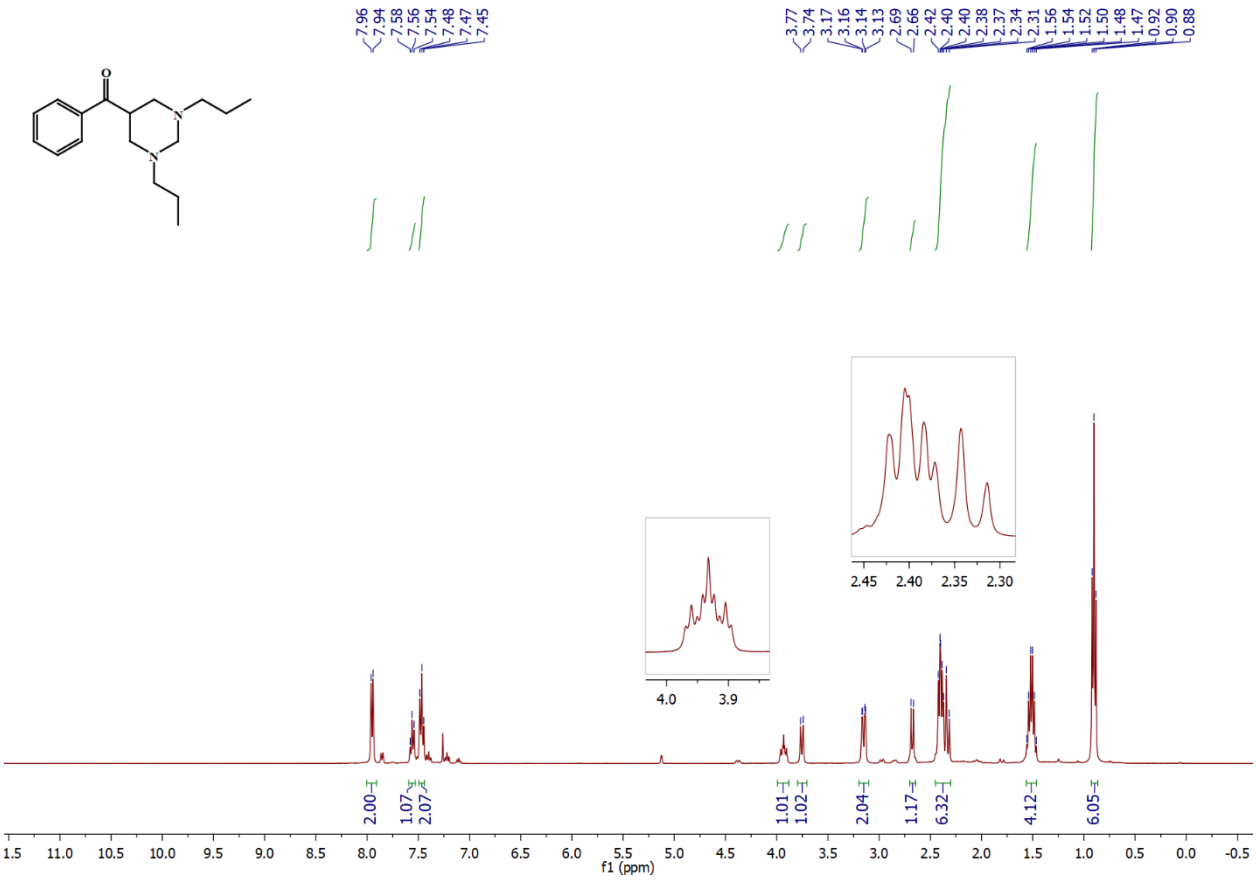
^{1}H NMR (400 MHz, $CDCl_3$) of **7**



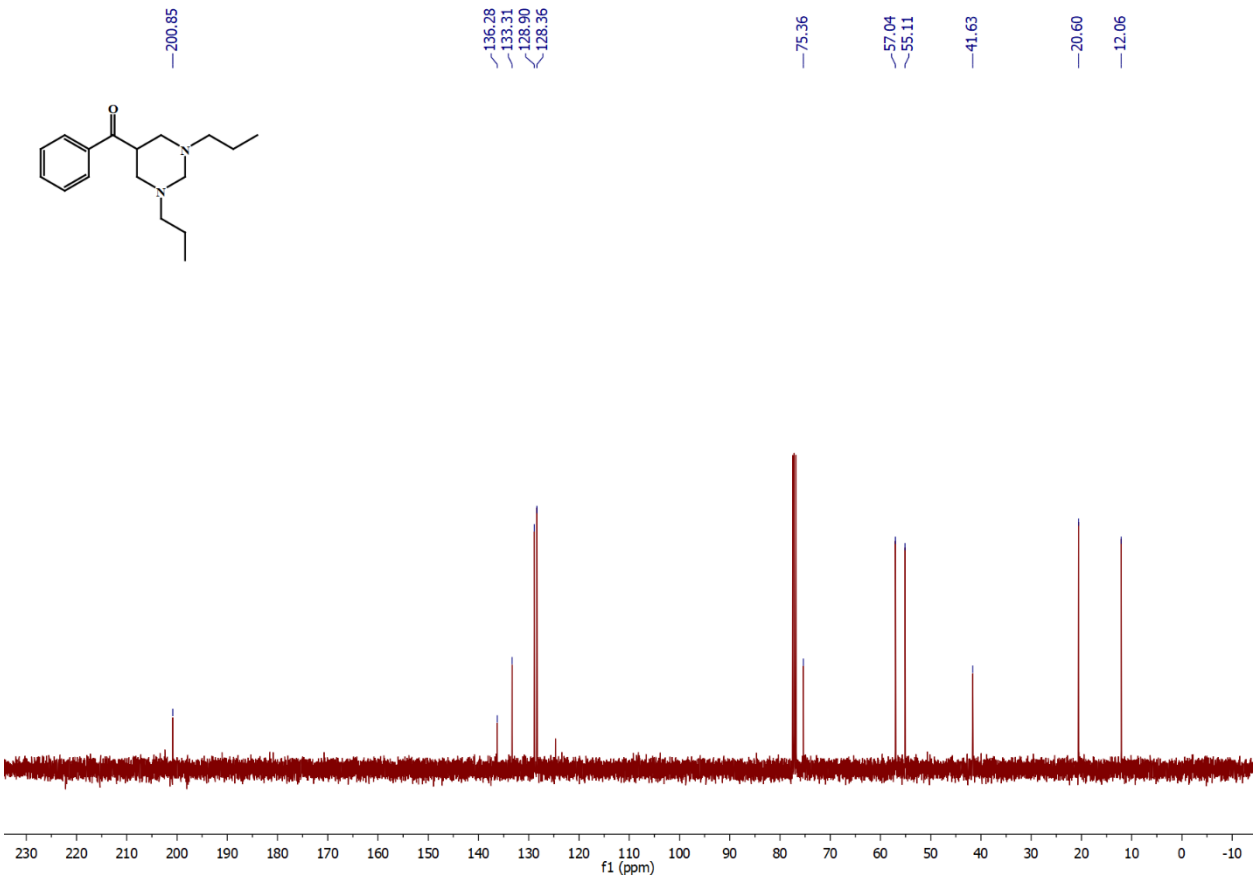
^{13}C NMR (101 MHz, $CDCl_3$) of **7**



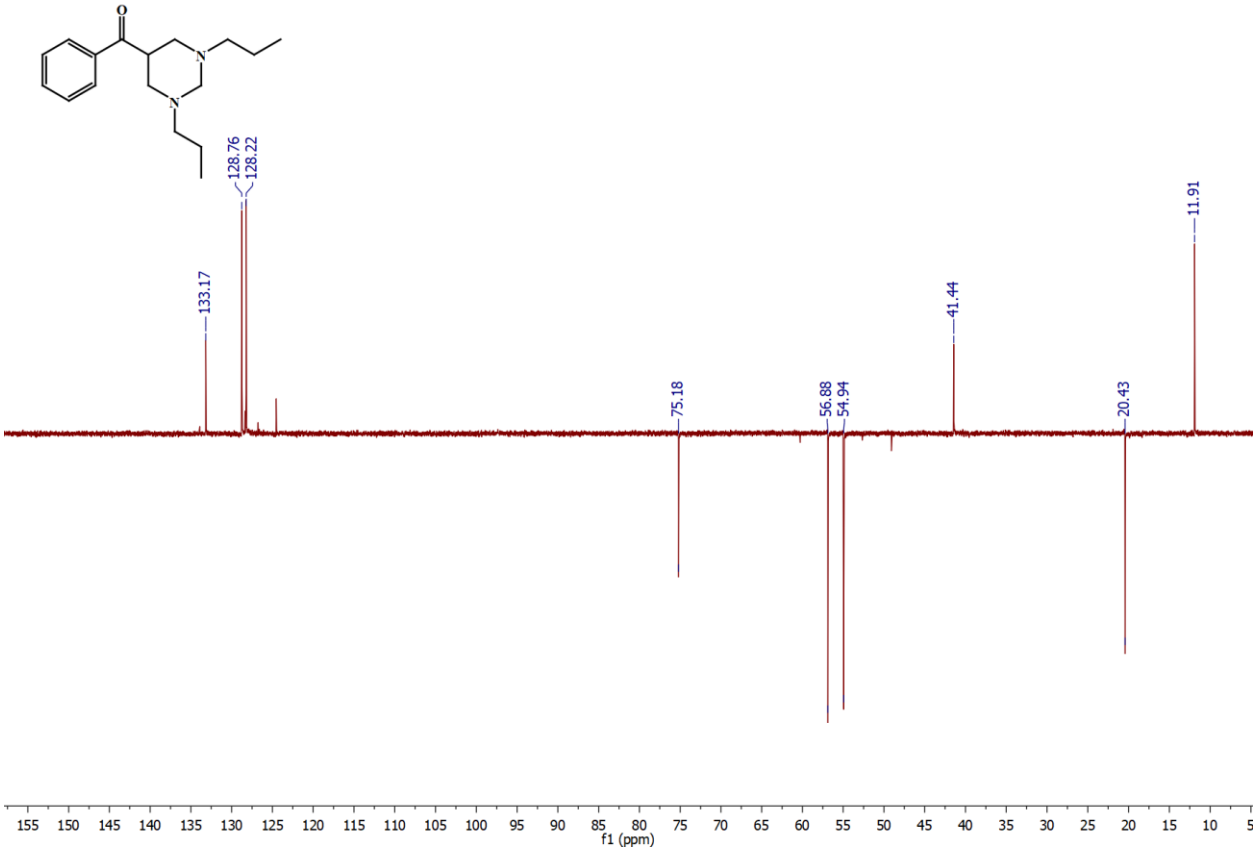
^{1}H NMR (400 MHz, $CDCl_3$) of **6a**



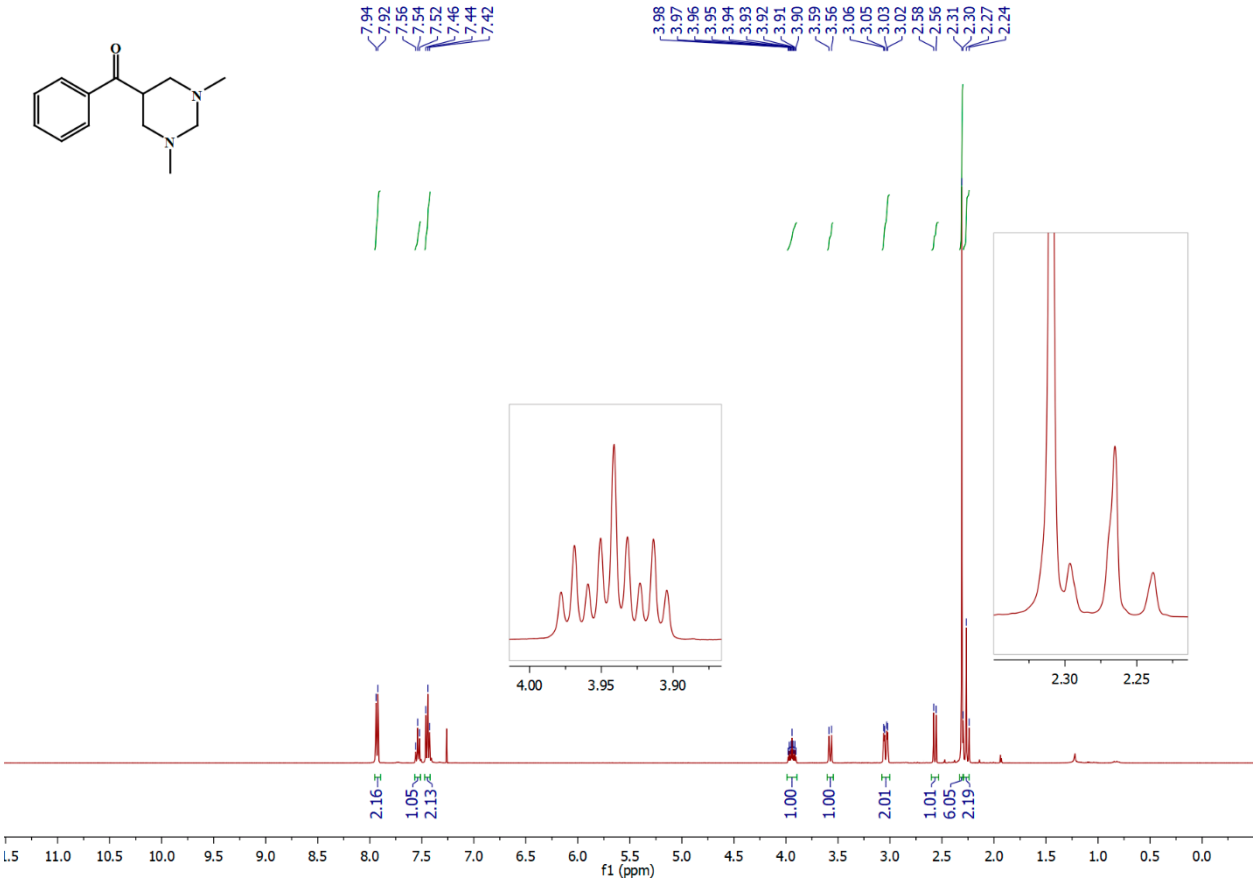
^{13}C NMR (101 MHz, $CDCl_3$) of **6a**



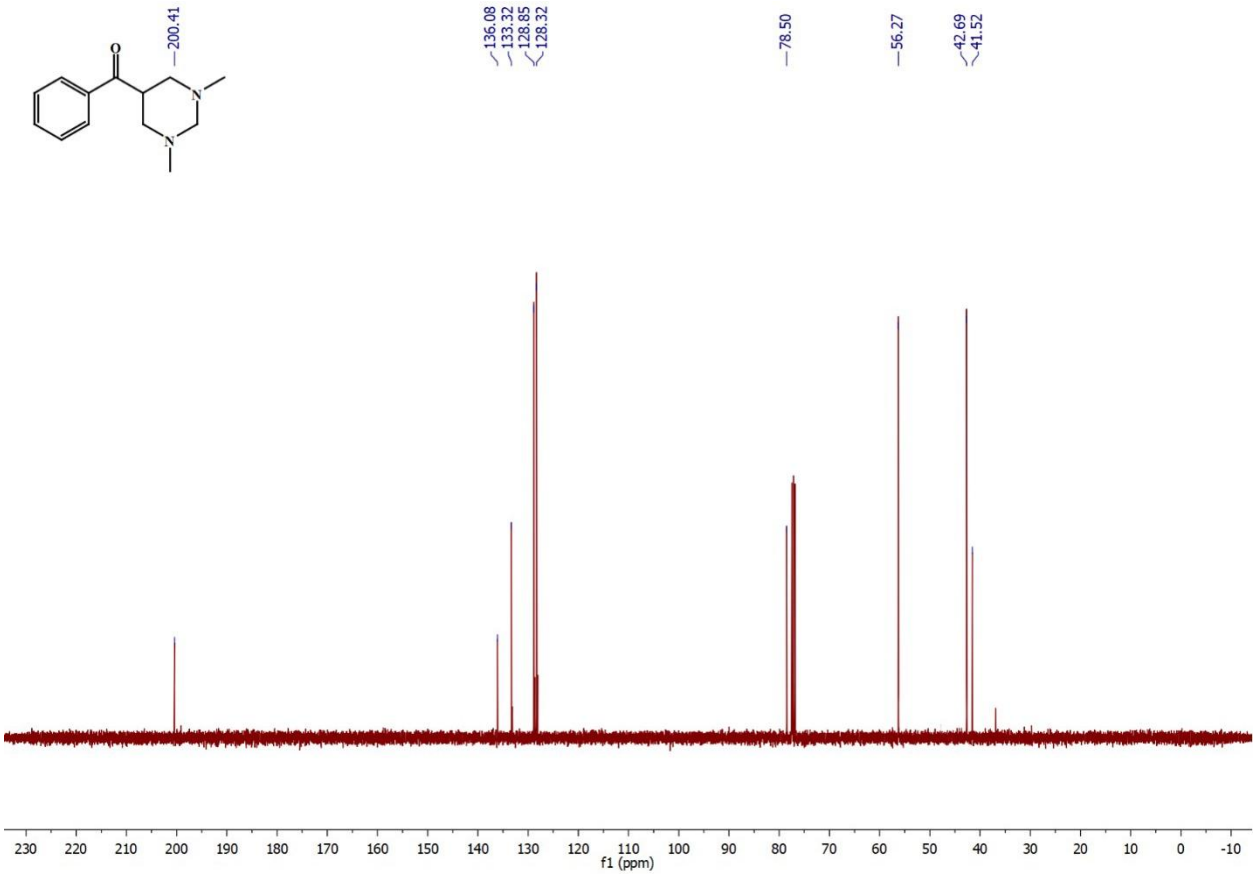
^{13}C-DEPT ($CDCl_3$) of **6a**



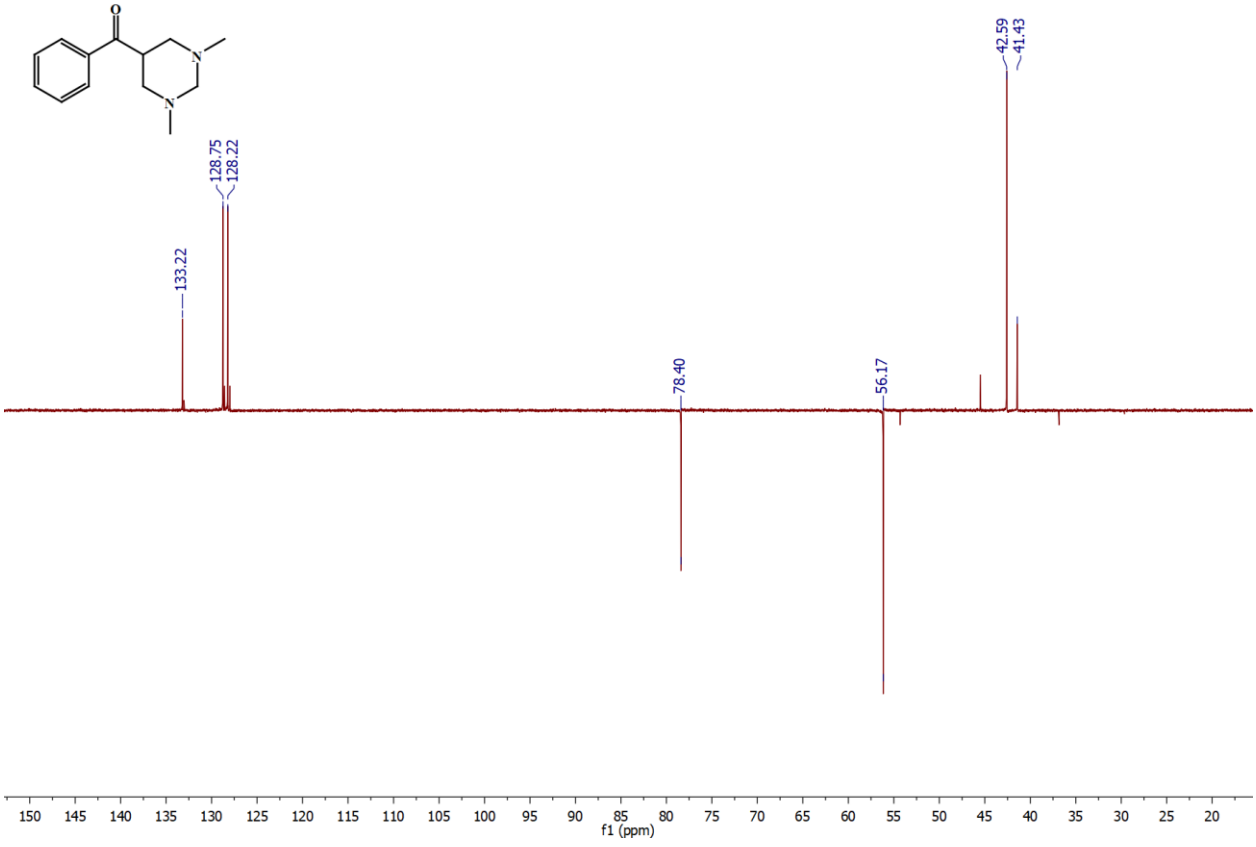
^{1}H NMR (400 MHz, $CDCl_3$) of **6b**



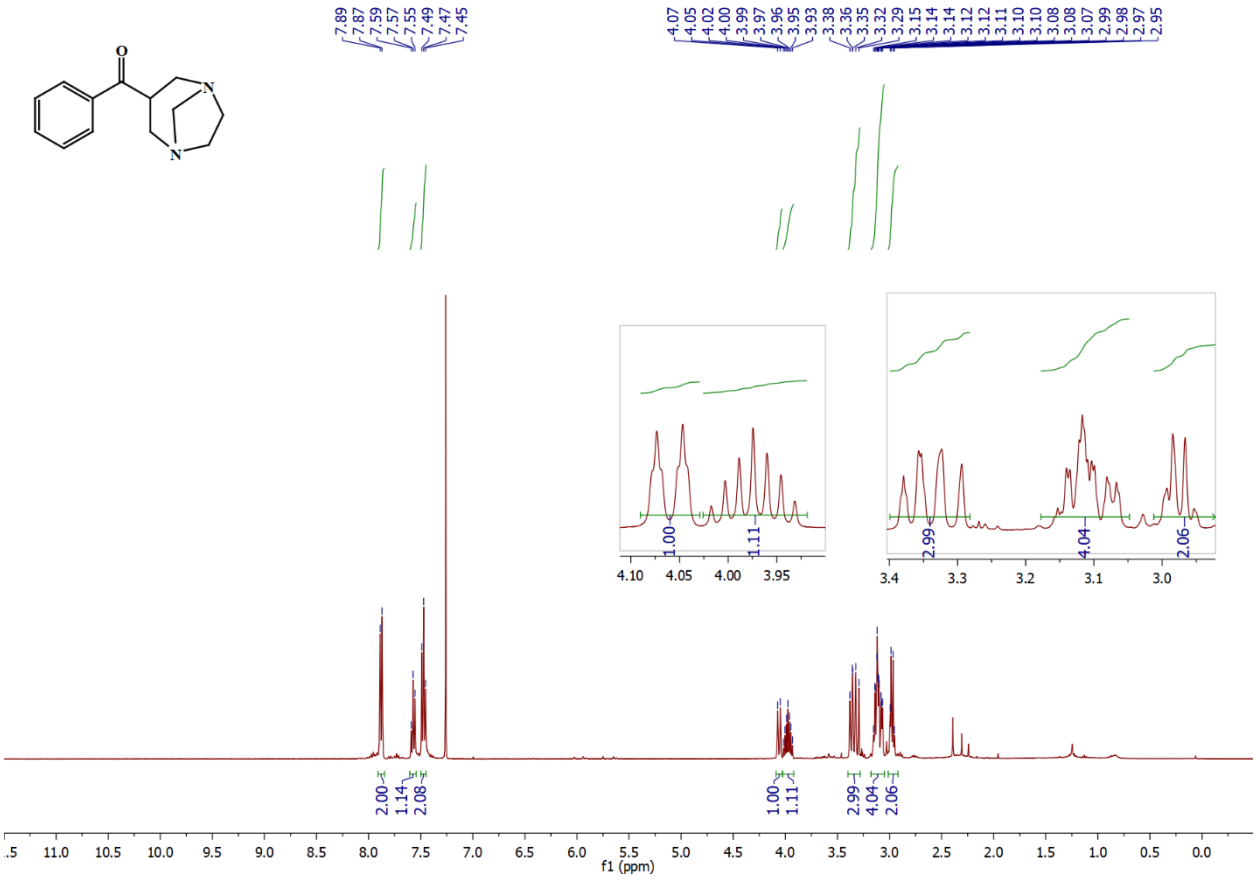
^{13}C NMR (101 MHz, $CDCl_3$) of **6b**



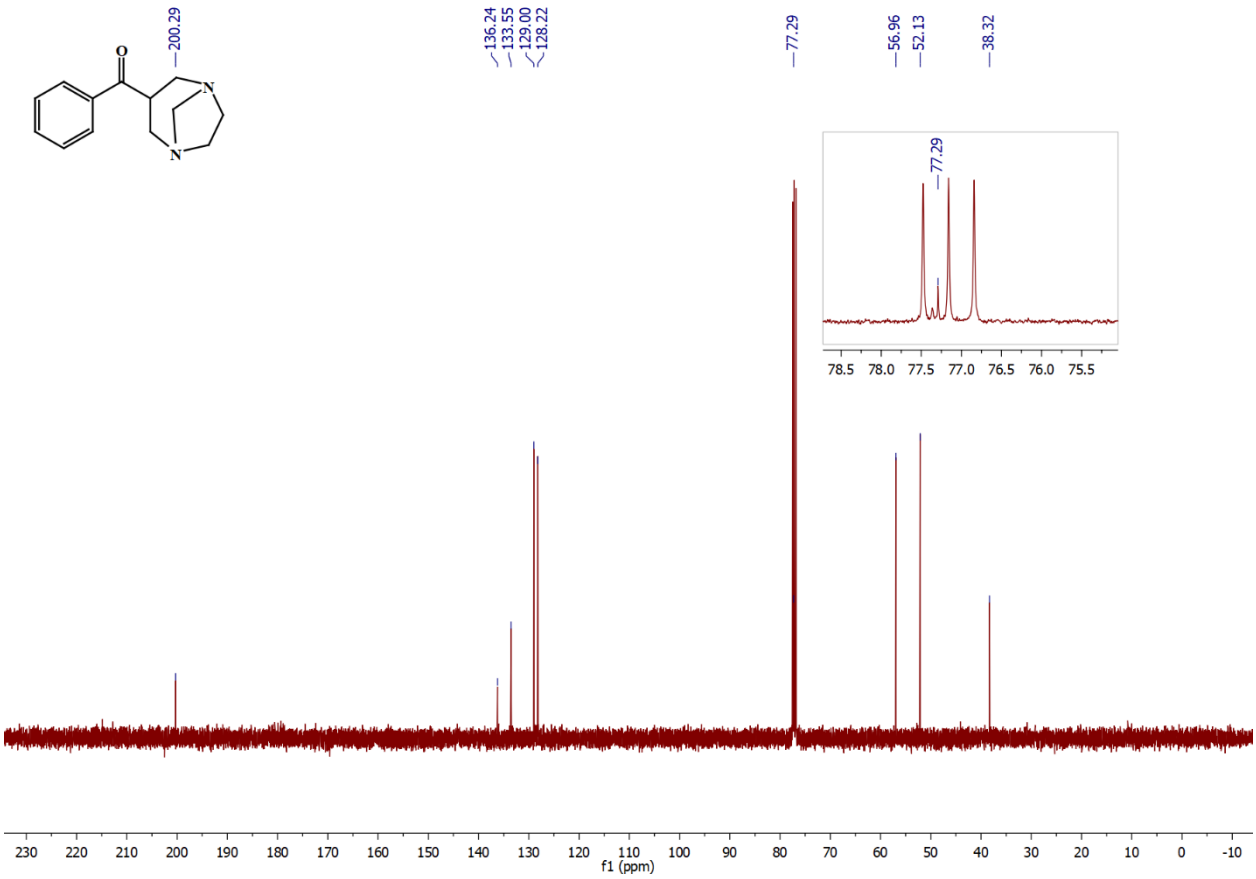
^{13}C-DEPT ($CDCl_3$) of **6b**



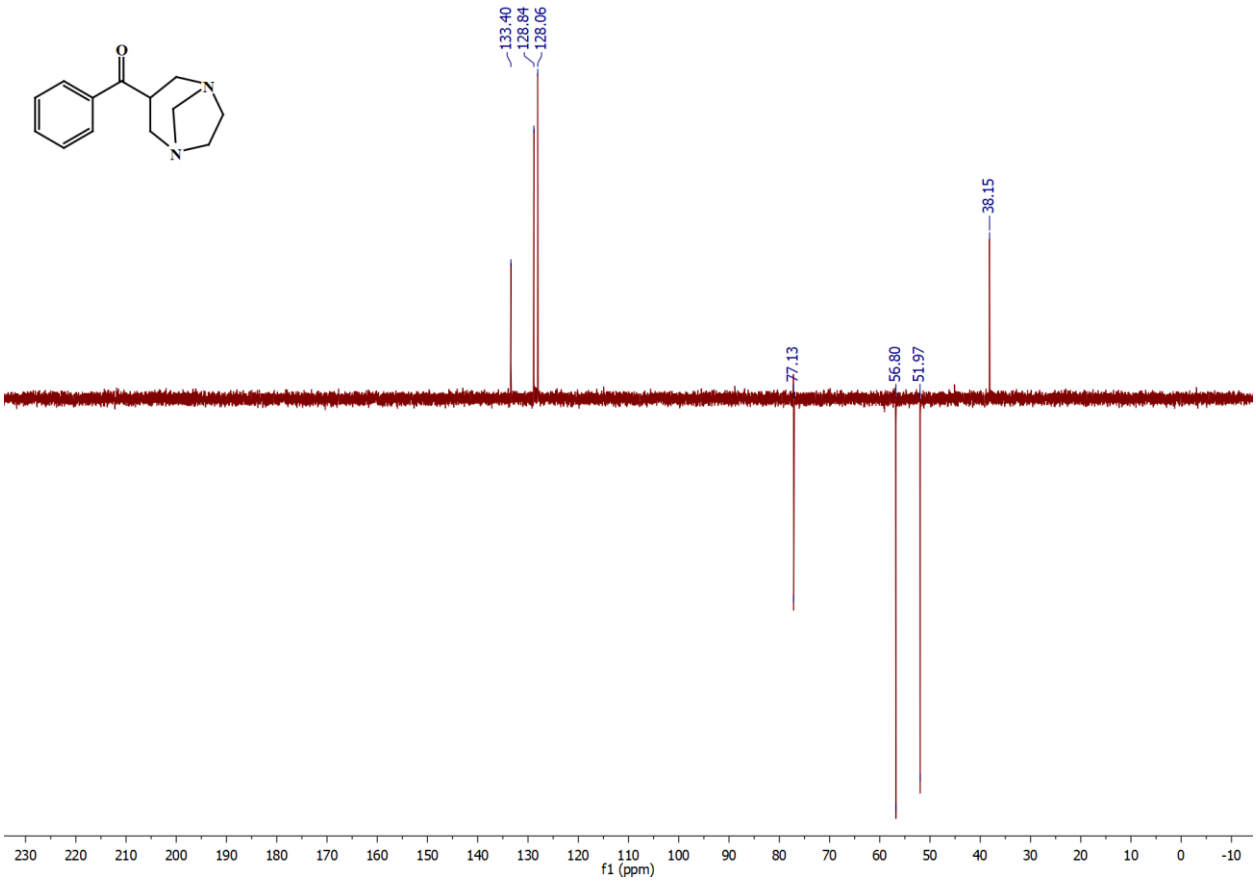
^{1}H NMR (400 MHz, $CDCl_3$) of **8**



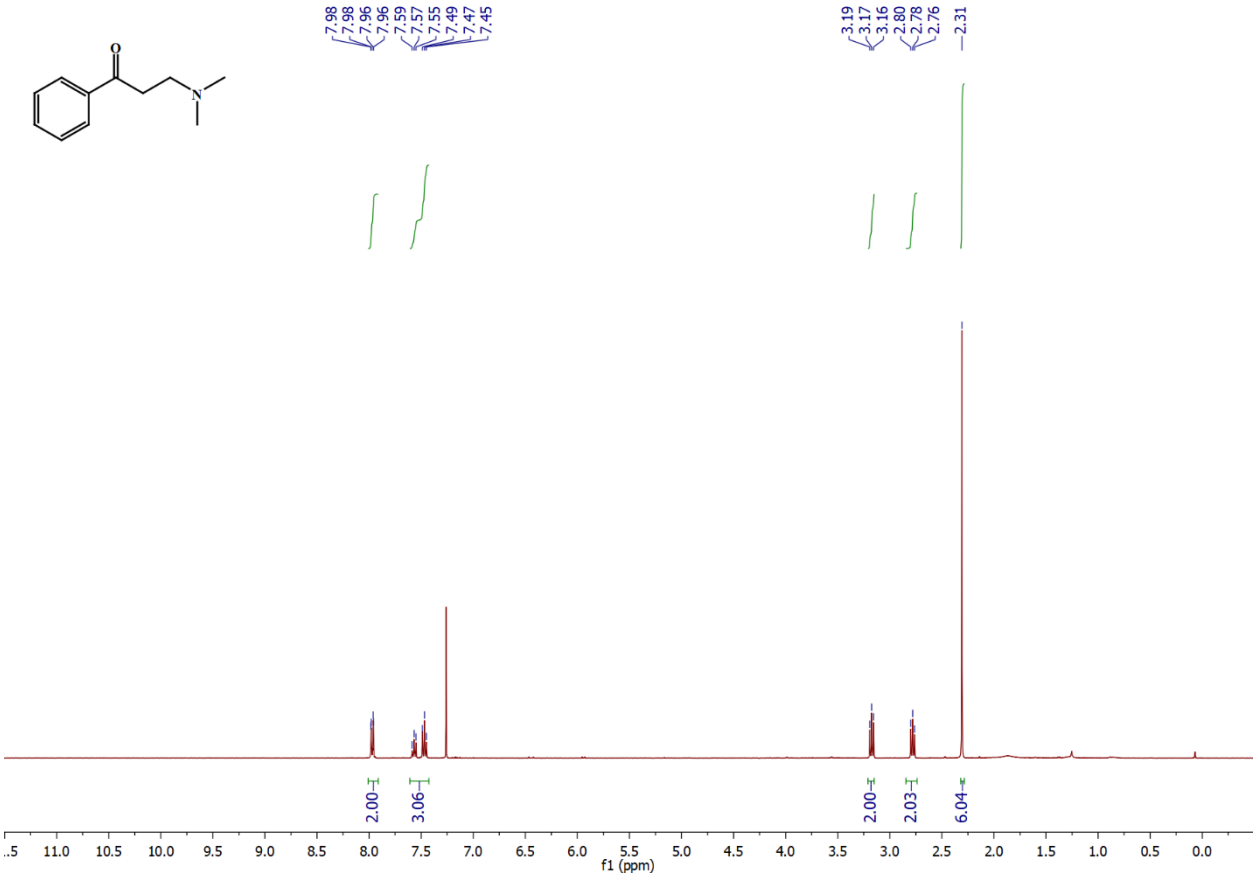
^{13}C NMR (101 MHz, $CDCl_3$) of **8**



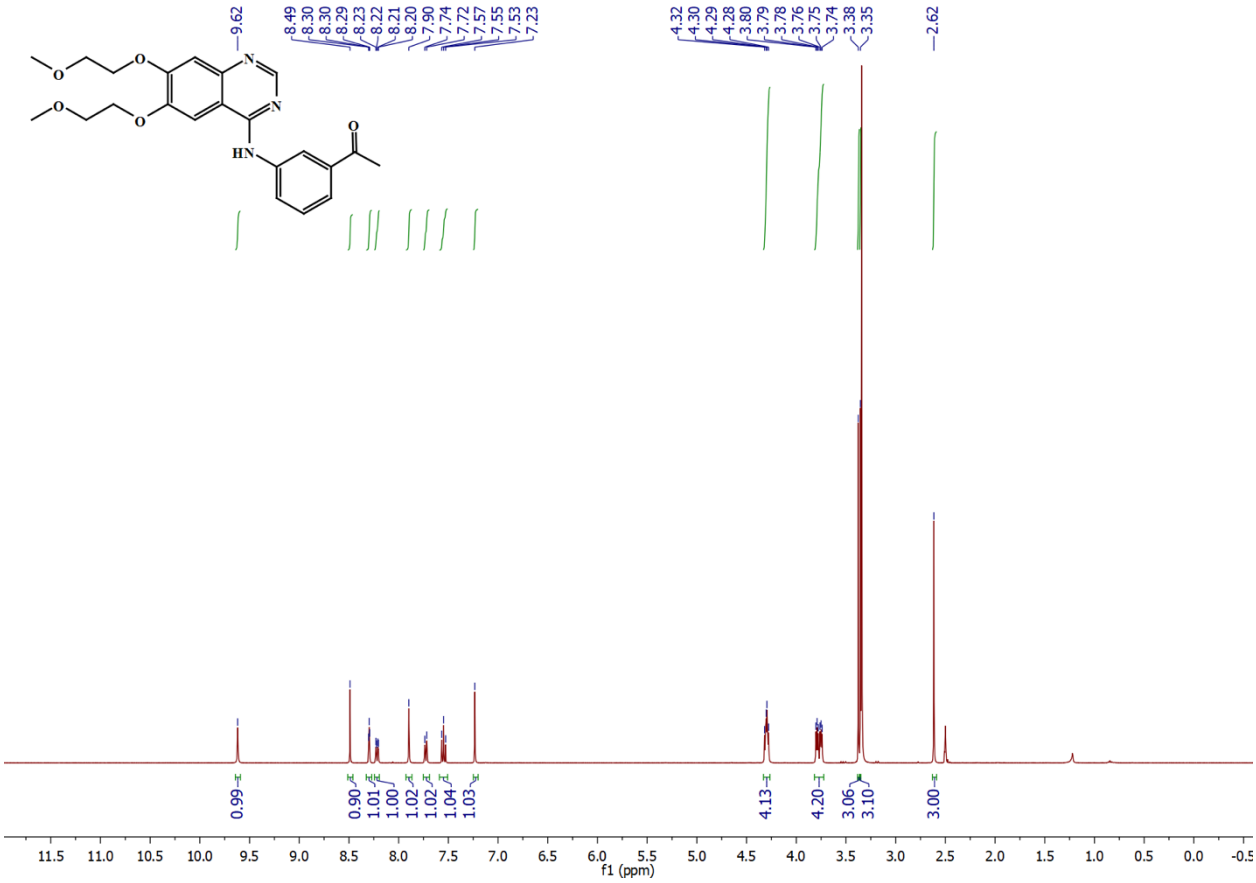
^{13}C-DEPT ($CDCl_3$) of **8**



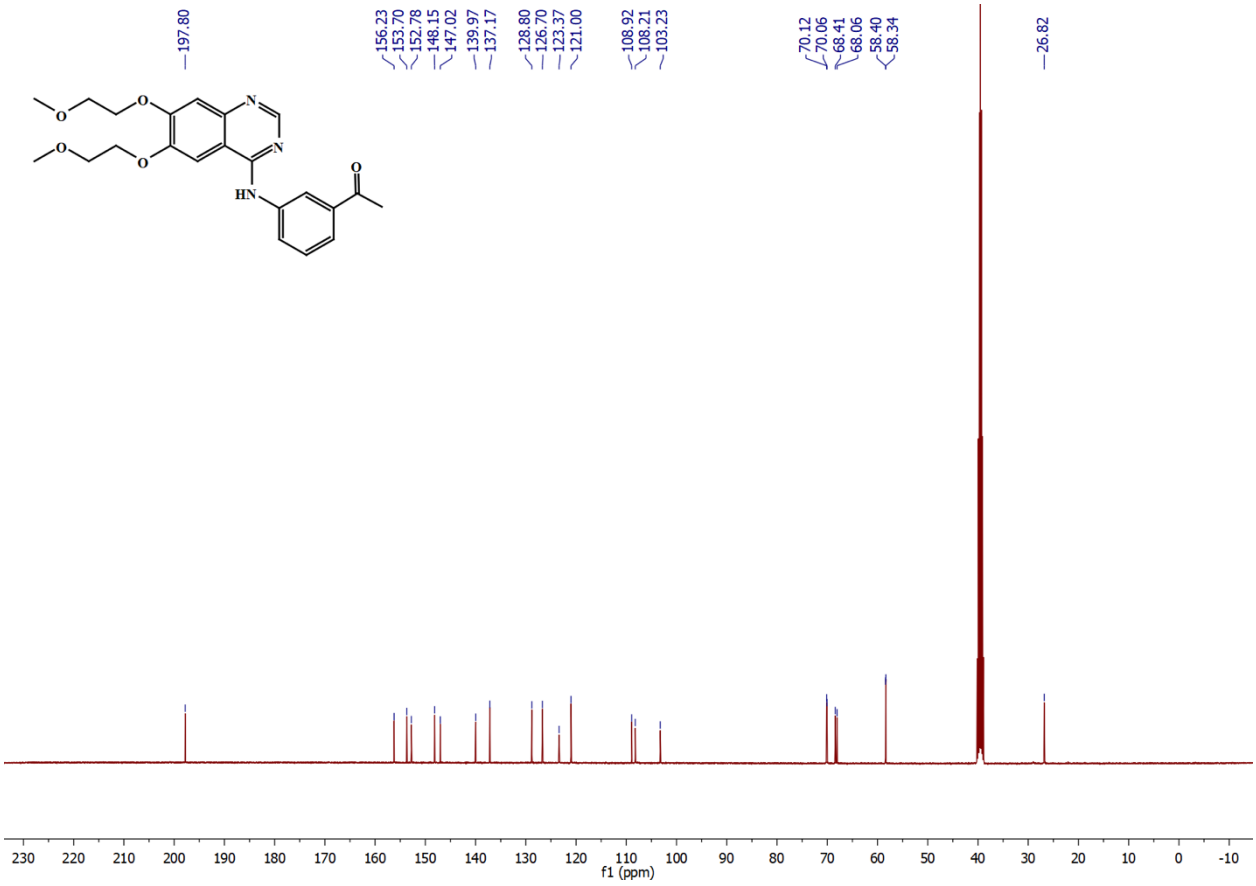
^{1}H NMR (400 MHz, $CDCl_3$) of **11**



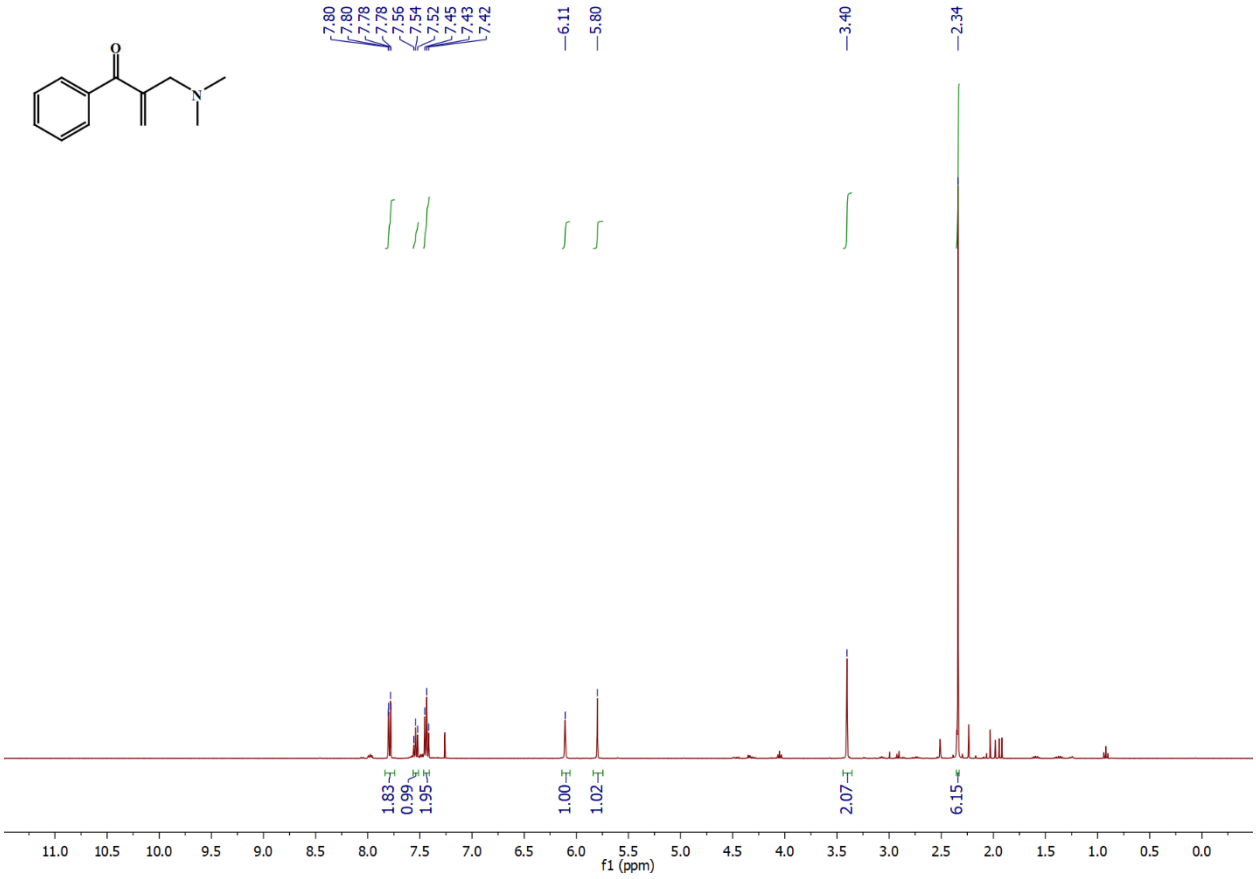
^{1}H NMR (400 MHz, DMSO-d6) of **10**



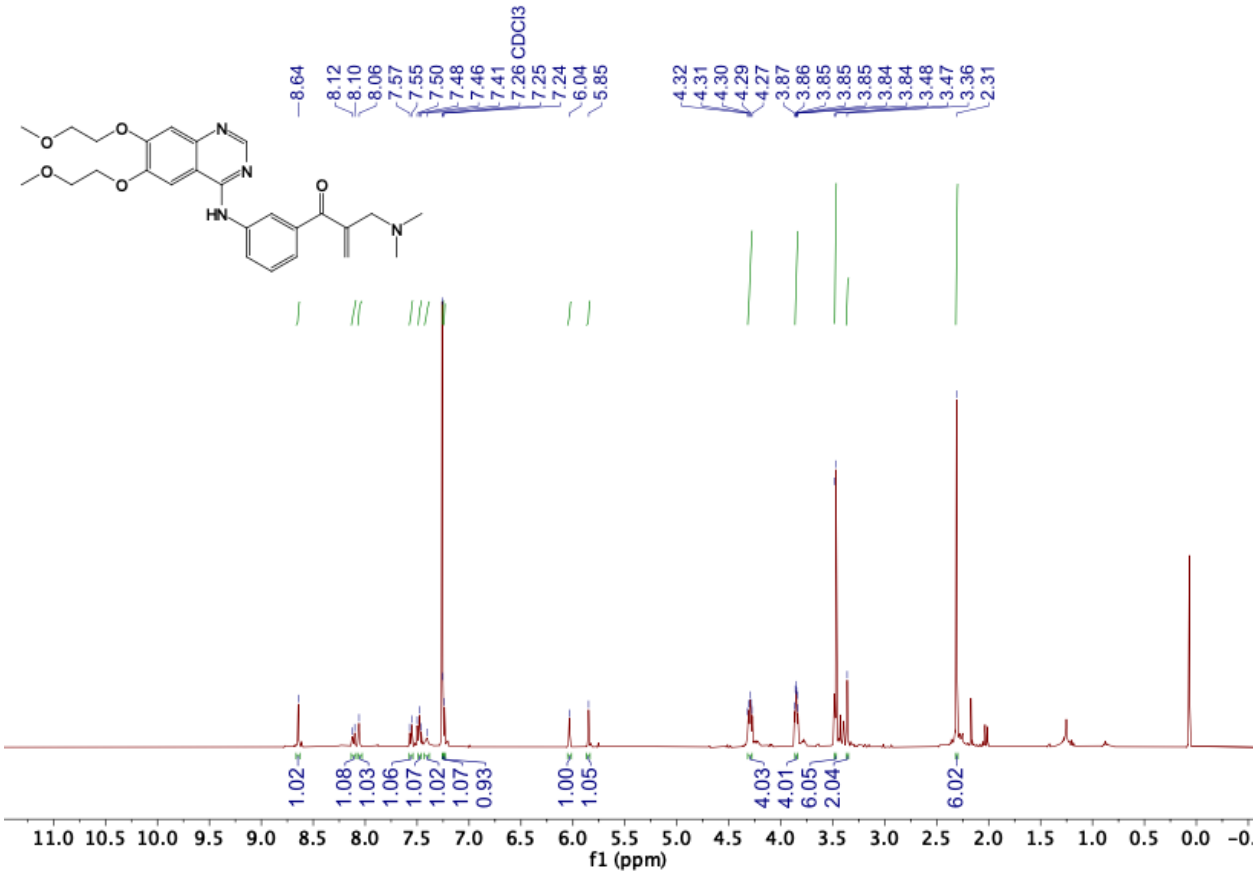
^{13}C NMR (101 MHz, DMSO-d6) of **10**



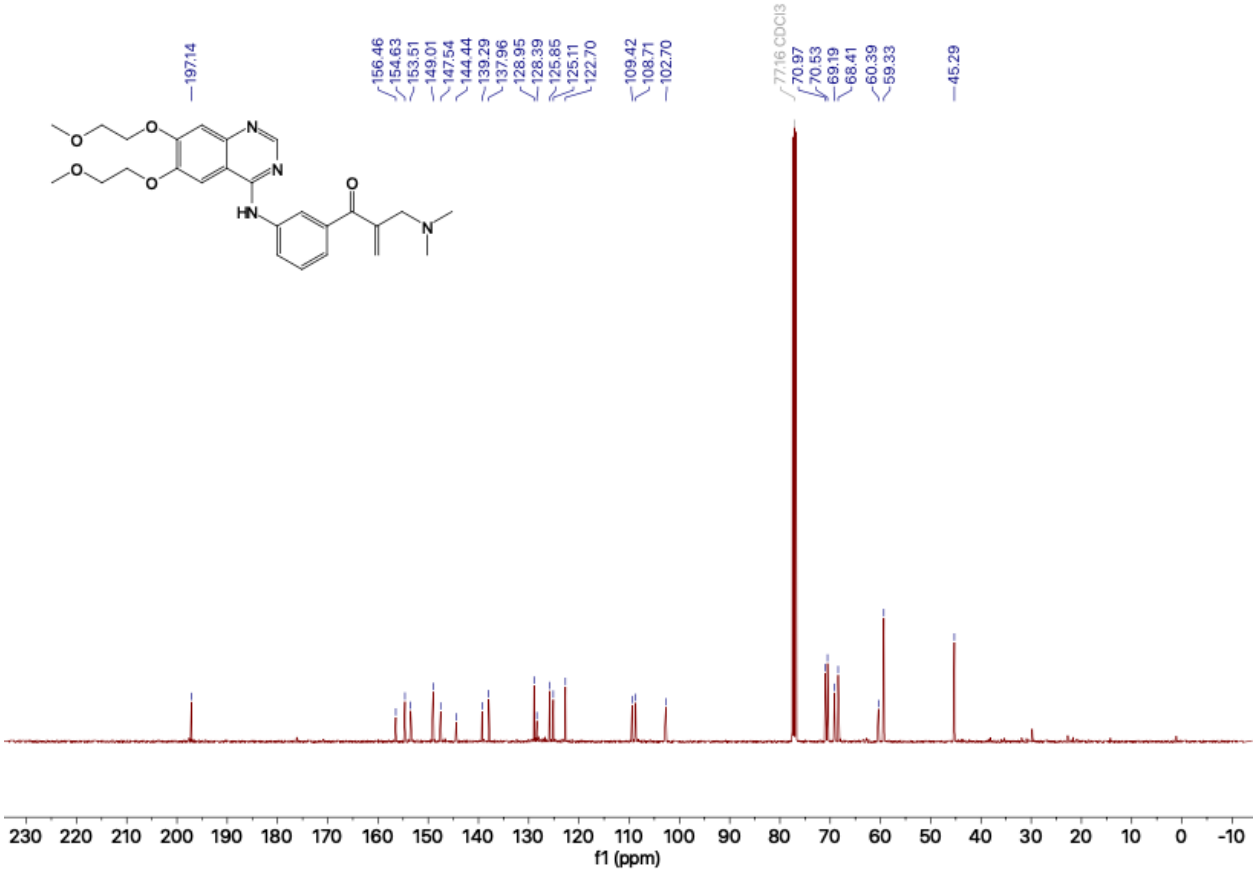
^{1}H NMR (400 MHz, $CDCl_3$) of **14**



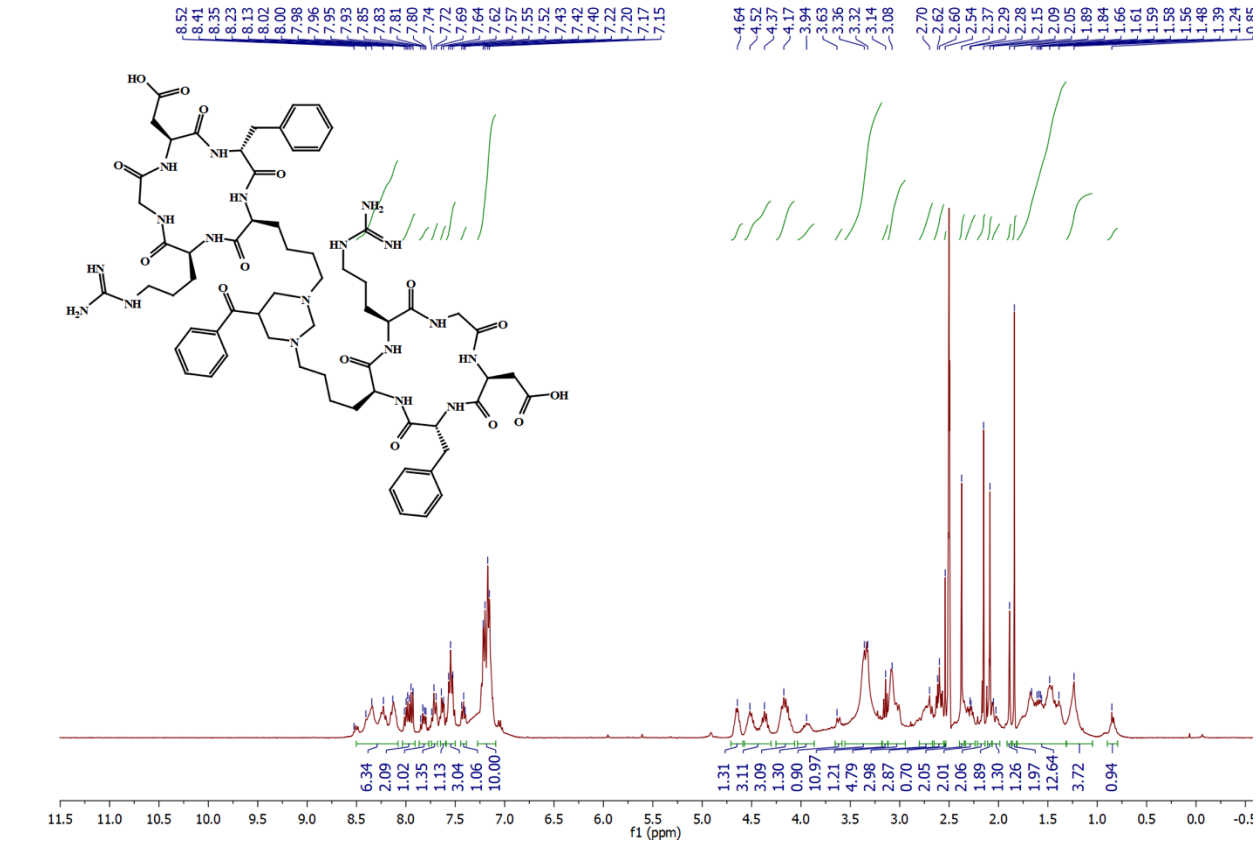
^{1}H NMR (400 MHz, $CDCl_3$) of **21**



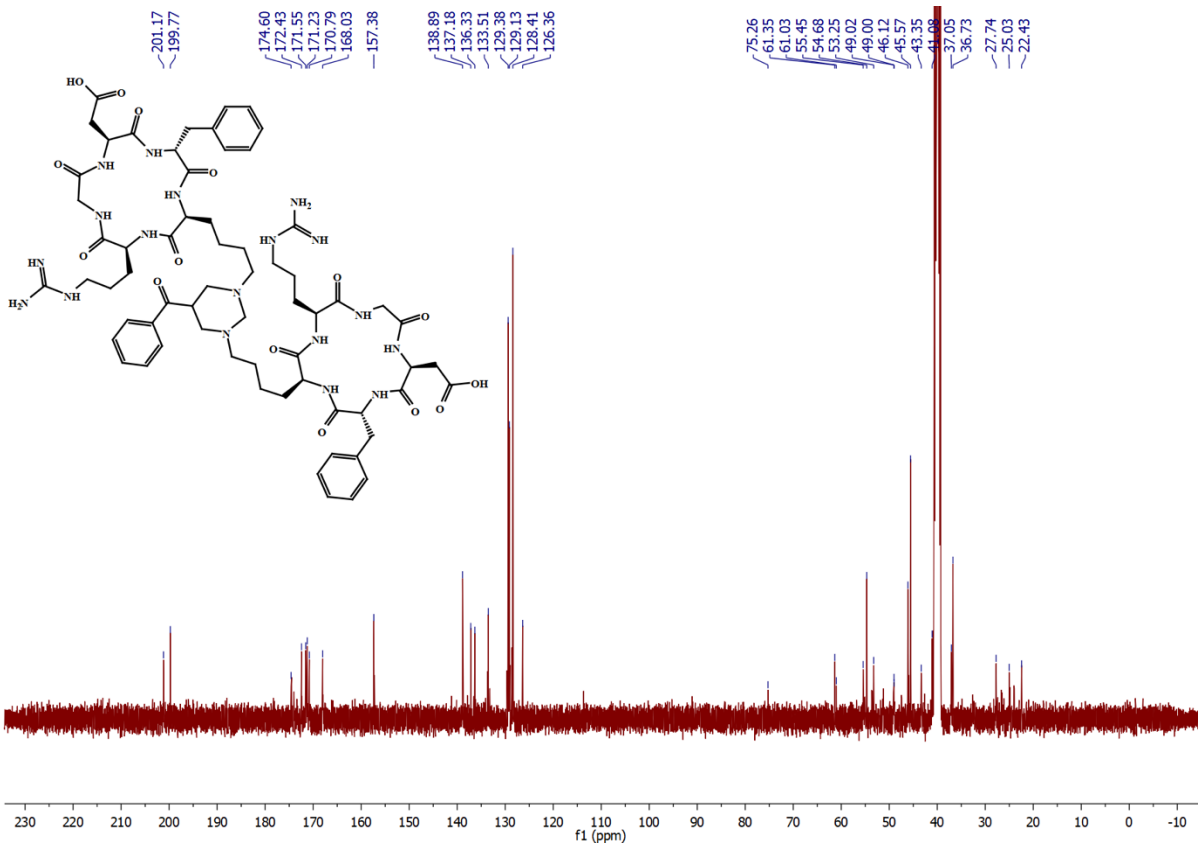
^{13}C NMR (101 MHz, $CDCl_3$) of **21**



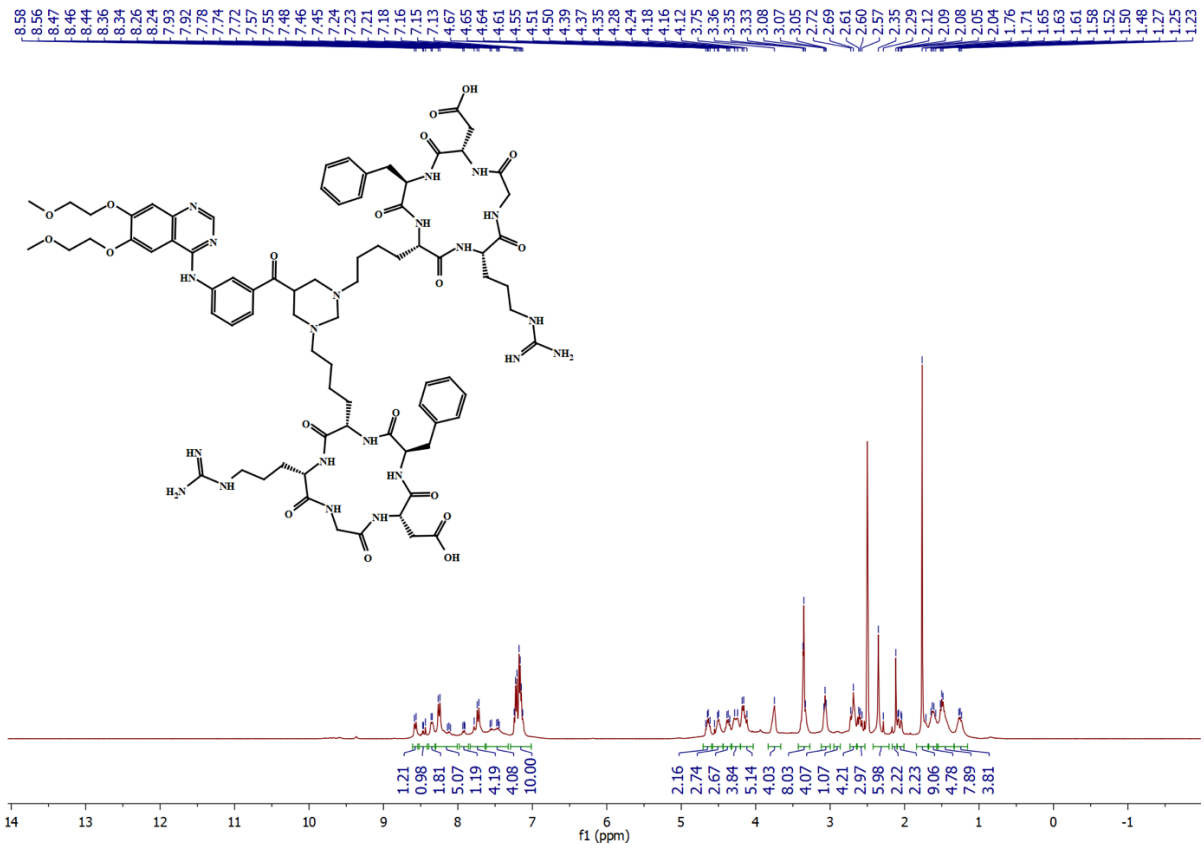
^{1}H NMR (400 MHz, DMSO-d6) of **19**



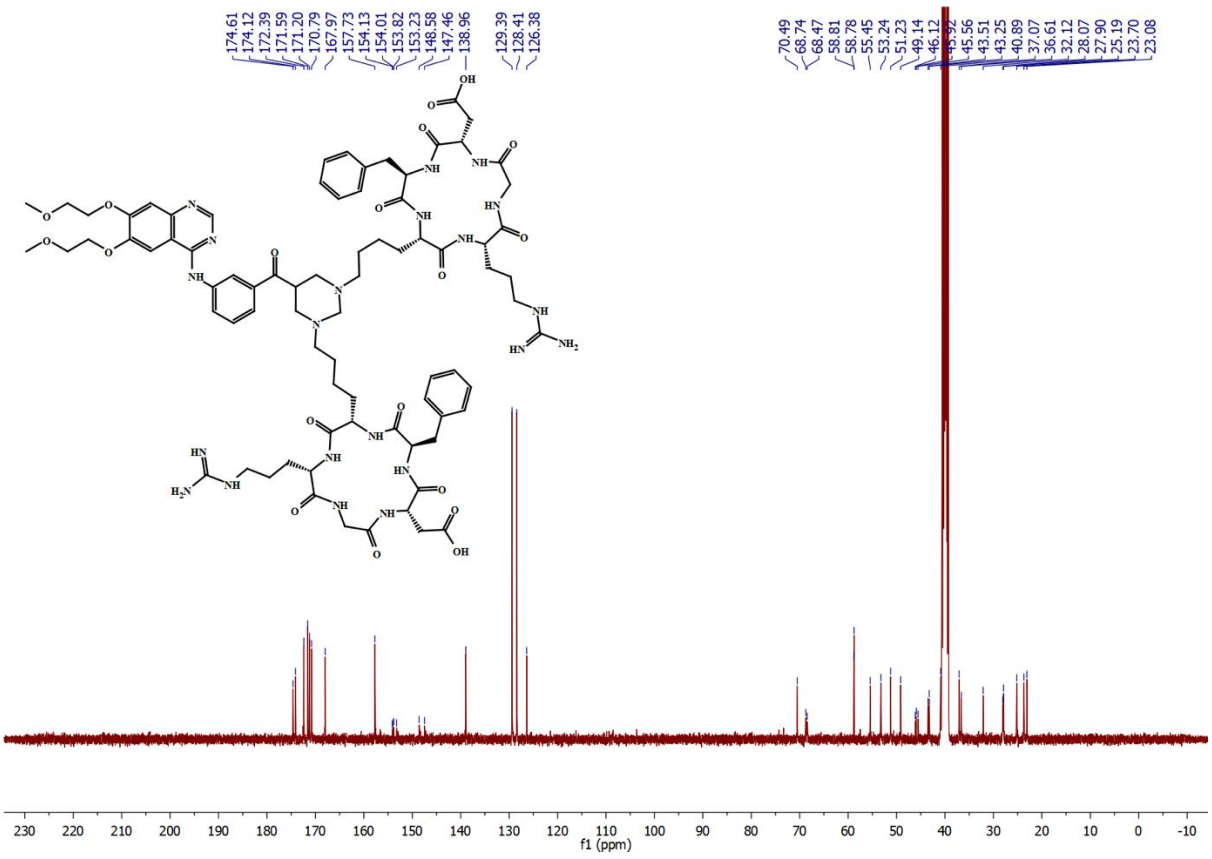
^{13}C NMR (101 MHz, DMSO-d6) of **19**



^{1}H NMR (400 MHz, DMSO-d6) of **20**

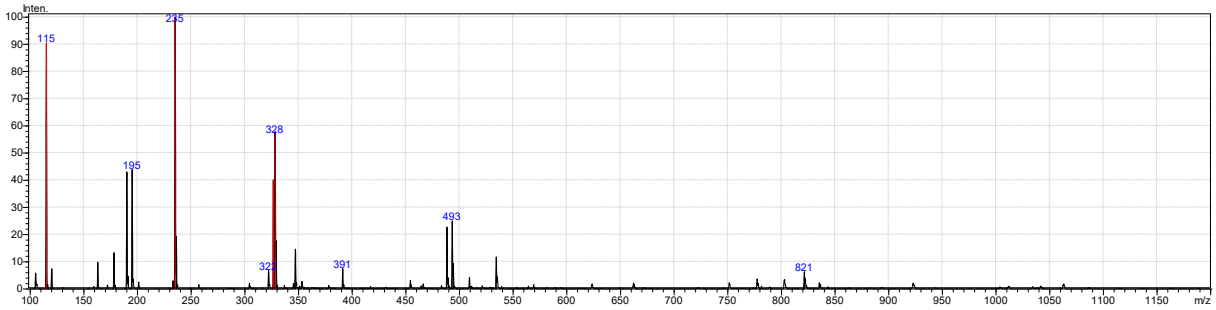


^{13}C NMR (101 MHz, DMSO-d6) of **20**



7.1 Copies of Mass Spectra

ESI-MS of **4a**



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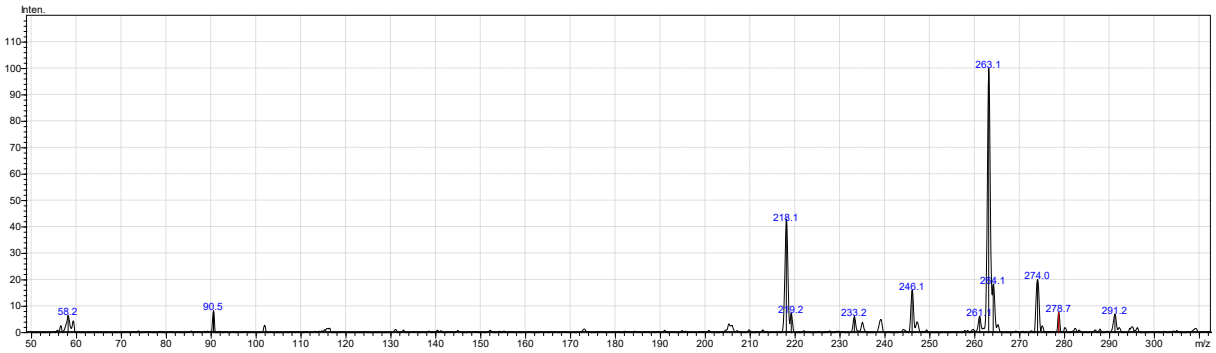

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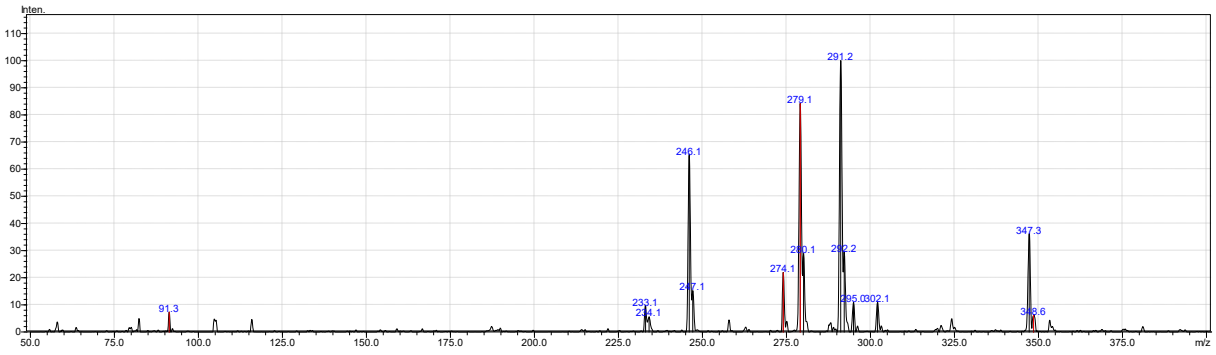

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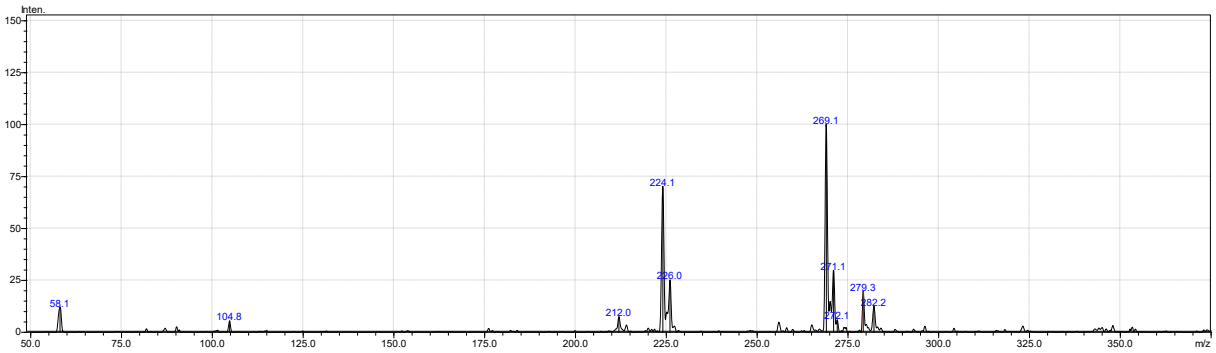

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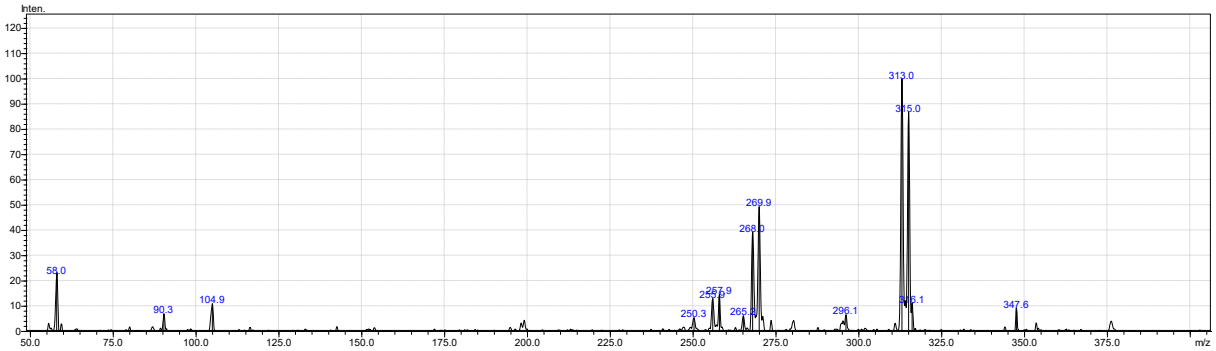

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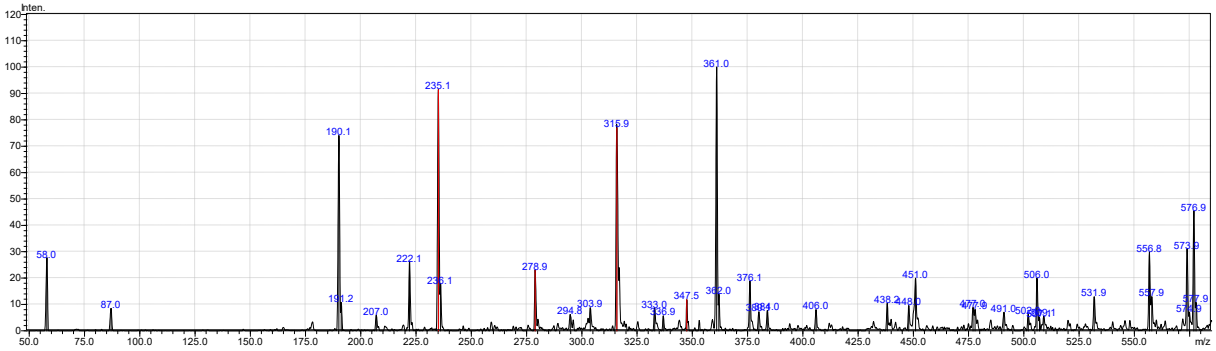

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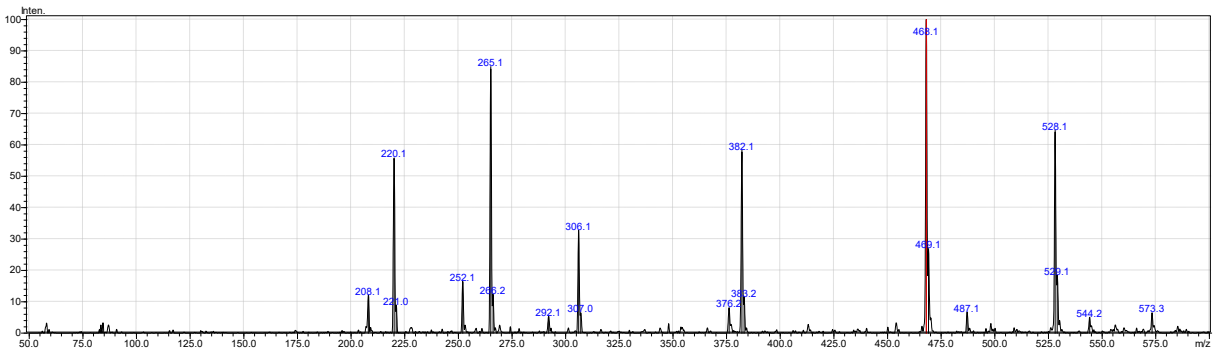

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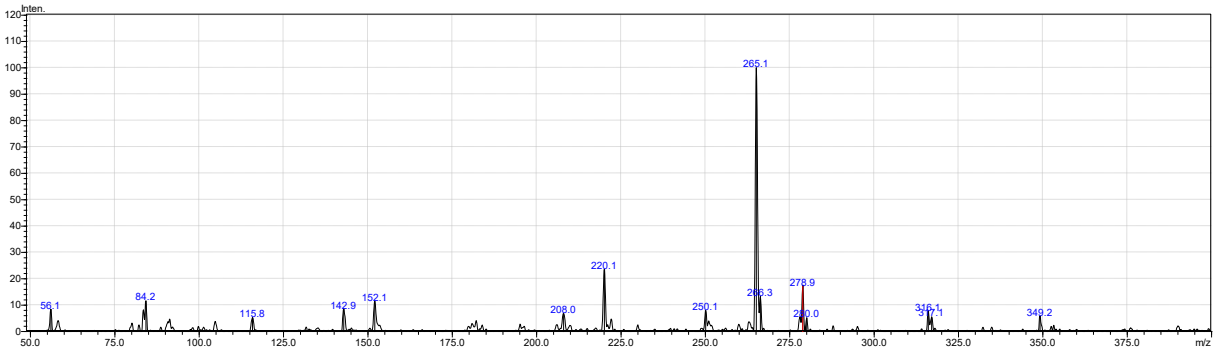

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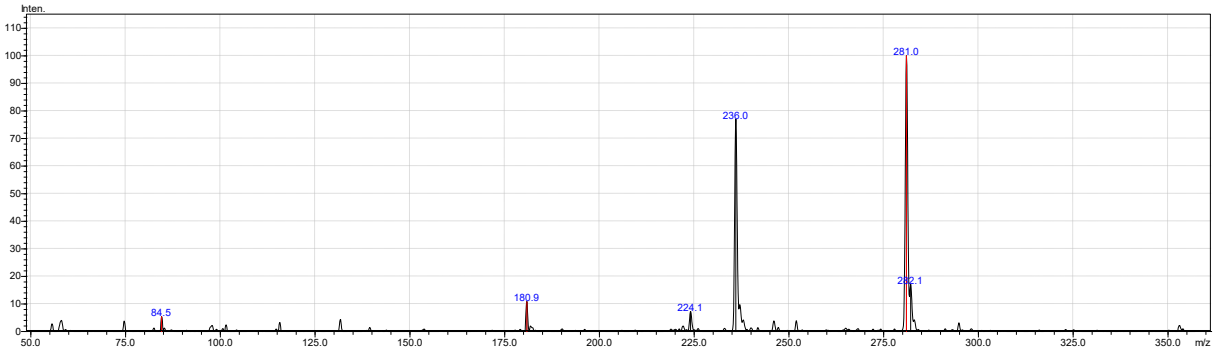
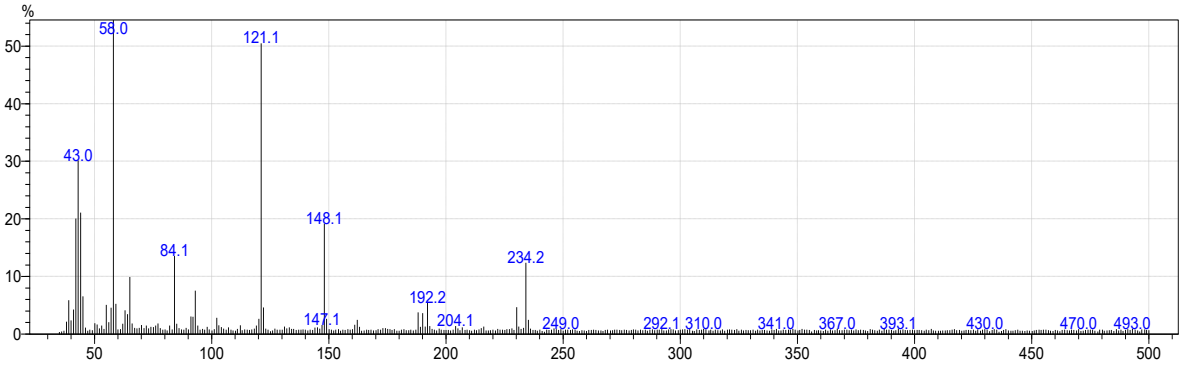


EI-MS of **4k**



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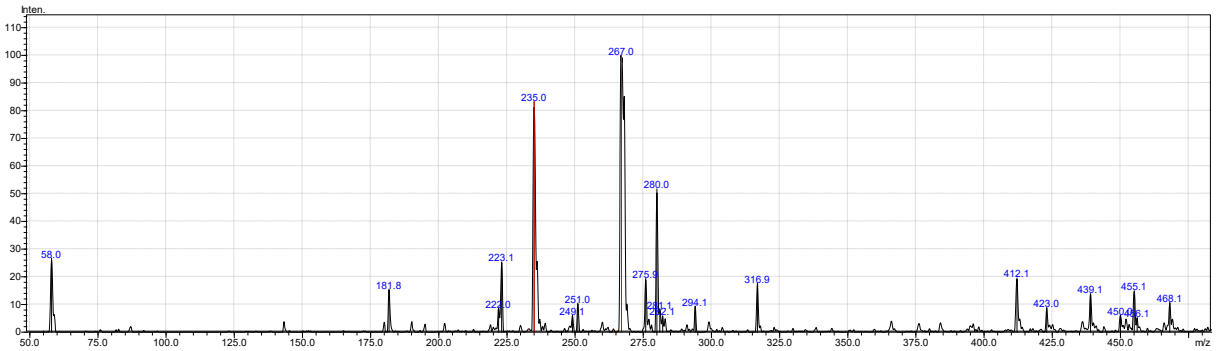

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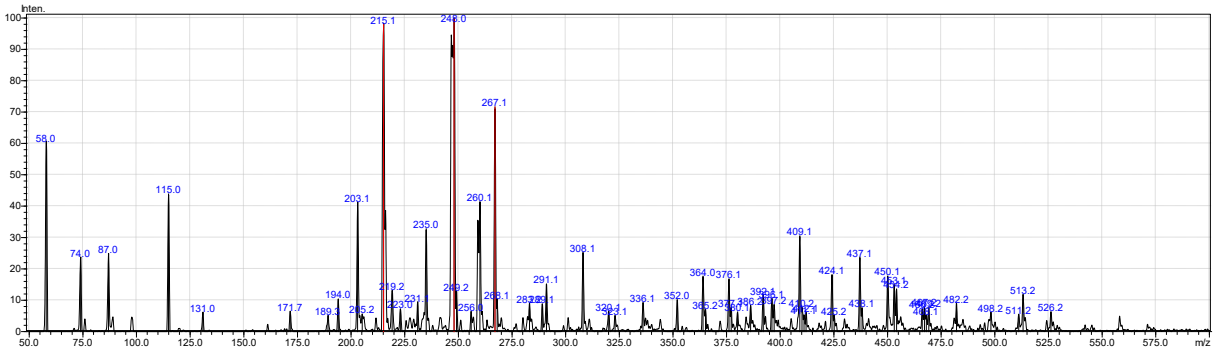

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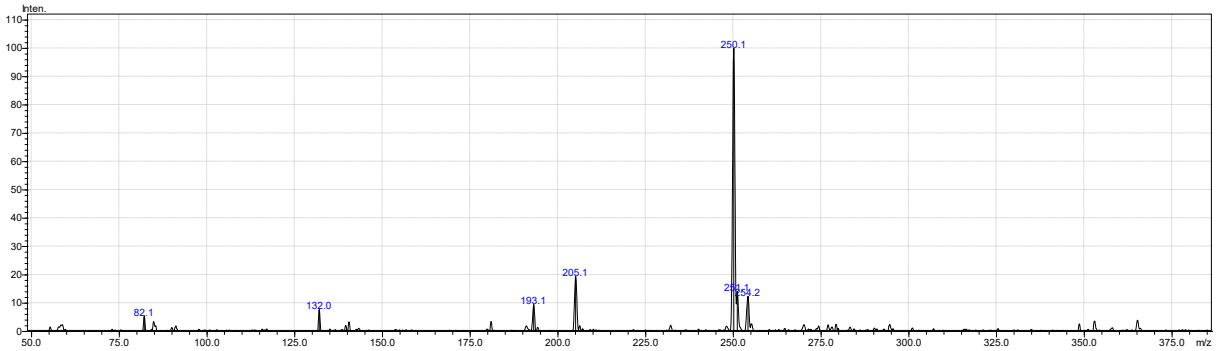

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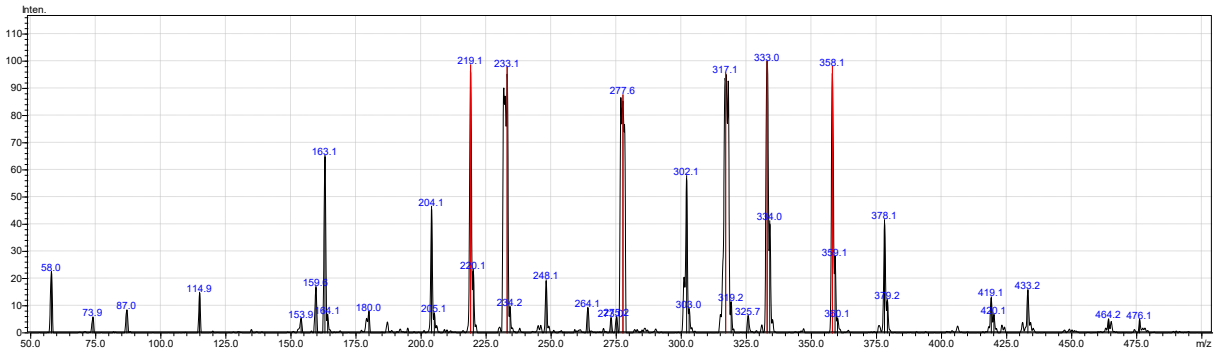

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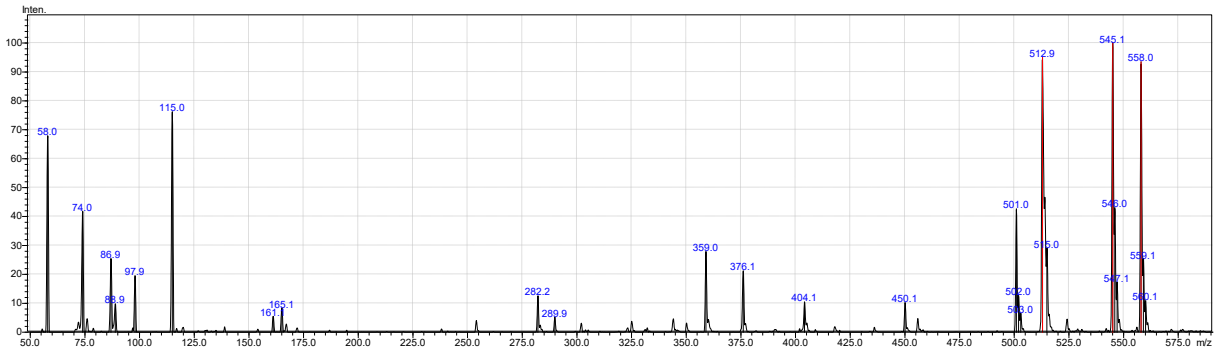

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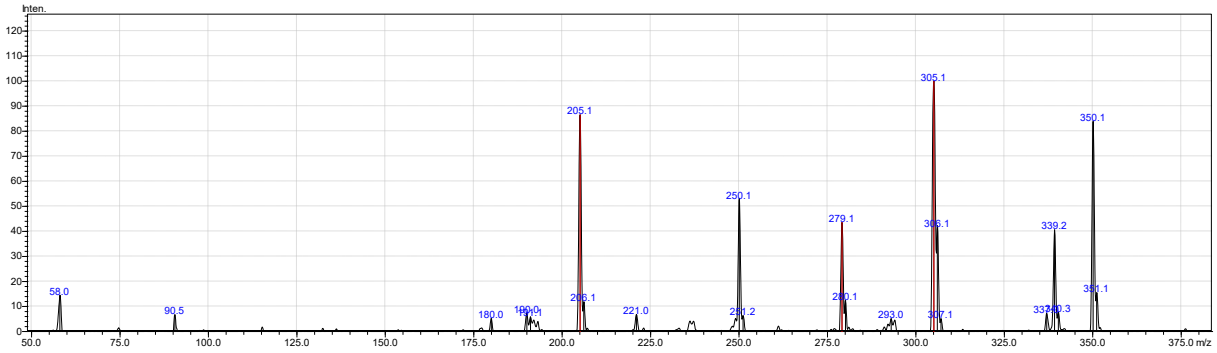

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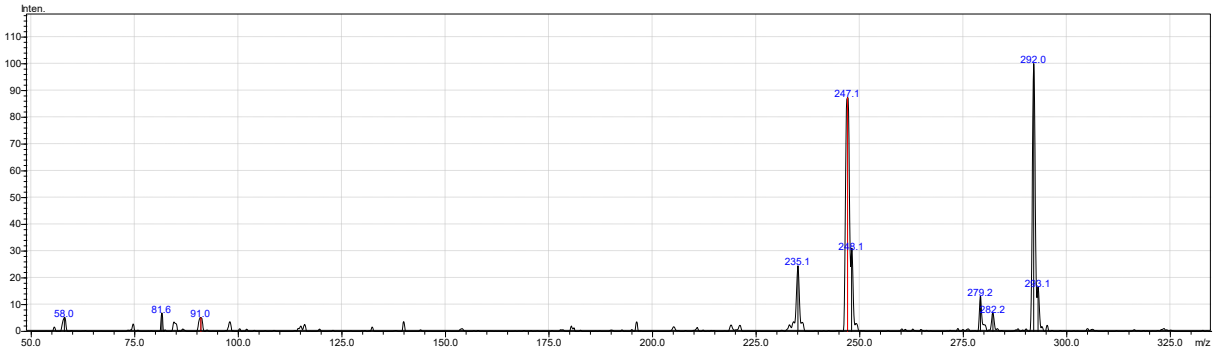

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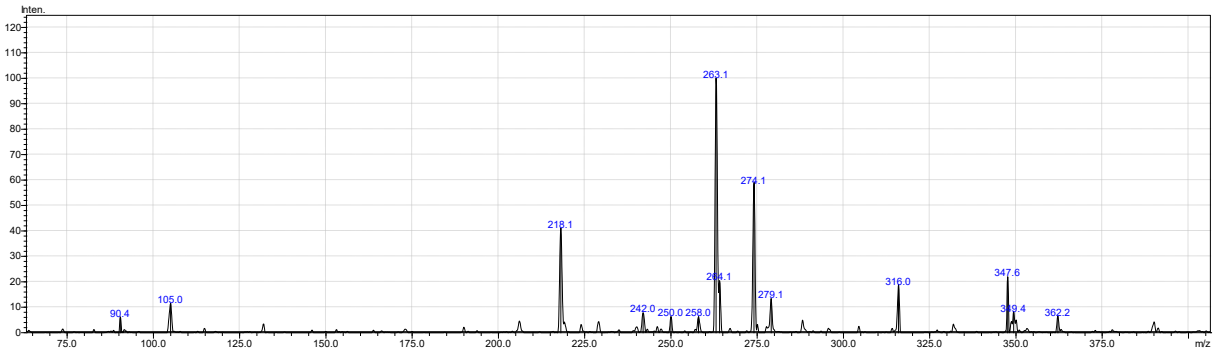
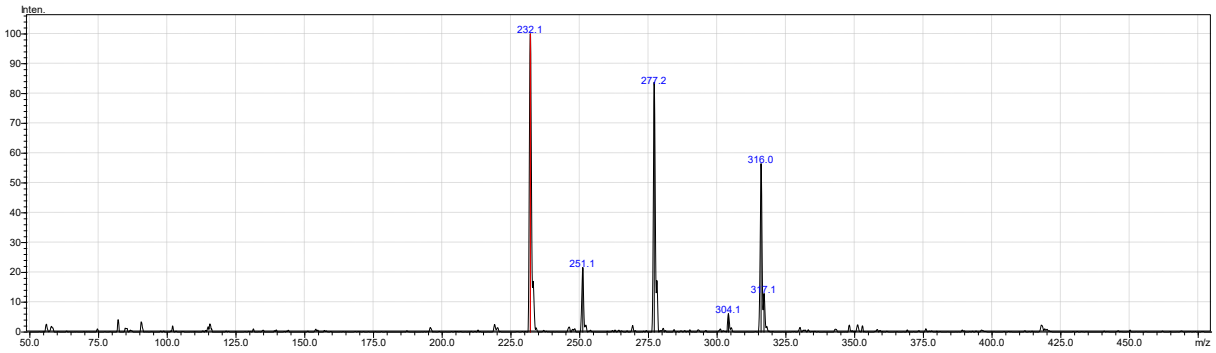
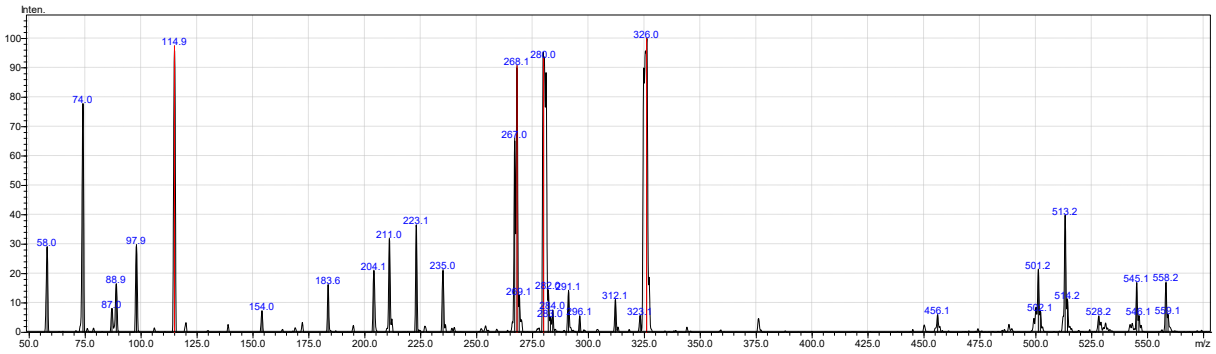


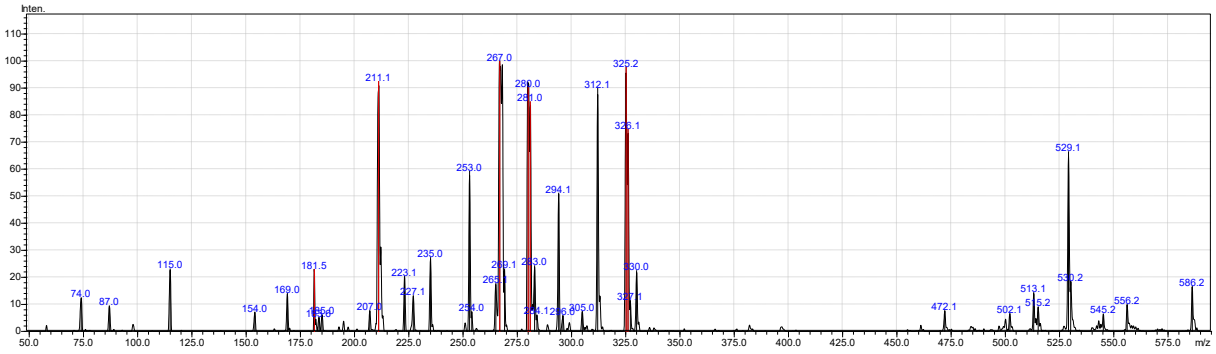
ESI-MS of **4t**



ESI-MS of **4u**



ESI-MS of **4v**



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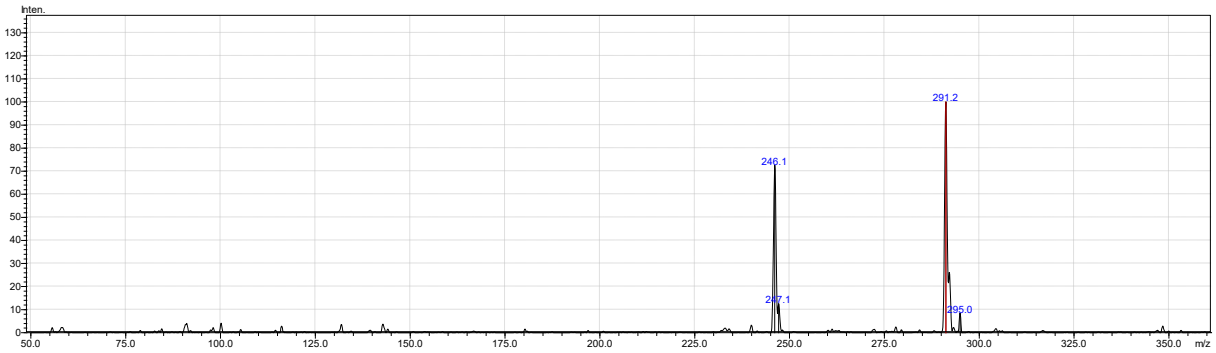
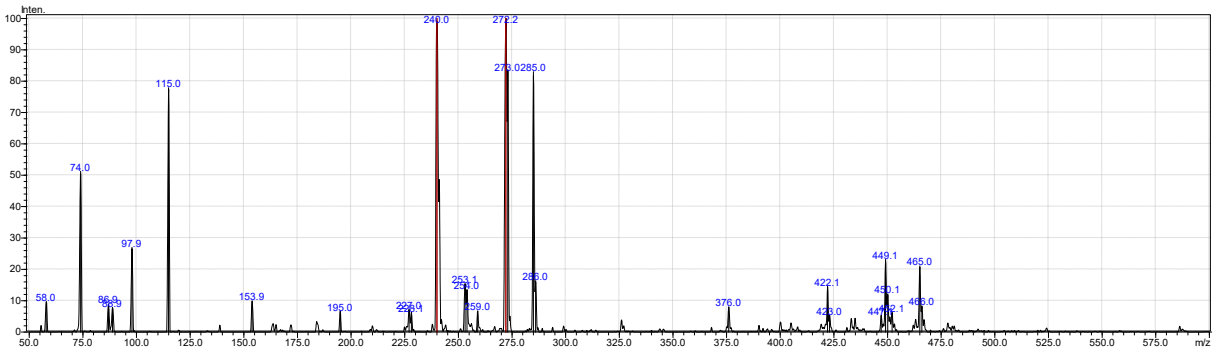


ESI-MS of **4x**



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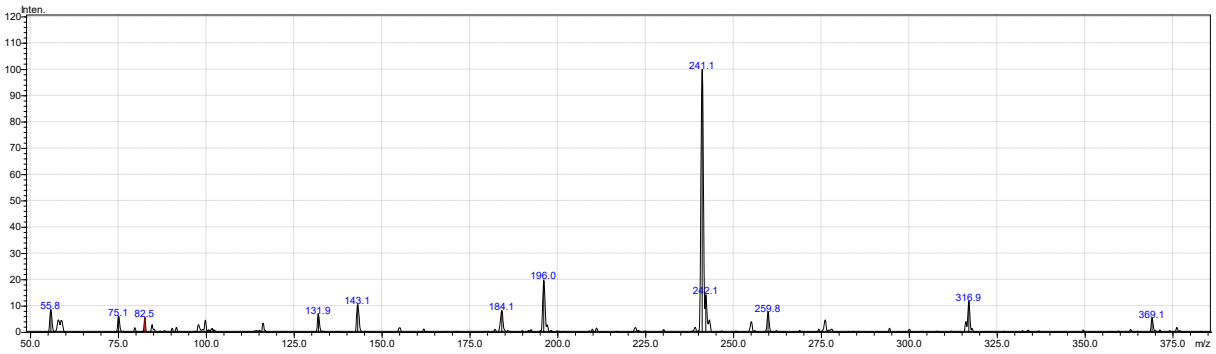
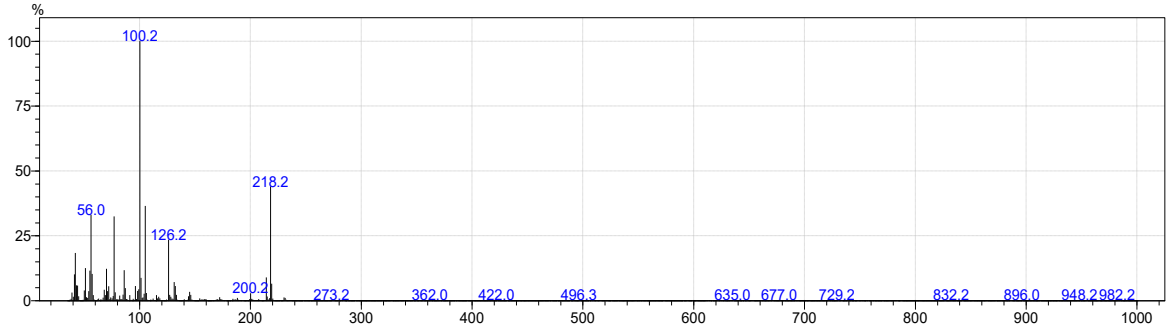
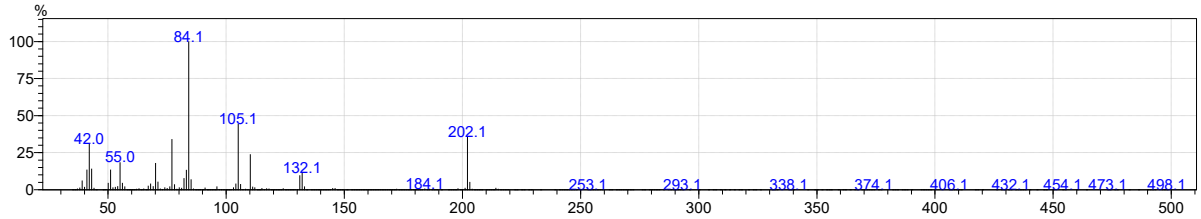


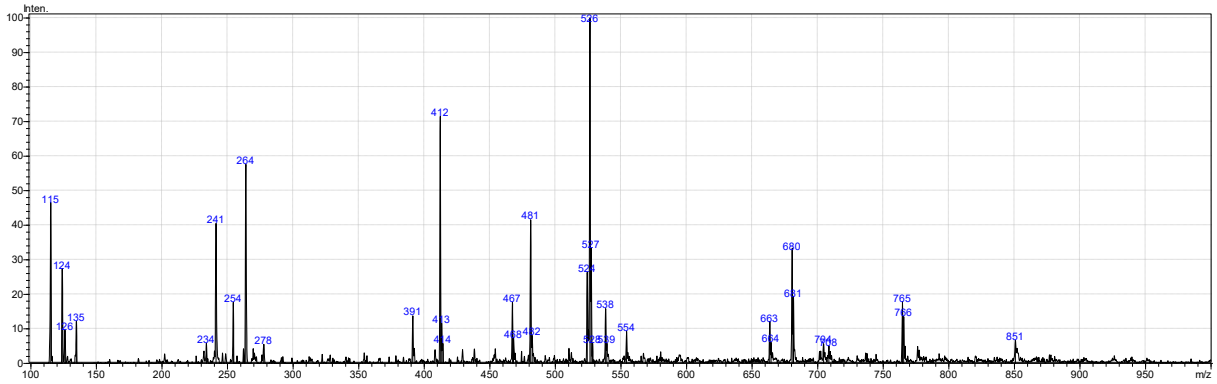
EI-MS of **4z**



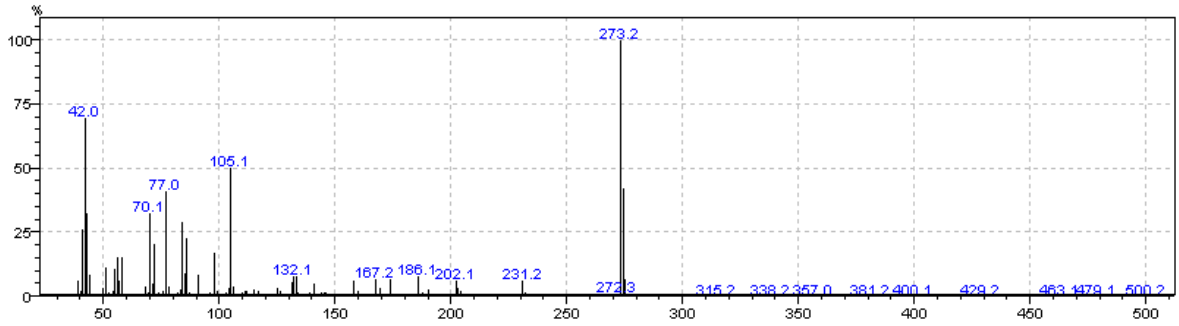
EI-MS of **4za**



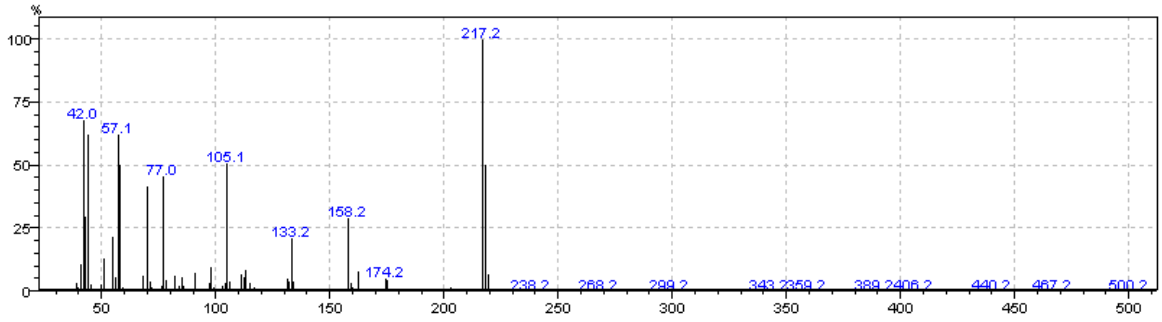
ESI-MS of **7**



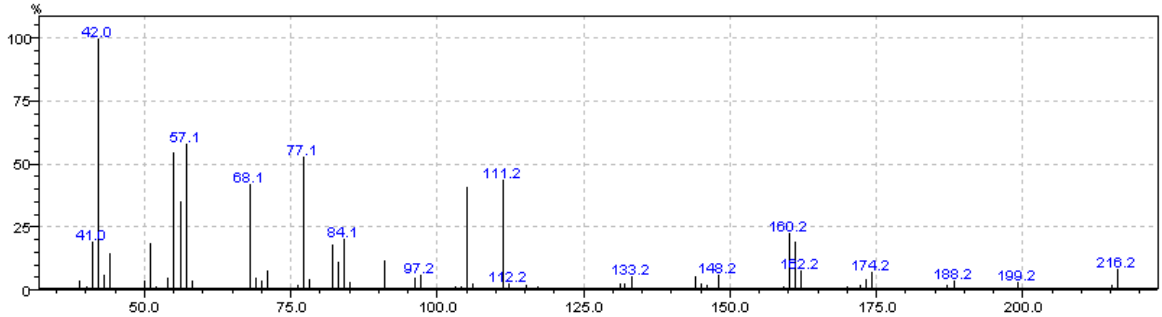
EI-MS of **6a**



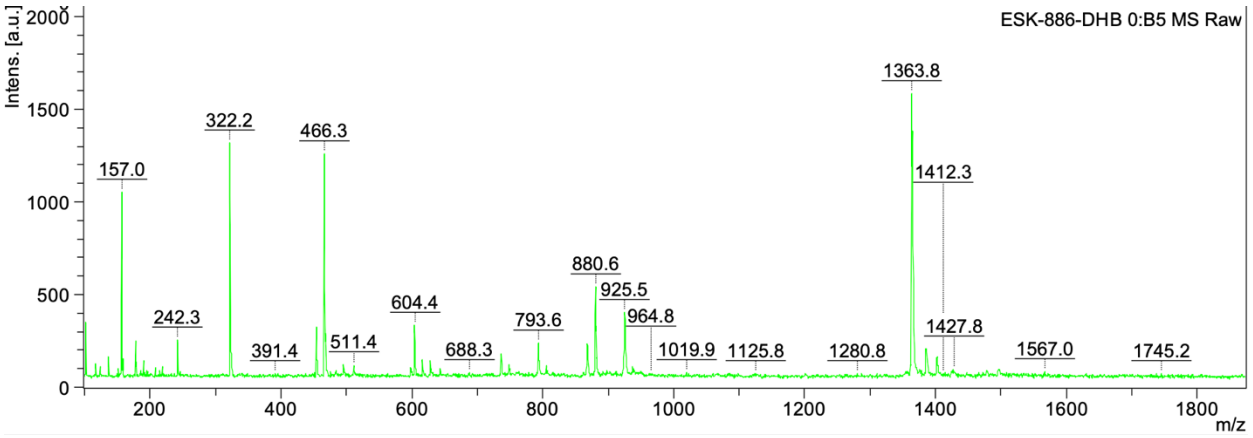
EI-MS of **6b**



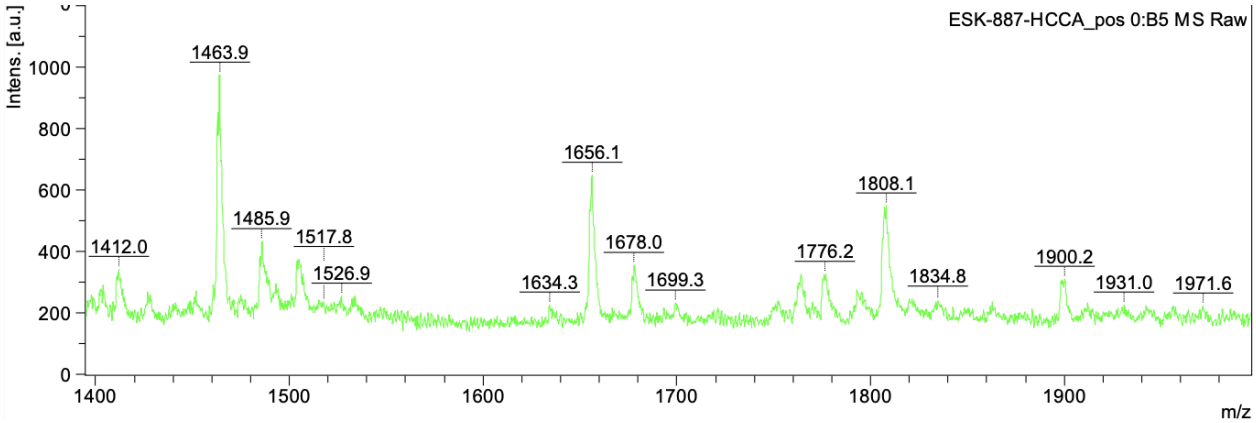
EI-MS of **8**



MALDI-TOF of **19**



MALDI-TOF of **20**



References

1. W.L.F. Armarego, Christina Chai. Butterworth-Heinemann, **2003**, p. 760.

2. Borisova, N. E.; Ivanov, A. V.; Matveev, P. I.; Smirnova, A. A.; Belova, E. V.; Kalmykov, S. N.; Myasoedov, B. F. *ChemistrySelect*, **2018**, *3*(7), 1983-1989.

3. Zhang, Y.; Li, J.; Li, X.; He, J. *Macromolecules*, **2014**, *47*(18), 6260-6269.

4. Cvijetić, I. N.; Tanç, M.; Juranić, I. O.; Verbić, T. Ž.; Supuran, C. T.; Drakulić, B. J. *Bioorganic & Medicinal Chemistry*, **2015**, *23*(15), 4649-4659.

5. Wang, S. K.; You, X.; Zhao, D. Y.; Mou, N. J.; Luo, Q. L. *Chemistry–A European Journal*, **2017**, *23*(49), 11757-11760.

6. Blau, L.; Menegon, R. F.; Trossini, G. H.; Molino, J. V. D.; Vital, D. G.; Cicarelli, R. M. B.; Chin, C. M. *European Journal of Medicinal Chemistry*, **2013**, *67*, 142-151.

7. Liu, Y.; Yan, Y.; Xue, D.; Wang, Z.; Xiao, J.; Wang, C. *ChemCatChem*, 2020, *12*(8), 2221-2225.

8. Torti, E.; Protti, S.; Merli, D.; Dondi, D.; Fagnoni, M. *Chemistry–A European Journal*, **2016**, *22*(47), 16998-17005.

9. Lu, Y.; Kasahara, A.; Hyodo, T.; Ohara, K.; Yamaguchi, K.; Otani, Y.; Ohwada, T. *Organic Letters*, **2023**, *25*(19), 3482-3486.

10. Liu, F.; Wu, N.; Cheng, X. *Organic Letters*, **2021**, *23*(8), 3015-3020.

11. Bains, A. K.; Kundu, A.; Maiti, D.; Adhikari, D. *Chemical Science*, **2021**, *12*(42), 14217-14223.

12. Zhang, W. J.; Wu, J. F.; Zhou, P. F.; Wang, Y.; Hou, A. J. *Tetrahedron*, **2013**, *69*(29), 5850-5858.

13. Organic Syntheses, Coll. Vol. 3, p.14 (1955); Vol. 28, p.1 (1948).
14. Lv, K.; Wang, L. L.; Zhou, X. B.; Liu, M. L.; Liu, H. Y.; Zheng, Z. B.; Li, S. *Medicinal Chemistry Research*, **2013**, *22*, 1723-1729.

15. Kuang, Jianming; Zhang, Shanjun; Ma, Huan; Liu, Lichao; Xiang, Xianshuai; Zeng, Mei. CN109574940, 2019

16. Meindl, W.; Laske, R.; Böhm, M. *Archiv der Pharmazie,* **1987**, *320*(8), 730-737.

17. Pati, H. N.; Das, U.; Ramirez-Erosa, I. J.; Dunlop, D. M.; Hickie, R. A.; Dimmock, J. R. *Chemical and Pharmaceutical bulletin*, **2007**, *55*(4), 511-515.

18. Chung, F.; Tisné, C.; Lecourt, T.; Seijo, B.; Dardel, F.; Micouin, L. *Chemistry–A European Journal*, **2009**, *15*(29), 7109-7116.

19. Sheldrick G.M. *Acta Crystallogr. A*, **2015**, 71, 3–8.

20. Sheldrick G.M. *Acta Crystallogr. C*, **2015**, 71, 3–8.

21. Kudriashova, E. S.; Yarushina, M. A.; Gavryushin, A. E.; Grishin, I. D.; Malysheva, Y. B.; Otvagin, V. F.; Fedorov, A. Y. *Org. Lett.* **2023**, *25*(27), 4996-5000.

22. Mosmann, T. *J. Immunol. Methods,* **1983**, *65* (1−2), 55−63.

23. C. Angeli, B. Bories, A. Cavallini, R. Cimiraglia, *J. Chem. Phys.*, **2006**, *124* (5), 054108.

24. Neese,F. *Comput. Molec. Sci.,* **2022,** 12(1)e1606.

25. Neese,F. *J. Comp. Chem.,* **2003**, *24*(14), 1740-1747.

26. Neese,F.; Wennmohs,F.; Hansen,A.; Becker,U. *Chem. Phys.,* **2009,** *356*(1-3), 98-109.

27. Bykov,D.; Petrenko,T.; Izsak,R.; Kossmann,S.; Becker,U.; Valeev,E.; Neese,F. *Molec. Phys.*, **2015**, *113*, 1961-1977.

28. Garcia-Rates,M.; Neese,F. *J. Comput. Chem.*, **2019,** *40,* 1816-1828.

29. Garcia-Rates,M.; Neese,F. *J. Comput. Chem.*, **2020**, *41,* 922-939.

30. 28. Helmich-Paris,B.; de Souza,B.; Neese,F. *J. Chem. Phys.,* **2021**, *155*, 104109. DOI: 10.1063/5.0058766. (h) Neese,F. The SHARK Integral Generation and Digestion System. *J. Comp. Chem.*, **2022**, 1-16

31. C. Y. Legault, CYLview, 1.0 b (http://www. cylview. org). *Université de Sherbrooke*. **2009**

32. R. A. Angnes, MechaSVG. *GitHub repository*, **2020**.