Supporting Information

A "One-Pot" Multicomponent Approach to a New Series of Morphine Derivatives and Their Biological Evaluation

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I. General Information

All solvents were purified according to standard methods. Melting points were recorded on a BüCHI B-540 melting point apparatus. NMR spectra were recorded for ^{1}H NMR at 400 MHz (or 500 MHz) and for ^{13}C NMR at 100 MHz (or 125 MHz). For ^{1}H NMR, tetramethylsilane (TMS) served as internal standard ($\delta = 0$) and data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t= triplet, q = quartet, m= multiplet), coupling constant in Hz and integration. For ^{13}C NMR, TMS ($\delta = 0$) or $CDCl_3$ (δ =77.26) was used as internal standard and spectra were obtained with complete proton decoupling. HRMS data were obtained on an Agilent 1290 HPLC-6224 Time of Flight Mass Spectrometer.

II. General procedure of 2

A mixture of hydromorphone hydrochloride salt or naloxone hydrochloride salt (0.33 mmol, 1.0 equiv), paraformaldehyde (1.65 mmol, 5.0 equiv) and primary amine (0.69 mmol, 2.1 equiv) were stirred in 2mL DMSO at room temperature for 36 hours. After the completeness of the reaction, the reaction mixture was diluted with 10 mL DCM. The above mixture was then washed with 5 mL water, the organic extracts were collected and concentrated. Purification of the crude product was carried out by chromatography (silica gel, methanol : dichloromethane = 1 : 20) or recrystallization (methanol was used as recrystallization solvent) to afford **2a**-**2v**.

III. General procedure of 3

A mixture of hydromorphone hydrochloride salt (0.33 mmol, 1.0 equiv) and primary amine R_1NH_2 (0.36 mmol, 1.1 equiv) was stirred in 2mL DMSO at room temperature for 12 hours. Paraformaldehyde (1.65 mmol, 5.0 equiv) and the second primary amine R_2NH_2 (0.36 mmol, 1.1 equiv) was then added into the above mixture and stirred for another 36 hours. After the completeness of the reaction, the reaction mixture was diluted with 10 mL DCM. The above mixture was then washed with 5 mL water, the organic extracts were collected and concentrated. Purification of the crude product was carried out by chromatography (silica gel, methanol : dichloromethane = 1 : 20) to afford **3a**-**3i**.

IV. General procedure of biological evaluation

Radioligand competition binding assay

MOR binding assay: rat cortices were homogenized using 50mM Tris, pH 7.4, and centrifuged at 16,500 rpm for 10 min. The pellets were resuspended in fresh buffer and incubated at 37 ^{o}C for 30 min. Following incubation, the suspensions were centrifuged as before, the resulting pellets were then resuspended in 100 volumes of 50mM Tris, pH 7.4 plus 2 mg/mL bovine serum and the suspensions combined. Each assay tube contained 0.5 mL of membrane suspension, 2 nM [^{3}H]-DAMGO, and 0.02 mg/mL mixture in a total volume of 0.65 mL. DOR binding assay: rat cortices were homogenized using 50mM Tris, pH 7.4, 10mM $MgCl_2$-$6H_2O$, 200 mM PMSF, centrifuged and incubated as above. Each assay tube contained 2 nM [^{3}H]-DPDPE, Assay tubes were incubated for 2.5 h at 25 ^{o}C. Unlabeled DPDPE was used as a competitor to generate a standard curve and determine nonspecific binding. KOR binding assay: Guinea pig cortices and cerebella were homogenized using 50 mM Tris, pH 7.4, 10 mM $MgCl_2$-$6H_2O$, 200 mM PMSF,

centrifuged and incubated as above. Each assay tube contained 2 nM [^{3}H]-U69,593. Assay tubes were incubated for 2 h at 25 ºC. Unlabeled U50,488 was used as a competitor to generate a standard curve and determine nonspecific binding. All three binding assays were terminated by filtration through GF/B filters, soaked in 5 mg/mL bovine serum albumin, 50mM Tris, pH 7.4, on a Tomtec Mach II Harvester 96. The filters were subsequently washed with 6 mL of assay buffer. Bound radioactivity was counted on a Wallac Betaplate Liquid Scintillation Counter.

Animal Studies

All animal studies were preapproved by the Torrey Pines Institute for Molecular Studies (Port St. Lucie, FL, USA), operating under the OLAW approval number A4618-01 and in accordance with the 2011 National Institute of Health Guide for the Care and Use of Laboratory Animals (8th edition). Animal studies are reported in compliance with the ARRIVE guidelines. Sample sizes (i.e .number of animals) were not predetermined by a statistical method, and animals were assigned to groups randomly. Drug treatment experiments were conducted in a blinded fashion. No animals were excluded from statistical analysis.

Antinociception test

The 55 ºC warm-water tail-withdrawal assay was performed as described in McLaughlin et al. [1], although modified by the collection of tail-withdrawal latencies over time. Briefly, each mouse was tested for baseline tail-withdrawal latency before drug administration. Tested compound was administered by the i.p. route. Latency to withdraw the tail was subsequently measured in 10-min post-drug administration intervals as indicated in the text, with the tail-withdrawal latency in dose-response lines reported 20 min after compound administration or 30 min after morphine administration (by the i.c.v. route), as this time point corresponds with the peak antinociceptive effect of the respective agents. A maximum response time of 15 s was utilized to prevent tissue damage.

Determination of in vivo opioid receptor agonist activity

To determine the opioid receptor selectivity of the agonist activity of compounds **2n, 2q** and **2r**, MOR KO and KOR KO mice were administered either compound **2n**, **2q** or **2r**, additional wild-type C57BL/6J mice were pretreated 15 min with a single dose of the DOR-selective antagonist naltrindole (20 mg/kg, i.p.) before administration of each compound. Antinociception was tested 30 min later.

Oxymax/CLAMS measurement of respiration rate and locomotor activity.

Respiration rates were recorded using the automated, computer-controlled Comprehensive Lab Animal Monitoring System (CLAMS; Columbus Instruments, Columbus, OH) as described previously [2]. Mice were placed in closed apparatus cages (23.5 cm×11.5 cm×13 cm). Before testing, mice were confined to the chambers for 60 minutes to habituate the animals to the apparatus. Mice were administered vehicle (10% DMSO/90% saline, i.p.), morphine (10 mg/kg, i.p.) or a 5 mg/kg, i.p. dose of either hydromorphone, compound **2n, 2q** or **2r** returned to chambers for 120 min. Using a pressure transducer built into the sealed CLAMS cage, the respiration rate (breaths/min) of each occupant mouse was counted.

Hydrolytic stability evaluation of 2r

To 300 μL PBS solution (pH = 7.4) in polystyrene tube and pre-incubated at 37 ℃ for 5 min, was added a 300 μL solution of **2r** in acetonitrile (2 μM), and the sample were incubated at 37 ℃. At defined times the solution was analyzed and samples were run on a Agilent 1290 HPLC-6224 time-of-flight mass spectrometer using PhenomenexLuna 5 μ C_{18}, 100 Å, 150 mm × 4.60 mm 5 μm column at a flow rate of 0.5 mL/min using liner gradients buffer B in A (B, CH_3OH containing 0.1% formic acid; A, H_2O containing 0.1% formic acid) at 254 nm. Mobile phase B was increased linearly from 5% to 95% over 7 min and 95% over the next 2 min, after which the column was equilibrated to 5% for 1 min. The remaining percentage of **2r** is calculated by area normalization method.

Human Specimens

Human serum sample was from Innovative Research (Saint Louis, MO, USA). The use of human serum samples was preapproved by the Torrey Pines Institute for Molecular Studies (Port St. Lucie, FL, USA), operating under the OLAW approval number A4618-01 and in accordance with federal regulations.

Serum stability evaluation of 2r

Human serum was spiked with **2r** for a 1.0 μM concentration. Sample was incubated in a water bath at 37 °C. At time points 0, 30, 60, 120, and 240 minutes, 200 μL of the serum sample was added to 400 μL of cold methanol with 10 μM concentration of internal standard. Blank serum samples were made in the same manner prior to the serum being spiked with the compound. Each time point was prepared in triplicate. Samples were centrifuged at 10,000 rpm for 10 minutes. The supernatant was dried in a speed vacuum. Samples were then reconstituted in 100 μL of 10 % acetonitrile in water. Next, samples were centrifuged at 13,000 rpm for 5 minutes. A volume of 80 μL supernatant was transferred to a vial and 10 μL was injected for analysis. Analysis was conducted by using High Performance Liquid Chromatography (HPLC, 20AD Shimadzu Prominence)/ Tandem Mass Spectrophotometry MS/MS, AbSciex 3200 QTrap® triple-quadrupole linear ion trap mass spectrometer fitted with a TurboIonSpray interface (Applied Biosystems/MDS Sciex, Darmstadt, Germany). In brief, to achieve separation on the HPLC of the analyte and the internal standard, reverse phase mode with a gradient of 20-70% acetonitrile over 8 minutes was used on a C_{18} reverse phase column (Phenomenex Gemini NX 110A 50 × 4.6 mm). Mobile phase A was LCMS grade water with 0.1% formic acid. Mobile phase B was acetonitrile with 0.1% formic acid. The MS/MS analysis was performed in Multiple Reaction Monitoring (MRM) mode using the two largest fragments of the parent ions. MS instrument parameters were spray voltage 5.5 kV, curtain gas 20 psi, source temperature 500 °C, ion source gas1-30 psi and gas 2-20 psi. Blank solvent injections were run between each sample to minimize analyte carry over. The counts for the ion transitions were summed to give the total peak area. The ratio of the analyte peak area to the internal standard peak area was calculated for each sample. The average ratio of the blank samples was calculated and used to normalize the time point signals, then the average was calculated and plotted for each time point.

Statistical Analysis

All dose–response lines were analyzed by regression and ED_{50} (dose producing 50% antinociception) values and 95% confidence limits determined using each individual data point with the Prism 5.0 software package (GraphPad, La Jolla, California, USA). Data for

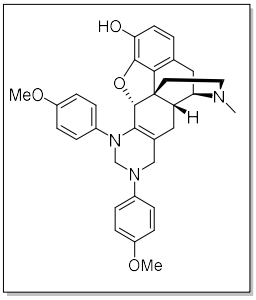
antinociception experiments were analyzed with Student's t-tests and analysis of variance (ANOVA) with Dunnett's *post hoc* test using Prism 5.0 software. Analyses examined the main effect of baseline and post-treatment tail-withdrawal latencies to determine statistical significance for all tail-withdrawal data. Statistical significance of ED_{50} values was determined by evaluation of the ED_{50} value shift via nonlinear regression modeling using Prism 5.0. Respiration data collected with CLAMS were analyzed via two-way matching-samples ANOVA, with treatment and time as factors, and Holm-Sidak's *post-hoc* test used to assess group differences. Effects were considered significant when $p < 0.05$. All effects are expressed as mean ± SEM.

Reference:

[1] J. P. McLaughlin, K.P. Hill, Q. Jiang, A. Sebastian, S. Archer, J. M. Bidlack, *J. Pharmacol. Exp. Ther*. 1999, **289**, 304.

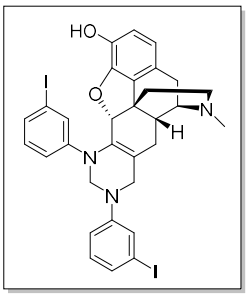
[2] C. J. Armishaw, J. Banerjee, M. L. Ganno, K. J. Reilley, S. O. Eans, E. Mizrachi, M. R. Hoot, R. Gyanda, R. A. Houghten, J. P. McLaughlin: *ACS Comb. Sci.,* 2013, **15**, 153.

V. Characterization Data of compound 2 and 3



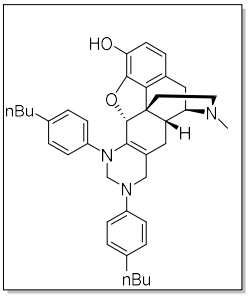
(4bS,13bR)-11,13-bis(4-methoxyphenyl)-7-methyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol（**2a**）

White solid, m. p.:190.3-190.9 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.9 Hz, 2H), 6.72-6.69 (m, 3H), 6.59-6.55 (m, 3H), 4.84 (s, 1H), 4.57 (d, J = 11.6 Hz, 1H), 4.20 (d, J = 11.6 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 3.51 (dd, J = 2.4, 1.3 Hz, 1H), 3.46 – 3.37 (m, 1H), 3.22 (dd, J = 6.2, 2.8 Hz, 1H), 3.04 (d, J = 18.6 Hz, 1H), 2.59 – 2.48 (m, 2H), 2.44 (s, 3H), 2.43 – 2.30 (m, 2H), 1.99-1,86 (m, 1 H), 1.76 – 1.71 (m, 2H), 1.68 – 1,66 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.28, 152.52, 143.85, 142.21, 140.33, 139.46, 133.39, 128.94, 125.04, 124.59, 122.41, 118.21, 116.72, 116.21, 114.35, 114.17, 84.53, 70.26, 58.02, 55.19, 55.15, 51.66, 46.06, 42.67, 41.66, 40.43, 35.60, 27.10, 19.87. HRMS (ESI): m/z calcd for $C_{33}H_{36}N_3O_4[M+H]^+$: 538.2700, found:538.2709.



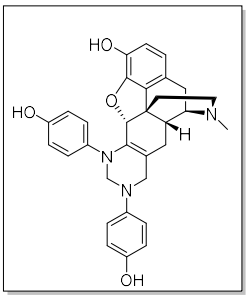
(4bS,13bR)-11,13-bis(3-iodophenyl)-7-methyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**2b**)

White solid, m. p.:191.1-193.4℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 2H), 7.04-7.01 (m, 3H), 6.88 (dd, J = 2.3, 1.7 Hz, 1H), 6.83 – 6.79 (t, J = 8.1Hz 1H), 6.70 (d, J = 8.1Hz 1H), 6.58 (d, J = 8.1Hz, 1H), 6.54 – 6.49 (m, 1H), 4.84 (s, 1H), 4.81 (d, J = 12.1 Hz, 1H), 4.23 (d, J = 11.7 Hz, 1H), 3.68 – 3.63 (m, 1H), 3.48 (d, J = 15.4 Hz, 1H), 3.21 (dd, J = 5.9, 2.7 Hz, 1H), 3.04 (d, J = 13.8 Hz, 1H), 2.52 – 2.45 (m, 2H), 2.43 (s, 3H), 2.40 – 2.30 (m, 2H), 2.01 – 1.90 (m, 1H), 1.79-1.73(m, 2H), 1.72 – 1.68 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.93, 148.38, 143.54, 139.30, 133.30, 132.83, 132.48, 130.68, 130.53, 128.66, 127.95, 125.67, 124.66, 123.25, 122.88, 119.26, 117.12, 113.85, 95.27, 94.67, 86.11, 68.72, 58.82, 50.88, 46.50, 42.86, 42.30, 39.39, 35.58, 27.60, 20.37. HRMS (ESI): m/z calcd for $C_{31}H_{30}I_2N_3O_2[M+H]^+$: 730.0422, found:730.0426.



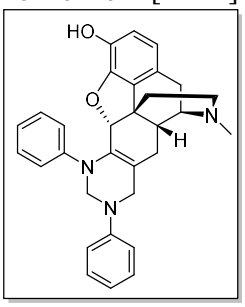
(4bS,13bR)-11,13-bis(4-butylphenyl)-7-methyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol. (**2c**)

White solid, m. p.:179.9-181.7℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 8.0 Hz, 2H), 7.05 (m, J = 8.8 Hz, 2H), 6.91 (m, J = 8.0 Hz, 2H), 6.56 (m, 3H), 6.50 (d, J = 7.9 Hz, 1H), 5.12 (d, J = 12.0 Hz, 1H), 4.82 (s, 1H), 4.03 (d, J = 12.0 Hz, 1H), 3.80 – 3.66 (m, 1H), 3.36 (d, J = 17.2 Hz, 1H), 3.14 (dd, J = 6.1, 2.8 Hz, 1H), 2.94 (d, J =18.7 Hz, 1H), 2.56 – 2.48 (m, 1H), 2.48 – 2.43 (m, 2H), 2.40 (dt, J = 10.7, 5.1 Hz, 3H), 2.34 (s, 3H), 2.33 – 2.26 (m, 2H), 2.17 (dd, J = 12.2, 8.7 Hz, 1H), 1.90 – 1.82 (m, 1H), 1.66 (dd, J = 8.7, 7.2 Hz, 1H), 1.59 – 1.48 (m, 3H), 1.48 – 1.38 (m, 2H), 1.36 – 1.17 (m, 4H), 0.93 – 0.79 (m, 7H).^{13}C NMR (100 MHz, $CDCl_3$) δ 145.83, 144.69, 143.83, 139.49, 136.21, 133.17, 131.97, 128.85, 128.70, 128.65, 128.61, 124.97, 123.91, 122.34, 118.28, 116.74, 114.09, 84.26, 68.39, 58.03, 50.84, 40.13, 39.92, 39.71, 39.50, 39.29, 39.09, 38.88, 33.35, 33.19, 27.07, 21.77, 21.65, 21.57, 19.91, 13.77, 13.72. HRMS (ESI): m/z calcd for $C_{39}H_{48}N_3O_2[M+H]^+$: 590.3741, found:590.3742.



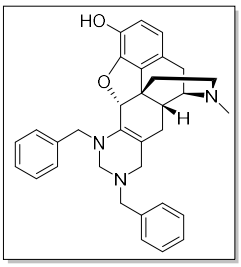
4,4'-((4bS,13bR)-1-hydroxy-7-methyl-7,8,8a,9-tetrahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazoline-11,13(6H,10H,12H,13bH)-diyl)diphenol (**2d**)

White solid, m. p.:200.4-201.4℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, J = 8.8 Hz, 2H), 6.72 (d, J = 8.8 Hz, 2H), 6.70 – 6.47 (m, 6H), 4.81 (s, 1H), 4.65 (d, J = 16.0 Hz, 2H), 3.97 (d, J = 11.6 Hz, 1H), 3.57 (d, J = 14.4 Hz, 1H), 3.33 – 3.28 (m, 1H), 3.09 – 3.01 (m, 1H), 2.94 – 2.85 (m, 1H), 2.49 – 2.39 (m, 2H), 2.35 (s, 3H), 2.19 – 2.15 (m, 2H), 2.17 – 2.00 (m, 1H), 1.81 – 1.63 (m, 2H), 1.68 – 1.55 (m, 1H). ^{13}C NMR (100MHz, $CDCl_3$) δ 153.43, 150.54, 143.89, 141.04, 139.41, 138.95, 133.52, 130.33, 124.96, 124.45, 121.51, 119.18, 118.14, 116.82, 115.48, 115.40, 84.58, 70.97, 58.28, 52.09, 46.16, 42.48, 41.63, 40.01, 39.64, 24.96, 19.51. HRMS (ESI): m/z calcd for $C_{31}H_{32}N_3O_4[M+H]^+$: 510.2387, found:510.2395.



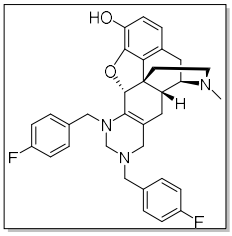
(4bS,13bR)-7-methyl-11,13-diphenyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**2e**)

White solid, m. p.:189.4-192.6℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 2H), 7.15 – 7.08 (m, 5H), 6.75 – 6.68 (m, 2H), 6.63 – 6.53 (m, 3H), 4.92 (d, J = 11.9 Hz, 1H), 4.31 (d, J = 11.9 Hz, 1H), 3.69 – 3.60 (m, 1H), 3.55 – 3.44 (m, 2H), 3.23 (dd, J = 6.1, 2.8 Hz, 1H), 3.06 (d, J = 18.6 Hz, 1H), 2.56 (dd, J = 7.6, 2.7 Hz, 2H), 2.44 (s, 3H), 2.34 (ddd, J = 17.0, 15.7, 4.8 Hz, 2H), 1.96 (td, J = 12.4, 4.9 Hz, 1H), 1.84 – 1.75 (m, 2H), 1.72 (ddd, J = 12.6, 3.6, 1.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.88, 147.36, 143.77, 139.42, 133.78, 129.16, 129.10, 128.93, 125.65, 123.87, 123.83, 123.77, 119.08, 118.96, 117.09, 114.60, 86.47, 69.81, 58.82, 51.08, 46.55, 42.86, 42.31, 39.52, 35.62, 27.76, 20.40. HRMS (ESI): m/z calcd for $C_{31}H_{32}N_3O_2$ $[M+H]^+$: 478.2489, found:478.2493.



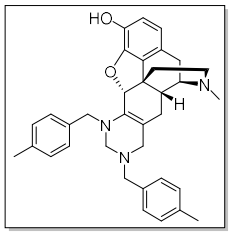
(4bS,13bR)-11,13-dibenzyl-7-methyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**2h**)

White solid, m. p.:190.3-192.2℃.^{1}H NMR (400 MHz, DMSO) δ 8.92 (s, 1H), 7.52 – 7.11 (m, 10H), 6.66 (d, J = 8.0 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 5.11 (s, 1H), 4.63 (d, J = 14.6 Hz, 1H), 3.96 (d, J = 14.6 Hz, 1H), 3.67 – 3.53 (m, 1H), 3.41 – 3.31 (m, 2H), 3.25 – 3.10 (m, 1H), 3.00 (d, J = 18.4 Hz, 1H), 2.96 – 2.79 (m, 2H), 2.65 – 2.57 (m, 1H), 2.52 (dd, J = 12.1, 4.6 Hz, 1H), 2.41 (s, 3H), 2.36 – 2.19 (m, 2H), 1.97 (td, J = 12.2, 5.0 Hz, 1H), 1.81 – 1.66 (m, 2H), 1.53 (dd, J = 15.9, 12.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 143.59, 139.86, 139.45, 138.13, 134.70, 129.14 , 129.00, 128.42, 127.95, 127.80, 126.73, 126.42, 125.09, 118.07, 117.29, 116.55, 89.43, 67.40, 58.13, 57.83, 56.23, 53.55, 48.64, 46.04, 42.69, 42.19, 35.69, 26.93, 19.80. HRMS (ESI): m/z calcd for $C_{33}H_{36}N_3O_2$ $[M+H]^+$: 506.2802, found:506.2807.



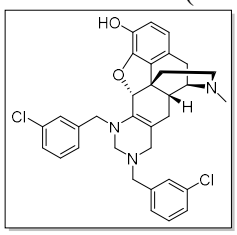
(4bS,13bR)-11,13-bis(4-fluorobenzyl)-7-methyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**2i**)

White solid, m. p.:137.5-139.1℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, $J_{(H-H)}$ = 8.4 Hz, $J_{(F-H)}$ = 5.6 Hz, 2H), 7.10(dd, $J_{(H-H)}$ =8.4 Hz, $J_{(F-H)}$ =5.6 Hz, 2H), 6.96(dd, $J_{(H-H)}$ = 8.8 Hz, $J_{(F-H)}$ = 8.8 Hz, 2H), 6.89 (dd, $J_{(H-H)}$ = 8.8 Hz, $J_{(F-H)}$ = 8.8 Hz, 2H), 6.65 (d, J = 8.0 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 5.03 (s, 1H), 4.29 (d, J = 14.4 Hz, 1H), 3.97 (d, J = 14.3 Hz, 1H), 3.43 – 3.37 (m, 1H), 3.37– 3.30 (m, 2H), 3.27 – 3.18 (m,2H), 3.14 (dd, J = 6.3, 2.8 Hz, 1H), 2.99 (d, J = 18.6 Hz, 1H), 2.86 – 2.71 (m, 2H), 2.61 – 2.52 (m, 1H), 2.45 – 2.40 (m, 1H), 2.39 (s, 3H), 2.36 – 2.24 (m, 2H), 2.02 – 1.89 (m, 1H), 1.76 (ddd, J = 12.5, 3.7, 1.8 Hz, 1H), 1.58 (t, J = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.01(d, J= 242 Hz), 161.94(d, J= 242 Hz), 144.01, 139.48, 135.16(d, J= 3.1 Hz), 134.85, 133.75(d, J = 3.1 Hz), 130.56(d, J =7.9 Hz), 130.29(d, J =7.9 Hz), 129.15, 125.76, 118.91, 118.58, 117.29, 115.13(d, J= 5.5 Hz), 114.92(d, J= 5.5 Hz), 89.32, 67.46, 58.87, 57.87, 56.42, 53.37, 50.47, 46.59, 42.78, 42.64, 35.71 , 27.51, 20.40. HRMS (ESI): m/z calcd for $C_{33}H_{34}F_2N_3O_2$ $[M+H]^+$: 542.2614, found:542.2618.



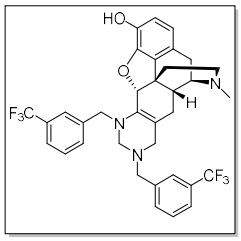
(4bS,13bR)-7-methyl-11,13-bis(4-methylbenzyl)-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**2j**)

White solid, m. p.:168.3-170.6℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 6.96 (m, 8H), 6.62 (d, J = 8.2 Hz, 1H), 6.55 – 6.46 (d, J = 8.2 Hz, 1H), 6.05 (bs, 1H). 5.02 (s, 1H), 4.41 (d, J = 16 Hz, 1H), 3.95 (d, J = 14.5 Hz, 1H), 3.41 (d, J = 12.9 Hz, 1H), 3.32 (dd, J = 11.7, 8.7 Hz, 2H), 3.24 (d, J = 10.7 Hz, 1H), 3.16 (dd, J = 5.7, 2.5 Hz, 1H), 2.95 (d, J = 18.6 Hz, 1H), 2.83 – 2.72 (m, 2H), 2.61 (m, 2H), 2.42 (s, 3H), 2.39 – 2.35 (m, 2H), 2.33 (s, 3H), 2.30 (s, 3H), 2.01 – 1.89 (m, 1H), 1.75 (m, 1H), 1.65 – 1.46 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 144.16, 139.53, 136.76, 136.63, 136.25, 135.01, 134.90, 129.12, 129.05, 128.91, 128.86, 128.69, 125.48, 118.68, 117.47, 117.20, 89.74, 67.90, 58.93, 58.46, 56.35, 53.83, 46.61, 42.67, 42.59, 40.08, 39.27, 35.64, 27.50, 21.12, 20.51. HRMS (ESI): m/z calcd for $C_{35}H_{40}N_3O_2$ $[M+H]^+$: 524.3115, found:534.3122.



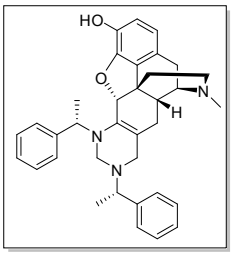
(4bS,13bR)-11,13-bis(3-chlorobenzyl)-7-methyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**2k**)

White solid, m. p.:149.2-150.5℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 6.98 (m, 8H), 6.57 (d, J = 8.0 Hz, 1H), 6.47 (d, J = 8.1 Hz, 1H), 4.94 (s, 1H), 4.31 (d, J = 14.9 Hz, 1H), 3.94 (d, J = 14.7 Hz, 1H), 3.38 – 3.22 (m, 2H), 3.18 – 3.04 (m, 3H), 2.90 (m, 1H), 2.78 – 2.66 (m, 2H), 2.56 – 2.44 (m, 1H), 2.38 – 2.33 (m, 1H), 2.31 (s, 3H), 2.27 – 2.17 (m, 2H), 1.93 – 1.81 (m, 1H), 1.73 – 1.63 (m, 1H), 1.58 – 1.41 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.00, 140.89, 139.19, 138.47, 133.68, 133.19, 133.11, 128.51, 128.44, 128.02, 127.77, 127.51, 126.42, 126.31, 126.09, 125.95, 125.70, 124.64, 124.59, 117.88, 116.30, 88.62, 66.91, 57.81, 57.00, 55.38, 52.76, 45.53, 41.68, 38.16, 34.61, 26.42, 19.40. HRMS (ESI): m/z calcd for $C_{33}H_{34}Cl_2N_3O_2$ $[M+H]^+$: 574.2023, found:574.2020.



(4bS,13bR)-7-methyl-11,13-bis(4-(trifluoromethyl)benzyl)-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**2l**)

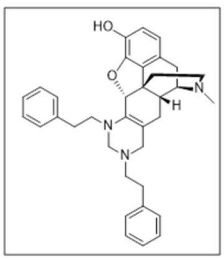
White solid, m. p.:151.2-153.6℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.12 (m, 8H), 6.61 – 6.52 (d, J = 8.1 Hz, 1H), 6.45 (d, J = 8.1 Hz, 1H), 4.93 (s, 1H), 4.39 (d, J = 15.3 Hz, 1H), 3.97 (d, J = 15.1 Hz, 1H), 3.44 – 3.26 (m, 2H), 3.18 – 2.96 (m, 3H), 2.88 (m, 1H), 2.74 (m, 2H), 2.47 (m, 1H), 2.34 (m, 1H), 2.33 – 2.28 (s, 3H), 2.25 – 2.10 (m, 2H), 1.94 – 1.81 (m, 1H), 1.66 (d, J = 12.1 Hz, 1H), 1.57 – 1.38 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.92, 139.87, 138.40, 138.12, 133.64, 131.12, 130.81, 129.63(q, J= 32 Hz), 129.52(q, J = 28Hz), 128.04, 127.69, 127.59, 127.13(q, J = 220 Hz), 126.78(q, J = 220 Hz), 124.71, 124.38 (q, J = 3.5 Hz), 123.95(q, J = 3.6 Hz), 123.10(q, J = 3.6 Hz), 122.74(q, J = 3.6 Hz), 117.88, 117.53, 116.10, 88.94, 67.00, 57.85, 57.04, 55.51, 52.87, 45.53, 41.71, 41.67, 38.24, 34.63, 26.40, 19.41. HRMS (ESI): m/z calcd for $C_{35}H_{34}F_6N_3O_2$ $[M+H]^+$: 642.2550, found:642.2551.



(4bS,13bR)-7-methyl-11,13-bis((S)-1-phenylethyl)-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**2m**)

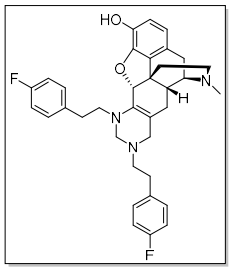
White solid, m. p.:173.4-176.0℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.2 Hz, 2H), 7.41–7.34 (m, 2H), 7.33 – 7.24 (m, 6H), 6.73 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 5.18 (s, 1H), 5.16 – 5.08 (m, 1H), 3.73 (d, J = 11.1 Hz, 1H), 3.25 – 3.12 (m, 2H), 3.05 (dd, J = 17.9, 14.8 Hz, 2H), 2.76 – 2.68(m, 2H), 2.63 – 2.51 (m, 2H), 2.45 (s, 3H), 2.43 – 2.28 (m, 3H), 2.01 (td, J = 12.4, 4.9 Hz, 1H), 1.84 (ddd, J = 12.4, 3.7, 1.7 Hz, 1H), 1.56 (d, J = 6.9 Hz, 3H), 1.52 – 1.43 (m, 2H), 1.25 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.37, 144.12, 143.68, 139.14, 132.71, 129.48, 128.23, 128.11, 127.95, 127.45, 126.85, 126.64, 126.21, 118.64, 116.63, 116.60, 91.77, 63.09, 62.64, 59.03, 57.16, 55.31, 46.61, 42.97, 42.83, 39.63, 35.85, 27.66, 20.53, 20.15, 16.69. HRMS (ESI): m/z calcd for $C_{35}H_{40}N_3O_2$ $[M+H]^+$: 534.3115, found:534.3117

(4bS,13bR)-11,13-diphenethyl-7-methyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**2n**)



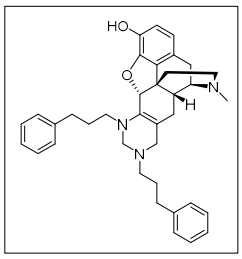
White solid, m.p.: 198.6-199.7 ℃； ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.11 (m, 6H), 7.11 (d, J = 7.9 Hz, 4H), 6.56 (d, J= 8.0 Hz, 1H), 6.44 (d, J = 8.1 Hz, 1H), 4.74 (s, 1H), 3.50 (q, J = 10.7 Hz, 2H), 3.37 – 3.30 (m, 2H), 3.20 – 3.01 (m, 1H), 2.91 (d, J = 18.6 Hz, 1H), 2.85-2.70 (m, 6H),

2.48 (dd, J = 7.4, 4.3 Hz, 3H), 2.35 (s, 3H), 2.35-2.23 (m, 3H), 1.81 (td, J = 12.4, 4.8 Hz, 1H), 1.67 (d, J = 11.3 Hz, 1H), 1.49 (m, 2H)； ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.13, 140.54, 140.36, 139.77, 133.39, 129.11, 129.03, 128.81, 128.63, 128.33, 126.07, 125.96, 118.60, 117.05, 114.58, 88.42, 70.66, 59.08, 58.90, 56.38, 56.33, 53.22, 46.66, 42.68, 42.34, 38.97, 35.47, 35.40, 34.07, 27.42, 20.56； m/z calcd for $C_{35}H_{40}N_3O_2$ $[M+H]^+$: 534.3115, found: 534.3110.



(4bS,13bR)-11,13-bis(4-fluorophenethyl)-7-methyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**2o**)

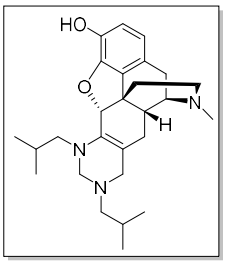
White solid, m. p.:182.2-183.9℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.16 (m, 2H), 7.15 – 7.08 (m, 2H), 6.98– 6.91 (m, 4H), 6.61 (d, J = 8.0 Hz, 1H), 6.52 (d, J = 8.1 Hz, 1H), 4.83 (s, 1H), 3.52 (q, J = 10.7 Hz, 2H), 3.33 (t, J = 7.9 Hz, 2H), 3.12 (dd, J = 5.7, 2.6 Hz, 1H), 2.99 (d, J = 18.6 Hz, 1H), 2.83 – 2.74 (m, 5H), 2.70 (d, J = 6.9 Hz, 1H), 2.55 (ddd, J = 10.7, 9.9, 5.2 Hz, 3H), 2.40 (s, 3H), 2.37 – 2.30 (m, 3H), 1.88 (td, J = 12.3, 4.8 Hz, 1H), 1.75 (d, J = 10.8 Hz, 1H), 1.66 – 1.49 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 161.96 (d, J = 243Hz), 161.38 (d, J = 243 Hz,), 144.17, 139.65, 136.05 (d, J = 3.1 Hz), 135.77 (d, J = 3.0 Hz), 133.37, 130.23 (d, J = 7.9 Hz), 129.98 (d, J = 7.9 Hz), 129.28, 125.59, 118.71, 117.08, 115.57, 115.21 (d, J = 5.5 Hz), 115.01 (d, J = 5.2 Hz), 88.59, 70.81, 58.92, 56.38, 56.31, 53.43, 46.60, 42.81, 42.54, 39.20, 35.73, 34.49, 33.18, 27.53, 20.47. HRMS (ESI): m/z calcd for $C_{35}H_{38}F_2N_3O_2$ $[M+H]^+$: 570.2927, found:570.2933.



(4bS,8R,8aR,13bR)-7-methyl-11,13-bis(3-phenylpropyl)-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8 methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol(**2p**)

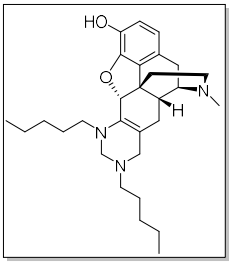
White solid, m. p.:184.7-187.3℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31– 7.13 (m, 10H), 6.65 (d, t, J = 8.0 Hz, 1H), 6.52 (d, J = 8.1 Hz, 1H), 4.84 (s, 1H), 3.51– 3.41 (m, 3H), 3.27 – 3.18 (m, 2H), 3.07-2.95 (m, 2H), 2.74 – 2.61 (m, 7H), 2.43 (s, 3H), 2.40 – 2.28 (m, 5H), 1.97 – 1.94 (m, 3H), 1.79 – 1.74 (m, 3H), 1.56 (d, J = 6.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.96, 142.19, 142.08, 139.23, 134.11, 129.36, 129.08, 128.44, 128.42 128.38, 128.30, 125.83, 125.73, 118.68, 116.86, 116.22, 88.84, 70.14, 65.85, 59.01, 56.56, 54.08, 50.70, 46.66, 42.71, 39.24, 35.62, 33.58, 30.49, 28.89, 27.49, 20.49, 15.27. HRMS (ESI): m/z calcd for $C_{37}H_{44}N_3O_2$ $[M+H]^+$: 562.3428,

found:562.3430.



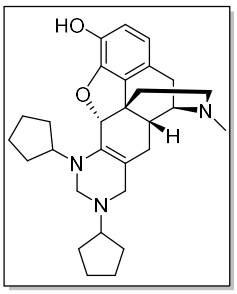
(4bS,13bR)-11,13-diisobutyl-7-methyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**2q**)

White solid, m. p.:168.8-171.7℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (d, J = 8.0 Hz, 1H), 6.53 (d, J = 8.1 Hz, 1H), 4.93 (s, 1H), 3.35 (q, J = 10.7 Hz, 2H), 3.16 (dd, J = 5.7, 2.8 Hz, 1H), 3.01 (d, J = 7.0 Hz, 1H), 2.68 – 2.55 (m, 3H), 2.42 (s, 3H), 2.35 (m, 3H), 2.08 – 1.91 (m, 5H), 1.79 (m, 3H), 1.57 – 1.52 (m, 2H), 0.97 (dd, J = 6.5, 5.0 Hz, 6H), 0.89 (dd, J = 4.1, 2.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.13, 139.05, 135.23, 129.35, 126.06, 118.59, 116.86, 116.42, 89.05, 70.13, 63.23, 58.90, 58.53, 51.15, 46.65, 42.83, 42.55, 39.48, 35.84, 28.30, 27.61, 25.96, 20.95, 20.89, 20.45. HRMS (ESI): m/z calcd for $C_{27}H_{40}N_3O_2$ $[M+H]^+$: 438.3115, found:438.3117.



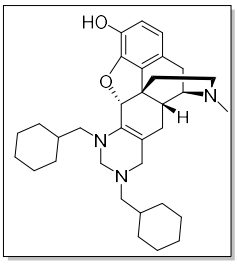
(4bS,13bR)-7-methyl-11,13-dipentyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**2r**)

White solid, m. p.:188.6-190.9℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 8.1 Hz, 1H), 4.91 (s, 1H), 3.40 (q, J = 10.6 Hz, 2H), 3.17 (ddd, J = 9.0, 7.1, 3.4 Hz, 2H), 3.02 – 2.89 (m, 2H), 2.77 (d, J = 16.1 Hz, 1H), 2.65 (d, J = 16.1 Hz, 1H), 2.59 – 2.52 (m, 1H), 2.40 (s, 3H), 2.38 – 2.20 (m, 5H), 1.98 – 1.88 (m, 1H), 1.81 – 1.72 (m, 1H), 1.62 – 1.40 (m, 6H), 1.38 – 1.22 (m, 8H), 0.94 – 0.83 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.14, 139.48, 134.24, 129.24, 125.59, 118.56, 117.03, 115.34, 88.43, 69.91, 58.88, 56.64, 54.76, 51.02, 46.65, 42.77, 42.48, 39.30, 35.84, 29.69, 29.62, 28.63, 27.60, 26.93, 22.67, 22.57, 20.41, 14.18, 14.04. HRMS (ESI): m/z calcd for $C_{29}H_{44}N_3O_2$ $[M+H]^+$: 466.3428, found:466.3430.



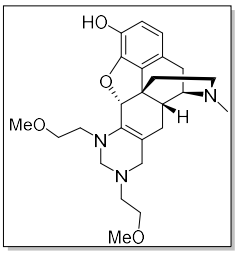
(4bS,13bR)-13-dicyclopentyl-7-methyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**2s**)

White solid, m. p.:181.3-183.4℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (d, J = 8.0 Hz, 1H), 6.51 (d, J = 8.0 Hz, 1H), 5.06 (s, 1H), 4.24 – 4.06 (m, 1H), 3.58 (d, J = 10.5 Hz, 1H), 3.40 (d, J = 10.6 Hz, 1H), 3.23-3.19 (m, 1H), 2.99 (d, J = 18.6 Hz, 1H), 2.81-2.76 (m, 3H), 2.67 – 2.58 (m, 3H), 2.45 (s, 3H), 2.43 – 2.38 (m, 3H), 1.99 (td, J = 13.2, 4.2 Hz, 1H), 1.81 – 1.77(m, 5H), 1.70 – 1.48 (m, 13H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.16, 139.44, 133.90, 129.45, 125.53, 118.77, 117.08, 112.62, 89.02, 64.71, 59.57, 55.90, 46.89, 42.83, 42.61, 39.11, 35.76, 30.60, 30.5, 29.99, 29.55, 27.70, 24.73, 24.59, 20.72. HRMS (ESI): m/z calcd for $C_{29}H_{40}N_3O_2$ $[M+H]^+$: 462.3115, found:462.3117.



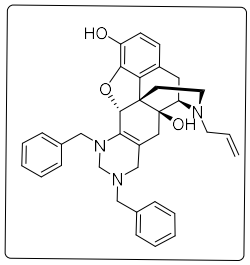
(4bS,13bR)-11,13-bis(cyclohexylmethyl)-7-methyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**2t**)

White solid, m. p.:194.5-196.4℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (d, J = 8.0 Hz, 1H), 6.48 (d, J = 8.1 Hz, 1H), 4.88 (s, 1H), 3.31 (s, 2H), 3.08 (dt, J = 14.1, 4.7 Hz, 2H), 2.95(d, J = 10.0 Hz, 1H), 2.77 – 2.61 (m, 3H), 2.57 – 2.48 (m, 2H), 2.42 – 2.32 (m, 4H), 2.32 – 2.23 (m, 2H), 2.06 – 1.99 (m, 2H), 1.95 – 1.78 (m, 3H), 1.75-1.65 (m, 9H), 1.54 – 1.47 (m, 2H), 1.27 – 1.08 (m, 6H), 0.97 – 0.74 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.18, 139.26, 135.17, 129.35, 125.78, 118.40, 116.85, 115.85, 89.04, 70.49, 61.81, 58.96, 57.34, 57.23, 46.64, 42.87, 42.52, 40.96, 39.63, 37.96, 35.93, 35.57, 31.87, 31.80, 31.72, 27.60, 26.79, 26.73, 26.27, 26.07, 20.41. HRMS (ESI): m/z calcd for $C_{33}H_{48}N_3O_2$ $[M+H]^+$: 518.3741, found:518.3741.



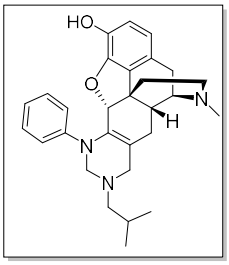
(4bS,13bR)-11,13-bis(2-methoxyethyl)-7-methyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**2u**)

White solid, m. p.:172.1-173.6℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (d, J = 8.0 Hz, 1H), 6.49 (d, J = 8.1 Hz, 1H), 4.94 (s, 1H), 3.61-3.58 (m,1H), 3.53 – 3.40 (m, 9H), 3.34 (s, 3H), 3.29 (s, 1H), 3.27 – 3.21 (m, 2H), 3.02 – 2.93 (m, 1H), 2.76 (m, 2H), 2.65 (dd, J = 12.3, 3.3 Hz, 1H), 2.52 (m, 3H), 2.44 (s, 3H), 2.42 – 2.31 (m, 3H), 2.03 – 1.93 (m, 1H), 1.83 – 1.72 (m, 1H), 1.58 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.10, 139.90, 133.51, 128.95, 124.78, 118.70, 117.25, 115.64, 89.288, 71.73, 71.30,70.00, 58.99, 58.83, 58.72, 56.50, 55.86, 46.53, 42.36, 42.30, 38.60, 35.12, 27.24, 23.37, 20.65. HRMS (ESI): m/z calcd for $C_{25}H_{36}N_3O_4$ $[M+H]^+$: 442.2700, found:442.2701.



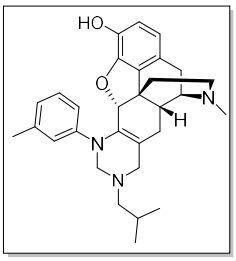
14- (hydroxyl) -1’,3’-dibenzyl -17- (allyl) - 6, 7-didehydro- 4, 5 α-epoxy-3- hydroxyl-1’,2’,3’,4’-tetrahydropyrimido [5’,6’:6,7] – morphinan(**2v**)

White solid, m. p.:141.4-143.8℃.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.12 (m, 10H), 6.68 (d, J = 8.1 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 5.89 – 5.76 (m, 1H), 5.30 (s, 1H), 5.25 – 5.08 (m, 3H), 4.28 (d, J = 14.4 Hz, 1H), 4.11 (t, J = 11.1 Hz, 1H), 3.45-3.39 (m, 2H), 3.26 (d, J = 10.7 Hz, 1H), 3.15 – 3.07 (m, 2H), 2.97 (dd, J = 20.4, 11.2 Hz, 2H), 2.79 (d, J = 16.8 Hz, 1H), 2.64 – 2.54 (m, 3H), 2.26 (d, J = 8.1 Hz, 2H), 2.03 (d, J = 17.1 Hz, 2H), 1.74 (d, J = 16.4 Hz, 1H), 1.66 (d, J = 8.7 Hz, 1H). ^{13}C NMR (125 MHz, DMSO) δ 143.76, 140.48, 140.23, 138.78, 136.45, 133.88, 131.98, 129.17, 128.98, 128.58, 128.43, 127.34, 124.51, 118.42, 117.85, 117.37, 115.34, 89.16,70.87, 67.93, 61.78, 60.21, 58.16, 57.62, 56.85, 53.98, 46.76, 43.45, 34.91, 31.49, 23.22, 21.21, 14.55. HRMS (ESI): m/z calcd for $C_{35}H_{38}N_3O_3$ $[M+H]^+$: 548.2908, found:548.2916.



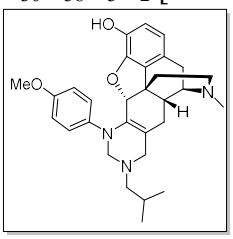
4bS,13bR)-11-isobutyl-7-methyl-13-phenyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**3a**)

White solid, m. p.:215.0-217.2℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.19 (m, 2H), 6.81 – 6.74 (m, 3H), 6.67 (d, J = 8.1 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 4.94 (s, 1H), 4.17 (d, J = 11.8 Hz, 1H), 4.09 (d, J = 11.8 Hz, 1H), 3.38 (dd, J = 39.8, 16.2 Hz, 2H), 3.19 (d, J = 3.3 Hz, 1H), 3.12 – 2.97 (m, 2H), 2.69 (dd, J = 13.9, 7.0 Hz, 1H), 2.61 – 2.56 (m, 2H), 2.42 (s, 3H), 2.40 – 2.28 (m, 2H), 2.06 – 1.85 (m, 2H), 1.80 (d, J = 11.6 Hz, 1H), 1.73 – 1.57 (m, 2H), 1.04 – 0.96 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.73, 144.14, 139.33, 136.59, 129.23, 129.13, 125.74, 118.86, 118.73, 117.81, 117.09, 114.61, 88.91, 66.19, 58.90, 59.30, 51.09, 46.59, 42.79, 42.46, 39.51, 35.79, 28.27, 27.54, 20.97, 20.90, 20.47. HRMS (ESI): m/z calcd for $C_{29}H_{36}N_3O_2$ $[M+H]^+$: 458.2802, found:458.2807.



(4bS,13bR)-11-isobutyl-7-methyl-13-(m-tolyl)-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**3b**)

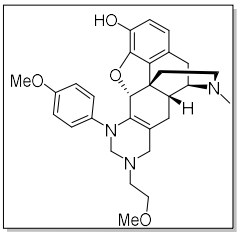
White solid, m. p.:165.8-167.9℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (t, J = 7.7 Hz, 1H), 6.71 – 6.65 (m, 1H), 6.64 – 6.48 (m, 4H), 4.94 (s, 1H), 4.16 (d, J = 11.8 Hz, 1H), 4.08 (d, J = 11.8 Hz, 1H), 3.38 (dd, J = 40.4, 16.3 Hz, 2H), 3.20 (dd, J = 5.9, 2.7 Hz, 1H), 3.11 – 2.97 (m, 2H), 2.69 (dd, J = 13.9, 7.0 Hz, 1H), 2.62-2.58 (m, 2H), 2.43 (s, 3H), 2.40 – 2.31 (m, 2H), 2.29 (s, 3H), 2.04 – 1.87 (m, 2H), 1.80 (dd, J = 12.5, 1.7 Hz, 1H), 1.75 – 1.58 (m, 2H), 1.04 – 0.96 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.82, 144.12, 139.32, 138.92, 136.54, 129.11, 129.06, 125.71, 119.78, 118.72, 117.89, 117.07, 115.33, 111.836, 88.92, 66.14, 58.93, 58.29, 51.21, 46.60, 42.78, 42.45, 39.50, 35.77, 28.27, 27.54, 21.82, 20.98, 20.91, 20.48. HRMS (ESI): m/z calcd for $C_{30}H_{38}N_3O_2$ $[M+H]^+$: 472.2959, found:472.2964.



(4bS,13bR)-11-isobutyl-13-(4-methoxyphenyl)-7-methyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**3c**)

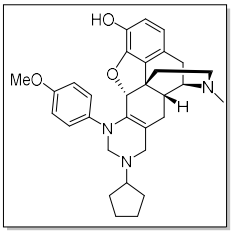
White solid, m. p.:185.7-187.3℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, J = 8.5 Hz, 2H), 6.76 (d, J = 8.5 Hz, 2H), 6.69 (d, J = 8.1 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 4.97 (s, 1H), 4.07 (d, J = 11.5 Hz, 1H), 3.99 (d, J = 11.5 Hz, 1H), 3.75 (s, 3H), 3.38 (d, J = 16.2 Hz, 1H), 3.26 (d, J = 16.2 Hz, 1H), 3.17 (dd, J = 5.8, 2.7 Hz, 1H), 3.09 – 2.94 (m, 2H), 2.72 (dd, J = 13.9, 7.0 Hz, 1H), 2.59 (dd,

J = 12.0, 3.8 Hz, 1H), 2.43 (s, 3H), 2.40 – 2.24 (m, 3H), 2.06 – 1.73 (m, 4H), 1.74 – 1.57 (m, 2H), 1.01 (dd, *J* = 6.5, 5.4 Hz, 6H).^{13}C NMR (100 MHz, $CDCl_3$) δ 153.59, 143.16, 138.89, 136.09, 126.33, 118.84, 117.54, 117.25, 116.69, 114.62, 114.54, 114.28, 89.11, 68.32, 58.99, 58.33, 52.49, 46.64, 42.90, 42.56, 39.55, 35.82, 28.29, 27.50, 20.92, 20.87, 20.46. HRMS (ESI): m/z calcd for $C_{30}H_{37}N_3O_3$ $[M+H]^+$: 488.2908, found:488.2910.



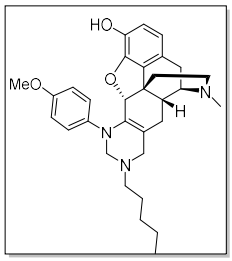
(4bS,13bR)-11-(2-methoxyethyl)-13-(4-methoxyphenyl)-7-methyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**3d**)

White solid, m. p.:166.4-169.8℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 – 6.75 (m, 4H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.55 (d, *J* = 8.1 Hz, 1H), 4.99 (s, 1H), 4.16 (d, *J* = 11.6 Hz, 1H), 4.07 (d, *J* = 11.6 Hz, 1H), 3.74 (s, 3H), 3.54 (dt, *J* = 5.0, 2.9 Hz, 2H), 3.41 (ddd, *J* = 17.9, 8.3, 3.8 Hz, 2H), 3.35 (s, 3H), 3.30 – 3.24 (m, 1H), 3.23 – 3.16 (m, 1H), 3.01 (d, *J* = 18.6 Hz, 1H), 2.59 – 2.53 (m, 3H), 2.41 (s, 3H), 2.39 – 2.27 (m, 3H), 2.00 – 1.91 (m, 1H), 1.77 (ddd, *J* = 21.5, 14.1, 3.5 Hz, 2H), 1.60 (d, *J* = 11.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.65, 143.91, 142.81, 139.46, 134.39, 129.23, 125.87, 118.94, 118.52, 117.49, 117.11, 114.66, 89.79, 71.71, 69.71, 58.96, 58.94, 55.62, 52.35, 51.21, 46.60, 42.87, 40.92, 39.29, 35.57, 27.42, 20.42. HRMS (ESI): m/z calcd for $C_{29}H_{36}N_3O_4$ $[M+H]^+$: 490.2700, found:490.2703.



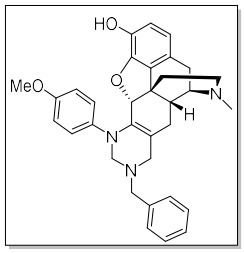
(4bS,13bR)-11-cyclopentyl-13-(4-methoxyphenyl)-7-methyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**3e**)

White solid, m. p.:214.1-216.2℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 2H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.55 (d, *J* = 8.2 Hz, 1H), 5.08 (s, 1H), 4.10 (d, *J* = 5.1 Hz, 2H), 3.74 (s, 3H), 3.40 (d, *J* = 16.0 Hz, 1H), 3.24 – 3.14 (m, 2H), 3.01 (d, *J* = 18.6 Hz, 1H), 2.61-2.49 (m 3H), 2.42 (s, 3H), 2.39 – 2.27 (m, 2H), 1.97 (td, *J* = 12.4, 4.9 Hz, 1H), 1.89 – 1.76 (m, 4H), 1.73 – 1.52 (m, 8H).^{13}C NMR (100 MHz, $CDCl_3$) δ 153.37, 142.87, 139.41, 134.90, 125.84, 118.85, 117.23, 117.11, 116.27, 114.67, 114.54, 114.34, 88.64, 63.40, 60.14, 58.95, 52.47, 46.65, 42.88, 42.53, 39.11, 35.85, 29.61, 27.59, 24.34, 24.12, 20.41. HRMS (ESI): m/z calcd for $C_{31}H_{38}N_3O_3$ $[M+H]^+$: 500.2908, found:500.2910.



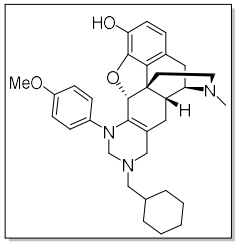
(4bS,13bR)-13-(4-methoxyphenyl)-7-methyl-11-pentyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**3f**)

White solid, m. p.:159.3-161.2℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 – 6.72 (m, 4H), 6.68 (d, J = 8.1 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 4.96 (s, 1H), 4.09 (d, J = 11.5 Hz, 1H), 4.02 (d, J = 11.5 Hz, 1H), 3.74 (s, 3H), 3.37 (d, J = 16.3 Hz, 1H), 3.28 – 3.16 (m, 3H), 3.02 (dt, J = 14.3, 4.5 Hz, 2H), 2.58 – 2.49 (m, 2H), 2.41 (s, 3H), 2.38 – 2.25 (m, 3H), 1.96 (td, J = 12.3, 4.8 Hz, 1H), 1.85 – 1.75 (m, 1H), 1.71 – 1.52 (m, 4H), 1.42 – 1.28 (m, 3H), 0.90 (t, J = 6.9 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 153.51, 143.85, 143.03, 139.58, 139.27, 135.29, 126.39, 119.17, 117.60, 117.29, 116.98, 114.58, 88.53, 68.44, 59.32, 59.29, 55.62, 55.49, 50.95, 42.56, 42.25, 41.01, 30.91, 29.67, 28.47, 27.27, 22.67, 19.91, 14.16. HRMS (ESI): m/z calcd for $C_{31}H_{40}N_3O_3$ $[M+H]^+$: 502.3064, found:502.3067.



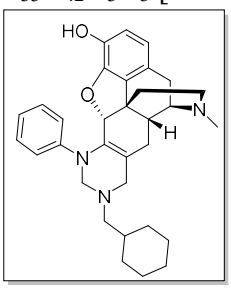
(4bS,13bR)-11-benzyl-13-(4-methoxyphenyl)-7-methyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**3g**)

White solid, m. p.:167.1-168.7℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 7.1 Hz, 2H), 7.33 (t, J = 7.3 Hz, 2H), 7.30 – 7.23 (m, 1H), 6.75 (d, J = 9.1 Hz, 2H), 6.70 – 6.61 (m, 3H), 6.55 (d, J = 8.1 Hz, 1H), 5.08 (s, 1H), 4.51 (d, J = 14.8 Hz, 1H), 4.10 (d, J = 14.8 Hz, 1H), 3.96 – 3.86 (m, 2H), 3.75 (s, 3H), 3.33 (dd, J = 39.4, 16.3 Hz, 2H), 3.23 – 3.16 (m, 1H), 3.07 – 2.94 (m, 1H), 2.61 – 2.51(m, 2H), 2.45(s, 3H), 2.38 – 2.25 (m, 3H), 1.98 (td, J = 12.4, 4.8 Hz, 1H), 1.84 – 1.69 (m, 2H), 1.69 – 1.57 (m, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 153.44, 143.99, 143.07, 139.74, 139.41, 135.88, 129.10, 128.61, 128.47, 127.13, 125.75, 119.34, 118.83, 117.21, 114.58, 89.92, 67.13, 58.94, 55.38, 54.20, 52.36, 46.61, 42.84, 42.67, 39.55, 35.75, 27.50, 20.44. HRMS (ESI): m/z calcd for $C_{33}H_{36}N_3O_3$ $[M+H]^+$: 522.2751, found:522.2757.



(4bS,13bR)-11-(cyclohexylmethyl)-13-(4-methoxyphenyl)-7-methyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**3h**)

White solid, m. p.:210.1-211.4℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 8.5 Hz, 2H), 6.67 (d, J = 7.9 Hz, 1H), 6.48 (d, J = 8.1 Hz, 1H), 4.90 (s, 1H), 3.96 (dd, J = 22.7, 11.5 Hz, 2H), 3.70 (s, 3H), 3.45 (d, J = 3.3 Hz, 1H), 3.29 (d, J = 16.2 Hz, 1H), 3.15 (dd, J = 14.5, 6.6 Hz, 2H), 2.95 (d, J = 19.0 Hz, 1H), 2.87 (dd, J = 11.9, 3.5 Hz, 1H), 2.73 – 2.61 (m, 2H), 2.51 (s, 3H), 2.48 – 2.37 (m, 2H), 2.14 – 2.02 (m, 1H), 1.82 (dd, J = 25.2, 12.2 Hz, 2H), 1.67 (dd, J = 15.6, 5.0 Hz, 5H), 1.59 – 1.44 (m, 2H), 1.30 – 1.09 (m, 3H), 0.94 (dd, J = 22.5, 10.8 Hz, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 153.55, 144.34, 143.09, 140.30, 136.13, 128.32, 123.28, 118.75, 117.55, 117.19, 115.90, 114.60, 88.78, 68.47, 59.09, 57.05, 55.59, 52.36, 46.36, 41.77, 41.51, 37.94, 37.75, 34.36, 31.60, 26.70, 26.21, 26.17, 22.82. HRMS (ESI): m/z calcd for $C_{33}H_{42}N_3O_3$ $[M+H]^+$: 528.3221, found:528.3227.



(4bS,13bR)-11-(cyclohexylmethyl)-7-methyl-13-phenyl-6,7,8,8a,9,10,11,12,13,13b-decahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinazolin-1-ol (**3i**)

White solid, m. p.:203.4-204.9℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 2H), 6.82 – 6.75 (m, 3H), 6.67 (d, J = 8.1 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 4.93 (s, 1H), 4.17 (d, J = 11.7 Hz, 1H), 4.07 (d, J = 11.7 Hz, 1H), 3.54 – 3.26 (m, 2H), 3.17 (dd, J = 5.9, 2.7 Hz, 1H), 3.13 – 2.98 (m, 2H), 2.77 – 2.62 (m, 1H), 2.56 (d, J = 5.2 Hz, 1H), 2.42 (s, 3H), 2.39 – 2.26 (m, 3H), 2.03 – 1.49 (m, 10H), 1.34 – 1.12 (m, 3H), 0.98 (dt, J = 12.2, 7.6 Hz, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 148.81, 144.05, 139.23, 136.72, 129.22, 129.17, 125.91, 118.92, 118.76, 117.95, 117.00, 114.73, 88.96, 66.44, 58.90, 57.12, 51.08, 46.60, 42.87, 42.50, 39.63, 37.90, 35.87, 31.78, 31.71, 27.55, 26.71, 26.21,20.43. HRMS (ESI): m/z calcd for $C_{32}H_{40}N_3O_2$ $[M+H]^+$: 498.3115, found:498.3115.

VI. Binding Affinities of the compounds at DOR, MOR, and KOR

Compound	K_i(nM)			Selectivity	
	MOR [^{3}H]DAMGO	KOR [^{3}H]U69,593	DOR [^{3}H]DPDPE	κ/μ	δ/μ
2a	2.57	56.52	28.77	22.0	11.2

2b	5.02	1622.86	21.71	323.3	4.3
2c	6.78	357.63	37.48	52.7	5.5
2d	11.35	304.25	21.86	26.8	1.9
2e	3.09	315.55	13.95	102.1	4.5
2h	2.05	70.79	10.98	34.5	5.4
2i	3.18	87.23	23.32	27.4	7.3
2j	2.22	60.54	14.57	27.3	6.6
2k	2.41	163.86	14.45	68.0	6.0
2l	3.78	377.70	24.24	100.0	59.3
2m	1.96	89.25	14.57	45.5	7.43
2n	1.37	28.53	3.83	20.8	2.8
2o	2.61	30.79	16.22	11.8	6.2
2p	2.18	14.97	11.94	6.9	5.4
2q	2.37	13.62	5.40	5.7	2.3
2r	2.21	26.00	6.24	11.7	2.8
2s	1.75	60.61	10.27	34.6	5.9
2t	3.11	38.75	21.67	12.5	7.0
2u	3.18	87.23	16.02	27.4	5.0
3a	2.71	49.57	7.67	18.3	2.8
3b	1.80	136.66	23.92	76.9	13.3
3c	1.62	164.77	13.73	101.8	8.5
3d	2.97	250.82	19.62	84.5	6.6
3e	3.13	296.31	20.87	94.7	6.7
3f	10.29	1784.09	79.81	173.3	7.7

3g	2.97	250.82	19.62	84.5	6.6
3h	4.22	53.96	25.70	12.8	6.1
3i	1.11	24.35	7.20	21.9	6.5
Morphine	1.27	46.00	140.00	36.2	110.2

VII. In vitro stability data of compound 2r

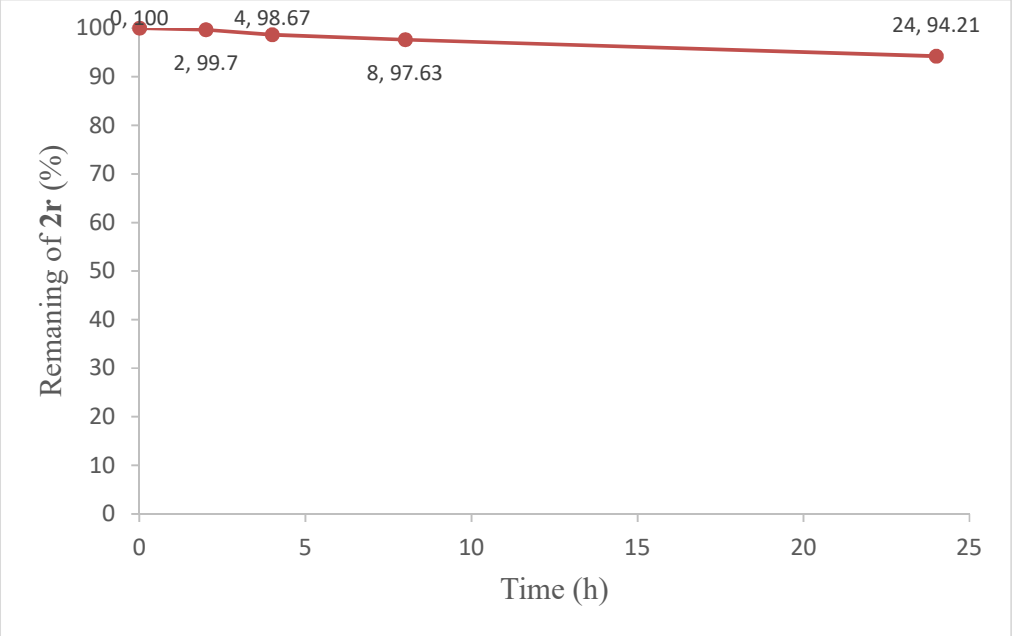


Figure SI 1. The hydrolytic stability of compound **2r** under the condition of pH 7.4

Serum stability data of 2r

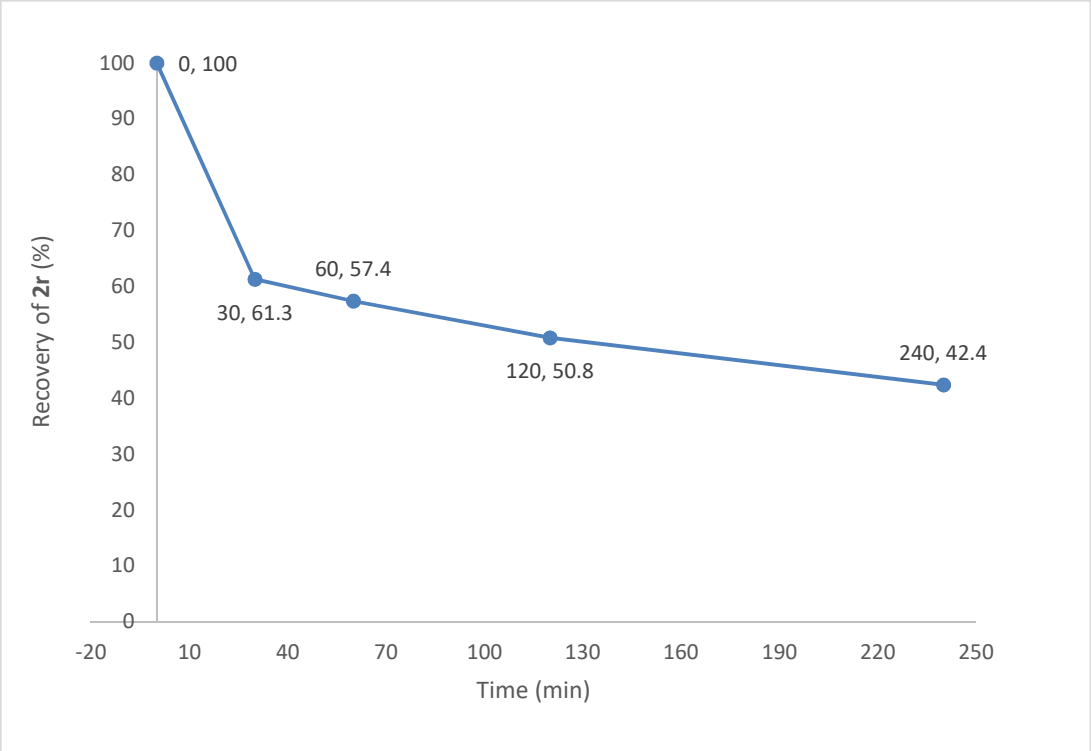
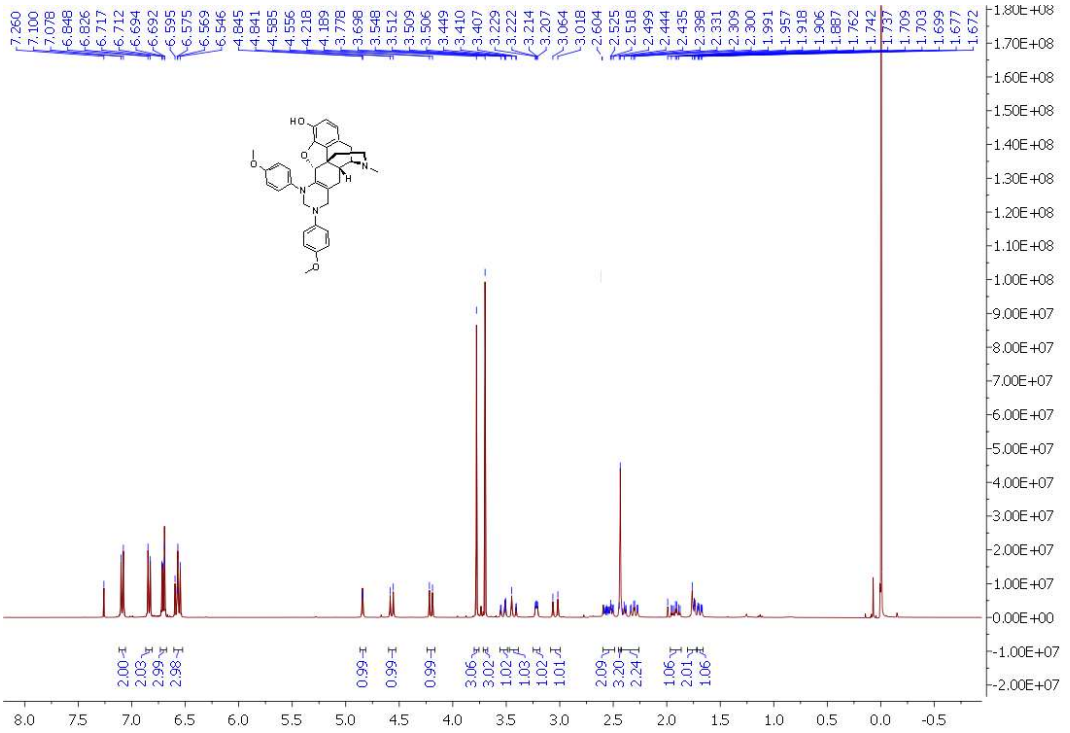
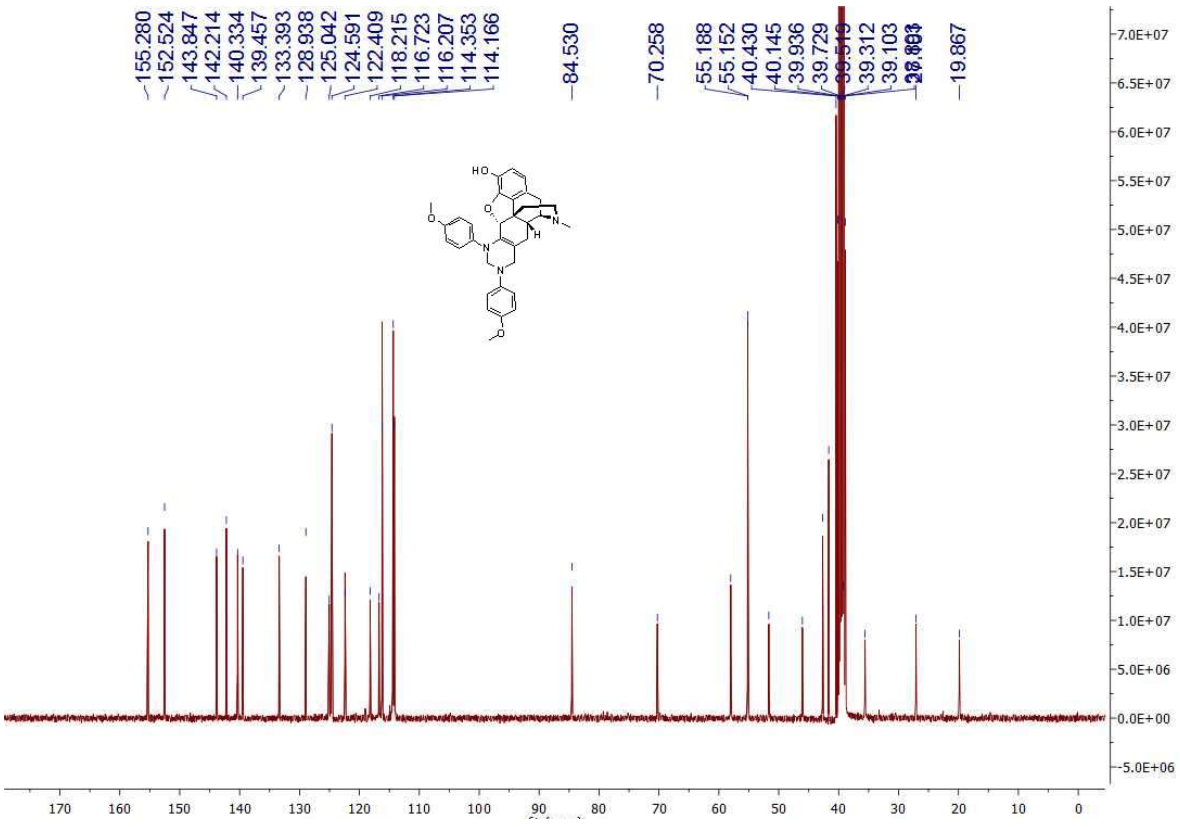
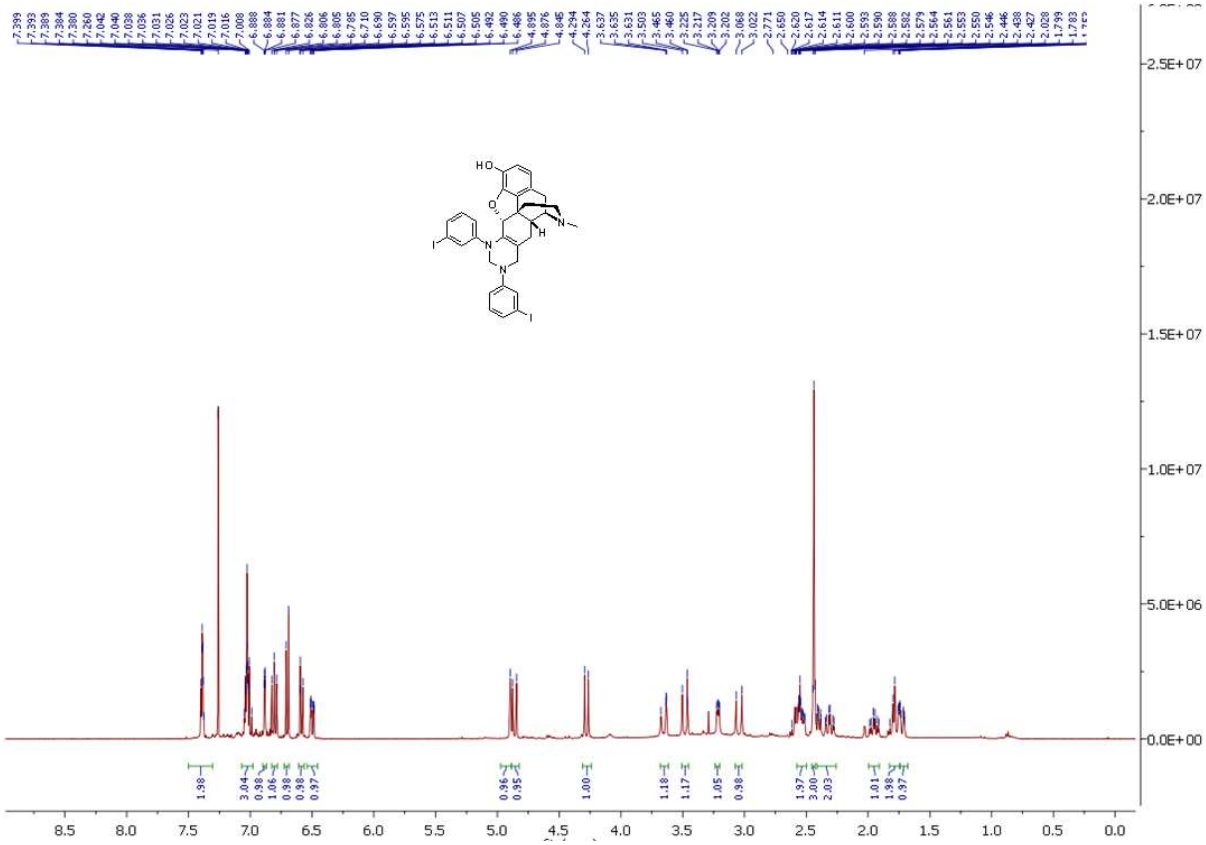


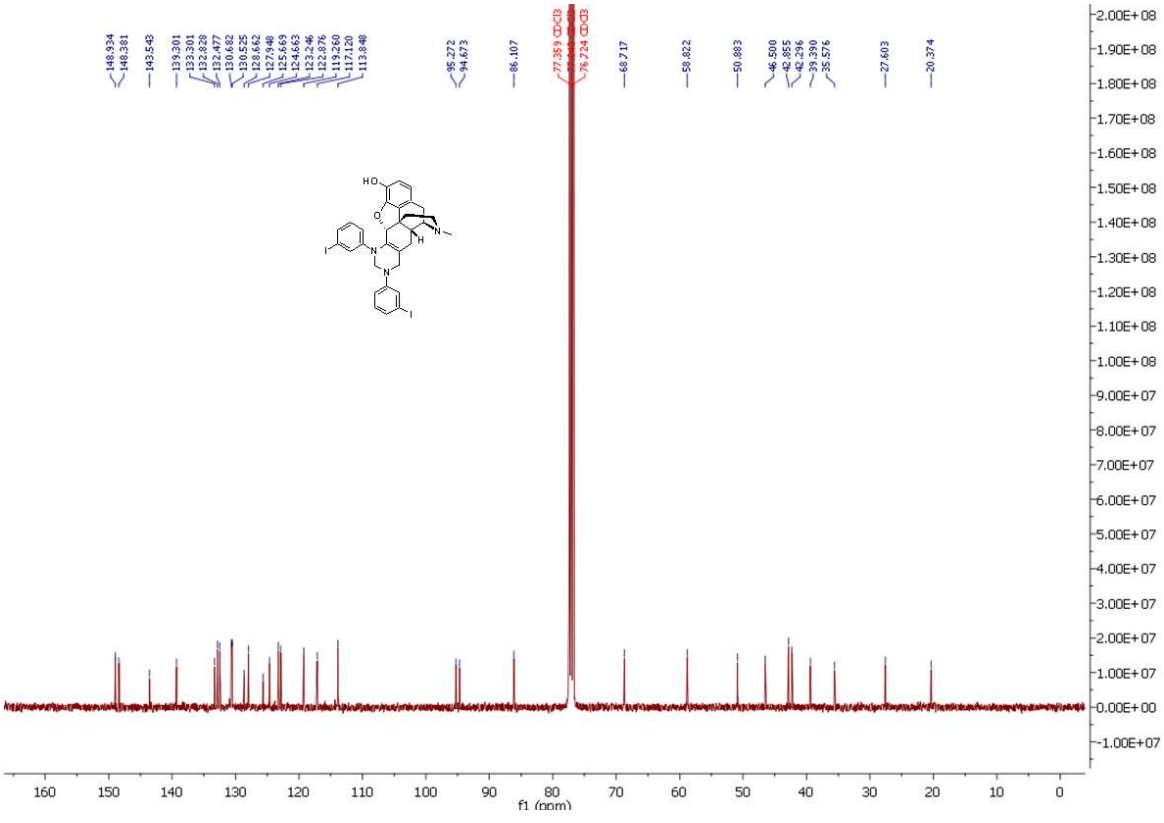
Figure SI 2. Time course of the recovery rates of **2r** after incubation in human serum. Data were determined in triplicate.

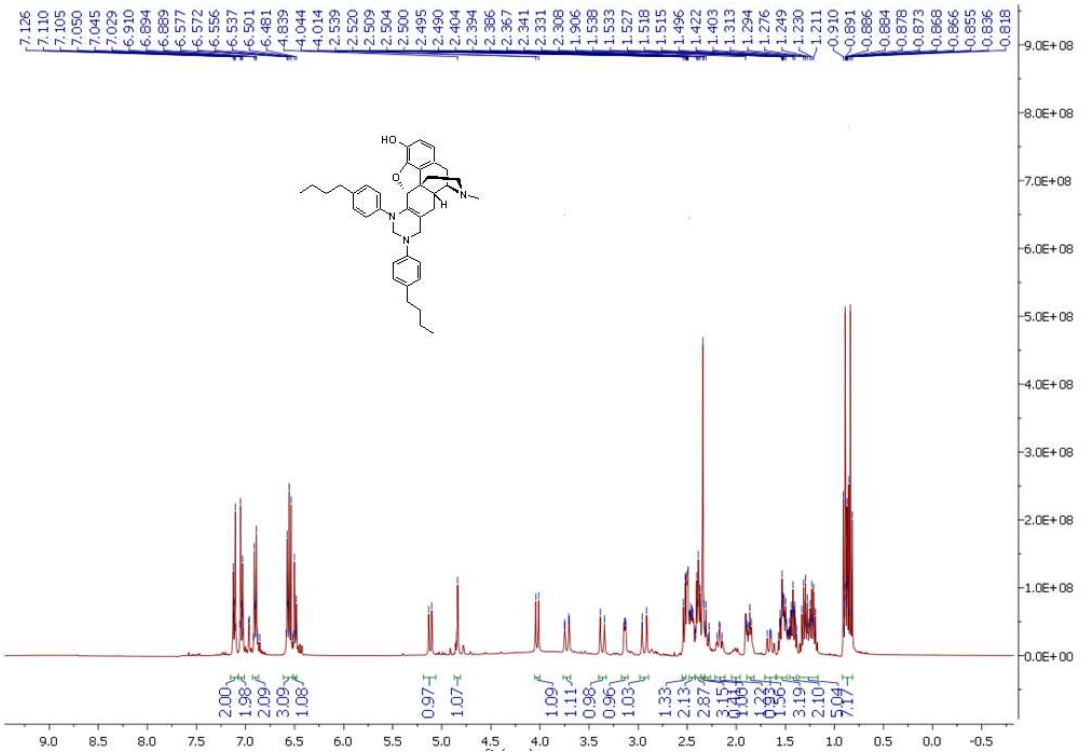
VIII. ^{1}H and ^{13}C NMR Spectra of Final Products

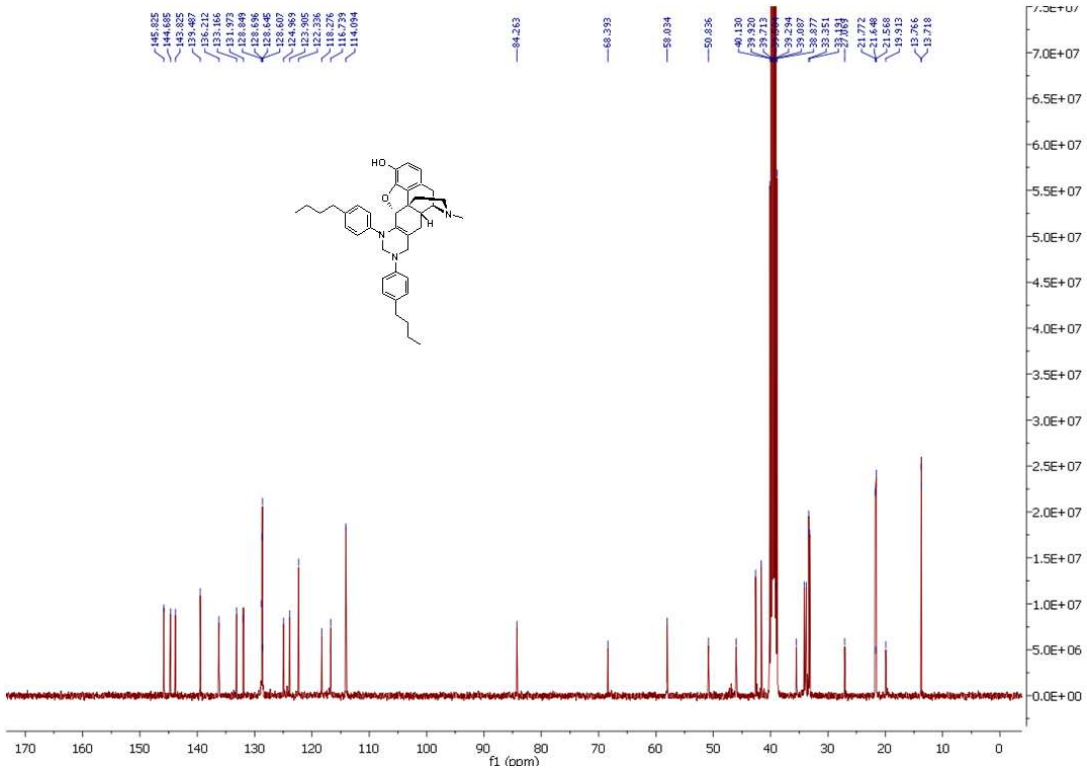


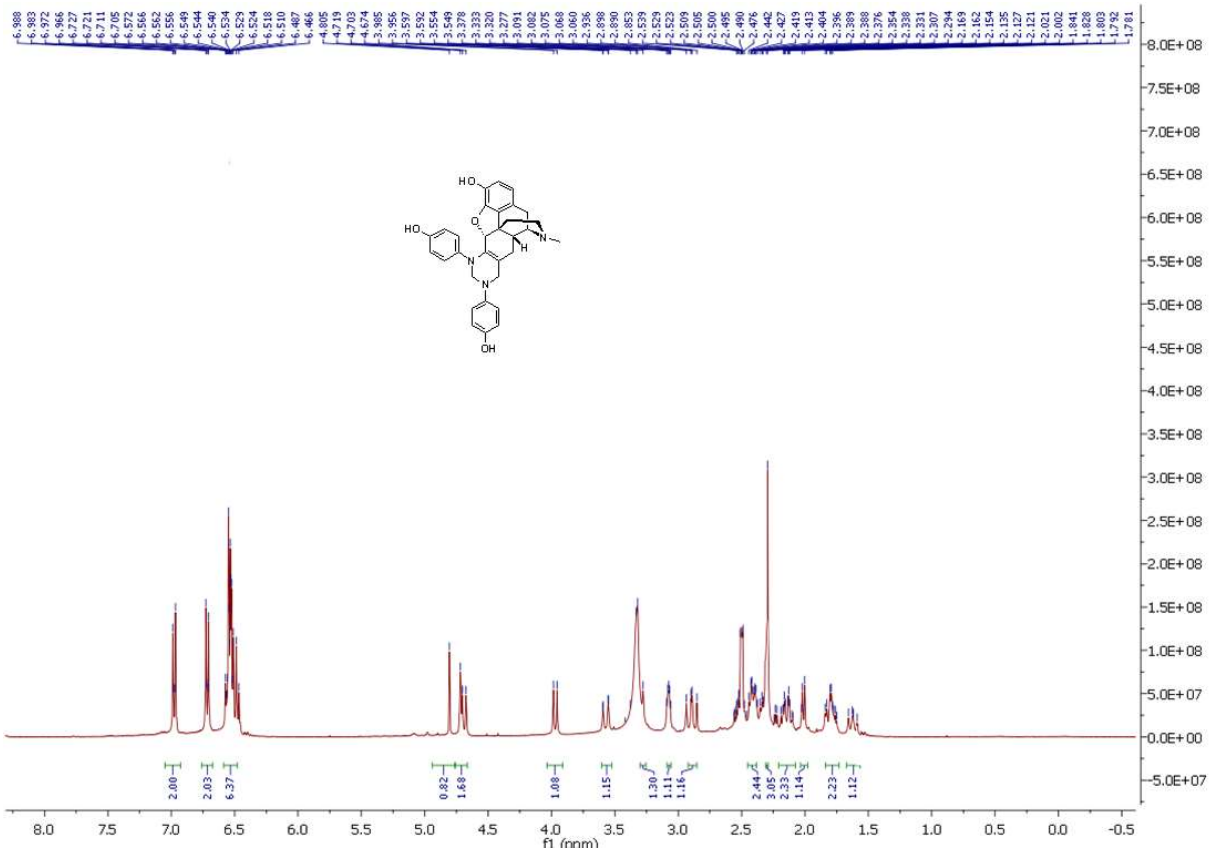








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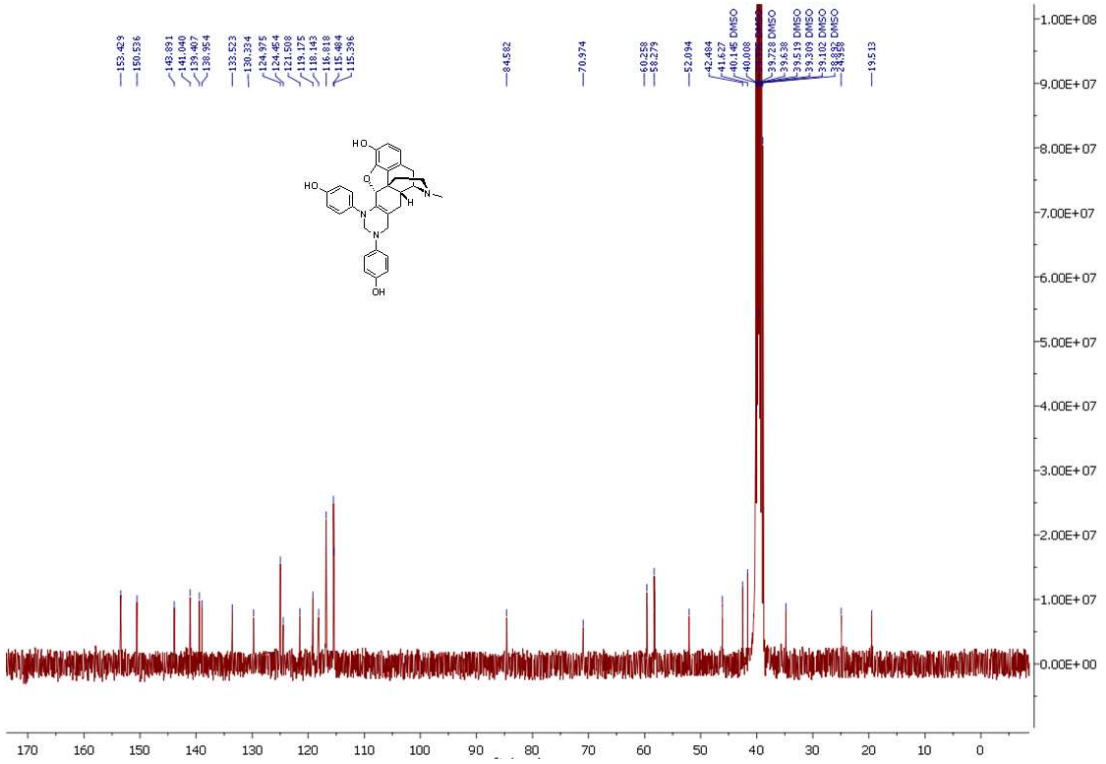

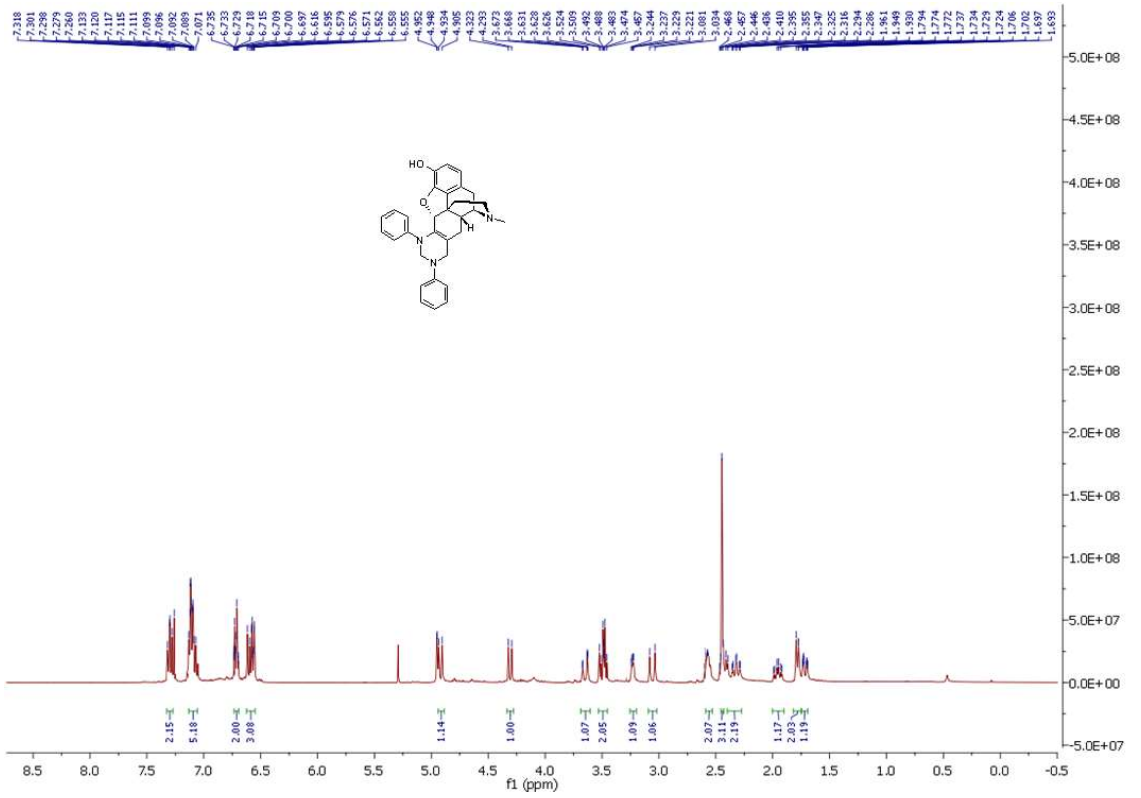
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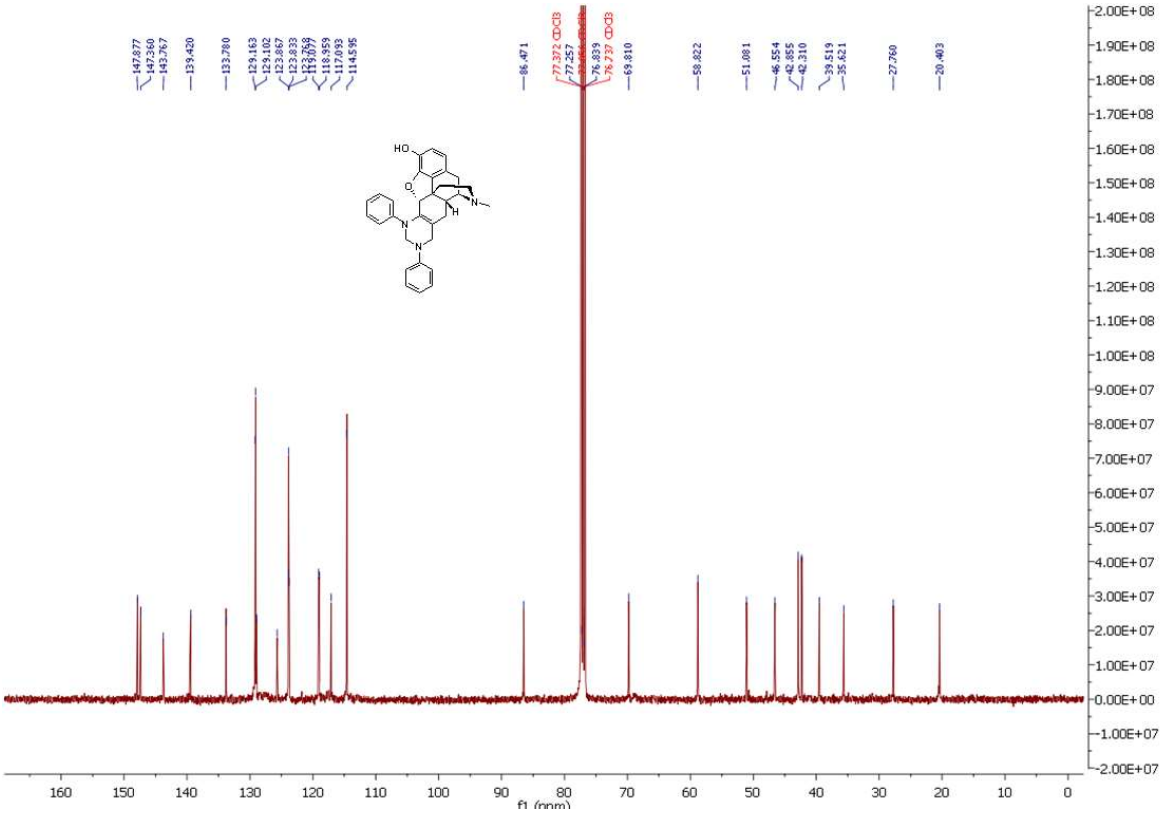
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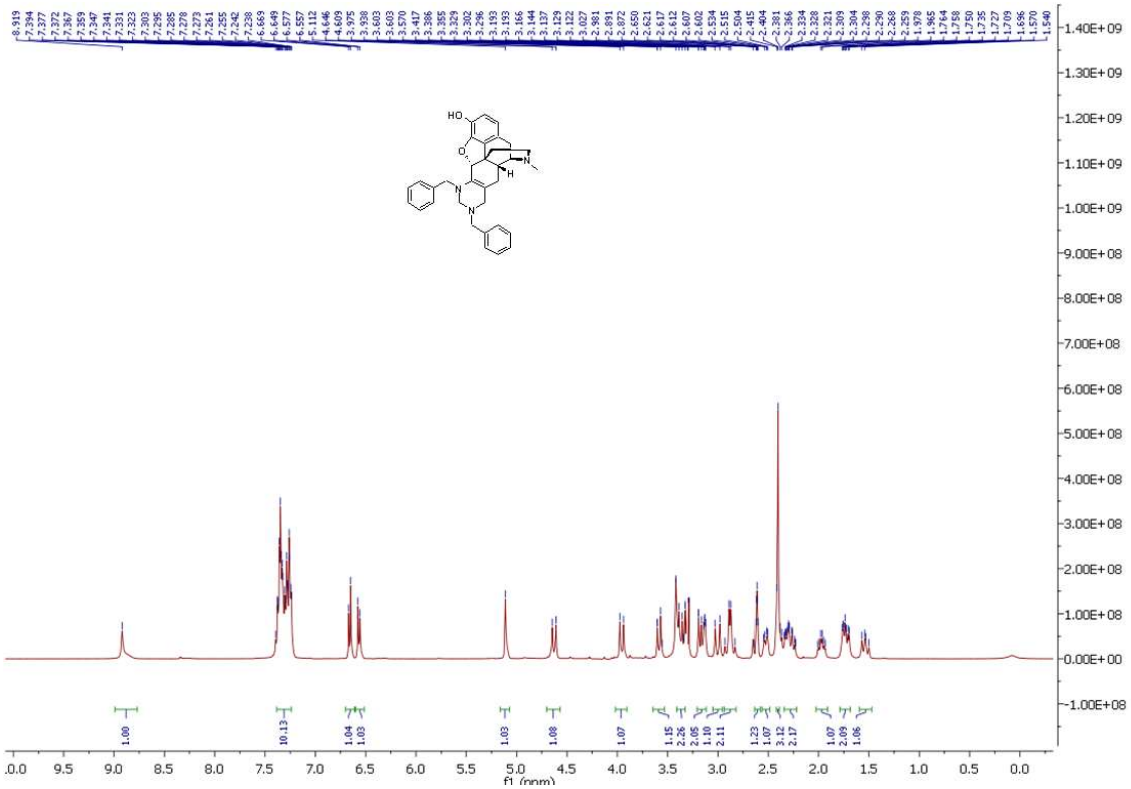

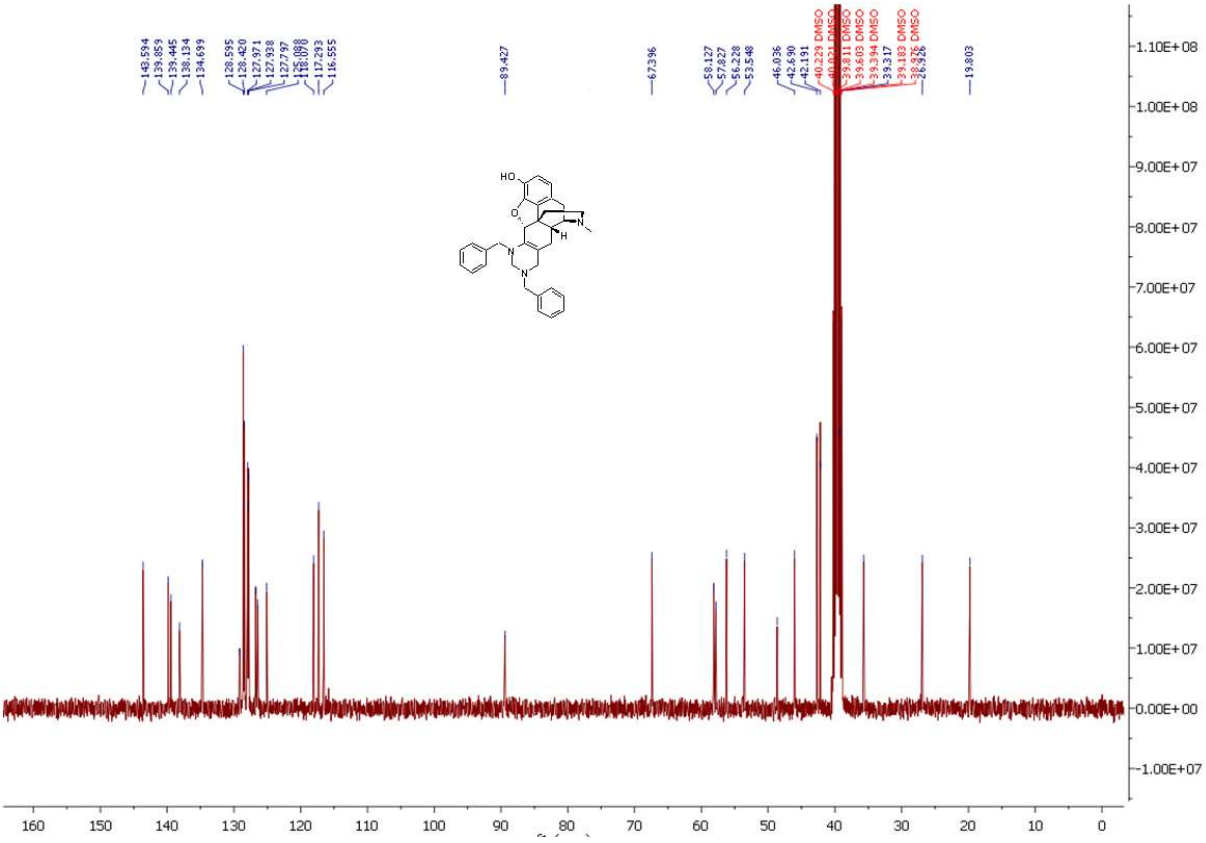

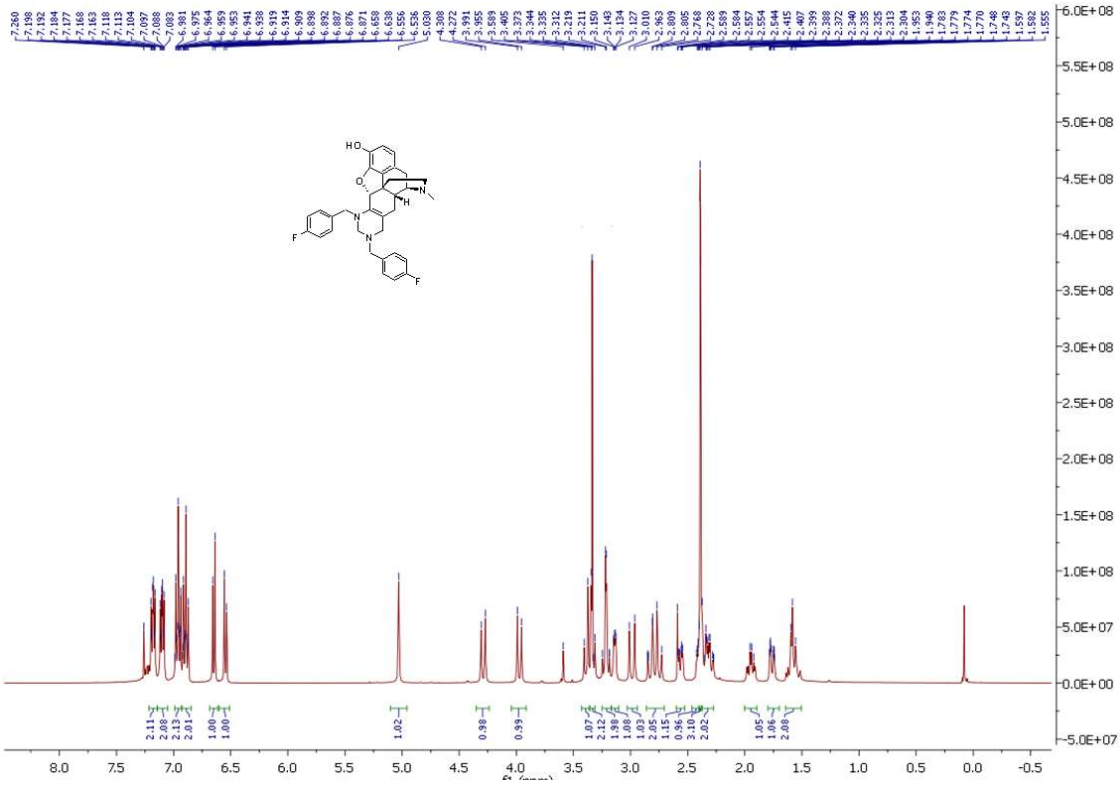

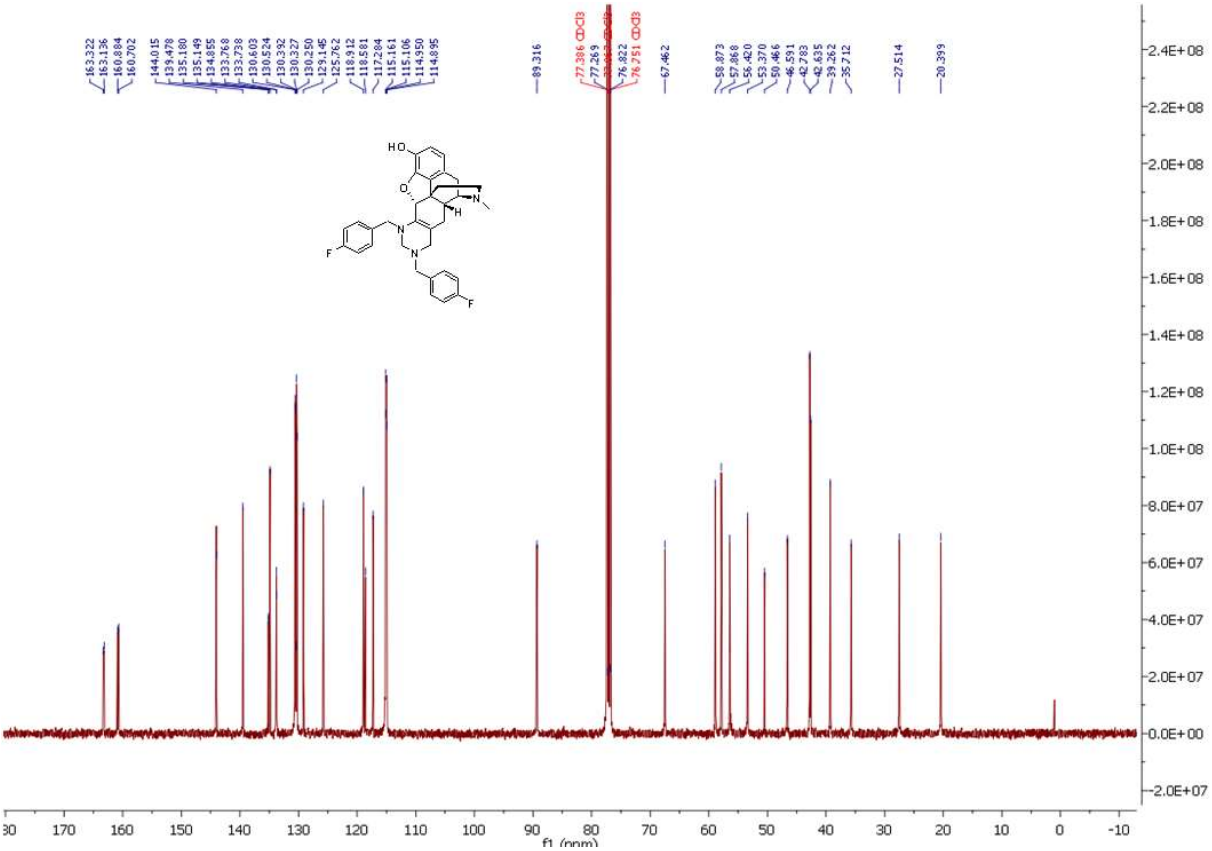

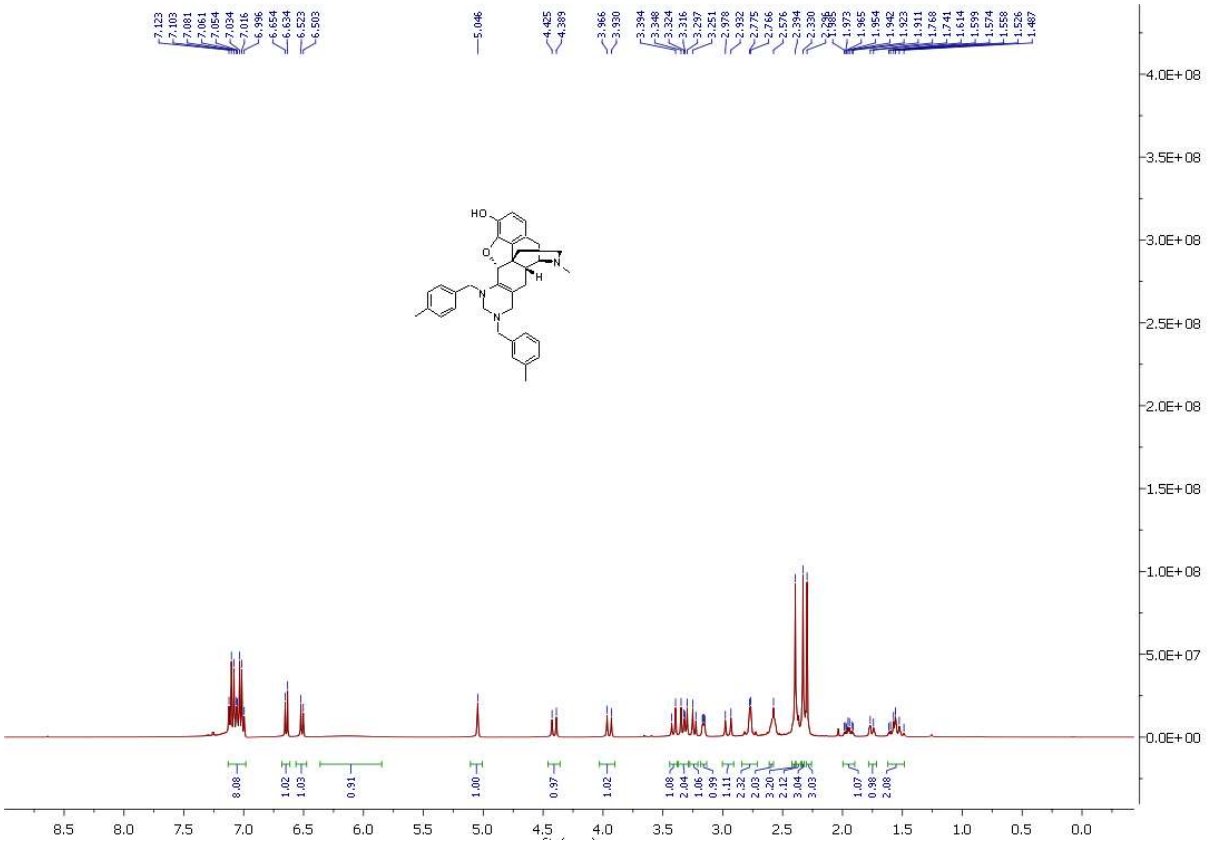
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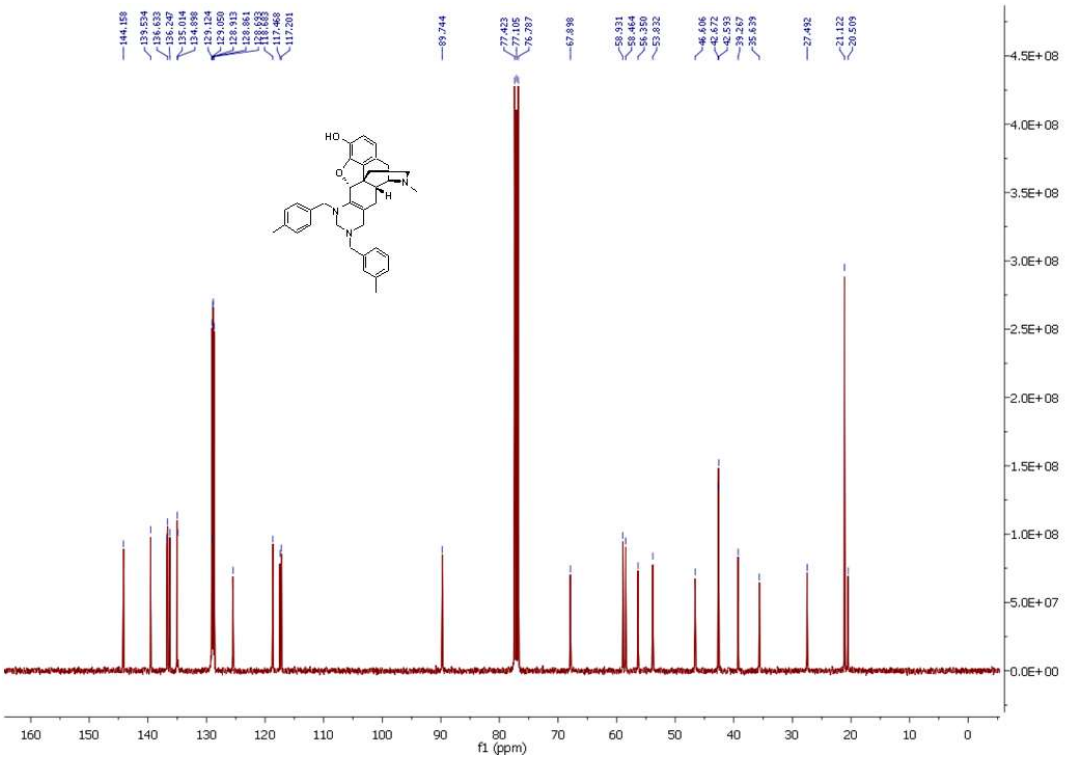
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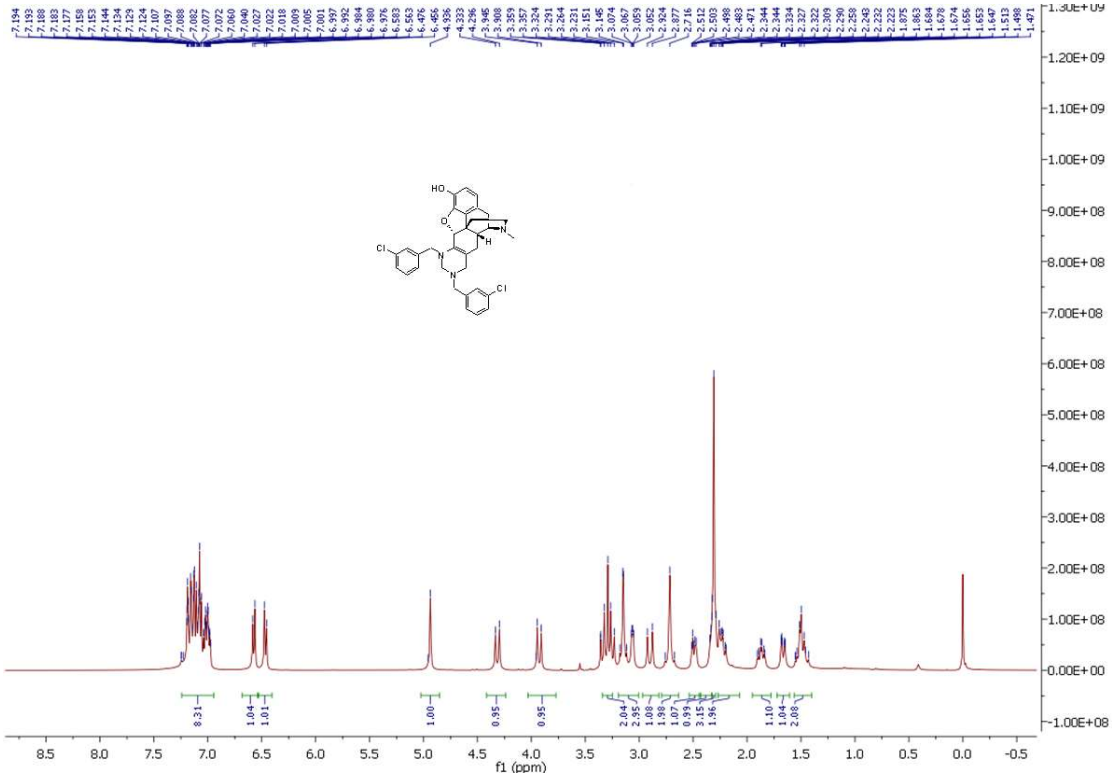
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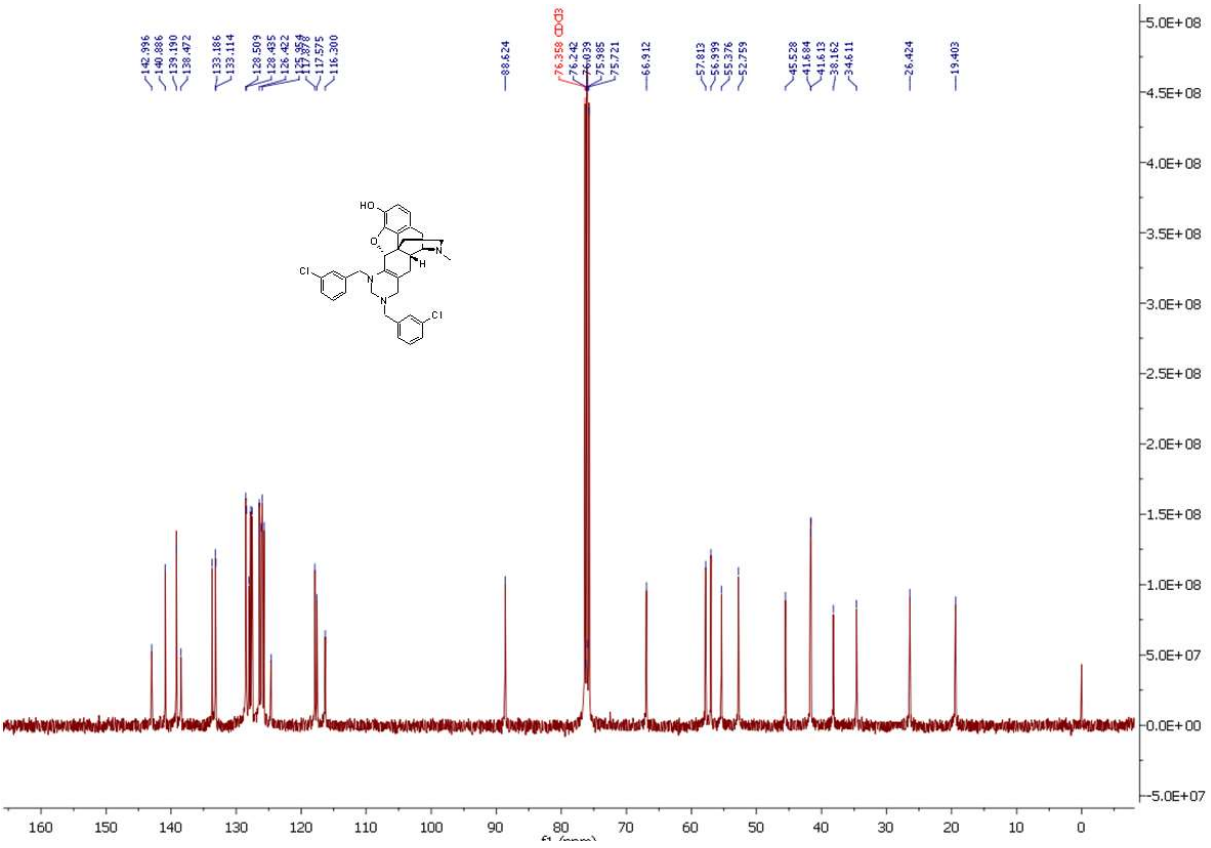
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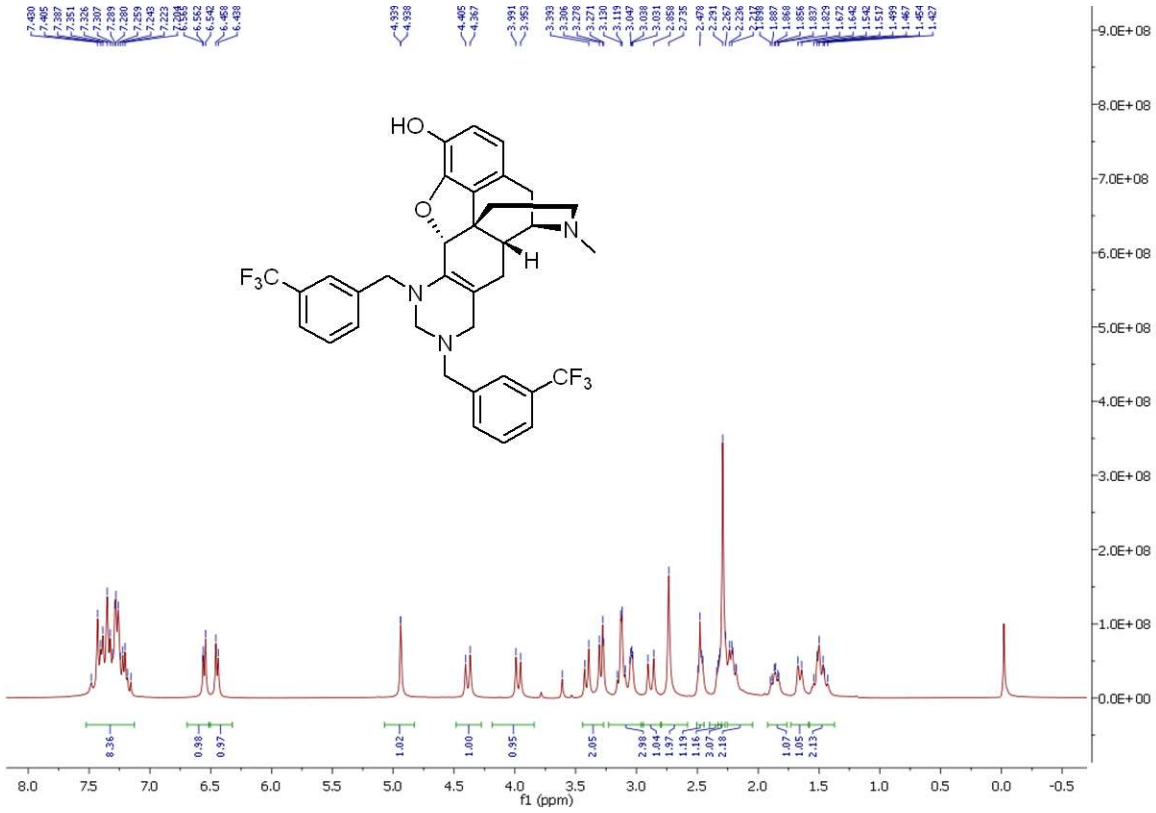
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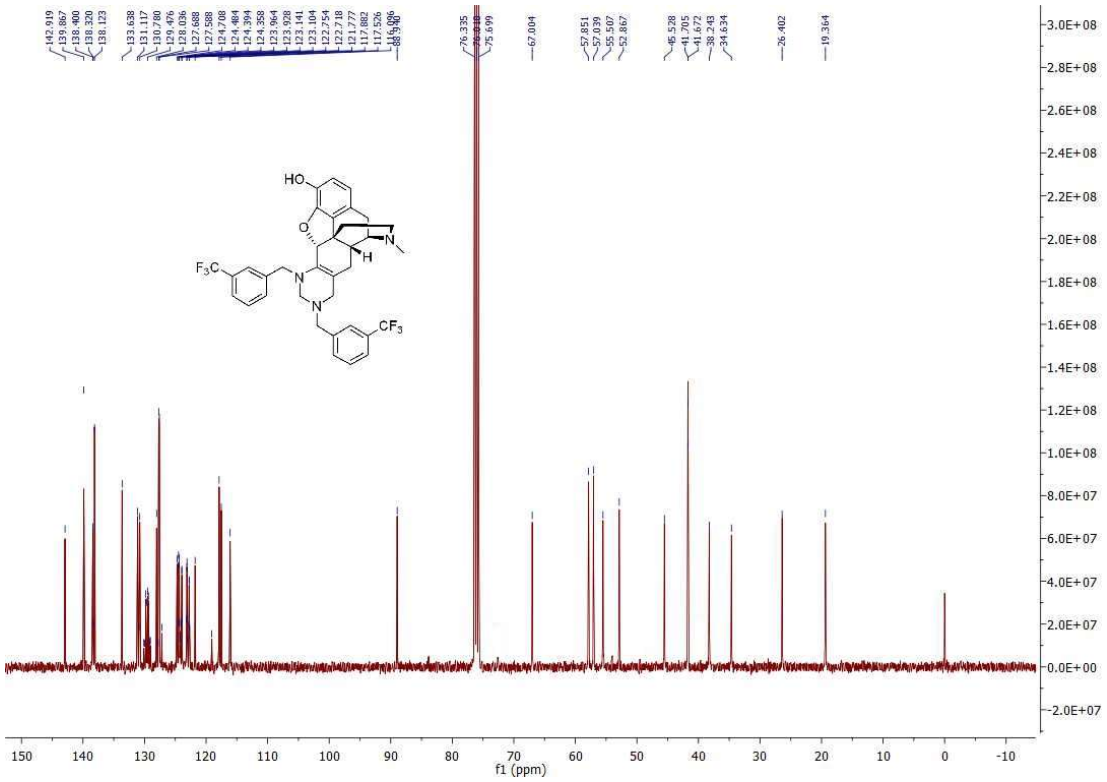
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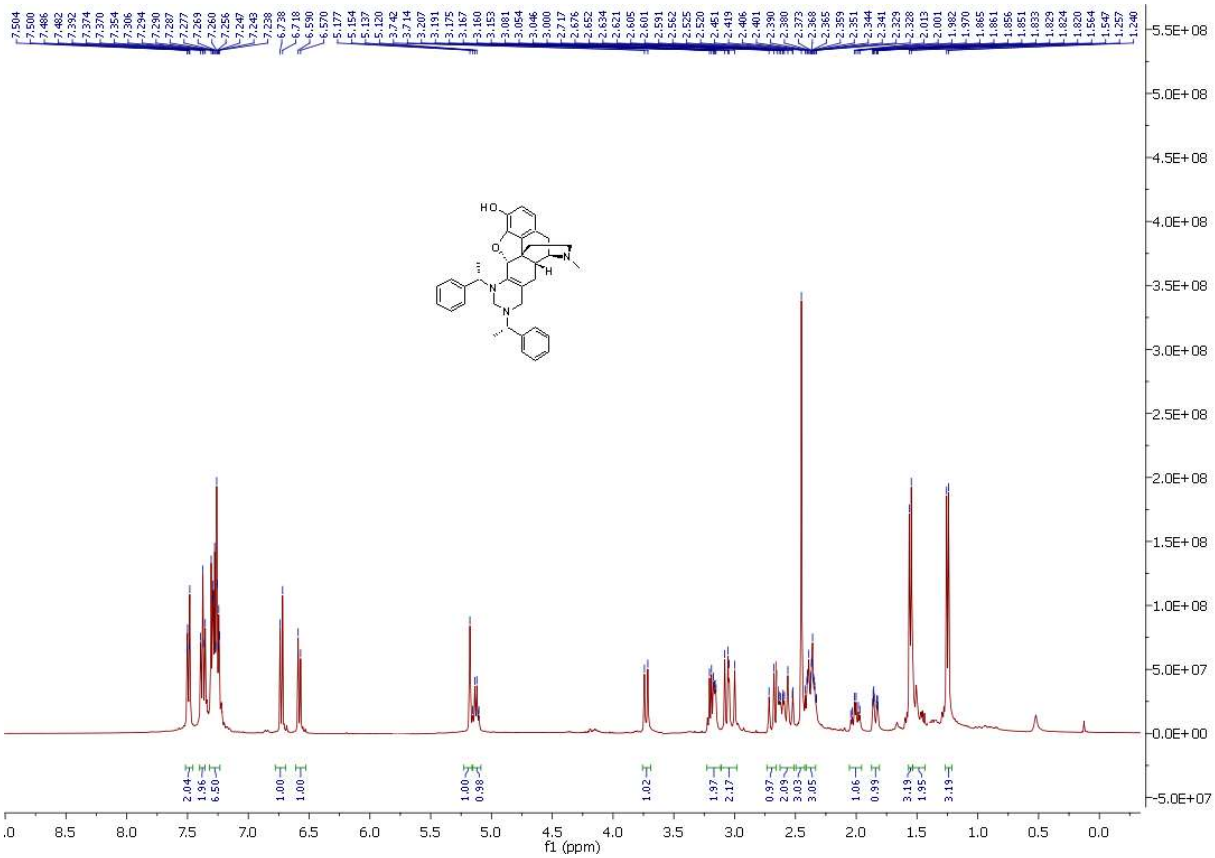
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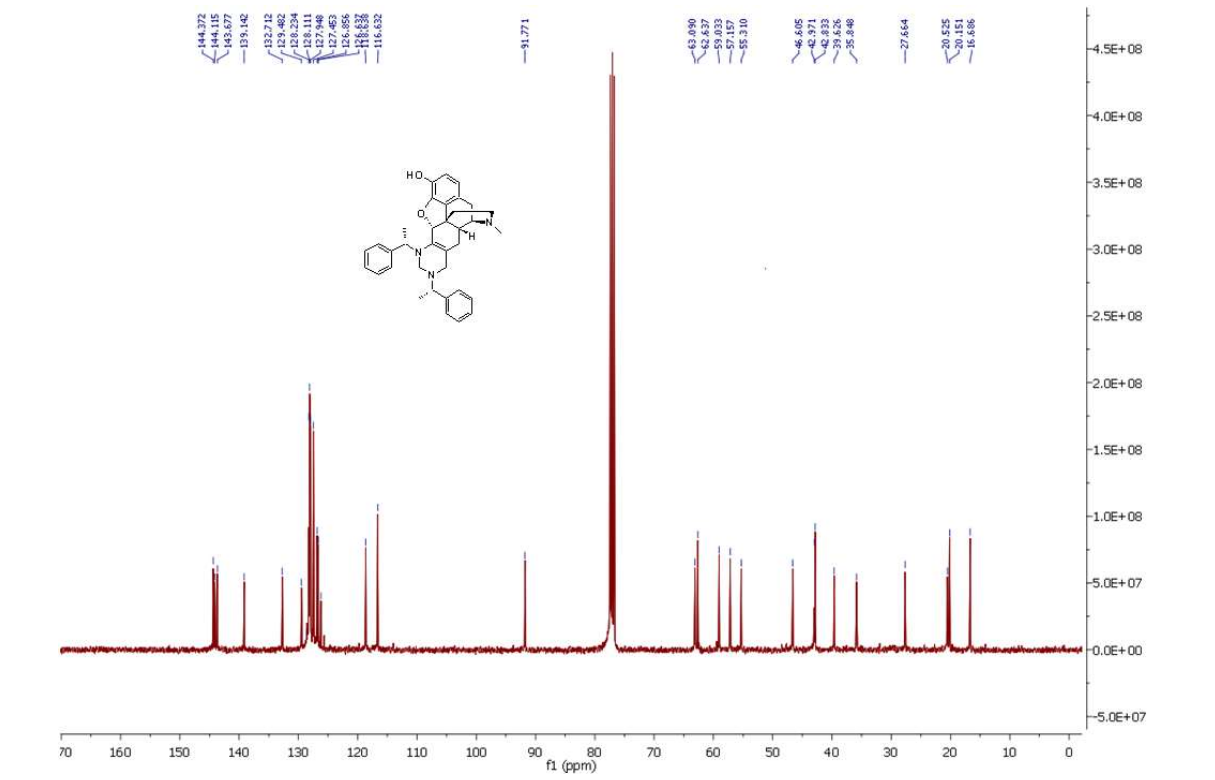
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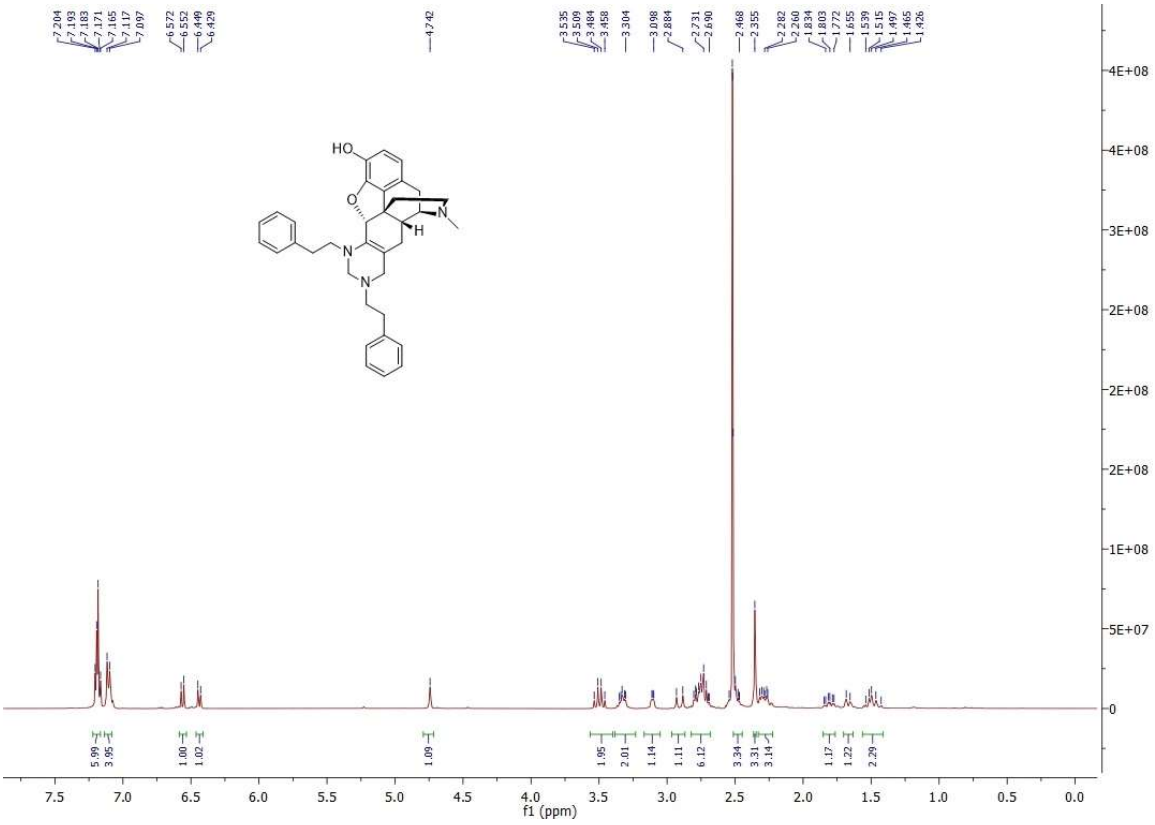
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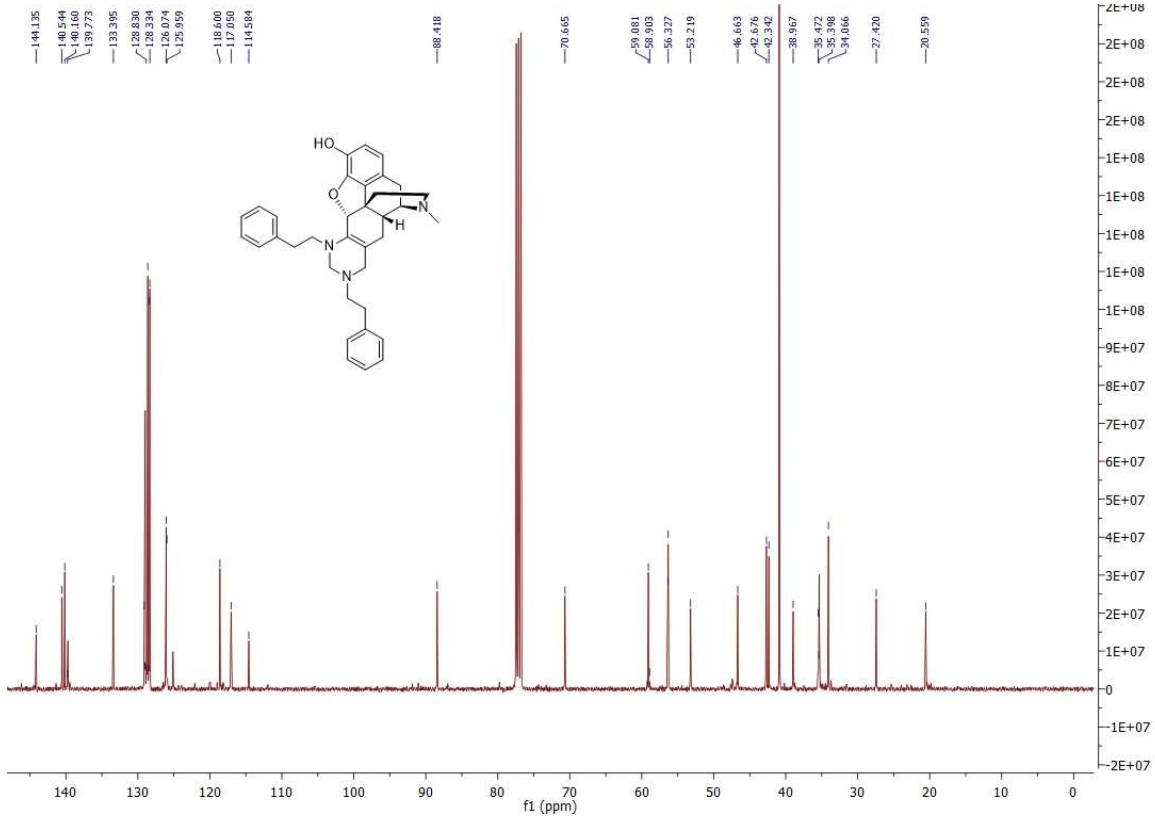
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114.584
88.418
70.665
59.081
58.903
56.327
53.219
46.663
42.676
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35.398
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20.559
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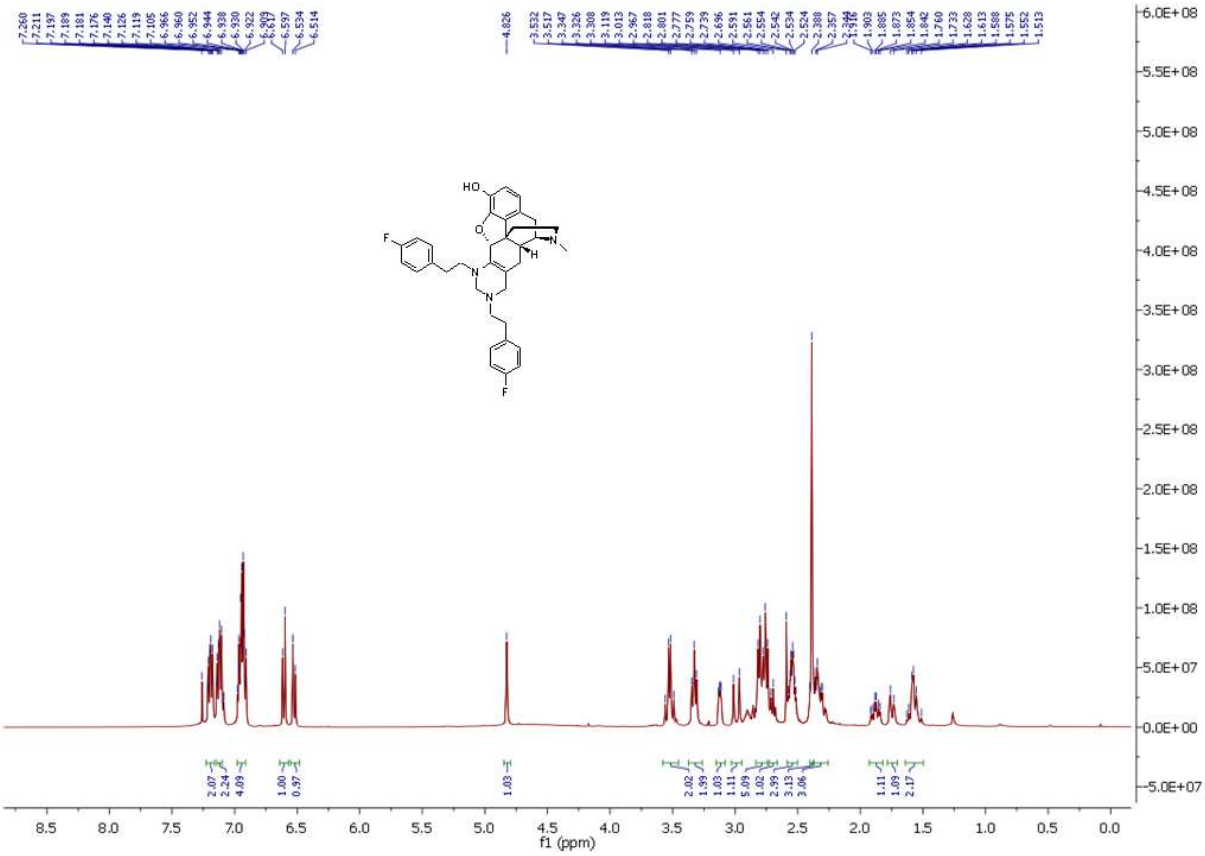
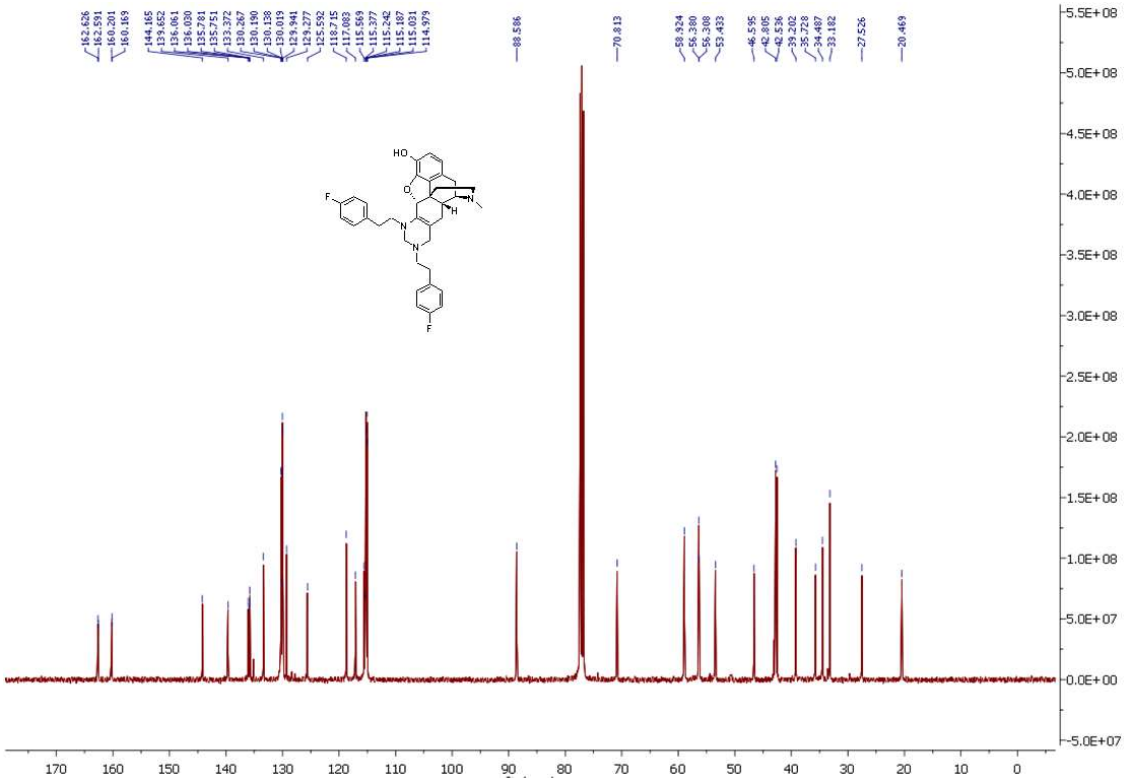
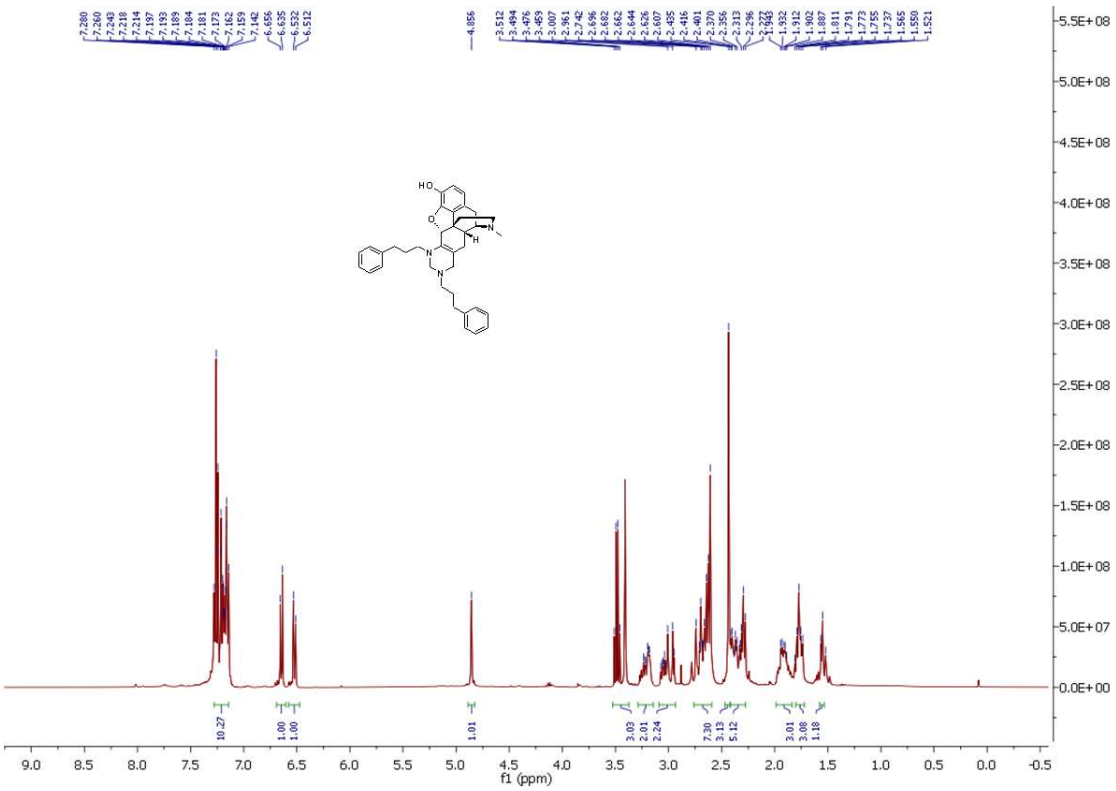
N
H
N
N
f1 (ppm)


f1 (ppm)

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7.214
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7.189
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7.181
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7.162
7.159
7.148
6.655
6.635
6.532
6.512
4.856
3.512
3.494
3.476
3.459
3.007
2.961
2.742
2.696
2.662
2.662
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2.435
2.416
2.401
2.370
2.356
2.313
2.296
1.932
1.912
1.902
1.887
1.811
1.791
1.773
1.755
1.737
1.565
1.550
1.521
HO
O
N
H
N
N
10.27
1.00
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2.01
2.24
7.30
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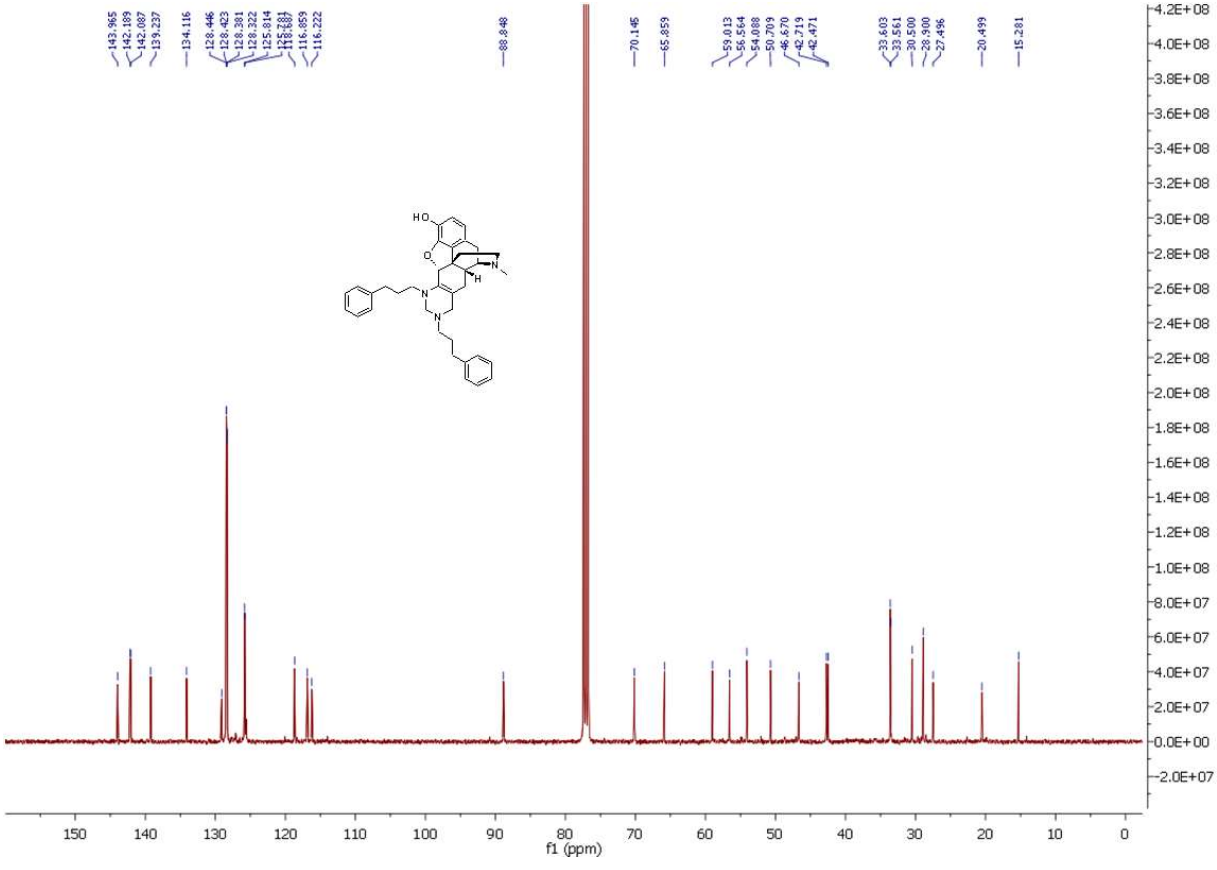
3.01
3.08
1.18
f1 (ppm)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70.145
65.859
59.013
56.564
54.088
50.709
46.670
42.719
42.471
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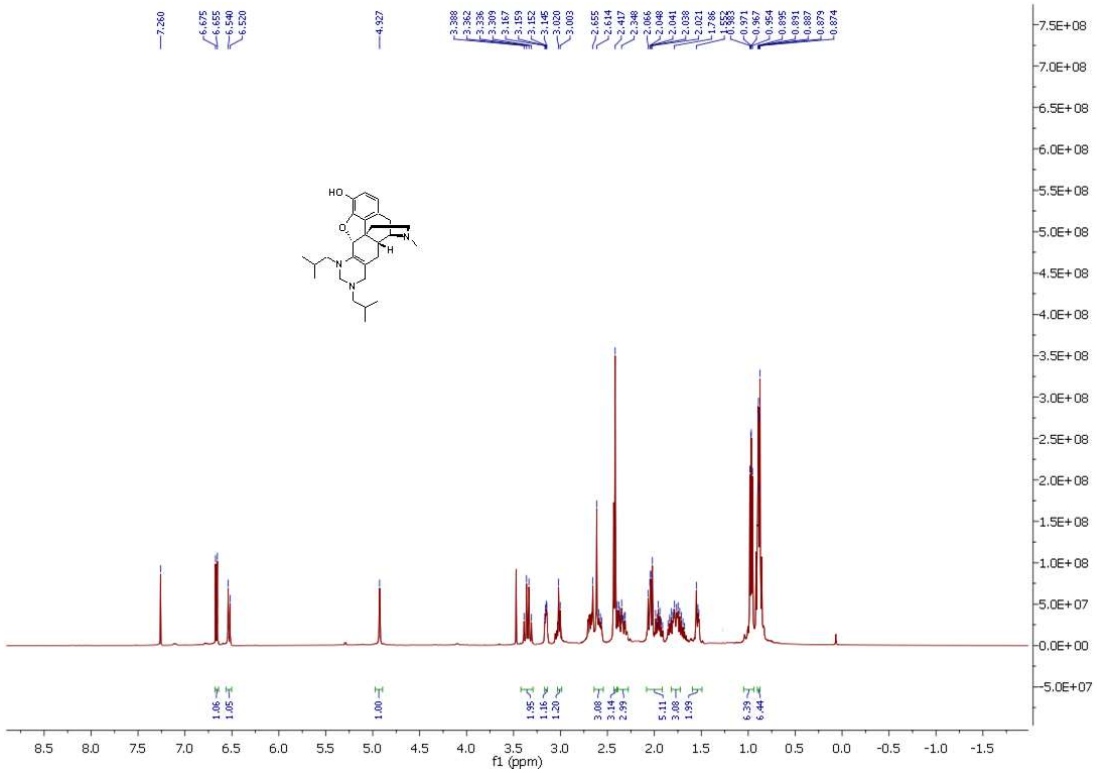
27.496
20.499
15.281
HO
O
N
H
N
N
f1 (ppm)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3.159
3.152
3.145
3.026
3.003
2.655
2.614
2.417
2.348
2.066
2.048
2.041
2.038
2.021
1.776
1.555
1.553
0.971
0.967
0.954
0.895
0.893
0.887
0.879
0.874
HO
O
N
H
N
N
1.06
1.05
1.00
1.95
1.16
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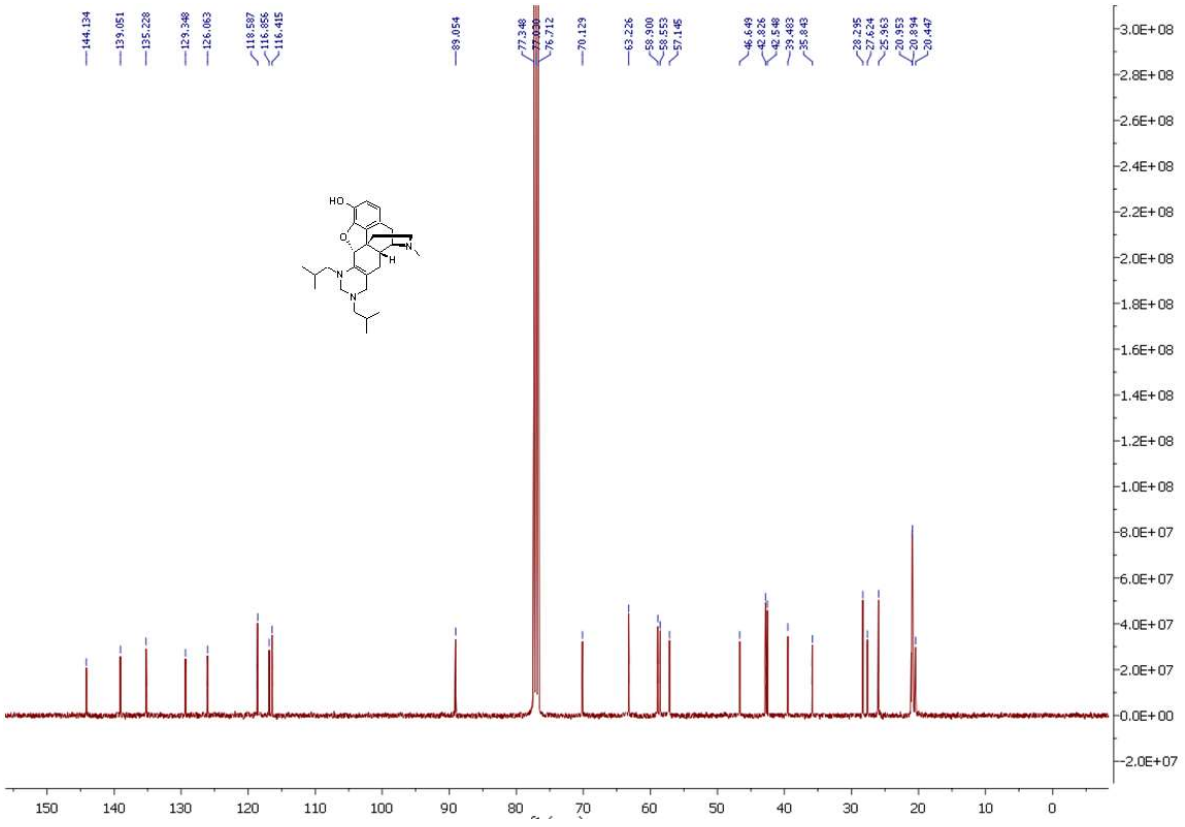
3.08
3.14
2.99
5.11
3.08
1.99
6.39
6.44
f1 (ppm)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70.129
63.226
58.900
58.553
57.145
46.649
42.826
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20.447
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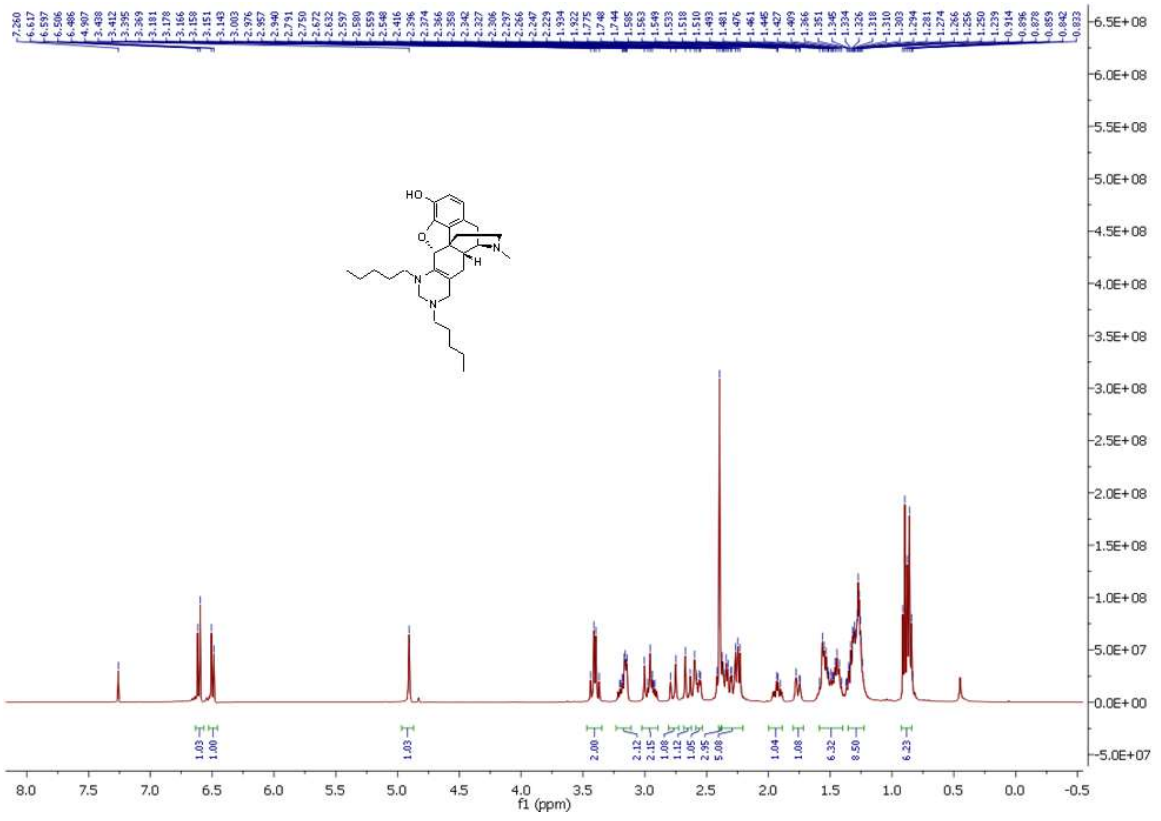
O
N
H
N
N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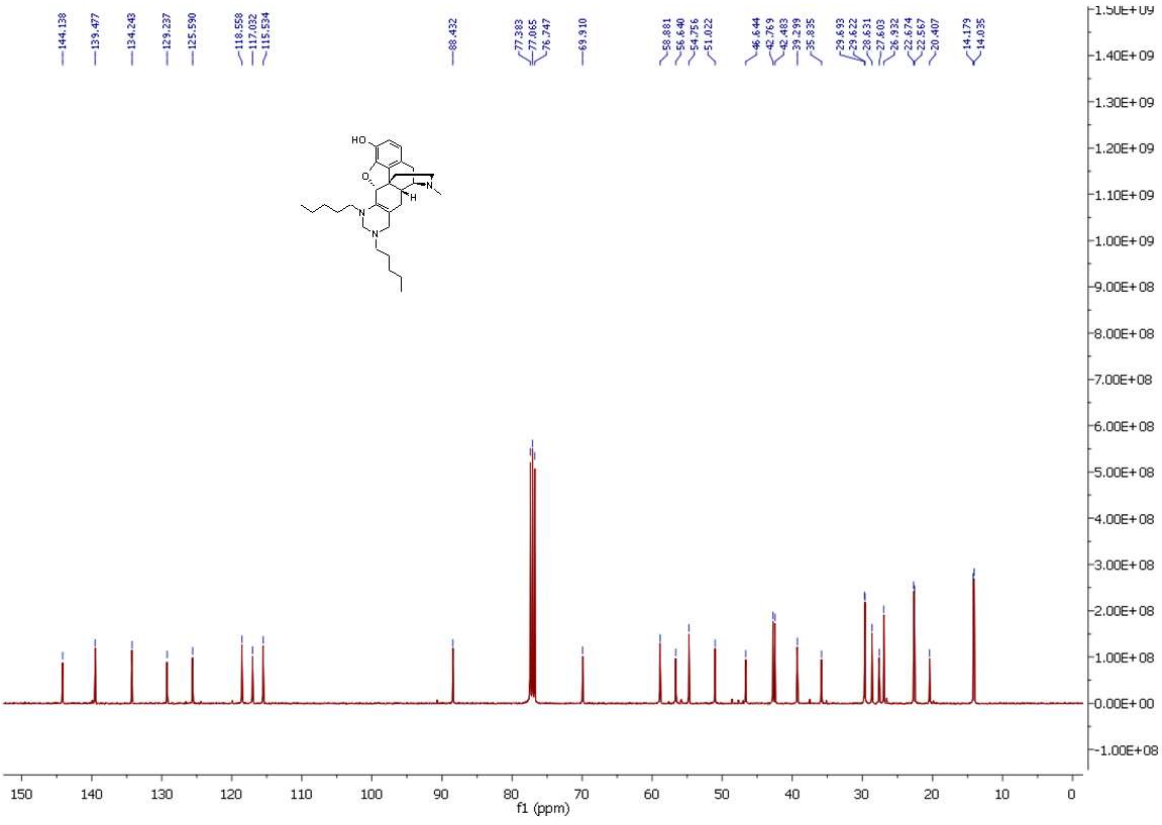
N
N
f1 (ppm)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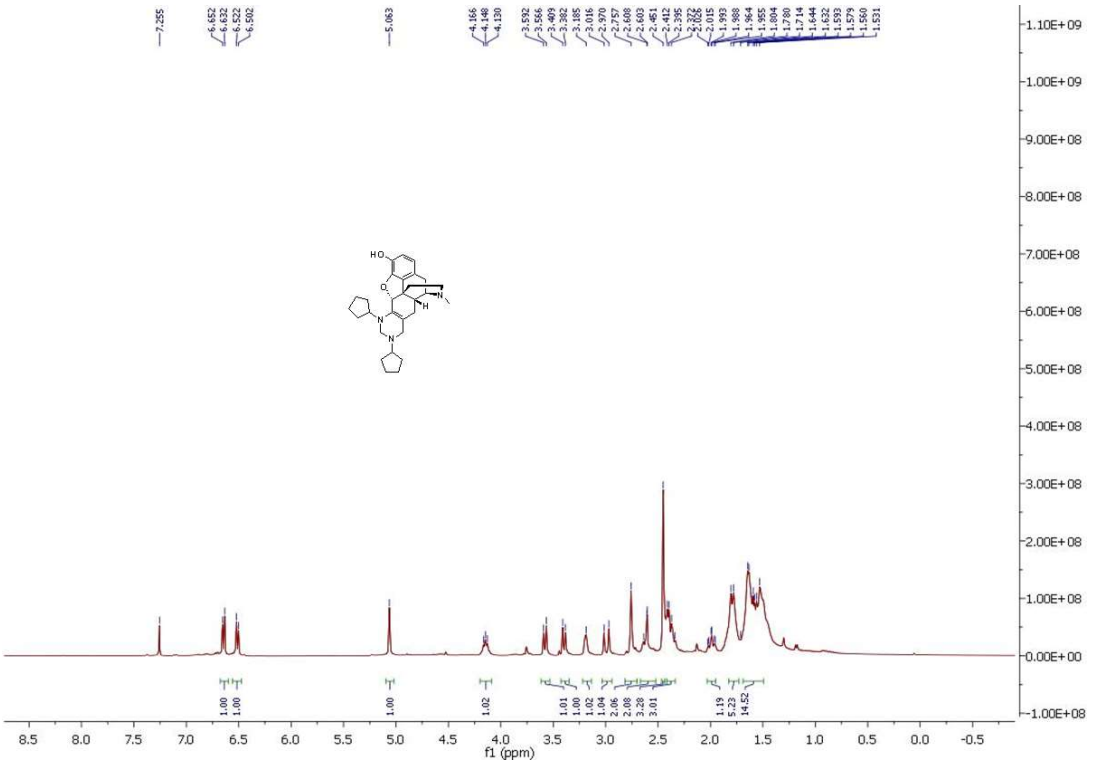
O
N
H
N
N
f1 (ppm)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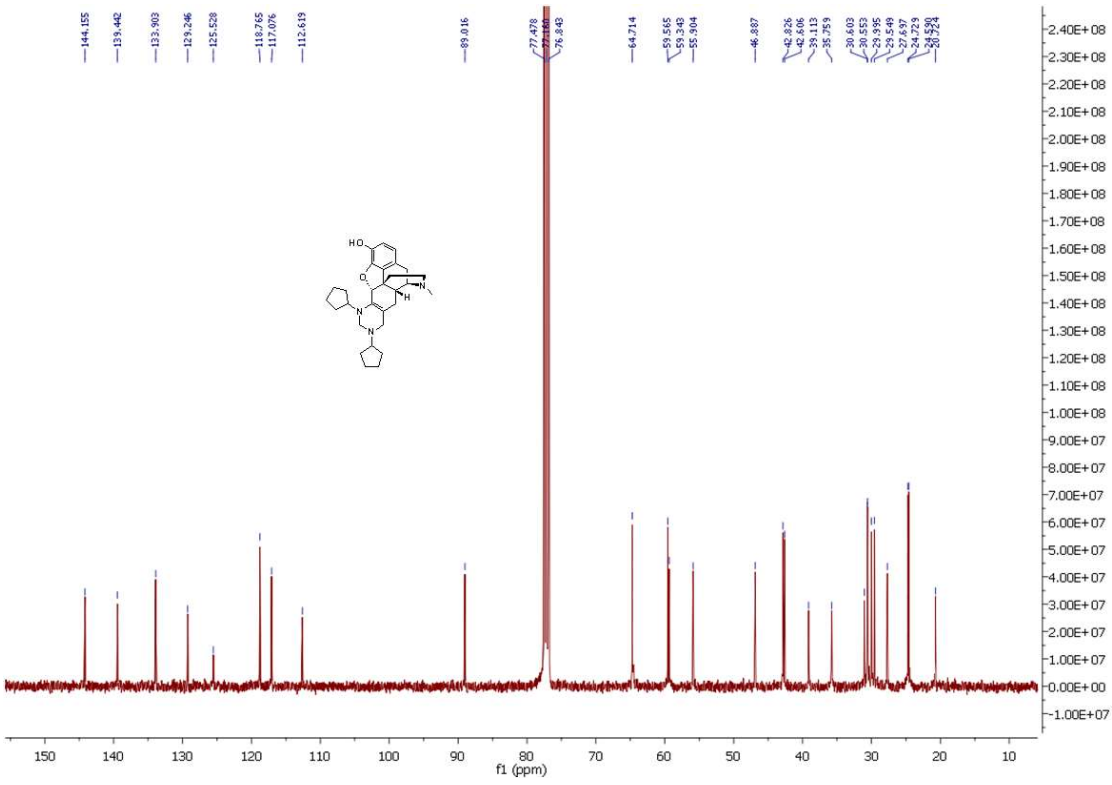
6.632
6.522
6.502
5.063
4.166
4.148
4.130
3.592
3.566
3.409
3.382
3.185
3.016
2.970
2.757
2.608
2.603
2.461
2.412
2.395
2.015
1.993
1.988
1.964
1.955
1.804
1.780
1.714
1.644
1.632
1.593
1.579
1.560
1.531
HO
O
N
H
N
N
1.00
1.00
1.00
1.02
1.01
1.00
1.02
1.04
2.06
2.08
3.28
3.01
1.19
5.23
14.62
f1 (ppm)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133.903
129.246
125.528
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117.076
112.619
89.016
77.478
77.160
76.843
64.714
59.565
59.343
55.904
46.807
42.826
42.606
39.113
35.759
30.603
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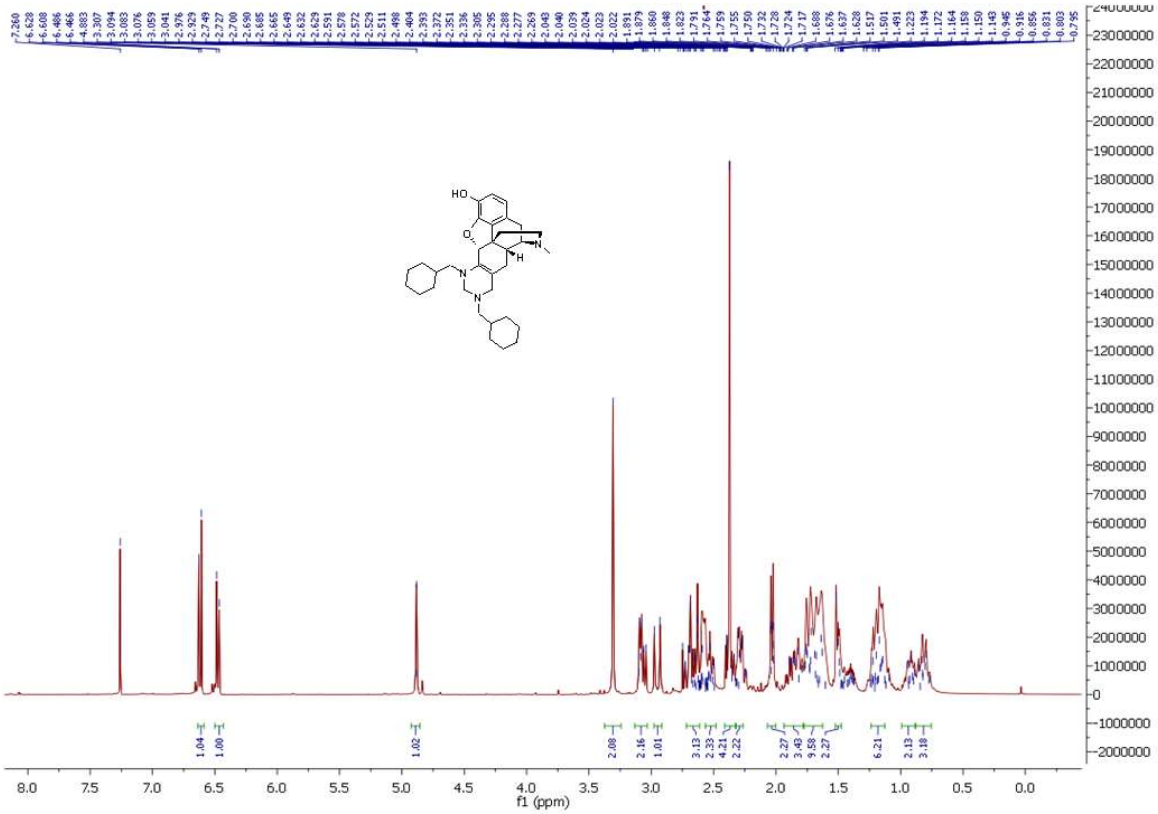
29.549
27.697
24.729
20.724
HO
O
N
H
N
N
f1 (ppm)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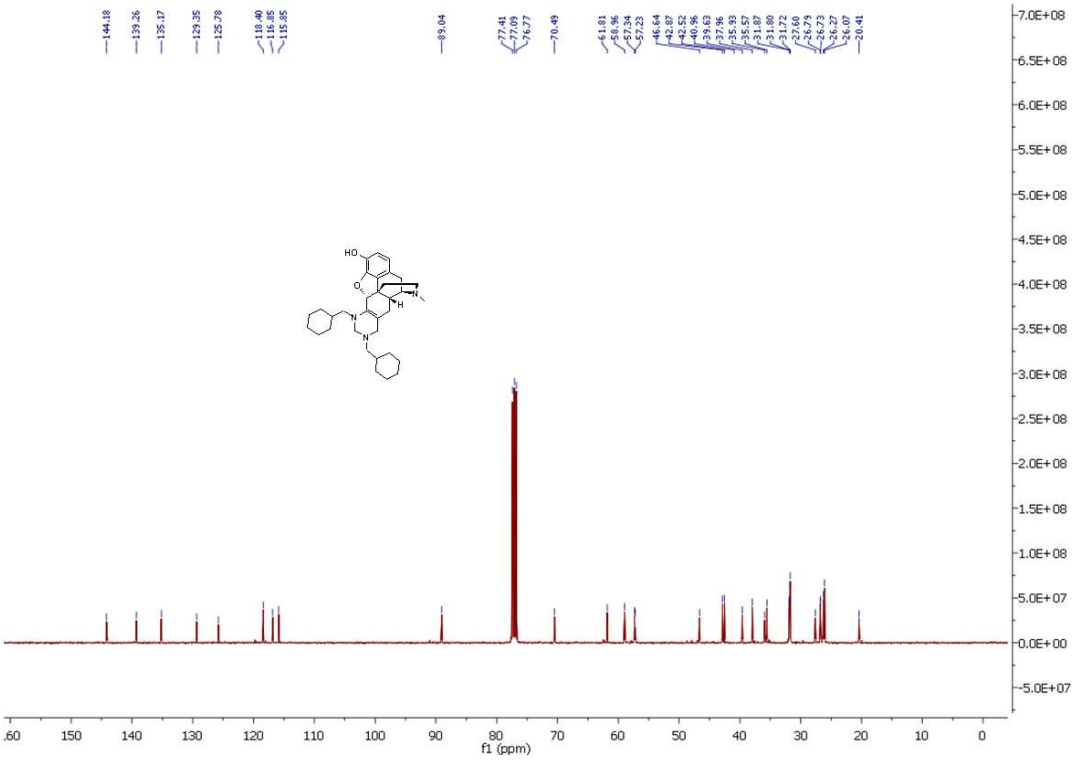
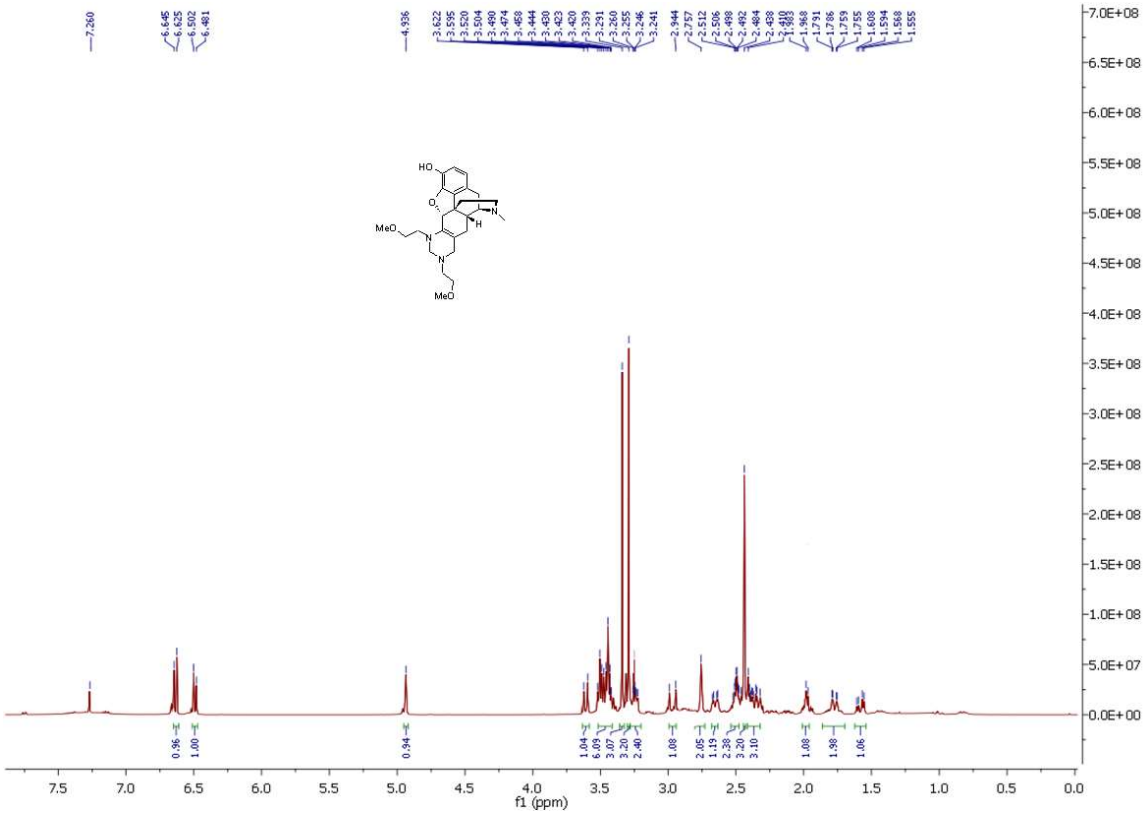
O
N
H
N
N
f1 (ppm)


HO
O
N
H
N
N
f1 (ppm)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4.936
3.622
3.595
3.520
3.504
3.490
3.474
3.458
3.444
3.430
3.423
3.420
3.339
3.291
3.260
3.255
3.246
3.241
2.944
2.757
2.512
2.506
2.498
2.492
2.484
2.438
2.410
2.383
1.968
1.791
1.786
1.759
1.755
1.608
1.594
1.568
1.555
HO
O
N
H
MeO
N
N
MeO
0.96
1.00
0.94
1.04
6.09
3.07
3.20
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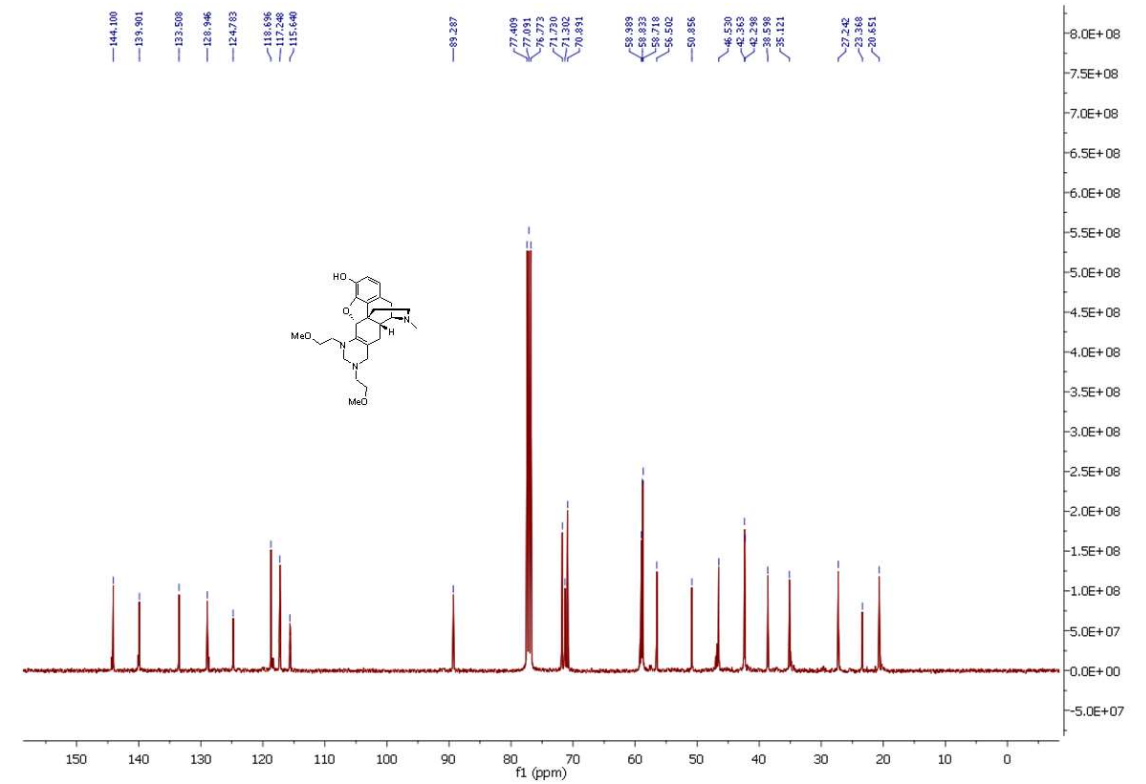
1.08
2.05
1.19
2.38
3.20
3.10
1.08
1.98
1.06
f1 (ppm)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71.730
71.302
70.891
58.389
58.833
58.718
56.502
50.856
46.530
42.363
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27.242
23.368
20.651
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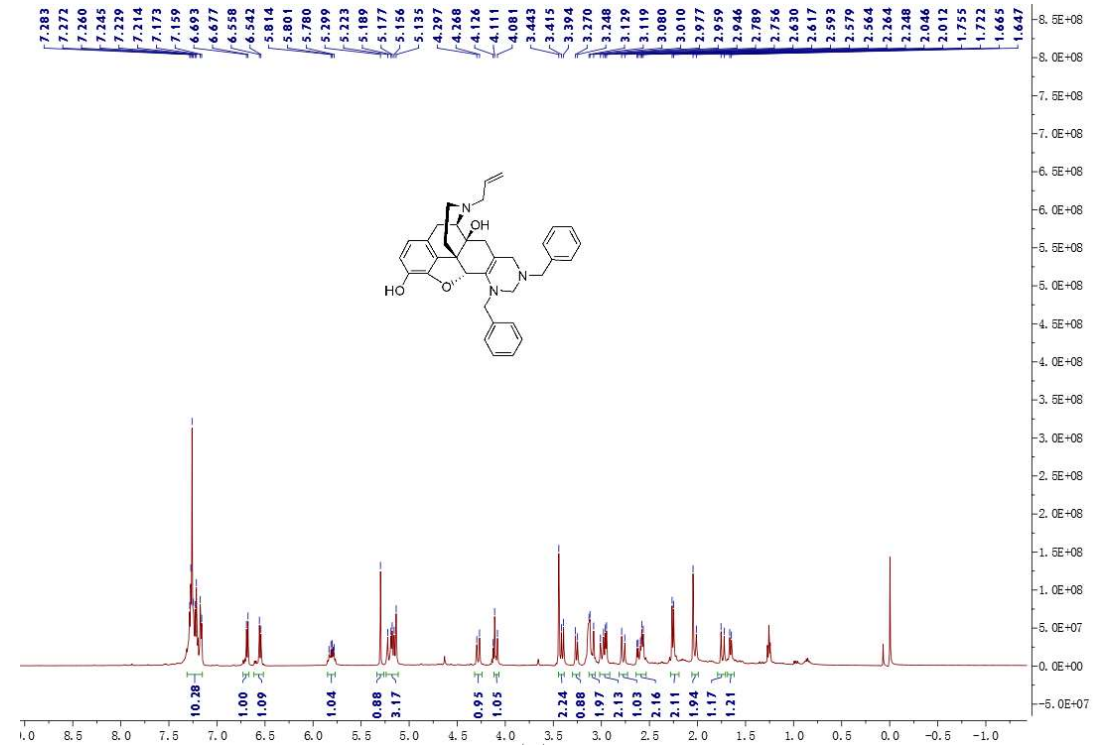
O
N
H
MeO
N
N
MeO
f1 (ppm)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7.229
7.214
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7.159
6.693
6.677
6.558
6.542
5.814
5.801
5.780
5.299
5.223
5.189
5.177
5.156
5.135
4.297
4.268
4.126
4.111
4.081
3.443
3.415
3.394
3.270
3.248
3.129
3.119
3.080
3.010
2.977
2.959
2.946
2.789
2.756
2.630
2.617
2.593
2.579
2.564
2.264
2.248
2.046
2.012
1.755
1.722
1.665
1.647
HO
OH
N
O
10.28
1.00
1.09
1.04
0.88
3.17
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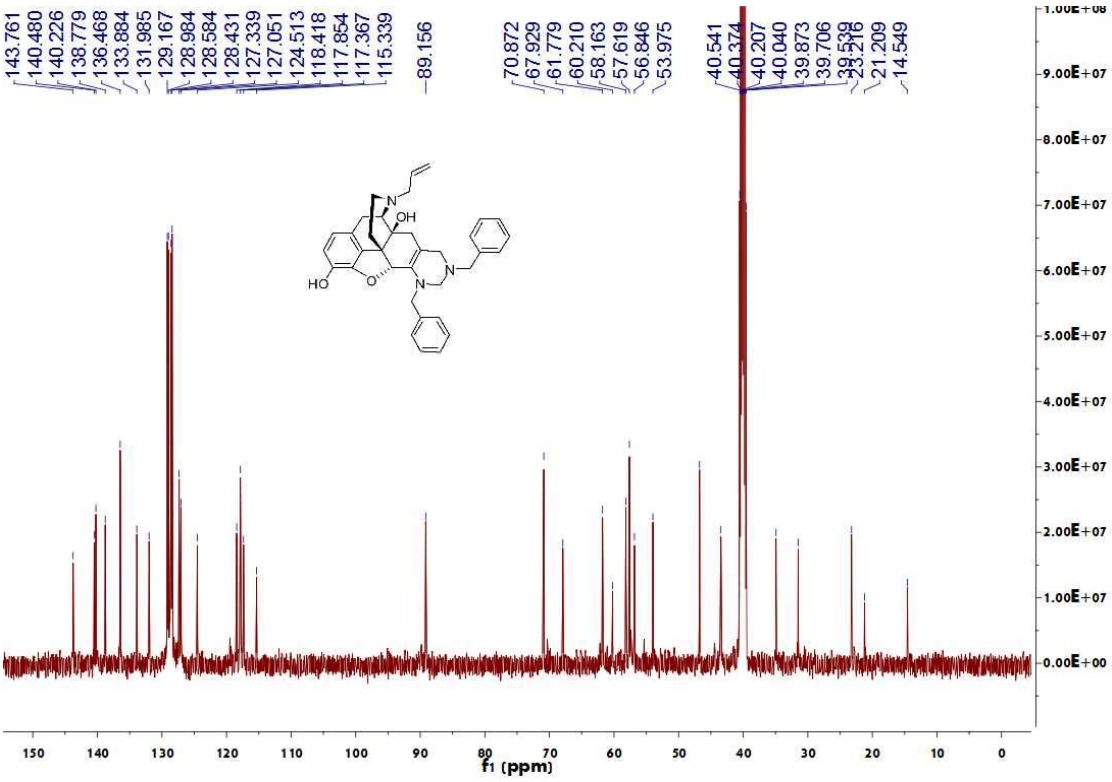
1.94
1.17
1.21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127.339
127.051
124.513
118.418
117.854
117.367
115.339
89.156
70.872
67.929
61.779
60.210
58.163
57.619
56.846
53.975
40.541
40.374
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39.706
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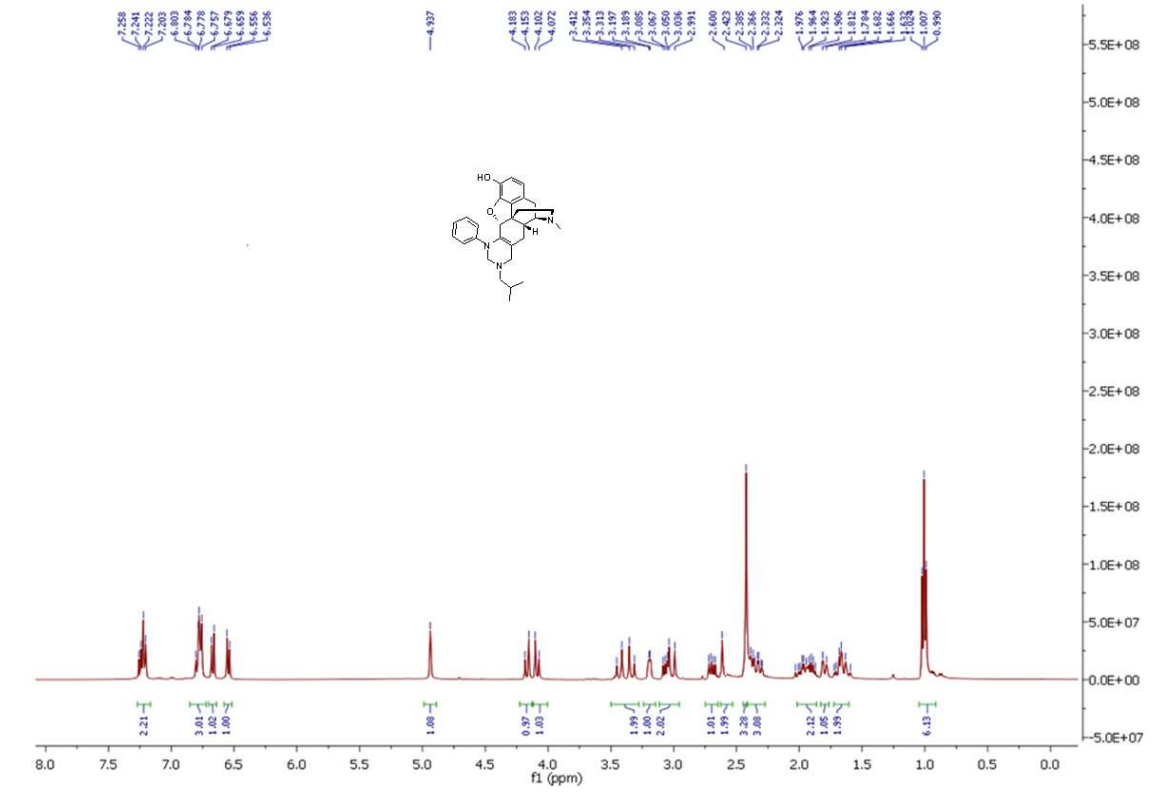
14.549
HO
OH
N
O
f1 (ppm)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6.659
6.656
6.636
4.937
4.183
4.153
4.102
4.072
3.412
3.354
3.313
3.197
3.189
3.085
3.067
3.050
3.036
2.991
2.600
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2.366
2.332
2.324
1.976
1.964
1.923
1.906
1.812
1.784
1.682
1.666
1.007
0.990
HO
O
N
H
N
N
2.21
3.01
1.02
1.00
1.00
0.97
1.03
1.99
1.00
2.02
1.01
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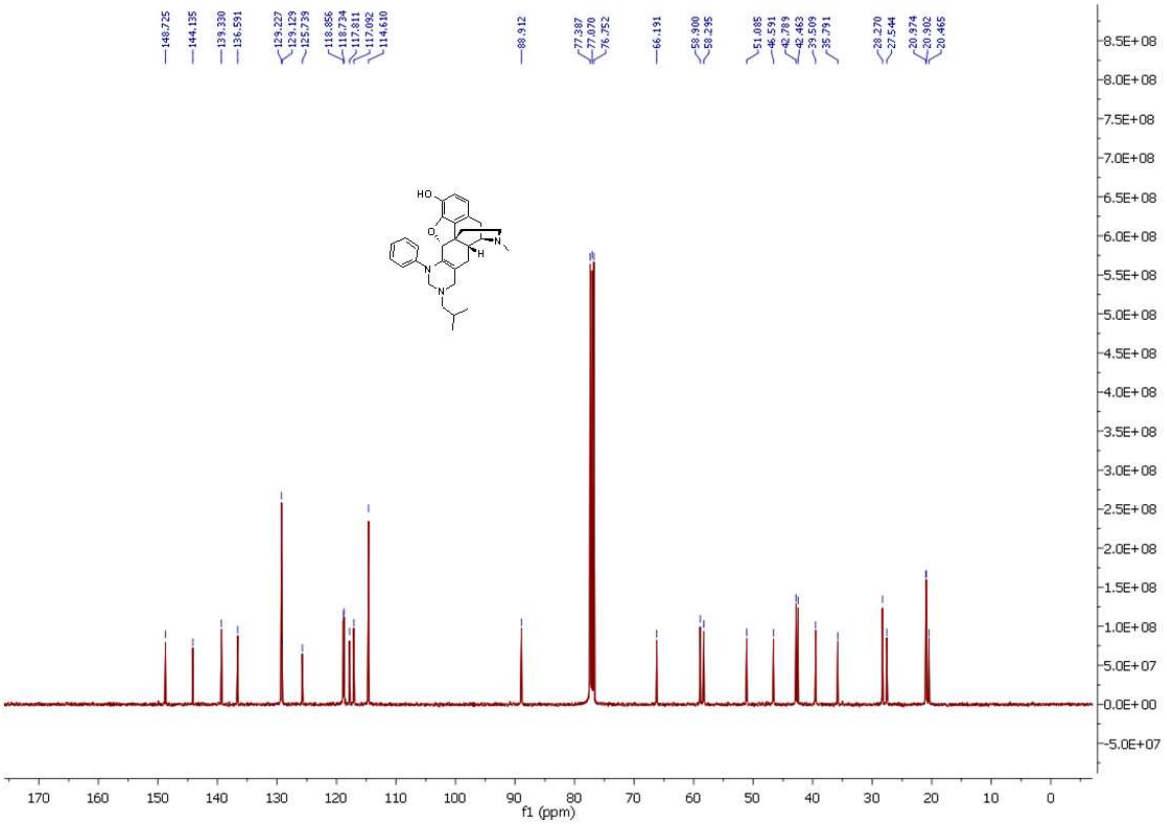
3.28
3.00
2.12
1.05
1.99
6.13
f1 (ppm)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117.092
114.610
88.912
77.387
77.070
76.752
66.191
58.300
58.295
51.085
46.591
42.709
42.465
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27.544
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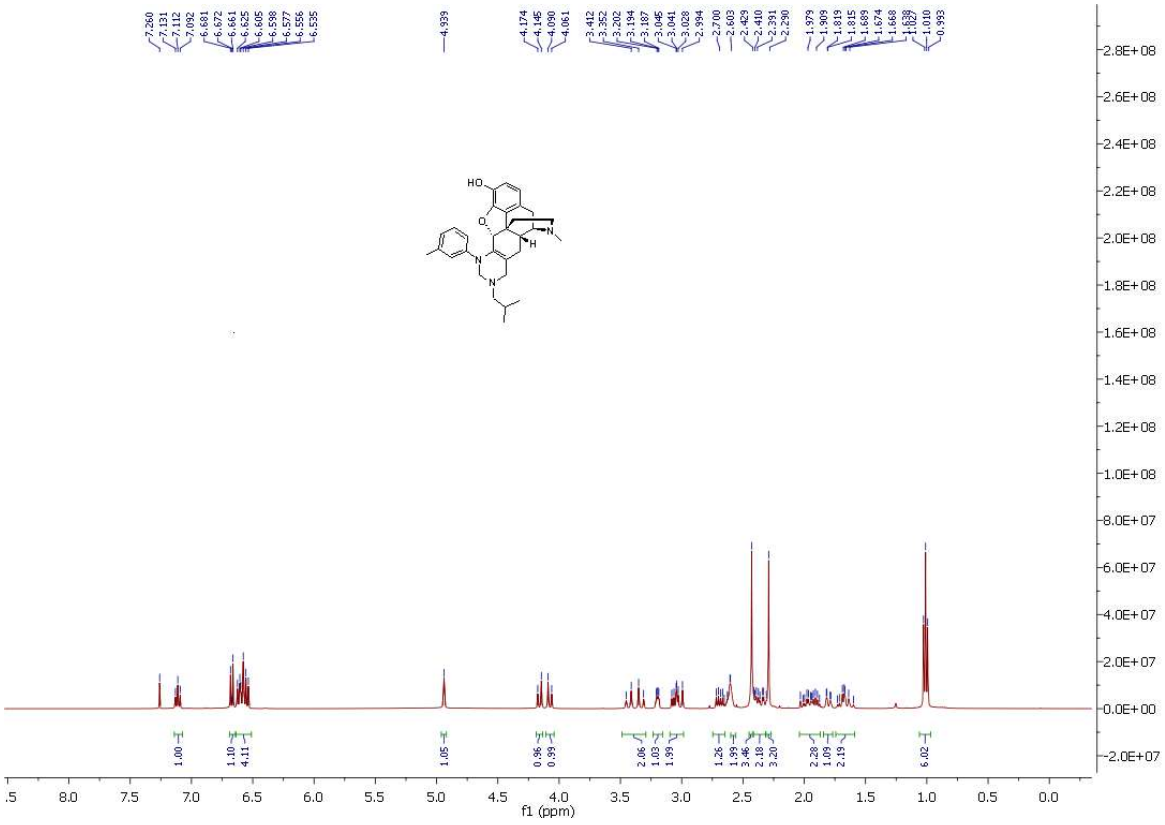
20.465
HO
O
N
H
N
N
f1 (ppm)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6.598
6.577
6.556
6.535
4.939
4.174
4.145
4.090
4.061
3.412
3.352
3.202
3.194
3.187
3.045
3.041
3.028
2.994
2.700
2.603
2.429
2.410
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2.290
1.979
1.909
1.819
1.815
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1.638
1.027
1.010
0.993
HO
O
N
H
N
N
1.00
1.10
4.11
1.05
0.96
0.99
2.06
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1.09
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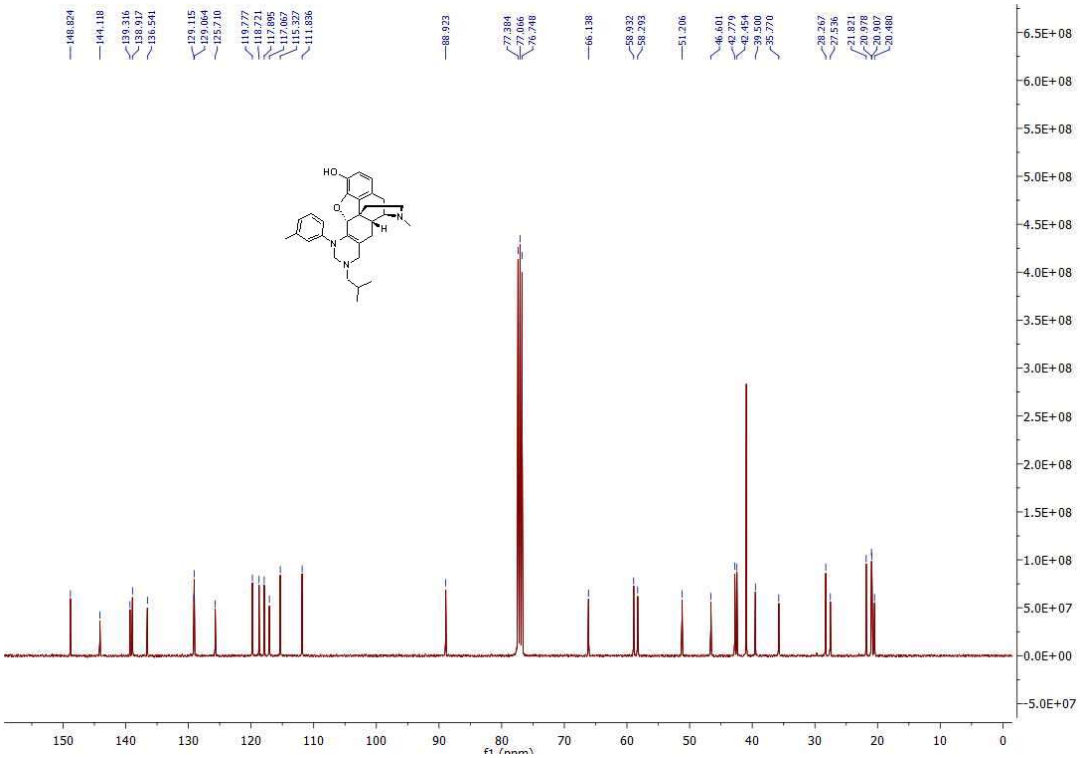
6.02
f1 (ppm)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115.327
111.836
88.923
77.384
77.066
76.748
66.138
58.932
58.293
51.206
46.601
42.779
42.454
39.500
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O
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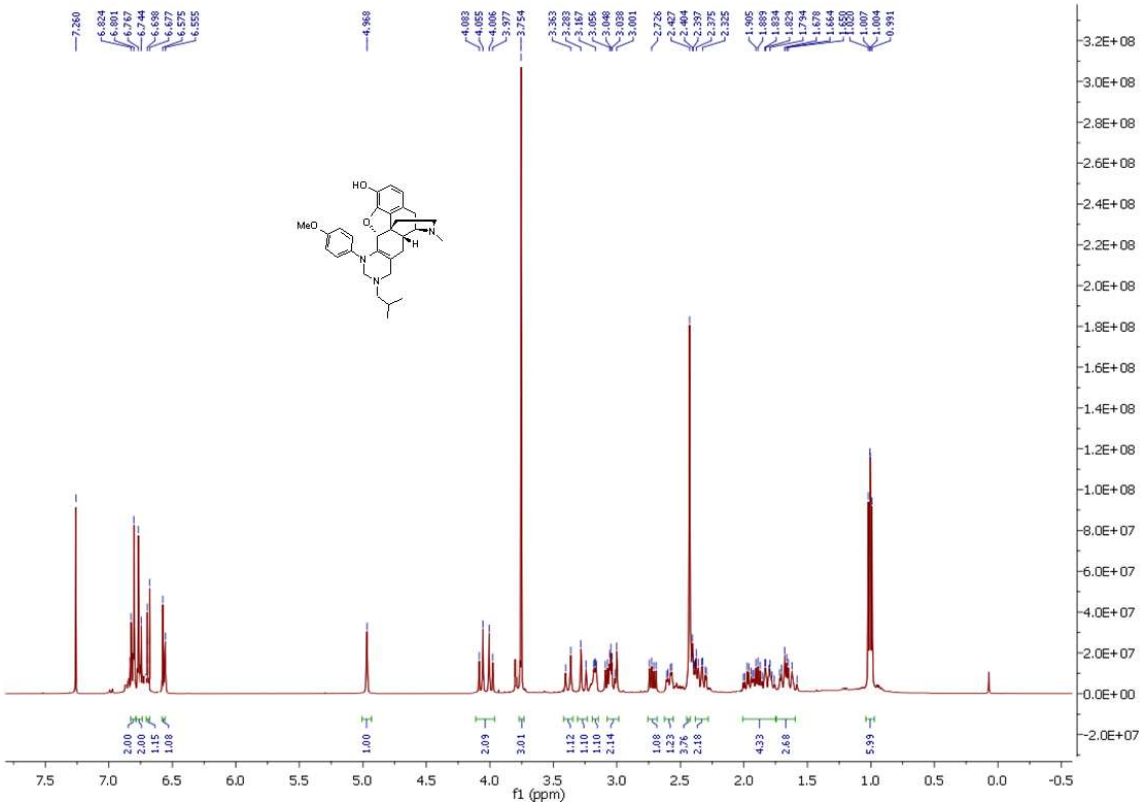
H
N
N
f1 (ppm)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4.055
4.006
3.977
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3.283
3.167
3.055
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3.038
3.001
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2.427
2.404
2.397
2.375
2.325
1.905
1.889
1.834
1.829
1.794
1.670
1.664
1.007
1.004
0.991
HO
MeO
N
O
H
2.00
2.00
1.15
1.08
1.00
2.09
3.01
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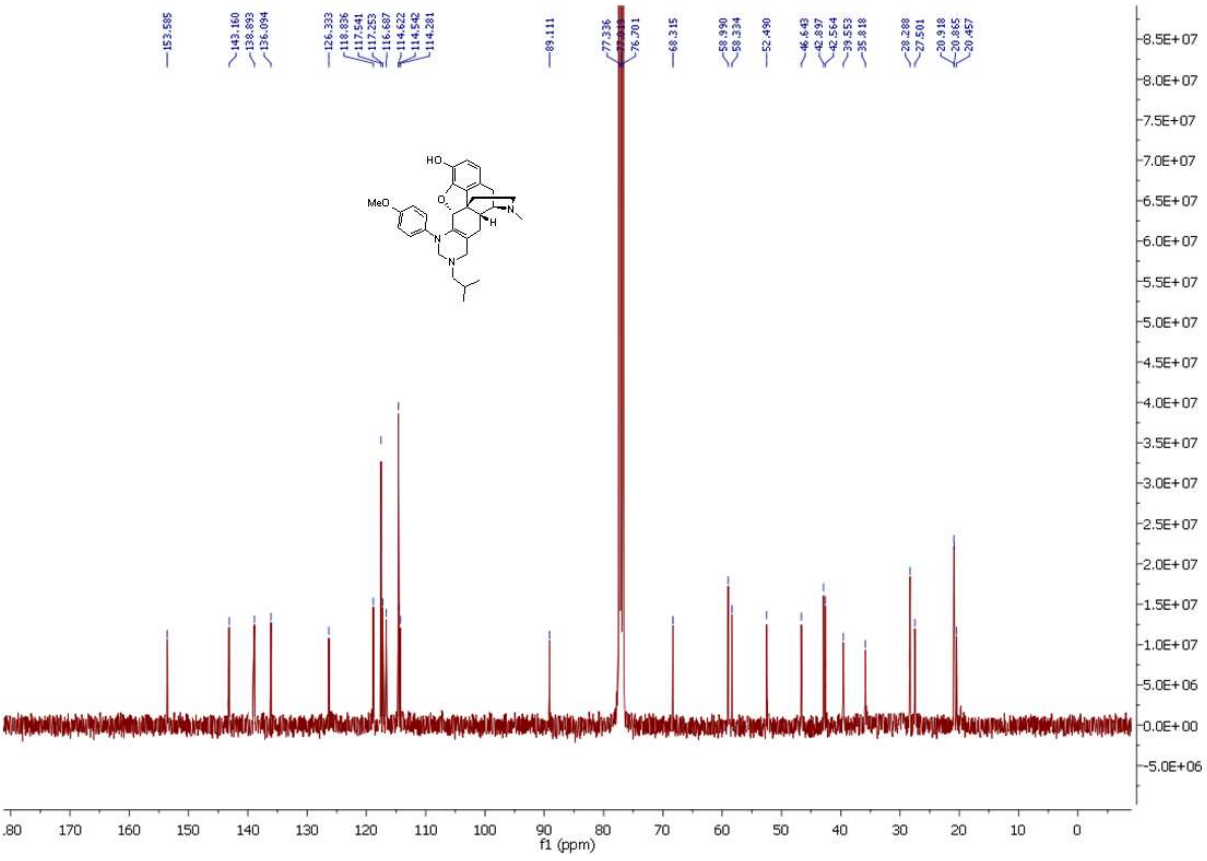
4.33
2.68
5.99
f1 (ppm)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126.333
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117.253
116.687
114.622
114.542
114.281
69.111
77.336
76.701
68.315
58.990
58.334
52.490
46.643
42.897
42.564
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27.501
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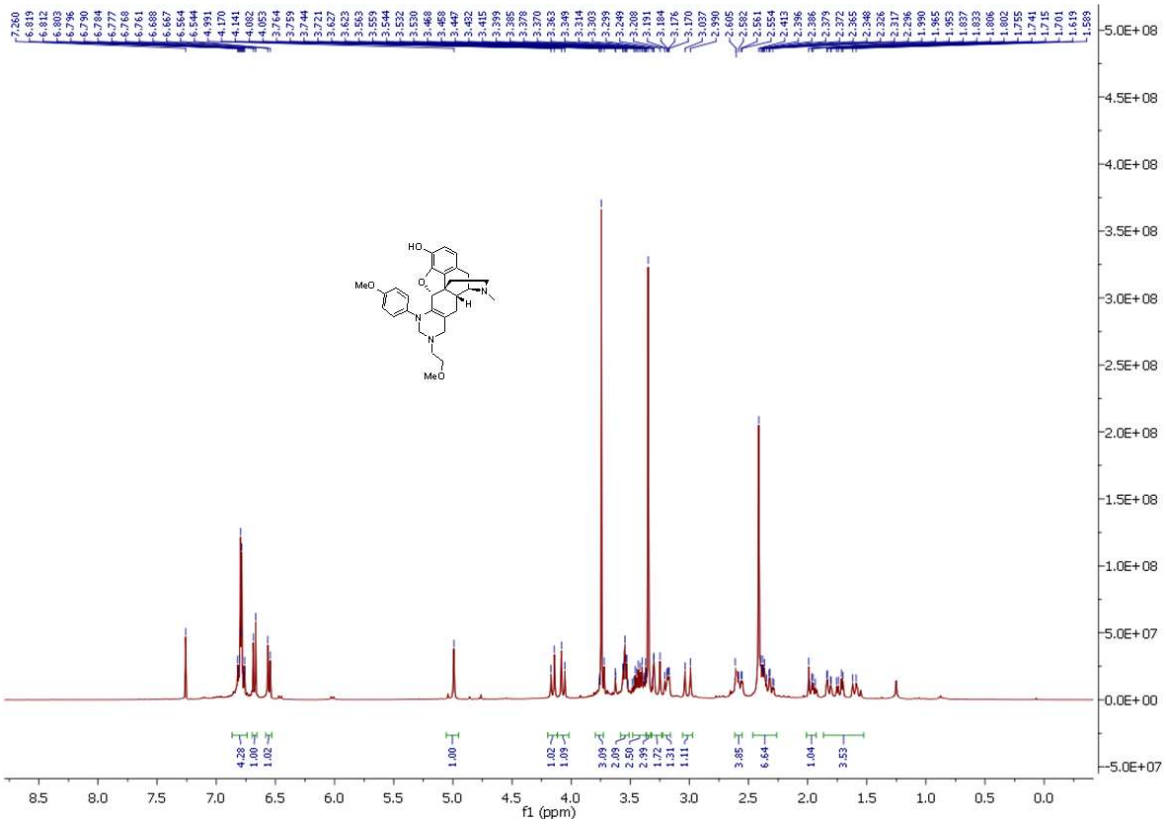
20.865
20.457
HO
MeO
N
O
H
f1 (ppm)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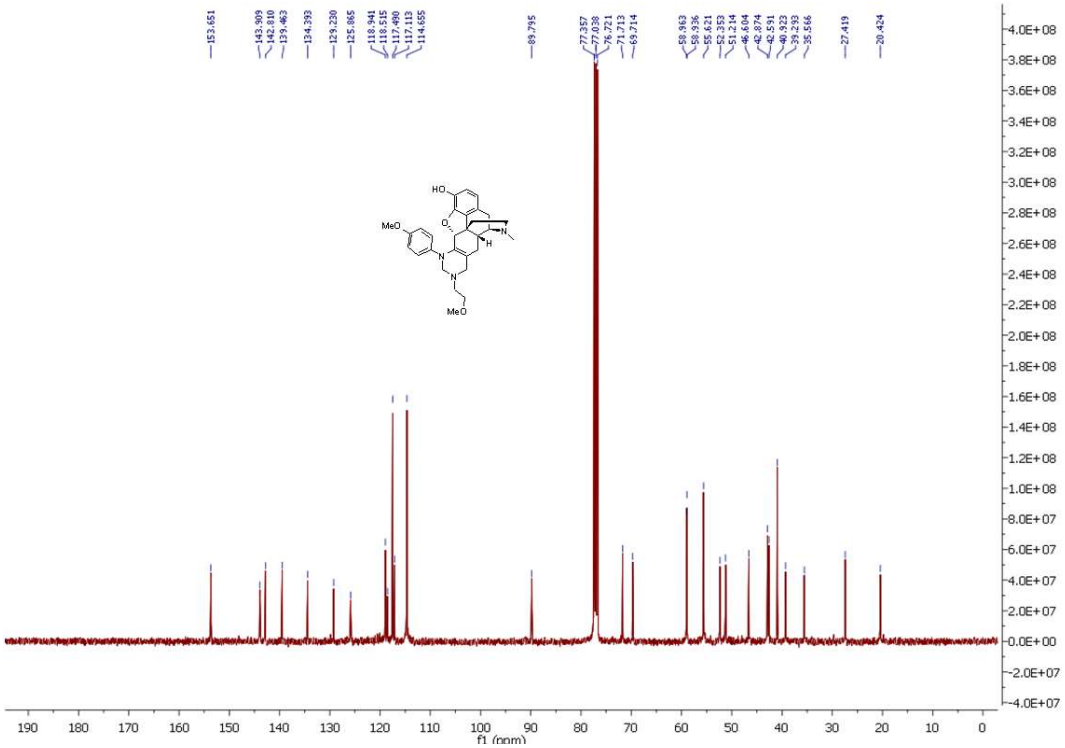
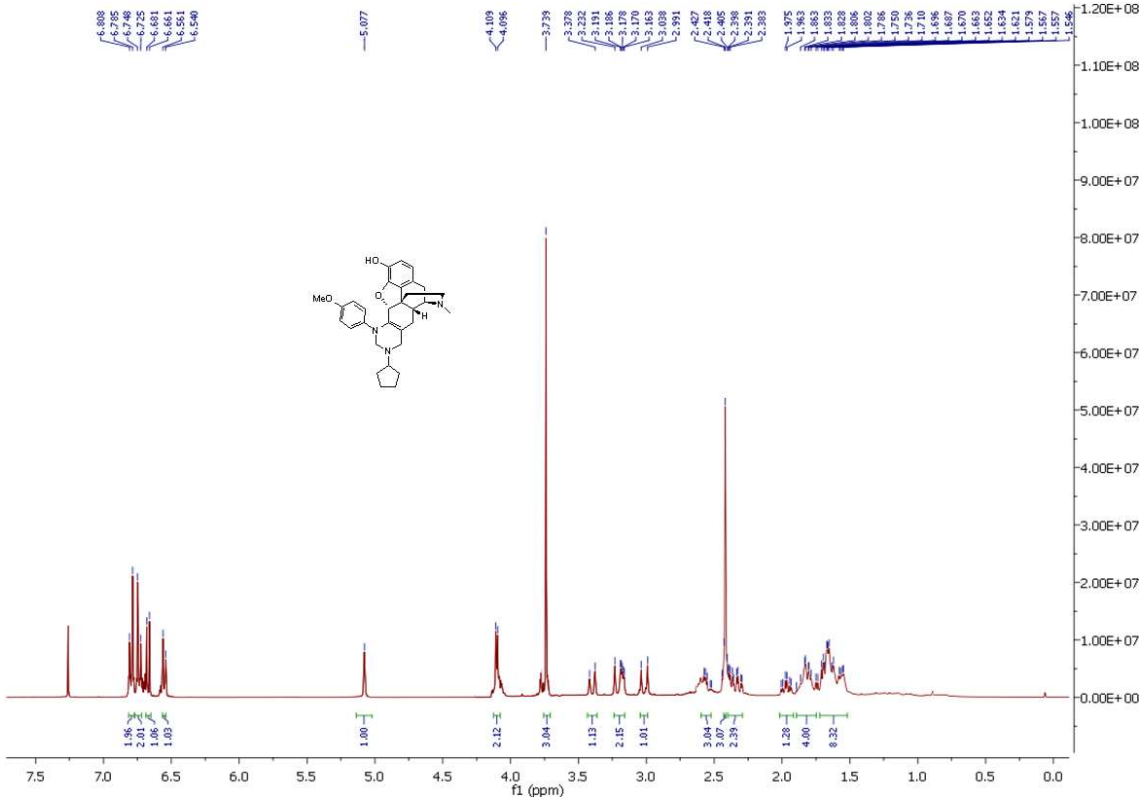
MeO
MeO
f1 (ppm)


HO
MeO
MeO
f1 (ppm)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3.232
3.191
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3.178
3.170
3.163
3.038
2.991
2.427
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2.405
2.398
2.391
2.383
1.975
1.963
1.883
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1.802
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1.736
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1.687
1.670
1.663
1.652
1.634
1.621
1.579
1.567
1.557
1.546
HO
MeO
1.96
2.01
1.06
1.03
1.00
2.12
3.04
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2.15
1.01
3.04
3.07
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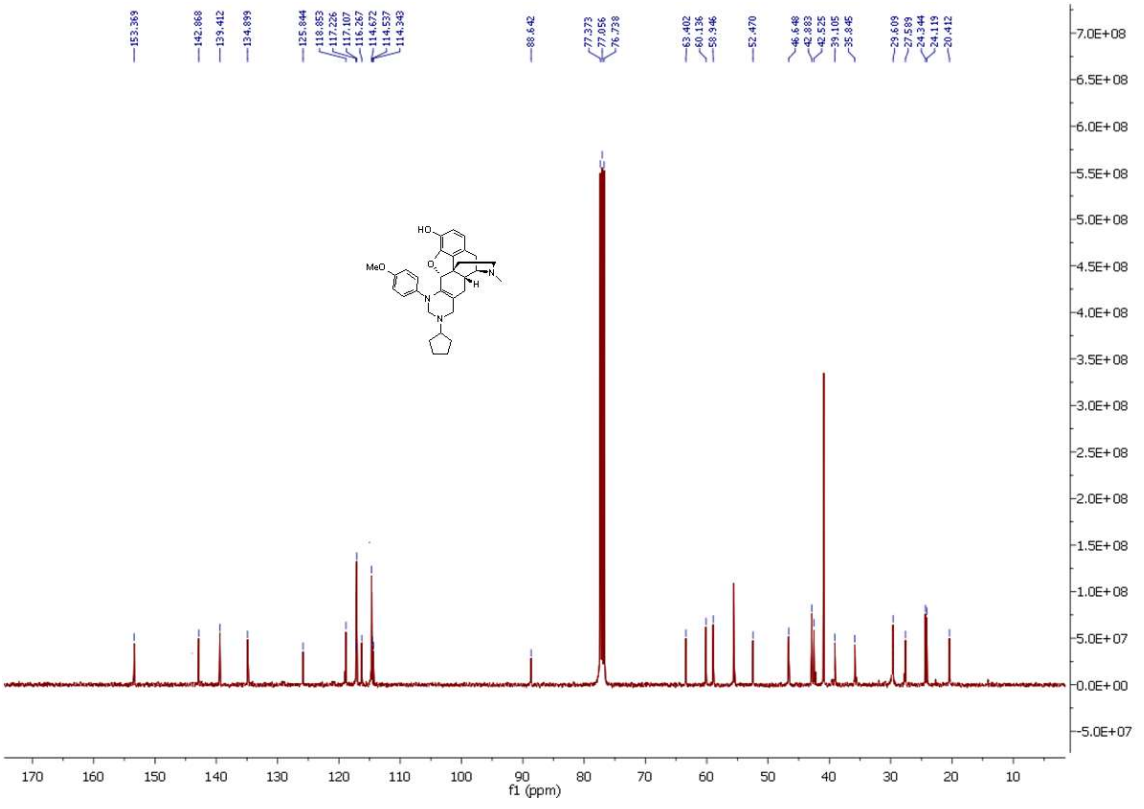
1.28
4.00
8.32
f1 (ppm)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125.844
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77.373
77.056
76.738
63.402
60.136
58.946
52.470
46.648
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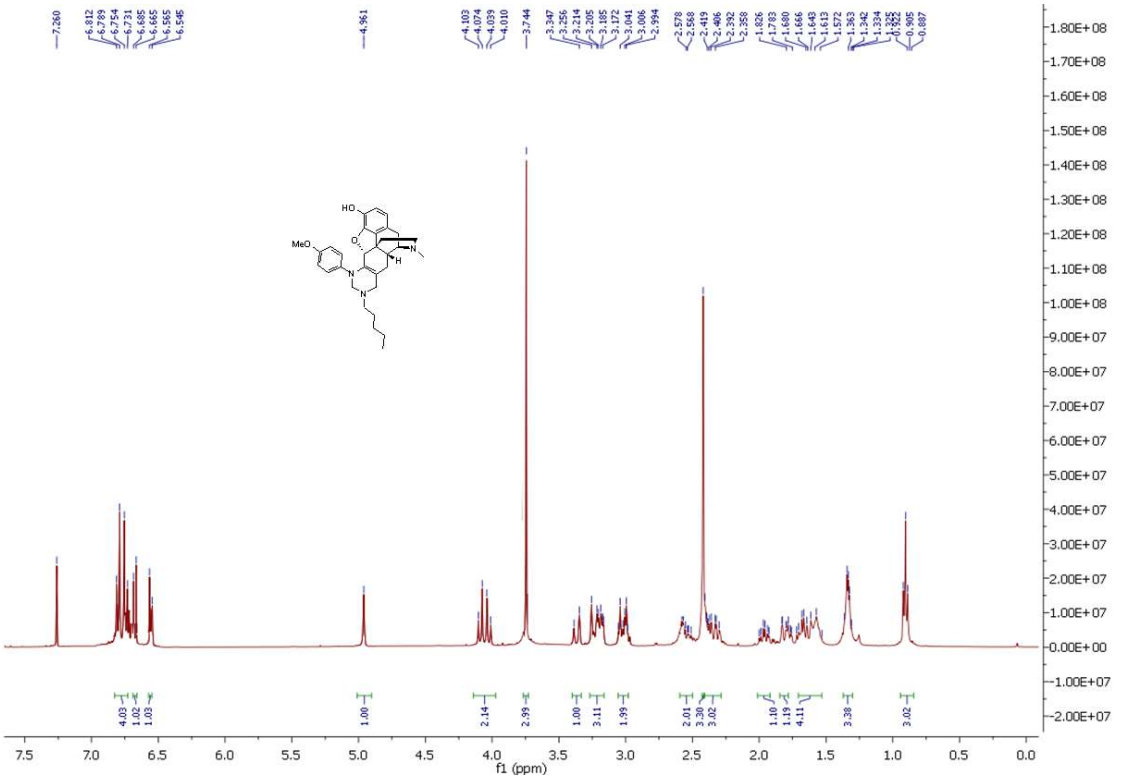
24.344
24.119
20.412
HO
MeO
f1 (ppm)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6.565
6.546
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4.074
4.039
4.010
3.744
3.347
3.256
3.214
3.205
3.185
3.172
3.041
3.006
2.994
2.578
2.568
2.419
2.406
2.392
2.358
1.826
1.793
1.680
1.666
1.643
1.613
1.572
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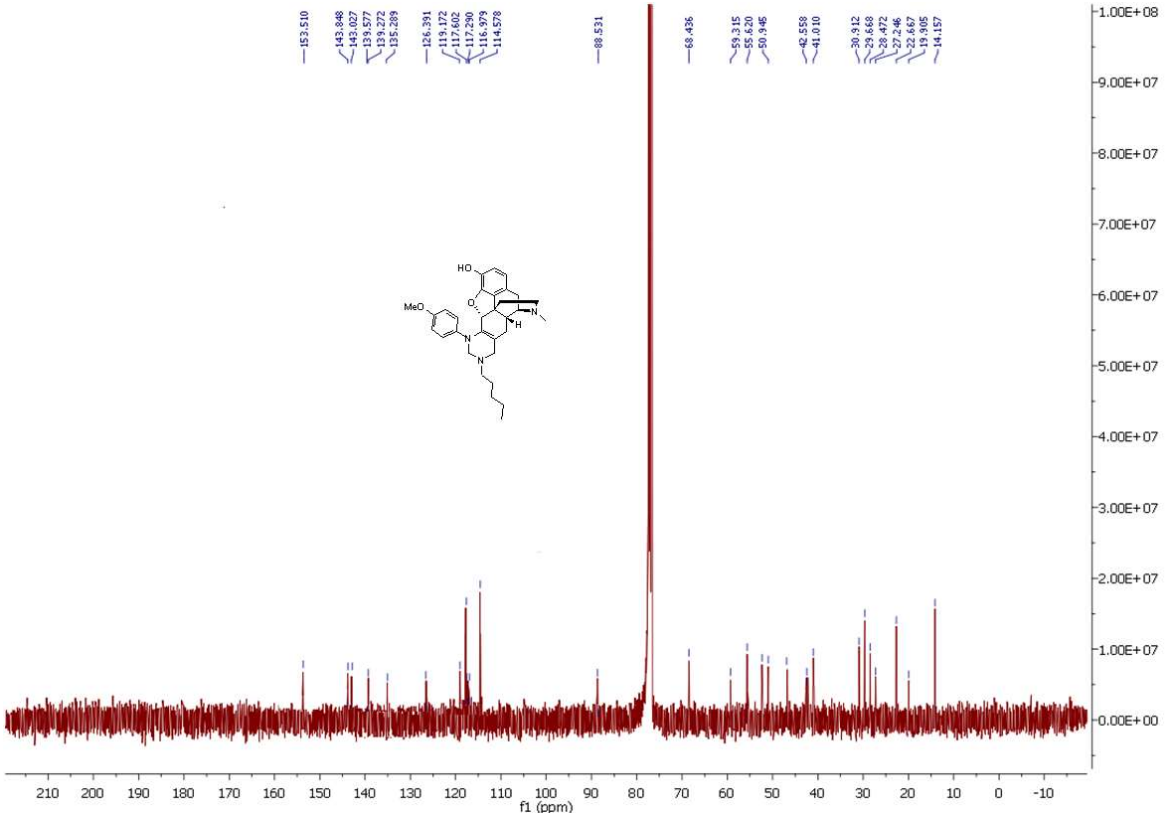
1.334
1.325
0.902
0.895
0.887
HO
MeO
O
N
H
f1 (ppm)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139.577
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135.289
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119.172
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117.290
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68.436
59.315
55.620
50.946
42.558
41.010
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28.472
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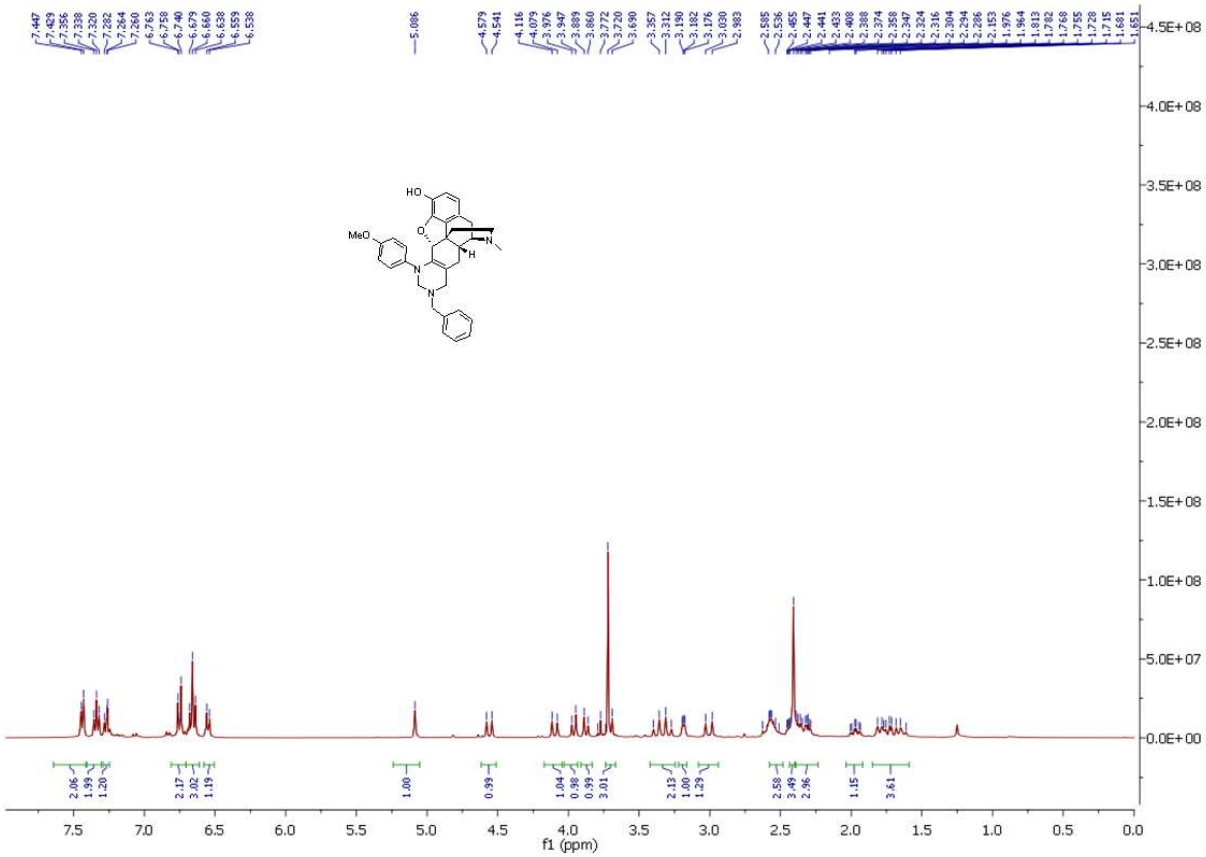
HO
MeO
O
N
H
f1 (ppm)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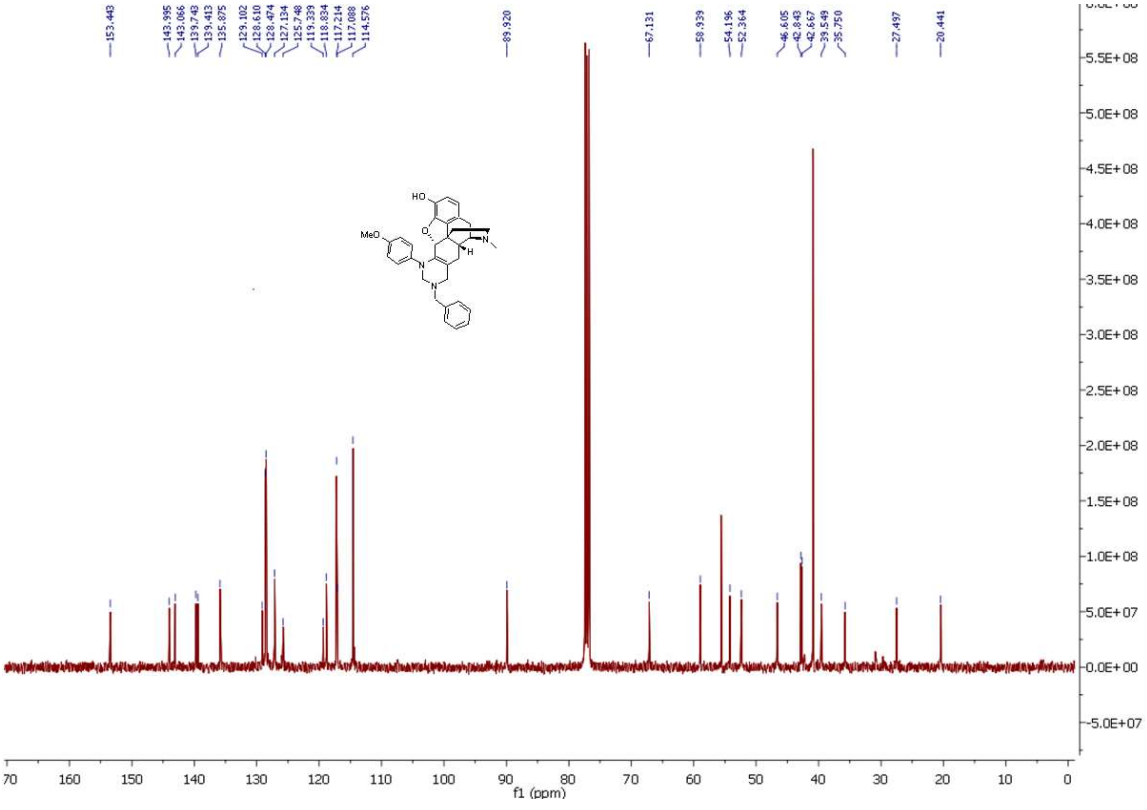
MeO
O
N
H
f1 (ppm)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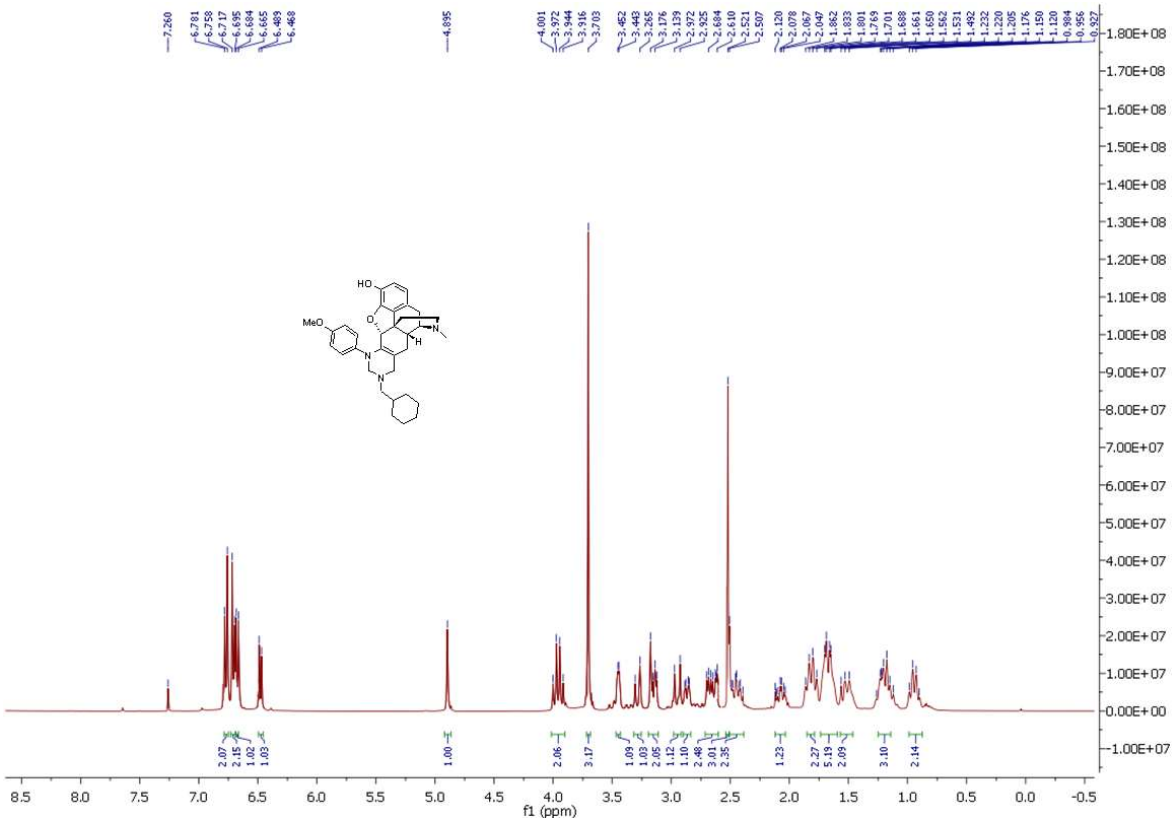
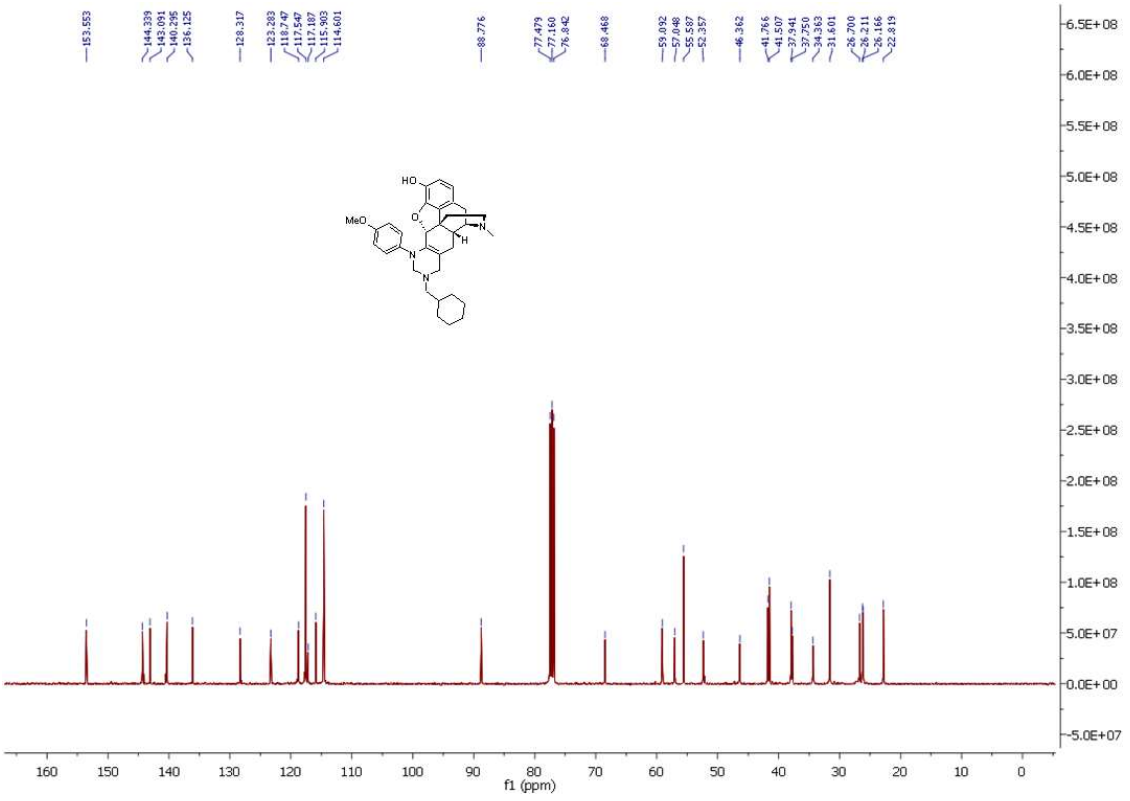
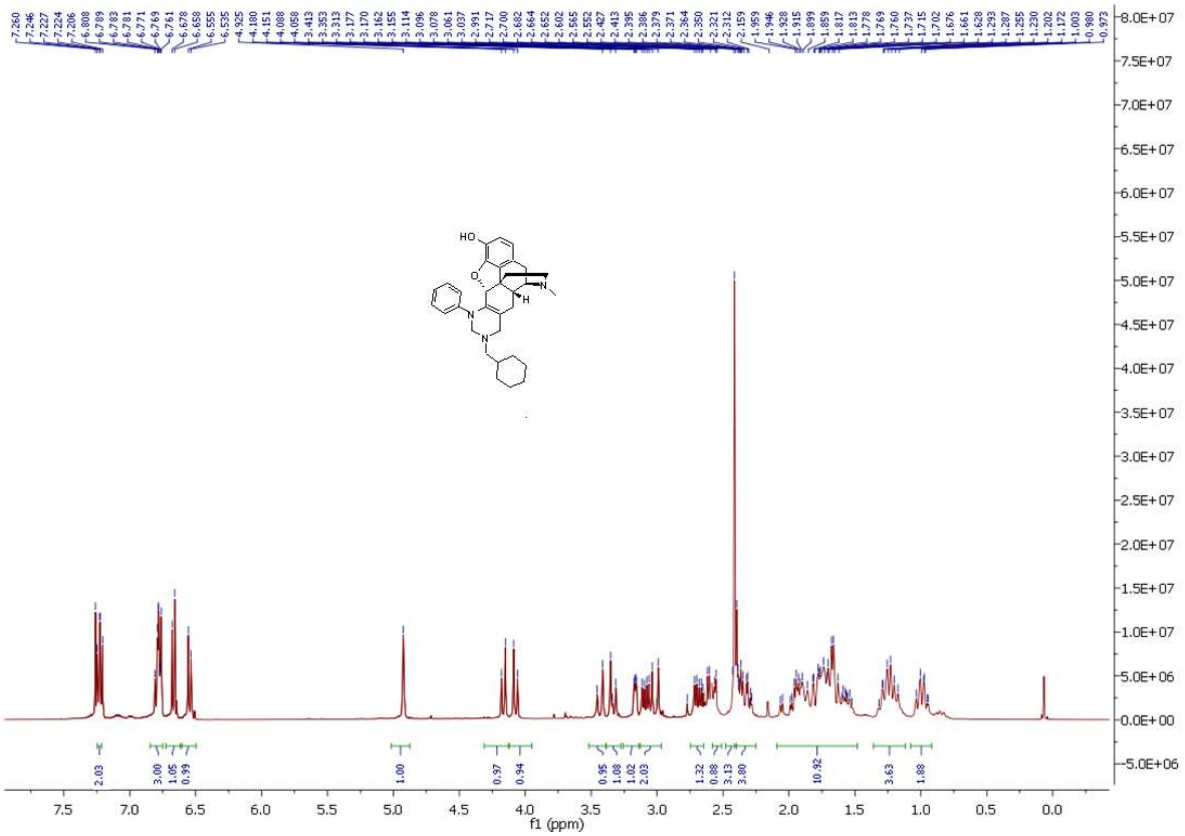
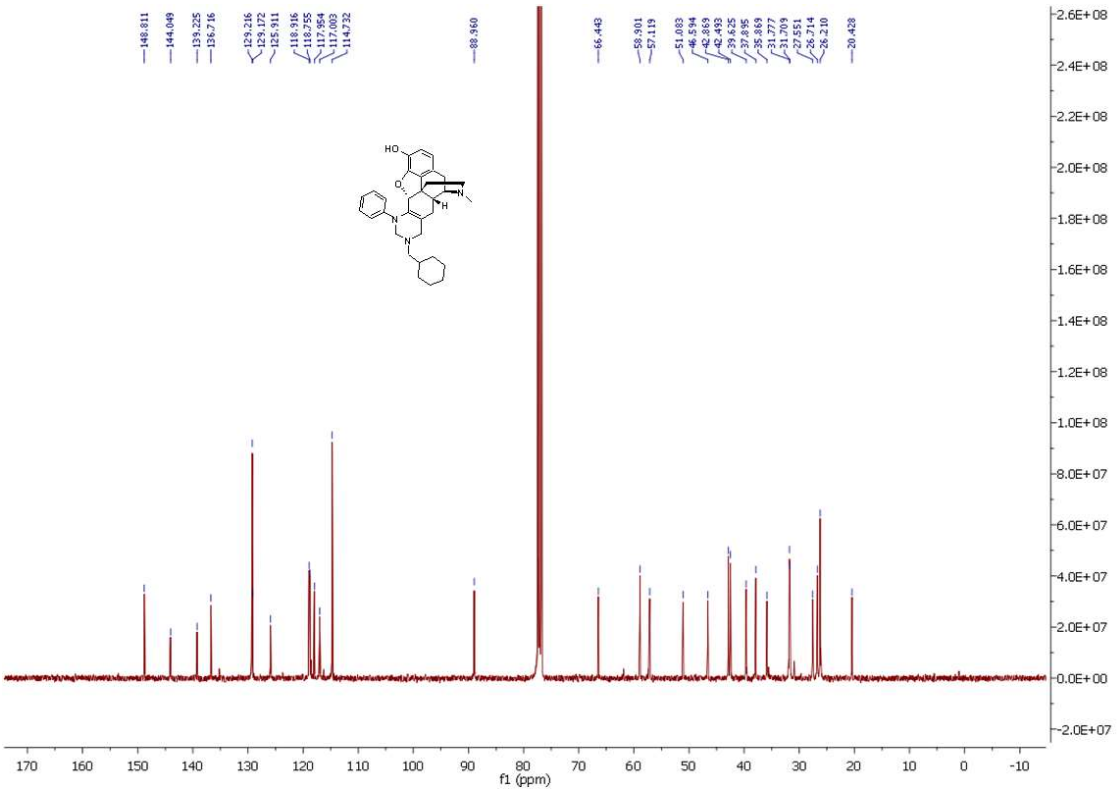
MeO
O
N
H
f1 (ppm)


HO
MeO
N
O
H
f1 (ppm)


HO
MeO
N
O
H
f1 (ppm)


HO
O
N
H
N
N
f1 (ppm)


HO
O
N
H
N
N
f1 (ppm)