Supplementary Information

Identification of novel small-molecule inhibitors targeting menin-MLL interaction, repurposing the antidiarrheals loperamide

Liyan Yue,‡[a,b] Juanjuan Du,‡[c] Fei Ye,‡[d] Zhifeng Chen,[e] Lianchun Li,[f] Fulin Lian,[a,b] Bidong Zhang,[a,b] Yuanyuan Zhang,[a,b,*] Hualiang Jiang,[a,b] Kaixian Chen,[a,e] Yuanchao Li,[c] Bing Zhou,[c] Yaxi Yang, [c,*] and Cheng Luo[a,e,*]

[a.] State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China.

[b.] University of Chinese Academy of Sciences， No.19A Yuquan Road, Beijing 100049, China

[c.] Department of Medicinal Chemistry, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China.

[d.] Zhejiang Sci-Tech University, College of Life Sciences, Hangzhou, China.

[e.] School of Life Science and Technology, Shanghai Tech University, Shanghai 200031, China.

[f.] Guangxi Key Laboratory of Functional Phytochemicals Research and Utilization, Guangxi Institute of Botany, Guangxi Zhuang Autonomous Region and Chinese Academy of Sciences, Guilin 541006, China.

‡ These authors contributed equally to this work.

* Correspondence: Yaxi Yang (yangyaxi@simm.ac.cn), Yuanyuan Zhang (10110700070@fudan.edu.cn) and Cheng Luo (cluo@simm.ac.cn)

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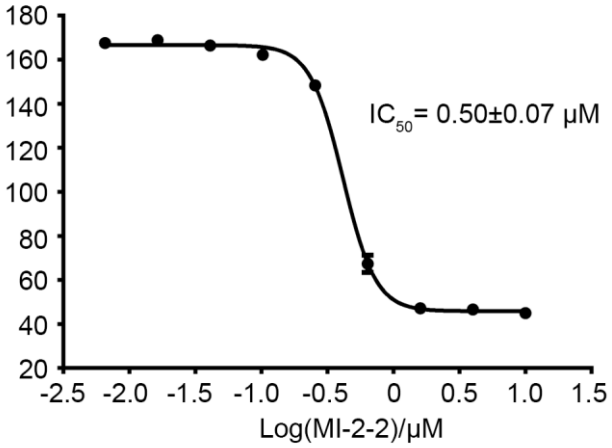
Supplementary Table 1. Protein thermal shift assay demonstrated the binding of loperamide-based analogues to menin. ∆ Tm values were calculated as a Tm difference between menin mixed with the 20 μM compound and menin mixed with DMSO.

Compound	∆ Tm (℃)
DMSO	—
DC_YM22	5.04±0.65
DC_YM23	2.20±0.31
DC_YM24	2.01±0.40
DC_YM26	4.81±0.51
DC_YM27	3.49±0.60
MBM1	4.28±0.36

Supplementary Table 2. AlamarBlue cell viability assay of human leukemia cells MV4;11 after 7 day's treatment with inhibitors.

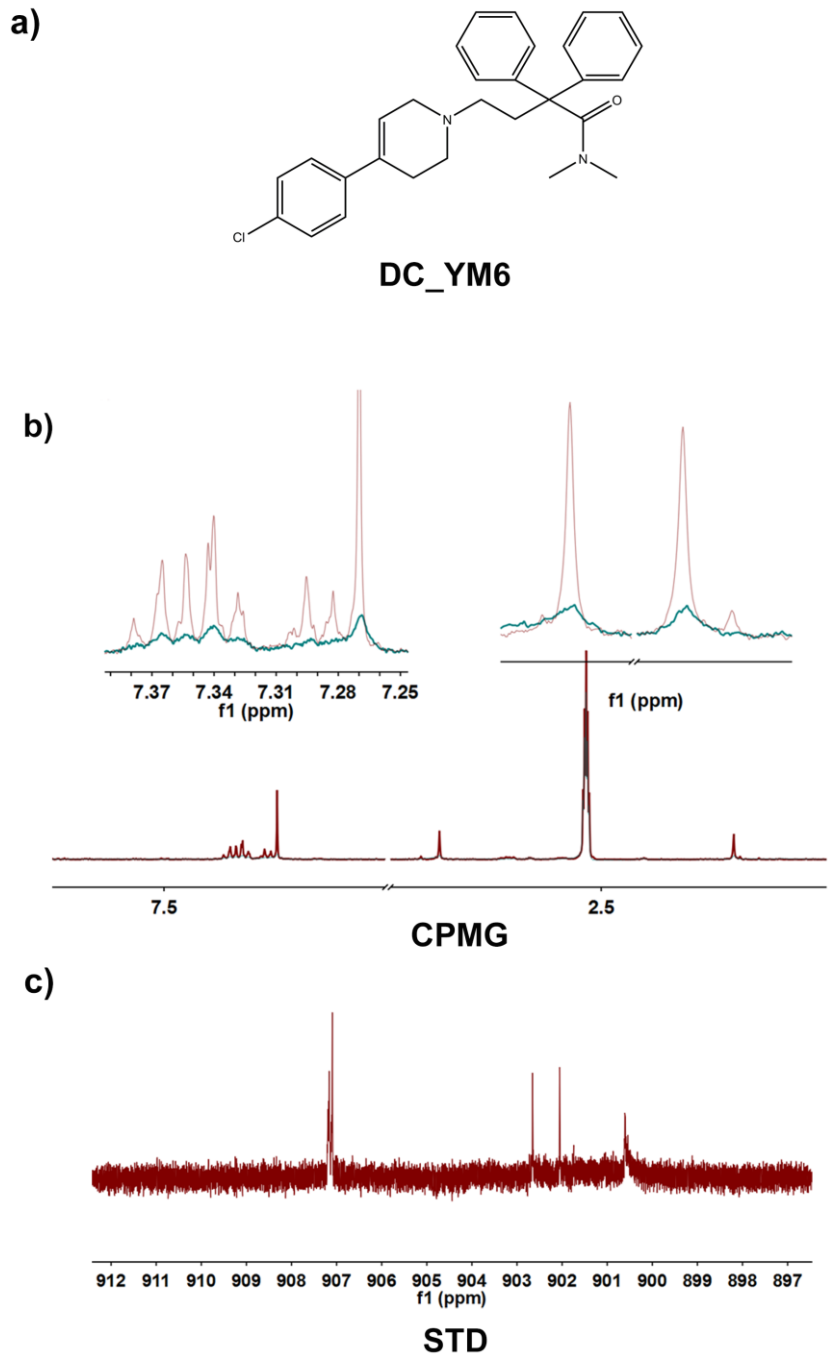
Compound	GI_{50} (μM)
DC_YM22	3.20±0.20
DC_YM24	3.34±1.06
DC_YM26	2.96±0.91
MI-2-2	2.37±0.81

Supplementary Figure 1.



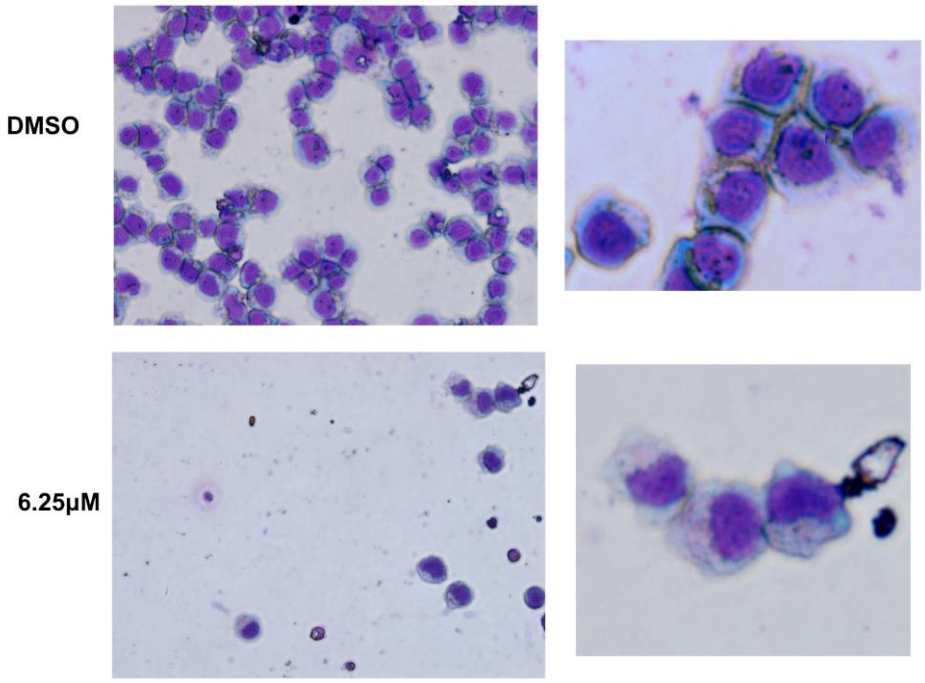
Supplementary Figure 1. FP assays determine the IC_{50} value of MI-2-2.

Supplementary Figure 2.



Supplementary Figure 2. NMR CPMG (b) and STD (c) experiments demonstrate direct binding of DC_YM6 to menin.

Supplementary Figure 3.



Supplementary Figure 3. DC_YM21 treatment induces human MLL leukemia cells KOPN-8 (MLL-ENL) differentiation. Wright-Giemsa stained cytospins on KOPN-8 cells after 10 days of treatment with **DC_YM21** and DMSO.

Procedures and Products

All reagents were purchased from commercial sources and used without further purification, unless otherwise indicated.

Loperamide and **DC_YM1~DC_YM3** are commercially available:

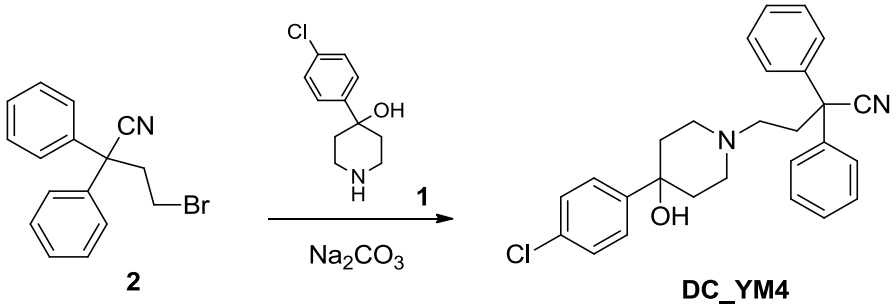
Loperamide Hydrochloride: CAS Number: 34552-83-5, Bought from Tokyo Chemical Industry (TCI) Shanghai, Catalogue Number: L0154, Melting Point: 223-225 ℃, Purity: > 98%.

DC_YM1: Loperamide *N*-Oxide, CAS Number：106900-12-3 Bought from TLC PharmaChem, Source Lot Number: 1045-029A3; Melting Point: 169-173 ℃, Purity: 97.9%.

DC_YM2: *N*-Desmethyl Loperamide, CAS Number: 66164-07-6, Bought from Toronto Research Chemicals (TRC), Catalogue Number: D291840; Melting Point: 214-216 ℃, Purity: 98%.

DC_YM3: *N*-Didesmethyl Loperamide, CAS Number: 66164-06-5, Bought from Toronto Research Chemicals (TRC), Catalogue Number: D441135. Melting Point: 200-203 ℃, Purity: 98%.

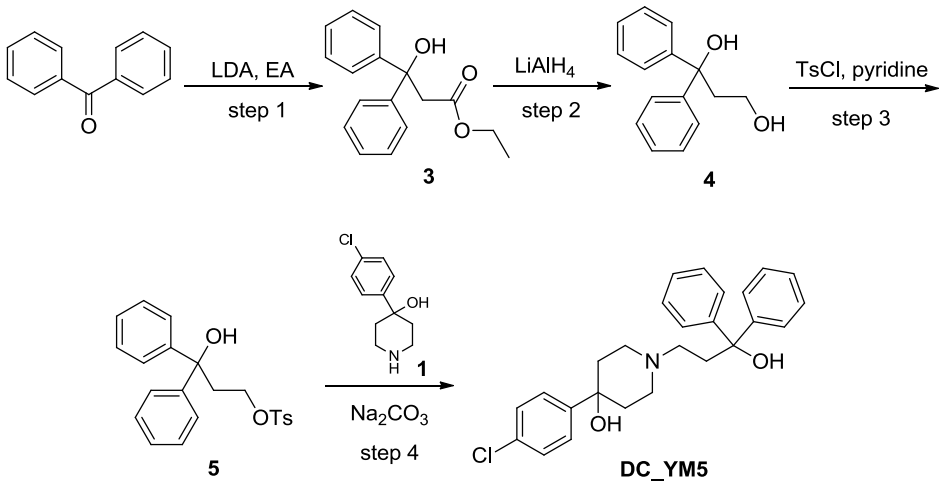
1. Synthesis of 4-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)-2,2-diphenylbutane nitrile (**DC_YM4**)



A solution of 4-bromo-2,2-diphenylbutanenitrile (**2**, 299 mg, 1 mmol) in CH_3CN (5 mL) was added 4-(4-chlorophenyl)-4-hydroxypiperidine (**1**, 211 mg, 1 mmol) and

Na_2CO_3 (318 mg, 3 mmol), and the mixture was stirred at 80 ℃ for 4 h. Then the solvent was removed in vacuo. The residue was diluted with EtOAc and washed with water. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane/methanol = 20/1) to give compound **DC_YM4**. Yield, 83%; mp 216 – 218 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.30 (m, 14H), 2.83-2.75 (m, 2H), 2.71-2.64 (m, 2H), 2.59-2.52 (m, 2H), 2.51-2.43 (m, 2H), 2.11 (td, J = 13.3, 4.4 Hz, 2H), 1.76-1.68 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.8, 140.0, 132.8, 129.0, 128.4, 128.0, 126.8, 126.1, 122.1, 71.0, 54.8, 50.1, 49.6, 38.4, 36.6; HRMS (EI) calcd. for $C_{27}H_{27}ClN_2O$ $[M]^+$: 430.1812. Found: 430.1807.

2. Synthesis of 4-(4-chlorophenyl)-1-(3-hydroxy-3,3-diphenylpropyl)piperidin-4-ol (**DC_YM5**)



Step 1: To a solution of diisopropylamine (0.5 mL) in THF (10 mL) was added *n*-butyllithium solution in hexane (2.2 mL, 1.6 M in hexane) at -78 ℃. The mixture was stirred at -78℃ for 15 min to get a LDA solution, then EtOAc (0.34 mL) was slowly added to the reaction mixture at -78 ℃. After 20 min, a solution of benzophenone (637 mg, 3.5 mmol) in THF (10 mL) was slowly added to the mixture. The reaction mixture was stirred at -78 ℃ for 2 h. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc. The combined organic layers

were washed with brine, and dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography with petroleum ether/ethyl acetate (100/1, v/v) to obtain the title compound **3** (95% yield); LRMS (EI) m/z 270 $[M]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38-7.45 (m, 4H), 7.15-7.35 (m, 6H), 5.10 (s, 1H), 4.02 (q, J = 7.20, 2H), 3.25 (s, 2H), 1.13 (t, J = 7.20, 3H).

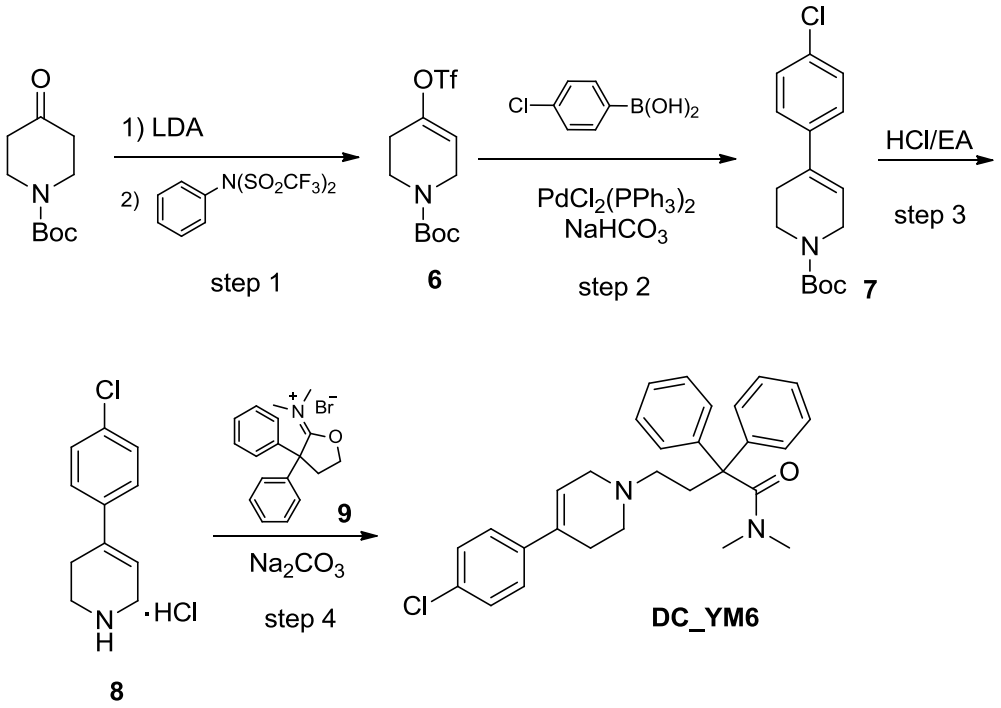
Step 2: To a solution of ester **3** (200 mg, 0.74 mmol) in THF (5 mL) was slowly added the suspension of $LiAlH_4$ in dry THF (1 mL, 1M) at 0 ℃, and the mixture was stirred at 0 ℃ for 1h . After complete consumption of the starting material, the mixture was quenched with water and exacted with ethyl acetate. The combined organic layers was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford the crude product, which was purified by flash column chromatography with petroleum ether/ethyl acetate (3/1, v/v) to give compound **4** (90% yield); LRMS (EI) m/z 228 $[M]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 4H), 7.37 – 7.31 (m, 4H), 7.28 – 7.23 (m, 2H), 4.23 (s, 1H), 3.74 (dd, J = 9.8, 4.9 Hz, 2H), 2.66 (t, J = 4.3 Hz, 1H), 2.59 – 2.53 (m, 2H).

Step 3: The *p*-toluenesulfonyl chloride (125 mg, 0.66 mmol) was added to the solution of the diol **4** (100 mg, 0.44 mmol) in dry pyridine (3 mL) at 0 ℃ under atomosphere of argon, and the mixture was stirred at 0 ℃ for 4 h. The mixture was diluted with EtOAc and washed with hydrochloric acid (2 M), the combined organic layers were washed with brine, and dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography with petroleum ether/ethyl acetate (6/1, v/v) to obtain the compound **5** (72%); LRMS (EI) m/z 382 $[M]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8.1 Hz, 2H), 7.33 – 7.21 (m, 12H), 4.09 (t, J = 7.3 Hz, 2H), 2.71 (t, J = 7.3 Hz, 2H), 2.44 (s, 3H).

Step 4: A solution of tosylate **5** (382 mg, 1 mmol) in CH_3CN (5 mL) was added 4-(4-chlorophenyl)-4-hydroxypiperidine (211 mg, 1 mmol) and Na_2CO_3 (318 mg, 3 mmol), and the mixture was stirred at 80 ℃ for 4 h. Then the solvent was removed in

vacuo. The residue was diluted with EtOAc and washed with water. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane/methanol = 20/1) to give compound **DC_YM5.** Yield, 80%; mp 230 – 232 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (brs, 1H), 7.50-7.45 (m, 4H), 7.45-7.40 (m, 2H), 7.35-7.28 (m, 6H), 7.20 (t, J = 7.3 Hz, 2H), 2.83 (d, J = 11.4 Hz, 2H), 2.58-2.40 (m, 6H), 2.13 (td, J = 13.4, 4.0 Hz, 2H), 1.74 (d, J = 12.6 Hz, 2H), 1.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 146.4, 133.0, 128.5, 128.1, 126.5, 126.1, 125.8, 79.1, 70.9, 55.0, 49.3, 38.5, 35.3; HRMS (EI) calcd. for $C_{26}H_{28}ClNO_2$ $[M]^+$: 421.1809. Found: 421.1811.

3. Synthesis of 4-(4-(4-chlorophenyl)-3,6-dihydropyridin-1(2H)-yl)-*N*,*N*-dimethyl-2,2-diphenylbutanamide (**DC_YM6**)



Step 1: To a solution of diisopropylamine (0.7 mL) in THF (10 mL) was added n-butyllithium solution in hexane (3.1 mL, 1.6 M in hexane) at -78 ℃. The mixture was stirred at -78 ℃ for 15 min to get a LDA solution, then 1-Boc-4-piperidone (1.0 g,

5.02 mmol) in THF (10 mL) was slowly added to the reaction mixture at -78 ℃. After 20 min, a solution of 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethylsulfonyl)methane sulfonamide (1.8 g, 5.02 mmol) in THF (10 mL) was slowly added to the mixture. The reaction mixture was stirred at 0 ℃ for 3 h. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography with petroleum ether/ethyl acetate (10/1, v/v) to obtain the compound **6** (92% yield); LRMS (EI) m/z 331 $[M]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80-5.72 (m, 1H), 4.06-4.02 (m, 2H), 3.63 (t, J = 5.6 Hz, 2H), 2.48-2.40 (m, 2H), 1.47 (s, 9H).

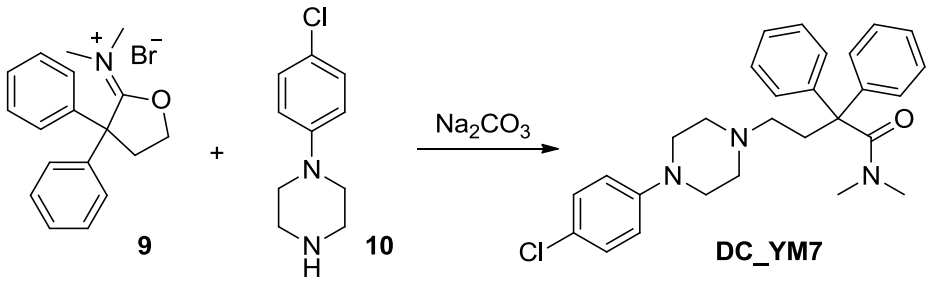
Step 2: To a solution of enol triflate **6** (331 mg, 1 mmol) in THF (4 mL) were added 4-chlorobenzeneboronic acid (187 mg, 1.2 mmol), saturated $NaHCO_3$ solution (1 mL) and $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), and the mixture was stirred at reflux for 2 h. The mixture was diluted with EtOAc and the aqueous layer was separated and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 2/1) to give compound **7** (95%); LRMS (EI) m/z 293 $[M]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 4H), 6.01 (brs, 1H), 4.06 (brs, 2H), 3.63 (brs, 2H), 2.47 (brs, 2H), 1.48 (s, 9H).

Step 3: A round-bottom flask was placed a solution of compound **7** (293 mg, 1 mmol) in ethyl acetate (5 mL), hydrogen chloride (gas) was bubbled through the solution and the resulting mixture was stirred for 1 h at room temperature. The formed precipitate was collected by filtration and dried to yield 206 mg (90%) of a white solid **8**; LRMS (EI) m/z 229 $[M]^+$.

Step 4: A solution of compound **8** (55 mg, 0.24 mmol) in CH_3CN (5 mL) was added dihydro-*N*,*N*-dimethyl-3,3-diphenyl-2(3H)-furaniminium bromide (**9**, 65 mg, 0.19 mmol) and Na_2CO_3 (60 mg, 0.57 mmol), and the mixture was stirred at 80 ℃ for 4h.

Then the solvent was removed in vacuo. The residue was diluted with EtOAc and washed with water. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane/methanol = 20/1) to give compound **DC_YM6**. Yield, 80%; mp 130 – 132 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.33 (m, 8H), 7.31-7.22 (m, 6H), 5.96-5.91 (m, 1H), 3.18-3.11 (m, 2H), 2.98 (brs, 3H), 2.69 (t, J = 5.6 Hz, 2H), 2.60-2.46 (m, 4H), 2.33 (brs, 3H), 2.32-2.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 140.7, 139.3, 133.7, 132.4, 128.3, 128.2, 128.0, 126.7, 126.1, 122.7, 59.7, 55.4, 53.1, 50.2, 42.6, 39.1, 37.2, 28.0; HRMS (EI) calcd. for $C_{29}H_{31}ClN_2O$ $[M]^+$: 458.2125. Found: 458.2122.

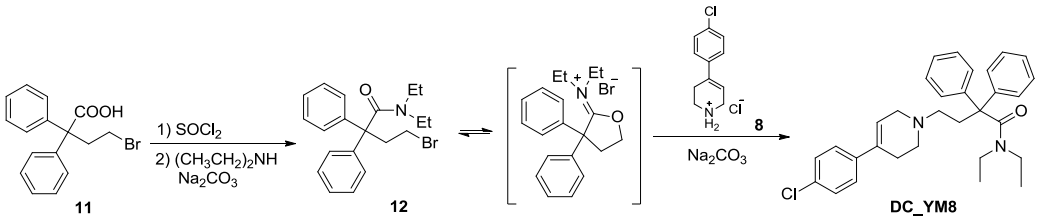
4. Synthesis of 4-(4-(4-chlorophenyl)piperazin-1-yl)-*N*,*N*-dimethyl-2,2-diphenylbutan amide (**DC_YM7**)



A solution of compound **9** (50 mg, 0.14 mmol) in CH_3CN (5 mL) was added 1-(4-chlorophenyl)piperazine (**10**) (43 mg, 0.22 mmol) and Na_2CO_3 (46 mg, 0.43 mmol), and the mixture was stirred at 80 ℃ for 4 h. Then the solvent was removed in vacuo. The residue was diluted with EtOAc and washed with water. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane/methanol = 20/1) to give compound **DC_YM7**. Yield, 82%; mp 172 – 174 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.36 (m, 8H), 7.33-7.28 (m, 2H), 7.20-7.15 (m, 2H), 6.82-6.77 (m, 2H), 3.12-3.06 (m, 4H), 3.01 (brs, 3H), 2.57-2.45 (m, 6H), 2.35 (brs, 3H), 2.17-2.10 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 150.0,

140.7, 128.8, 128.4, 128.1, 126.8, 124.1, 117.0, 59.7, 55.8, 53.0, 49.0, 42.5, 39.2, 37.2; HRMS (EI) calcd. for $C_{28}H_{32}ClN_3O$ $[M]^+$: 461.2234. Found: 461.2231.

5. Synthesis of 4-(4-(4-chlorophenyl)-3,6-dihydropyridin-1(2H)-yl)-*N*,*N*-diethyl-2,2-diphenylbutanamide (**DC_YM8**)

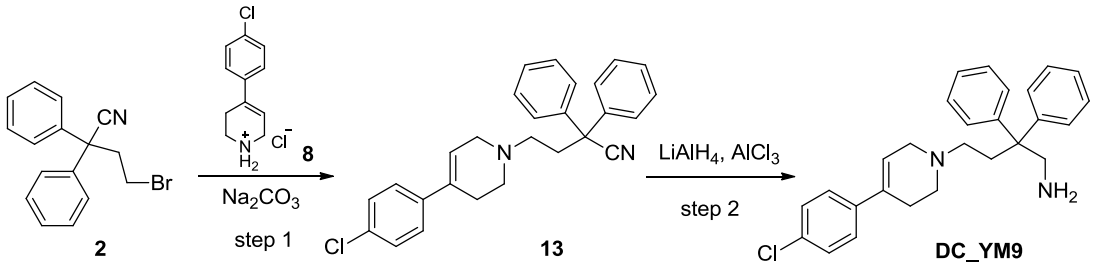


Step 1: To a solution of 4-bromo-2,2-diphenylbutyric acid (**11**, 2 g, 6.3 mmol) in $CHCl_3$ (15 mL) was added $SOCl_2$ (2 mL) dropwise. The mixture was refluxed for 4 h and allowed to cool, and the solvent was removed in vacuo. The crude acid chloride was used without purification. To a solution of diethylamine (0.77 mL) and Na_2CO_3 (1.6 g, 15 mmol) in H_2O (10 mL) was added dropwise a solution of 4-bromo-2,2-diphenylbutyroyl chloride in PhMe (7 mL), while the temperature was kept between 0 and 5 ℃. The mixture was stirred for an additional 2 h and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and the solvent removed in vacuo. The crude compound **12** was used in the next step without purification.

Step 2: A solution of compound **12** (373 mg, 1 mmol) in CH_3CN (5 mL) was added compound **8** (229 mg, 1 mmol) and Na_2CO_3 (318 mg, 3 mmol), and the mixture was stirred at 80 ℃ for 4 h. Then the solvent was removed in vacuo. The residue was diluted with EtOAc and washed with water. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane/methanol = 20/1) to give compound **DC_YM8**. Yield, 70%; mp 165 – 167 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.33 (m, 8H), 7.31-7.22 (m, 6H), 5.91 (s, 1H), 3.42-3.24 (m, 4H), 2.90-2.78 (m, 4H), 2.65-2.51 (m, 4H), 2.44-2.33 (m, 2H), 1.18 (t, J = 7.0 Hz, 3H),

-0.01 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 140.4, 138.5, 134.2, 133.1, 128.6, 128.4, 128.2, 127.0, 126.3, 59.6, 55.0, 53.5, 52.1, 49.7, 43.6, 40.7, 12.3, 11.2; HRMS (EI) calcd. for $C_{31}H_{35}ClN_2O$ $[M]^+$: 486.2438. Found: 486.2433.

6. Synthesis of 4-(4-(4-chlorophenyl)-3,6-dihydropyridin-1(2H)-yl)-2,2-diphenyl butan-1-amine (**DC_YM9**)

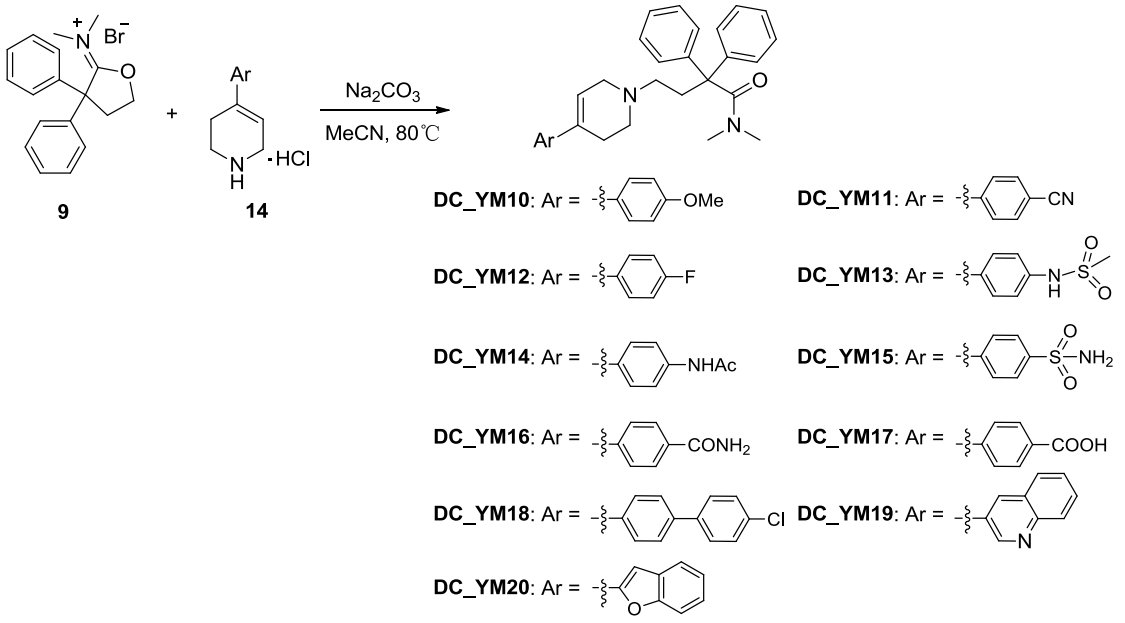


Step 1: A solution of 4-bromo-2,2-diphenylbutanenitrile (**2**, 299 mg, 1 mmol) in CH_3CN (5 mL) was added compound **8** (229 mg, 1 mmol) and Na_2CO_3 (318 mg, 3 mmol), and the mixture was stirred at 80 ℃ for 4 h. Then the solvent was removed in vacuo. The residue was diluted with EtOAc and washed with water. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 2/1) to give compound **13** (80%); LRMS (EI) m/z 412 $[M]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.23 (m, 14H), 6.03 (s, 1H), 3.16 (d, J = 3.1 Hz, 2H), 2.76-2.66 (m, 4H), 2.64-2.48 (s, 1H).

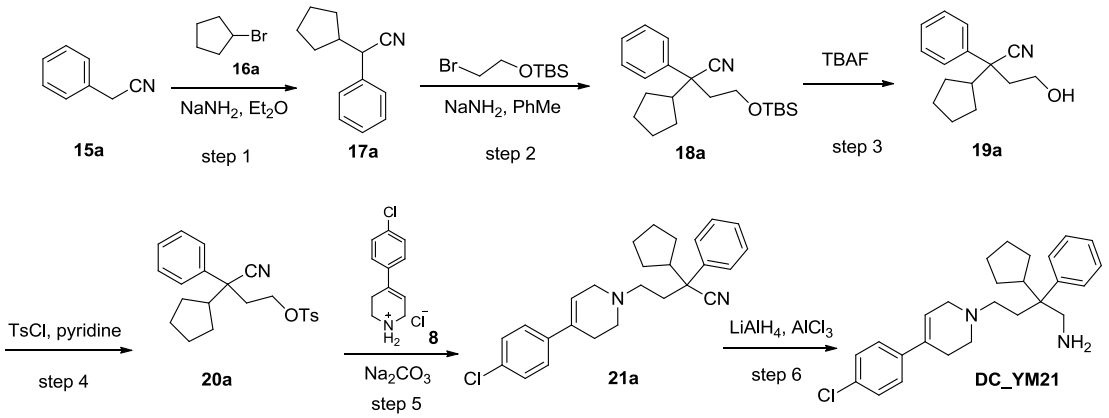
Step 2: LAH (0.15 mL, 2.4 M in THF) was slurried in anhydrous THF (5 mL), and the solution was cooled in an ice bath to 0 ℃ under nitrogen. $AlCl_3$ (49 mg, 0.37 mmol) was dissolved in anhydrous THF (5mL). The $AlCl_3$ solution was added to the LAH slurry via an addition funnel over 15 min. Compound **12** (52 mg, 0.13 mmol) was dissolved in anhydrous THF (5 mL). This solution was added to the LAH/$AlCl_3$ mixture slowly. The resulting mixture was stirred at ambient temperature for 1 h and then heated to reflux for 7 h. When cooled to 0 ℃ the reaction was quenched with water and extracted with Et_2O. The combined organic layers were washed with brine,

and dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography with dichloromethane/methanol (30/1, v/v) to obtain the compound **DC_YM9**. Yield, 60%; mp 147 – 149 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.17 (m, 14H), 6.00 (s, 1H), 3.35 (s, 2H), 3.10-3.03 (m, 2H), 2.61 (t, J = 5.4 Hz, 2H), 2.53-2.39 (m, 4H), 2.23-2.14 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.3, 139.2, 134.0, 132.7, 128.4, 128.2, 128.1, 126.2, 122.3, 53.9, 53.4, 51.0, 50.6, 49.1, 33.5, 28.1; HRMS (EI) calcd. for $C_{27}H_{29}ClN_2$ $[M]^+$: 416.2019. Found: 416.2011.

7. **DC_YM10 to DC_YM20** were synthesized according to the procedure for synthesis of **DC_YM6** using various of 4-aryl substituted-1,2,3,6-tetrahydropyridine (**14**)



8. General procedure for the synthesis of **DC_YM21 to DC_YM27** (taking **DC_YM21** as an example):



Step 1: A solution of 2-phenylacetonitrile (**15a**, 3 g, 25 mmol) in Et_2O (50 mL) was added bromocyclopentane (**16a** 2.7 mL) and $NaNH_2$ (1 g, 25 mmol), the mixture was refluxed for 3 h then quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography with petroleum ether/ethyl acetate (30/1, v/v) to obtain the compound **17a** (90% yield).

Step 2: To a solution of compound **17a** (253 mg, 1.4 mmol) in PhMe (10 mL) was added 2-(tert-butyldimethylsilyloxy)ethyl bromide (327 g, 1.4 mmol) and $NaNH_2$ (164 mg, 4.2 mmol), the mixture was stirred at 120 ℃ for 3 h then quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography with petroleum ether/ethyl acetate (30/1, v/v) to obtain the compound **18a** (85% yield)

Step 3: To a stirred solution of compound **18a** (343 mg, 1 mmol) in THF (5 mL) was added tetrabutylammonium fluoride (1 mL, 1M in THF), the reaction was stirred at room temperature for 2 h. The mixture was diluted with EtOAc and washed with water. The organic layers were combined, washed with brine, dried over Na_2SO_4 and

concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether /acetone = 2/1) to give compound **19a** (90%).

Step 4: The *p*-toluenesulfonyl chloride (191 mg, 1mmol) was added to the solution of the compound **19a** (206 mg, 0.9mmol) in dry pyridine (5mL) at 0 ℃ under atomosphere of argon, and the mixture was stirred at 0 ℃ for 4 h. The mixture was diluted with EtOAc and washed with hydrochloric acid (2 M), the combined organic layers were washed with brine, and dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography with petroleum ether/ethyl acetate (6/1, v/v) to obtain the compound **20a** (85% yield).

Step 5: A solution of compound **20a** (383 mg, 1mmol) in CH_3CN (5mL) was added compound **8** (229 mg, 1mmol) and Na_2CO_3 (318 mg, 3mmol), and the mixture was stirred at 80 ℃ for 4 h. Then the solvent was removed in vacuo. The residue was diluted with EtOAc and washed with water. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether /acetone = 3/1) to give compound **21a** (70%).

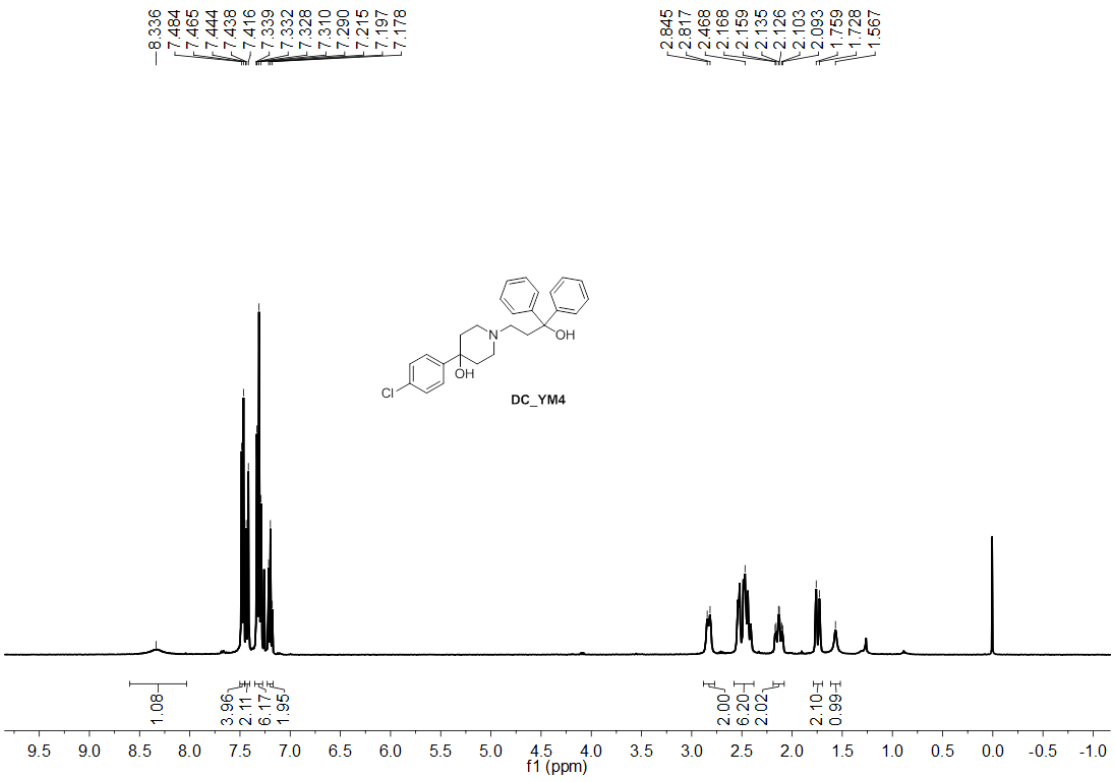
Step 6: LAH (0.15 mL, 2.4 M in THF) was slurried in anhydrous THF (5 mL), and the solution was cooled in an ice bath to 0 ℃ under nitrogen. $AlCl_3$ (49 mg, 0.37 mmol) was dissolved in anhydrous THF (5 mL). The $AlCl_3$ solution was added to the LAH slurry via an addition funnel over 15 min. Compound **21a** (50 mg, 0.12 mmol) was dissolved in anhydrous THF (5mL). This solution was added to the LAH/$AlCl_3$ mixture slowly. The resulting mixture was stirred at ambient temperature for 1 h and then heated to reflux for 7 h. When cooled to 0 ℃ the reaction was quenched with water and extracted with Et_2O. The combined organic layers were washed with brine, and dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography with dichloromethane/methanol (15/1, v/v) to obtain the compound **DC_YM21** (53%).

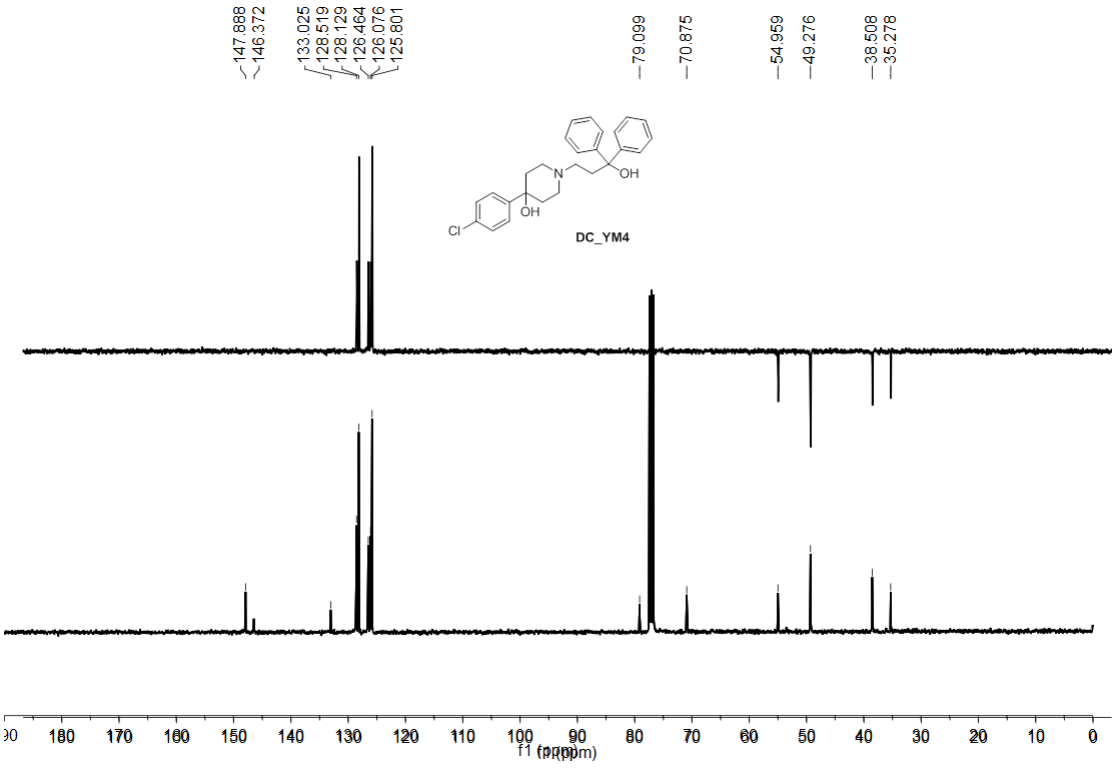
Supplementary Table 3. HPLC analysis data of synthesized compounds

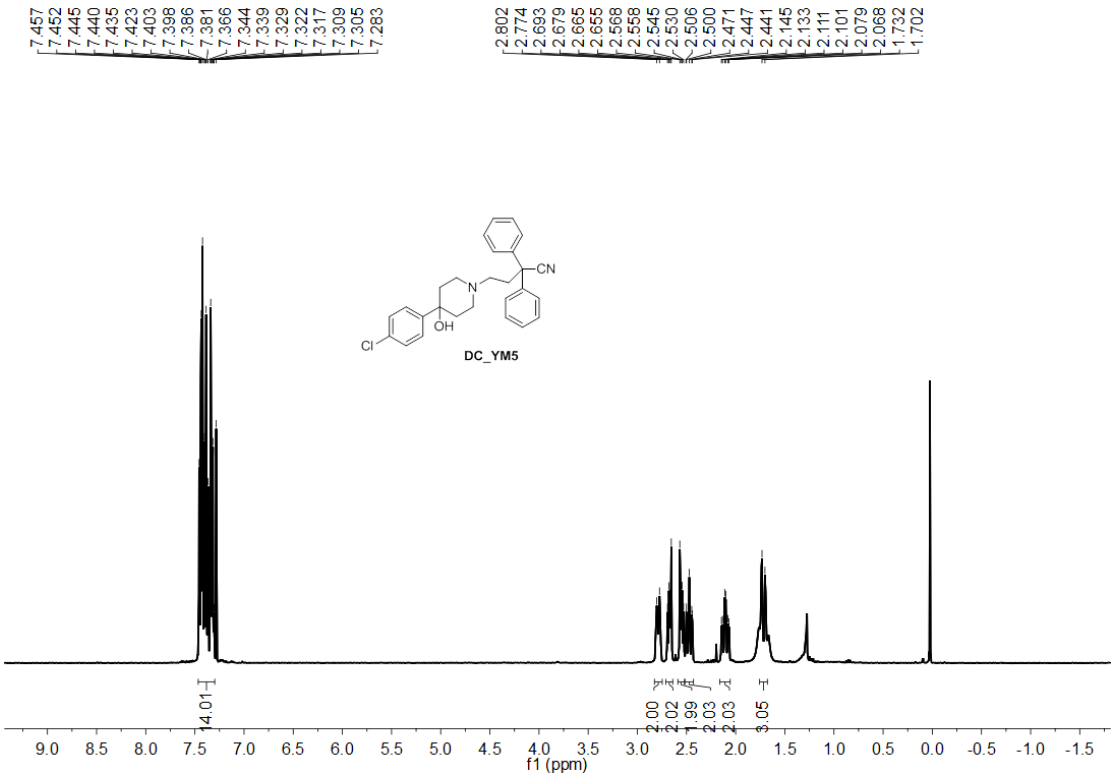
Compound	Retention Time (min, t_R)	Relative Purity (%)
DC_YM4	11.892	96.12
DC_YM5	9.786	97.39
DC_YM6	11.370	95.54
DC_YM7	10.669	97.10
DC_YM8	11.731	95.34
DC_YM9	11.412	95.13
DC_YM10	10.677	95.08
DC_YM11	9.263	95.21
DC_YM12	10.333	96.42
DC_YM13	8.532	95.55
DC_YM14	9.711	95.91
DC_YM15	8.372	97.14
DC_YM16	8.018	95.17
DC_YM17	6.322	96.59
DC_YM18	13.347	97.23
DC_YM19	10.091	96.02
DC_YM20	11.827	95.31
DC_YM21	12.213	96.43
DC_YM22	11.907	95.32
DC_YM23	11.814	95.07
DC_YM24	11.942	96.06
DC_YM25	11.461	95.08
DC_YM26	9.361	96.11
DC_YM27	9.725	95.04

Mobile phase: MeOH ($NH_3.H_2O$ 0.5‰)/H_2O ($NH_3.H_2O$ 0.5‰) with gradient elution (0 ~ 5 min: 50% MeOH ($NH_3.H_2O$ 0.5‰) ~ 95% MeOH ($NH_3.H_2O$ 0.5‰); 5 ~ 15 min: 95% MeOH ($NH_3.H_2O$ 0.5‰)) at 20 ^oC.

^{1}H and ^{13}C NMR spectra



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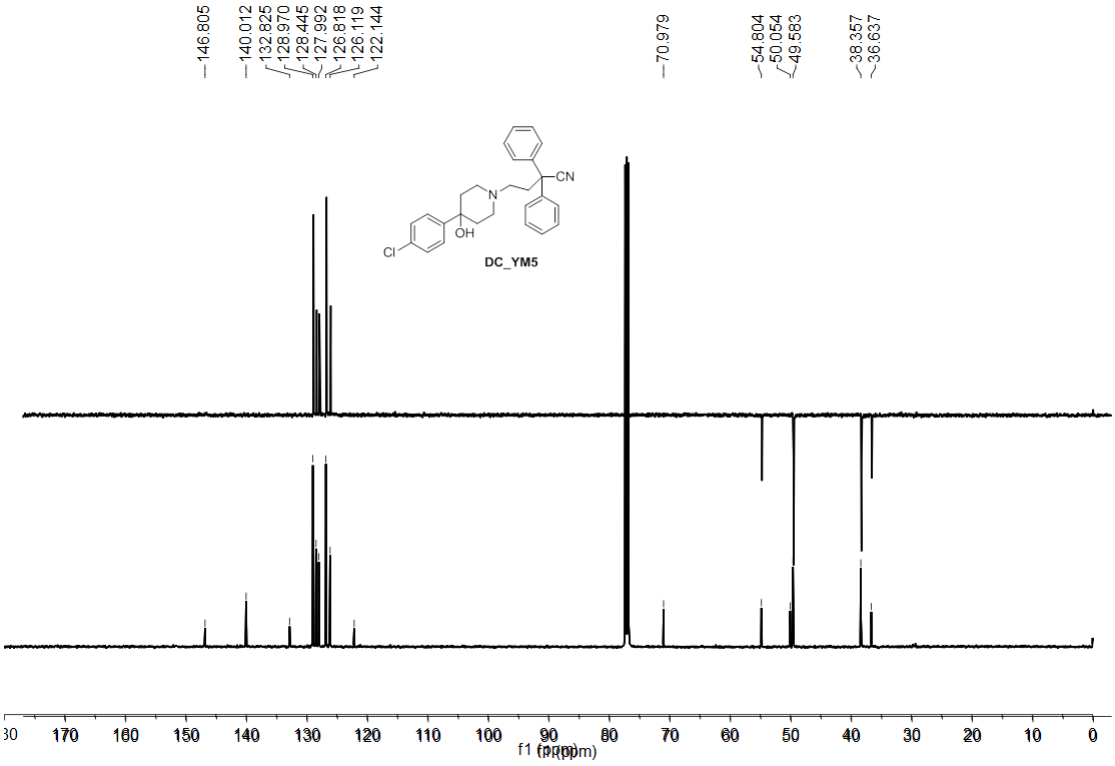
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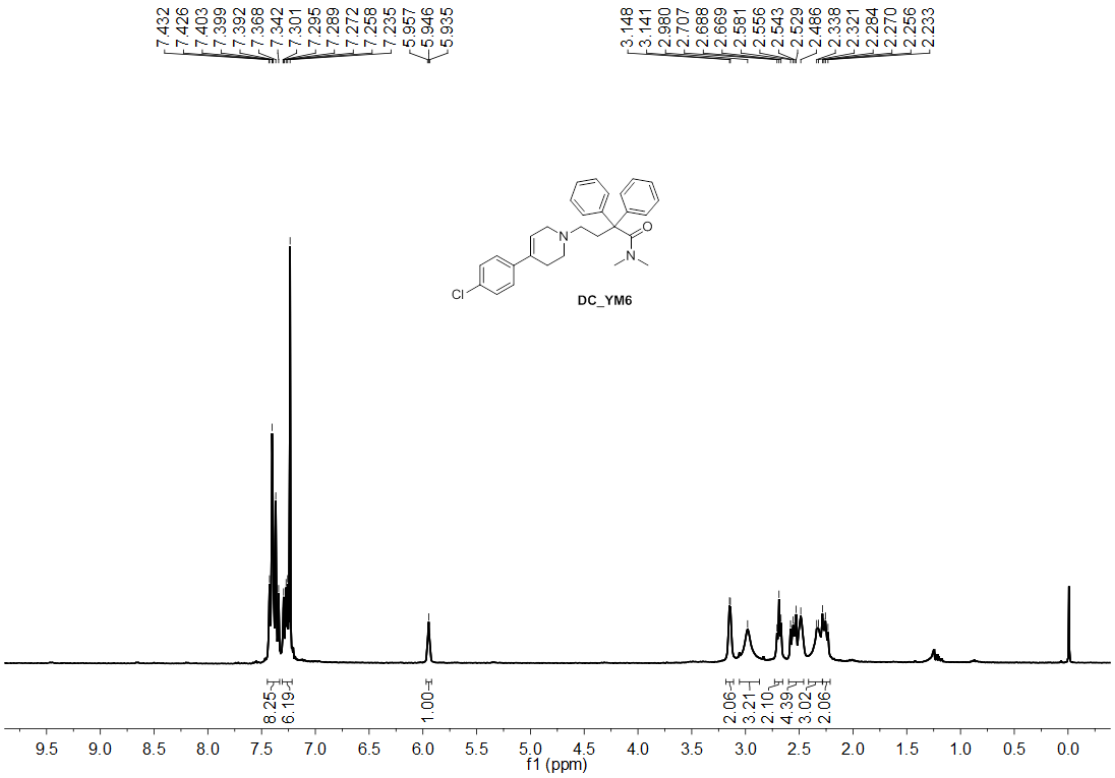
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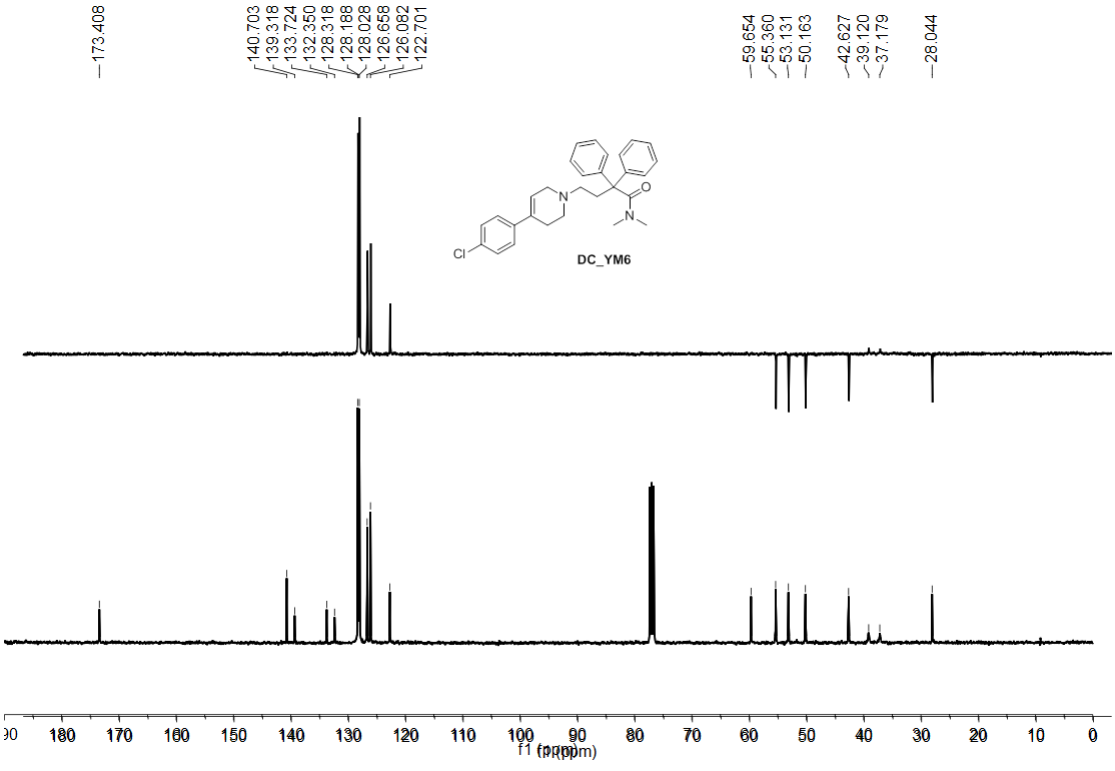
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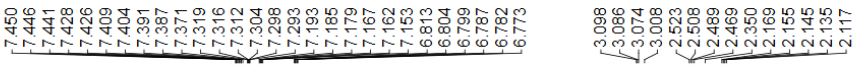
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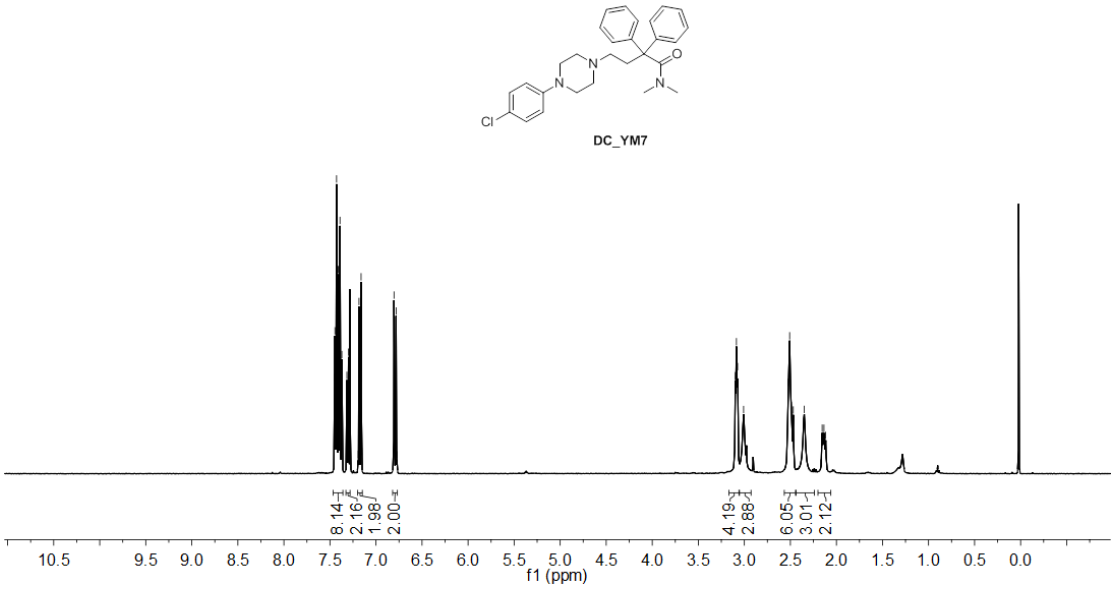
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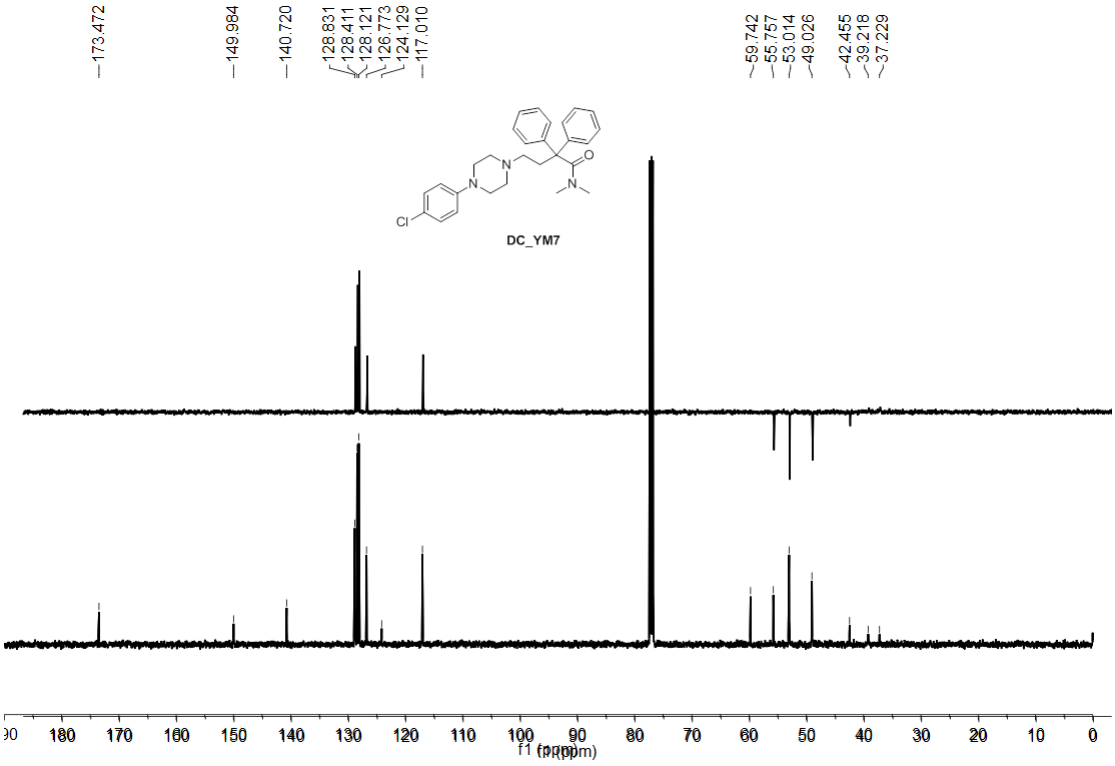
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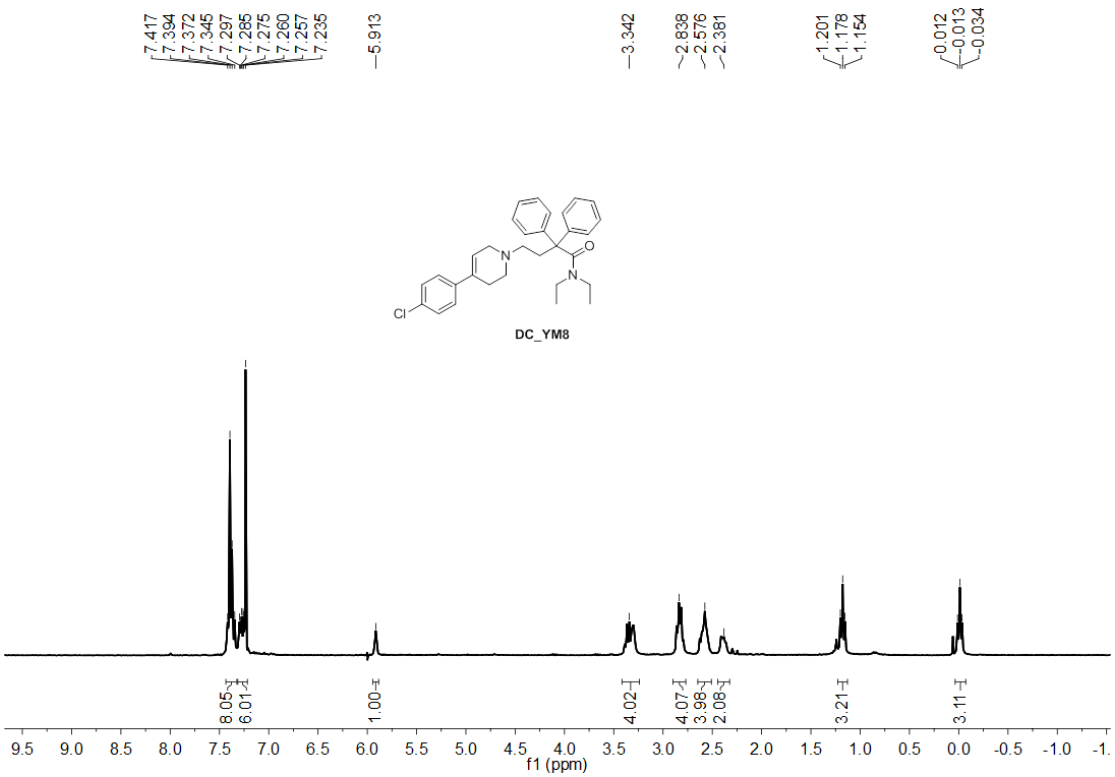
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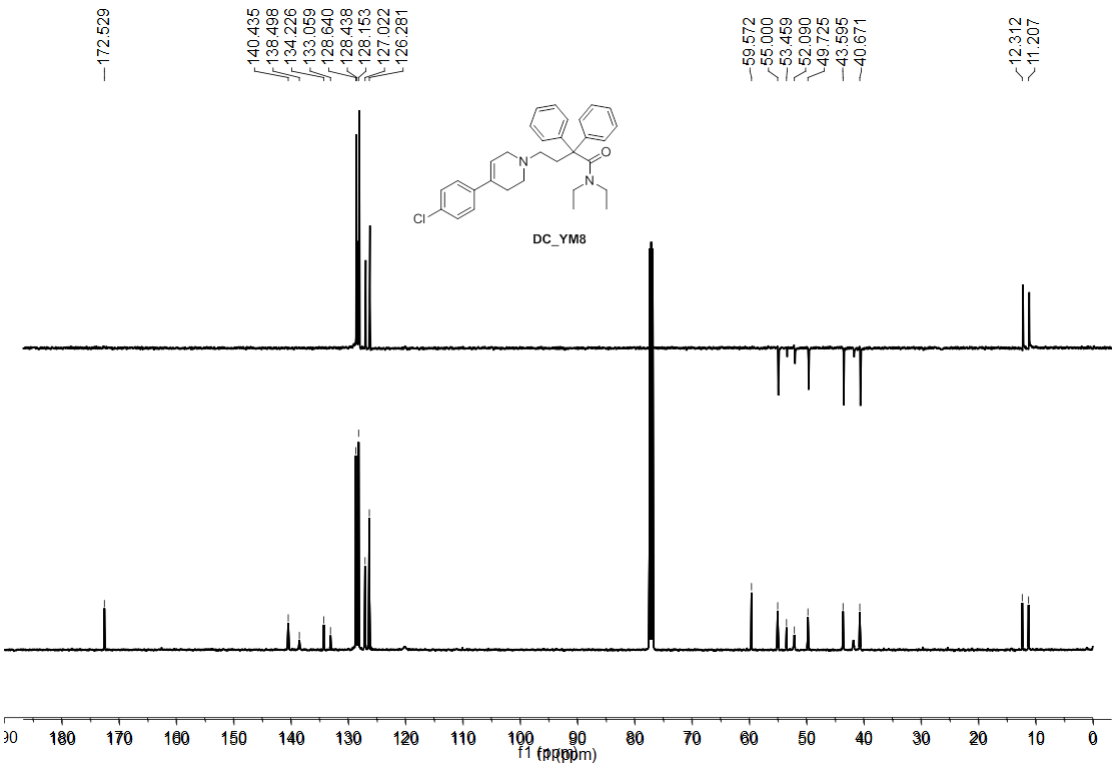
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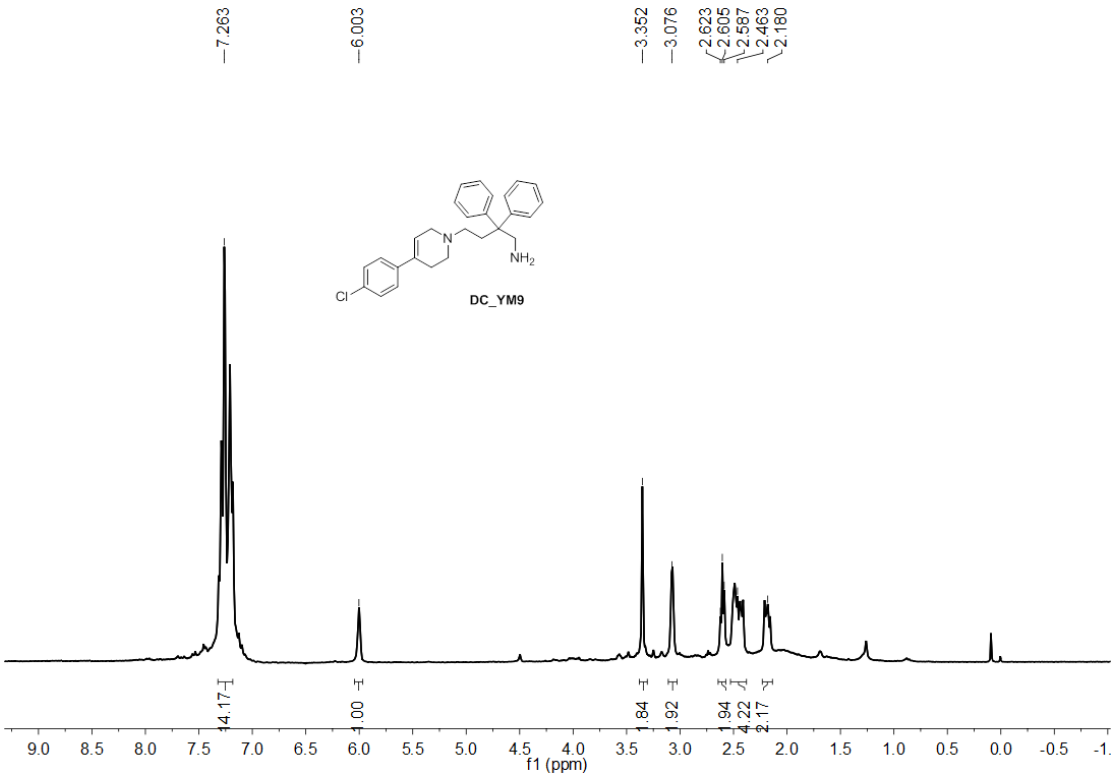
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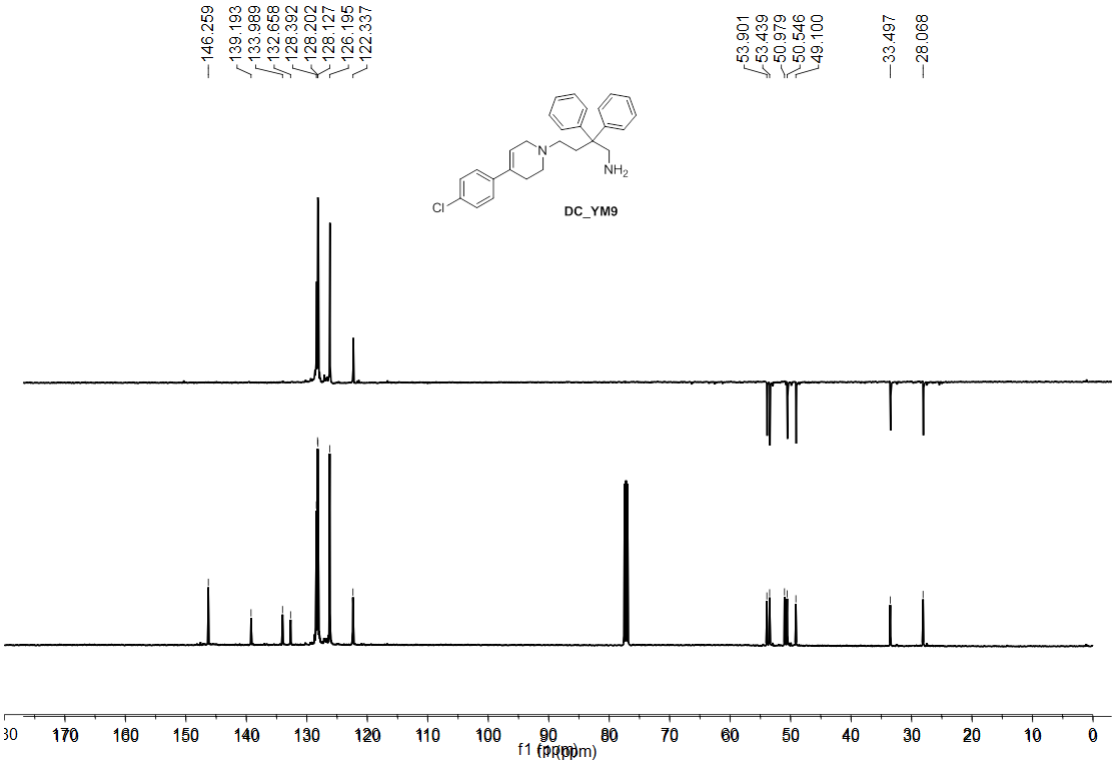
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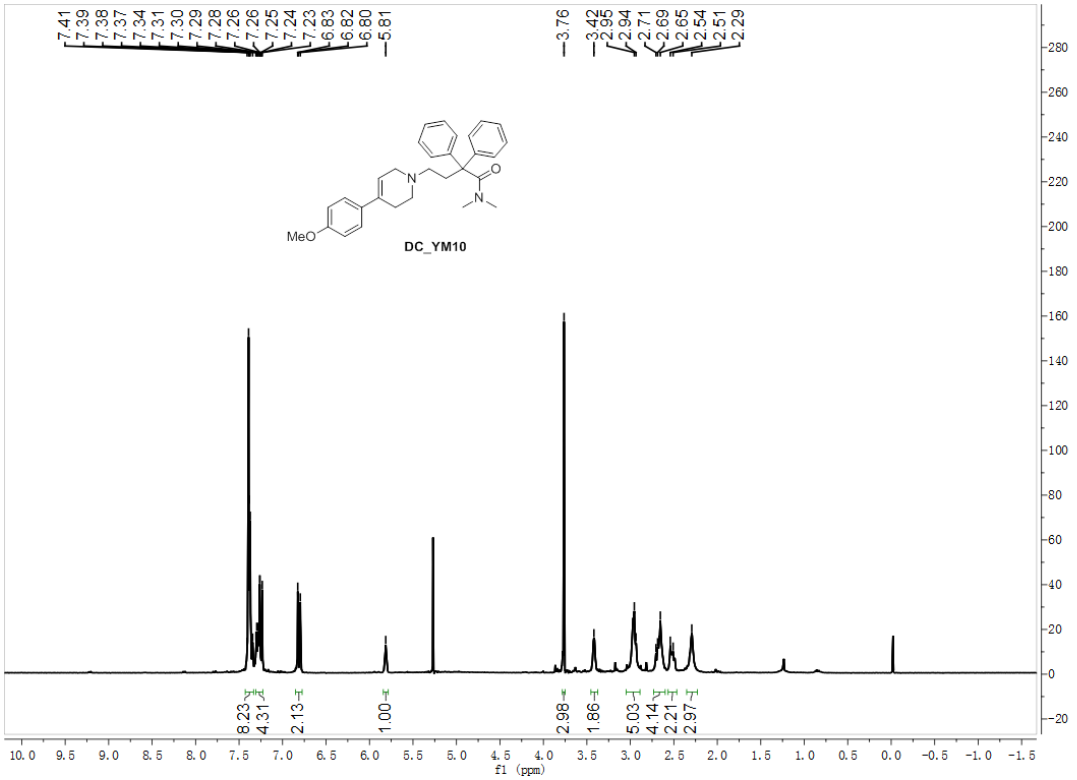
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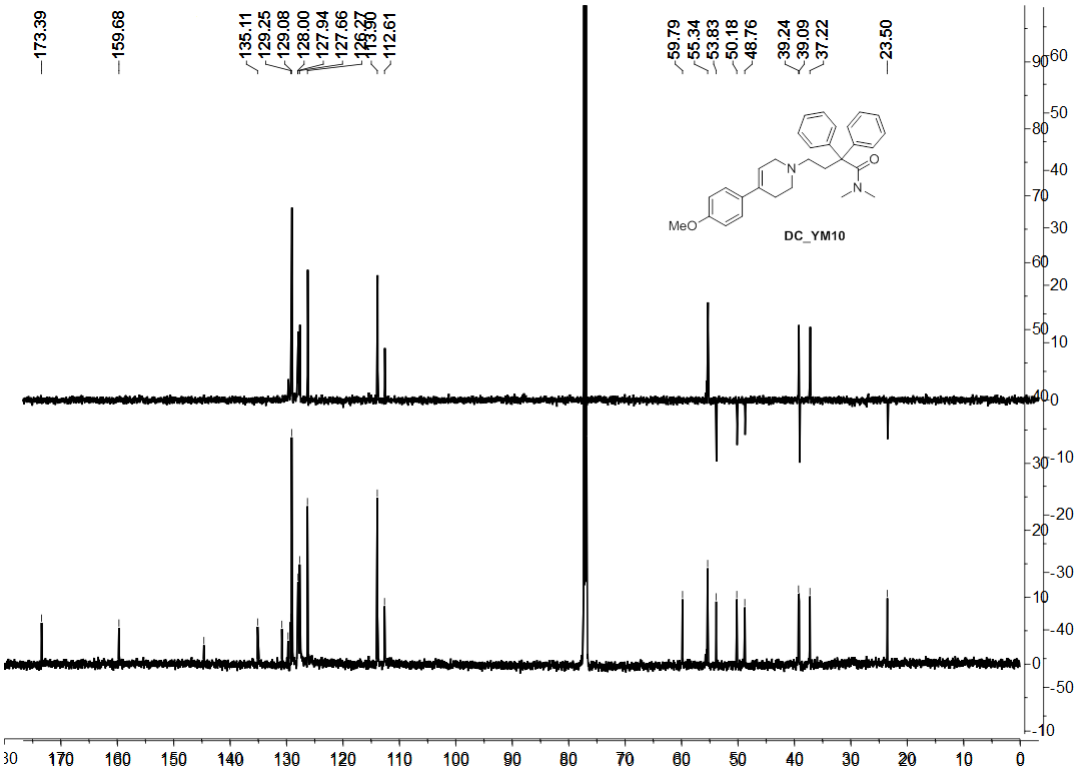
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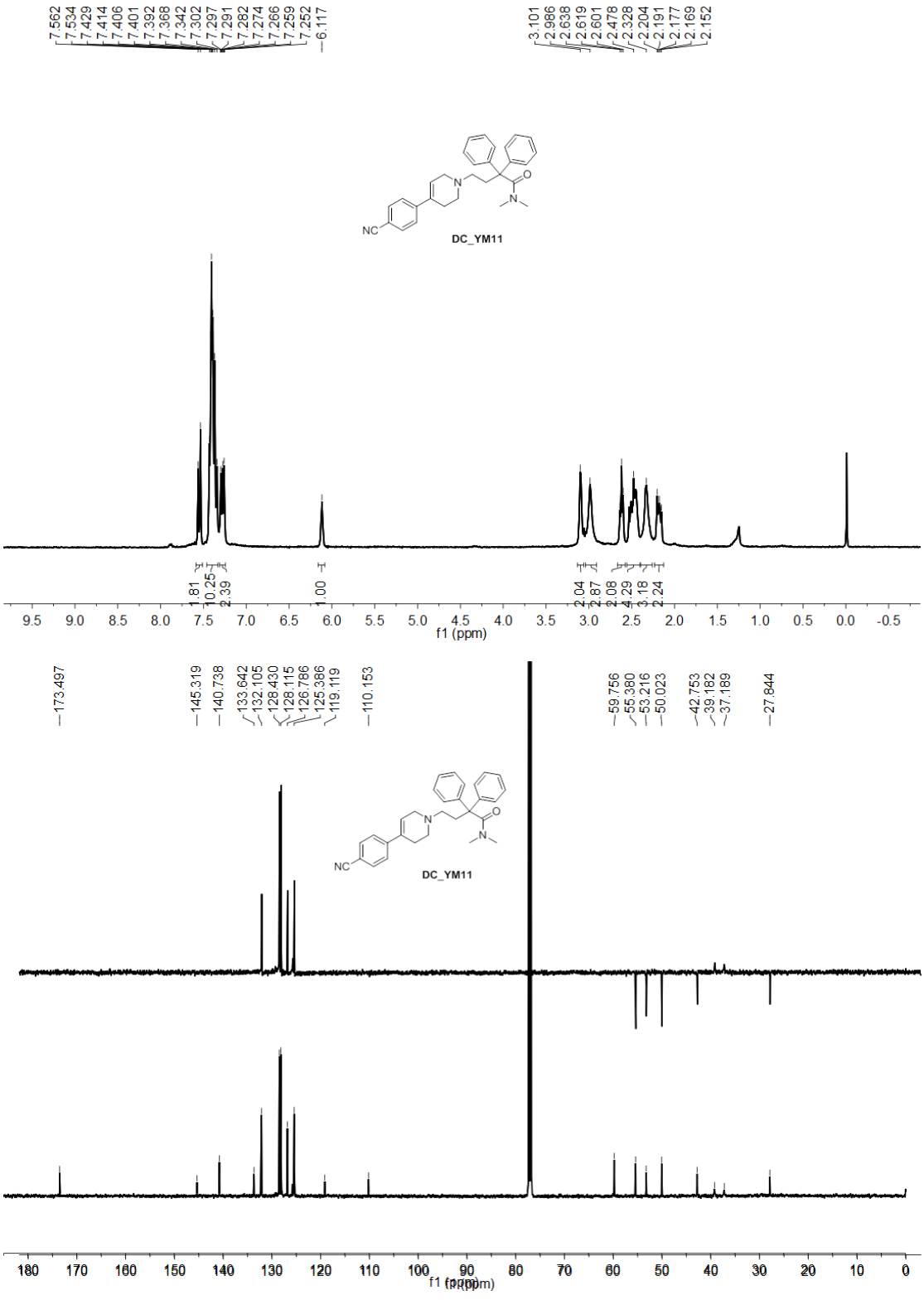
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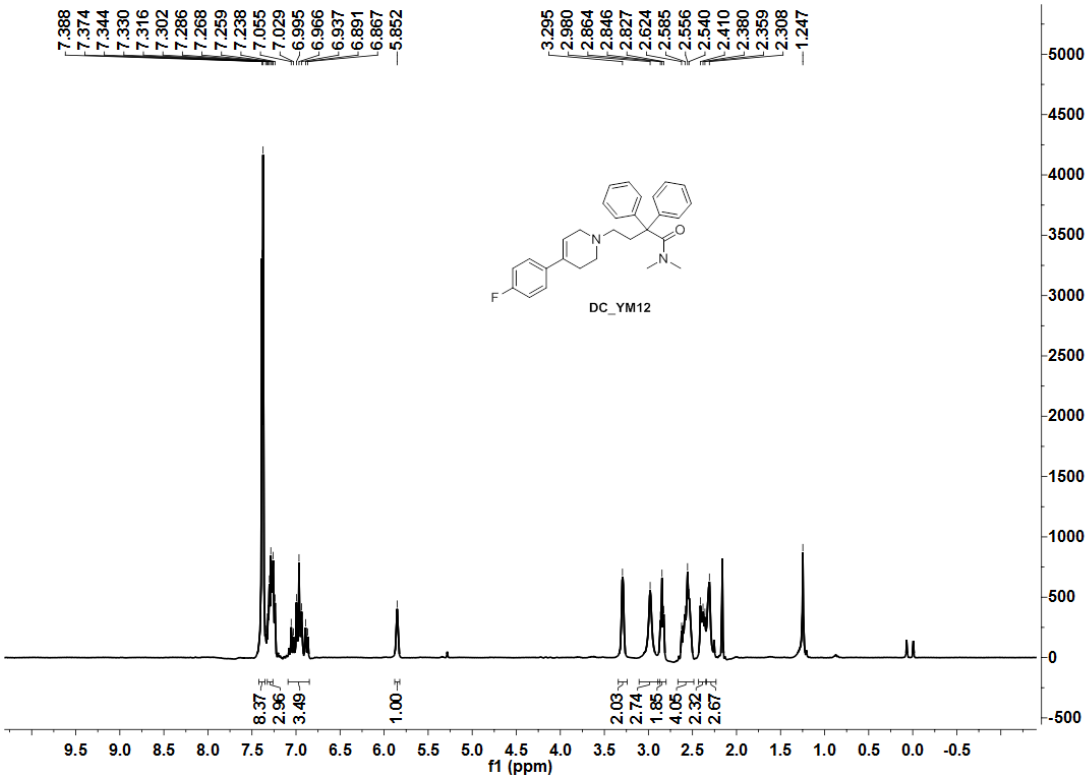
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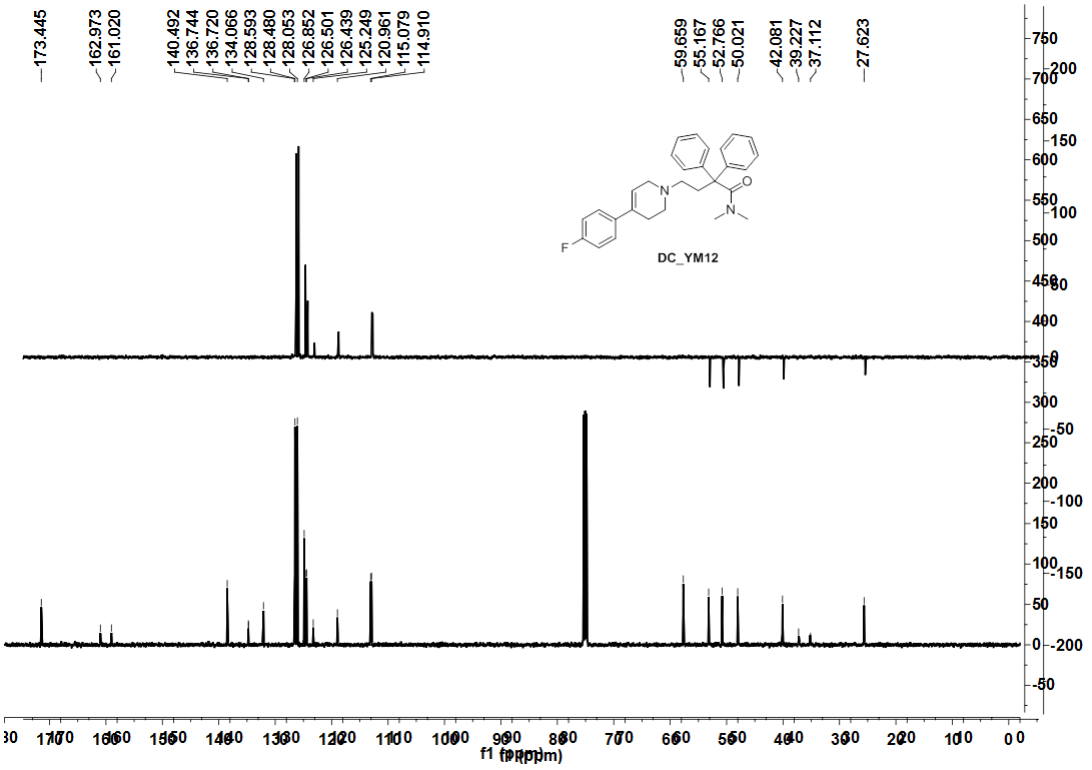
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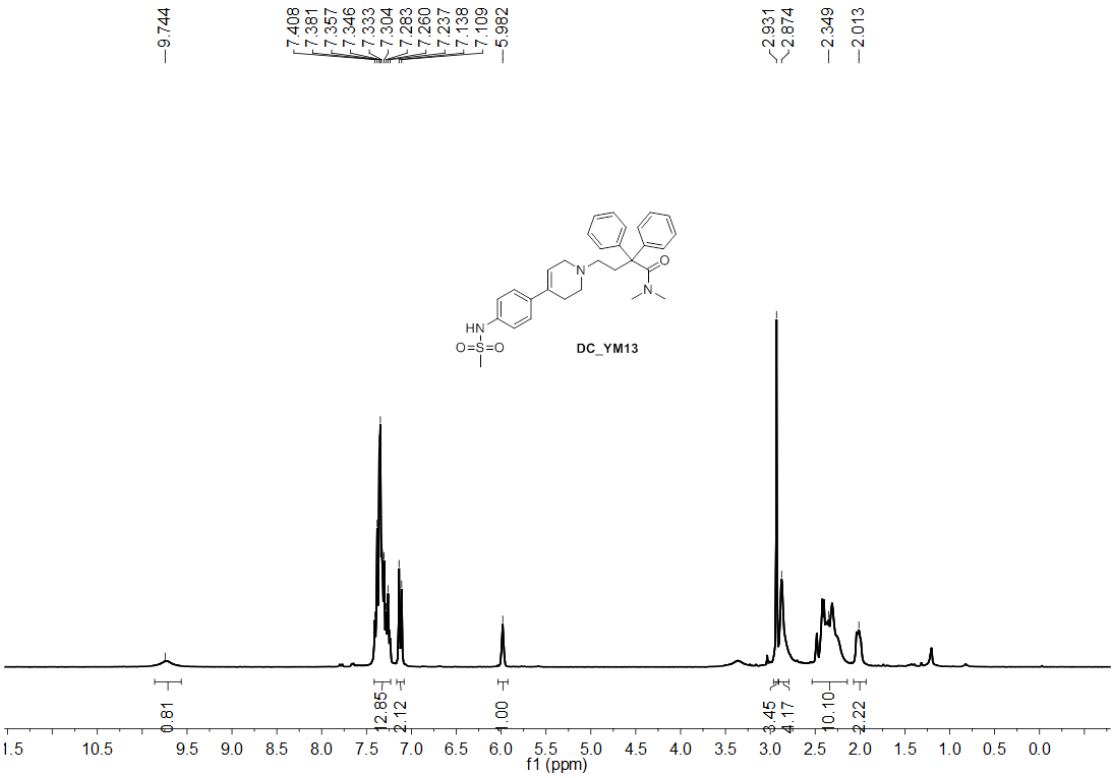
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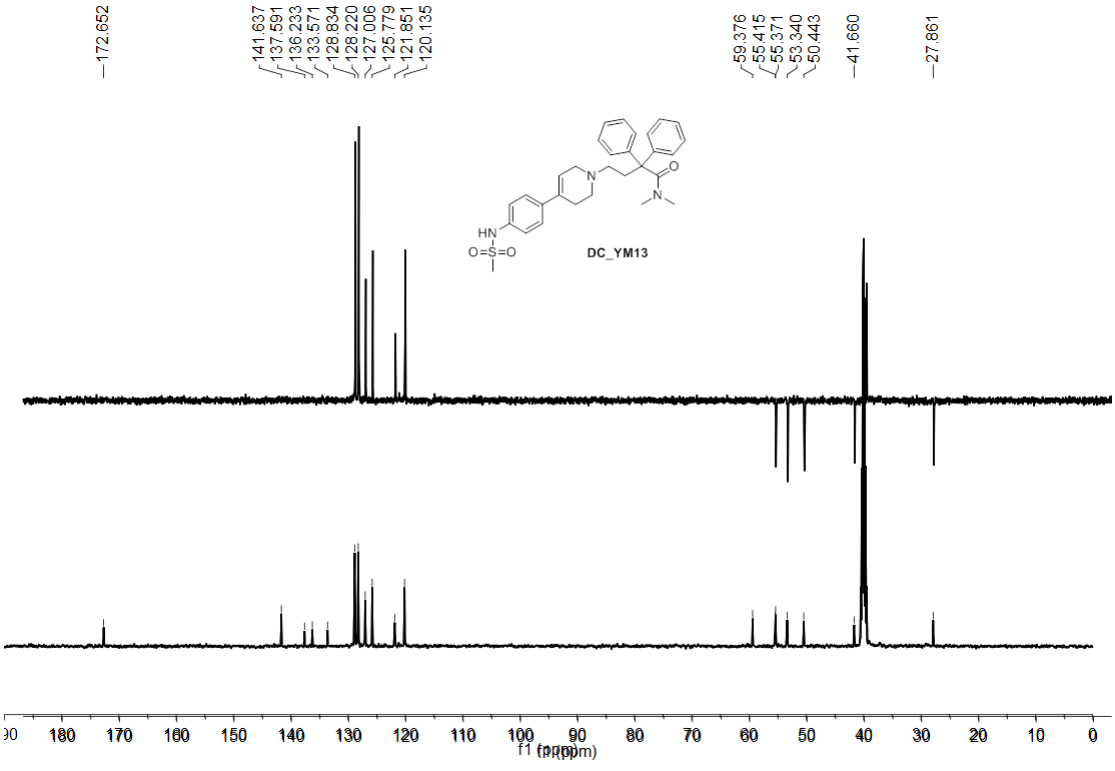
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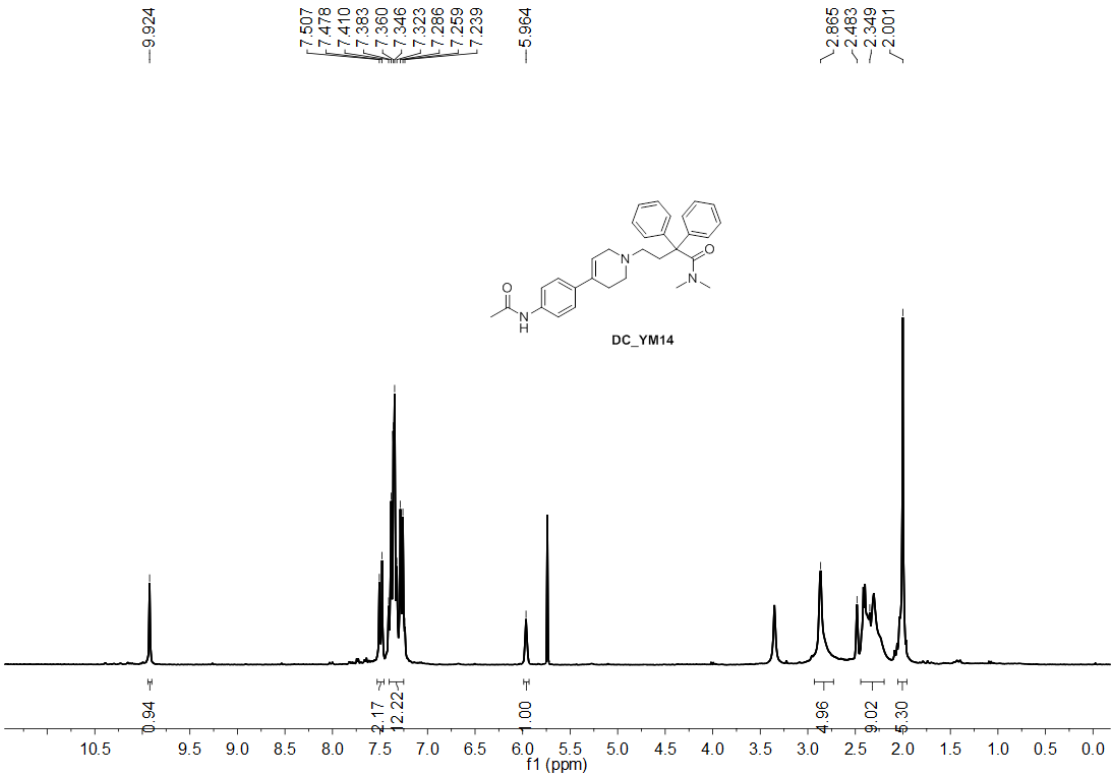
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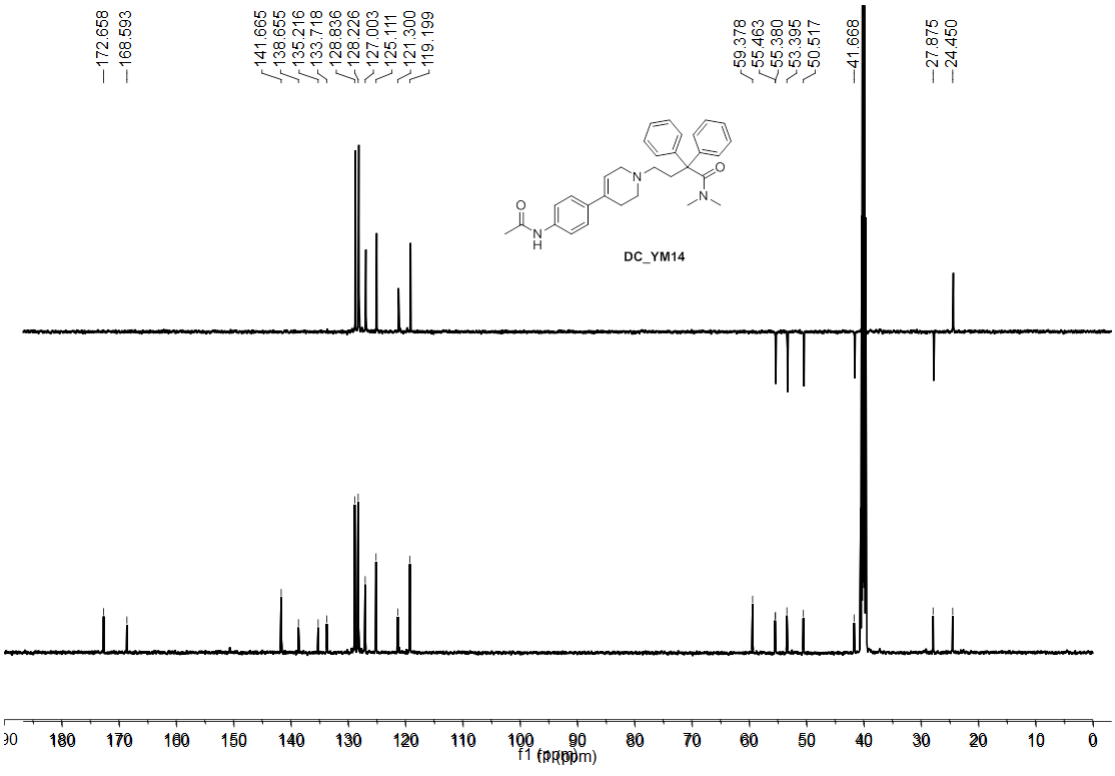
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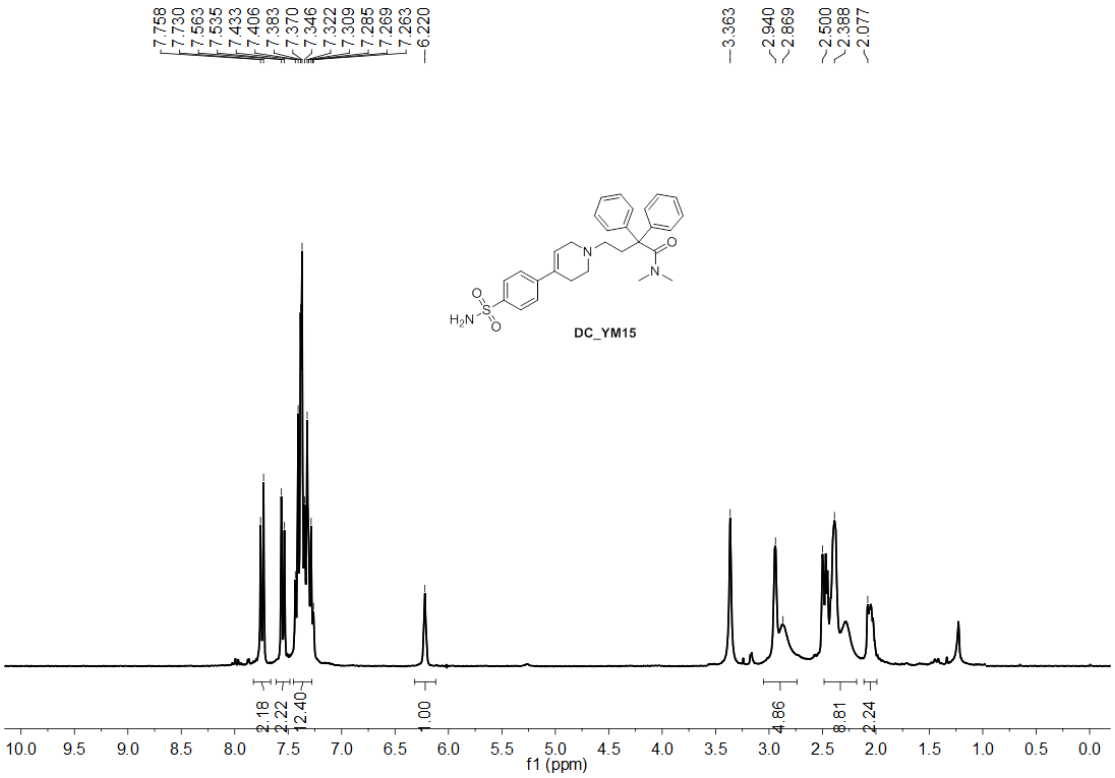
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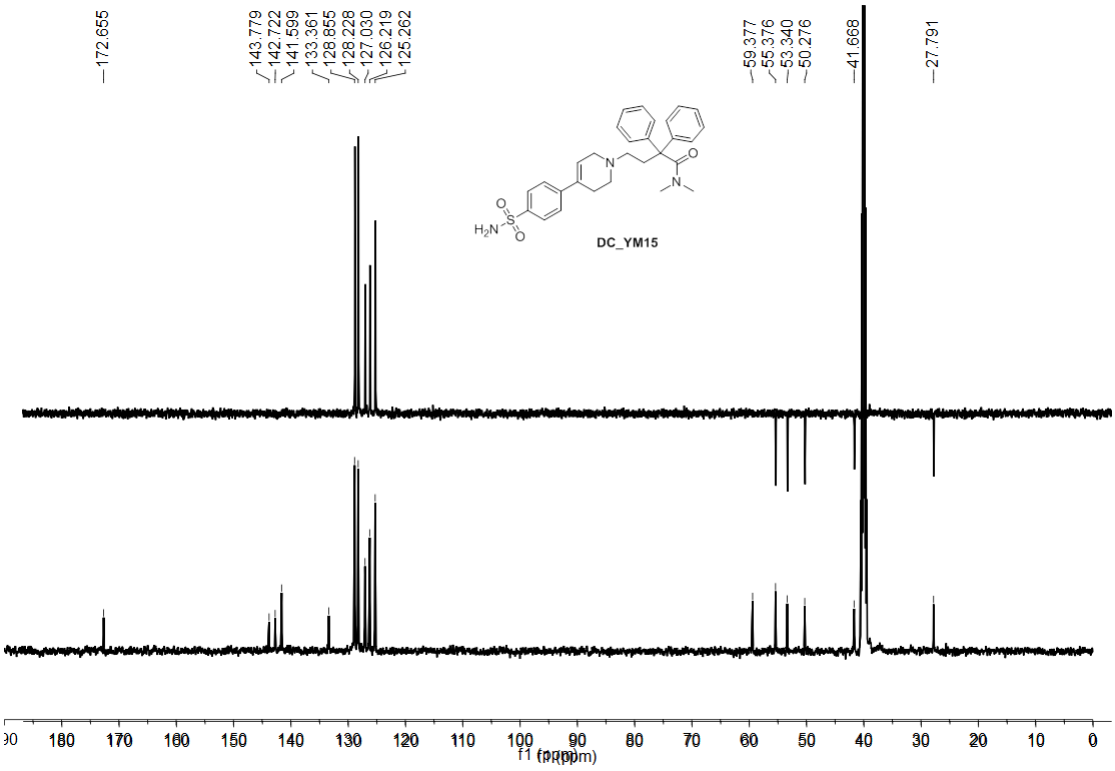
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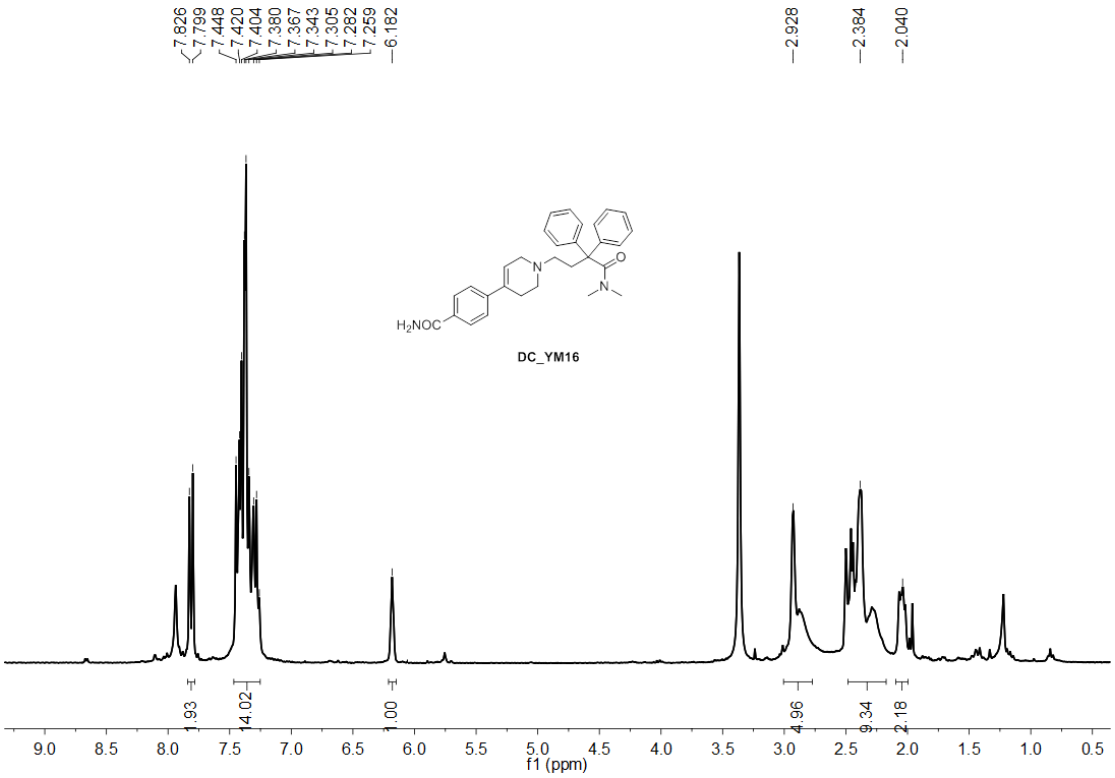
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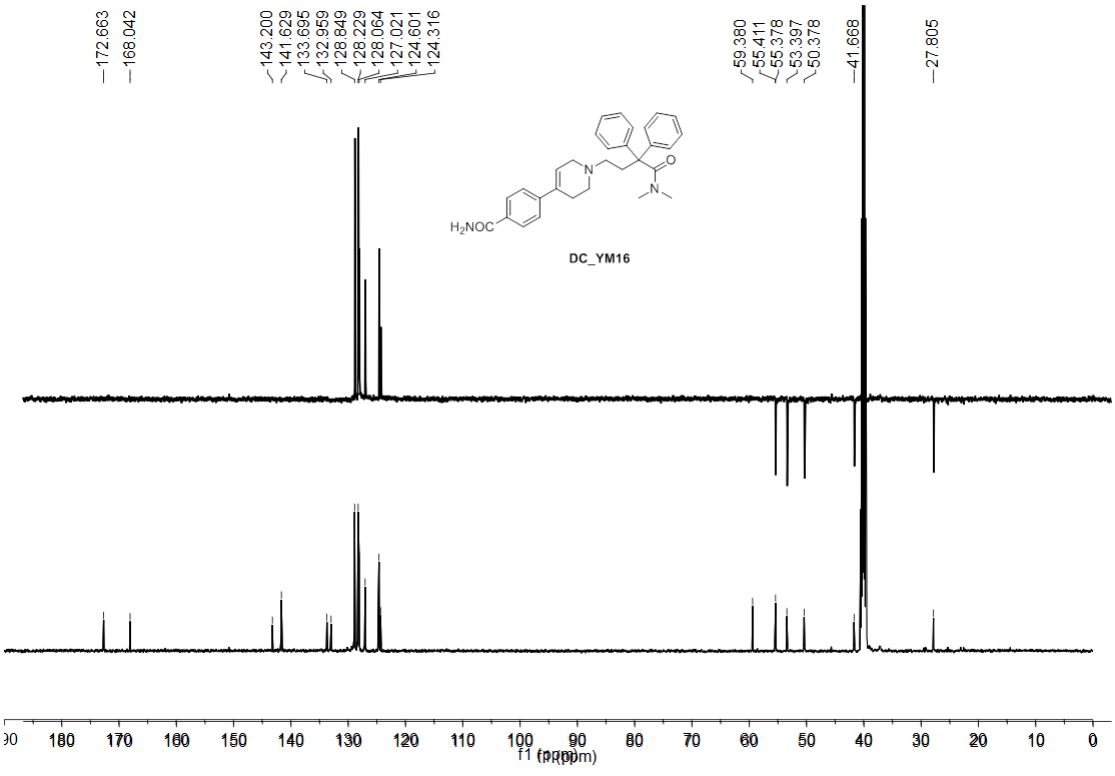
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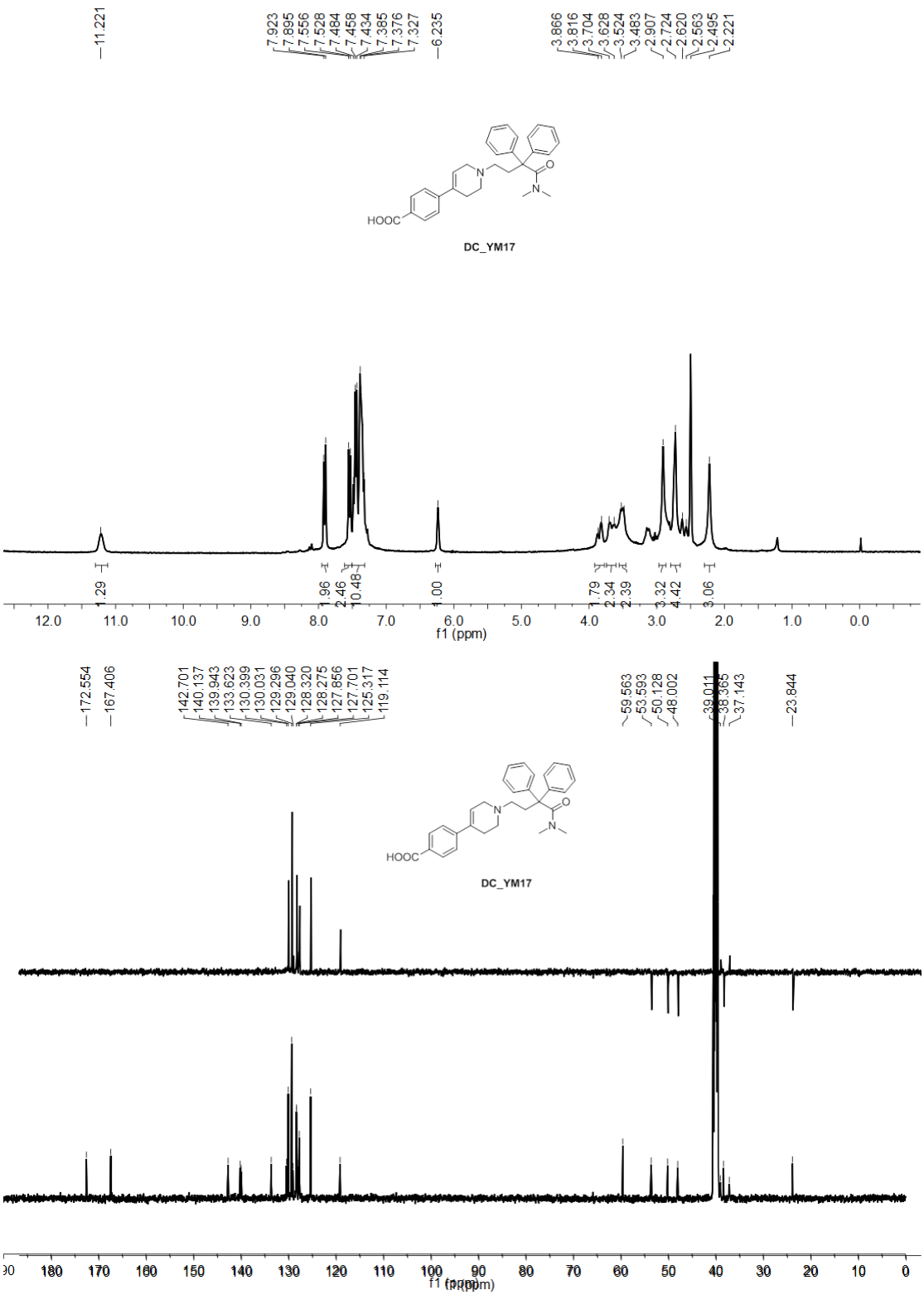
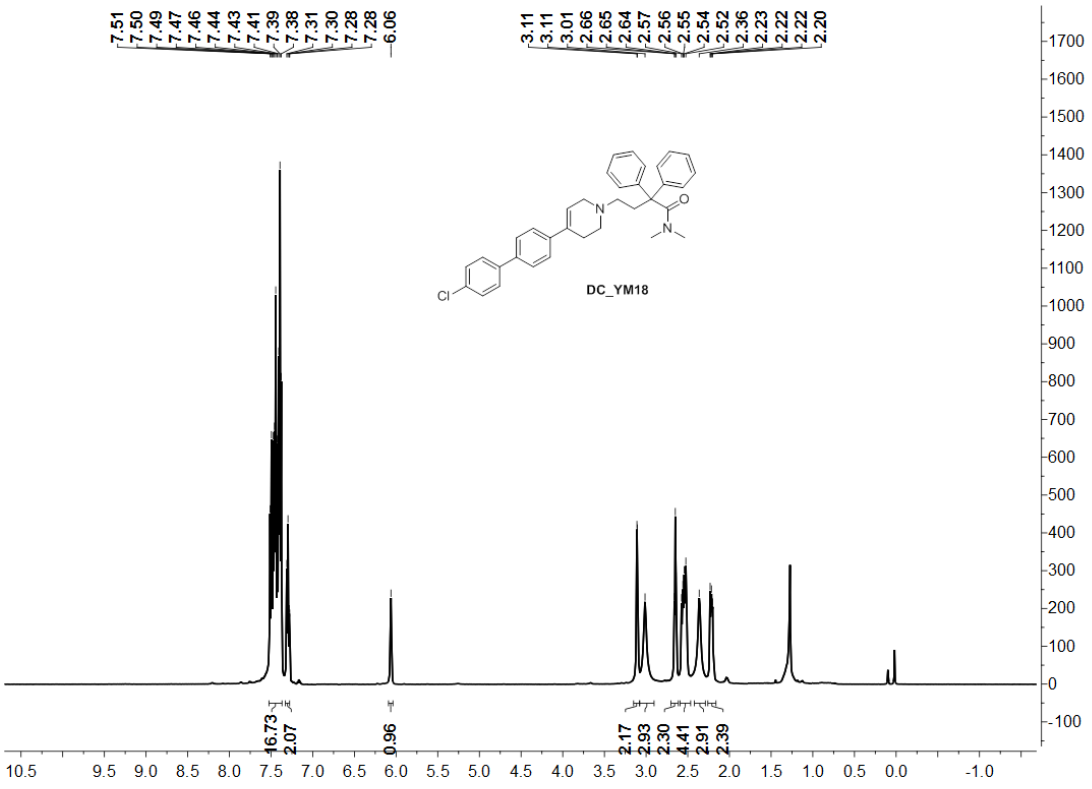
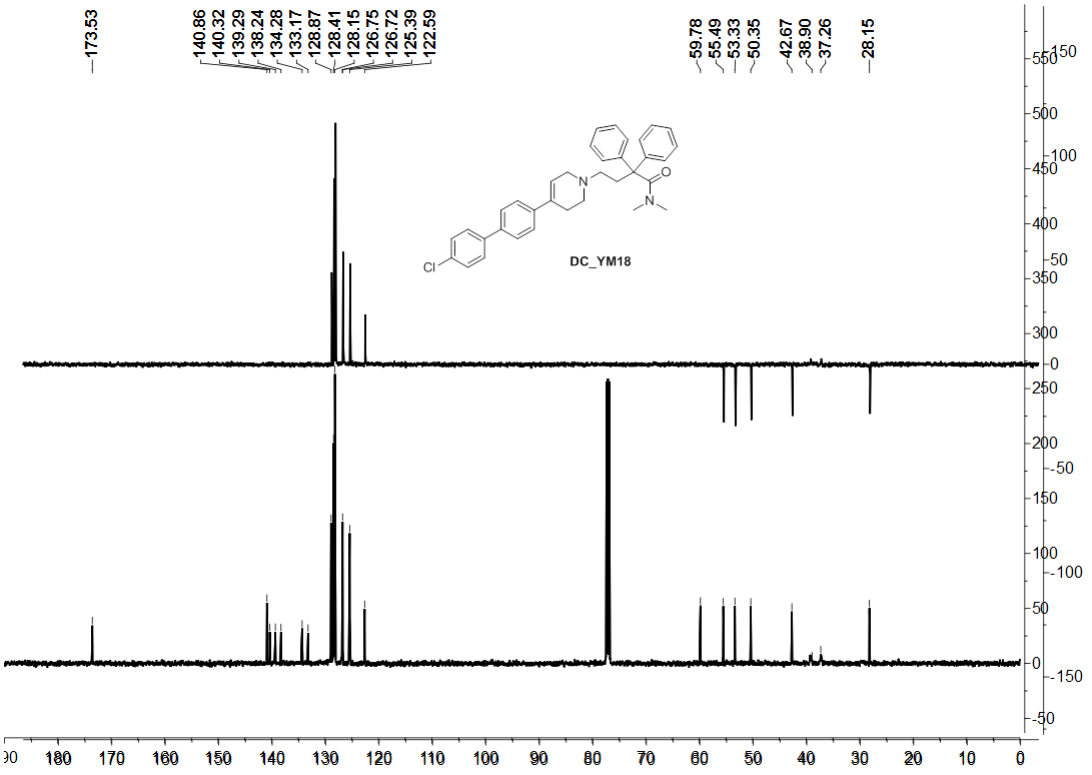
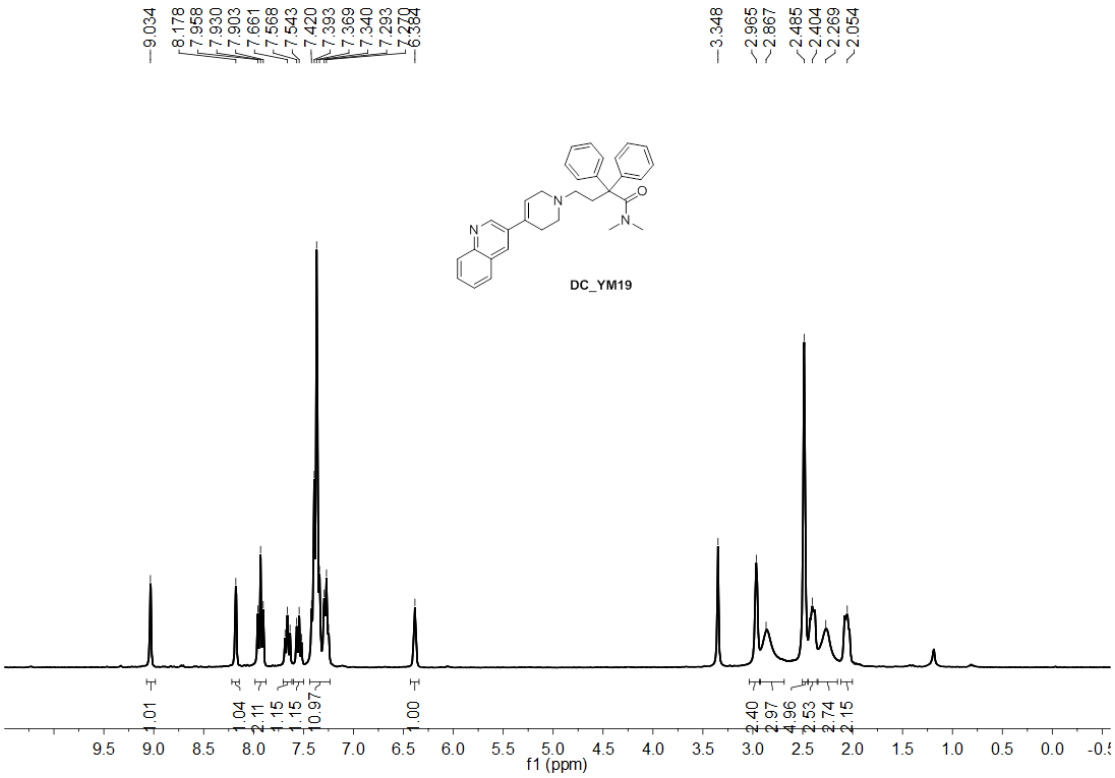
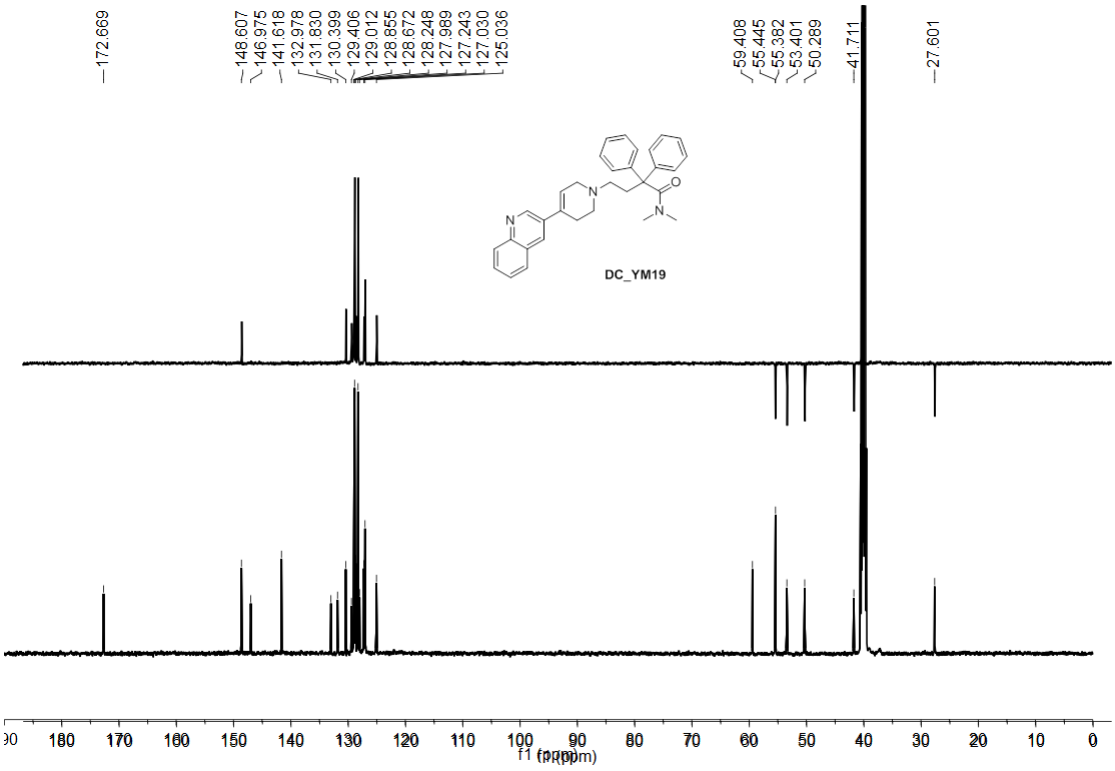
DC_YM16
f1 (ppm)


11.221
7.923
7.895
7.556
7.528
7.484
7.458
7.434
7.385
7.376
7.327
6.235
3.866
3.816
3.704
3.628
3.524
3.483
2.907
2.724
2.620
2.563
2.495
2.221
HOOC
N
O
N
DC_YM17
1.29
1.96
2.46
10.48
1.00
1.79
2.34
2.39
3.32
4.42
3.06
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)
172.554
167.406
142.701
140.137
139.943
133.623
130.399
130.031
129.296
129.040
128.320
128.275
127.856
127.701
125.317
119.114
59.563
53.593
50.128
48.002
39.011
38.365
37.143
23.844
HOOC
N
O
N
DC_YM17
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.51
7.50
7.49
7.47
7.46
7.44
7.43
7.41
7.39
7.38
7.31
7.30
7.28
7.28
6.06
3.11
3.11
3.01
2.66
2.65
2.64
2.57
2.56
2.55
2.54
2.52
2.36
2.23
2.22
2.22
2.20
DC_YM18
16.73
2.07
0.96
2.17
2.93
2.30
4.41
2.91
2.39


173.53
140.86
140.32
139.29
138.24
134.28
133.17
128.87
128.41
128.15
126.75
126.72
125.39
122.59
59.78
55.49
53.33
50.35
42.67
38.90
37.26
28.15
DC_YM18


9.034
8.178
7.958
7.930
7.903
7.661
7.568
7.543
7.420
7.393
7.369
7.340
7.293
7.270
6.384
3.348
2.965
2.867
2.485
2.404
2.269
2.054
DC_YM19
1.01
1.04
2.11
1.15
1.15
10.97
1.00
2.40
2.97
4.96
2.53
2.74
2.15
f1 (ppm)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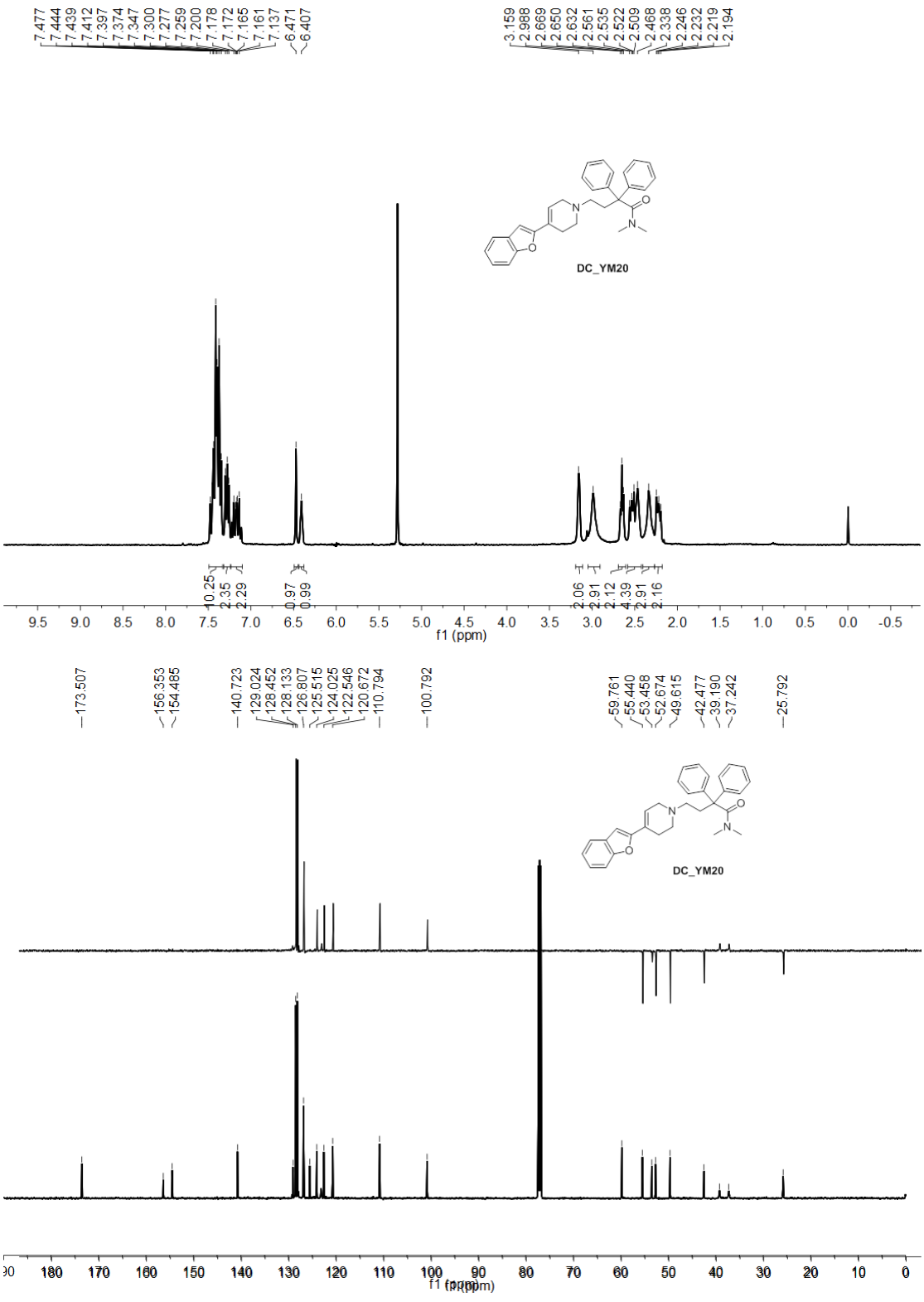
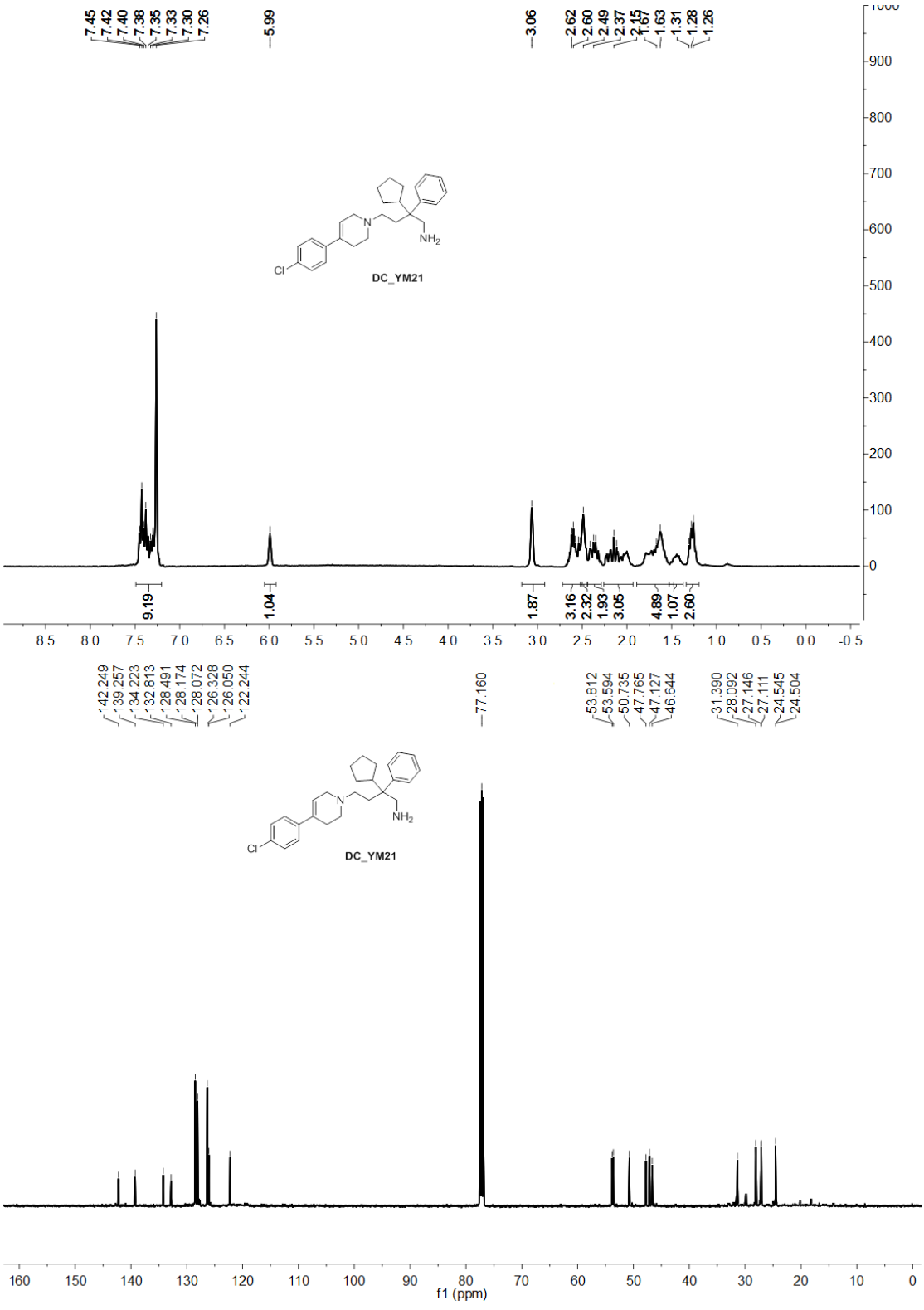
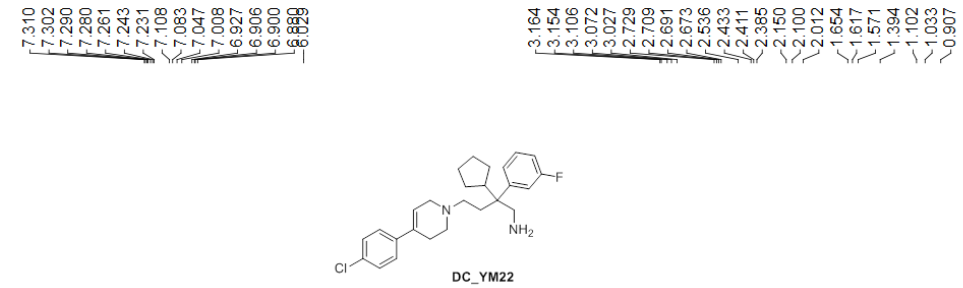
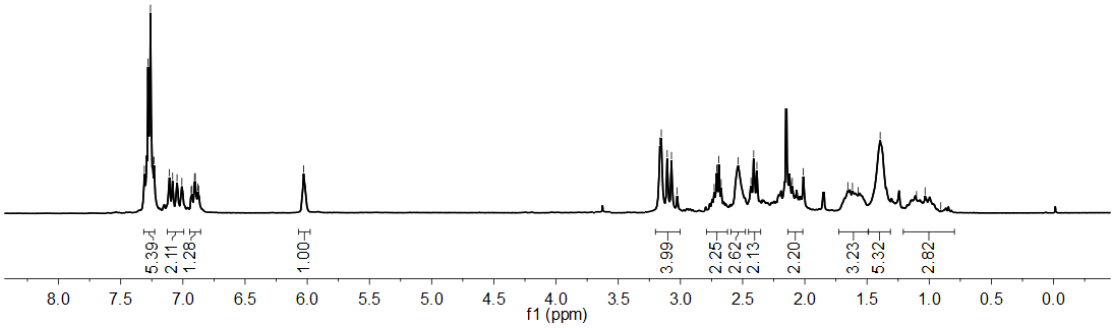
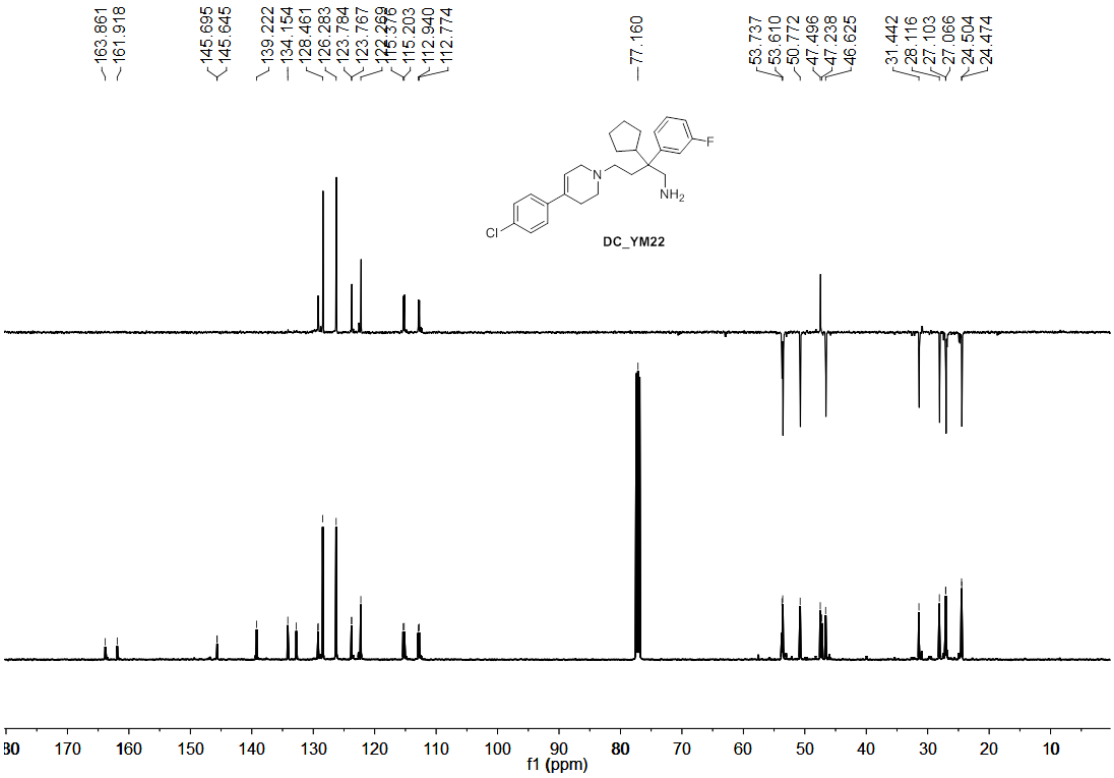
148.607
146.975
141.618
132.978
131.830
130.399
129.406
129.012
128.855
128.672
128.248
127.989
127.243
127.030
125.036
59.408
55.445
55.382
53.401
50.289
41.711
27.601
DC_YM19
f1 (ppm)

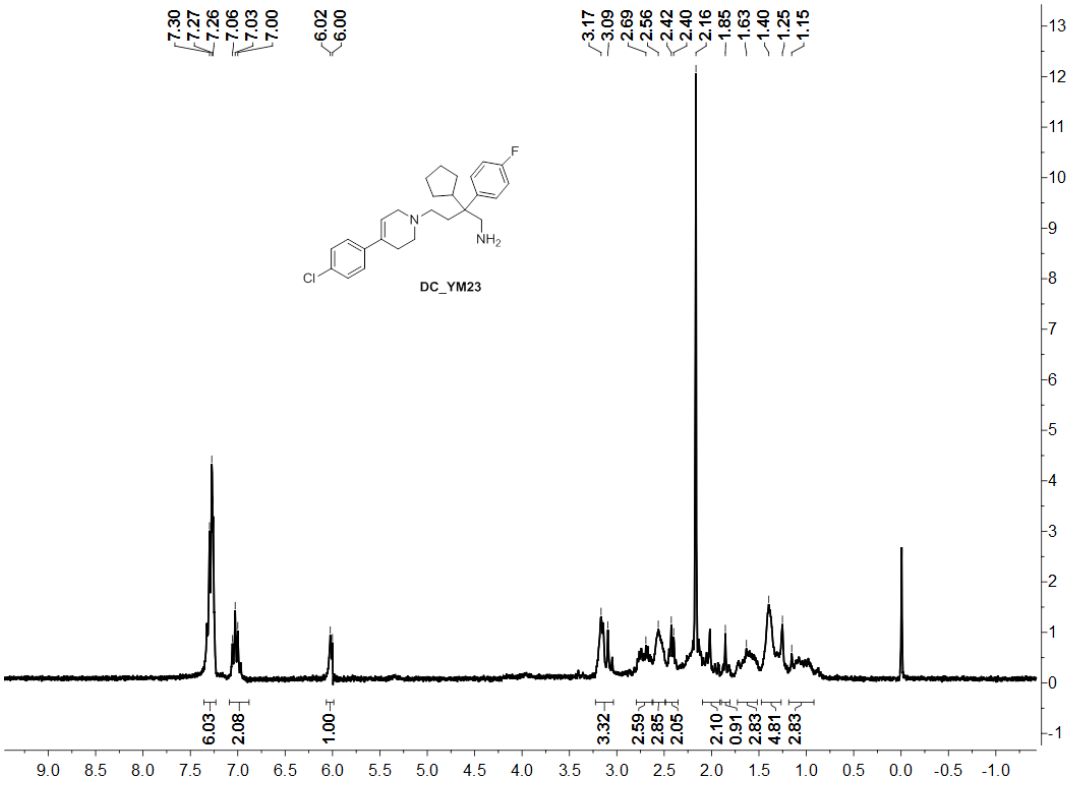

7.477
7.444
7.439
7.412
7.397
7.374
7.347
7.300
7.277
7.259
7.200
7.178
7.172
7.165
7.161
7.137
6.471
6.407
3.159
2.988
2.669
2.650
2.632
2.561
2.535
2.522
2.509
2.468
2.338
2.246
2.232
2.219
2.194
DC_YM20
10.25
2.35
2.29
0.97
0.99
2.06
2.91
2.12
4.39
2.91
2.16
f1 (ppm)
173.507
156.353
154.485
140.723
129.024
128.452
128.133
126.807
125.515
124.025
122.546
120.672
110.794
100.792
59.761
55.440
53.458
52.674
49.615
42.477
39.190
37.242
25.792
DC_YM20
f1 (ppm)

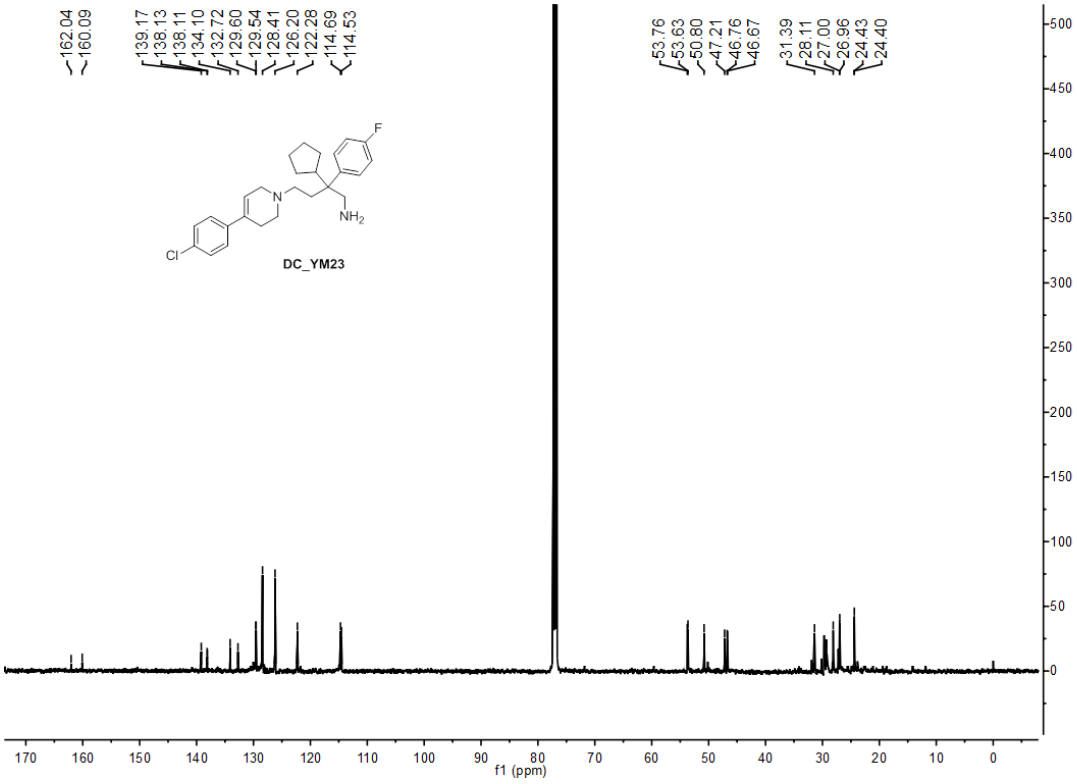

7.45
7.42
7.40
7.38
7.35
7.33
7.30
7.26
5.99
3.06
2.62
2.60
2.49
2.37
2.15
1.67
1.63
1.31
1.28
1.26
DC_YM21
9.19
1.04
1.87
3.16
2.32
1.93
3.05
4.89
1.07
2.60
142.249
139.257
134.223
132.813
128.491
128.174
128.072
126.328
126.050
122.244
77.160
53.812
53.594
50.735
47.765
47.127
46.644
31.390
28.092
27.146
27.111
24.545
24.504
DC_YM21
f1 (ppm)

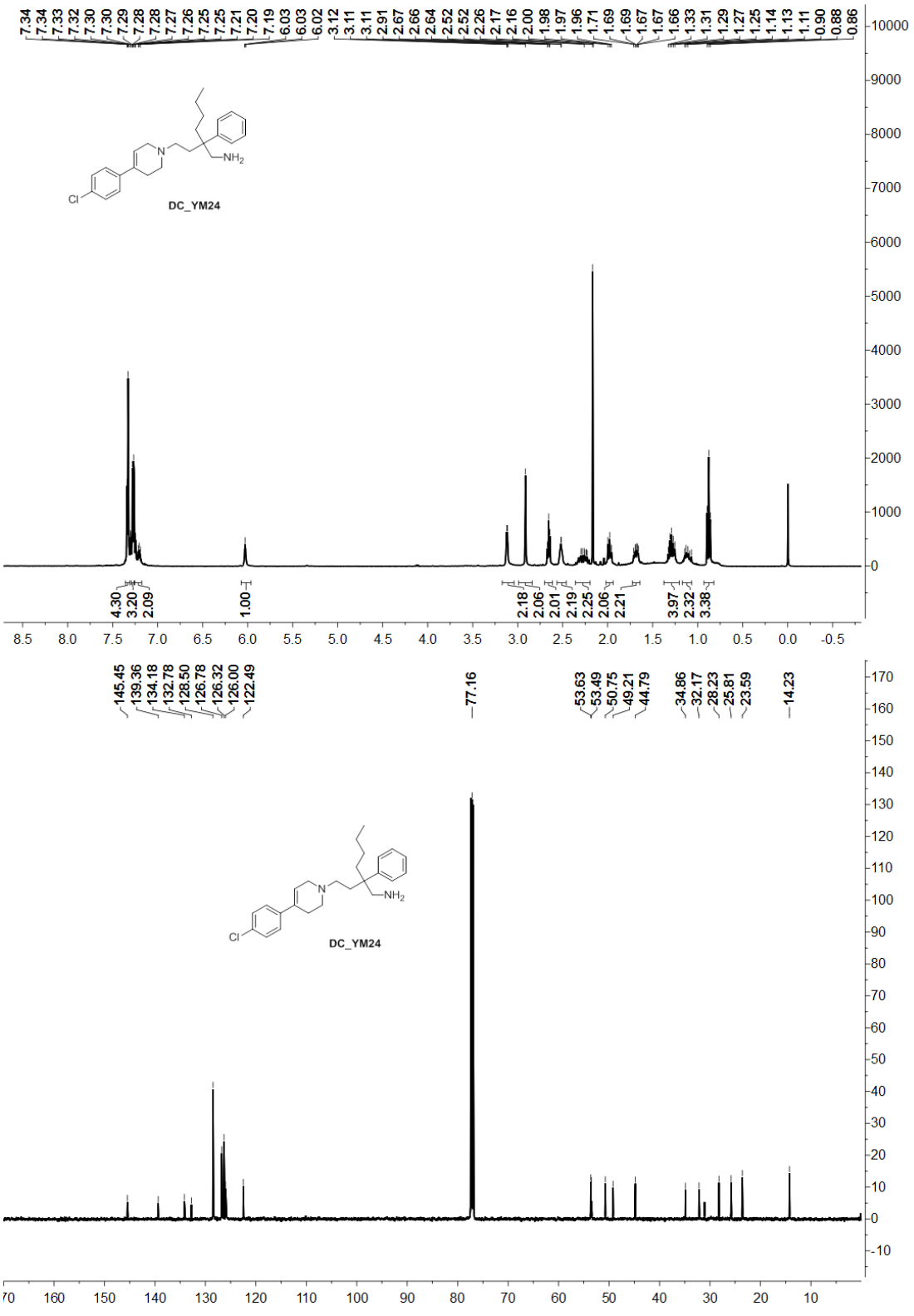

7.310
7.302
7.290
7.280
7.261
7.243
7.231
7.108
7.083
7.047
7.008
6.927
6.906
6.900
3.164
3.154
3.106
3.072
3.027
2.729
2.709
2.691
2.673
2.536
2.433
2.411
2.385
2.150
2.100
2.012
1.654
1.617
1.571
1.394
1.102
1.033
0.907
F
N
NH2
Cl
DC_YM22

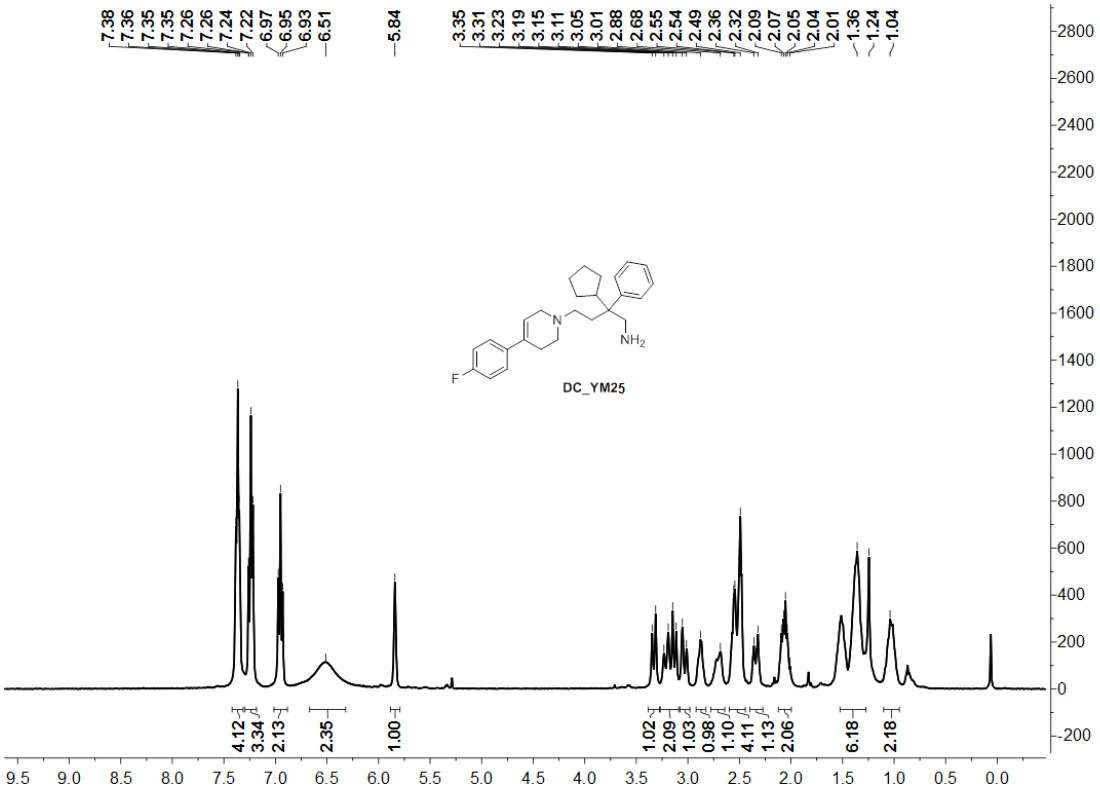

5.39
2.11
1.28
1.00
3.99
2.25
2.62
2.13
2.20
3.23
5.32
2.82
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

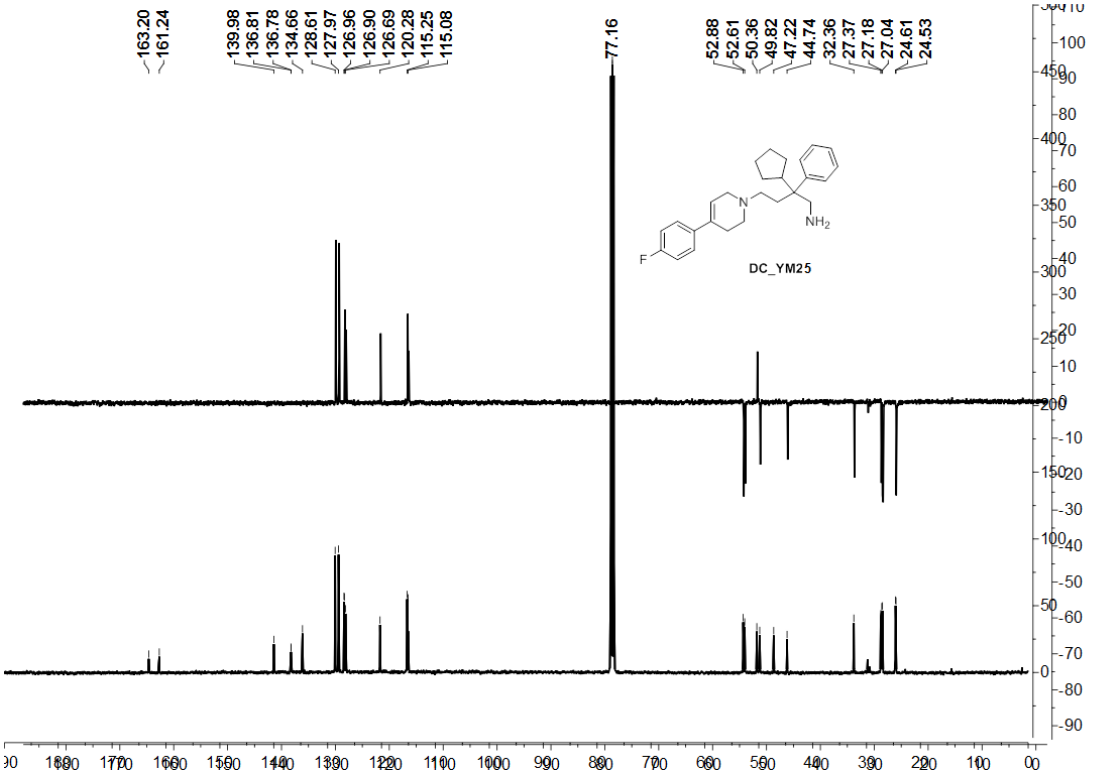

163.861
161.918
145.695
145.645
139.222
134.154
128.461
126.283
123.784
123.767
115.203
112.940
112.774
77.160
53.737
53.610
50.772
47.496
47.238
46.625
31.442
28.116
27.103
27.066
24.504
24.474
F
N
NH2
Cl
DC_YM22
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


7.30
7.27
7.26
7.06
7.03
7.00
6.02
6.00
3.17
3.09
2.69
2.56
2.42
2.40
2.16
1.85
1.63
1.40
1.25
1.15
F
N
NH2
Cl
DC_YM23
6.03
2.08
1.00
3.32
2.59
2.85
2.05
2.10
0.91
2.83
4.81
2.83


162.04
160.09
139.17
138.13
138.11
134.10
132.72
129.60
129.54
128.41
126.20
122.28
114.69
114.53
53.76
53.63
50.80
47.21
46.76
46.67
31.39
28.11
27.00
26.96
24.43
24.40
F
N
NH2
Cl
DC_YM23
f1 (ppm)


DC_YM24
DC_YM24


7.38
7.36
7.35
7.35
7.26
7.26
7.24
7.22
6.97
6.95
6.93
6.51
5.84
3.35
3.31
3.23
3.19
3.15
3.11
3.05
3.01
2.88
2.68
2.55
2.54
2.49
2.36
2.32
2.09
2.07
2.05
2.04
2.01
1.36
1.24
1.04
DC_YM25
4.12
3.34
2.13
2.35
1.00
1.02
2.09
1.03
0.98
1.10
4.11
1.13
2.06
6.18
2.18


163.20
161.24
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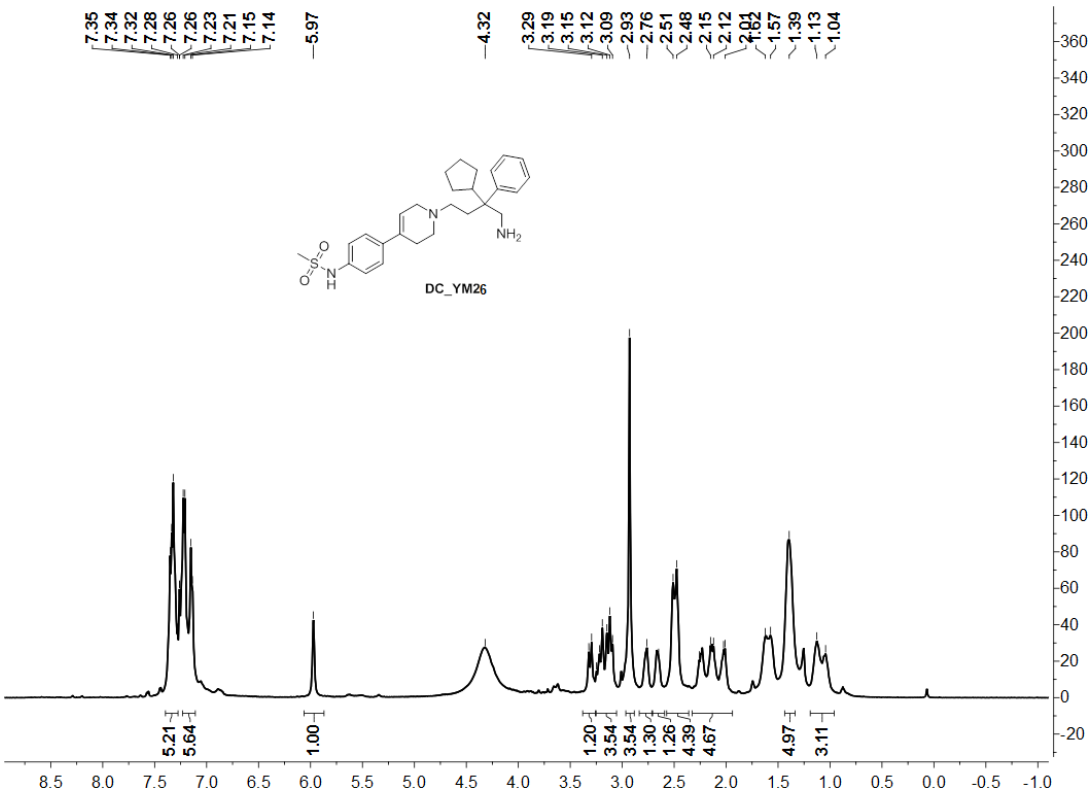
136.81
136.78
134.66
128.61
127.97
126.96
126.90
126.69
120.28
115.25
115.08
77.16
52.88
52.61
50.36
49.82
47.22
44.74
32.36
27.37
27.18
27.04
24.61
24.53
DC_YM25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7.34
7.32
7.28
7.26
7.26
7.23
7.21
7.15
7.14
5.97
4.32
3.29
3.19
3.15
3.12
3.09
2.93
2.76
2.51
2.48
2.15
2.12
2.01
1.82
1.57
1.39
1.13
1.04
DC_YM26
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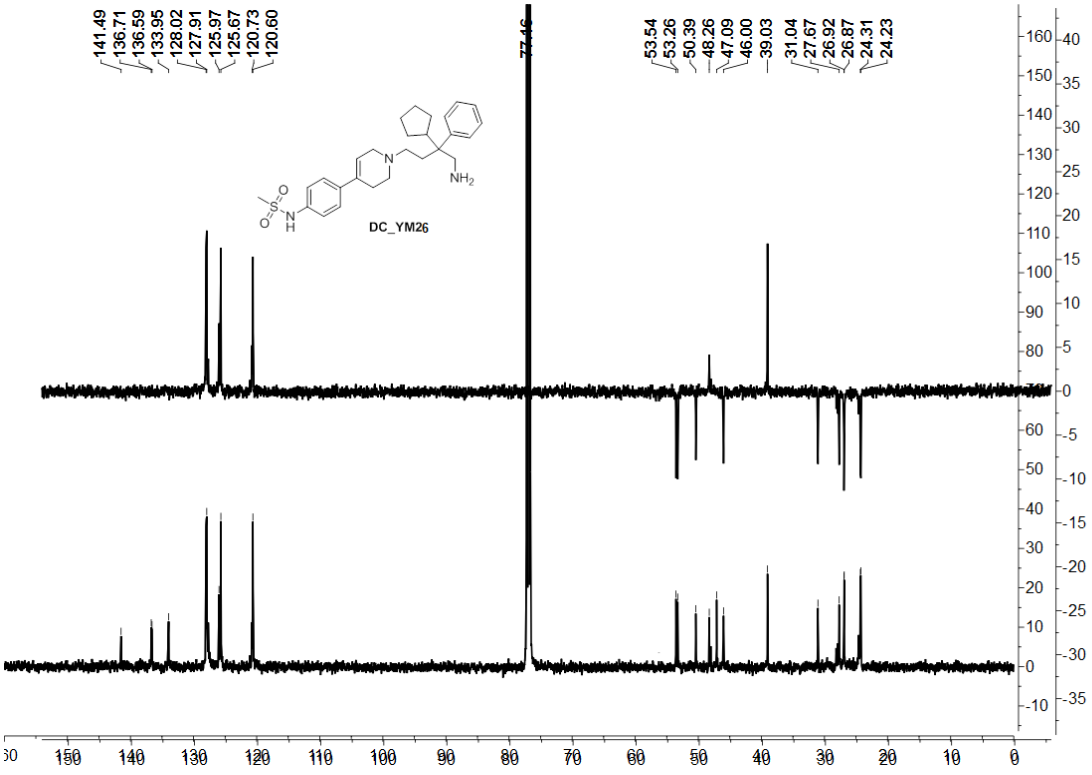
5.64
1.00
1.20
3.54
3.54
1.30
1.26
4.39
4.67
4.97
3.11


141.49
136.71
136.59
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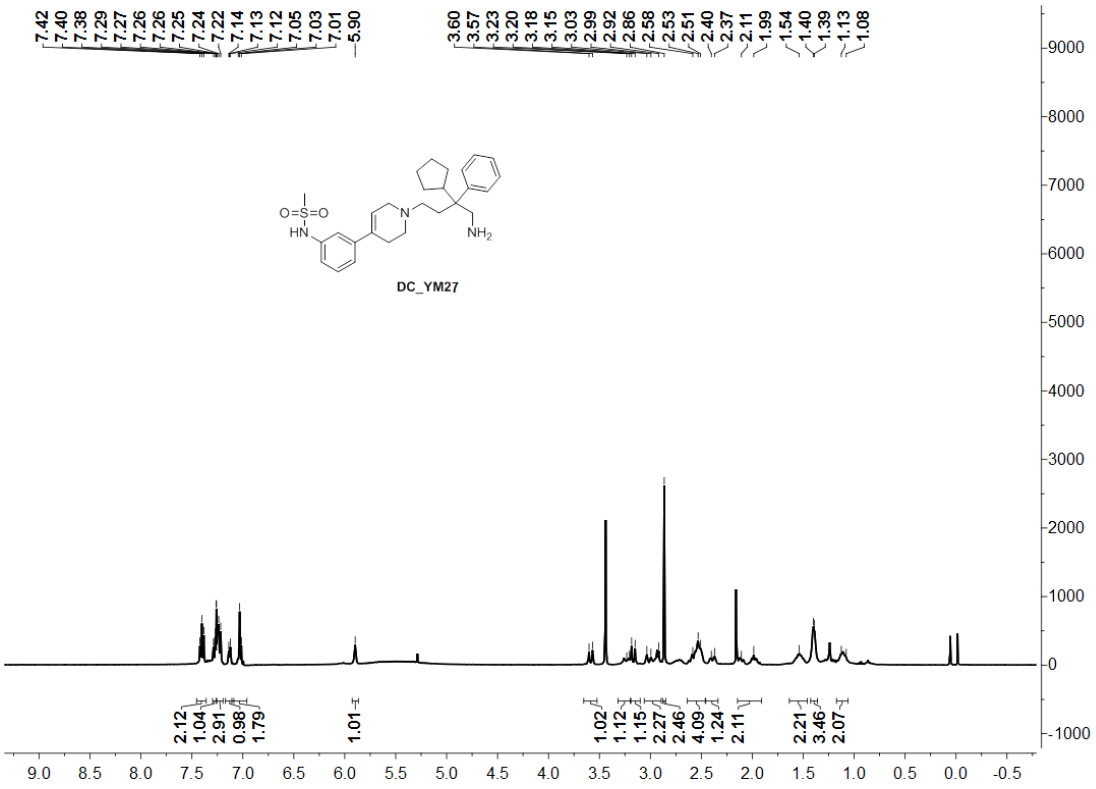
128.02
127.91
125.97
125.67
120.73
120.60
77.46
53.54
53.26
50.39
48.26
47.09
46.00
39.03
31.04
27.67
26.92
26.87
24.31
24.23
DC_YM26


7.42
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7.26
7.26
7.25
7.24
7.22
7.14
7.13
7.12
7.05
7.03
7.01
5.90
3.60
3.57
3.23
3.20
3.18
3.15
3.03
2.99
2.92
2.86
2.58
2.53
2.51
2.40
2.37
2.11
1.99
1.54
1.40
1.39
1.13
1.08
O=S=O
HN
N
NH2
DC_YM27
2.12
1.04
2.91
0.98
1.79
1.01
1.02
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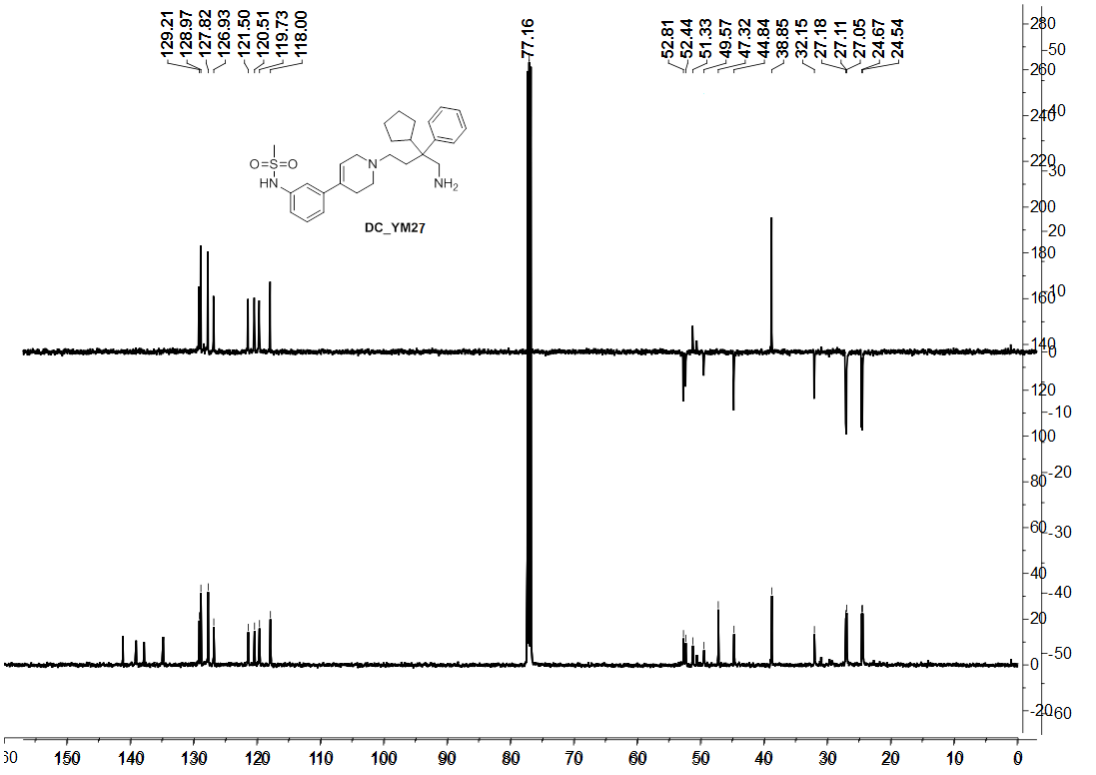
1.15
2.27
2.46
4.09
1.24
2.11
2.21
3.46
2.07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128.97
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126.93
121.50
120.51
119.73
118.00
77.16
52.81
52.44
51.33
49.57
47.32
44.84
38.85
32.15
27.18
27.11
27.05
24.67
24.54
O=S=O
HN
N
NH2
DC_YM27