Electronic Supplementary Material (ESI) for MedChemComm.

Supporting Information

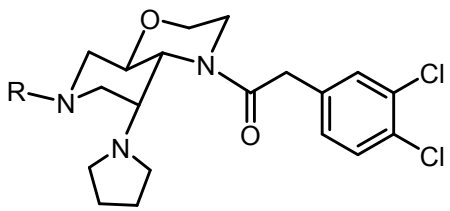
Synthesis and pharmacological evaluation of conformationally restricted κ-opioid receptor agonists

Yvonne Wenker,[a] Michael Soeberdt,[b] Constantin Daniliuc,[c] Sonja Ständer,[d] Dirk Schepmann,[a] Bernhard Wünsch*[a,e]

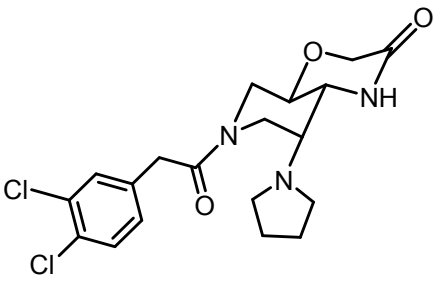
[a] Institut für Pharmazeutische und Medizinische Chemie der Westfälischen Wilhelms-Universität Münster, Corrensstraße 48, D-48149 Münster, Germany
Tel.: +49-251-8333311; Fax: +49-251-8332144; E-mail: wuensch@uni-muenster.de
[b] Dr. August Wolff GmbH & Co. KG Arzneimittel, Sudbrackstr. 56, D-33611 Bielefeld, Germany
[c] Organisch-Chemisches Institut der Westfälischen Wilhelms-Universität Münster, Corrensstr. 40, D-48149 Münster, Germany
[d] Center for Chronic Pruritus and Department of Dermatology, University Hospital Münster, von-Esmarch-Straße 58, D-48149 Münster, Germany
[e] Cells-in-Motion Cluster of Excellence ((EXC 1003 – CiM), Westfälische Wilhelms-Universität Münster, Germany

*To whom correspondence should be addressed:
Tel: #49-251-8333311;
Fax: #49-251-8332144;
Email: wuensch@uni-muenster.de

Table SI1: Affinity data of 17 and 18



17a-h



18

compd.	R	K_i ± SEM [nM]				
		κ	μ	δ	σ_1	σ_2
		[^{3}H]U-69,593	[^{3}H]DAMGO	[^{3}H]DPDPE	[^{3}H]-(+)-pentazocine	[^{3}H]DTG
17a	H	132 ± 44	26 %	5 %	10 %	0 %
17b	CH_3	286 ± 63	6 %	6 %	19 %	13 %
17c	CH_2CH_3	1300[b]	20 %	15 %	391	102
17d	$(CH_2)_3CH_3$	8 %	502	47 %	192	316
17e	cyclopentyl	5 %	447	717	181	45
17f	CH_2-phenyl	912[b]	261 ± 79	260	983	29 %
17g	CH_2-3-pyridyl	0 %	633	666	291	1.4 μM
17h	DCPA[a]	0 %	4 %	0 %	991	8 %
18	-	0 %	0 %	0 %	0 %	13 %
U-69,593		0.97 ± 0.40	-	-	-	-
naloxone		6.9 ± 0.5	2.1 ± 0.5	2.4 ± 0.5	-	-
morphine		35 ± 6.0	3.9 ± 2.1	2.0 ± 0.3	-	-
(+)-pentazocine		-	-	-	5.4 ± 0.5	-
haloperidol		-	-	-	6.6 ± 0.9	78 ± 2.3

[a)] DCPA = dichlorophenylacetyl;

K_i values are given as mean values ± SEM of three experiments (n = 3); due to low affinity the K_i values of some compounds were determined only once; values in % reflect the inhibition of the radioligand binding at a test compound concentration of 1 μM.

2. Experimental, chemistry

2.1. General

Unless otherwise noted, moisture sensitive reactions were conducted under dry nitrogen. THF was dried with sodium/benzophenone and was freshly distilled before use. Thin layer chromatography (tlc): Silica gel 60 F_{254} plates (Merck). Flash chromatography (fc): Silica gel 60, 40–64 µm (Merck); parentheses include: diameter of the column, eluent, fraction size, R_f value. Melting point: Melting point apparatus SMP 3 (Stuart Scientific), uncorrected. MS: MAT GCQ (Thermo-Finnigan); IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): Unity Mercury Plus 400 spectrometer (Varian); δ in ppm related to tetramethylsilane; coupling constants are given with 0.5 Hz resolution.

2.2. Synthetic procedures

2.2.1. (4*r*)-(3,5-Dihydroxy-4-nitropiperidin-1-yl)-(phenyl)methanone (8b)

Nitromethane (0.19 mL, 3.57 mmol) was added to a solution of iminodiacetaldehyde **7b** (488 mg, 2.38 mmol) in a mixture of THF (2 mL) and *tert*-butanol (0.5 mL). NaOH (15 mg, 0.38 mmol) was added and the mixture was stirred for 20 h at rt. The solution was neutralized using Amberlite® ion exchange resin (IR-120), filtered and the solvent was removed under reduced pressure. The product was purified by fc (∅ = 4 cm, h = 16 cm, CH_2Cl_2/ethyl acetate = 2/1, V = 30 mL, R_f = 0.34 (cyclohexane/ethyl acetate = 2/1)). Colorless solid, mp 135 °C (decomposition), yield 316 mg (50 %). $C_{12}H_{14}N_2O_5$ (M = 266.3 g/mol). ^{1}H NMR (d_6-DMSO): δ (ppm) = 2.66 – 2.77 (m, 1 H, NCH_2), 2.93 – 3.09 (m, 1 H, NCH_2), 3.25 – 3.33 (m, 1 H, NCH_2), 3.55 – 3.70 (m, 1 H, NCH_2), 3.78 – 3.94 (m, 2 H, 2 x C*H*OH), 4.47 (t, ^3J = 9.8 Hz, 1 H, C*H*NO_2), 5.58 – 6.12 (m, 2 H, 2 x O*H*), 7.37 – 7.53 (m, 5 H, 5 x CH_{ar}). ^{13}C NMR (d_6-DMSO): δ (ppm) = 45.6.1 (N*C*H_2), 50.9 (N*C*H_2), 66.9 (*C*HOH), 67.6 (*C*HOH), 96.3 (*C*HNO_2), 127.0 (2 C, C_{ar}), 128.6 (2 C, C_{ar}), 129.9 (C_{ar}), 135.2 (C_q), 169.6 (*C*=O). MS (ESI): m/z = 289 [M + Na], 555 [2 M + Na].

2.2.2. (4*r*)-1-Allyl-4-nitropiperidine-3,5-diol (8d)

At 0 °C allyl bromide (38.5 µL, 0.45 mmol) was added to a solution of nitropiperidinediol **8c** (72.1 mg, 0.45 mmol) and K_2CO_3 (61.5 mg, 0.45 mmol) in THF (2 mL). After 24 h stirring at rt, the solvent was removed under reduced pressure and the product was purified by fc (∅ = 2 cm, h = 17 cm, cyclohexane/ethyl acetate = 2/1,

V = 10 mL, R_f = 0.64 (CH_2Cl_2/CH_3OH = 9/1)). Colorless crystals, yield 14.1 mg (15 %). $C_8H_{14}N_2O_4$ (M = 202.2 g/mol). ^{1}H NMR (d_6-DMSO): δ (ppm) = 1.87 (t, ^2J = 10.8 Hz, ^3J = 10.8 Hz, 2 H, 2-CH_{2ax}, 6-CH_{2ax}), 2.92 (dd, ^2J = 11.2 Hz, ^3J = 4.6 Hz, 2 H, 2-CH_{2eq}, 6-CH_{2eq}), 3.01 (d broad, ^3J = 6.4 Hz, 2 H, NCH_2CH=CH_2), 3.80 – 3.94 (m, 2 H, 2 x C*H*OH), 4.14 (t, ^3J = 9.8 Hz, 1 H, C*H*NO_2), 5.11 – 5.25 (m, 2 H, NCH_2CH=CH_2), 5.63 (d broad, 2 H, 2 x O*H*), 5.71 – 5.88 (m, 1 H, NCH_2C*H*=CH_2). MS (EM, ESI): m/z = calcd. for $C_8H_{15}N_2O_4$ [M + H] 203.1031, found 203.1019. IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3514/3287 (*m*, O-H), 2924/2855 (*w*, C-H), 1559/1373 (*s*, C-NO_2). Purity (HPLC): 93.2 %, t_R = 3.41 min (method CH_3CN).

2.2.3. (4*r*)-1-Benzyl-4-nitropiperidine-3,5-diol (8e)

Trifluoroacetic acid (0.12 mL, 1.52 mmol) was added to a solution of nitropiperidinediol **8c** (80.0 mg, 0.30 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 3 h at rt. The solvent was removed under reduced pressure and the residue was dissolved in in CH_3CN (1 mL). Triethylamine (42 µL, 0.30 mmol) was added to the solution and the mixture was stirred for 10 min. Then benzaldehyde (33 µL, 0.33 mmol) and after 30 min $NaBH(OAc)_3$ (89.0 mg, 0.42 mmol) were added to the mixture. After 20 h the transformation was stopped by addition of a small amount of water, the solvent was removed under reduced pressure and the product was purified by fc (∅ = 3 cm, h = 20 cm, CH_2Cl_2/ethyl acetate = 4/1, V = 20 mL, R_f = 0.20 (CH_2Cl_2/CH_3OH = 10/1)). Colorless resin, yield 39.0 mg (50 %). $C_{12}H_{16}N_2O_4$ (M = 252.3 g/mol). ^{1}H NMR (d_6-DMSO): δ (ppm) = 1.89 (t, ^2J = 10.8 Hz, ^3J = 10.8 Hz, 2 H, 2-CH_{2ax}, 6-CH_{2ax}), 2.89 (dd, ^2J = 11.4 Hz, ^3J = 4.7 Hz, 2 H, 2-CH_{2eq}, 6-CH_{2eq}), 3.44 – 3.54 (m, 2 H, ArCH_2), 3.83 – 3.92 (m, 2 H, 2 x C*H*OH), 4.15 (t, ^3J = 9.8 Hz, 1 H, C*H*NO_2), 5.63 (d, ^3J = 6.2 Hz, 2 H, 2 x O*H*), 7.25 – 7.36 (m, 5 H, CH_{ar}). ^{13}C NMR (d_6-DMSO): δ (ppm) = 57.6 (2 x N*C*H_2), 60.6 (Ar*C*H_2), 68.2 (2 x *C*HOH), 97.3 (*C*HNO_2), 127.3 (C_{ar}), 128.4 (2 C, C_{ar}), 128.9 (2 C, C_{ar}), 137.8 (C_q). MS (ESI): m/z = 253 [M + H], 275 [M + Na]. IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3433 (*w*, O-H), 2932/2844 (*w*, C-H), 1544 (*s*, C-NO_2), 752/705 (*s*, Ar), 641 (*m*, Ar). Purity (HPLC): 97.5 %, t_R = 4.57 min (method CH_3CN).

2.2.4. (4*r*)-1-(4-Methoxybenzyl)-4-nitropiperidine-3,5-diol (8f)

Trifluoroacetic acid (0.12 mL, 1.52 mmol) was added to a solution of nitropiperidinediol **8c** (80.0 mg, 0.31 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 3 h at rt. The solvent was removed under reduced pressure and the residue was dissolved in in THF (1 mL). Then 4-methoxybenzyldehyde (36 µL, 0.30 mmol) and triethylamine (42 µL, 0.3 mmol) were added to the solution. After stirring for 30 min, $NaBH(OAc)_3$ (89.3 mg, 0.42 mmol) was added and the mixture was stirred for 1 h. The transformation was stopped by addition of a small amount of water and the solvent was removed under reduced pressure. The product was purified by fc (∅ = 2 cm, h = 15 cm, CH_2Cl_2/ethyl acetate = 3/1, V = 10 mL, R_f = 0.28). Colorless resin, yield 32.2 mg (38 %). $C_{13}H_{18}N_2O_5$ (M = 282.3 g/mol). ^{1}H NMR (d_6-DMSO): δ (ppm) = 1.85 (t, ^2J = 10.8 Hz, ^3J = 10.8 Hz, 2 H, 2-CH_2, 6-CH_2), 2.88 (dd, ^2J = 11.2 Hz, ^3J = 4.6 Hz, 2 H, 2-CH_2, 6-CH_2), 3.47 (s, 2 H, ArCH_2), 3.73 (s, 3 H, OCH_3), 3.78 – 3.93 (m, 2 H, 2 x C*H*OH), 4.13 (t, ^3J = 9.8 Hz, 1 H, C*H*NO_2), 5.62 (d, ^3J = 6.2 Hz, 2 H, 2 x O*H*), 6.89 (d, ^3J = 8.7 Hz, 2 H, 2 x CH_{ar}), 7.20 (d, ^3J = 8.7 Hz, 2 H, 2 x CH_{ar}). MS (EI): m/z = 282 [M], 236 [M − NO_2], 121 [C_8H_9O]. IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3340 (*w*, O-H), 2930 (*w*, C-H), 2822 (*w*, O-CH_3), 1542 (*s*, C-NO_2), 1377 (*w*, C-NO_2), 815 (*s*, Ar), 755/642 (*m*, Ar). Purity (HPLC): 94.2 %, t_R = 6.31 min (method CH_3CN).

2.2.5. (4a*RS*,8*RS*,8a*RS*)-6-Butyl-8-(pyrrolidin-1-yl)-4a,5,6,7,8,8a-hexahydro-1*H*-pyrido[3,4-b][1,4]oxazin-2(3*H*)-one (15d)

According to **General Procedure A** Boc-protected pyridooxazines **14** (115 mg, 0.36 mmol) was reacted with trifluoroacetic acid (0.82 mL, 10.6 mmol) in CH_2Cl_2 (3.5 mL). Then, alkylation was performed with *n*-butanal (32.5 µL, 0.36 mmol), $NaBH(OAc)_3$ (107 mg, 0.5 mmol) and THF (6 mL). The secondary amine was completely converted after 18 h and the product was purified by fc (∅ = 2 cm, h = 18 cm, CH_2Cl_2/CH_3OH/NH_3 = 9.5/0.47/0.03, V = 10 mL, R_f = 0.33). Colorless solid, mp 151 – 154 °C, yield 75.2 mg (74 %). $C_{15}H_{27}N_3O_2$ (M = 281.4 g/mol). ^{1}H NMR (CD_3OD): δ (ppm) = 0.94 (t, ^3J = 7.3 Hz, 3 H, CH_3), 1.28 – 1.41 (m, 2 H, $CH_2CH_2CH_2CH_3$), 1.42 – 1.59 (m, 2 H, $CH_2CH_2CH_2CH_3$), 1.72 – 1.82 (m, 4 H, N(CH_2CH_2)$_2$), 2.03 (t, ^2J = 10.1 Hz, ^3J = 10.1 Hz, 1 H, 5-C$H_{2\text{-ax}}$), 2.09 (dd, ^2J = 12.8 Hz, ^3J = 1.9 Hz, 1 H, 7-CH_{2ax}), 2.32 – 2.47 (m, 2 H, $CH_2CH_2CH_2CH_3$), 2.69 – 2.81 (m, 5 H, 8-C*H*, N(CH_2CH_2)$_2$), 3.16 – 3.18 (m, 1 H, 5-C$H_{2\text{-eq}}$), 3.19 – 3.23

(m, 1 H, 7-C$H_{2\text{-eq}}$), 3.38 (dd, ^{3}J = 9.8 Hz, ^{3}J = 3.1 Hz, 1 H, 8a-C*H*), 3.97 – 4.06 (m, 1 H, 4a-C*H*), 4.16 (s, 2 H, 3-CH_2). A signal for N*H* proton is not observed in the ^{1}H NMR spectrum. ^{13}C NMR (CD_3OD): δ (ppm) = 14.3 (*C*H_3), 21.8 ($CH_2CH_2CH_2CH_3$), 24.1 (2 C, N(CH_2CH_2)$_2$), 29.9 ($CH_2CH_2CH_2CH_3$), 54.2 (2 C, N(CH_2CH_2)$_2$), 56.3 (*C*-7), 57.7 (*C*-5), 59.0 ($CH_2CH_2CH_2CH_3$), 60.9 (*C*-8a), 62.7 (*C*-8), 68.4 (*C*-3), 71.4 (*C*-4a), 171.2 (*C*=O). MS (EM, APCI): m/z = calcd. for $C_{15}H_{28}N_3O_2$ [M + H] 282.2182, found 282.2154; calcd. for $C_{11}H_{21}N_2O_2$ [(M – pyrrolidine) + 2 H] 213.1603, found 213.1572. IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3197/3066 (*w*, N-H), 2959/2928/2870 (*m*, C-H), 1678 (*s*, C=O).

2.2.6. (4a*RS*,8*RS*,8a*RS*)-6-Cyclopentyl-8-(pyrrolidin-1-yl)-4a,5,6,7,8,8a-hexahydro-1*H*-pyrido[3,4-b][1,4]oxazin-2(3*H*)-one (15e)

According to **General Procedure A** Boc-protected pyridooxazines **14** (65.0 mg, 0.20 mmol) was reacted with cyclopentanone (18 µL, 0.20 mmol), trifluoroacetic acid (15 µL, 0.20 mmol) and $NaBH(OAc)_3$ (59.3 mg, 0.28 mmol) in THF (4 mL). After 1 h the amine was completely converted and the product was purified by fc (∅ = 2 cm, h = 18 cm, $CH_2Cl_2/CH_3OH/NH_3$ = 9.5/0.47/0.03, V = 10 mL, R_f = 0.24 (CH_2Cl_2/CH_3OH = 9/1)). Colorless solid, mp 168 °C (decomposition), yield 47.8 mg (81 %). $C_{16}H_{27}N_3O_2$ (M = 293.4 g/mol). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.34 – 1.92 (m, 12 H, CH(CH_2)$_4$, N(CH_2CH_2)$_2$), 1.95 – 2.05 (m, 2 H, 5-C$H_{2\text{-ax}}$, 7-C$H_{2\text{-ax}}$), 2.53 – 2.69 (m, 4 H, C*H*(CH_2)$_4$, 8-C*H*, N(C$H_2$$CH_2$)$_2$), 2.70 – 2.79 (m, 2 H, N(C$H_2$$CH_2$)$_2$), 3.17 – 3.25 (m, 1 H, 5-C$H_{2\text{-eq}}$ or 7-C$H_{2\text{-eq}}$), 3.28 – 3.33 (m, 1 H, 5-C$H_{2\text{-eq}}$ or 7-C$H_{2\text{-eq}}$), 3.36 (dd, ^{3}J = 9.7 Hz, ^{3}J = 3.4 Hz, 1 H, 8a-C*H*), 3.94 – 4.02 (m, 1 H, 4a-C*H*), 4.18 (d, ^{2}J = 16.7 Hz, 1 H, 3-CH_2), 4.26 (d, ^{2}J = 16.7 Hz, 1 H, 3-CH_2), 6.76 (s broad, 1 H, N*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 23.4/24.2/29.8/30.4 (6 C, CH(*C*H_2)$_4$, N(CH_2*C*H_2)$_2$), 53.4 (2 C, N(*C*$H_2$$CH_2$)$_2$), 54.0 (*C*-5 or *C*-7), 55.6 (*C*-5 or *C*-7), 59.9 (*C*-8a), 61.5 (*C*-8 or C*H*(CH_2)$_4$), 67.3 (*C*H(CH_2)$_4$ or *C*-8), 67.9 (*C*-3), 71.1 (*C*-4a), 169.1 (*C*=O). MS (EM, APCI): m/z = calcd. for $C_{16}H_{28}N_3O_2$ [M + H] 294.2182, found 294.2162. IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2959/2901/2866 (*m*, C-H), 1682 (*s*, C=O).

2.2.7. (4a*RS*,8*RS*,8a*RS*)-6-Benzyl-8-(pyrrolidin-1-yl)-4a,5,6,7,8,8a-hexahydro-1*H*-pyrido[3,4-b][1,4]oxazin-2(3*H*)-one (15f)

According to **General Procedure A** Boc-protected pyridooxazines **14** (140 mg, 0.43 mmol) was reacted with trifluoroacetic acid (1.0 mL, 12.9 mmol) in CH_2Cl_2 (4 mL). The alkylation was performed with benzaldehyde (65.1 µL, 0.65 mmol),

$NaBH(OAc)_3$ (127.6 mg, 0.6 mmol) and THF (10 mL). The conversion was complete after 3 h and the product was purified by fc (∅ = 2 cm, h = 16 cm, CH_2Cl_2/CH_3OH = 9/1, V = 10 mL, R_f = 0.30). Colorless solid, mp 191 – 194 °C, yield 121.6 mg (90 %). $C_{18}H_{25}N_3O_2$ (M = 315.4 g/mol). ^{1}H NMR (CD_3OD): *δ* (ppm) = 1.77 – 1.85 (m, 4 H, $N(CH_2CH_2)_2$), 2.14 (t, ^2J = 10.1 Hz, ^3J = 10.1 Hz, 1 H, 5-C$H_{2\text{-ax}}$), 2.20 (dd, ^2J = 13.2 Hz, ^3J = 1.9 Hz, 1 H, 7-C$H_{2\text{-ax}}$), 2.77 – 2.86 (m, 2 H, $N(CH_2CH_2)_2$), 2.88 – 2.96 (m, 2 H, $N(CH_2CH_2)_2$), 2.96 – 3.00 (m, 1 H, 8-C*H*), 3.06 – 3.12 (m, ^2J = 13.1 Hz, ^3J = 1.8 Hz, 1 H, 7-C$H_{2\text{-eq}}$), 3.22 (dd, ^2J = 10.3 Hz, ^3J = 4.7 Hz, 1 H, 5-C$H_{2\text{-eq}}$), 3.46 – 3.52 (m, 1 H, 8a-C*H*), 3.49 (d, ^2J = 12.7 Hz, 1 H, ArCH_2), 3.69 (d, ^2J = 12.7 Hz, 1 H, ArCH_2), 4.03 (m, 1 H, 4a-C*H*), 4.18 (s, 2 H, 3-CH_2), 7.26 – 7.36 (m, 5 H, Ar). A signal for the N*H* proton is not observed in the ^{1}H NMR spectrum. ^{13}C NMR (CD_3OD): *δ* (ppm) = 23.8 (2 C, $N(CH_2CH_2)_2$), 54.6 (2 C, $N(CH_2CH_2)_2$), 54.8 (*C*-7), 57.3 (*C*-5), 60.0 (*C*-8a), 63.0 (*C*-8), 63.1 (ArCH_2), 68.5 (*C*-3), 71.2 (*C*-4a), 128.7 (C_{ar}), 129.4 (2 C, C_{ar}), 130.7 (2 C, C_{ar}), 138.6 (C_q), 171.2 (*C*=O). MS (EM, APCI): m/z = calcd. for $C_{18}H_{26}N_3O_2$ [M + H] 316.2025, found 316.2007. IR (neat): *v* (cm^{-1}) = 3183/3067 (*w*, N-H), 2954/2905/2774 (*m*, C-H), 1670 (*s*, C=O), 737/694 (*s,* Ar). Purity (HPLC): 98.3 %, t_R = 12.89 min (method CH_3CN).

2.2.8. (4a*RS*,8*RS*,8a*RS*)-6-(Pyridin-3-ylmethyl)-8-(pyrrolidin-1-yl)-4a,5,6,7,8,8a-hexahydro-1*H*-pyrido[3,4-b][1,4]oxazin-2(3*H*)-one (15g)

According to **General Procedure A** Boc-protected pyridooxazines **14** (80.4 mg, 0.25 mmol) was reacted with trifluoroacetic acid (0.57 mL, 7.4 mmol) in CH_2Cl_2 (2.5 mL). Then alkylation was performed with pyridine-3-carbaldehyde (35 µL, 0.38 mmol), $NaBH(OAc)_3$ (74.2 mg, 0.35 mmol) and THF (4 mL). The transformation was complete after 20 h and the product was purified by fc (∅ = 2 cm, h = 16 cm, $CH_2Cl_2/CH_3OH/NH_3$ = 9.2/0.7/0.1, V = 10 mL, R_f = 0.48 ($CH_2Cl_2/CH_3OH/NH_3$ = 9.5/0.47/0.3)). Pale yellow crystals, mp 78 – 81 °C, yield 75.5 mg (95 %). $C_{17}H_{24}N_4O_2$ (M = 316.4 g/mol). ^{1}H NMR (CD_3OD): *δ* (ppm) = 1.66 – 1.76 (m, 4 H, $N(CH_2CH_2)_2$), 2.10 (t, ^2J = 10.1 Hz, ^3J = 10.1 Hz, 1 H, 5-C$H_{2\text{-ax}}$), 2.17 (dd, ^2J = 12.7 Hz, ^3J = 2.1 Hz, 1 H, 7-C$H_{2\text{-ax}}$), 2.52 – 2.61 (m, 2 H, $N(CH_2CH_2)_2$), 2.62 – 2.72 (m, 3 H, $N(CH_2CH_2)_2$, 8-C*H*), 3.04 (dt, ^2J = 12.7 Hz, ^3J = 2.0 Hz, 1 H, 7-C$H_{2\text{-eq}}$), 3.15 (dd, ^2J = 10.1 Hz, ^3J = 4.6 Hz, 1 H, 5-C$H_{2\text{-eq}}$), 3.37 (dd, ^3J = 9.8 Hz, ^3J = 3.2 Hz, 1 H, 8a-C*H*), 3.54 (d, ^2J = 13.3 Hz, 1 H, PyrCH_2), 3.68 (d, ^2J = 13.3 Hz, 1 H, PyrCH_2), 3.99 – 4.08 (m, 1 H, 4a-C*H*), 4.15 (s, 2 H, 3-CH_2), 7.42 (dd, ^3J = 7.8 Hz,

^{3}J = 4.9 Hz, 1 H, 5-CH_{pyr}), 7.85 (dt, ^{3}J = 7.8 Hz, ^{2}J = 1.8 Hz, 1 H, 6-CH_{pyr}), 8.45 (dd, ^{3}J = 4.9 Hz, ^{4}J = 1.6 Hz, 1 H, 4-CH_{pyr}), 8.51 (dd, ^{4}J = 1.7 Hz, 1 H, 2-CH_{pyr}). A signal for the N*H* proton is not observed in the ^{1}H NMR spectrum. ^{13}C NMR (CD_3OD): δ (ppm) = 24.1 (2 C, N(CH_2CH_2)$_2$), 54.0 (2 C, N(CH_2CH_2)$_2$), 55.8 (*C*-7), 57.3 (*C*-5), 60.2 (PyrCH_2), 60.8 (*C*-8a), 62.4 (*C*-8), 68.3 (*C*-3), 71.4 (*C*-4a), 125.9 (C_{pyr}-5), 135.6 (C_q), 139.4 (C_{pyr}-6), 149.1 (C_{pyr}-4), 150.9 (C_{pyr}-2), 171.2 (*C*=O). MS (EM, APCI): m/z = calcd. for $C_{17}H_{25}N_4O_2$ [M + H] 317.1978, found 317.1955. IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2956/2909/2801 (*m*, C-H), 1670 (*s*, C=O), 714 (*s,* Ar). Purity (HPLC): 98.5 %, t_R = 4.49 min (method CH_3CN).

2.2.9. 6-Butyl (4a*RS*,8*RS*,8a*RS*)-8-(pyrrolidin-1-yl)-2,3,4a,5,6,7,8,8a-octahydro-1*H*-pyrido[3,4-b][1,4]oxazine (16d)

A solution of AlH_3 (1.33 mmol) was freshly prepared by **General Procedure B**. Lactam **15d** (47.9 mg, 0.17 mmol) dissolved in THF (3 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 45 min at 0 °C and for additional 20 min at rt. 2 M NaOH (5 mL) was added carefully at 0 °C. CH_2Cl_2 (5 mL) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure. Yellow oil, yield 54.0 mg (> 99 %). $C_{15}H_{29}N_3O$ (M = 267.4 g/mol). ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.91 (t, ^{3}J = 7.3 Hz, 3 H, CH_3), 1.24 – 1.35 (m, 2 H, $CH_2CH_2CH_2CH_3$), 1.36 – 1.53 (m, 2 H, $CH_2CH_2CH_2CH_3$), 1.61 – 1.80 (m, 5 H, N(CH_2CH_2)$_2$, N*H*), 1.83 (t, ^{2}J = 10.1 Hz, ^{3}J = 10.1 Hz, 1 H, 5-C$H_{2\text{-ax}}$), 2.00 (dd, ^{2}J = 12.5 Hz, ^{3}J = 2.9 Hz, 1 H, 7-C$H_{2\text{-ax}}$), 2.20 – 2.29 (m, 1 H, $CH_2CH_2CH_2CH_3$), 2.30 – 2.38 (m, 1 H, $CH_2CH_2CH_2CH_3$), 2.45 (dd, ^{3}J = 9.7 Hz, ^{3}J = 4.2 Hz, 1 H, 8a-C*H*), 2.66 – 2.76 (m, 3 H, 8-C*H*, N(CH_2CH_2)$_2$), 2.80 – 2.89 (m, 2 H, N(CH_2CH_2)$_2$), 2.90 – 3.06 (m, 3 H, 2-CH_2, 5-C$H_{2\text{-eq}}$ or 7-C$H_{2\text{-eq}}$), 3.09 (m, 1 H, 5-C$H_{2\text{-eq}}$ or 7-C$H_{2\text{-eq}}$), 3.49 – 3.62 (m, 2 H, 3-CH_2), 3.80 (m, 1 H, 4a-C*H*). MS (EM, APCI): m/z = calcd. for $C_{15}H_{30}N_3O$ [M + H] 268.2389, found 268.2406. IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2955/2932/2870 (*m*, C-H), 1119/1092 (*s*, C-O_{ether}).

2.2.10. (4a*RS*,8*RS*,8a*RS*)-6-Benzyl-8-(pyrrolidin-1-yl)-2,3,4a,5,6,7,8,8a-octahydro-1*H*-pyrido[3,4-b][1,4]-oxazine (16f)

A solution of AlH_3 (1.33 mmol) was freshly prepared by **General Procedure B**. Lactam **15f** (57.8 mg, 0.18 mmol) dissolved in THF (3 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 15 min at 0 °C, then 2 M NaOH (5 mL) was added carefully at 0 °C. CH_2Cl_2 (5 mL) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure. R_f = 0.21 (CH_2Cl_2/MeOH = 9/1). Colorless oil, yield 53.8 mg (> 99 %). $C_{18}H_{27}N_3O$ (M = 301.4 g/mol). ^{1}H NMR (CD_3OD): δ (ppm) = 1.65 – 1.74 (m, 4 H, N(CH_2CH_2)$_2$), 1.81 – 1.90 (m, 2 H, 5-C$H_{2\text{-ax}}$, N*H*), 2.10 (dd, ^2J = 12.7 Hz, ^3J = 3.0 Hz, 1 H, 7-C$H_{2\text{-ax}}$), 2.42 (dd, ^3J = 9.9 Hz, ^3J = 4.4 Hz, 1 H, 8a-C*H*), 2.65 – 2.74 (m, 2 H, N(CH_2CH$_2$)$_2$), 2.76 – 2.86 (m, 3 H, N(CH_2CH$_2$)$_2$, 8-C*H*), 2.87 – 2.92 (m, 2 H, 2-CH_2), 2.92 – 2.95 (m, 1 H, 5-C$H_{2\text{-eq}}$), 3.08 (dt, ^2J = 12.7 Hz, ^3J = 2.1 Hz, 1 H, 7-C$H_{2\text{-eq}}$), 3.44 (d, ^2J = 12.8 Hz, 1 H, ArCH_2), 3.49 (d, ^2J = 12.8 Hz, 1 H, ArCH_2), 3.51 – 3.57 (m, 1 H, 3-CH_2), 3.58 – 3.65 (m, 1 H, 4a-C*H*), 3.71 – 3.77 (m, 1 H, 3-CH_2), 7.21 – 7.33 (m, 5 H, Ar-*H*). MS (EM, APCI): m/z = calcd. for $C_{18}H_{28}N_3O$ [M + H] 302.2232, found 302.2233. IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2959/2909/2870 (*m*, C-H), 1107/1088 (*s*, C-O$_{ether}$), 791/698 (*s*, Ar).

2.2.11. 2-(3,4-Dichlorophenyl)-1-[(4a*RS*,8*RS*,8a*RS*)-6-ethyl-8-(pyrrolidin-1-yl)-2,3,4a,5,6,7,8,8a-octahydropyrido[3,4-b][1,4]oxazin-1-yl]ethanone (17c)

A solution of AlH_3 (1.33 mmol) was freshly prepared by **General Procedure B**. After cooling to 0 °C a solution of lactam **15c** (53.1 mg, 0.21 mmol) in THF (3 mL) was added dropwise. The reaction mixture was stirred for 45 min at 0 °C and additional 20 min at rt. 2 M NaOH (5 mL) was carefully added at 0 °C. CH_2Cl_2 (5 mL) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The residue (**16c**) was dissolved in CH_2Cl_2 (5 mL), 2-(3,4-dichlorophenyl)acetyl chloride (39.1 µL, 0.25 mmol) was added and the mixture was stirred for 30 min. Then 2 M NaOH (5 mL) was added and the mixture was stirred vigorously for 30 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and the

solvent was removed under reduced pressure. The product was purified by fc (∅ = 2 cm, h = 17 cm, CH_2Cl_2/CH_3OH = 9.7/0.3 → CH_2Cl_2/CH_3OH = 9.5/0.5, V = 10 mL, R_f = 0.07 (CH_2Cl_2/CH_3OH = 9/1)). Colorless resin, yield 76.6 mg (86 %). $C_{21}H_{29}Cl_2N_3O_2$ (M = 426.4 g/mol). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.06 (t, ^3J = 7.2 Hz, 3 H, CH_3), 1.60 – 1.87 (m, 4 H, N(CH_2CH_2)$_2$), 1.94 (t, ^2J = 9.9 Hz, ^3J = 9.9 Hz, 1 H, 5-C$H_{2\text{-ax}}$), 2.04 – 2.22 (m, 1 H, 7-C$H_{2\text{-ax}}$), 2.29 – 2.81 (m, 6 H, CH_2CH_3, N(CH_2CH_2)$_2$), 3.08 (d, ^2J = 12.8 Hz, 1 H, 7-C$H_{2\text{-eq}}$), 3.19 (dd, ^2J = 10.0 Hz, ^3J = 2.9 Hz, 1 H, 5-C$H_{2\text{-eq}}$), 3.48 – 4.08 (m, 8 H, 2-CH_2, 3-CH_2, 8-CH, 8a-CH, ArCH_2), 4.28 – 4.73 (m, 1 H, 4a-CH), 7.09 (dd, ^3J = 8.2 Hz, ^4J = 2.0 Hz, 1 H, 6-CH_{ar}), 7.35 (d, ^4J = 2.0 Hz, 1 H, 2-CH_{ar}), 7.39 (d, ^3J = 8.2 Hz, 1 H, 5-CH_{ar}). ^{13}C NMR ($CDCl_3$): δ (ppm) = 12.1 (CH_3), 23.4 (2 C, N(CH_2CH_2)$_2$), 40.6 (ArCH_2), 41.2 (*C*-8a), 51.9 (CH_2CH_3), 53.6 (2 C, N(CH_2CH_2)$_2$), 55.5 (*C*-7), 58.2 (*C*-5), 60.6 (*C*-8), 64.5 (*C*-2), 65.8 (*C*-3), 66.8 (*C*-4a), 128.6 (C_{ar}-6), 130.6 (C_{ar}-2), 131.1 (C_{ar}-5), 131.4 (C_q), 132.8 (C_q), 134.7 (C_q), 170.5 (*C*=O). MS (EM, APCI): m/z = calcd. for $C_{21}H_{30}{}^{35}Cl_2N_3O_2$ [M + H] 426.1715, found 426.1690. IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2966/2870/2778 (*m*, C-H), 1636 (*s*, C=O), 1129/1111 (*s*, C-O_{ether}). Purity (HPLC): 98.4 %, t_R = 17.95 min (method CH_3CN).

2.2.12. 6-Butyl 1-[(4a*RS*,8*RS*,8a*RS*)-8-(pyrrolidin-1-yl)-2,3,4a,5,6,7,8,8a-octahydropyrido[3,4-b][1,4]oxazin-1-yl]-2-(3,4-dichlorophenyl)ethanone (17d)

2-(3,4-Dichlorophenyl)acetyl chloride (31.7 µL, 0.20 mmol) was added to a solution of amine **16d** (45.1 mg, 0.17 mmol) in CH_2Cl_2 (5.5 mL) and the mixture was stirred for 30 min at rt. 2 M NaOH (5.5 mL) was added and the mixture was stirred vigorously for 30 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The product was purified by fc (∅ = 2 cm, h = 16 cm, CH_2Cl_2/MeOH = 9.7/0.3, V = 10 mL, R_f = 0.65 (CH_2Cl_2/MeOH = 9/1)). Yellow oil, yield 71.4 mg (92 %). $C_{23}H_{33}Cl_2N_3O_2$ (M = 454.4 g/mol). ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.90 (t, ^3J = 7.3 Hz, 3 H, CH_3), 1.20 – 1.34 (m, 2 H, $CH_2CH_2CH_2CH_3$), 1.37 – 1.53 (m, 2 H, $CH_2CH_2CH_2CH_3$), 1.60 – 1.79 (m, 4 H, N(CH_2CH_2)$_2$), 1.92 (t, ^2J = 9.9 Hz, ^3J = 9.9 Hz, 1 H, 5-C$H_{2\text{-ax}}$), 2.04 – 2.13 (m, 1 H, 7-C$H_{2\text{-ax}}$), 2.21 – 2.31 (m, 1 H, $CH_2CH_2CH_2CH_3$), 2.33 – 2.42 (m, 1 H, $CH_2CH_2CH_2CH_3$), 2.44 – 2.66 (m, 4 H, N(CH_2CH_2)$_2$), 3.06 (d, ^2J = 12.9 Hz, 1 H, 7-C$H_{2\text{-eq}}$), 3.12 – 3.20 (m, 1 H, 5-C$H_{2\text{-eq}}$), 3.63 (d, ^2J = 15.2 Hz, 1 H, ArCH_2), 3.55 – 4.02 (m, 7 H, 2-CH_2, 3-CH_2, 8-CH, 8a-CH, ArCH_2), 4.35 – 4.51 (m, 1 H, 4a-CH), 7.09 (dd,

^{3}J = 8.2 Hz, ^{4}J = 2.1 Hz, 1 H, 6-CH_{ar}), 7.35 (d, ^{4}J = 2.0 Hz, 1 H, 2-CH_{ar}), 7.39 (d, ^{3}J = 8.2 Hz, 1 H, 5-CH_{ar}). ^{13}C NMR ($CDCl_3$): δ (ppm) = 14.2 (CH_3), 20.8 ($CH_2CH_2CH_2CH_3$), 23.4 (2 C, N(CH_2CH_2)$_2$), 29.2 ($CH_2CH_2CH_2CH_3$), 40.6 (ArCH_2), 41.5 (*C*-8a), 53.3 (2 C, N(CH_2CH_2)$_2$), 56.1 (*C*-7), 58.2 ($CH_2CH_2CH_2CH_3$), 58.7 (*C*-5), 60.3 (*C*-8), 64.9 (*C*-2), 65.8 (*C*-3), 66.8 (*C*-4a), 128.6 (C_{ar}-6), 130.6 (C_{ar}-5), 131.1 (C_{ar}-2), 131.3 (C_q), 132.8 (C_q), 134.8 (C_q), 170.2 (*C*=O). MS (EM, APCI): m/z = calcd. for $C_{23}H_{34}{}^{35}Cl_2N_3O_2$ [M + H] 454.2028, found 454.2028; calcd. for $C_{15}H_{30}N_3O$ [M – (3,4-dichlorophenyl)acetyl + 2 H] 268.2389, found 268.2366. IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2955/2928/2870 (*m*, C-H), 1640 (*s*, C=O), 1131/1111 (*s*, C-O_{ether}). Purity (HPLC): 99.1 %, t_R = 20.0 min (method CH_3CN).

2.2.13. 1-[(4a*RS*,8*RS*,8a*RS*)-6-Cyclopentyl-8-(pyrrolidin-1-yl)-2,3,4a,5,6,7,8,8a-octahydropyrido[3,4-b][1,4]oxazin-1-yl]-2-(3,4-dichlorophenyl)-ethanone (17e)

A solution of AlH_3 (1.33 mmol) was freshly prepared by **General Procedure B**. After cooling down to 0 °C a solution of lactam **15e** (50.3 mg, 0.18 mmol) in THF (3 mL) was added dropwise. The reaction mixture was stirred for 45 min at 0 °C and additional 20 min at rt. The transformation was stopped carefully with 2 M NaOH (5 mL) at 0 °C. CH_2Cl_2 (5 mL) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure. The residue (**16e**) was dissolved in CH_2Cl_2 (5 mL), 2-(3,4-dichlorophenyl)acetyl chloride (33.5 µL, 0.22 mmol) was added and the mixture was stirred for 30 min. Then 2 M NaOH (5 mL) was added and the mixture was stirred vigorously for 30 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The product was purified by fc (∅ = 2 cm, h = 17 cm, CH_2Cl_2/CH_3OH = 9.7/0.3, V = 10 mL, R_f = 0.10 (CH_2Cl_2/CH_3OH = 9/1)). Pale yellow solid, mp 89 – 92 °C, yield 64.7 mg (77 %). $C_{24}H_{33}Cl_2N_3O_2$ (M = 466.4 g/mol). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.29 – 1.86 (m, 12 H, CH(CH_2)$_4$, N(CH_2CH_2)$_2$), 1.90 (t, ^{2}J = 9.9 Hz, ^{3}J = 9.9 Hz, 1 H, 5-C$H_{2\text{-}ax}$), 2.09 – 2.22 (m, 1 H, 7-C$H_{2\text{-}ax}$), 2.42 – 2.81 (m, 5 H, C*H*(CH_2)$_4$, N(CH_2CH_2)$_2$), 3.13 (d, ^{2}J = 9.8 Hz, 1 H, 7-C$H_{2\text{-}eq}$), 3.27 (dd, ^{2}J = 9.8 Hz, ^{3}J = 2.7 Hz, 1 H, 5-C$H_{2\text{-}eq}$), 3.56 (d, ^{2}J = 15.2 Hz, 1 H, ArCH_2), 3.51 – 4.09 (m, 7 H, 2-CH_2, 3-CH_2, 8-C*H*, 8a-C*H*, ArCH_2), 4.38 – 4.57 (m, 1 H, 4a-C*H*), 7.09 (dd, ^{3}J = 8.2 Hz, ^{4}J = 2.0 Hz, 1 H, 6-CH_{ar}),

7.35 (d, ^4J = 2.0 Hz, 1 H, 2-CH_{ar}), 7.38 (d, ^3J = 8.2 Hz, 1 H, 5-CH_{ar}). ^{13}C NMR ($CDCl_3$): δ (ppm) = 23.4/24.1/29.9/30.4 (6 C, N(CH_2CH_2)$_2$, CH(CH_2)$_4$), 40.6 (ArCH_2), 41.5 (*C*-8a), 53.6 (2 C, N(CH_2CH_2)$_2$), 55.0 (*C*-7), 57.2 (*C*-5), 60.6 (*C*-8), 64.6 (*C*-2), 65.8 (*C*-3), 66.6 (*C*-4a), 67.2 (*C*H(CH_2)$_4$), 128.6 (C_{ar}-6), 130.7 (C_{ar}-2), 131.1 (C_{ar}-5), 131.4 (C_q), 132.8 (C_q), 134.7 (C_q), 170.5 (*C*=O). MS (EM, APCI): m/z = calcd. for $C_{24}H_{34}{}^{35}Cl_2N_3O_2$ [M + H] 466.2028, found 466.1986. IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2951/2866/2781 (*m*, C-H), 1640 (*s*, C=O), 1132/1115 (*s*, C-O_{ether}). Purity (HPLC): 95.1 %, t_R = 19.40 min (method CH_3CN).

2.2.14. 2-(3,4-Dichlorophenyl)-1-[(4a*RS*,8*RS*,8a*RS*)-6-(pyridin-3-ylmethyl)-8-(pyrrolidin-1-yl)-2,3,4a,5,6,7,8,8a-octahydropyrido[3,4-b][1,4]oxazin-1-yl]-ethanone (17g)

A solution of AlH_3 (1.33 mmol) was freshly prepared by **General Procedure B**. Lactam **15g** (28.2 mg, 0.09 mmol) dissolved in THF (2 mL) was added dropwise at −5 °C and the mixture was stirred for 15 min. 2 M NaOH (5 mL) was added carefully at −5 °C. CH_2Cl_2 (5 mL) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The residue (**16g**) was dissolved in CH_2Cl_2 (3 mL), 2-(3,4-dichlorophenyl)acetyl chloride (16.7 µL, 0.11 mmol) was added and the mixture was stirred for 15 min at rt. Then 2 M NaOH (3 mL) was added and the mixture was stirred vigorously for 30 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The product was purified by fc (∅ = 2 cm, h = 17 cm, CH_2Cl_2/CH_3OH/NH_3 = 9.5/0.47/0.03, V = 10 mL, R_f = 0.50). Colorless solid, mp 140 °C (decomposition), yield 16.8 mg (38 %). $C_{25}H_{30}Cl_2N_4O_2$ (M = 489.4 g/mol). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.49 – 1.71 (m, 4 H, N(CH_2CH_2)$_2$), 1.97 (t, ^2J = 9.8 Hz, ^3J = 9.8 Hz, 1 H, 5-C$H_{2\text{-ax}}$), 2.22 (dd, ^2J = 12.8 Hz, ^3J = 1.2 Hz, 1 H, 7-C$H_{2\text{-ax}}$), 2.37 – 2.54 (m, 4 H, N(CH_2CH_2)$_2$), 2.95 (d, ^2J = 12.8 Hz, 1 H, 7-C$H_{2\text{-eq}}$), 3.12 (dd, ^2J = 10.0 Hz, ^3J = 2.9 Hz 1 H, 5-C$H_{2\text{-eq}}$), 3.15 – 3.28 (m, 1 H, 8-C*H*), 3.45 (d, ^2J = 13.1 Hz, 1 H, PyrCH_2), 3.54 (d, ^2J = 13.1 Hz, 1 H, PyrCH_2), 3.62 (d, ^2J = 15.3 Hz, 1 H, ArCH_2), 3.67 (d, ^2J = 15.4 Hz, 1 H, ArCH_2), 3.57 – 4.01 (m, 5 H, 2-CH_2, 3-CH_2, 8a-C*H*), 4.33 – 4.48 (m, 1 H, 4a-C*H*), 7.08 (dd, 1 H, ^3J = 8.2 Hz, ^4J = 1.7 Hz, 6-CH_{ar}),

7.22 – 7.27 (m, 1 H, 2-CH_{pyr}), 7.34 (d, 1 H, ^4J = 1.6 Hz, 2-CH_{ar}), 7.38 (d, 1 H, ^3J = 8.2 Hz, 5-CH_{ar}), 7.60 – 7.67 (m, 1 H, CH_{pyr}), 8.48 – 8.57 (m, 2 H, NCH_{pyr}). ^{13}C NMR ($CDCl_3$): δ (ppm) = 23.4 (2 C, N(CH_2CH_2)$_2$), 40.5 (ArCH_2), 40.6 (*C*-8a), 53.1 (2 C, N(CH_2CH_2)$_2$), 55.2 (*C*-7), 57.9 (*C*-5), 59.7 (*C*-8), 60.1 (PyrCH_2), 64.7 (*C*-2), 65.8 (*C*-3), 66.6 (*C*-4a), 123.4 (C_{pyr}), 128.5 (C_{ar}-6), 130.7 (C_{ar}-5), 131.1 (C_{ar}-2), 131.3 (C_q), 132.8 (C_q), 133.2 (C_q), 134. 8 (C_q), 137.1 (C_{pyr}), 149.1 (NC_{pyr}), 150.8 (NC_{pyr}), 170.1 (*C*=O). MS (EM, APCI): m/z = calcd. for $C_{25}H_{31}{}^{35}Cl_2N_4O_2$ [M + H] 489.1824, found 489.1826. IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2916/2866/2776 (*m*, C-H), 1628 (*s*, C=O), 1126/1111 (*s*, C-O_{ether}), 713/679 (*m*, Ar). Purity (HPLC): 94.9 %, t_R = 16.01 min (method CH_3CN).

2.2.15. 2-(3,4-Dichlorophenyl)-1-[(4a*RS*,8*RS*,8a*RS*)-6-(3,4-dichlorophenylacetyl)-8-(pyrrolidin-1-yl)-2,3,4a,5,6,7,8,8a-octahydropyrido[3,4-b][1,4]oxazin-1-yl]-ethanone (17h)

A solution of AlH_3 (1.33 mmol) was freshly prepared by **General Procedure B**. Amide **15g** (92.7 mg, 0.29 mmol) dissolved in THF (5.5 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 45 min at 0 °C and for additional 20 min at rt. The transformation was stopped carefully with 2 M NaOH (5 mL) at 0 °C. CH_2Cl_2 (5 mL) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure. The residue (**16a**) was dissolved in CH_2Cl_2 (9 mL), 2-(3,4-dichlorophenyl)acetyl chloride (54.5 µL, 0.35 mmol) was added and the mixture was stirred for 30 min. Then 2 M NaOH (5 mL) was added and the mixture was stirred vigorously for 12 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The product was purified by fc (∅ = 3 cm, h = 17 cm, CH_2Cl_2/CH_3OH = 9.8/0.2, V = 10 mL, R_f = 0.43). Yellow resin, yield 34.4 mg (20 %). $C_{27}H_{29}Cl_4N_3O_3$ (M = 585.4 g/mol). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.51 – 1.76 (m, 4 H, N(CH_2CH_2)$_2$), 2.40 – 2.61 (m, 4 H, N(CH_2CH_2)$_2$), 2.73 (d, ^2J = 14.3 Hz, 1 H, 7-C$H_{2\text{-ax}}$), 2.80 – 2.89 (m, 1 H, 5-C$H_{2\text{-ax}}$), 3.21 – 3.38 (m, 1 H, 8-C*H*), 3.42 – 4.03 (m, 10 H, 2-CH_2, 3-CH_2, 5-C$H_{2\text{-eq}}$, 8a-C*H*, 2 x ArCH_2), 4.06 – 4.23 (m, 1 H, 4a-C*H*), 4.84 – 4.75 (d, ^2J = 14.4 Hz, 1 H, 7-C$H_{2\text{-eq}}$), 7.03 – 7.11 (m, 2 H, 2 x 6-CH_{ar}), 7.30 – 7.44 (m, 4 H, 2 x 2-CH_{ar}, 2 x 5-CH_{ar}). ^{13}C NMR ($CDCl_3$):

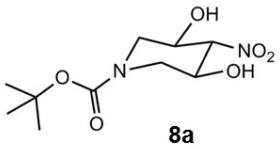
δ (ppm) = 23.5 (2 C, N(CH_2CH_2)$_2$), 40.2 (ArCH_2), 40.8 (ArCH_2), 41.4 (*C*-8a), 45.3 (*C*-7), 50.6 (*C*-5), 53.6 (2 C, N(CH_2CH_2)$_2$), 59.5 (*C*-8), 64.3 (*C*-2), 65.3 (*C*-4a), 65.7 (*C*-3), 128.4 (6-C_{ar}), 128.5 (6'-C_{ar}), 130.7 (C_{ar}), 130.8 (C_{ar}), 131.0 (2 C, 2 x C_{ar}), 131.3 (C_q), 131.5 (C_q), 132.8 (C_q), 132.9 (C_q), 134.4 (C_q), 135.1 (C_q), 168.7 (*C*=O), 170.4 (*C*=O). MS (EM, APCI): m/z = calcd. for $C_{27}H_{30}{}^{35}Cl_4N_3O_3$ [M + H] 584.1041, found 584.1002. IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2924/2874 (*w*, C-H), 1640 (*s*, C=O), 733/678 (*m*, Ar). Purity (HPLC): 95.1 %, t_R = 22.23 min (method CH_3CN).

2.2.16. (4a*RS*,8*RS*,8a*RS*)-6-[2-(3,4-Dichlorophenyl)acetyl]-8-(pyrrolidin-1-yl)-4a,5,6,7,8,8a-hexahydro-1*H*-pyrido[3,4-b][1,4]oxazin-2(3*H*)-one (18)

Trifluoroacetic acid (31 µL, 0.41 mmol) was added to a solution of Boc-protected pyridooxazines **14** (26.6 mg, 0.08 mmol) in CH_2Cl_2 (2 mL) and the mixture was stirred for 4 h at rt. After evaporation of the solvent in vacuum, the residue (**15a**) was dissolved in CH_2Cl_2 (2.5 mL) and 2-(3,4-dichlorophenyl)acetyl chloride (15.3 µL, 0.10 mmol) was added. The mixture was stirred for 30 min, then 2 M NaOH (2.5 mL) was added and the mixture was stirred for additional 20 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 3 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure and the product was purified by fc (∅ = 2 cm, h = 18 cm, CH_2Cl_2/CH_3OH = 9.8/0.2 → CH_2Cl_2/CH_3OH = 9.5/0.5, V = 10 mL), colorless oil, yield 28.5 mg. Since the product contained not converted carbamate **14** (~ 6 %, determined by ^{1}H NMR-spectroscopy), the mixture was dissolved in CH_2Cl_2 (2 mL) and trifluoroacetic acid (60 µL, 0.78 mmol) was added. After stirring for 16 h at rt the pH value of the solution was adjusted to pH 7 by addition of a saturated solution of $NaHCO_3$ and the solvent was removed under reduced pressure. The product was purified by fc (∅ = 1 cm, h = 16 cm, CH_2Cl_2/CH_3OH = 9.5/0.5, V = 5 mL, R_f = 0.58 (CH_2Cl_2/CH_3OH = 9/1)). Colorless crystals, mp 181 °C (decomposition), yield 23 mg (68 %). $C_{19}H_{23}Cl_2N_3O_3$ (M = 412.3 g/mol). ^{1}H NMR (CD_3OD): δ (ppm) = 1.69 – 1.75 (m, 4 H, N(CH_2CH_2)$_2$), 2.56 – 2.85 (m, 6 H, N(CH_2CH_2)$_2$, 7-CH_2, 8-C*H*), 3.05 (dd, ^2J = 12.9 Hz, ^3J = 10.3 Hz, 1 H, 5-CH_2), 3.63 (dd, ^3J = 9.9 Hz, ^3J = 2.6 Hz, 1 H, 8a-C*H*), 3.72 – 3.78 (m, 1 H, 4a-C*H*), 3.77 (d, ^2J = 15.7 Hz, 1 H, ArCH_2), 3.96 (d, ^2J = 15.7 Hz, 1 H, ArCH_2), 4.06 (d, ^2J = 16.7 Hz, 1 H, 3-CH_2), 4.14 – 4.22 (m, 1 H, 5-CH_2), 4.17 (d, ^2J = 16.7 Hz, 1 H, 3-CH_2), 4.60 (s, 1 H, N*H*), 4.82 – 4.94 (m, 1 H, 7-CH_2), 7.22 (dd, ^3J = 8.3 Hz, ^4J = 2.1 Hz, 1 H, 6-CH_{ar}), 7.45 (d, ^4J = 2.1 Hz, 1 H, 2-

CH_{ar}), 7.47 (d, ^{3}J = 8.4 Hz, 1 H, CH_{ar}). ^{13}C NMR (CD_3OD): δ (ppm) = 24.1 (2 C, N(CH_2CH_2)$_2$), 40.4 (ArCH_2), 45.9 (*C*-7), 50.1 (*C*-5), 54.4 (2 C, N(CH_2CH_2)$_2$), 60.8 (*C*-8a), 62.3 (*C*-8), 68.1 (*C*-3), 70.1 (*C*-4a), 130.1 (C_{ar}), 131.6 (C_{ar}), 131.8 (C_q), 132.0 (C_{ar}), 133.3 (C_q), 137.3 (C_q), 170.6 (*C*=O), 171.8 (*C*=O). MS (EM, APCI): m/z = calcd. for $C_{19}H_{24}{}^{35}Cl_2N_3O_3$ [M + H] 412.1195, found 412.1159. IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2951/2920/2793 (*w*, C-H), 1678 (*s*, C=O), 1643 (*s*, C=O). Purity (HPLC): 98.7 %, t_R = 15.93 min (method CH_3CN).

3. NMR Spectra



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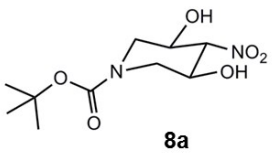

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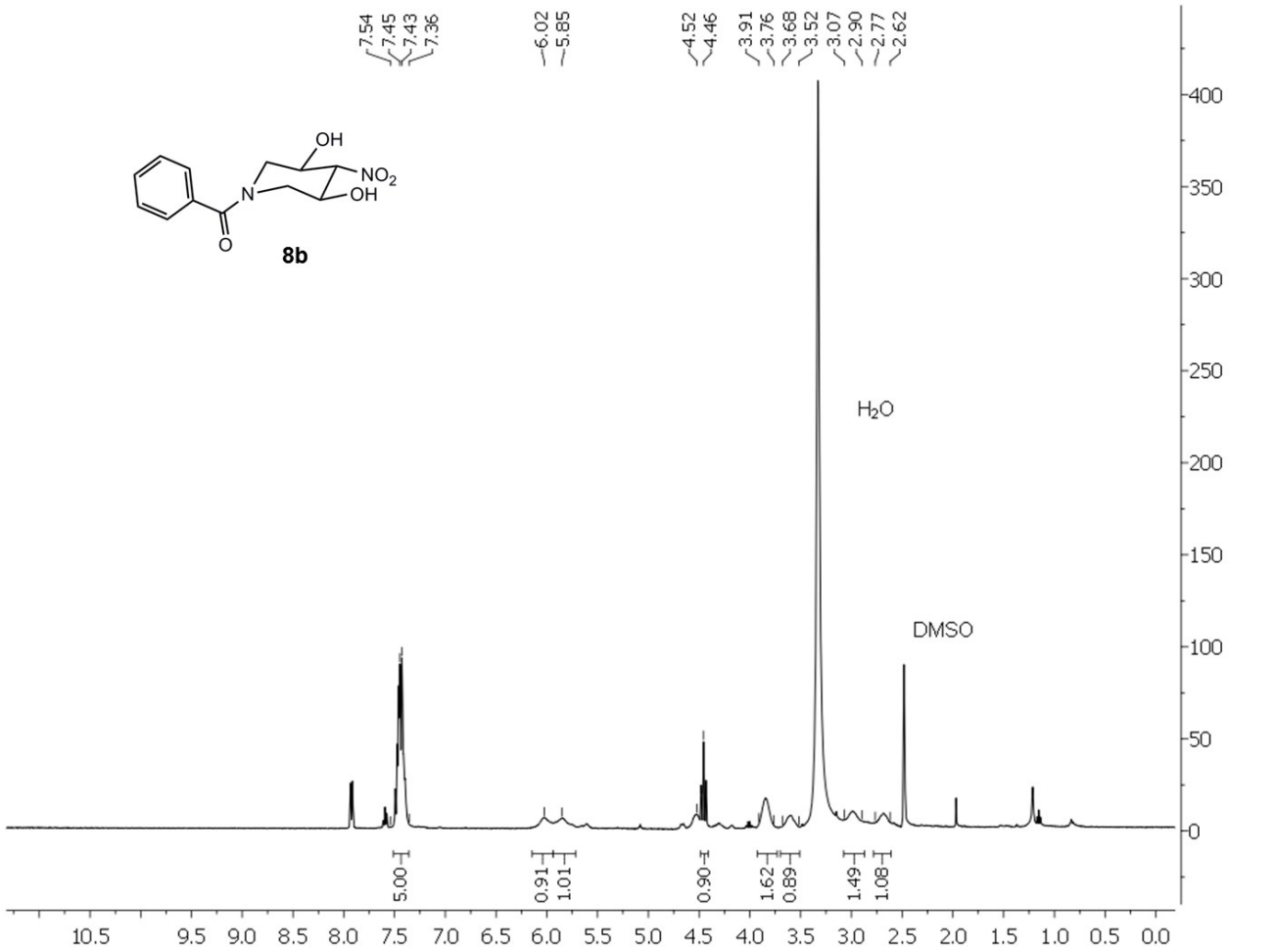
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2.77
2.62
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NO2
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N
O
8b
H2O
DMSO
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0.90
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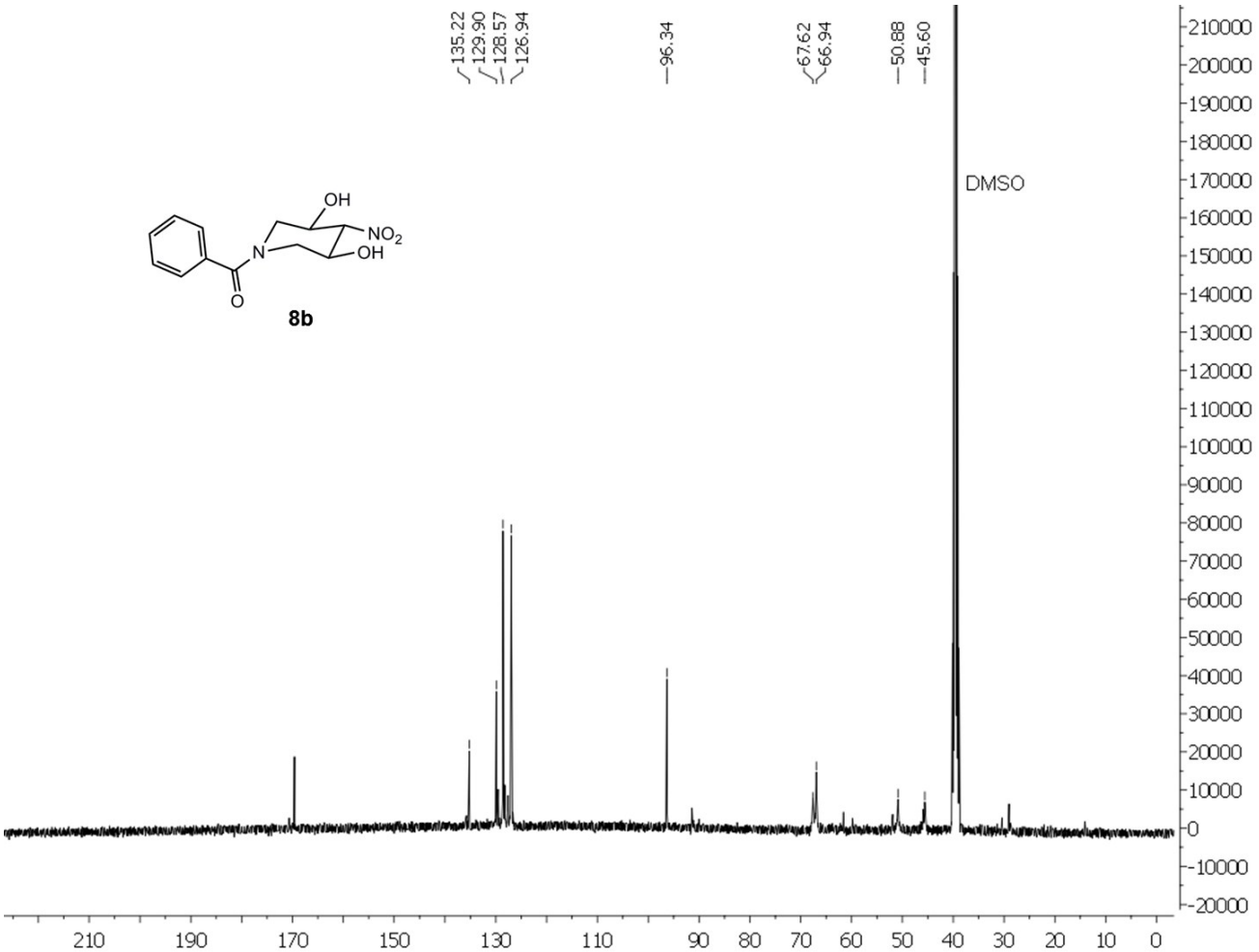
0.89
1.49
1.08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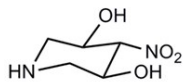
O
8b
DMSO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HN
OH

8c

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1.26
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11.5
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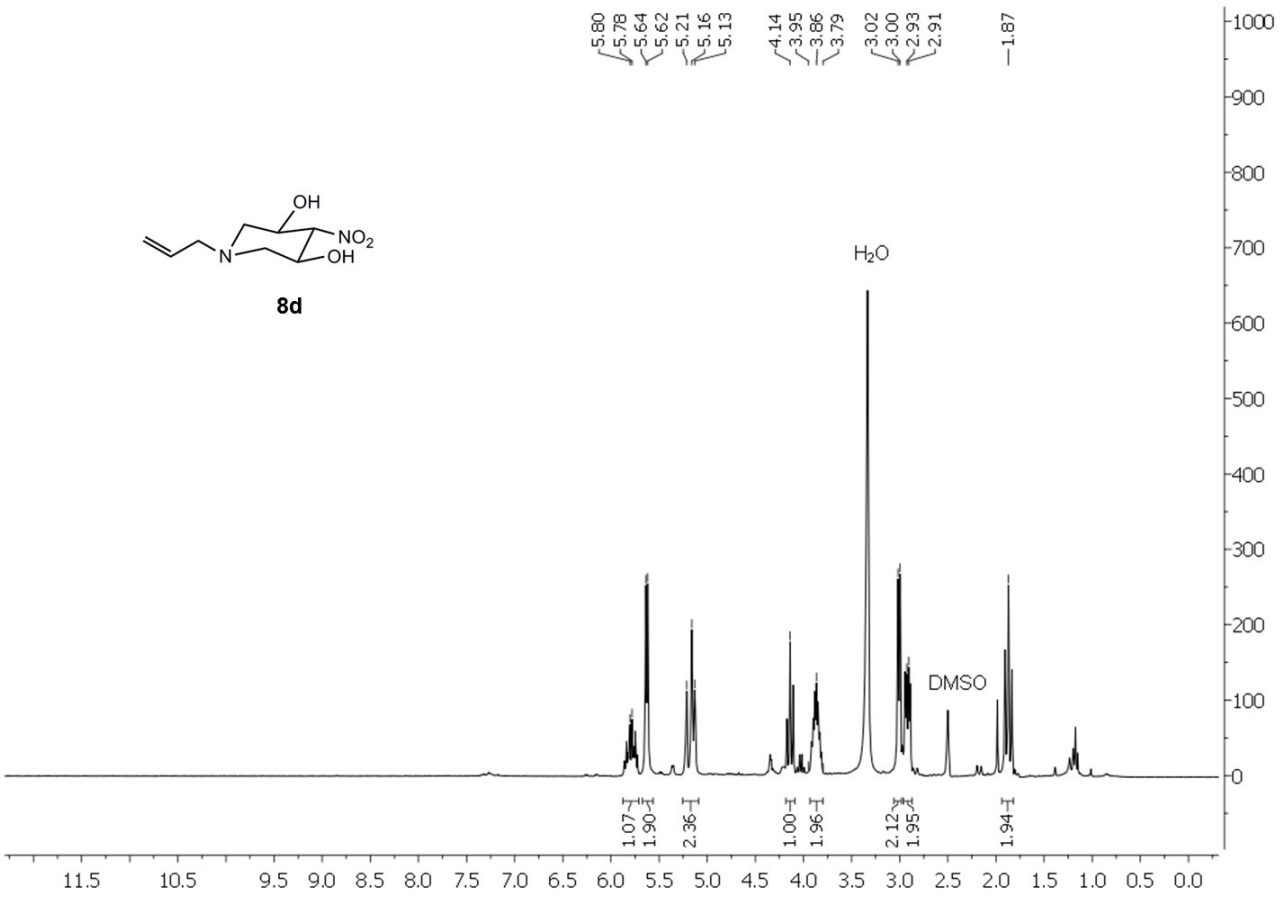
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3.02
3.00
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2.91
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DMSO
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2.36
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1.96
2.12
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1.94
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800
700
600
500
400
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200
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8.5
8.0
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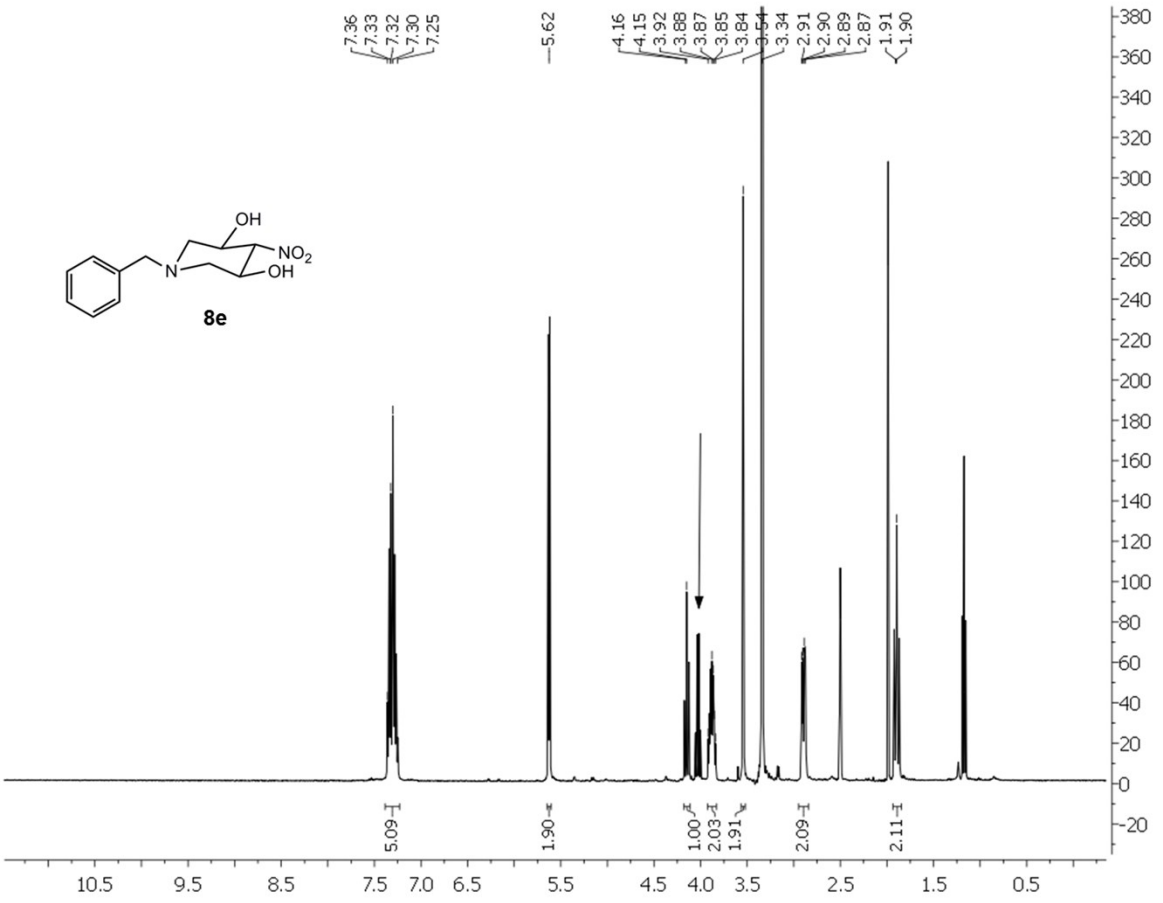
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3.84
3.54
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2.89
2.87
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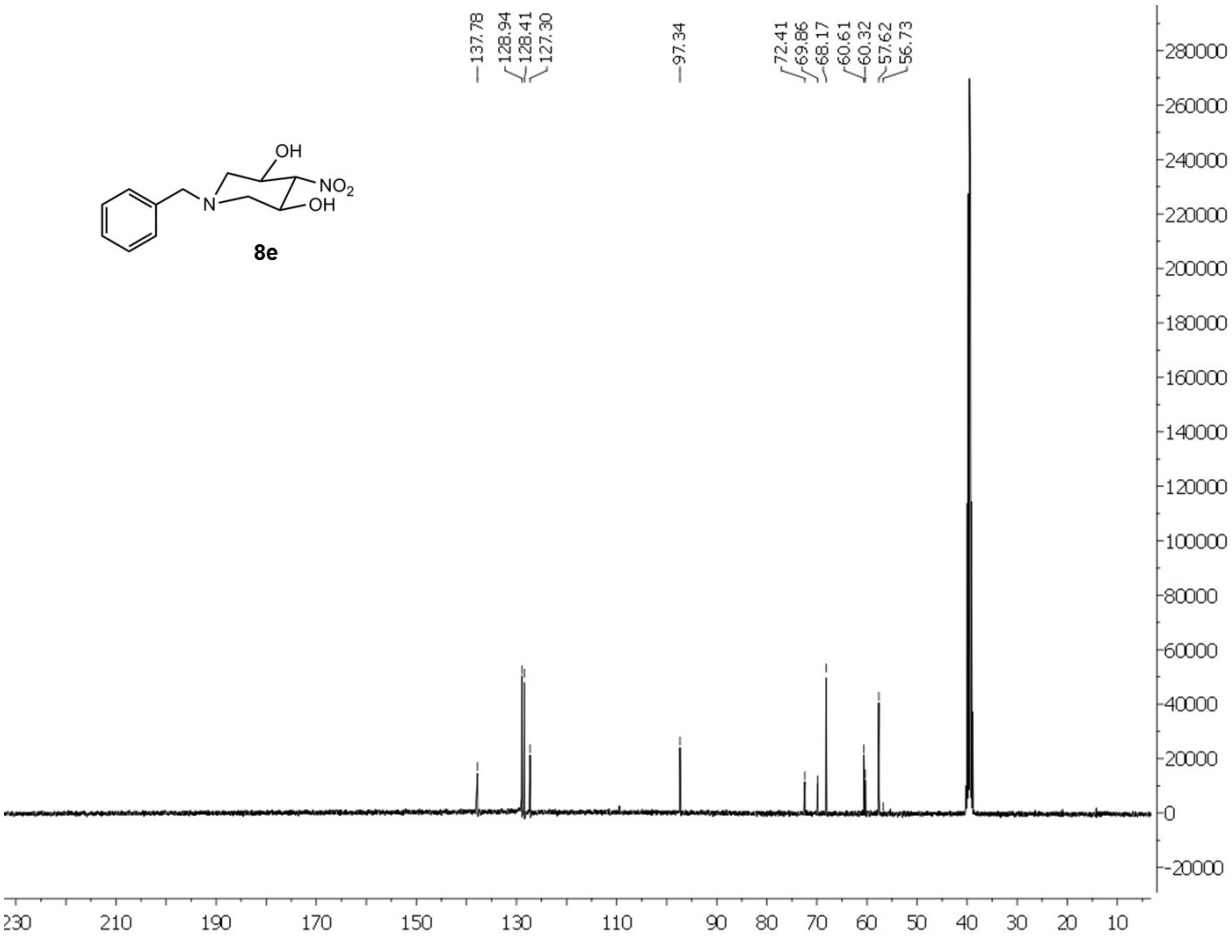
2.09
2.11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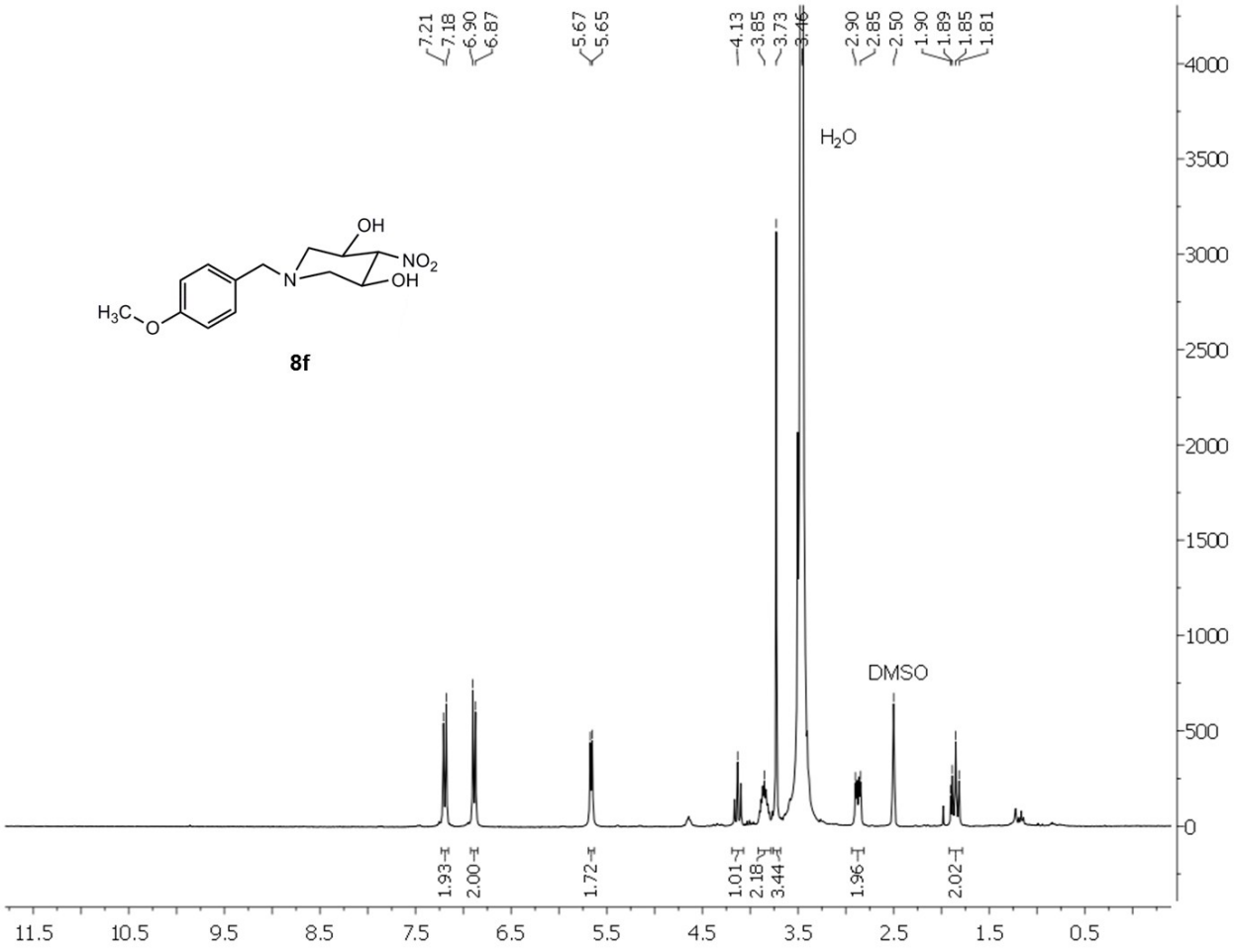
N
8e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DMSO
OH
NO2
OH
N
H3C
O
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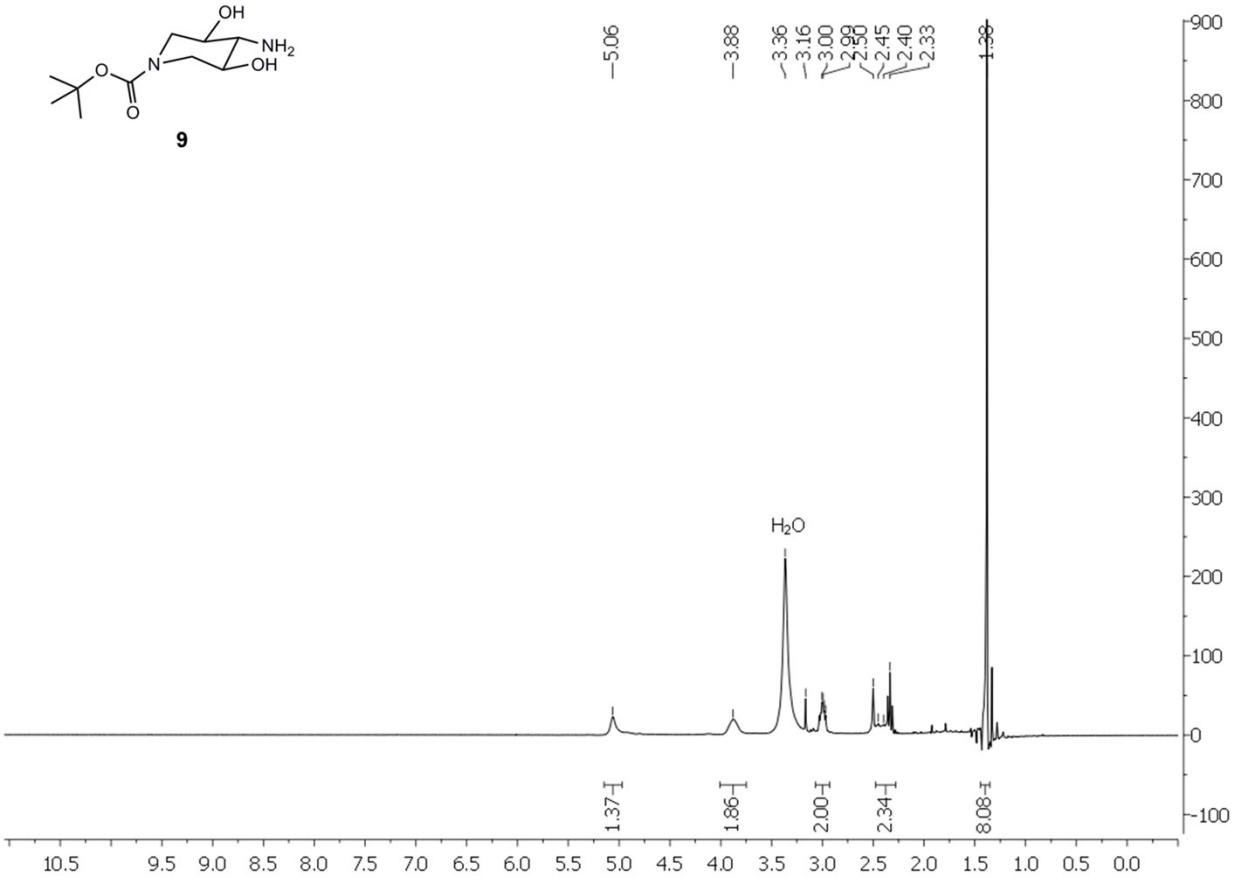
8f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2.34
8.08
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400
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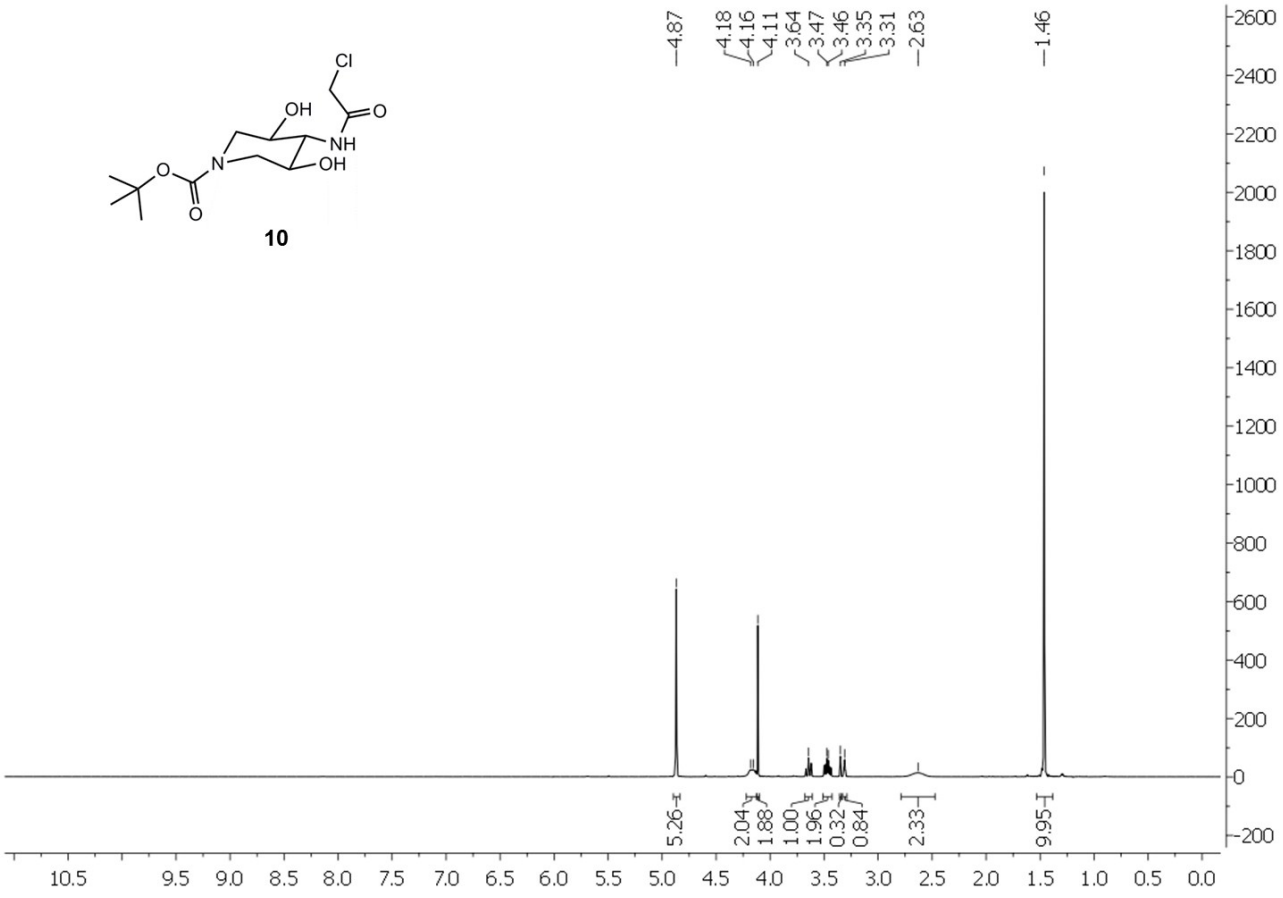
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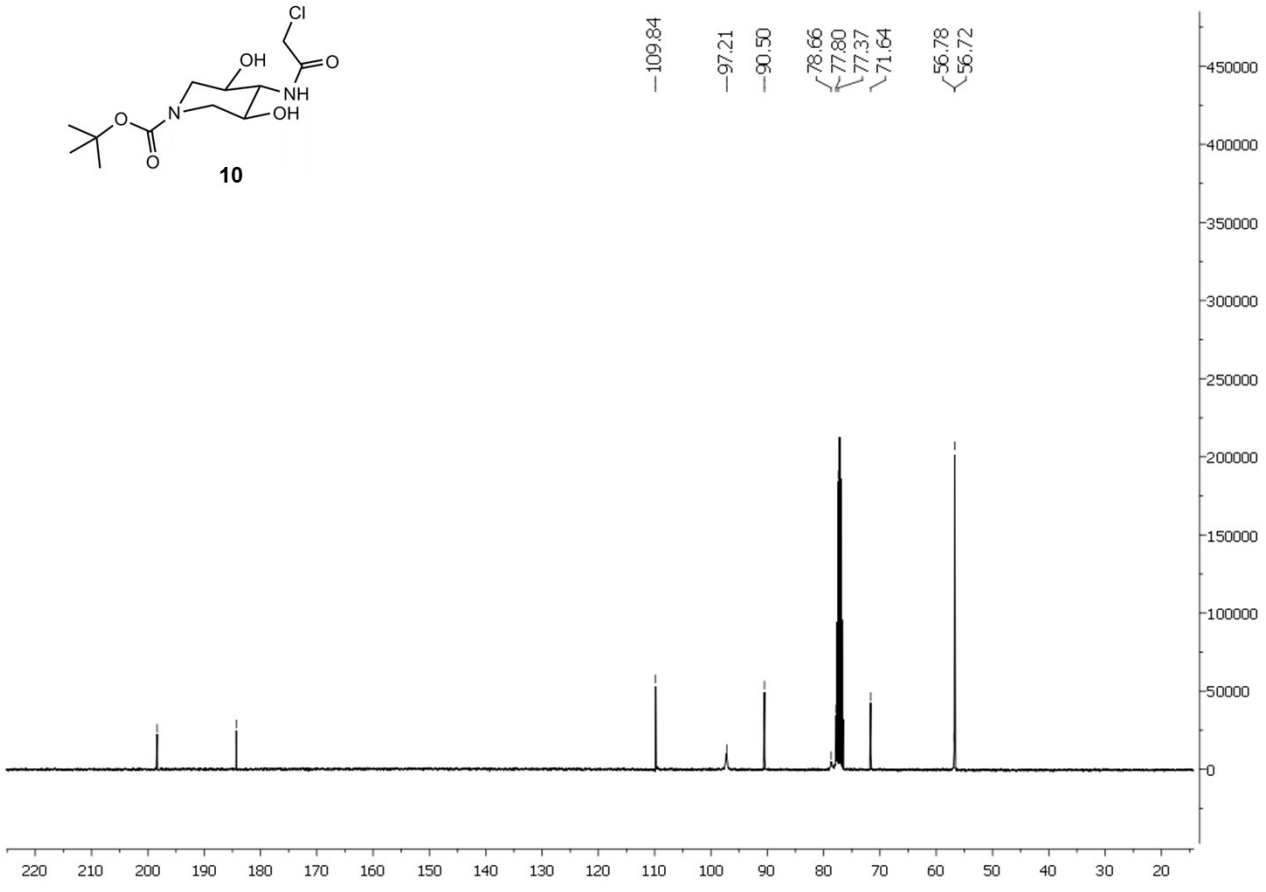
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56.72
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350000
300000
250000
200000
150000
100000
50000
0
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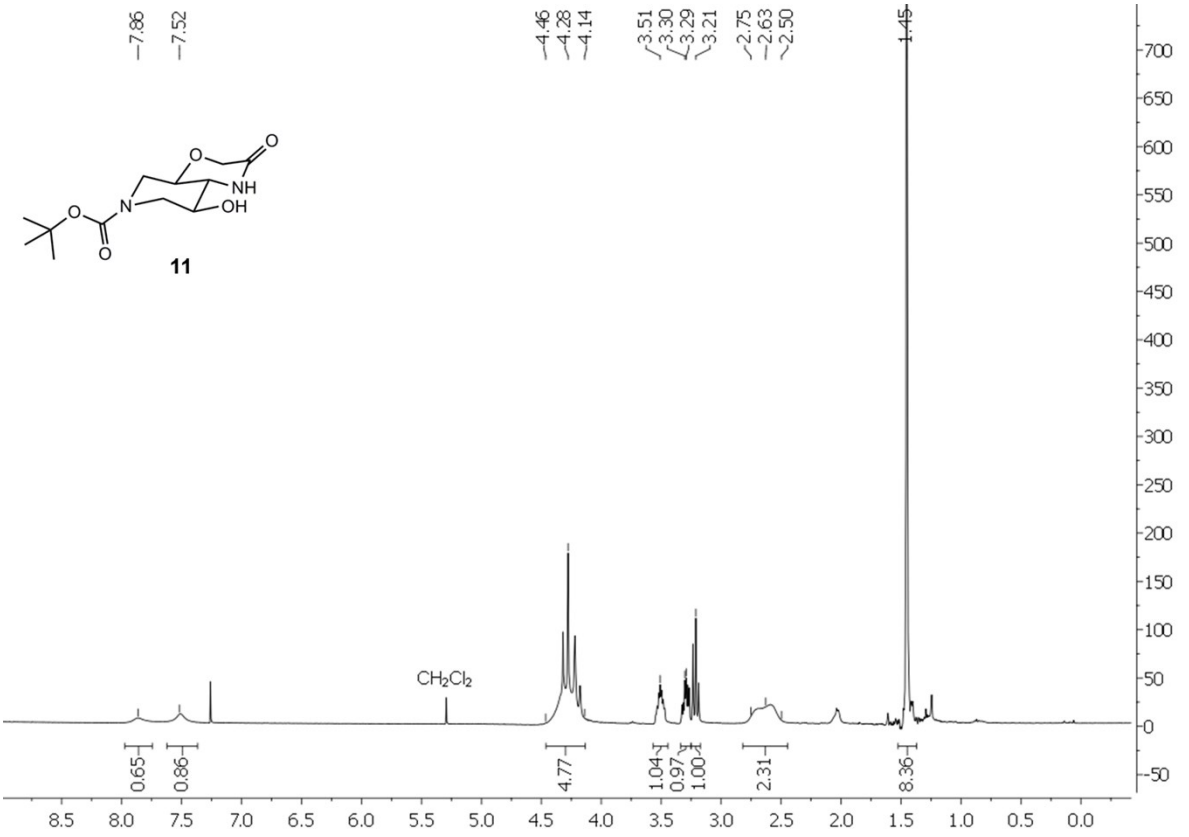
30
20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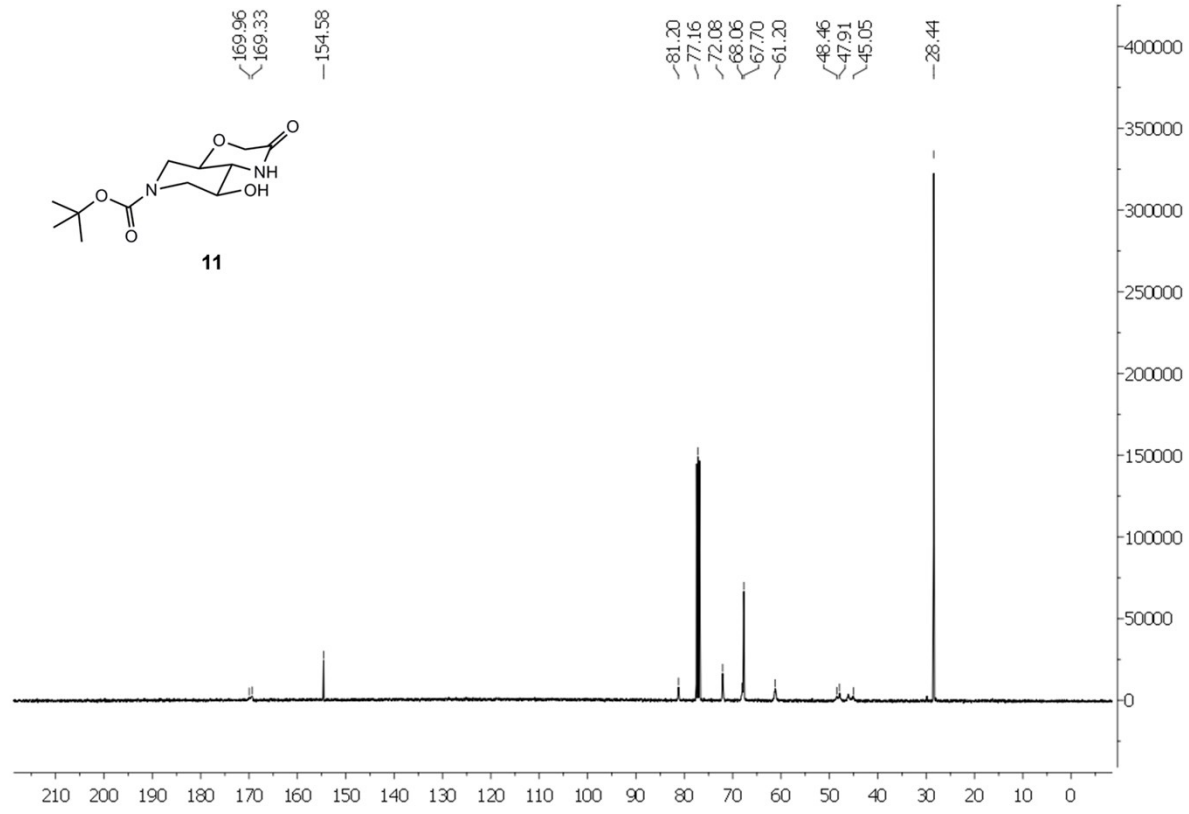
2.31
8.36
11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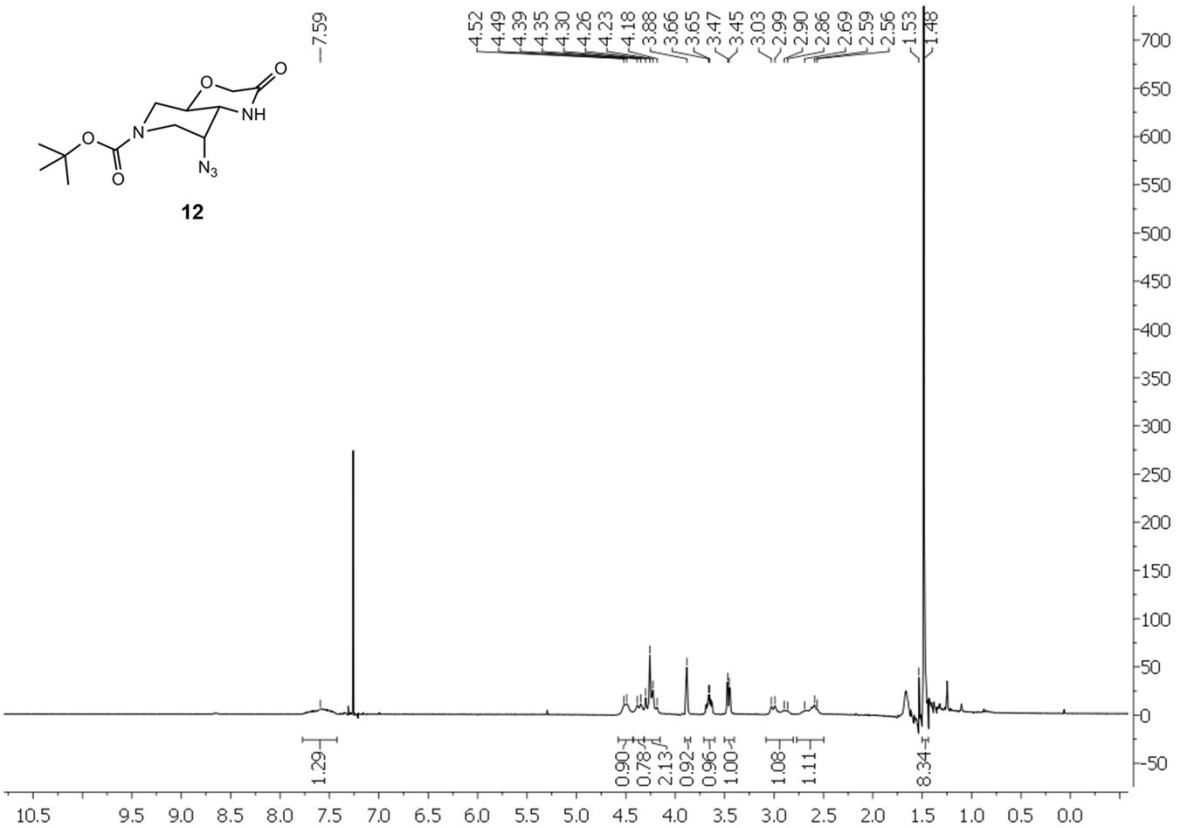
28.44
11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3.47
3.45
3.03
2.99
2.90
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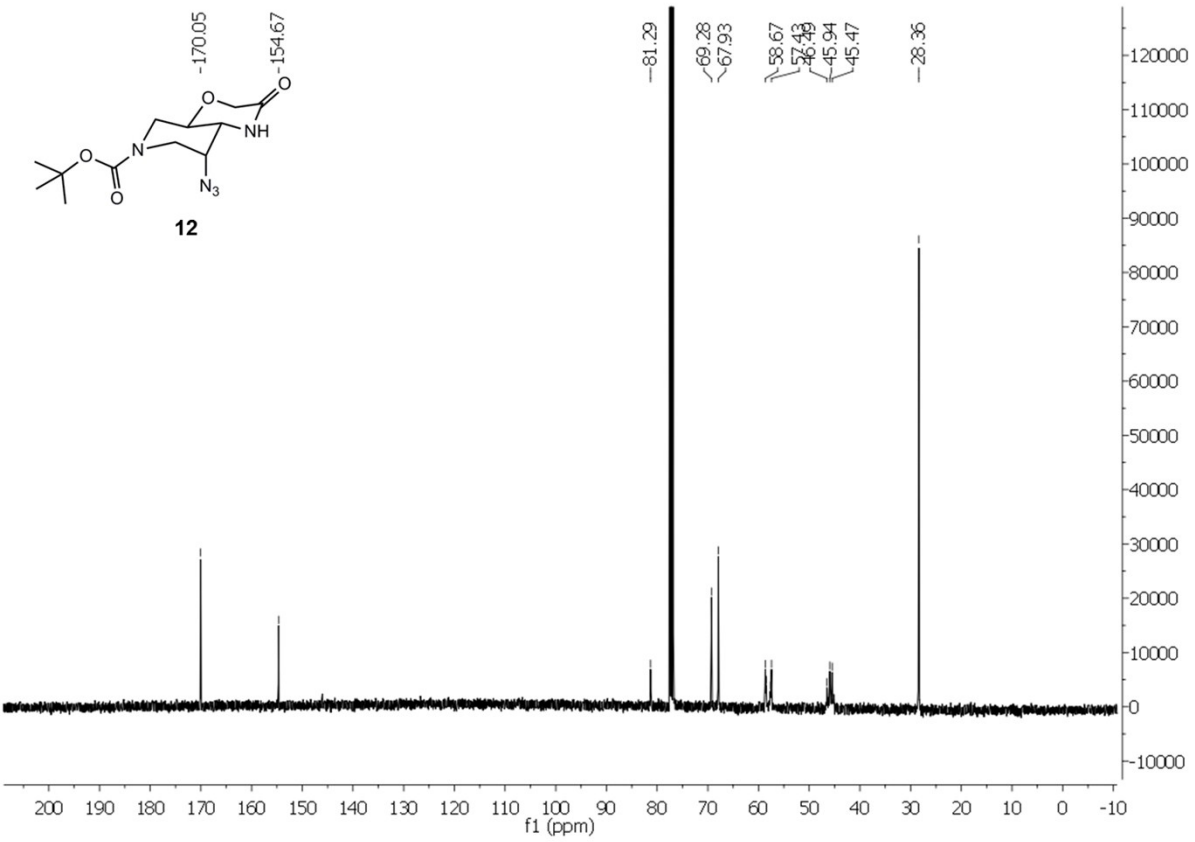
8.34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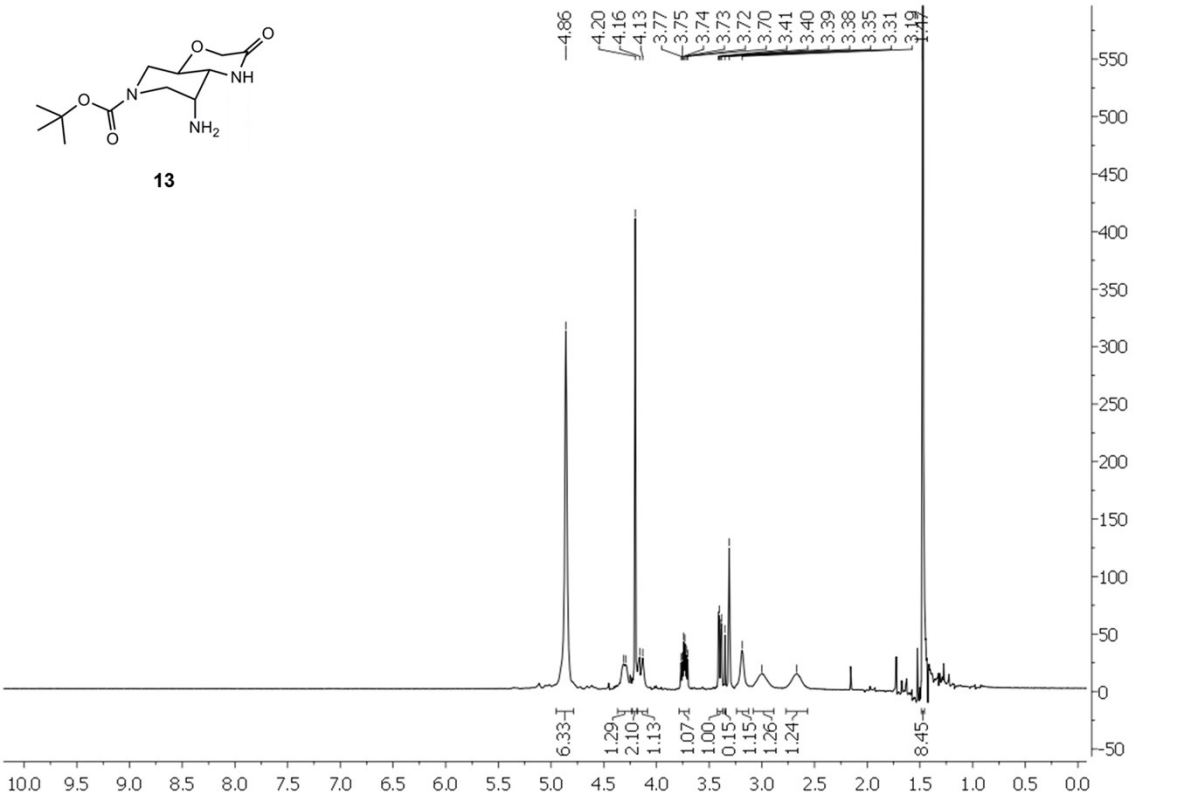
f1 (ppm)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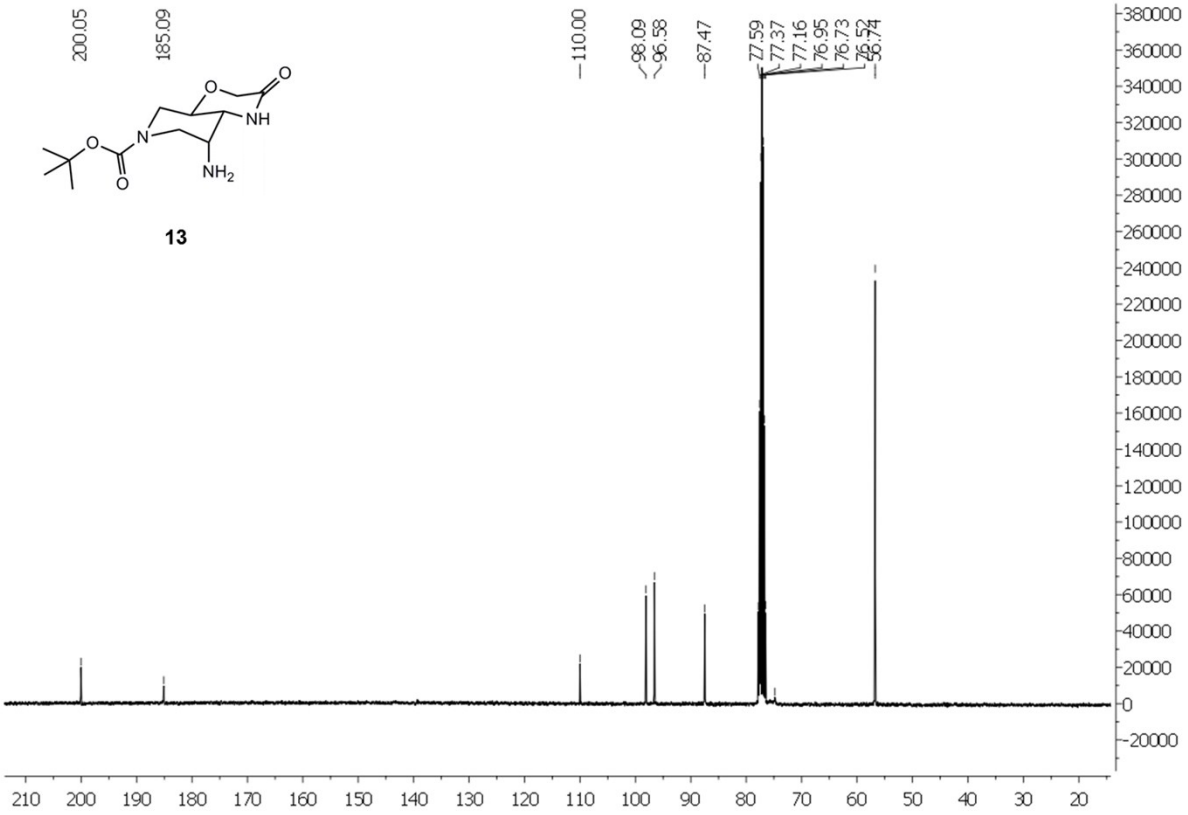
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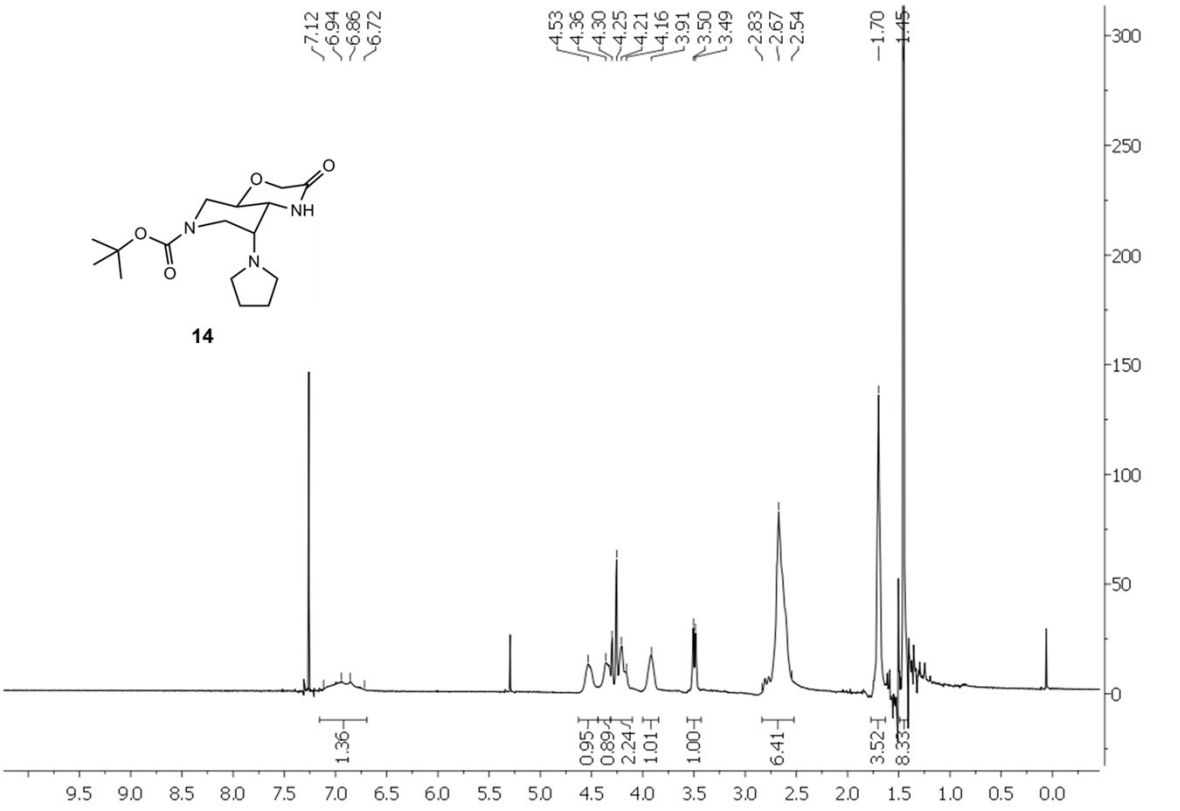
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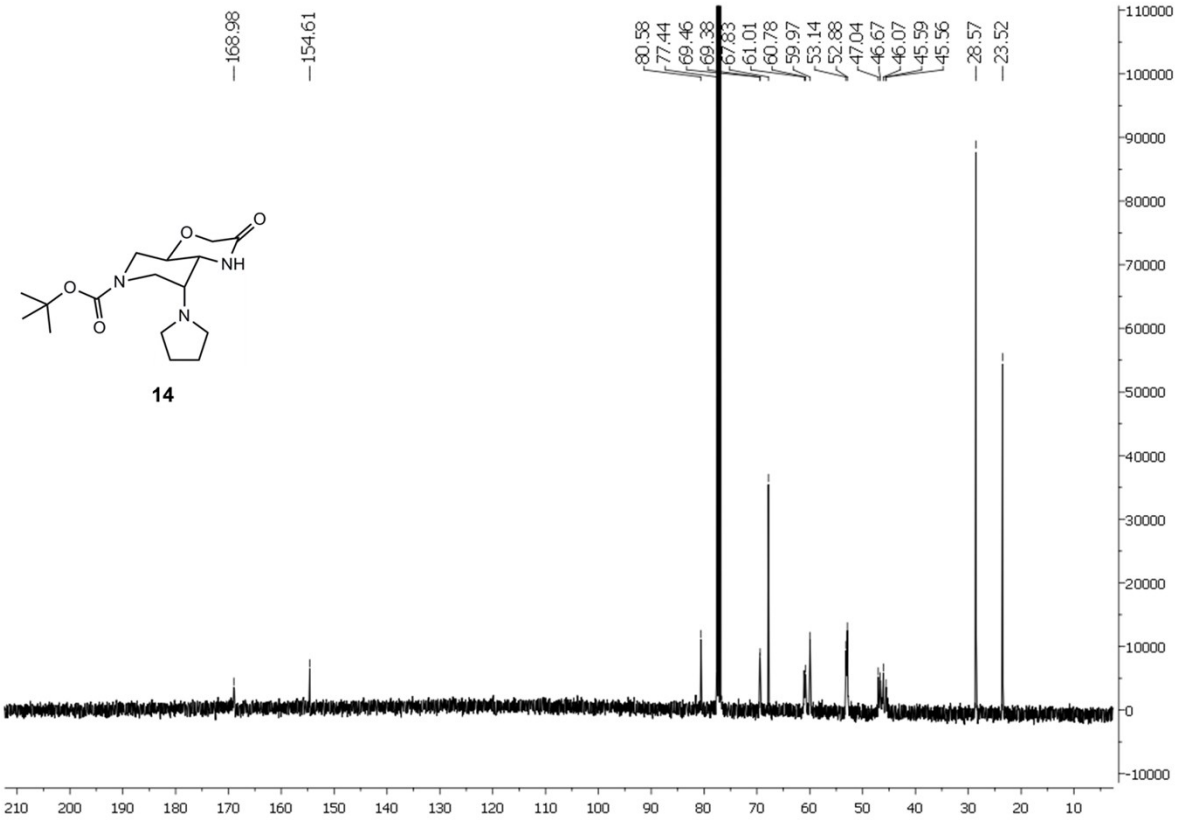
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46.07
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45.56
28.57
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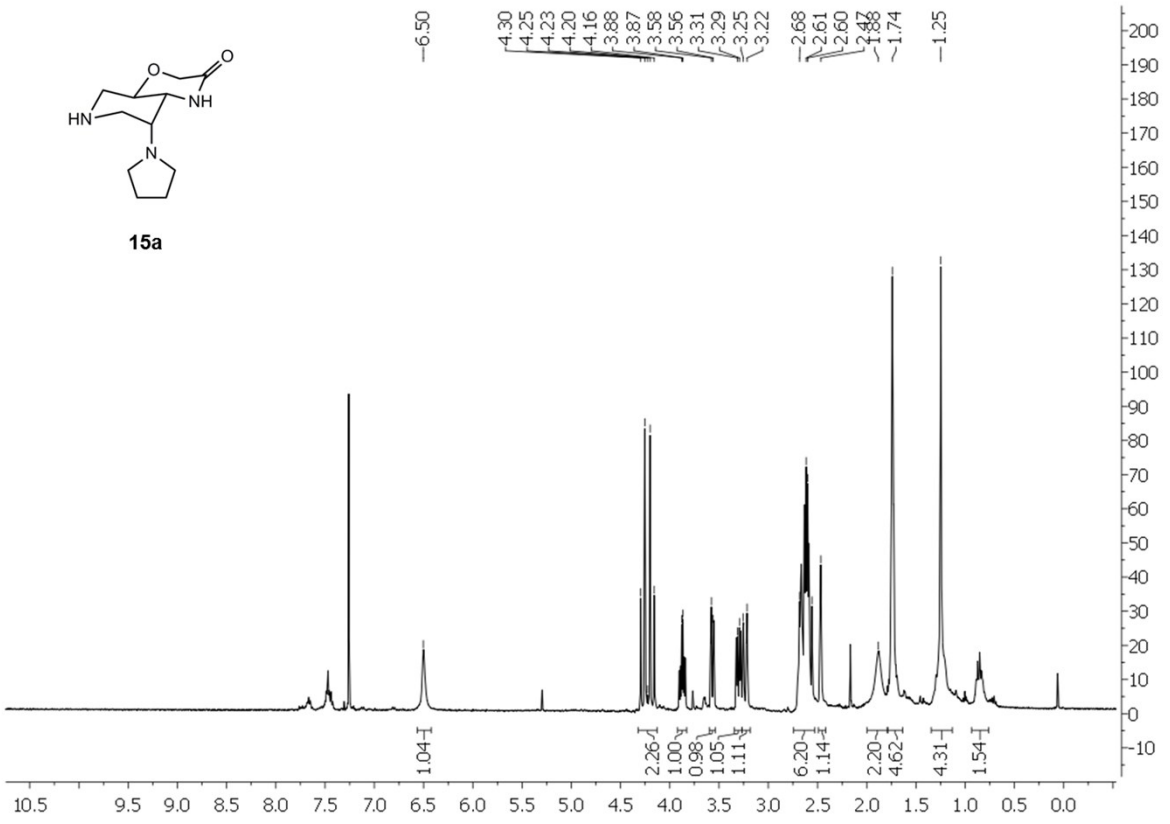
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N

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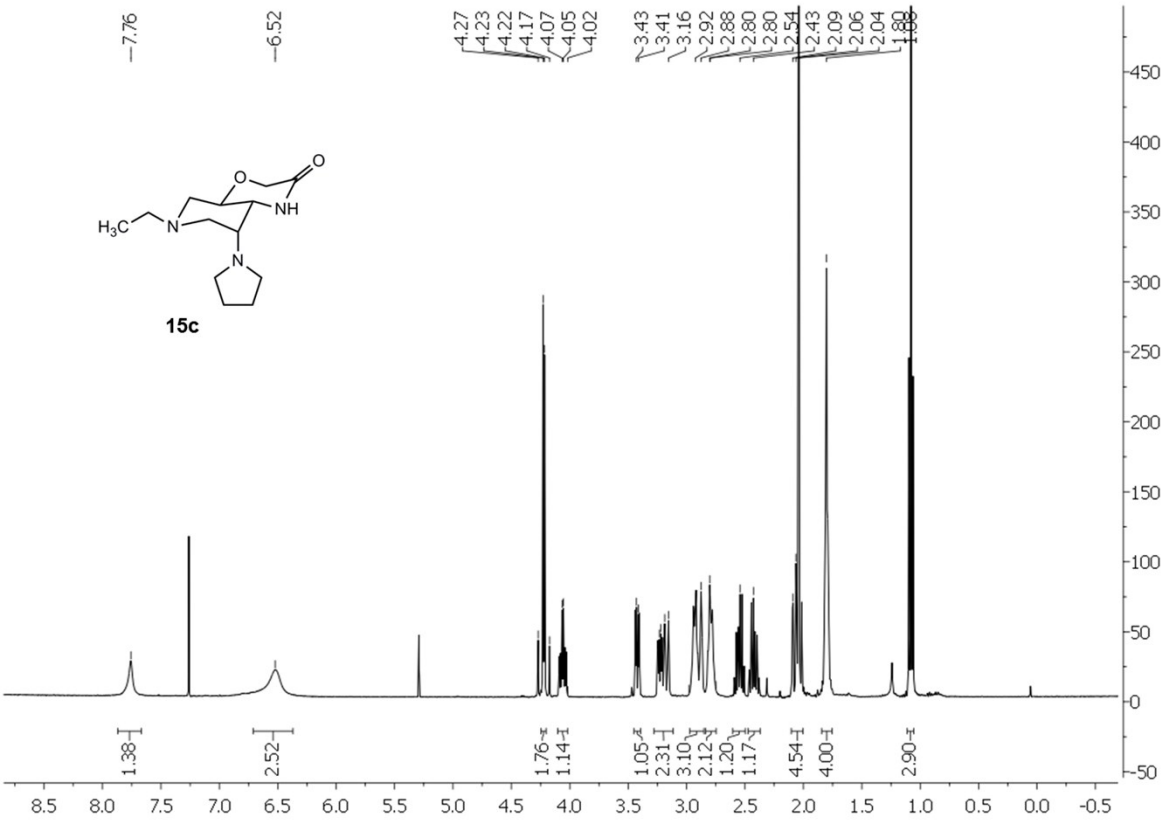
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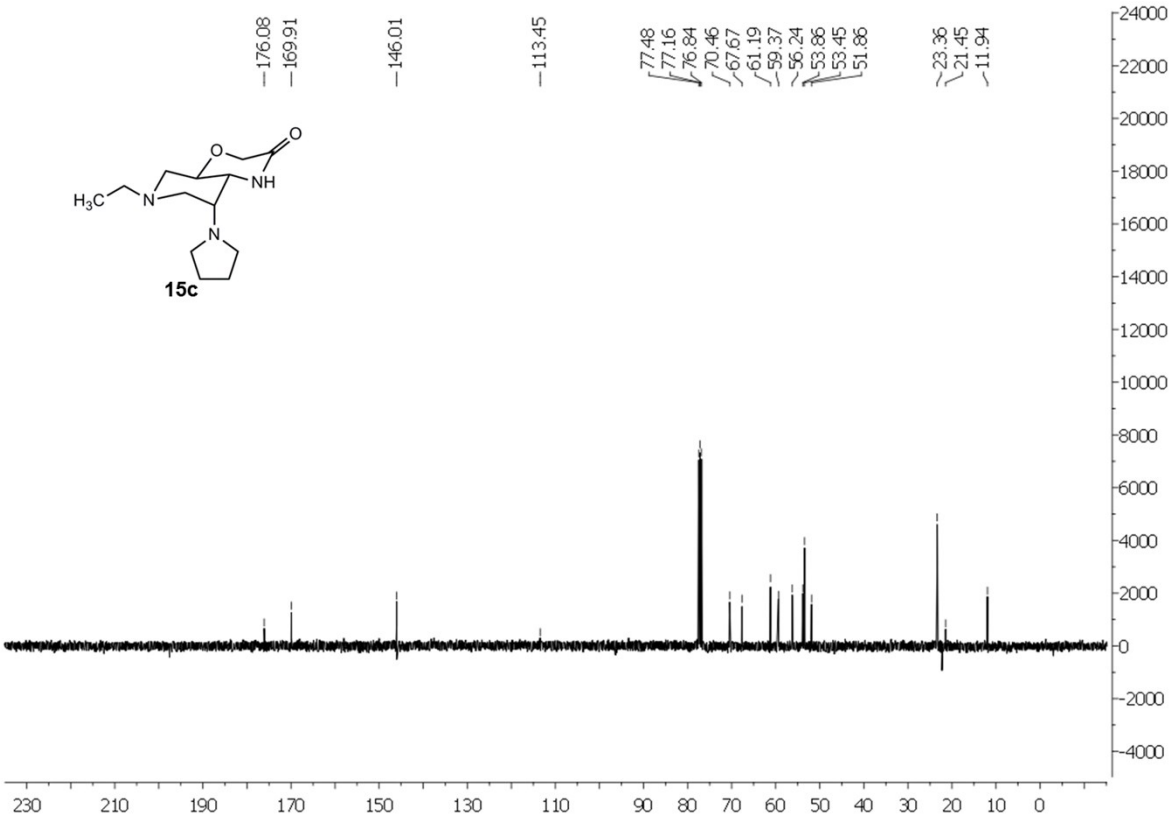
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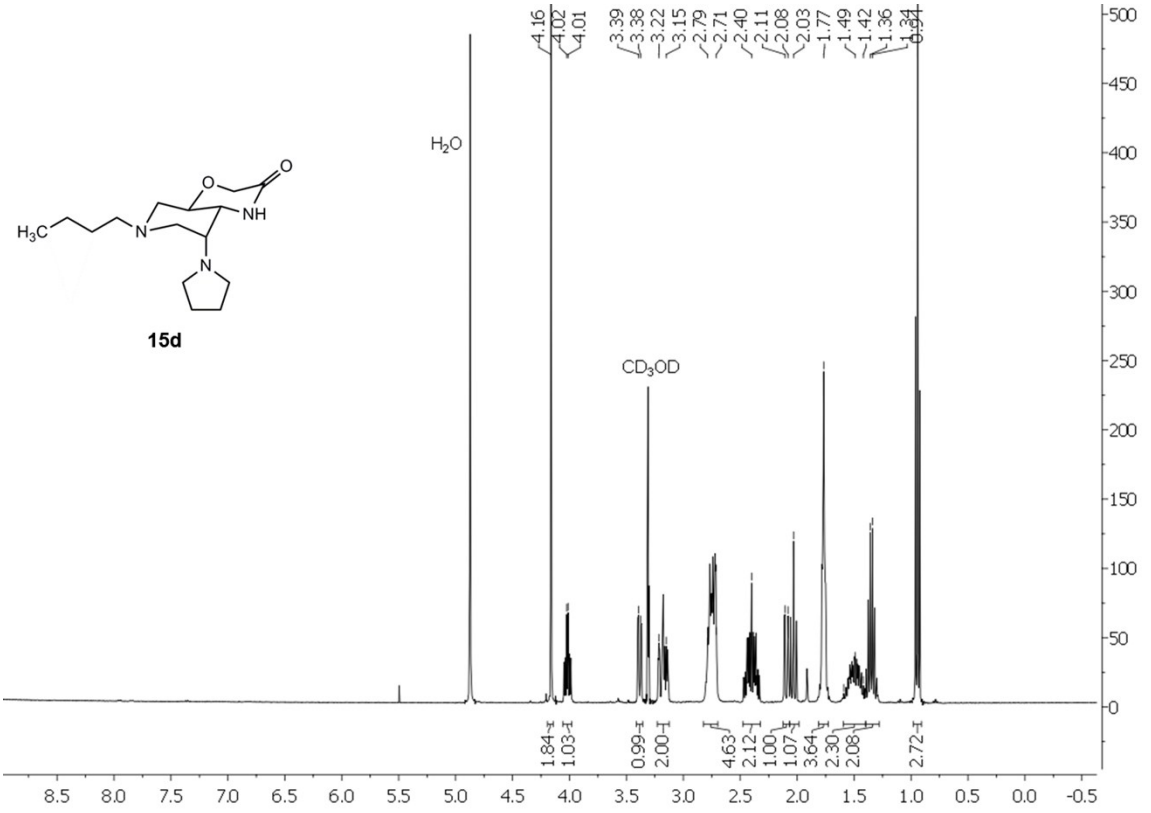
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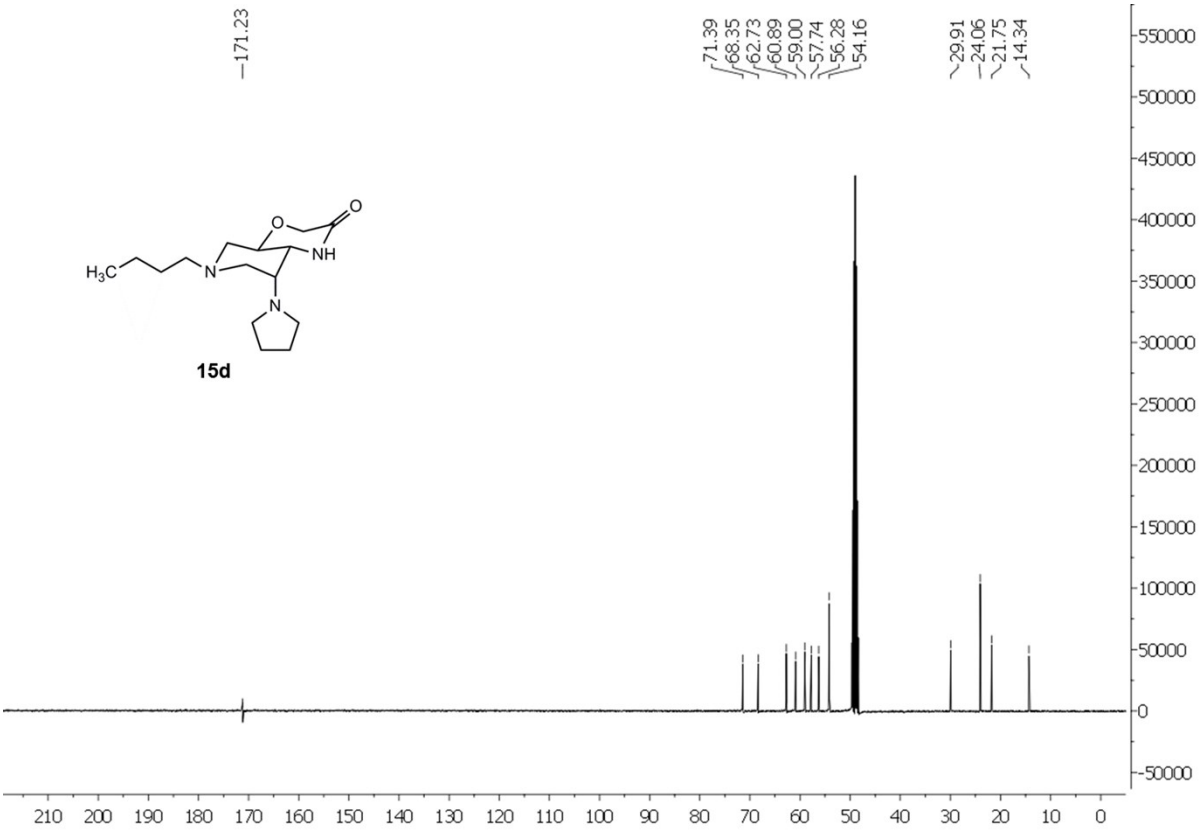
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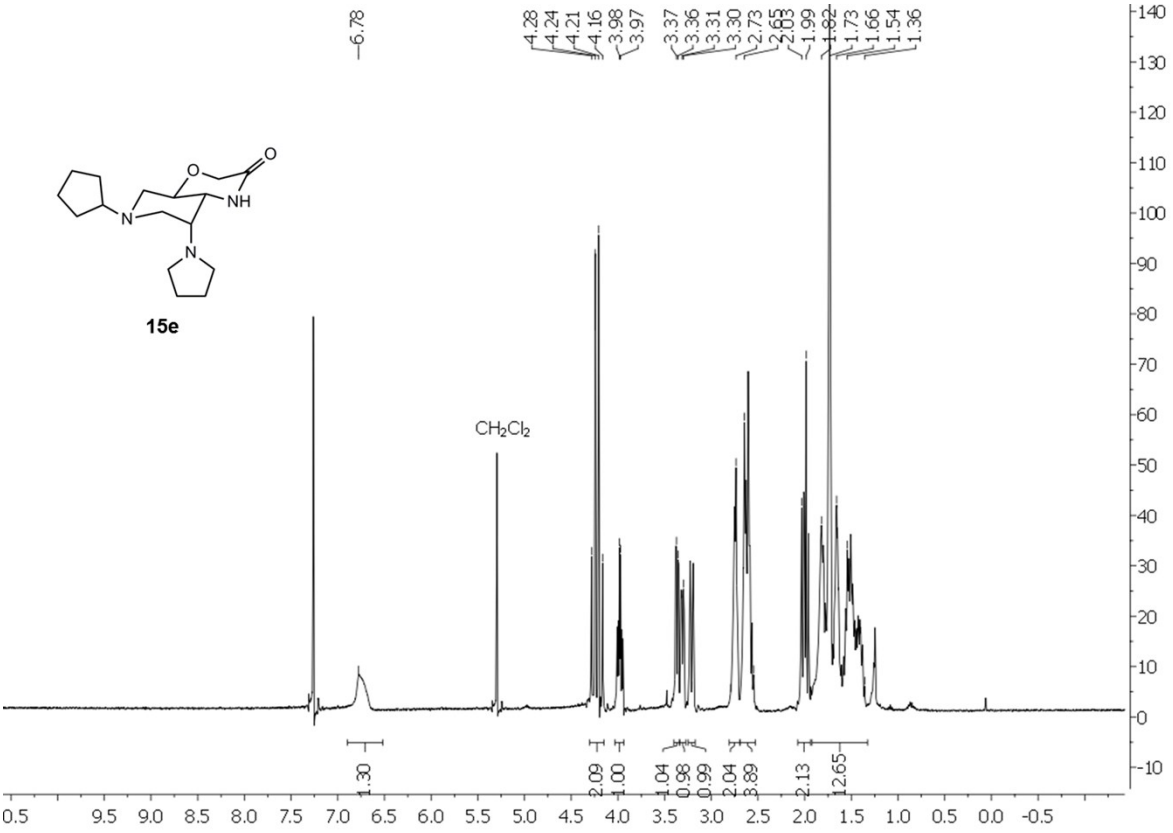
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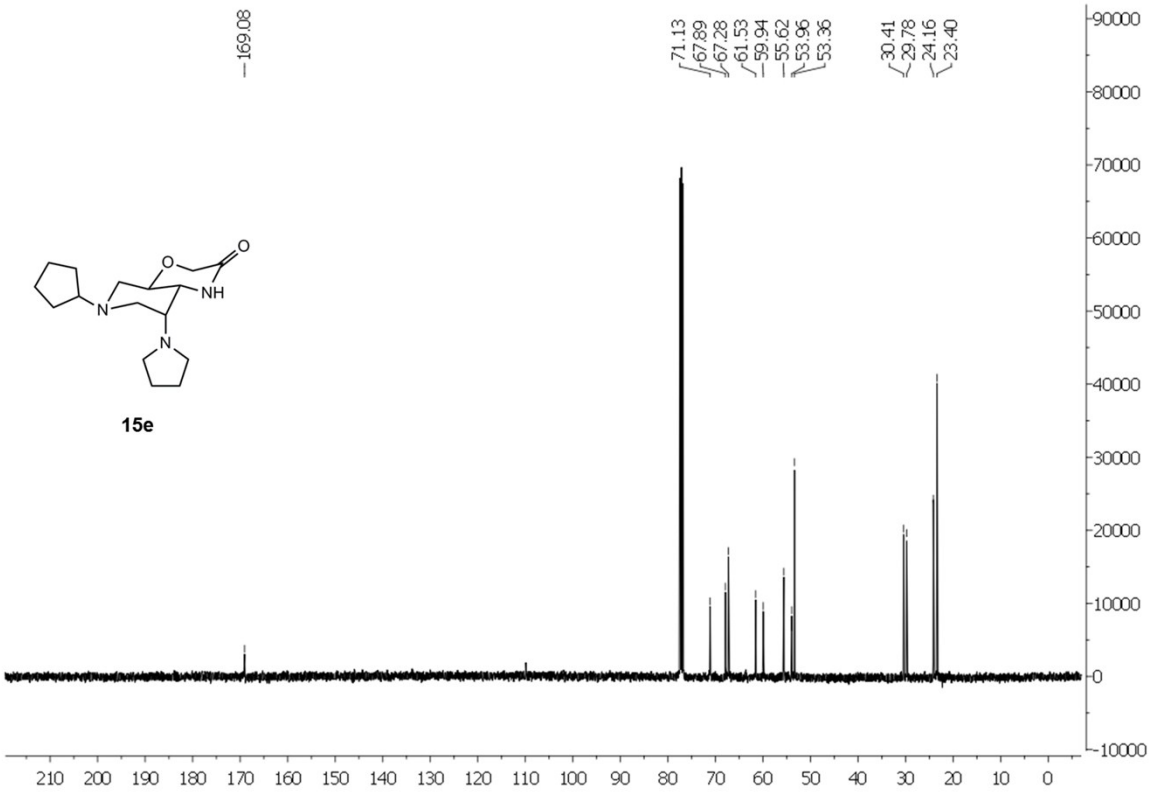
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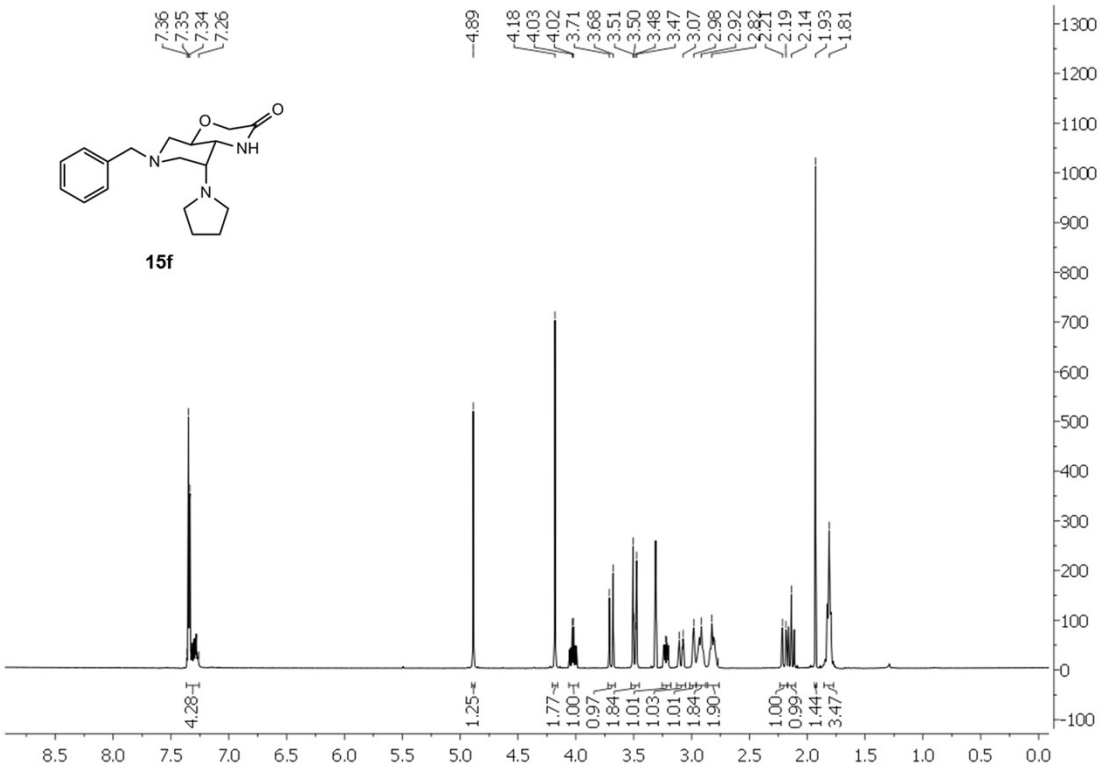
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3.47
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2.92
2.82
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2.19
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N
N
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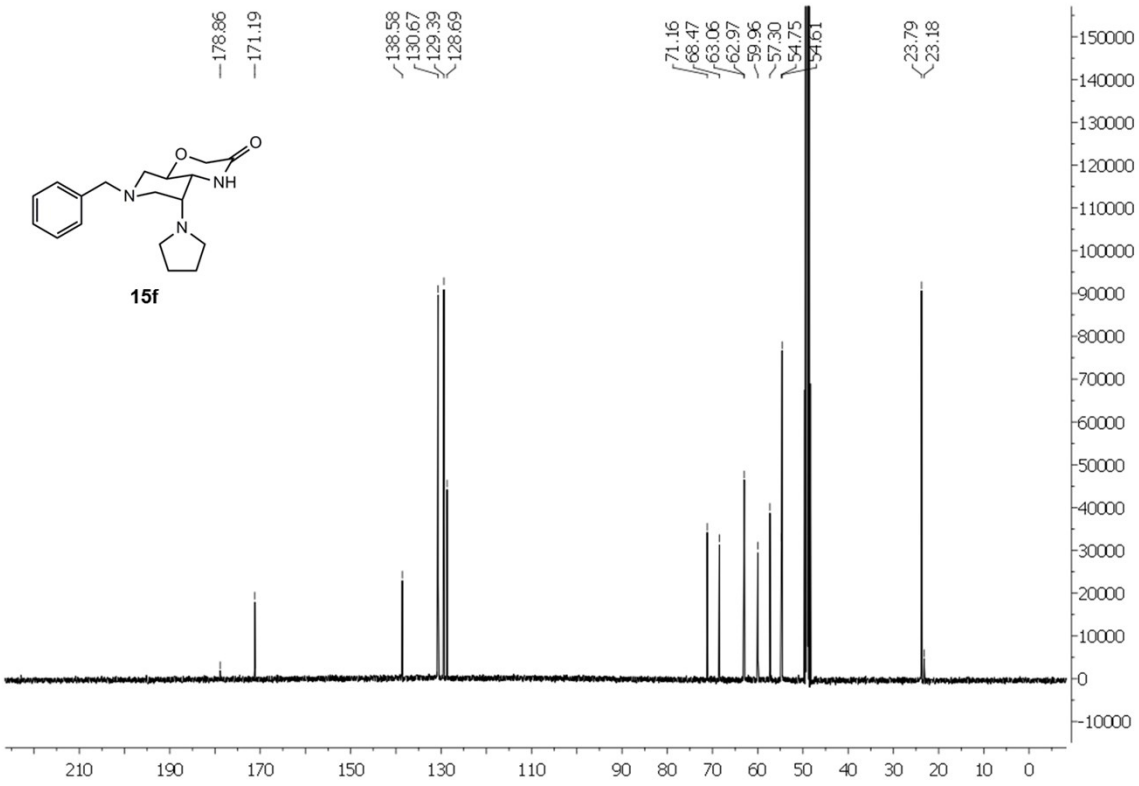
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N
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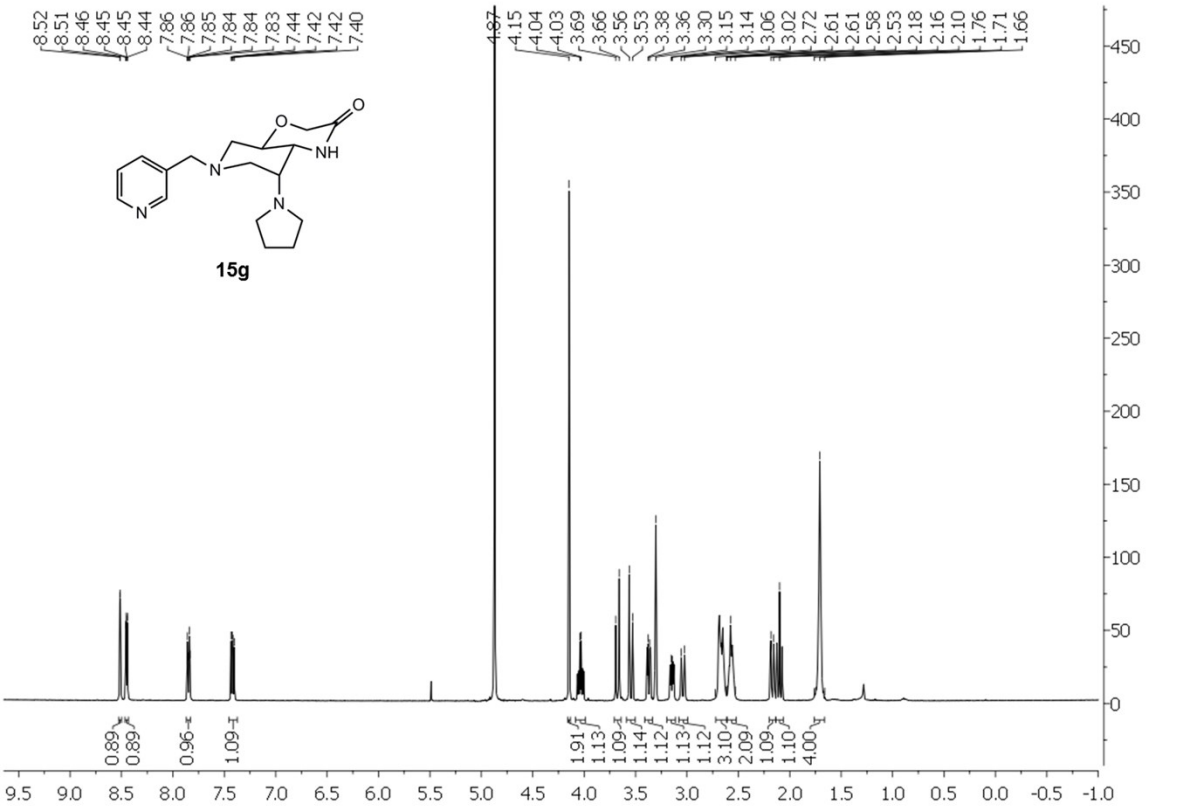
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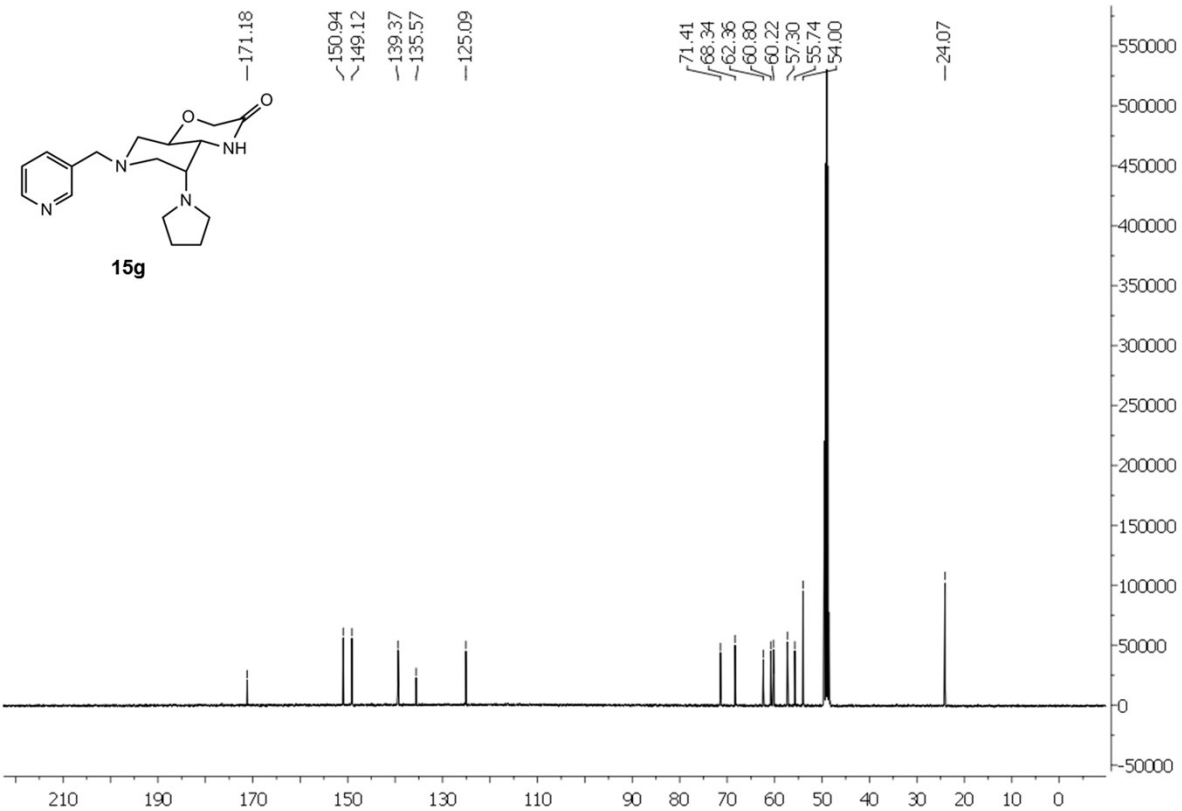
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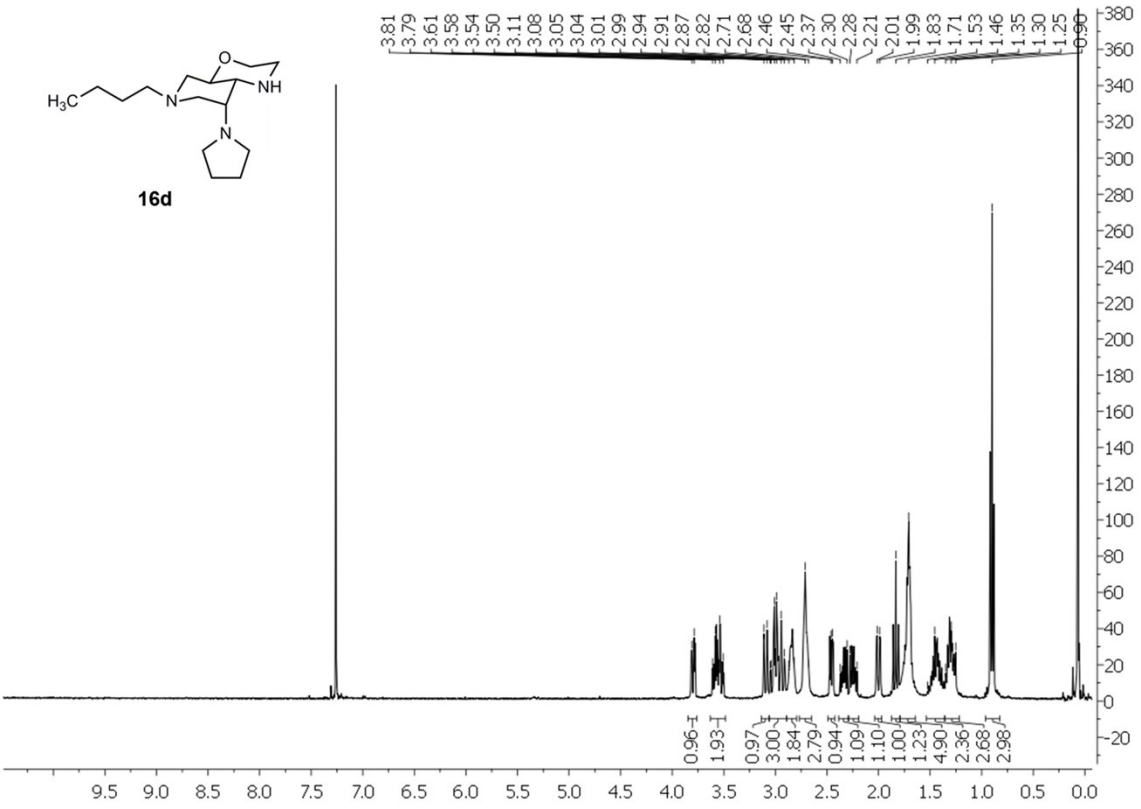
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2.91
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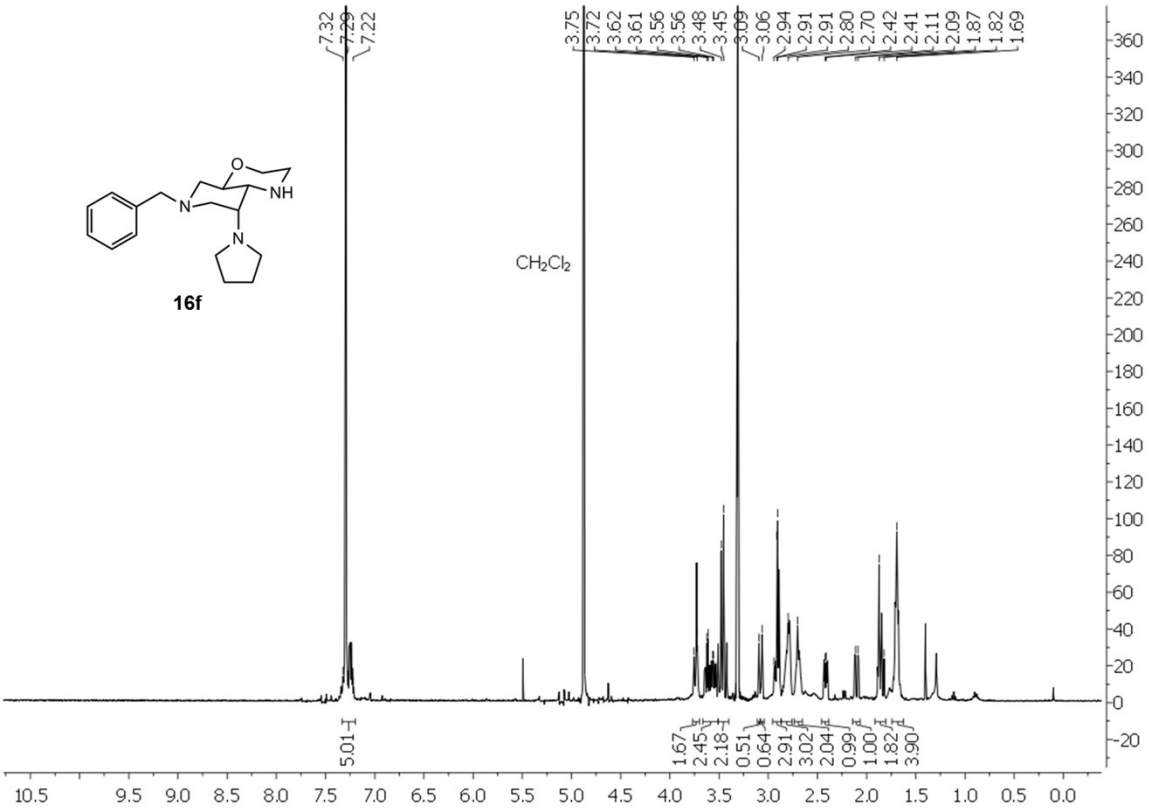
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3.45
3.09
3.06
2.94
2.91
2.91
2.80
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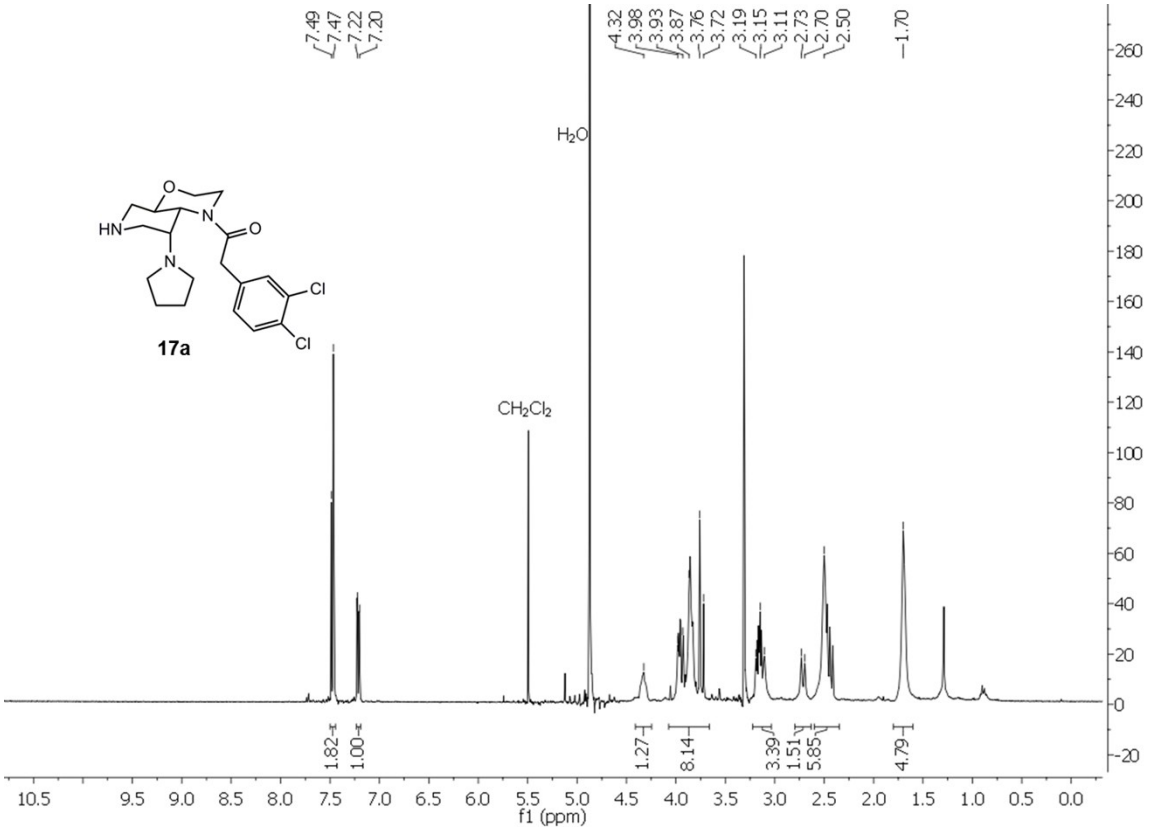
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2.70
2.50
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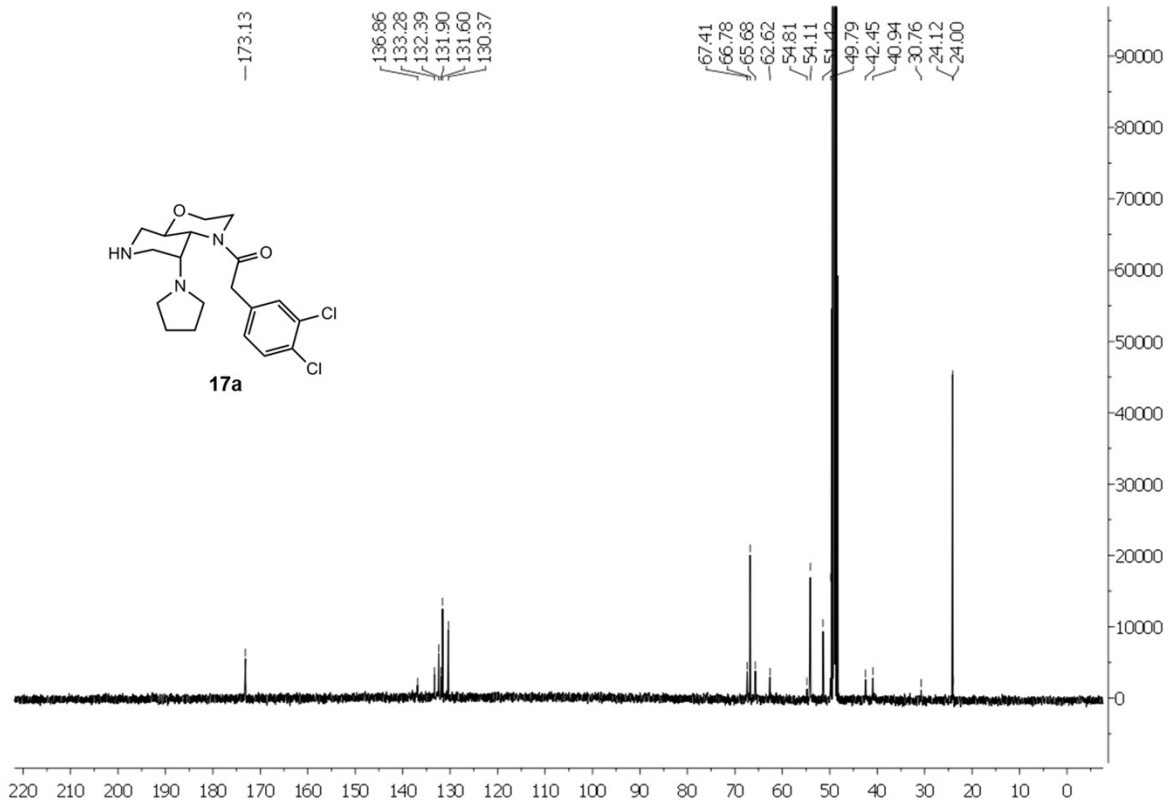
f1 (ppm)
17a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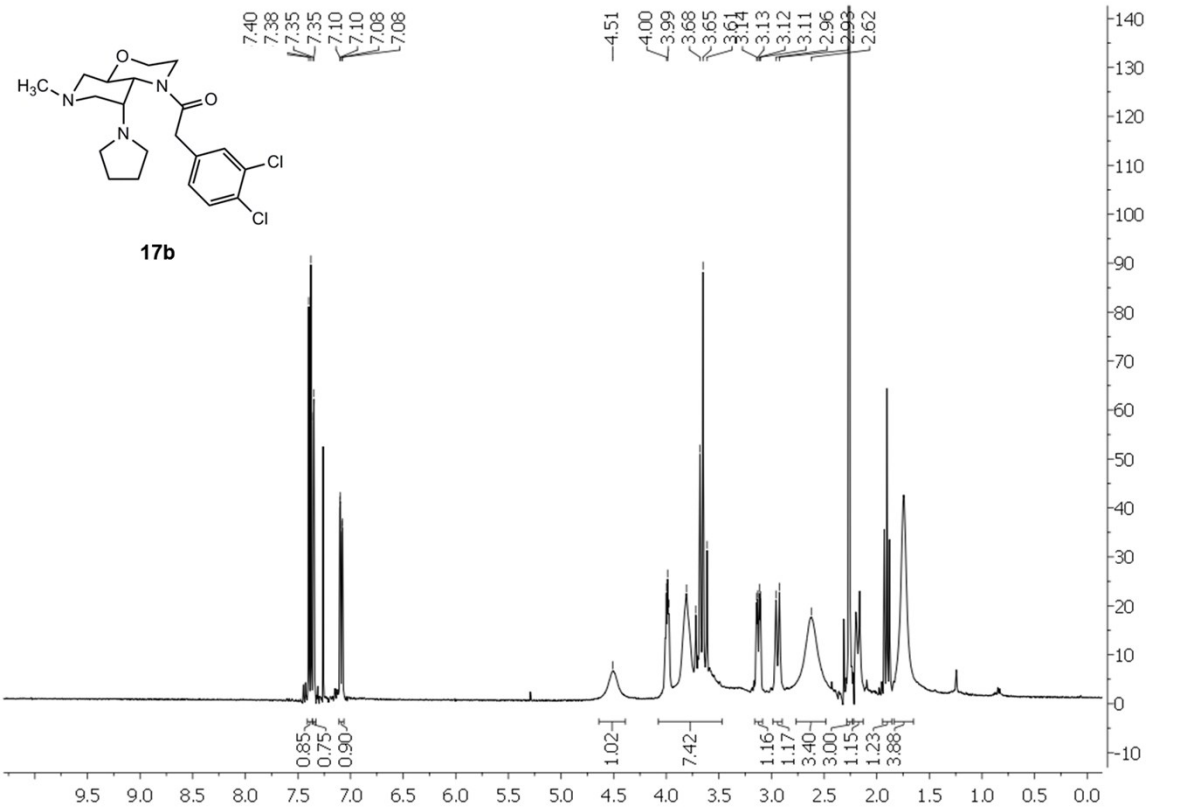
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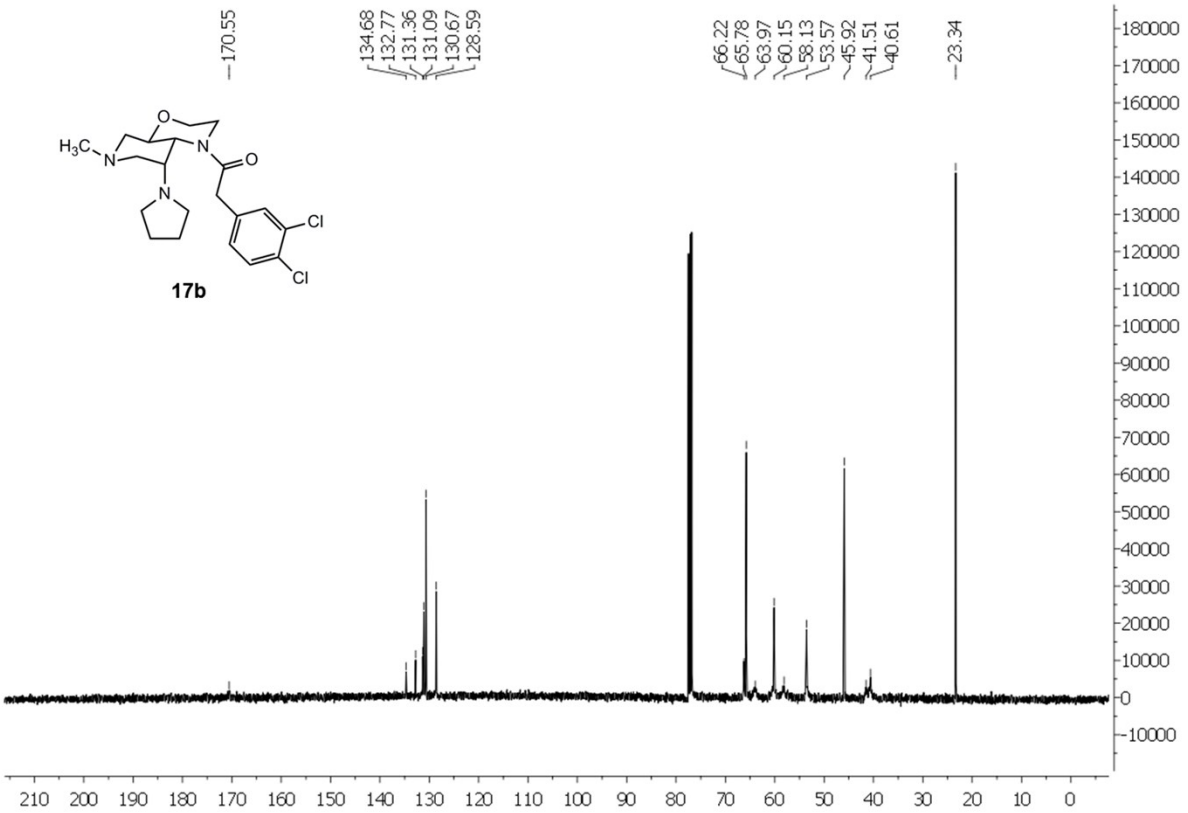
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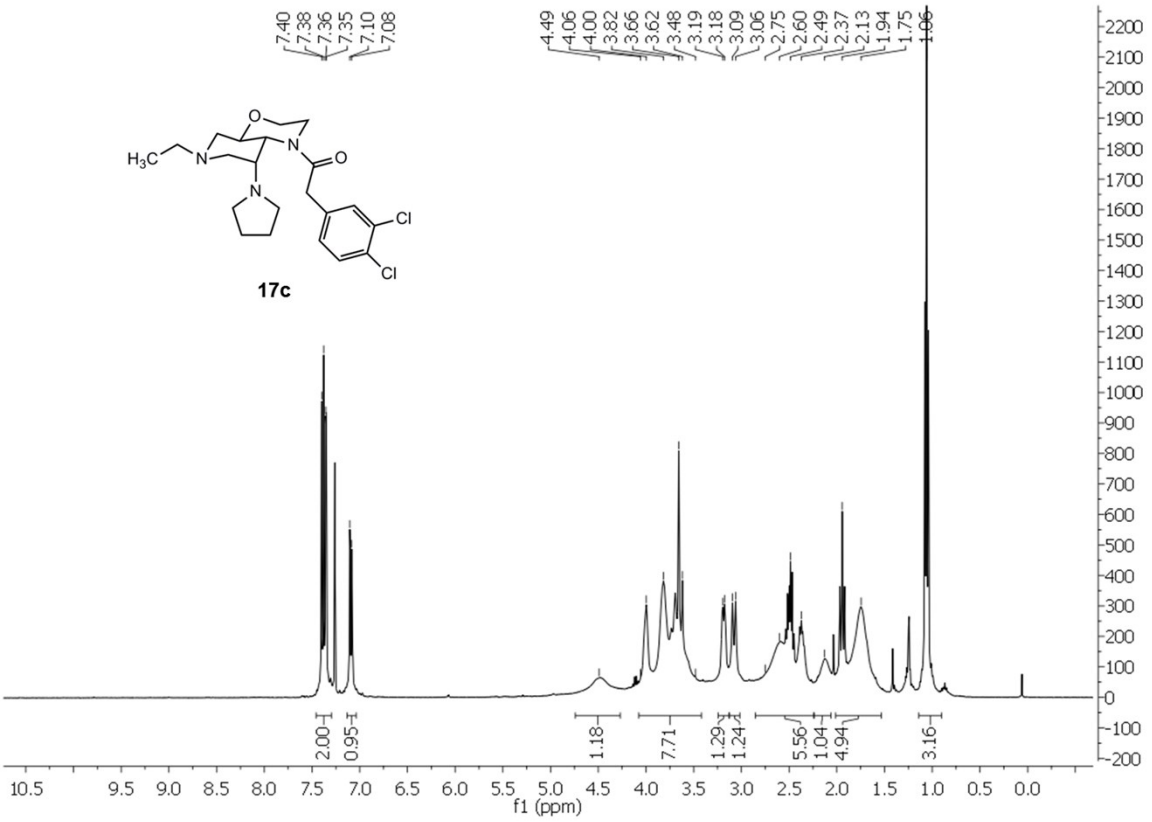
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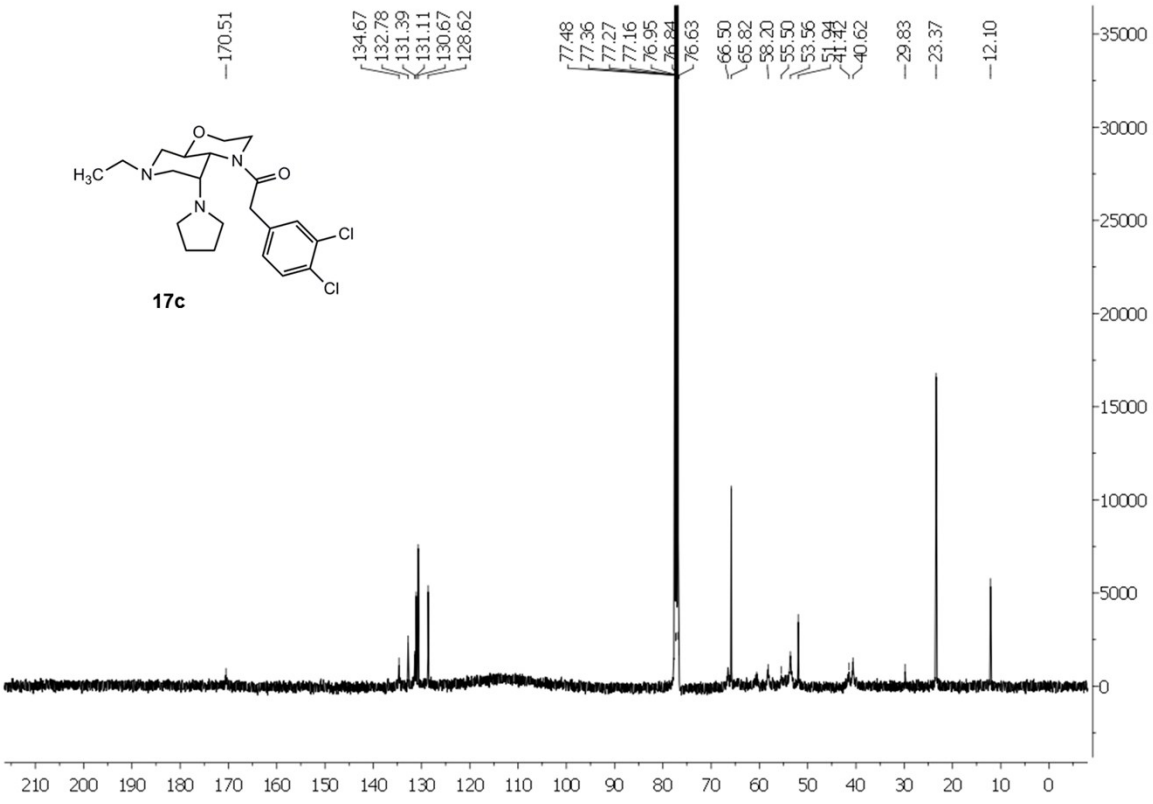
f1 (ppm)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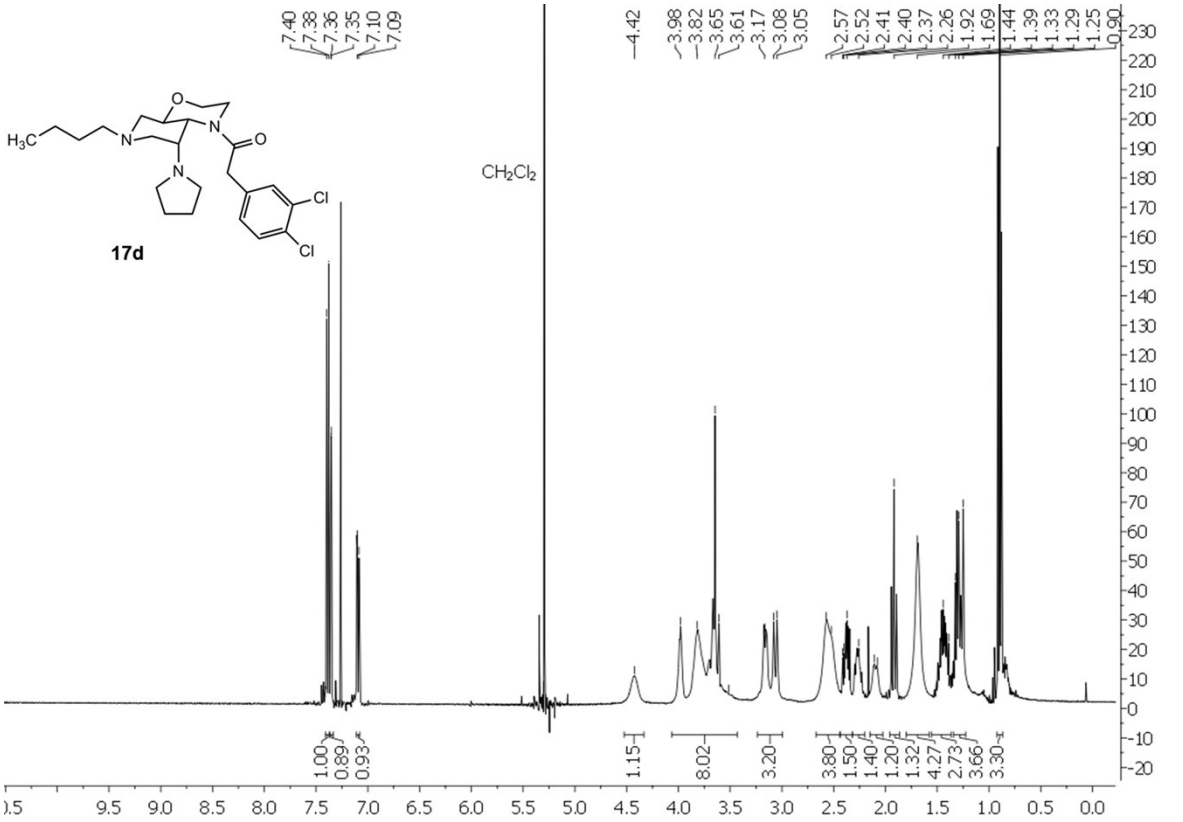
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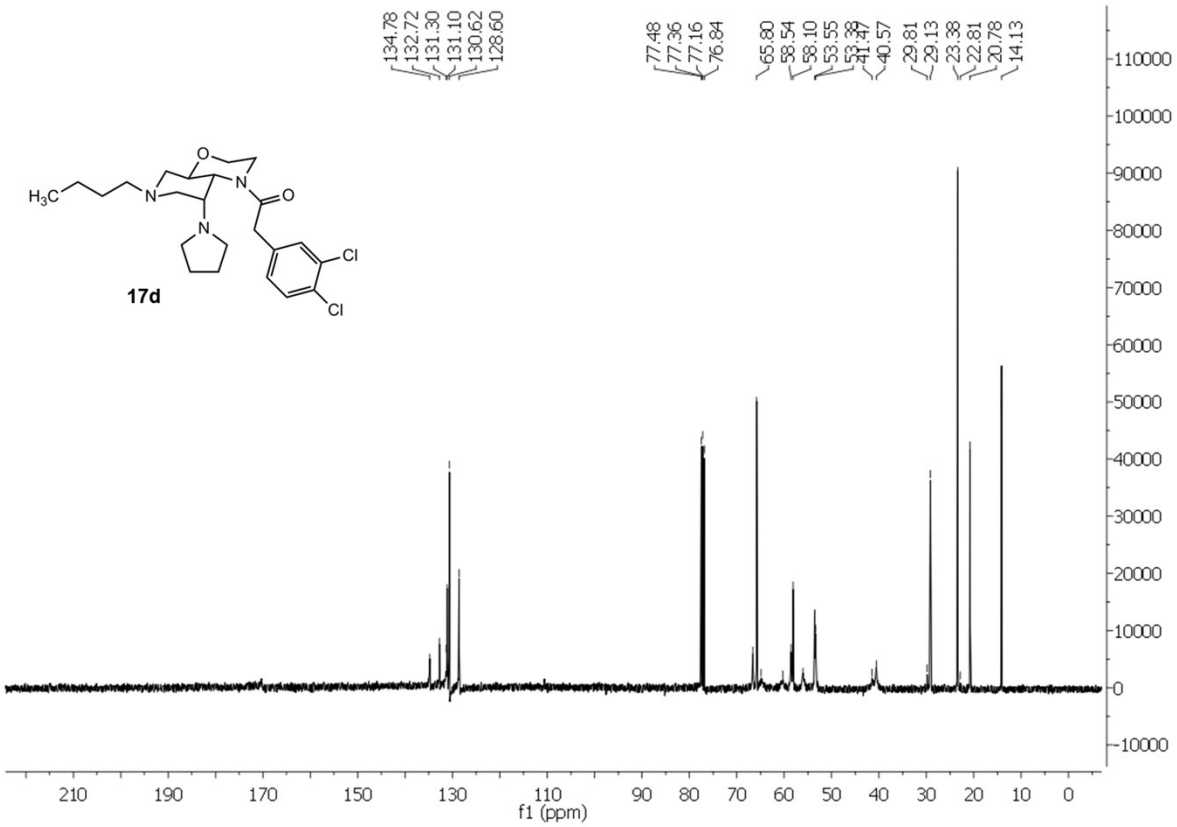
CH2Cl2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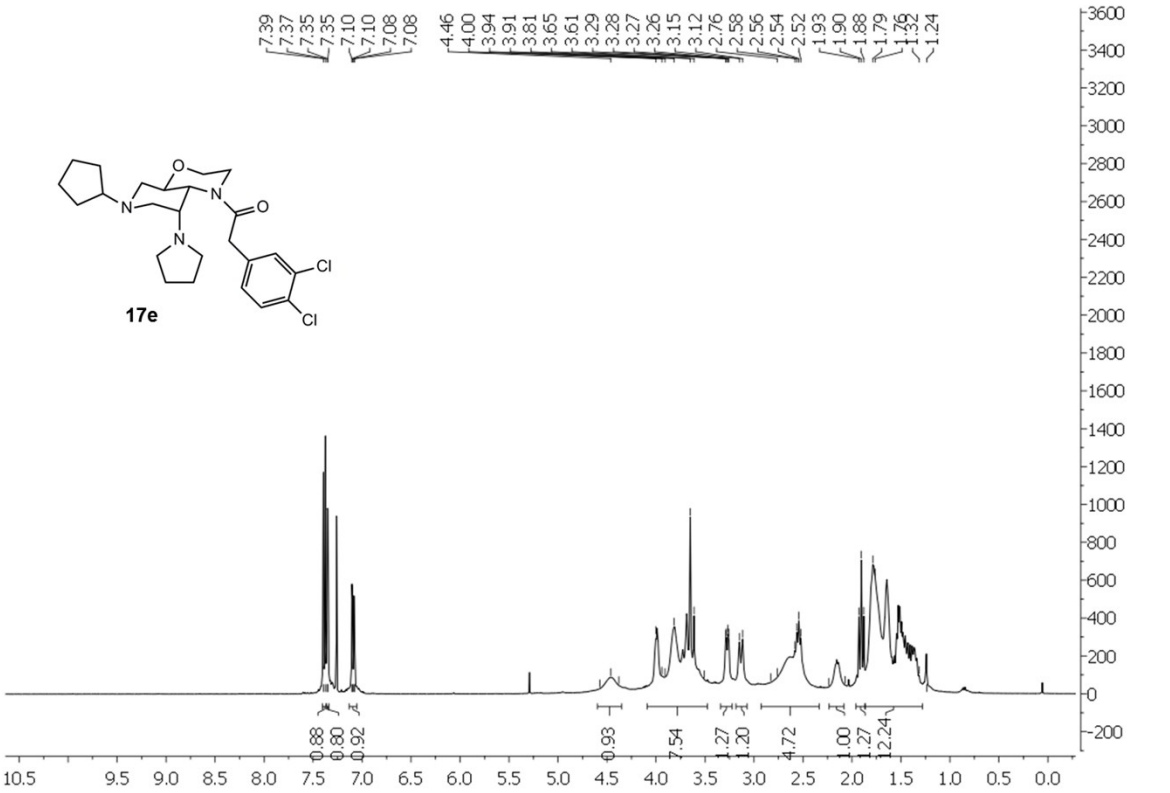
f1 (ppm)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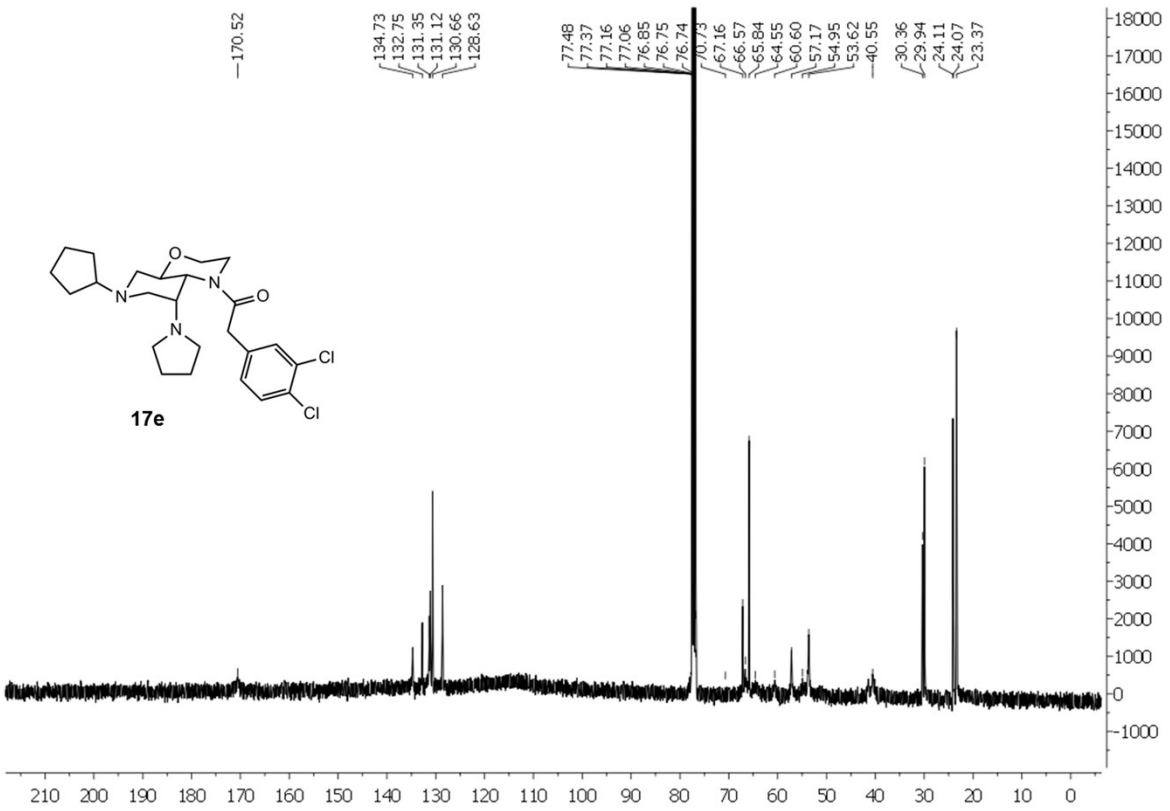
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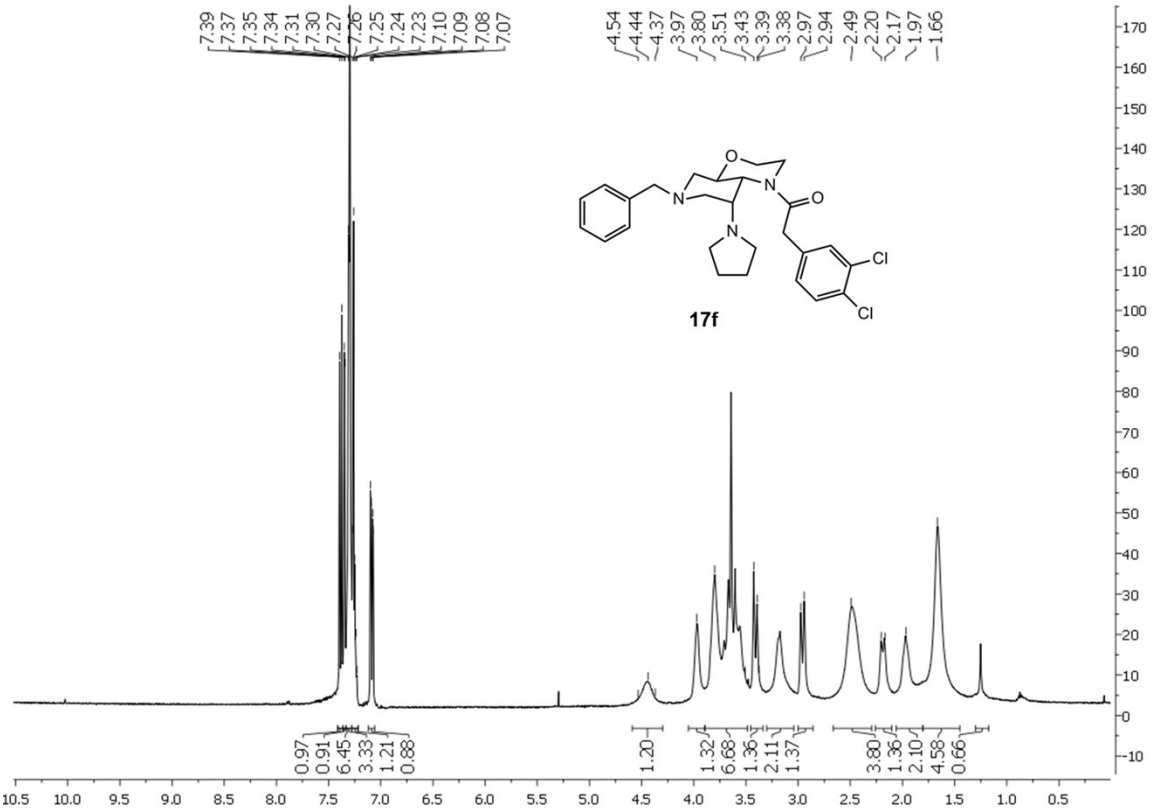
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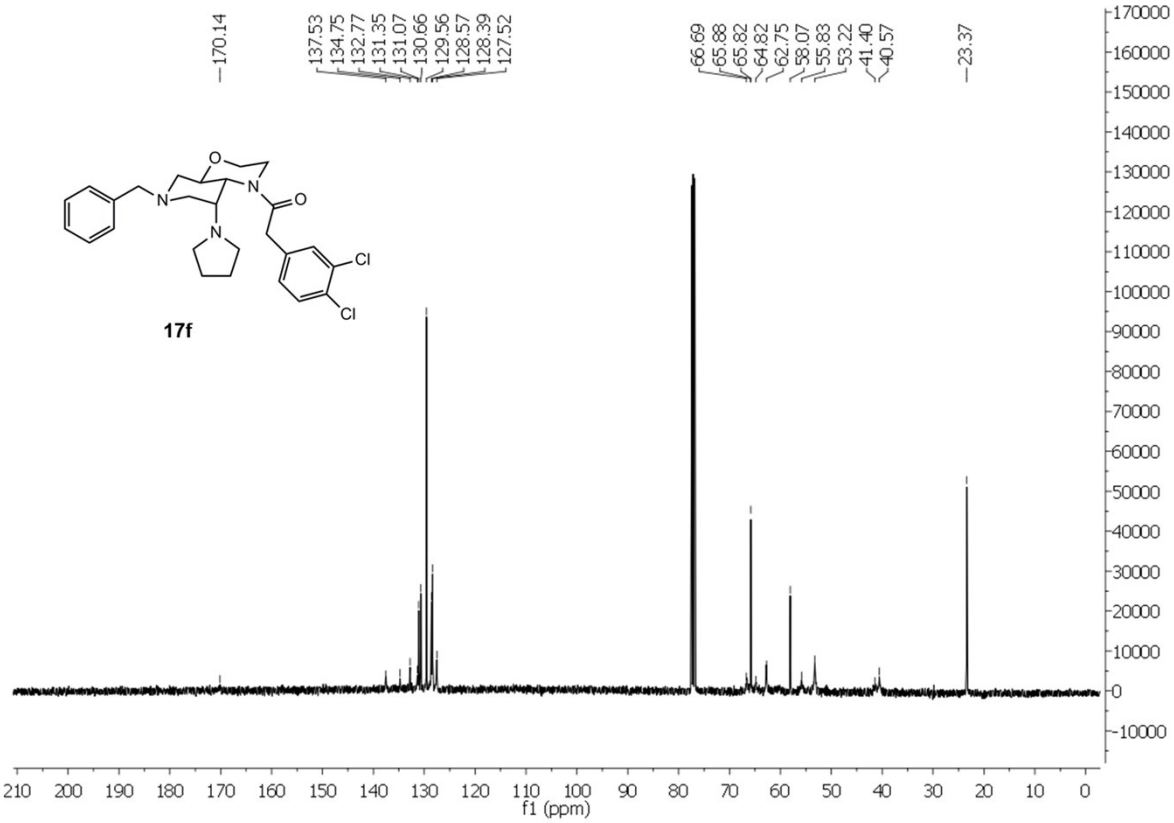
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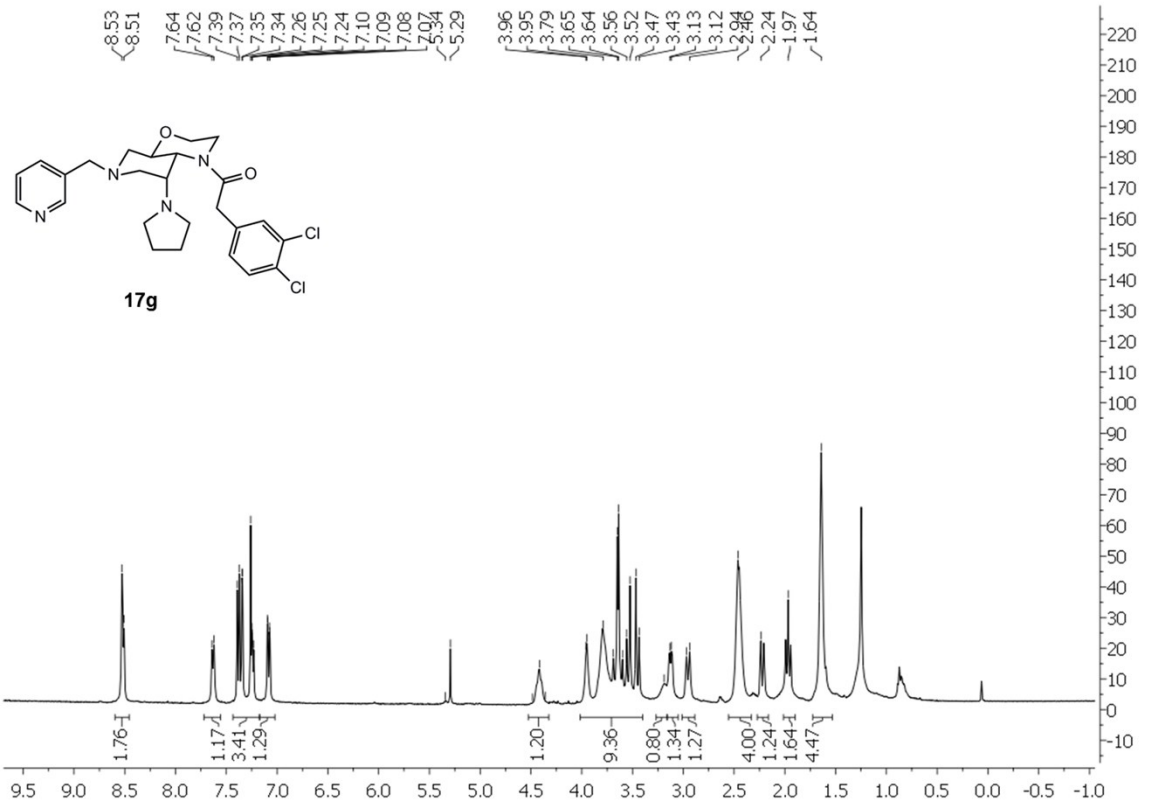
17f
f1 (ppm)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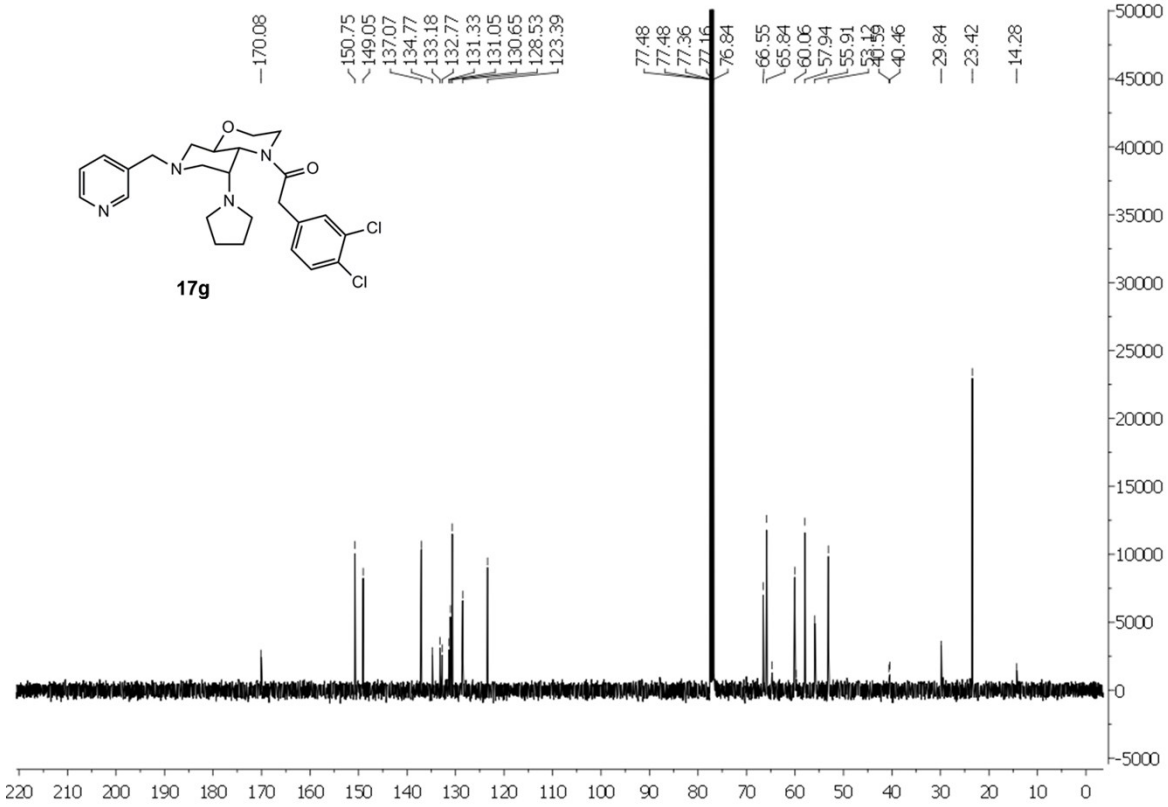
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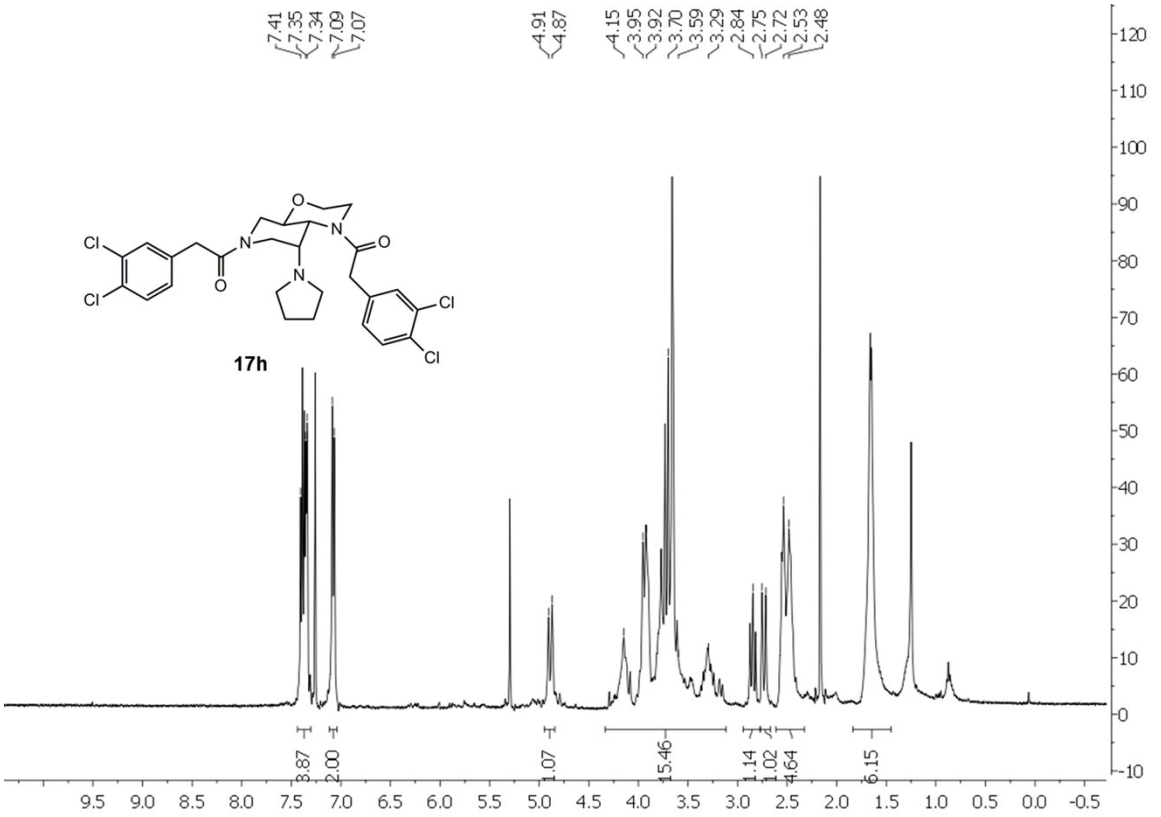
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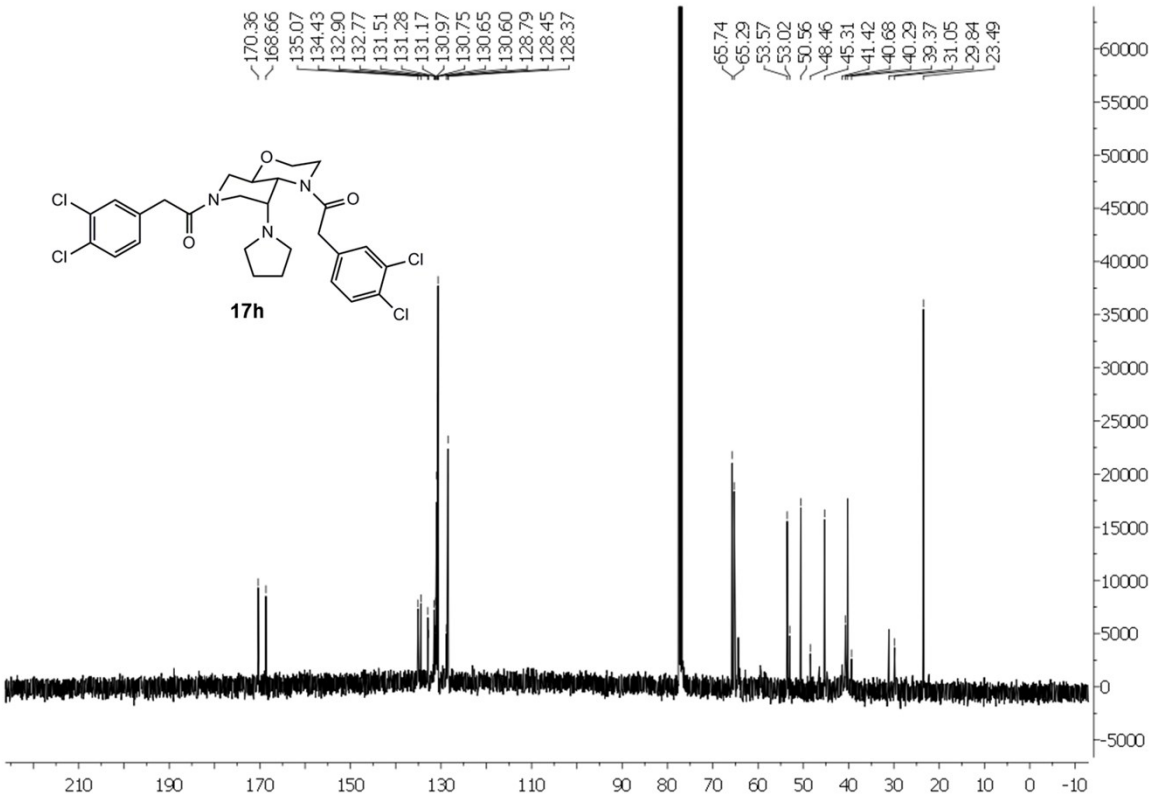
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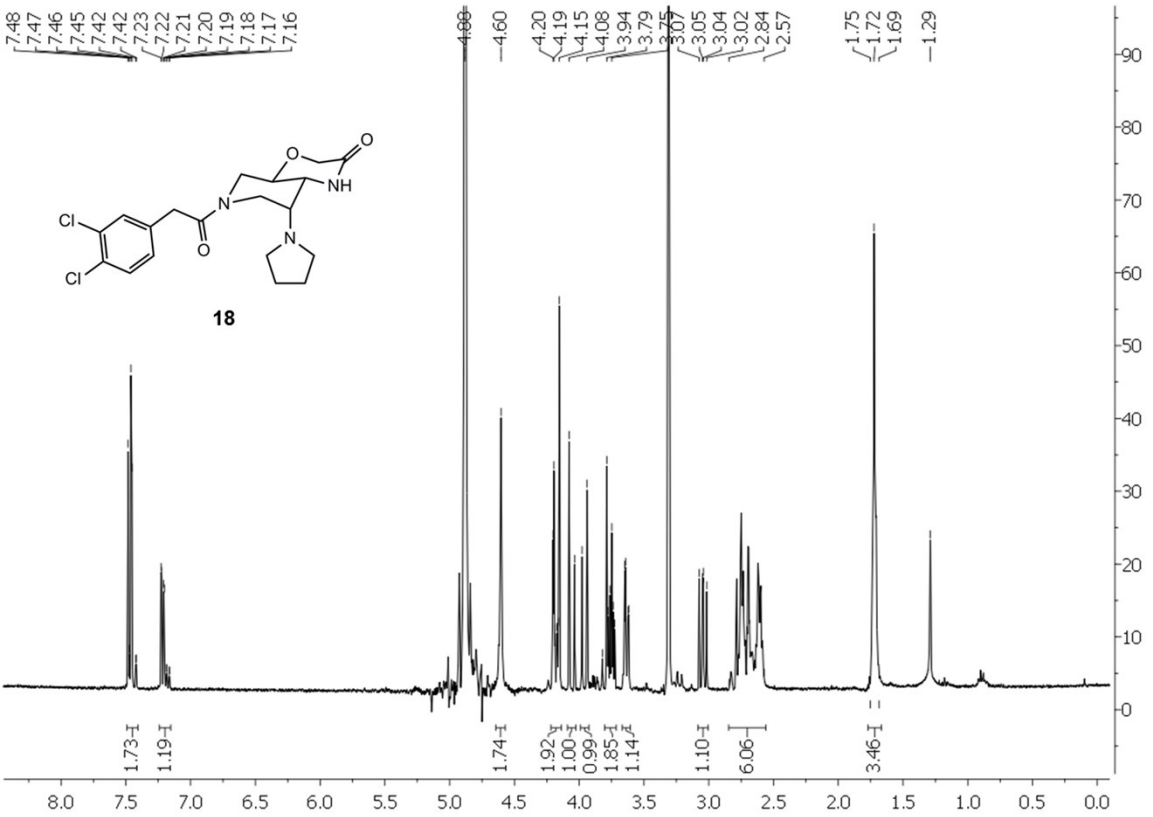
17h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Cl
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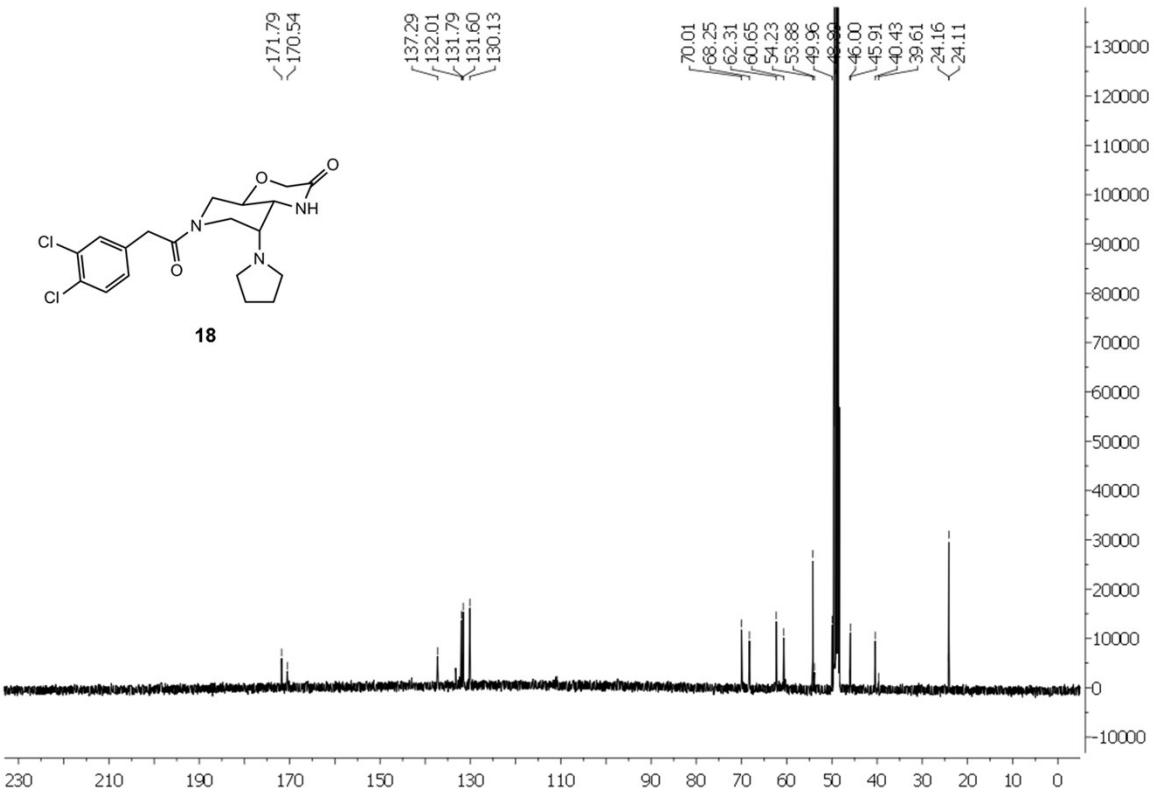
O
O
N
18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137.29
132.01
131.79
131.60
130.13
70.01
68.25
62.31
60.65
54.23
53.88
49.96
48.90
46.00
45.91
40.43
39.61
24.16
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