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Supporting Information

C(21)-Di- and monofluorinated scaffold for thevinol/orvinol-based opioid receptor ligands

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Content

1. General

All reactions were performed in an argon atmosphere in dried glassware. All solvents were purified (dried and distilled) before use according to literature methods. All reagents were used as supplied by commercial sources unless otherwise stated. Thevinone (**3**) and thevinal (**12**) were obtained from thebaine (**1**) and methyl vinyl ketone or acroleine, respectively, according to the method **[1]**. 21,21,21-Trifluorothevinone (**7**) was obtained according to the method **[2]**.

NMR spectra (^{1}H, ^{13}C, ^{19}F) were recorded using Brucker Avance™ 400 spectrometer (400 MHz for ^{1}H, 376.5 MHz for ^{19}F) or Bruker Avance™ 300 spectrometer (300 MHz for ^{1}H, 282 MHz for ^{19}F) in $CDCl_3$. ^{19}F chemical shifts were measured relative to $CFCl_3$ as an external standard. Multiplicities are abbreviated as follows: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, t = triplet, q = quartet, m = multiplet, br = broad; coupling constants, *J*, are reported in Hz. LC-MS (liquid chromatography–mass spectrometry) analysis of the reaction products was performed on Shimadzu LCMS-2020 High Performance Liquid Chromatograph Mass Spectrometer with electrospray ionization (ESI) method and single quadrupole detector (negative and positive ions). HRMS were recorded on a Bruker maXis instrument using electrospray ionization. Microanalyses (C, H, N, F) were performed using the Carlo-Erba CE-1106. Melting points were determined with an Electrorthermal 1002 MELTEMP® capillary melting point apparatus and are uncorrected. TLC was performed with precoated TLC sheets of silica gel 60 F254 (Merck®) and visualized by UV and iodine. Column liquid chromatography was performed using silica gel (particle size no more then 80 μm).

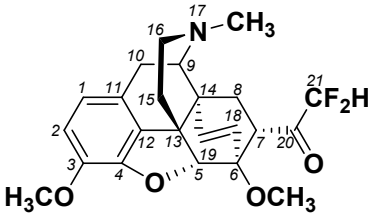
2. Experimental Section and Spectra Data

2.1. Deflourination of di- and trifluoromethylketones 7, 10 (general procedure A).

A flask with magnesium turnings (0.22 g, 9.2 mmol) was treated with ultrasound and dried in vacuo. DMF (15 ml) and Me_3SiCl (2.30 mL, 18.4 mmol) were added and cooled down to 0 °C. An appropriate ketone (0.50 g, ~1.2 mmol) was added and stirred for 4 h at 0 − -5 °C. A 15% aq. solution of HCl (15 ml) was then added, and the mixture was stirred for 1 h and poured into water (500 mL). The product was extracted with a $CHCl_3$ (3×50 mL), and the combined organic phases were washed with water (3×250 mL) and dried over Na_2SO_4. The drying agent was filtered off and the filtrate was evaporated to dryness. The resulted mixture was separated by column chromatography on silica gel (EtOAc : hexane : MeOH : NH_3(aq.) = 1600 : 1600 : 15 : 1).

(5*R*,6*R*,7*S*)-4,5-epoxy-7-(2,2-difluoro-1-oxoethyl)-3,6-dimethoxy-17-methyl-6,14-*endo*-ethenoisomorphinan (10).

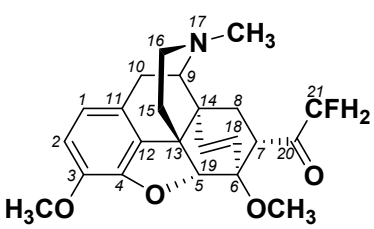
The ketone **7** was treated as described in procedure **A** to obtain **10** (0.31 g, 64%) as yellow oil.



^{1}H NMR (300 MHz, CDCl3): 6.63 + 6.55 (AB-system, J_{AB} = 7.7 Hz, 2H, H-2 + H-1), 5.89 (dd, ^2J = 54.4 Hz, 1H, CF_2H), 5.82 (d, ^3J = 8.8 Hz, 1H, H-18), 5.64 (d, ^3J = 8.8 Hz, 1H, H-19), 4.60 (s, 1H, H-5), 3.81 (s, 3H, 3-OCH3), 3.64 (s, 3H, 6-OCH_3), 3.35 (dd, 3J = 7.3 Hz, 1H, H-7β), 3.27-3.16 (m, 2H, H-9, H-10β), 2.91-2.81 (m, 1H, H-8β), 2.60-2.50 (m, 1H, H-16_{eq}), 2.48-2.30 (m, 2H, H-10α, H-16_{ax}), 2.37 (s, 3H, NCH_3), 2.01 (ddd, ^2J = 13.0 Hz, ^3J = 6.3 Hz, 1H, H-15_{eq}), 1.90-1.82 (m, 1H, H-15_{ax}), 1.55 (dd, 2J = 12.5 Hz, ^3J = 6.3 Hz, 1H, H-8α). **^{13}C NMR** (101 MHz, $CDCl_3$): 199.67 (t, J_{C-F} = 23.7 Hz, C-20), 147.74, 141.90, 137.39, 133.84, 128.12, 124.00, 119.65, 113.80, 110.52 (t, J_{C-F} = 252.1 Hz, CF_2H), 96.70, 82.71, 59.92, 56.71, 54.87, 47.53, 45.43, 44.72, 43.49, 43.32, 33.21, 29.07, 22.51. **^{19}F NMR** (282 MHz, $CDCl_3$): -129.40 (d, $^2J_{F-H}$ = 55.2 Hz, 2F, CF_2H). **LC-MS (ESI)**: m/z calcd for '$C_{23}H_{25}F_2NO_4$' $[M+H]^+$ 418.2; found: $[M+H]^+$ 418.4, $[M+H+CH_3CN]^+$ 459.4 (positive ion mode). **HRMS (ESI)** calcd for $C_{23}H_{25}F_2NO_4$ $[M+H]^+$: 418.1830, found: 418.1835.

(5*R*,6*R*,7*S*)-4,5-Epoxy-7-(2-fluoro-1-oxoethyl)-3,6-dimethoxy-17-methyl-6,14-*endo*-ethenoisomorphinan (11).

The ketone **10** was treated as described in procedure **A** to obtain **11** (0.26 g, 56%) as yellow oil.



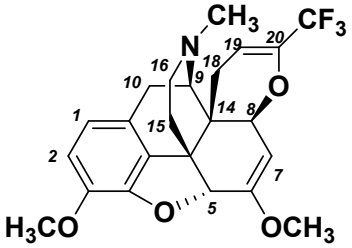
^{1}H NMR (400 MHz, $CDCl_3$): 6.62 + 6.53 (AB-system, J_{AB} = 8.5 Hz, 2H, H-2 + H-1), 5.86 (d, ^3J = 8.5 Hz, 1H, H-18),

5.61 (d, ^3J = 9.5 Hz, 1H, H-18), 5.04 + 4.92 (ABX-system, A = H-21$_A$, B = H-21$_B$, X = F, $^2J_{AB}$ = 16.9 Hz, $^2J_{AX}$ = 47.9 Hz, 1H, H-21$_A$), 4.85 + 4.73 (ABX-system, A = H-21$_A$, B = H-21$_B$, X = F, $^2J_{AB}$ = 16.1 Hz, $^2J_{BX}$ = 46.9 Hz, 1H, H-21$_B$), 4.55 (s, 1H, H-5), 3.81 (s, 3H, 3-OCH$_3$), 3.63 (s, 3H, 6-OCH$_3$), 3.26-3.18 (m, 2H, H-9, H-10β), 3.06-3.00 (m, 1H, H-8β), 2.89-2.81 (m, 1H, H-7β), 2.51 (dd, ^2J = 11.9 Hz, ^3J = 5.2 Hz, 1H, H-16$_{eq}$), 2.46-2.38 (m, 2H, H-10α, H-16$_{ax}$), 2.35 (s, 3H, NCH$_3$), 1.97 (ddd, ^2J = 12.9 Hz, ^3J = 5.07 Hz, 1H, H-15$_{eq}$), 1.87-1.80 (m, 1H, H-15$_{ax}$),1.49 (dd, ^2J = 12.6 Hz, ^3J = 6.6 Hz, 1H, H-8α). **^{13}C NMR** (101 MHz, $CDCl_3$): 205.72 (d, $^2J_{C\text{-}F}$ =16.2 Hz, C(O)), 147.82, 141.87, 137.03, 133.96, 128.24, 124.68, 119.57, 113.70, 94.63, 85.86 (d, $^1J_{C\text{-}F}$ = 182.0 Hz, $\underline{C}H_2F$), 81.56, 59.91, 56.69, 54.48, 47.51, 45.44 (C-14, C-16), 43.52, 43.27, 33.35, 29.30, 22.44. **^{19}F NMR** (282 MHz, $CDCl_3$): -224.9 (t, $J_{H\text{-}F}$ = 47.2 Hz, 1F, $CH_2\underline{F}$). **LC-MS (ESI):** m/z calcd for '$C_{23}H_{26}FNO_4$' $[M+H]^+$ 400.2; found: $[M+H]^+$ 400.3, $[M+H+CH_3CN]^+$ 441.4 (positive ion mode). **HRMS (ESI)** calcd for $C_{23}H_{26}FNO_4$ $[M+H]^+$: 400.1924, found: 400.1925.

2.2. Catalytic hydrogenation of 21,21,21-trifluorothevinone (7).

10% Pd/C catalyst (0.30 g) was added to a solution of 21,21,21-trifluorothevinone **7** (10.00 g, 0.023 mol) in acetic acid (250 ml). The reaction mixture was hydrogenated with H_2 (60 atm, 55-60 °C) for 45 h. The reaction progress was monitored by ^{1}H NMR. The conversion of **7** was 15% after 25 h and did not change further even after an additoin of another portion of the catalyst (0.30 g). The reaction mixture was filtered and evaporated. The product was separated by column chromatography on silica gel (60A, 40-63 micron, eluent $CHCl_3$: MeOH: NH_3(aq.) (25% aq. solution) = 1500:15:1) affording product **15** (1.10 g, 11 %) as colourless solid.

(8*S*,14*R*)-8,14-[(*Z*)-1-oxabut-2-eno]-8,14-dihydrothebaine (15):



MP: 143-145 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.65 + 6.73 (AB-system, J_{AB} = 8.2 Hz, 2H, H-1 + H-2), 5.48 (m, 1H, H-19), 4.78 (d, ^3J = 1.3 Hz, 1H, H-7), 4.63 (d, ^3J = 1.3 Hz, 1H, H-8), 4.39 (s, 1H, H-5), 3.86 (s, 3H, 3-OCH$_3$), 3.53 (s, 3H, 6-OCH$_3$), 3.29-3.36 (m, 1H, H-16$_{eq}$), 3.17 (d, ^2J = 18.8 Hz, 1H, H-10*β*), 3.02 (d, ^3J = 5.7 Hz, 1H, H-9), 2.45-2.59 (m, 2H, H-10*α* + H-16$_{ax}$), 2.36 (s, 3H, NCH$_3$), 2.25 (ddd, ^2J = 12.4 Hz, ^3J = 5.0 Hz, 1H, H-18$_{ax}$), 2.10 (ddd, ^2J = 12.2 Hz, ^3J = 3.4 Hz, 1H, H-15$_{ax}$), 1.88 (dt, 1H, H-15$_{eq}$), 1.63 (m, 1H, H-18$_{eq}$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 153.11, 144.59, 143.41, 139.89 (q, $^2J_{C,F}$ = 35.6 Hz, $\underline{C}H\text{-}CF_3$), 128.99, 126.95, 119.96 (q, $^1J_{C,F}$ = 270.0 Hz, $\underline{C}F_3$), 118.86, 113.76, 103.15, 101.33, 87.11, 73.70, 57.59, 56.38, 54.99, 45.81, 44.71, 43.33, 39.76, 29.80, 22.17, 20.31; **^{19}F NMR** (282 MHz,

$CDCl_3$): δ -72.53 (s, 3F, CF_3); **HRMS (ESI)** calcd for $C_{23}H_{24}F_3NO_4$ $[M + H]^+$: 436.1736, found: 436.1730.

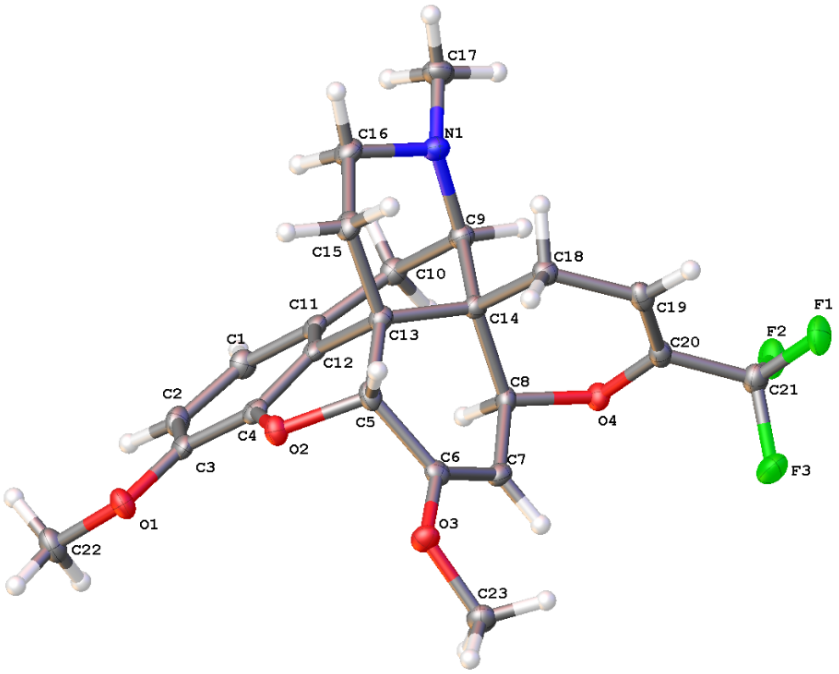
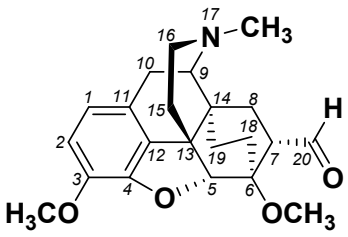


Fig. S1 Molecular structure of **15**.

2.3. Catalytic hydrogenation of thevinal (12).

10% Pd/C (0.10 g) was added to a solution of thevinal (**12**) (1.00 g, 2.72 mmol) in EtOH (75 mL) and the mixture was hydrogenated with H_2 (1 atm, 20 °C) for 0.4 h. The mixture was filtered and evaporated to deliver a mixture of 18,19-dihydrothevinal (**18**) and thevinyl alcohol (**19**) in a 10:1 ratio (1.00 g) as yellow oil.

(5*R*,6*R*,7*S*)-4,5-Epoxy-18,19-dihydro-3,6-dimethoxy-17-methyl-6,14-*endo*-ethanomorphinan-7-carboxaldehyde (18):

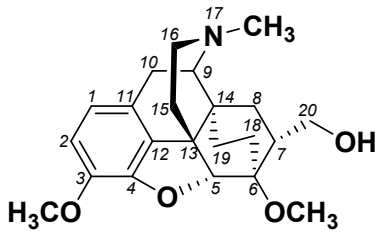


^{1}H NMR (400 MHz, $CDCl_3$): 9.90 (s, 1H, H-20), 6.72 + 6.60 (AB-system, J_{AB} = 8.6 Hz, 2H, H-2 + H-1), 4.59 (s, 1H, H-5), 3.87 (s, 3H, 3-OCH_3), 3.50 (s, 3H, 6-OCH_3), 3.11 (dd, ^2J = 18.2 Hz, 1H, H-10β), 2.96-2.87 (m, 1H, H-7β), 2.74 (d, ^3J = 6.1 Hz, H-9), 2.70-2.60 (m, 1H, H-8β), 2.45 (dd, 1H, ^2J = 11.5 Hz, ^3J = 4.8 Hz, 1H, H-16_{eq}), 2.37-2.20 (m, 2H, H-10α, H-16_{eq}), 2.30 (s, 3H, NCH_3), 2.03 (dd, ^2J = 12.6 Hz, ^3J = 5.7 Hz, 1H, H-15_{ax}), 1.92 (dd, ^2J = 13.6 Hz, ^3J = 5.51 Hz, 1H, H-8α), 1.72-1.52 (m, 2H, H-15_{eq}, H-18), 1.44-1.31 (m, 1H, H-18), 1.14 (ddd, ^2J = 12.2 Hz, ^3J = 6.1 Hz, 1H, H-19), 0.85-0.70 (m, 1H, H-19). **^{13}C NMR** (101 MHz, $CDCl_3$): 203.11, 146.70, 141.85, 132.14, 128.46, 119.38, 113.83, 92.14, 77.29, 61.35, 56.65, 51.64, 48.59, 45.30, 45.18, 43.53, 35.55, 35.17, 28.50, 26.66, 21.99,

19.98. **LC-MS (ESI):** m/z calcd for '$C_{22}H_{27}NO_4$' $[M+H]^+$ 370.2; found: $[M+H]^+$ 370.4, $[M+H+CH_3CN]^+$ 411.4 (positive ion mode).

The mixture of 18 and 19 (10:1): Found (%): C 71.15, H 7.31, N 3.71. $C_{22}H_{27}NO_4$. Calculated (%): C 71.52, H 7.37, N 3.79.

(5*R*,6*R*,7*R*)-4,5-Epoxy-18,19-dihydro-3,6-dimethoxy-17-methyl-6,14-*endo*-ethenomorphinan-7-methanol (19):



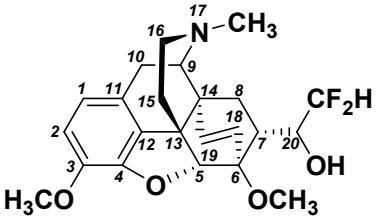
^{1}H NMR (400 MHz, $CDCl_3$): 6.69 + 6.56 (AB-system, J_{AB} = 8.1 Hz, 2H, H-2 + H-1), 4.46 (s, 1H, H-5), 3.85 (s, 4H, H-20, 3-OCH_3), 3.68 (br.s., 1H, OH), 3.47 (br. s, 4H, H-20, 6-OCH_3), 3.08 (d, ^2J = 18.2 Hz, 1H, H-10β), 2.85-2.75 (m, 1H, H-8β), 2.61 (d, ^3J = 6.5 Hz, 1H, H-9), 2.42 (dd, ^2J = 12.3 Hz, ^3J = 5.5 Hz, 1H, H-16_{eq}), 2.31-2.16 (m, 2H, H-10α, H-16_{ax}), 2.27 (s, 3H, NCH_3), 2.11-1.98 (m, 2H, H-7β, H-15_{eq}), 1.72-1.59 (m, 2H, H-15_{ax}, H-18), 1.55-1.46 (m, 1H, H-18), 0.97 (ddd, ^2J = 12.3 Hz, ^3J = 6.1 Hz, 1H, H-19), 0.80-0.67 (m, 2H, H-8α, H-19). **^{13}C NMR** (101 MHz, $CDCl_3$): 146.80, 141.77, 132.46, 128.59, 119.16, 113.97, 94.90, 79.20, 64.91, 61.29, 56.76, 52.29, 45.30, 45.22, 43.53, 38.27, 35.59, 35.16, 31.29, 28.99, 21.89, 21.89, 17.29. **LC-MS (ESI):** m/z calcd for '$C_{22}H_{29}NO_4$' $[M+H]^+$ 372.2; found: $[M+H]^+$ 372.4 (positive ion mode). Found (%): C 70.44, H 7.66, N 3.62; $C_{22}H_{29}NO_4$. Calculated (%): C 71.13, H 7.87, N 3.77.

2.4. Difluoromethylation of aldehydes (General procedure B).

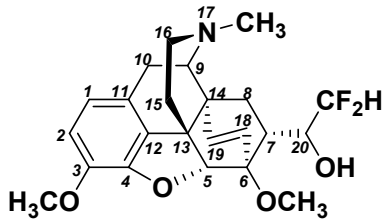
CsF (0.05 g, 0.35 mmol) was added to a solution of an aldehyde (2.71 mmol) and Me_3SiCF_2H (1.0 g, 8.13 mmol) in DMF (10 mL). The mixture was stirred overnight at room temperature. An aqueous solution of HCl (15% aq., 15 ml) was added and the mixture was stirred for 1 h. The products were extracted with $CHCl_3$ (3×50 mL) and the combined organic layers were washed with brine (3×100 mL) and dried over Na_2SO_4. The drying agent was filtered off and the filtrate was evaporated to dryness. The resulted mixture was separated by column chromatography on silica gel (EtOAc : hexane : MeOH : NH_3(aq.) = 1600 : 1600 : 15 : 1).

The reaction of the aldehyde **12** (1.00 g, 2.71 mmol) according to procedure **B** afforded products **26** (two C(20)-epimers), **27**, and **28**.

(5*R*,6*R*,7*R*)-4,5α-Epoxy-7-(1-hydroxy-1-(difluoromethyl)methyl)-3,6-dimethoxy-17-methyl-6,14-*endo*-ethenoisimorphinan (26):

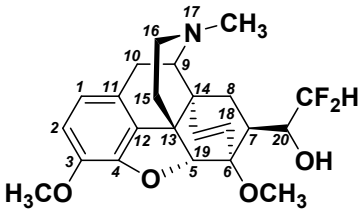


26 [1st C(20)-epimer]: yellow oil, 0.155 g (14%).
^{1}H NMR (400 MHz, $CDCl_3$): 6.61 + 6.52 (AB-system, J_{AB} = 8.5 Hz, 2H, H-2 + H-1), 5.83 (d, ^3J = 7.8 Hz, 1H, H-18), 5.63 (ddd, ^2J = 55.1 Hz, ^3J = 4.5 Hz, 1H, $CF_2\underline{H}$), 5.49 (d, ^3J = 9.0 Hz, H-19), 4.61 (s, 1H, H-5), 4.15-4.08 (m, 1H, H-20), 3.85 (s, 3H, 3-OCH_3), 3.64 (s, 3H, 3-OCH_3), 3.24-3.17 (m, 2H, H-9, H-10β), 2.87-2.82 (m, 1H, H-8β), 2.57-2.50 (m, 1H, H-16_{eq}), 2.46-2.38 (m, 2H, H-10α, H-16_{ax}), 2.39 (s, 3H, NCH_3), 2.18-2.15 (m, 1H, H-7β), 2.03-1.98 (m, 2H, H-15_{eq}, OH), 1.87-1.84 (m, 1H, H-15_{ax}), 1.41 (dd, ^2J = 12.4 Hz, ^3J = 7.8 Hz, 1H, H-8α). **^{13}C NMR** (101 MHz, $CDCl_3$): 148.11, 141.90, 136.45, 133.95, 126.91, 119.45, 115.87 (t, $J_{C\text{-}F}$ = 239.0 Hz), 113.46, 94.66, 79.71, 68.99 (t, J = 23.7 Hz, C-20), 60.09, 56.59, 52.77, 47.26, 45.58, 43.53, 42.92, 36.73, 36.69, 33.54, 29.27, 25.56, 22.39. **^{19}F NMR** (282 MHz, $CDCl_3$): -130.12 + -131.97 (AB-system, $J_{F\text{-}F}$ = 287.3 Hz, 2F, $C\underline{F_2}H$). **LC-MS (ESI):** m/z calcd for '$C_{23}H_{27}F_2NO_4$' $[M+H]^+$ 420.2; found: $[M+H]^+$ 420.3, $[M+H+CH_3CN]^+$ 461.3 (positive ion mode). **HRMS (ESI)** calcd for $C_{23}H_{27}F_2NO_4$ $[M+H]^+$: 420.1986, found: 420.1987.



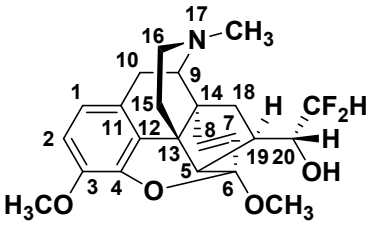
26 [2nd C(20)-epimer]: yellow oil, 0.032 g (3%)
^{1}H NMR (300 MHz, $CDCl_3$): 6.62 + 6.52 (AB-system, J_{AB} = 8.1 Hz, 2H, H-2 + H-1), 5.84 (m, 1H, H-18), 6.64 (ddd, ^2J = 56.3 Hz, ^3J = 5.3 Hz, 1H, $\underline{C}F_2H$), 5.50 (d, ^3J = 8.8 Hz, 1H, H-19), 4.59 (s, 1H, H-5), 4.18-4.08 (m, 1H, H-20), 3.81 (s, 3H, 3-OCH_3), 3.60 (s, 3H, 6-OCH_3), 3.25-3.17 (m, 2H, H-9, H-10β), 2.86-2.79 (m, 1H, H-8β), 2.55-2.50 (m, 1H, H-16_{eq}), 2.45-2.37 (m, 5H, NCH_3, H-10α, H-16_{ax}), 2.18-2.15 (m, 1H, H-7β), 2.05-1.95 (m, 2H, H-15_{eq}, OH), 1.87-1.84 (m, 1H, H-15_{ax}), 1.41 (dd, ^2J = 13.2 Hz, ^3J = 7.0 Hz, 1H, H-8α). **^{13}C NMR** (101 MHz, $CDCl_3$): 148.13, 141.92, 136.45, 133.96, 128.12, 126.92, 119.46, 115.87 (t, $J_{C\text{-}F}$ = 244.8 Hz, $\underline{C}F_2H$), 113.47, 94.67, 79.72, 68.99 (t, J = 21.5 Hz, C-20), 60.01, 56.60, 52.77, 47.27, 45.58, 43.53, 42.92, 36.59, 33.54, 25.51, 22.36. **^{19}F NMR** (282 MHz, $CDCl_3$): -127.43 + -129.39 (AB-system, $^2J_{F\text{-}F}$ = 287.9 Hz, 2F, $C\underline{F_2}H$). **LC-MS (ESI):** m/z calcd for '$C_{23}H_{27}F_2NO_4$' $[M+H]^+$ 420.2; found: $[M+H]^+$ 420.0, (positive ion mode). **HRMS (ESI)** calcd for $C_{23}H_{27}F_2NO_4$ $[M+H]^+$: 420.1986, found: 420.1976.

(5*R*,6*R*,7*S*)-4,5α-Epoxy-7-(1-hydroxy-1-(difluoromethyl)methyl)-3,6-dimethoxy-17-methyl-6,14-*endo*-ethenoisimorphinan (27): yellow oil, 0.015 g (1%).



^{1}H NMR (300 MHz, $CDCl_3$): 6.62 + 6.52 (AB-system, J_{AB} = 285.6 Hz, 2H, H-2 + H-1), 6.12 (d, ^{3}J = 8.9 Hz, H-18), 5.68 (ddd, $^{2}J_{F\text{-}H}$ = 56.8 Hz, $^{3}J_{F\text{-}H}$ = 5.6 Hz, $CF_2\underline{H}$), 5.46 (d, ^{3}J = 9.0 Hz, H-19), 5.11 (s, 1H, H-5), 4.38-4.29 (m, 1H, H-20), 3.84 (s, 3H, 3-OCH_3), 3.61 (s, 3H, 6-OCH_3), 3.28-3.19 (m, 2H, H-9, H-10β), 2.96-2.85 (m, 2H, H-8β, H-7α), 2.54-2.49 (m, 1H, H-16$_{eq}$), 2.46-2.42 (m, 1H, H-16$_{ax}$), 2.41-2.35 (m, 1H, H-10α), 2.37 (s, 3H, NCH_3), 1.95-2.05 (m, 1H, H-15$_{eq}$), 1.59-1.54 (m, 1H, H-15$_{ax}$), 1.36-1.27 (m, 1H, H-8α). **^{13}C NMR** (101 MHz, $CDCl_3$): 147.69, 142.12, 136.38, 135.93, 128.54, 127.76, 119.07, 116.43 (t, $J_{C\text{-}F}$ = 243.7 Hz, $\underline{C}F_2H$), 113.69, 93.47, 80.70, 67.57 (t, J = 23.7 Hz, C-20), 60.92, 56.87, 52.55, 46.97, 45.56, 43.56, 43.22, 40.14, 29.72, 29.23, 22.46. **^{19}F NMR** (282 MHz, $CDCl_3$): -126.50 + -129.39 (AB-system, $^{2}J_{F\text{-}F}$ = 279.7 Hz, 2F, $C\underline{F_2}H$). **LC-MS (ESI):** m/z calcd for '$C_{23}H_{27}F_2NO_4$' $[M+H]^+$ 420.2; found: $[M+H]^+$ 420.0. **HRMS (ESI)** calcd for $C_{23}H_{27}F_2NO_4$ $[M+H]^+$: 420.1986, found: 420.2001.

5,14-Ethano-4(*O*)-6-dehydro-l9-(1-hydroxy-2,2-difluoroethyl)-6-*O*-methylthebainol [(1*R*)-1-((4a*R*,6*R*,7*S*,12b*S*)-7,9-dimethoxy-3-methyl-1,2,3,4,5,6,6a,7-octahydro-4a,7-etheno-4,12-methanochromeno[4',3':2,3]cyclopenta[1,2-*c*]pyridin-6-yl)-2,2-difluoroethan-1-ol] **(28):** yellow oil (0.015 g, 1%).



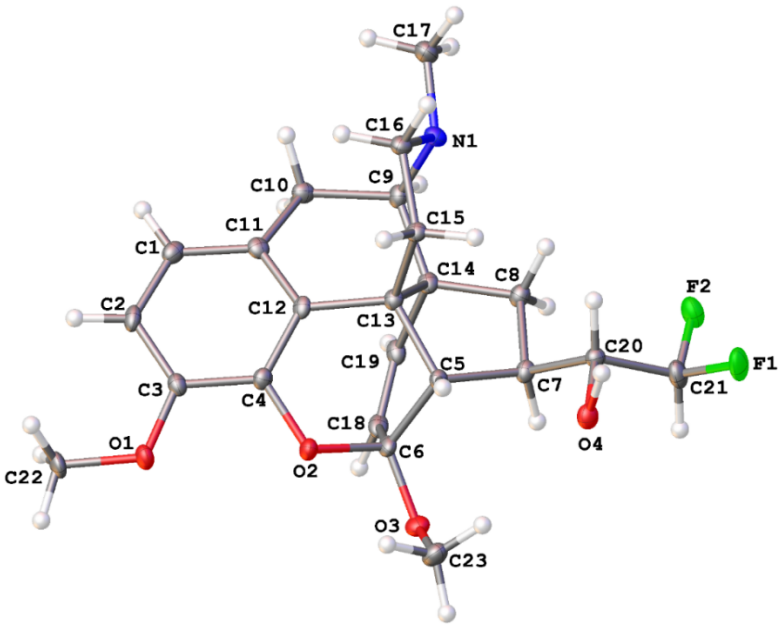
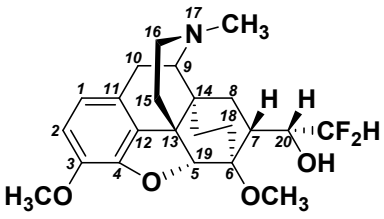


Fig. S2. General view of the compound **28** in representation of atoms *via* thermal ellipsoids at 40% probability level. The minor component of the disordered 1-hydroxy-1-(difluoromethyl)ethyl group is omitted. Based on the absolute configuration of the

asymmetric centres in the parent compound, the absolute configuration of the atom C(20) was identified as *R*.

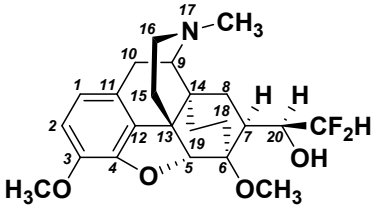
The reaction of the aldehyde **18** (1.00 g, 2.70 mmol) according to procedure **B** afforded compounds **24** and **25**.

(5*R*,6*R*,7*R*,20*R*)-4,5α-Epoxy-7-(1-hydroxy-1-(difluoromethyl)methyl)-3,6-dimethoxy-17-methyl-6,14-*endo*-ethanoisomorphinan (24): 0.524 g (46%), yellow oil.



^{1}H NMR (300 MHz, $CDCl_3$): 6.71 + 6.59 (AB-system, J_{AB} = 7.9 Hz, 2H, H-2 + H-1), 5.67 (ddd, $^{2}J_{F\text{-}H}$ = 56.7 Hz, $^{3}J_{F\text{-}H}$ = 5.5 Hz, 1H, $CF_2\underline{H}$), 4.48 (s, 1H, H-5), 4.30-4.18 (m, 1H, H-20), 3.87 (s, 3H, 3-OCH_3), 3.41 (s, 3H, 6-OCH_3), 3.11 (d, ^{2}J = 18.2 Hz, 1H, H-10β), 2.72 (d, ^{3}J = 5.5 Hz, 1H, H-9), 2.68-2.56 (m, 1H, H-8β), 2.51-2.38 (m, 2H, H-7β, H-16_{eq}), 2.37-2.21 (m, 2H, H-10α, H-16_{ax}), 2.31 (s, 3H, NCH_3), 2.12-1.97 (m, 2H, H-15_{eq}, OH), 1.81-1.65 (m, 3H, H-8α, H-15_{ax}, H-18), 1.39-1.52 (m, 1H, H-18), 1.23-1.11 (m, 1H, H-19), 0.79-0.66 (m, 1H, H-19). **^{13}C NMR** (101 MHz, $CDCl_3$): 146.93, 141.76, 132.43, 128.62, 119.14, 116.11 (t, $J_{C\text{-}F}$ = 243.9 Hz, $\underline{C}F_2H$), 113.60, 92.03, 75.71, 68.16 (t, $J_{C\text{-}F}$ = 24.8 Hz, C-20), 61.58, 56.59, 50.77, 45.33, 45.16, 43.55, 35.73, 35.45, 34.80 28.83, 25.76, 21.94, 20.36. **^{19}F NMR** (282 MHz, $CDCl_3$): -126.50 + -129.39 (AB-system, $^{2}J_{F\text{-}F}$ = 279.7 Hz, 2F, $C\underline{F_2}H$). **LC-MS (ESI):** m/z calcd for '$C_{23}H_{29}F_2NO_4$' $[M+H]^+$ 422.2; found: $[M+H]^+$ 422.4, $[M+H+CH_3CN]^+$ 463.4 (positive ion mode). **HRMS (ESI)** calcd for $C_{23}H_{29}F_2NO_4$ $[M+H]^+$: 422.2143, found: 422.2153. Found (%): C 64.98, H 6.87, N 3.65, F 8.43; $C_{23}H_{29}F_2NO_4$. Calculated (%): C 65.54, H 6.94, N 3.32, F 9.01.

(5*R*, 6*R*, 7*S*, 20*S*)-4,5α-Epoxy-7-(1-hydroxy-1-(difluoromethyl)methyl)-3,6-dimethoxy-17-methyl-6,14-*endo*-ethanoisomorphinan (25): 0.091 g (8%), colorless crystals (from MeOH).



MP: 193-194 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): 6.70 + 6.57 (AB-system, J_{AB} = 7.9 Hz, 2H, H-2 + H-1), 5.70 (ddd, ^{2}J = 56.9 Hz, ^{3}J = 5.8 Hz, 1H, $CF_2\underline{H}$), 5.01 (s, 1H, H-5), 4.39-4.08 (m, 2H, H-20, OH), 3.87 (s, 3H, 3-OCH_3), 3.35 (s, 3H, 6-OCH_3), 3.12 (d, ^{2}J = 18.9 Hz, 1H, H-10β), 3.00-2.89 (m, 1H, H-7α), 2.88-2.70 (m, 2H, H-8β, H-9), 2.49-2.39 (m, 1H, H-16_{eq}), 2.39-2.17 (m, 3H, H-10α, H-15_{eq}, H-16_{ax}), 2.31 (s, 3H, NCH_3), 1.54-1.32 (m, 4H, H-8α, H-15_{ax}, H-18, H-18), 1.28-1.13 (m, 1H, H-19), 1.00-0.86 (m, 1H, H-19). **^{13}C NMR** (101 MHz, $CDCl_3$): 146.60, 141.73, 133.76, 128.22, 118.83, 116.44 (t, $J_{C\text{-}F}$ = 244.0 Hz, $\underline{C}F_2H$), 114.37, 92.64,

76.04, 68.01 (t, $J_{C\text{-}F}$ = 25.5 Hz, C-20), 62.24, 57.02, 51.03, 45.22, 43.86, 43.59, 39.20, 36.05, 32.04, 28.86, 26.89, 22.12, 21.42. **^{19}F NMR** (282 MHz, $CDCl_3$): -126.53 + -130.22 (AB-system, $^2J_{F\text{-}F}$ = 287.7 Hz, $^2J_{F\text{-}H}$ = 57.1 Hz, $^3J_{F\text{-}H}$ = 14.0 Hz, 2F, C$\underline{F_2}$H). **LC-MS (ESI):** m/z calcd for '$C_{23}H_{29}F_2NO_4$' $[M+H]^+$ 422.2; found: $[M+H]^+$ 422.4, $[M+H+CH_3CN]^+$ 463.4 (positive ion mode). Found (%): C 65.69, H 6.70, N 3.37, F 8.96; $C_{23}H_{29}F_2NO_4$. Calculated (%): C 65.54, H 6.94, N 3.32, F 9.01.

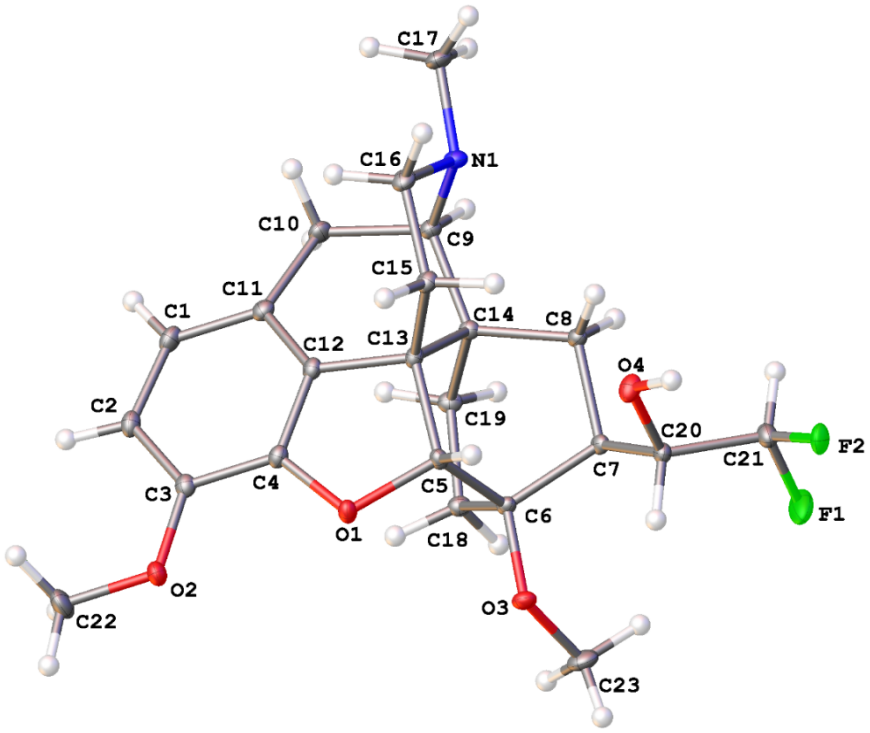


Fig. S3. General view of the compound **25** in representation of atoms *via* thermal ellipsoids at 40% probability level. The minor component of the disordered difluoromethyl group is omitted. Based on the absolute configuration of the asymmetric centres in the parent compound, the absolute configuration of the atom C(20) was identified as *S*.

2.5. Dess-Martin oxidation of secondary 21,21-difluoro substituted alcohols (general procedure C).

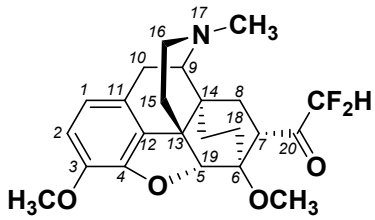
Dess-Martin periodinane reagent (3.00 g, 7.10 mmol) was added to a solution of an appropriate alcohol (1.00 g, ~2.4 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred for 24 h. After addition of NaOH (1 N aq. solution, 40 mL), the mixture was stirred for 1 h. The product was extracted with $CHCl_3$ (3×50 mL), and the combined organic layers were washed with water (3×50 mL) and dried over Na_2SO_4. The drying agent was filtered off and the filtrate was evaporated to dryness.

(5*R*,6*R*,7*S*)-4,5-epoxy-7-(2,2-difluoro-1-oxoethyl)-3,6-dimethoxy-17-methyl-6,14-*endo*-ethenoisomorphinan (10).

The C(20)-epimeric mixture of alcohols **26** (0.07 g, 0.17 mmol) was treated as described in procedure **C** to obtain **10** (0.045 g, 64%) as yellow oil.

(5*R*,6*R*,7*S*)-4,5-Epoxy-7-(2,2-difluoro-1-oxoethyl)-3,6-dimethoxy-17-methyl-6,14-*endo*-ethanoisomorphinan (13):

The alcohol **25** (3.40 g, 8.00 mmol) was treated as described in procedure **C** to obtain **13** (2.80 g, 84%) as yellow oil.



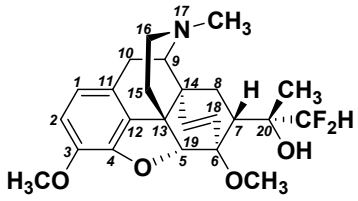
^{1}H NMR (300 MHz, $CDCl_3$): 6.72 + 6.60 (AB-system, J_{AB} = 8.1 Hz, 2H, H-2 + H-1), 5.88 (dd, ^2J = 54.4 Hz, 1H, $CF_2\underline{H}$), 4.51 (s, 1H, H-5), 3.87 (s, 3H, 3-OCH_3), 3.45-3.35 (m, 4H, H-7β, 6-OCH_3), 3.11 (d, ^2J = 18.4 Hz, 1H, H-10β), 2.78-2.66 (m, 2H, H-8β, H-9), 2.49-2.41 (m, 1H, H-16_{eq}), 2.36-2.20 (m, 2H, H-10α, H-16_{ax}), 2.29 (s, 3H, NCH_3), 2.04 (ddd, ^2J = 12.9 Hz, ^3J = 6.0 Hz, 1H, H-15_{eq}), 1.81 (dd, ^2J = 13.0 Hz, ^3J = 6.3 Hz, 1H, H-8α), 1.73-1.59 (m, 2H, H-15_{ax}, H-18), 1.43-1.29 (m, 2H, H-18, H-19), 0.81-0.70 (m, 1H, H-19). **^{13}C NMR** (101 MHz, $CDCl_3$): 201.08 (t, $J_{C\text{-}F}$ = 24.2 Hz, C-20), 146.60, 141.84, 132.13, 128.65, 119.45, 114.10, 110.76, 94.97, 78.49, 61.15, 56.77, 52.81, 46.20, 45.11, 44.96, 43.48, 35.62, 29.53, 28.42, 22.00, 17.01. **^{19}F NMR** (282 MHz, $CDCl_3$): -130.04 (d, $^2J_{F\text{-}H}$ = 53.2 Hz, 2F, $C\underline{F_2}H$). **LC-MS (ESI):** m/z calcd for '$C_{23}H_{29}F_2NO_4$' $[M+H]^+$ 422.2; found: $[M+H]^+$ 422.4 (positive ion mode). **HRMS (ESI)** calcd for $C_{23}H_{27}F_2NO_4$ $[M+H]^+$: 420.1986, found: 420.1982.

2.6. Difluoromethylation of enolizable ketones (general procedure D).

CsF (0.4 g, 2.62 mmol) was added to a solution of a ketone (2.62 mmol), HMPA (2.2 mL), and DMPU (1.6 mL) in THF (15 mL). After an addition of Me_3SiCF_2H (0.98 g, 7.86 mmol), the mixture was stirred at reflux for 24 h. An aqueous solution (15%) of HCl (15 ml) was added, the mixture was stirred for 1 h and was then poured into water (200 mL). The product was extracted with a mixture of hexanes-ethyl acetate (1:1, 3×50 mL), and the combined organic layers were washed with brine (3×100 mL) and dried over Na_2SO_4. The drying agent was filtered off and the filtrate was evaporated to dryness. The resulted mixture was separated by column chromatography on silica gel (EtOAc : hexane : MeOH : NH_3(aq.) = 1600 : 1600 : 15 : 1).

The ketone **3** (1.00 g, 2.62 mmol) was treated as described in procedure **D** to obtain 20*R*-**31**, 20*S*-**31**, and **32**.

(5*R*,6*R*,7*R*,20*R*)-4,5α-Epoxy-7-(1-hydroxy-1-(difluoromethyl)ethyl)-3,6-dimethoxy-17-methyl-6,14-*endo*-ethenoisomorphinan (20*R*-31): 0.083 g (7%), colorless crystals (from MeOH).



MP: 155-156 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): 6.63 + 6.53 (AB-system, J_{AB} = 8.4 Hz, 2H, H-2 + H-1), 5.93 (d, ^3J = 8.8 Hz, 1H, H-18), 5.69 (dd, ^2J = 55.9 Hz, 1H, $CF_2\underline{H}$), 5.54 (d, ^3J = 9.0 Hz, 1H, H-19), 4.86 (s, 1H, OH), 4.52 (s, 1H, H-5), 3.82 (s, 3H, 3-OCH_3), 3.78 (s, 3H, 6-OCH_3), 3.21 (d, ^2J = 18.5 Hz, 1H, H-10β), 3.15 (d, ^3J = 6.5 Hz, 1H, H-9), 2.90-2.82 (m, 1H, H-8β). 2.52 (dd, ^2J = 11.6 Hz, ^3J = 4.6 Hz, 1H, H-16_{eq}), 2.44-2.33 (m, 2H, H-10α, H-16_{ax}), 2.37 (m, 3H, NCH_3), 2.10 (ddd, ^2J = 8.7 Hz, ^3J = 4.0 Hz, 1H, H-7β), 1.95 (ddd, ^2J = 12.9 Hz, ^3J = 5.6 Hz, 1H, H-15_{ax}), 1.89-1.82 (m, 1H, H-15_{eq}), 1.27-1.18 (m, 1H, H-8α), 1.19 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): 147.87, 141.80, 137.15, 134.06, 128.26, 123.62, 119.51, 116.04 (t, $J_{C\text{-}F}$ = 249.4 Hz, $\underline{C}F_2H$), 113.84, 98.87, 83.17, 74.65 (t, $J_{C\text{-}F}$ = 19.2 Hz, C-20), 59.87, 56.79, 55.41, 46.90, 46.54, 45.44, 43.53, 42.69, 33.62, 28.98, 22.23, 19.40. **^{19}F NMR** (282 MHz, $CDCl_3$): -125.17 + -130.50 (AB-system, $J_{F\text{-}F}$ = 280.7 Hz, 2F, $CF_2\underline{H}$). **HRMS (ESI)** calcd for $C_{24}H_{29}F_2NO_4$ $[M+H]^+$: 434.2143, found: 434.2143.

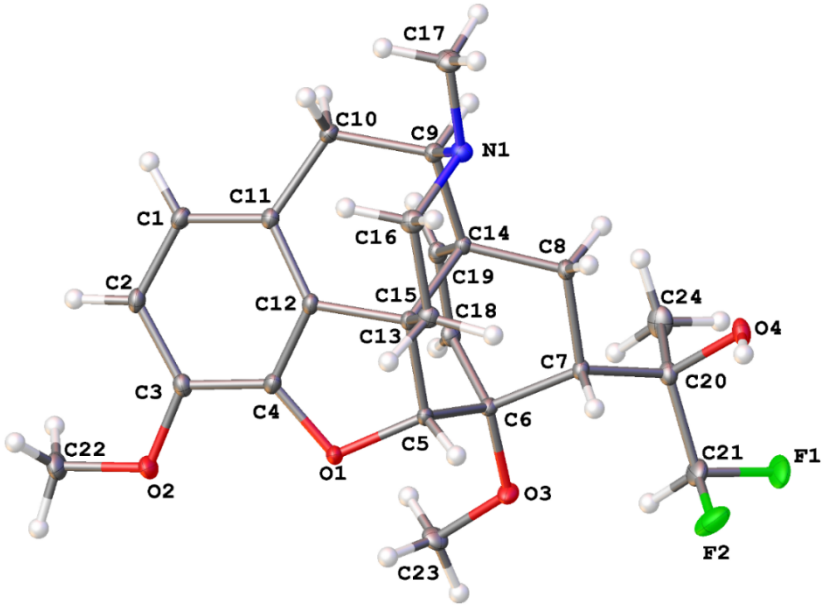
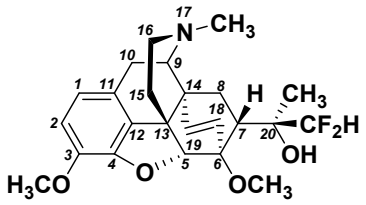


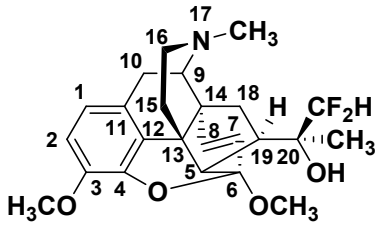
Fig. S4. General view of the compound 20*R*-**31** in representation of atoms *via* thermal ellipsoids at 40% probability level. The lattice molecule of methanol is omitted. Based on the absolute configuration of the asymmetric centres in the parent compound, the absolute configuration of the atom C(20) was identified as *R*.

(5*R*,6*R*,7*R*,20*S*)-4,5α-Epoxy-7-(1-hydroxy-1-(difluoromethyl)ethyl)-3,6-dimethoxy-17-methyl-6,14-*endo*-ethenoisomorphinan (20*S*-**31):** 0.023 g (3%), yellow oil.



^{1}H NMR (400 MHz, $CDCl_3$): 6.63 + 6.53 (AB-system, J_{AB} = 8.5 Hz, 2H, H-2 + H-1), 5.97 (d, ^{3}J = 8.5 Hz, 1H, H-18), 5.66 (dd, ^{2}J = 55.7 Hz, 1H, $CF_2\underline{H}$), 5.51 (d, ^{3}J = 8.5 Hz, 1H, H-19), 5.09 (s, 1H, OH), 4.56 (s, 1H, H-5), 3.82 (s, 3H, 3-OCH_3), 3.79 (s, 3H, 6-OCH_3), 3.22 (d, ^{2}J = 18.5 Hz, 1H, H-10β), 3.14 (d, ^{3}J = 7.4 Hz, 1H, H-9), 2.88-2.97 (m, 1H, H-8β). 2.51 (dd, ^{2}J = 11.9 Hz, ^{3}J = 4.9 Hz, 1H, H-16_{eq}), 2. 36 (s, 3H, NCH_3), 2.33-2.42 (m, 2H, H-10α, H-16_{ax}), 2.23 (t, ^{2}J = 8.7 Hz, 1H, H-7β), 1.84 (d, ^{2}J = 12.3 Hz, 1H, H-15_{ax}), 1.09 (s, 3H, CH_3), 0.98-1.06 (m, 1H, H-15_{eq}), 0.89-0.96 (m, 1H, H-8α). **^{13}C NMR** (101 MHz, $CDCl_3$): 147.94, 141.77, 136.38, 134.10, 128.36, 124.56, 119.46, 117.66 (t, $J_{C\text{-}F}$ = 248.15 MHz, $\underline{C}F_2H$), 113.83, 99.38, 83.36, 74.92, 59.82, 56.80, 55.45, 46.97, 45.40, 43.53, 42.92, 42.61, 33.54, 29.04, 22.29, 18.82. **^{19}F NMR** (282 MHz, $CDCl_3$): -129.08 + -134.98 (AB-system, $J_{F\text{-}F}$ = 273.6 Hz, 2F, $C\underline{F_2}H$). **HRMS (ESI)** calcd for $C_{24}H_{29}F_2NO_4$ $[M+H]^+$: 434.2143, found: 434.2135.

5,14-Ethano-4(*O*)-6-dehydro-l9-(2-hydroxy-1,1-difluoroprop-2-yl)-6-*O*-methylthebainol [(2S)-2-((4aR,6R,7S,12bS)-7,9-dimethoxy-3-methyl-1,2,3,4,5,6,6a,7-octahydro-4a,7-etheno-4,12-methanochromeno[4',3':2,3]cyclopenta[1,2-c]pyridin-6-yl)-1,1-difluoropropan-2-ol] **(32):** 0.07 g (6%), white solid.



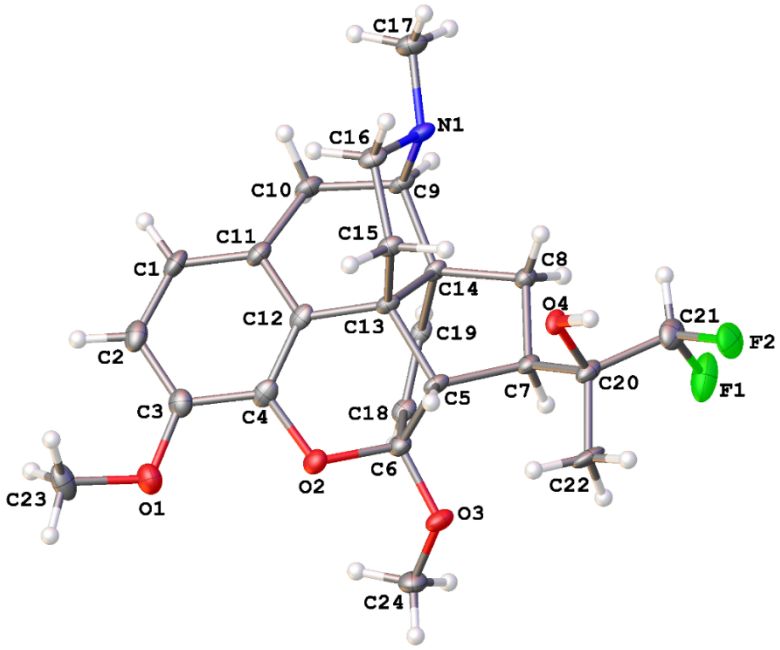
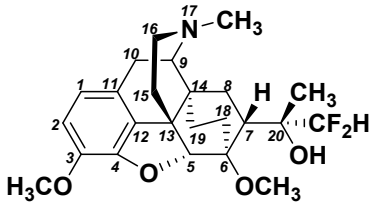


Fig. S5. General view of the compound **32** in representation of atoms *via* thermal ellipsoids at 40% probability level. The two lattice molecules of methanol and the minor component of the disordered methyl and 1-hydroxy-1-(difluoromethyl)ethyl groups are omitted. Based on the absolute configuration of the asymmetric centres in the parent compound, the absolute configuration of the atom C(20) was identified as *S*.

(5*R*,6*R*,7*R*,20*R*)-4,5α-Epoxy-7-[1-hydroxy-1-(difluoromethyl)ethyl]-3,6-dimethoxy-17-methyl-6,14-*endo*-ethanoisomorphinan (33). The ketone **30** (1.00 g, 2.62 mmol) was treated as described in procedure **D** to obtain **33** (0.391 g, 35%), white solid (from MeOH).



MP: 141-143 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): 6.71 + 6.58 (AB-system, J_{AB} = 8.8 Hz, 2H, H-2 + H-1), 6.00 (dd, ^{2}J = 55.4 Hz, 1H, $CF_2\underline{H}$), 4.95 (s, 1H, OH), 4.37 (d, ^{4}J = 2.1 Hz, 1H, H-5), 3.87 (s, 3H, 3-OCH_3), 3.55 (s, 3H, 6-OCH_3), 3.11 (d, ^{2}J = 18.5 Hz, 1H, H-10β), 2.79-2.72 (m, 1H, H-8β), 2.65 (d, ^{3}J = 6.4 Hz, 1H, H-9), 2.43 (dd, ^{2}J = 11.6 Hz, ^{3}J = 5.4 Hz, 1H, H-16$_{eq}$), 2.32-2.25 (m, 1H, H-16$_{ax}$), 2.30 (s, 3H, NCH_3), 2.21 (dd, ^{2}J = 12.5 Hz, ^{3}J = 5.4 Hz, 1H, H-10α), 2.09-2.04 (m, 1H, H-15$_{eq}$), 2.00-1.93 (ddd, ^{2}J = 12.8 Hz, ^{3}J = 5.9 Hz, 1H, H-7β), 1.92-1.83 (m, 1H, H-18), 1.69-1.65 (m, 1H, H-15$_{ax}$), 1.54-1.46 (m, 2H, H-8α, H-18), 1.31 (s, 3H, CH_3), 1.11 (ddd, ^{2}J = 12.5 Hz, ^{3}J = 5.5 Hz, 1H, H-19), 0.76-0.67 (m, 1H, H-19). **^{13}C NMR** (101 MHz, $CDCl_3$), 146.82, 141.74, 132.21, 128.84, 119.34, 116.96 (t, $J_{C\text{-}F}$ = 248 Hz, $\underline{C}F_2H$), 114.19, 97.07, 79.60, 75.25 (t, $J_{C\text{-}F}$ = 20.5 Hz, C-20), 61.12, 56.87, 52.97, 47.33, 46.12, 45.11, 43.50, 35.87, 35.58, 30.01, 29.05, 21.90, 19.00, 17.95. **^{19}F NMR** (282 MHz, $CDCl_3$): -121.35 + -130.16 (AB-system, $J_{F\text{-}F}$ = 282.9 Hz, 2F, $C\underline{F_2}H$). **LC-MS (ESI):** m/z

calcd for '$C_{24}H_{31}F_2NO_4$' $[M+H]^+$ 436.2; found: $[M+H]^+$ 436.4 (positive ion mode). **HRMS (ESI)** calcd for $C_{24}H_{31}F_2NO_4$ $[M+H]^+$: 436.2299, found: 436.2285. Found (%): C 66.04, H 7.19, N 3.21, F 8.68; $C_{24}H_{31}F_2NO_4$. Calculated (%): C 66.19, H 7.18, N 3.22, F 8.72.

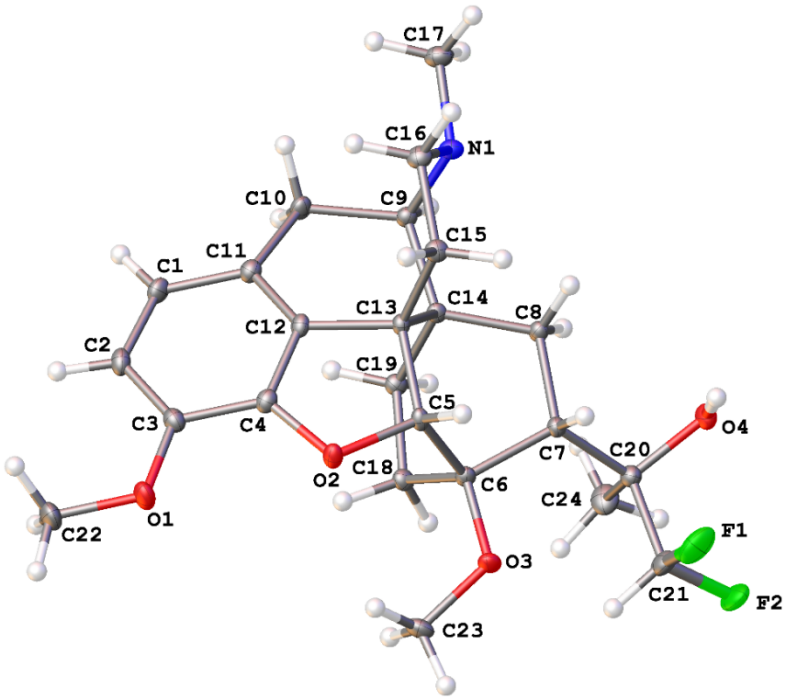
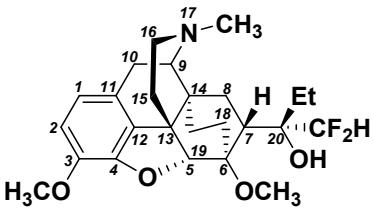


Fig. S6. General view of the compound **33** in representation of atoms *via* thermal ellipsoids at 40% probability level. The lattice molecule of methanol is omitted for clarity. Based on the absolute configuration of the asymmetric centres in the parent compound, the absolute configuration of the atom C(20) was identified as *R*.

(5*R*,6*R*,7*R*,20*R*)-4,5α-Epoxy-7-[1-hydroxy-1-(difluoromethyl)propyl]-3,6-dimethoxy-17-methyl-6,14-*endo*-ethanoisomorphinan (35). The ketone **34** (0.36 g, 0.90 mmol) was treated as described in procedure **D** to obtain after a column chromatography on silica gel (EtOAc : hexane : MeOH : NH_3(aq.) = 1600 : 1600 : 15 : 1) product **35** (0.018 g, 5%) as yellow oil.



^{1}H NMR (400 MHz, $CDCl_3$): 6.72 + 6.58 (AB-system, J_{AB} = 7.9 Hz, 2H, H-2 + H-1), 6.01 (dd, ^2J = 55.8 Hz, 1H, $CF_2\underline{H}$), 5.14 (s, 1H, OH), 4.39 (s, 1H, H-5), 3.88 (s, 3H, 3-OCH_3), 3.56 (s, 3H, 6-OCH_3), 3.11 (d, ^2J = 18.4 Hz, 1H, H-10β), 2.80-2.70 (m, 1H, H-8β), 2.64 (d, ^3J = 5.9 Hz, 1H, H-9), 2.43 (dd, ^2J = 12.0 Hz, ^3J = 5.2 Hz, 1H, H-16_{eq}), 2.29 (s, 3H, NCH_3), 2.26-2.34 (m, 1H, H-16_{ax}), 2.34-2.26 (m, 1H, H-10α), 2.11-2.02 (m, 1H, H-15_{eq}), 1.98-1.84 (m, 2H, H-7β, H-18), 1.84-1.75 (m, 1H, H-15), 1.73-1.63 (m, 2H, $\underline{CH_2}CH_3$), 1.59-1.49 (m, 2H, H-8α, H-18), 1.18-1.08 (m, 1H, H-19), 1.05 (t, ^3J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$), 0.77-0.66 (m,

1H, H-19). **^{13}C NMR** (101 MHz, $CDCl_3$): 146.82, 141.70, 132.19, 128.92, 119.31, 117.43 (t, $J_{C\text{-}F}$ = 247.3 Hz, $\underline{C}F_2H$), 114.05, 97.38, 79.64, 77.18, 61.06, 56.82, 53.02, 46.15, 45.08, 43.57, 35.84, 35.62, 29.22, 29.17, 29.00, 22.84, 21.88, 17.89, 7.03. **^{19}F NMR** (282 MHz, $CDCl_3$): -124.83 + -131.16 (AB-system, $J_{F\text{-}F}$ = 282.4 Hz, 2F, $C\underline{F_2}H$). **LC-MS (ESI):** m/z calcd for '$C_{25}H_{33}F_2NO_4$' $[M+H]^+$ 450.2; found: $[M+H]^+$ 450.4 (positive ion mode). **HRMS (ESI)** calcd for $C_{25}H_{33}F_2NO_4$ $[M+H]^+$: 450.2456, found: 450.2480.

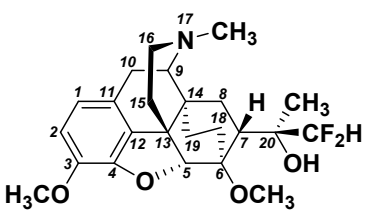
2.7. Reactions of RMgX with the 21,21-difluorinated ketones (general procedure E).

A solution of RMgX in Et_2O was added dropwise to a solution of an appropriate ketone in Et_2O at 20 °C and the mixture was stirred for the required time. The reaction mixture was quenched with NH_4Cl (saturated aqueous solution), and extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over Na_2SO_4. The drying agent was filtered off and the filtrate was evaporated to dryness.

Reaction of 10 with MeMgI. The ketone **10** (0.12 g, 0.29 mmol) was reacted with MeMgI (0.3 mL, 1.7 M in Et_2O) as described in procedure **E.** The reaction products were separated by column chromatography on silica gel (EtOAc : hexane : MeOH : NH_3(aq.) = 1600 : 1600 : 15 : 1) to afford 20*S*-**31** (0.10 g, 73%) and 20*R*-**31** (0.003 g, 3%).

(5*R*,6*R*,7*R*,20*S*)-4,5α-Epoxy-7-(1-hydroxy-1-(difluoromethyl)ethyl)-3,6-dimethoxy-17-methyl-6,14-*endo*-ethanoisomorphinan (20*S*-**36):**

The ketone **13** (0.5 g, 1.2 mmol) was reacted with MeMgI (1.1 mL, 1.7 M in Et_2O) as described in procedure **E** to afford the pure (NMR) crude product 20*S*-**36** (0.46 g, 88%). The colorless crystals of 20*S*-**36** (0.24 g, 46%) suitable for X-ray study were obtained after recrystallization from EtOH.



MP: 125-127 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): 6.71 + 6.58 (AB-system, J_{AB} = 7.9 Hz, 2H, H-2 + H-1), 5.68 (dd, ^2J = 56.2 Hz, 1H, $CF_2\underline{H}$), 4.88 (s, 1H, OH), 4.41 (s, 1H, H-5), 3.87 (s, 3H, 3-OCH_3), 3.54 (s, 3H, 6-OCH_3), 3.11 (d, ^2J = 18.5 Hz, 1H, H-10β), 2.88-2.77 (m, 1H, H-8β), 2.66 (d, ^3J = 6.1 Hz, 1H, H-9), 2.43 (dd, ^2J = 11.5 Hz, ^3J = 5.3 Hz, 1H, H-16_{eq}), 2.33-2.11 (m, 3H, H-10α, H-15_{eq}, H-16_{ax}), 2.29 (s, 3H, NCH_3), 2.01 (dd, ^2J = 12.5 Hz, ^3J = 6.7 Hz, 1H, H-7β), 1.80-1.72 (m, 2H, H-18, H-18), 1.64 (m, 1H, H-15_{ax}), 1.41-1.31 (m, 1H, H-8α), 1.39 (s, 3H, CH_3), 1.14-0.99 (m, 1H, H-19), 0.83-0.66 (m, 1H, H-19). **^{13}C NMR** (101 MHz, $CDCl_3$): 146.82, 141.70, 132.36, 128.79, 119.30, 117.68 (t, $J_{C\text{-}F}$ = 243.1 Hz, $\underline{C}F_2H$), 114.13, 96.26, 79.58, 75.72 (t, J = 21.6 Hz, C-20), 61.17, 56.84, 52.80, 45.86, 45.08,

43.52, 41.45, 35.82, 35.46, 30.21, 29.59, 21.94, 18.60, 18.08. **^{19}F NMR** (282 MHz, $CDCl_3$): -130.16 + -133.85 (AB-system, $^2J_{F\text{-}F}$ = 275.4 Hz, $^2J_{F\text{-}H}$ = 55.6 Hz, 2F, $C\underline{F_2}H$). **LC-MS (ESI):** m/z calcd for '$C_{24}H_{31}F_2NO_4$' $[M+H]^+$ 436.2; found: $[M+H]^+$ 436.4, $[M+H+CH_3CN]^+$ 477.4 (positive ion mode). **HRMS (ESI)** calcd for $C_{24}H_{31}F_2NO_4$ $[M+H]^+$: 436.2299, found: 436.2291.

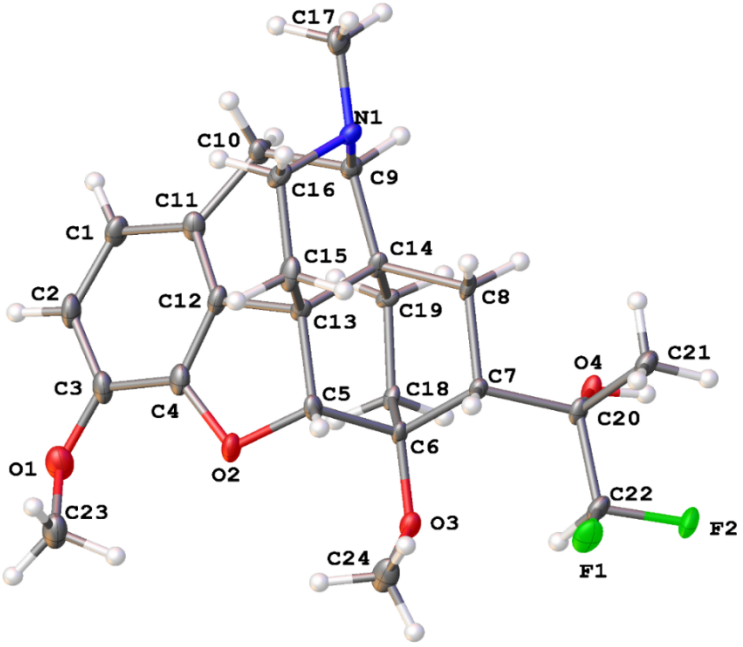
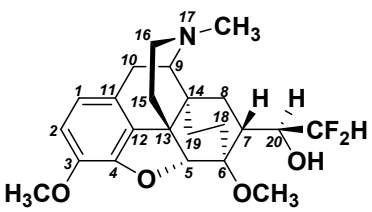


Fig. S7. General view of the compound 20*S*-**36** in representation of atoms *via* thermal ellipsoids at 40% probability level. Lattice molecules of water and ethanol are omitted. Based on the absolute configuration of the asymmetric centres in the parent compound, the absolute configuration of the atom C(20) was identified as *S*.

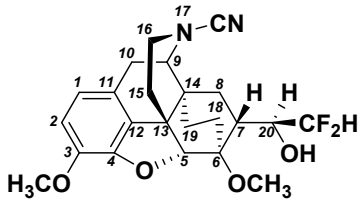
(5*R*,6*R*,7*R*,20*S*)-4,5α-Epoxy-7-(1-hydroxy-1-(difluoromethyl)methyl)-3,6-dimethoxy-17-methyl-6,14-*endo*-ethanoisimorphinan (37). The ketone **13** (0.10 g, 0.24 mmol) was reacted with EtMgBr (0.18 mL, 1.6 M in Et_2O) or *i*-PrMgI (0.10 mL, 2.9 M in Et_2O) as described in procedure **E**. The products were separated by column chromatography on silica gel (EtOAc : hexane : MeOH : NH_3(aq.) = 1600 : 1600 : 15 : 1) to afford compound **37** (0.06 g, 60%) as colorless oil.



^{1}H NMR (300 MHz, $CDCl_3$):6.73 + 6.60 (AB-system, J_{AB} = 8.1 Hz, 2H, H-2 + H-1), 5.86 (dd, ^2J = 54.4 Hz, 1H, $CF_2\underline{H}$), 5.55 (s, 1H, OH), 4.49 (s, 1H, H-5), 4.03 (dd, ^3J = 10.3 Hz, 1H, H-20), 3.88 (s, 3H, 3-OCH_3), 3.54 (s, 3H, 6-OCH_3), 3.11 (d, ^2J = 18.5 Hz, 1H, H-10β), 2.93-2.78 (m, 1H, H-8β), 2.66 (d, ^3J = 6.7 Hz, 1H, H-9), 2.45 (dd, ^2J = 12.2 Hz, ^3J = 5.8 Hz, 1H, H-16$_{eq}$), 2.36-1.96 (m, 5H, H-7β, H-10α, H-15$_{ax}$, H-15$_{eq}$, H-16$_{ax}$), 2.29 (s, 3H, NCH_3), 1.85-1.52 (m, 2H, H-18, H-18), 1.19 (dd, ^2J = 13.0 Hz, ^3J = 6.3 Hz, 1H, H-8α), 1.07 (ddd, ^2J = 12.2 Hz, ^3J = 6.0

Hz, 1H, H-19), 0.89-0.73 (m, 1H, H-19). **^{13}C NMR** 146.60, 141.86, 132.31, 128.50, 119.46, 116.20 (t, $J_{C\text{-}F}$ = 244.6 Hz, $\underline{C}F_2H$), 114.20, 94.48, 79.22, 73.73 (t, $J_{C\text{-}F}$ = 19.6 Hz, C-20), 61.22, 56.81, 52.58, 45.12, 44.91, 43.50, 36.18, 35.12, 35.01, 30.58, 28.97, 21.96, 17.65. **^{19}F NMR** (282 MHz, $CDCl_3$): -129.10 + -131.12 (AB-system, $^2J_{F\text{-}F}$ = 283.1 Hz, $^2J_{F\text{-}H}$ = 55.6 Hz, $^3J_{F\text{-}H}$ = 14.6 Hz, 2F, $C\underline{F_2}H$).

2.8. (5*R*,6*R*,7*R*,20*S*)-4,5α-Epoxy-7-(1-hydroxy-1-(difluoromethyl)methyl)-3,6-dimethoxy-17-cyano-6,14-*endo*-ethanoisimorphinan (38). A solution of BrCN (2.75 mL, 0.8 M in $CHCl_3$) was added to **37 (**0.23 g, 0.55 mmol) and the resulted solution was allowed to stay at room temperature for 24 h. The reaction mixture was washed with diluted HCl and water, dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. A crystallization of the residue from methanol afforded compound **38** (0.056 g, 24%) as colorless crystals.



MP 240-242 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): 6.78 + 6.65 (AB-system, J_{AB} = 7.4 Hz, 2H, H-2 + H-1), 5.88 (dd, ^2J = 54.2 Hz, 1H, $CF_2\underline{H}$), 5.20 (s, 1H, OH), 4.47 (s, 1H, H-5), 4.03 (dd, ^2J = 22.2 Hz, ^3J = 10.7 Hz, 1H, H-20), 3.88 (s, 3H, 3-OCH_3), 3.53 (s, 3H, 6-OCH_3), 3.40 (d, ^3J = 6.17 Hz, 1H, H-9), 3.30-3.22 (m, 2H, 2H-16), 3.15 (d, ^2J = 18.9 Hz, H-10β), 2.94 (dd, ^2J = 18.9 Hz, ^3J = 6.2 Hz, 1H, H-10α), 2.68-2.58 (m, 1H, H-8β), 2.21-2.07 (m, 2H, H-7β, H-15_{ax}), 1.87-1.71 (m, 2H, H-15_{eq}, H-18), 1.70-1.60 (m, 1H, H-18), 1.45 (dd, ^2J = 13.4 Hz, ^3J = 7.2 Hz, 1H, H-8α), 1.17 (ddd, ^2J = 12.7 Hz, ^3J = 6.2 Hz, 1H, H-19), 0.80-0.68 (m, 1H, H-19). **^{13}C NMR** (101 MHz, $CDCl_3$): 146.87, 142.53, 130.32, 125.71, 120.06, 117.89, 116.50 (t, $J_{C\text{-}F}$ = 242.11 Hz, $\underline{C}F_2H$), 114.84, 94.34, 78.55, 73.34 (t, $^2J_{C\text{-}F}$ = 20.20 Hz, C-20), 59.43, 56.73, 52.78, 44.59, 41.53, 36.33, 34.59, 32.94, 31.61, 29.75, 28.28, 17.32. **^{19}F NMR** (282 MHz, $CDCl_3$): -125.79 + -131.50 (AB-system, $^2J_{F\text{-}F}$ = 285.3 Hz, $^2J_{F\text{-}H}$ = 56.3 Hz, $^3J_{F\text{-}H}$ = 12.2 Hz, 2F, $C\underline{F_2}H$). Found (%): C 62.93, H 5.94, N 6.46, F 8.09; $C_{23}H_{26}N_2O_4$. Calculated (%): C 63.88, H 6.06, N 6.48, F 8.79.

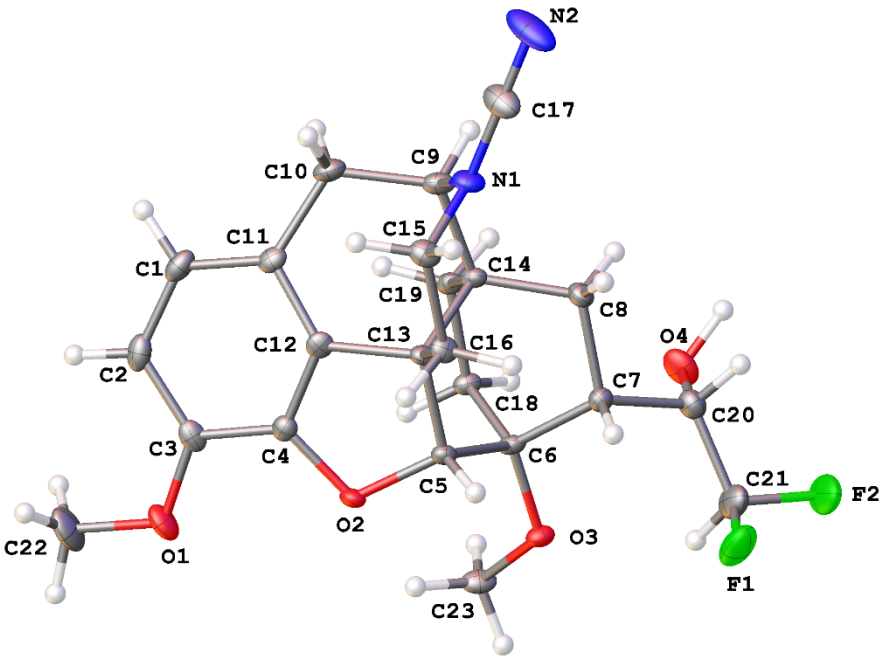


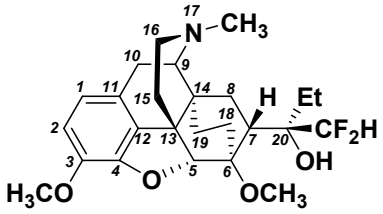
Fig. S8. General view of the compound **38** in representation of atoms *via* thermal ellipsoids at 40% probability level. The minor component of the disordered cyano group is omitted. Based on the absolute configuration of the asymmetric centres in the parent compound, the absolute configuration of the atom C(20) was identified as *S*.

2.9. Reactions of RLi with ketone 13 (general procedure F).

The solution of RLi was added dropwise to a solution of **13** in Et_2O or THF at -78 °C and the mixture was stirred for the required time. The reaction mixture was allowed to warm to the room temperature, quenched with NH_4Cl (saturated aqueous solution), and extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over Na_2SO_4. The drying agent was filtered off and the filtrate was evaporated to dryness.

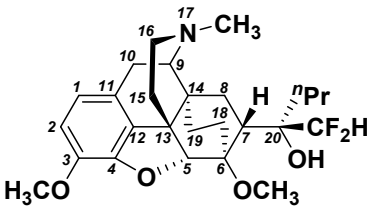
(5*R*,6*R*,7*R*,20*S*)-4,5α-Epoxy-7-[1-hydroxy-1-(difluoromethyl)ethyl]-3,6-dimethoxy-17-methyl-6,14-*endo*-ethanoisomorphinan (20*S*-36). The reaction of the ketone **13** (0.10 g, 0.24 mmol) with MeLi (0.5 mL, 0.9 M in Et_2O) according to procedure **F** afforded 20*S*-**36**, which was isolated by crystallization from EtOH (0.05 g, 32%).

(5*R*,6*R*,7*R*,20*S*)-4,5α-Epoxy-7-[1-hydroxy-1-(difluoromethyl)propyl]-3,6-dimethoxy-17-methyl-6,14-*endo*-ethanoisomorphinan (39, R = Et). The ketone **13** (0.10 g, 0.24 mmol) was reacted with EtLi (2.4 mL, 0.2 M in *n*-pentane) according to procedure **F** to afford compound **39** (R = Et), which was separated by column chromatography on silica gel (EtOAc : hexane : MeOH : NH_3(aq.) = 1600 : 1600 : 15 : 1) as colorless oil (0.046 g, 41%).



^{1}H NMR (300 MHz, $CDCl_3$):6.72 + 6.58 (AB-system, J_{AB} = 8.3 Hz, 2H, H-2 + H-1), 5.71 (dd, ^2J = 55.3 Hz, 1H, $CF_2\underline{H}$), 4.85 (s, 1H, OH), 4.42 (s, 1H, H-5), 3.54 (s, 3H, 3-OCH_3), 3.42 (s, 3H, 6-OCH_3), 3.11 (d, ^2J = 18.5 Hz, 1H, H-10β), 2.89-2.90 (m, 1H, H-8β), 2.65 (d, ^3J = 6.4 Hz, 1H, H-9), 2.42 (dd, ^2J = 12.0 Hz, ^3J = 5.6 Hz, 1H, H-16_{eq}), 2.28-2.17 (m, 3H, H-16_{ax}, $C\underline{H_2}CH_3$). 2.29 (s, 3H, NCH_3), 2.09-2.16 (m, 2H, H-7β, H-10α), 1.90-1.85 (m, 1H, H-18), 1.84-1.77 (m, 1H, H-15_{eq}), 1.77-1.71 (m, 1H, H-15_{ax}), 1.68-1.62 (m, 2H, H-8α, H-18), 1.48-1.39 (m, 1H, H-19), 1.04 (t, ^3J = 7.3 Hz, 3H, CH_3), 0.80-0.71 (m, 1H, H-19). **^{13}C NMR** (101 MHz, $CDCl_3$):146.85, 141.67, 132.47, 128.91, 119.24, 118.15 (t, $J_{C\text{-}F}$ = 247.8 Hz), 114.15, 96.71, 79.57, 77.31, 61.19, 56.88, 52.84, 45.90, 45.08, 43.53, 41.40, 41.36, 35.87, 35.46, 29.67, 25.83, 21.97, 18.21, 7.46. **^{19}F NMR** (282 MHz, $CDCl_3$): -127.93 + -137.53 (AB-system, $^2J_{F\text{-}F}$ = 277.0, 2F, $C\underline{F_2}H$). **HRMS (ESI)** calcd for $C_{25}H_{33}F_2NO_4$ $[M+H]^+$: 450.2456, found: 450.2454.

(5*R*,6*R*,7*R*,20*S*)-4,5α-Epoxy-7-[1-hydroxy-1-(difluoromethyl)butyl]-3,6-dimethoxy-17-methyl-6,14-*endo*-ethanoisomorphinan (39, R = *n*-Pr). The ketone **13** (0.10 g, 0.24 mmol) was reacted with *n*-PrLi (1.4 mL, 0.4 M in *n*-pentane) according to procedure **F** to afford product **39** (R = *n*-Pr), which was isolated as white solid (0.035 g, 32%) by crystallization from EtOH.



MP: 106-108 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): 6.72 + 6.58 (AB-system, J_{AB} = 8.4 Hz, H-2 + H-1), 5.70 (dd, ^2J = 55.7 Hz, 1H, $CF_2\underline{H}$), 4.93 (d, J = 4.9 Hz, 1H, OH), 4.42 (s, 1H, H-5), 3.88 (s, 3H, 3-OCH_3), 3.54 (s, 3H, 6-OCH_3), 3.11 (d, ^2J = 18.4 Hz, 1H, H-10β), 2.90-2.67 (m, 1H, H-8β), 2.65 (d, ^3J = 5.9 Hz, 1H, H-9), 2.43 (dd, ^2J = 11.2 Hz, ^3J = 5.5 Hz, 1H, H-16_{eq}), 2.29 (s, 3H, NCH_3), 2.33-2.14 (m, 3H, H-7β, H-10α, H-16_{ax}), 2.03 (ddd, ^2J = 12.6 Hz, ^3J = 5.5 Hz, 1H, H-15_{ax}), 1.95-1.87 (m, 1H, H-22), 1.85-1.60 (m, 5H, H-15_{eq}, H-18, H-18, H-22, H-23), 1.49-1.33 (m, 2H, H-8α, H-23), 1.09 (ddd, ^2J = 12.5 Hz, ^3J = 7.0 Hz, 1H, H-19), 0.95 (t, ^3J = 6.7 Hz, 3H, CH_3), 0.82-0.69 (m, 1H, H-19). **^{13}C NMR** (101 MHz, $CDCl_3$): 146.84, 141.66, 132.50, 128.95, 119.24, 118.16 (t, $J_{C\text{-}F}$ = 246.7 Hz, $C\underline{F_2}H$), 114.15, 96.69, 79.63, 77.25, 61.16, 56.90, 52.86, 45.92, 45.06, 43.54, 41.44, 36.63, 35.88, 35.50, 29.69, 29.65, 21.94, 18.22, 16.20, 15.12. **^{19}F NMR** (282 MHz, $CDCl_3$): -125.27 + -136.77 (AB-system, $^2J_{F\text{-}F}$ = 279.7, 2F, $C\underline{F_2}H$). **LC-MS (ESI):** m/z calcd for '$C_{26}H_{35}F_2NO_4$' $[M+H]^+$ 464.2; found: $[M+H]^+$ 464.4, $[M+H+CH_3CN]^+$ 505.5 (positive ion mode). **HRMS (ESI)** calcd for $C_{26}H_{35}F_2NO_4$ $[M+H]^+$: 464.2612, found: 464.2599.

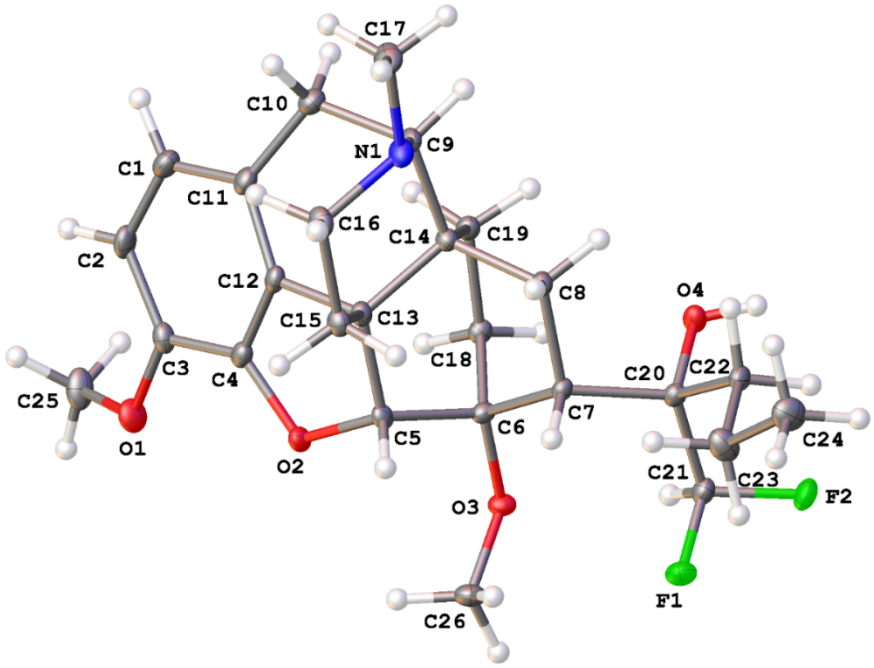
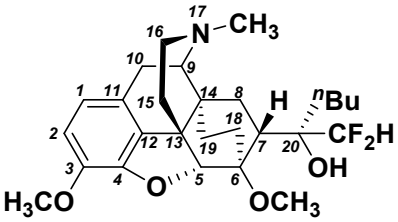


Fig. S9. General view of the compound **39** (R = *n*-Pr) in representation of atoms *via* thermal ellipsoids at 40% probability level. Lattice molecule of water is omitted. Based on the absolute configuration of the asymmetric centres in the parent compound, the absolute configuration of the atom C(20) was identified as *S*.

(5*R*,6*R*,7*R*,20*S*)-4,5α-Epoxy-7-[1-hydroxy-1-(difluoromethyl)pentyl]-3,6-dimethoxy-17-methyl-6,14-*endo*-ethanoisomorphinan (39, R = *n*-Bu). The ketone **13** (0.225 g, 0.54 mmol) was reacted with *n*-BuLi (0.8 mL, 1.6 M in *n*-hexane) according to procedure **F** to afford compound **39** (R = *n*-Bu), which was separated by column chromatography on silica gel (EtOAc : hexane : MeOH : NH_3(aq.) = 1600 : 1600 : 15 : 1) followed by recrystallization from EtOH as white solid (0.064 g, 25%).



MP: 106-108 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): 6.71 + 6.58 (AB-system, J_{AB} = 8.3 Hz, H-2 + H-1), 5.70 (dd, ^2J = 55.8 Hz, 1H, $CF_2\underline{H}$), 4.93 (d, J = 4.9 Hz, 1H, H-5), 4.42 (s, 1H, H-5), 3.88 (s, 3H, 3-OCH_3), 3.54 (s, 3H, 6-OCH_3), 3.11 (d, ^2J = 18.5 Hz, 1H, H-10β), 2.88-2.79 (m, 1H, H-8β), 2.65 (d, ^3J = 6.4 Hz, 1H, H-9), 2.43 (dd, ^2J = 11.8 Hz, ^3J = 5.1 Hz, 1H, H-16$_{eq}$), 2.31-2.17 (m, 3H, H-10α, H-15$_{eq}$, H-16$_{ax}$), 2.29 (s, 3H, NCH_3), 2.04 (dd, ^3J = 12.6 Hz, ^3J = 5.6 Hz, 1H, H-7β), 1.97-1.90 (m, 1H, H-16$_{ax}$), 1.86-1.59 (m, 6H, $(C\underline{H}_2)_3CH_3$), 1.47-1.39 (m, 1H, H-18), 1.36-1.30 (m, 2H, H-8α, H-18), 1.08 (ddd, ^2J = 12.1 Hz, ^3J = 6.0 Hz, 1H, H-19), 0.92 (t, ^3J = 6.9 Hz, 3H, CH_3), 0.81-0.70 (m, 1H, H-19). **^{13}C NMR** (101 MHz, $CDCl_3$): 146.82, 141.85, 132.47, 128.93, 119.24, 118.14 (t, $J_{C\text{-}F}$ = 248.6 Hz, $\underline{C}F_2H$), 114.12, 96.70, 79.62, 77.28, 61.15, 56.88, 52.86, 45.92, 45.05, 43.54, 41.48, 41.43, 35.87, 35.48, 33.04, 29.66, 25.00, 23.75, 21.94, 18.23, 14.07. **^{19}F NMR** (282 MHz, $CDCl_3$): -125.23 + -136.87 (AB-

system, $^{2}J_{F\text{-}F}$ = 275.5, 2F, C$\underline{F_2}$H). **LC-MS (ESI):** m/z calcd for '$C_{27}H_{37}F_2NO_4$' $[M+H]^+$ 478.3; found: $[M+H]^+$ 478.5, $[M+H+CH_3CN]^+$ 519.5 (positive ion mode). **HRMS (ESI)** calcd for $C_{27}H_{37}F_2NO_4$ $[M+H]^+$: 478.2769, found: 478.2761.

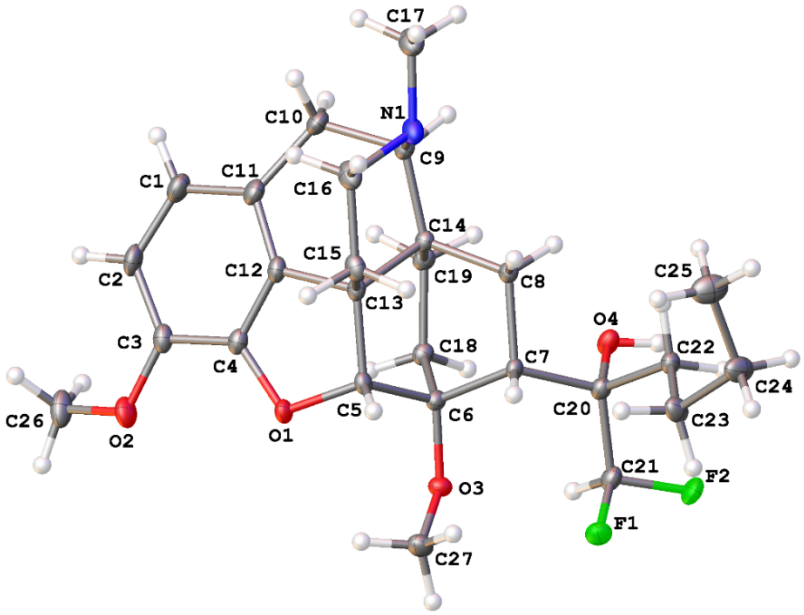
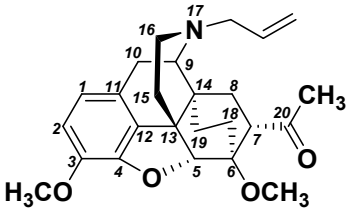


Fig. S10. General view of the compound **39** (R = *n*-Bu) in representation of atoms *via* thermal ellipsoids at 40% probability level. Lattice molecule of water and the minor component of the disordered n-butyl group are omitted. Based on the absolute configuration of the asymmetric centres in the parent compound, the absolute configuration of the atom C(20) was identified as *S*.

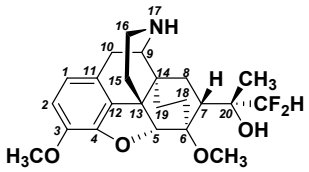
2.10. *N*-Allyl-*N*-nor-18,19-dihydrothevinone (45). Allyl bromide (0.16 g, 1.35 mmol) and $NaHCO_3$ (0.13 g, 1.60 mmol) were added to the solution of *N*-nor-18,19-dihydrothevinone hydrochloride (**44**) (0.50 g, 1.23 mmol) in DMF (10 mL). After stirring for 2 h at 90 °C, the reaction mixture was cooled to 20 °C and poured into water (25 mL). The product was extracted with $CHCl_3$ (3×50 mL) and the combined organic layers were washed with brine (3×100 mL) and dried over Na_2SO_4. The drying agent was filtered off and the filtrate was evaporated to dryness and afford **45** (0.36 g, 64%) as yellow oil.



^{1}H NMR (400 MHz, $CDCl_3$): 6.71 + 6.58 (AB-system, J_{AB} = 8.0 Hz, 2H, H-2 + H-1), 5.82-5.65 (m, 1H, $H_{allyl}(-CH_2-C\underline{H}=CH_2)$, 5.17 (d, ^{2}J = 17.0 Hz, 1H, $H_{allyl}(-CH_2-CH=C\underline{H_2}$ (*trans*)), 5.09 (d, ^{2}J = 10.4 Hz, 1H, $H_{allyl}(-CH_2-CH=C\underline{H_2}$ (*cis*)), 4.48 (s, 1H, H-5), 3.87 (s, 3H, 3-OCH_3), 3.43 (s, 3H, 3-OCH_3), 3.10-2.97 (m, 4H, H-10β, H-16$_{eq}$, $H_{allyl}(-C\underline{H_2}-CH=CH_2)$), 2.85 (d, ^{3}J = 6.3 Hz, 1H, H-9), 2.76-2.67 (m, 1H, H-8β), 2.53 (dd, ^{2}J = 11.8 Hz, ^{3}J = 5.2 Hz, 1H, H-16$_{ax}$), 2.37-2.23 (m, 5H, CH_3, H-10α, H-15$_{eq}$), 2.02 (ddd, ^{2}J = 12.9 Hz, ^{3}J = 6.1 Hz, 1H, H-7β), 1.76-1.63 (m, 2H, H-15$_{ax}$, H-18), 1.57-1.49 (m, 2H, H-8α, H-18),

1.34-1.23 (m, 1H, H-19), 0.75-0.64 (m, 1H, H-19). **^{13}C NMR** (101 MHz, $CDCl_3$): 210.92, 146.75, 141.79, 136.30, 132.58, 128.64, 119.21, 116.79, 113.88, 94.68, 77.64, 58.48, 58.22, 56.72, 52.28, 49.61, 46.37, 43.51, 35.52, 35.27, 33.81, 30.33, 28.59, 22.91, 17.46. **HRMS (ESI)** calcd for $C_{25}H_{31}NO_4$ $[M+H]^+$: 410.2331, found: 410.2346.

2.11. (5*R*,6*R*,7*R*,20*R*)-4,5α-Epoxy-7-[1-hydroxy-1-(difluoromethyl)ethyl]-3,6-dimethoxy-6,14-*endo*-ethanoisomorphinan hydrochloride (41). DEAD (0.42 mL, 2.2 mmol) was added dropwise to a stirred solution of 20*R*-**33** (0.50 g, 1.10 mmol) in acetonitrile (10 mL) at reflux. The reaction mixture was heated at reflux for 5 h. Pyridinium hydrochloride (0.40 g, 3.20 mmol) was added and the mixture was stirred for 30 min at room temperature. The precipitate, formed during overnight, was filtered off, washed with cold acetonitrile and dried *in vacuo* to afford **41** (0.40 g, 77%). A part of **41** (0.10 g, 0.20 mmol) was dissolved in water (15 mL), basified with concentrated aqueous ammonia and extracted with chloroform (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo* to afford free amine (0.07 g, 85%) as white solid.



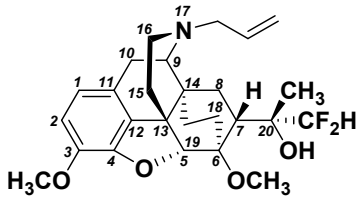
MP: 158–159 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): 6.74 + 6.59 (AB-system, J_{AB} = 8.0 Hz, 2H, H-2 + H-1), 6.02 (dd, ^2J = 57.0 Hz, 1H. $CF_2\underline{H}$), 4.93 (br. s, 1H, OH), 4.35 (s, 1H, H-5), 3.88 (s, 3H, 3-OCH_3), 3.55 (s, 3H, 6-OCH_3), 3.01-2.85 (m, 4H, H-9, H-10α, H-10β, H-16_{ax}), 2.78 (dd, ^2J = 12.6 Hz, ^3J = 4.6 Hz, 1H, H-16_{eq}), 2.71-2.58 (m, 1H, H-8β), 2.13-2.00 (m, 1H, H-7β), 1.97-1.81 (m, 2H, H-15_{eq}, H-18), 1.71-1.49 (m, 4H, H-8α, H-15_{ax}, H-18, NH), 1.32 (s, 3H, CH_3), 1.13 (ddd, ^2J = 12.5 Hz, ^3J = 5.8 Hz, 1H, H-19), 0.76-0.63 (m, 1H, H-19). **^{13}C NMR** (101 MHz, $CDCl_3$): 146.89, 141.82, 132.11, 128.77, 119.36, 116.92, 114.25, 97.41, 79.37, 56.84, 53.99, 52.96, 47.15, 47.11, 47.00, 37.00, 35.27, 35.22, 34.14, 29.70, 29.08, 18.94, 18.15. **^{19}F NMR** (300 MHz, $CDCl_3$): -130.28 + -122.92 (AB-system, J_{AB} = 283.3 Hz, 2F, $C\underline{F_2}H$). **HRMS (ESI)** calcd for $C_{23}H_{29}F_2NO_4$ $[M+H]^+$: 422.2065, found: 422.2150.

2.12. (5*R*, 6*R*, 7*R*, 20*R*)-17-Allyl-4,5α-epoxy-7-[1-hydroxy-1-(difluoromethyl)ethyl]-3,6-dimethoxy-6,14-*endo*-ethanoisomorphinan (42).

Method 1: Allyl bromide (0.29 g, 2.40 mmol) and $NaHCO_3$ (0.24 g, 2.90 mmol) were added to a solution of **41** (1.00 g, 2.20 mmol) in anhydrous DMF (20 mL) and the mixture was vigorously stirred at 90-95 °C. After 20 h, the reaction mixture was quenched with water (100 mL) and extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The

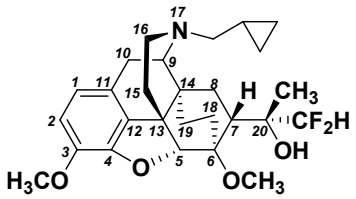
products were separated by column chromatography on silica gel (EtOAc : hexane : MeOH : NH_3(aq.) = 1600 : 1600 : 15 : 1) to afford **42** (0.49 g, 48%) as yellow oil.

Method 2: The ketone **45** (0.30 g, 0.70 mmol) was treated as described in procedure **D**. The products were separated by column chromatography on silica gel (EtOAc : hexane : MeOH : NH_3(aq.) = 1600 : 1600 : 15 : 1) to afford **42** (0.074 g, 23%) as yellow oil.



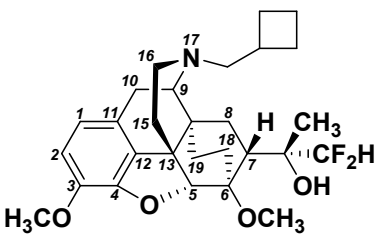
^{1}H NMR (400 MHz, $CDCl_3$): 6.71 + 6.57 (AB-system, J_{AB} = 7.8 Hz, 2H, H-2 + H-1), 6.01 (dd, ^2J = 56.5 Hz, 2H, $CF_2\underline{H}$), 5.84-5.71 (m, 1H, H_{allyl}(−CH_2−$C\underline{H}$=CH_2), 5.18 (d, ^2J = 16.7 Hz, 1H, H_{allyl}(−CH_2−CH=C$\underline{H_2}$ (*trans*)), 5.11 (d, ^2J = 9.5 Hz, 1H, H_{allyl}(−CH_2−CH=C$\underline{H_2}$ (*cis*)), 4.93 (s, 1H, OH), 4.37 (s, 1H, H-5), 3.87 (s, 3H, 3-OCH_3), 3.55 (s, 3H, 3-OCH_3), 2.98-3.11 (m, 3H, H-10β, H_{allyl}(−C$\underline{H_2}$−CH=CH_2)), 2.86-2.74 (m, 2H, H-8β, H-9), 2.57-2.48 (m, 1H, H-16_{eq}), 2.36-2.26 (m, 1H, H-7β), 2.22 (dd, ^2J = 18.4 Hz, ^3J = 6.4 Hz, 1H, H-10α), 1.98-1.81 (m, 2H, H-15_{eq}, H-16_{ax}), 1.74-1.62 (m, 2H, H-15_{ax}, H-18), 1.55-1.43 (m, 2H, H-8α, H-18), 1.31 (s, 3H, CH_3), 1.17-1.03 (m, 1H, H-19), 0.75-0.63 (m, 1H, H-19). **^{13}C NMR** (101 MHz, $CDCl_3$): 146.79, 141.71, 136.26, 132.30, 128.75, 119.33, 117.01, 116.94 (t, J_{C-F} = 248.5 Hz, $\underline{C}F_2H$), 114.10, 97.08, 79.61, 75.29 (t, J = 20.7 Hz, C-20), 58.25, 58.10, 56.83, 52.98, 47.31, 46.71, 43.46, 35.79, 35.63, 29.89, 29.06, 22.66, 18.90, 17.92. **^{19}F NMR** (282 MHz, $CDCl_3$): -122.91 + -130.18 (AB-system, J_{F-F} = 281.9 Hz, 2F, $C\underline{F_2}H$). **LC-MS (ESI):** m/z calcd for '$C_{26}H_{33}F_2NO_4$' $[M+H]^+$ 462.2; found: $[M+H]^+$ 462.4 (positive ion mode). **HRMS (ESI)** calcd for $C_{26}H_{33}F_2NO_4$ $[M+H]^+$: 462.2456, found: 462.2467.

(5*R*,6*R*,7*R*,20*R*)-17-(Cyclopropylmethyl)-4,5α-epoxy-7-[1-hydroxy-1-(difluoromethyl)ethyl]-3,6-dimethoxy-6,14-*endo*-ethanoisomorphinan (43). Cyclopropylcarbonyl chloride (0.17 g, 1.65 mmol) and anhydrous K_2CO_3 (0.71 g, 5.15 mmol) were added to a solution of **41** (0.30 g, 0.66 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 2 h at 20 °C and quenched with water (15 mL). After stirring the mixture for 10 min, the products were extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The dry residue was dissolved in THF (10 mL) and added dropwise to a vigorously stirred suspension of $LiAlH_4$ (0.30 g, 7.80 mmol) in THF (5 mL). The reaction mixture was heated under reflux for 1 h and cooled to 20 °C. A saturated aqueous solution of NH_4Cl (25 mL) was dropwise added to the mixture and the product was extracted with ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo* to afford **43** (0.21 g, 52%) as yellowish oil.



^{1}H NMR (400 MHz, $CDCl_3$): 6.71 + 6.56 (AB-system, J_{AB} = 8.0 Hz, 2H, H-2 + H-1), 6.03 (dd, ^2J = 56.0 Hz, 1H, $CF_2\underline{H}$), 4.96 (s, 1H, OH), 4.38 (s, 1H, H-5), 3.88 (s, 3H, 3-OCH_3), 3.56 (s, 3H, 6-OCH_3), 3.07-2.95 (m, 2H, H-9, H-10β), 2.88-2.79 (m, 1H, H-8β), 2.62 (dd, ^2J = 11.8 Hz, ^3J = 4.9 Hz, 1H, H-16_{ax}), 2.38 (dd, ^2J = 12.6 Hz, ^3J = 5.8 Hz, 1H, H-16_{eq}), 2.32-2.16 (m, 3H, H-10α, *cyclo*-C_3H_5-$C\underline{H}_2$), 2.12-1.94 (m, 2H, H-7β, H-15_{eq}), 1.89 (ddd, ^2J = 13.3 Hz, ^2J = 6.0 Hz, 1H, H-18), 1.72-1.64 (m, 1H, H-15_{ax}), 1.55-1.45 (m, 2H, H-8α, H-18), 1.32 (s, 3H, CH_3), 1.13 (ddd, ^2J = 12.6 Hz, ^3J = 5.7 Hz, 1H, H-19), 0.86-0.76 (m, 1H, C$\underline{H}$ (from *cyclo*-C_3H_5)), 0.76-0.67 (m, 1H, H-19), 0.55-0.45 + 0.14-0.07 (m + m, 2H + 2H, 2$C\underline{H}_2$ (from *cyclo*-C_3H_5)). **^{13}C NMR** (101 MHz, $CDCl_3$): 146.82, 141.69, 132.42, 128.92, 119.29, 116.97 (t, $^1J_{C\text{-}F}$ = 247.2 Hz, $\underline{C}F_2H$), 114.12, 97.16, 79.66, 75.31 (t, $^2J_{C\text{-}F}$ = 19.5 Hz, C-20), 59.88, 57.99, 56.85, 52.97, 47.35, 46.82, 43.67, 35.72, 35.68, 29.91, 29.17, 22.55, 18.92, 17.97, 9.41, 4.24, 3.34. **^{19}F NMR** (282 MHz, $CDCl_3$): -130.15 + -122.85 (AB-system, J_{AB} = 281.2 Hz, 2F, $C\underline{F}_2H$). **LC-MS (ESI):** m/z calcd for '$C_{27}H_{35}F_2NO_4$' $[M+H]^+$ 476.3; found: $[M+H]^+$ 476.4 (positive ion mode). Found (%): C 68.43, H 7.51, N 2.93, F 8.01; $C_{27}H_{35}F_2NO_4$. Calculated (%): C 68.19, H 7.42, N 2.95, F 7.99.

(5*R*,6*R*,7*R*,20*R*)-17-(Cyclobutylmethyl)-4,5α-epoxy-7-[1-hydroxy-1-(difluoromethyl)ethyl]-3,6-dimethoxy-6,14-*endo*-ethanoisomorphinan (44). Cyclobutylcarbonyl chloride (0.20 g, 1.65 mmol) and anhydrous K_2CO_3 (0.71 g, 5.15 mmol) were added to a solution of **41** (0.30 g, 0.66 mmol) in CH_2Cl_2 (10 mL). After stirring for 2 h at 20 °C, the mixture was quenched with water (15 mL), stirred for 10 min and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The dry residue was dissolved in THF (10 mL) and added dropwise to a vigorously stirred suspension of $LiAlH_4$ (0.26 g, 6.80 mmol) in THF (5 mL). The reaction mixture was refluxed for 1 h and cooled to 20 °C. A saturated aqueous solution of NH_4Cl (25 mL) was dropwise added to the mixture on stirring and the product was extracted with ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo* to afford **44** (0.17 g, 50%) as yellowish oil.



^{1}H NMR (400 MHz, $CDCl_3$): 6.71 + 6.56 (AB-system, J_{AB} = 7.9 Hz, 2H, H-2 + H-1), 6.01 (dd, ^2J = 56.2 Hz, 1H, $CF_2\underline{H}$), 4.93 (s, 1H, OH), 4.36 (s, 1H, H-5), 3.87 (s, 3H, 3-OCH_3), 3.54 (s, 3H, 6-OCH_3), 3.04 (d, ^2J = 18.5 Hz, 1H, H-10β), 2.85-2.75 (m, 1H, H-8β), 2.67 (d, ^3J = 6.2 Hz, 1H, H-9), 2.49-2.38 (m, 4H, H-16_{ax}, *cyclo*-C_4H_7-$C\underline{H}_2$, C$\underline{H}$ (from *cyclo*-C_4H_7)), 2.31 (ddd, ^2J = 11.8 Hz, ^3J = 3.8 Hz, H-16_{eq}), 2.22 (dd, ^2J = 18.7 Hz, ^3J = 6.5 Hz,

H-10α), 2.10-1.77 (m, 7H, H-15, 3C$\underline{H_2}$ (from *cyclo*-C_4H_7)), 1.73-1.59 (m, 3H, H-15, H-18, H-18), 1.54-1.39 (m, 1H, H-8α), 1.30 (s, 3H, CH_3), 1.08 (ddd, ^2J = 12.5 Hz, ^3J = 5.9 Hz, H-19), 0.74-0.62 (m, 1H, H-19). **^{13}C NMR** (101 MHz, $CDCl_3$): 146.80, 141.68, 132.42, 128.93, 119.32, 116.96 (t, $J_{C\text{-}F}$ = 248.1 Hz, $\underline{C}F_2H$), 114.13, 97.11, 79.69, 75.30 (t, $J_{C\text{-}F}$ = 20.1 Hz, C-20), 61.23, 58.50, 56.86, 52.95, 47.33, 46.70, 43.82, 35.76, 34.22, 29.87, 29.82, 29.12, 27.40, 26.88, 23.01, 18.82, 18.76, 17.95. **^{19}F NMR** (282 MHz, $CDCl_3$): -130.14 + - 122.86 (AB-system, J_{AB} = 283.7 Hz, 2F, $C\underline{F_2}H$). **LC-MS (ESI):** m/z calcd for '$C_{28}H_{37}F_2NO_4$' $[M+H]^+$ 490.3; found: $[M+H]^+$ 490.5 (positive ion mode). **HRMS (ESI)** calcd for $C_{28}H_{37}F_2NO_4$ $[M+H]^+$: 490.2769, found: 490.2781.

3. Crystal structure data

X-ray crystallography. X-ray diffraction data for **25**, **28**, 20*R*-**31**, **32**, **36**, **38**, **39b** and **39c** were collected at 100 K with a Bruker Quest D8 CMOS diffractometer; those for **15**, at 100 K and **33**, at 120 K with a Bruker APEXII DUO CCD diffractometer, both using graphite monochromated Mo-Kα radiation (lλ = 0.71073 Å). Using Olex2 [3], the structures were solved with the ShelXT [4] structure solution program using Intrinsic Phasing and refined with the XL [5] refinement package using Least-Squares minimization against F^2 in anisotropic approximation for non-hydrogen atoms. Hydrogen atoms of hydroxyl groups as well as those of lattice methanol in **31** and **32**, ethanol in **36** and water in **36**, **39b** and **39c** were located from difference Fourier synthesis while the positions of other hydrogen atoms were calculated, and they all were refined in isotropic approximation within the riding model. Disordered solvent molecules of methanol in **25** were treated as a diffuse contribution into the overall scattering without specific atom positions. Crystal data and structure refinement parameters are given in Table S1 CCDC 2296708 (**15**), 2291939 (**25**), 2291933 (**28**), 2291936 (20*R*-**31**), 2291934 (**32**), 2294268 (**33**), 2291940 (**36**), 2291935 (**38**), 2291938 (**39b**) and 2291937 (**39c**) contain the supplementary crystallographic data for this paper.

Table S1. Crystal data and structure refinement parameters for the compounds **15**, **25**, **28**, 20*R*-**31**, **32**, **33**, 20*S*-**36**, **38**, **39b** and **39c.**

Compound	15	25	28	20*R*-31	32	33	20*S*-36	38	39b	39c
Empirical formula	$C_{23}H_{24}F_3NO_4$	$C_{23}H_{29}F_2NO_4$	$C_{23}H_{27}F_2NO_4$	$C_{25}H_{33}F_2NO_5$	$C_{25}H_{33}F_2NO_5$	$C_{25}H_{35}F_2NO_5$	$C_{26}H_{39}F_2NO_6$	$C_{23}H_{26}F_2N_2O_4$	$C_{26}H_{37}F_2NO_5$	$C_{27}H_{39}F_2NO_5$
Formula weight	435.43	421.47	419.45	465.52	465.52	467.54	499.58	432.46	481.56	495.59
T, K	100	100	100	100	100	120	100	100	100	100
Crystal system	Orthorhombic	Orthorhombic	Monoclinic	Orthorhombic	Monoclinic	Orthorhombic	Orthorhombic	Orthorhombic	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12$	$P2_1$	$P2_12_12_1$	C2	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Z	4	4	2	4	4	4	4	4	4	4
a, Å	9.1217(3)	12.2544(3)	8.7371(4)	7.7954(2)	40.487(3)	7.888(5)	9.5587(9)	7.7726(4)	9.4825(3)	9.3792(2)
b, Å	11.2737(3)	24.9923(7)	13.1143(5)	12.3806(2)	7.3959(4)	12.342(8)	10.1828(8)	11.5067(6)	12.4436(4)	12.5351(2)
c, Å	19.5547(5)	7.2291(2)	8.7598(4)	23.4227(5)	7.5817(5)	23.321(15)	24.801(2)	22.6755(10)	19.8848(5)	20.4300(3)
α, °	90	90	90	90	90	90	90	90	90	90
β, °	90	90	107.946(3)	90	95.636(7)	90	90	90	90	90
γ, °	90	90	90	90	90	90	90	90	90	90
V, Å^3	2010.91(10)	2214.02(10)	954.87(7)	2260.57(8)	2259.3(2)	2271(3)	2414.0(4)	2028.03(17)	2346.33(12)	2401.94(7)
D_{calc} (g cm^{-1})	1.438	1.264	1.459	1.368	1.369	1.368	1.375	1.416	1.363	1.370
μ, cm^{-1}	1.16	0.97	1.12	1.05	1.05	1.05	1.06	1.09	1.04	1.03
F(000)	912	896	444	992	992	1000	1072	912	1032	1064
$2\Theta_{max}$, °	52	58	56	58	58	58	56	58	56	58
Reflections measured	20876	29109	11851	30248	20675	28460	59479	26533	29168	32636
Independent reflections	3938	5876	4617	6003	5921	6037	5837	5347	5664	6392
Observed reflections [I > 2σ(I)]	3938	5619	3566	5816	4773	5269	4932	4287	4926	5902
Parameters	283	285	287	303	344	303	332	289	311	331
R1	0.0321	0.0373	0.0565	0.0333	0.0729	0.0412	0.0982	0.0673	0.0382	0.0391
wR2	0.0742	0.0967	0.1279	0.0894	0.1674	0.1019	0.2272	0.1573	0.0888	0.1007
GOF	1.407	1.028	1.027	1.061	1.073	1.017	1.142	1.074	1.020	1.064
$\Delta\rho_{max}$/ $\Delta\rho_{min}$ (e*Å^{-3})	0.19/-0.19	0.348/-0.232	0.305/-0.303	0.426/-0.212	0.382/-0.311	0.342/-0.237	0.443/-0.608	0.361/-0.292	0.234/-0.187	0.327/-0.198

4. Copies of NMR spectra

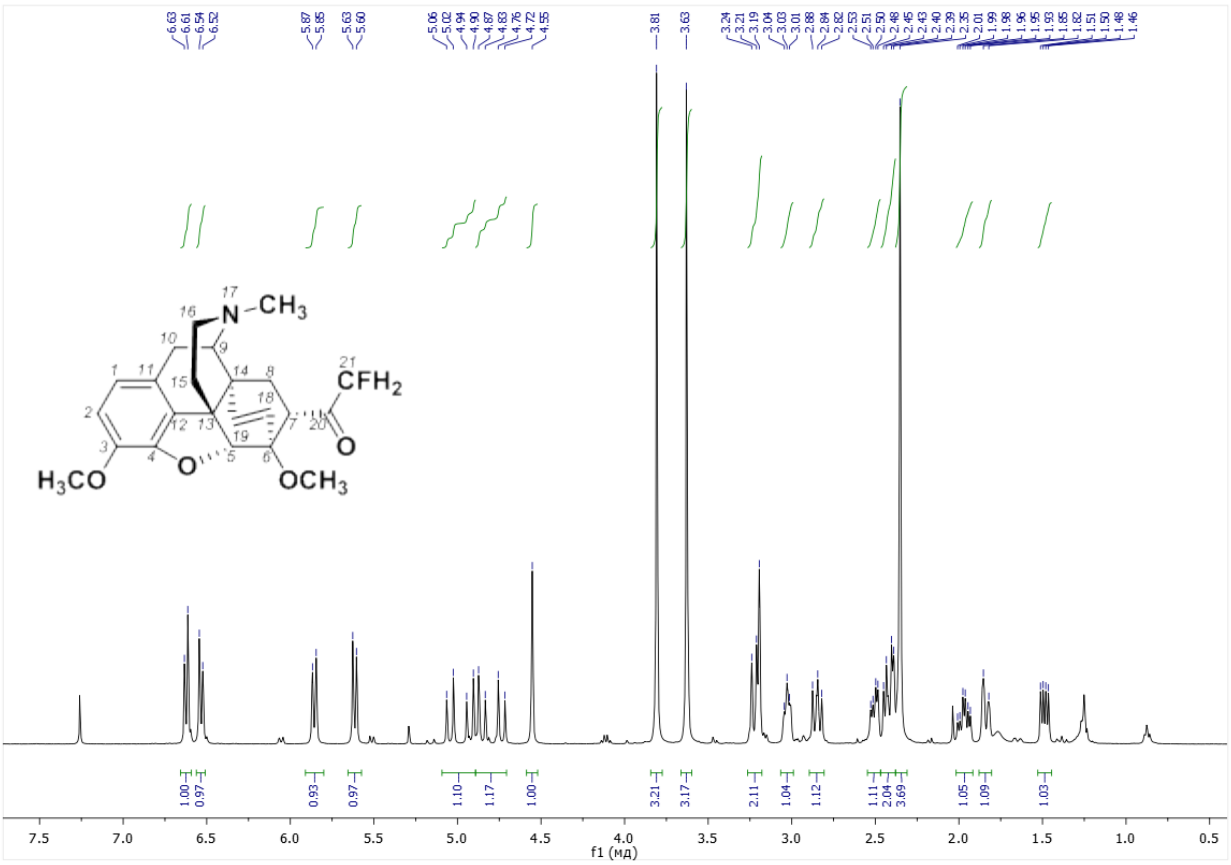


Figure S11. ^{1}H NMR spectra of compound **11**.

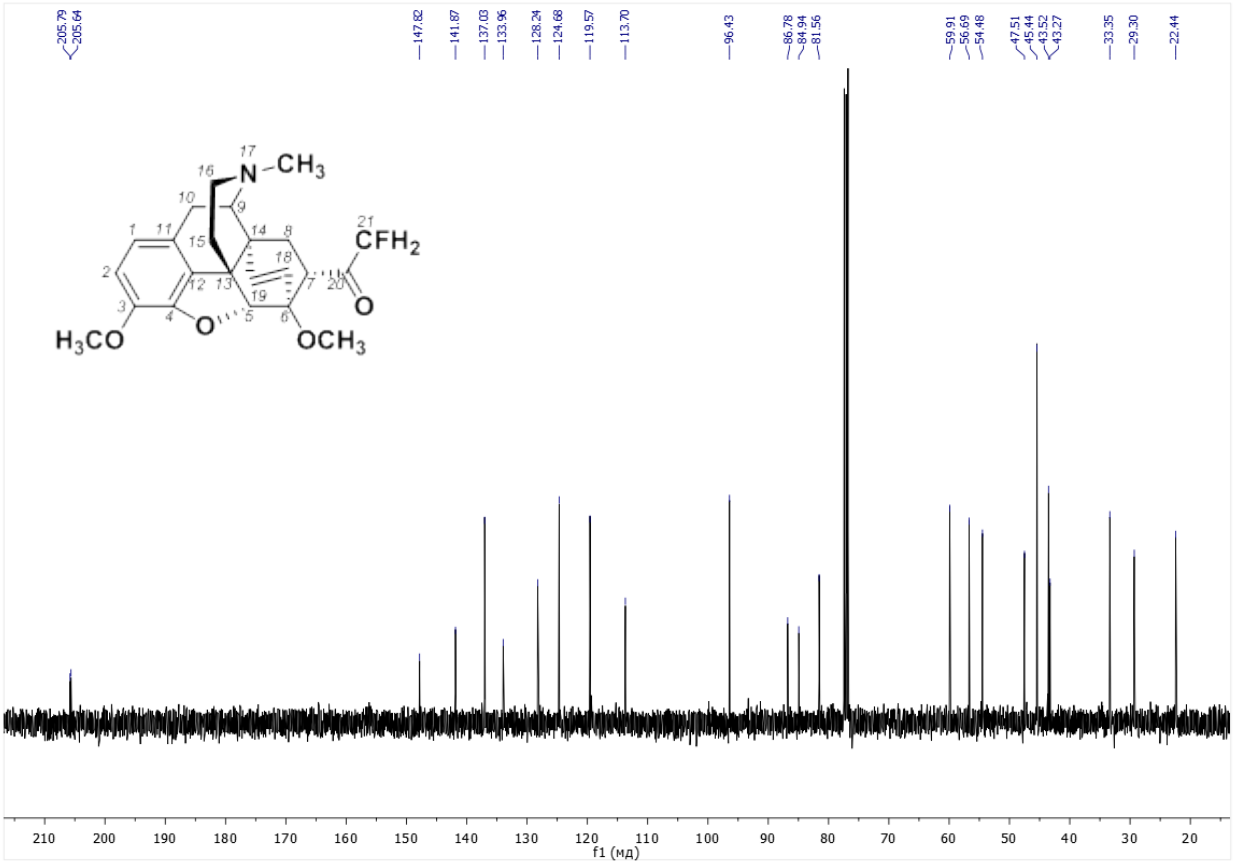


Figure S12. ^{13}C NMR spectra of compound **11**.

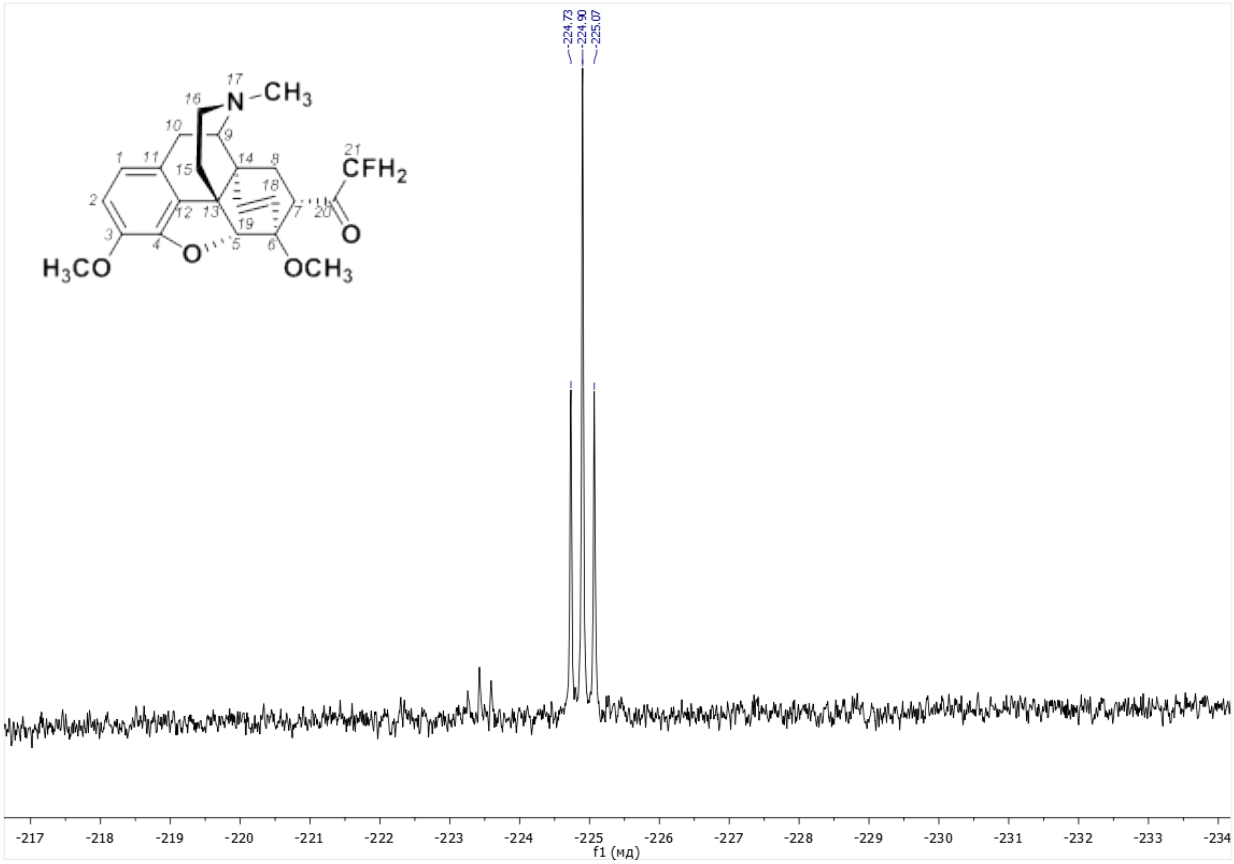


Figure S13. ^{19}F NMR spectra of compound **11**.

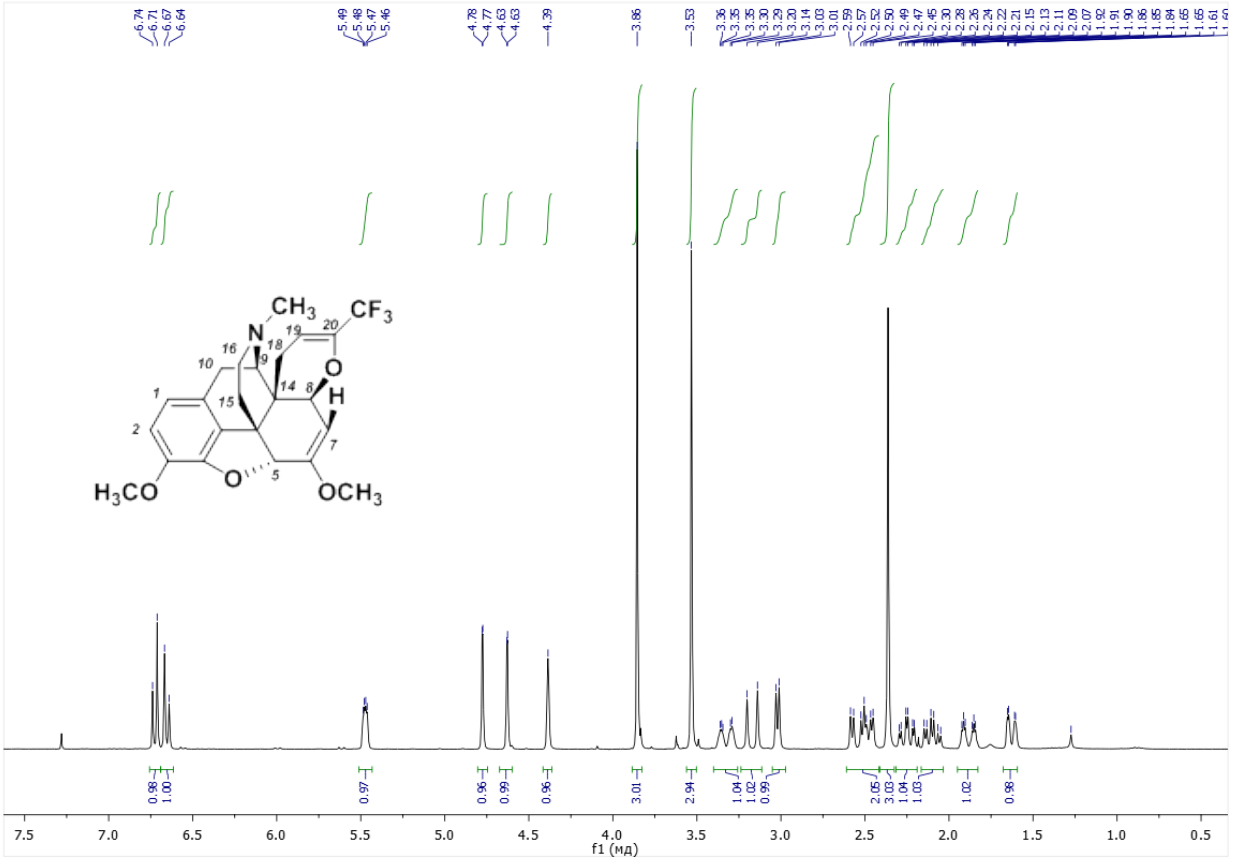


Figure S14. ^{1}H NMR spectra of compound **15**.

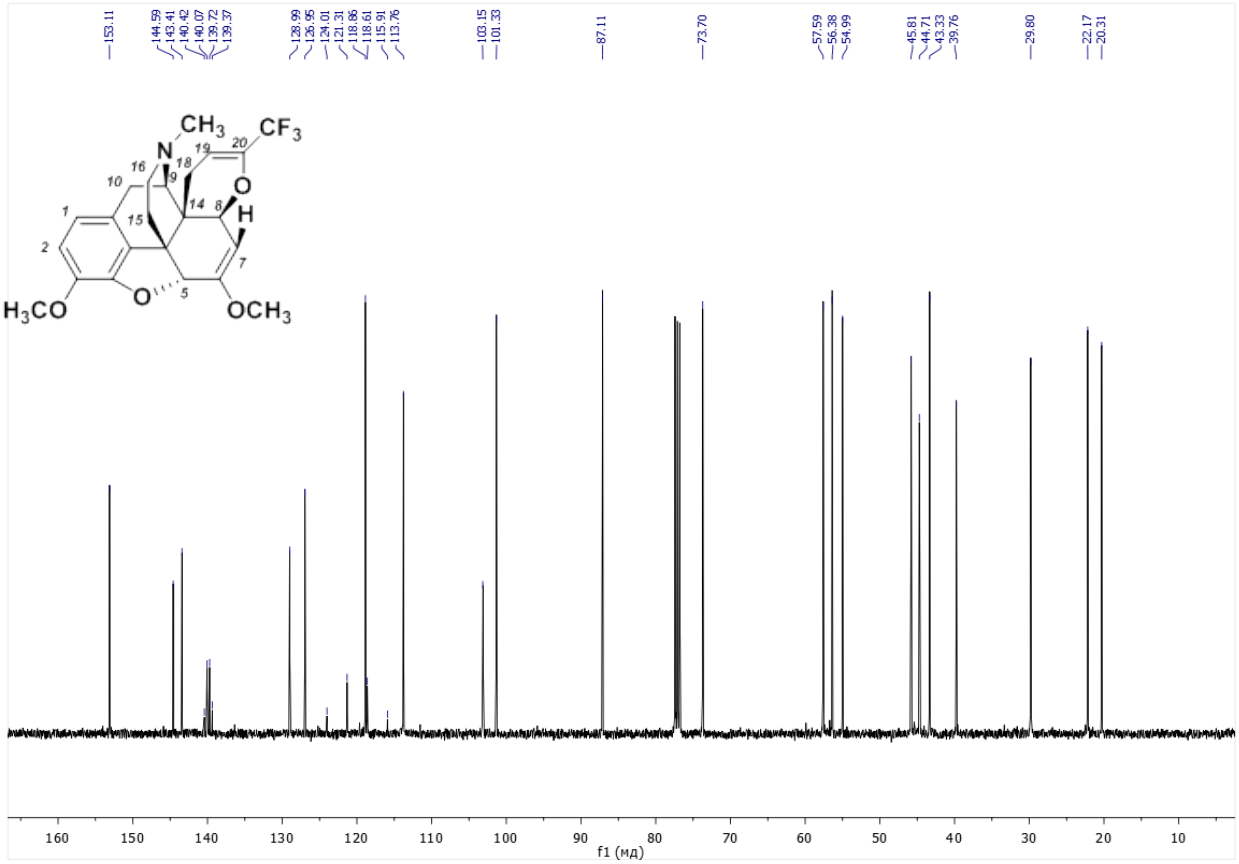


Figure S15. ^{13}C NMR spectra of compound **15**.

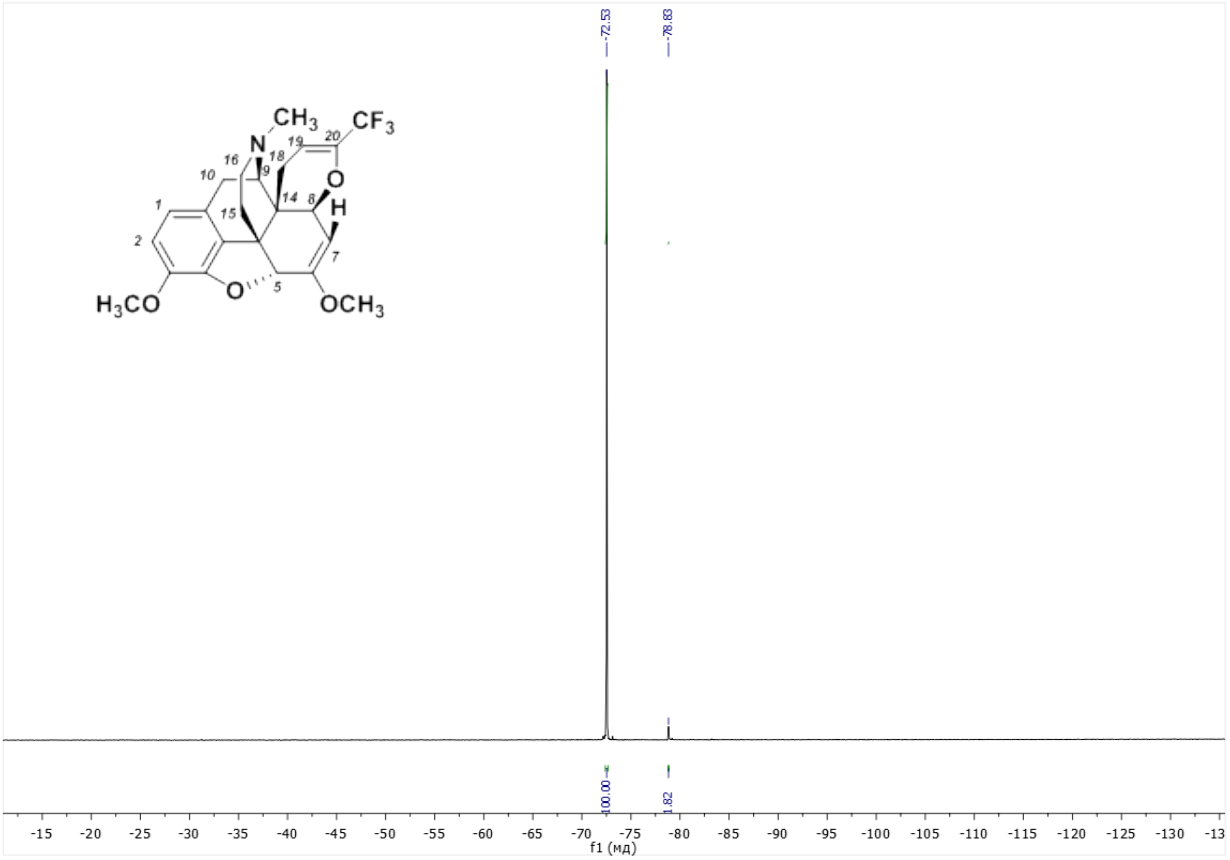


Figure S16. $^{19}F\{^{1}H\}$ NMR spectra of compound **15**.

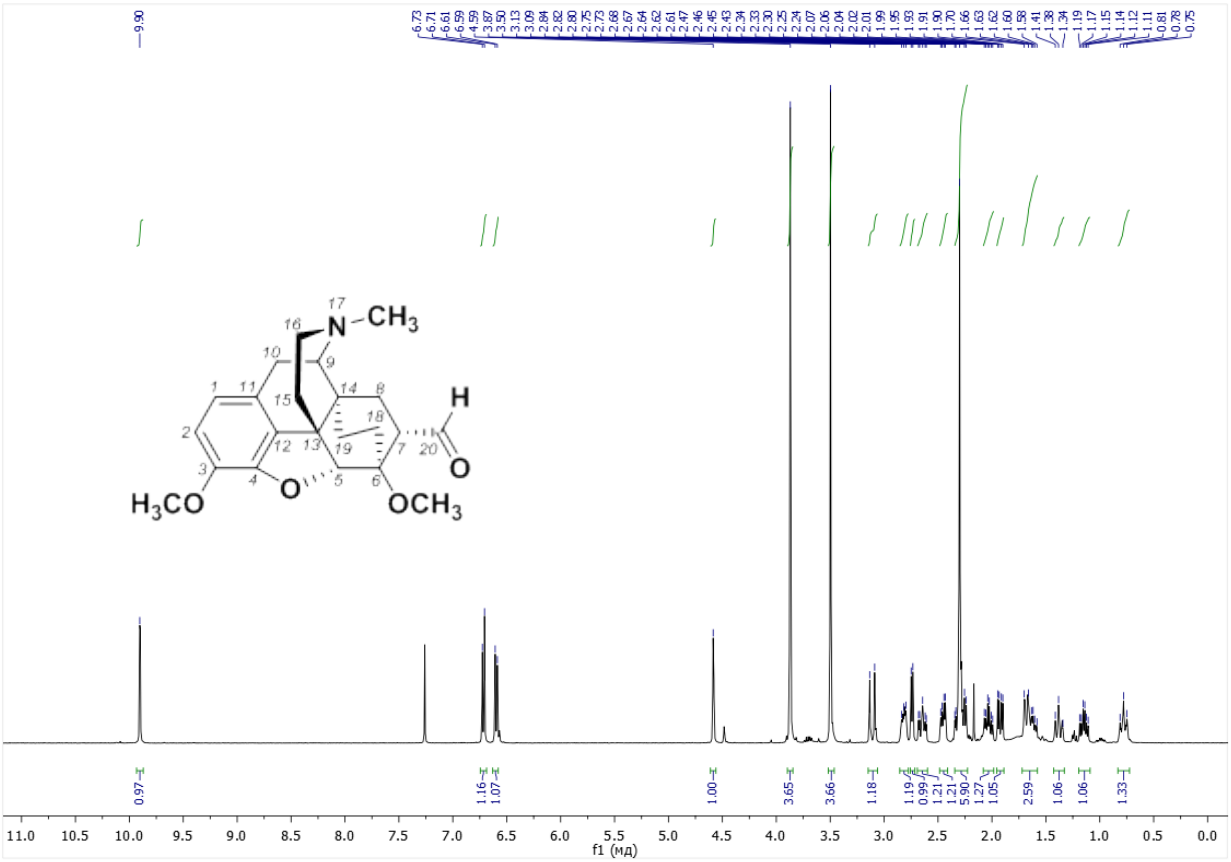


Figure S17. ^{1}H NMR spectra of compound **18**.

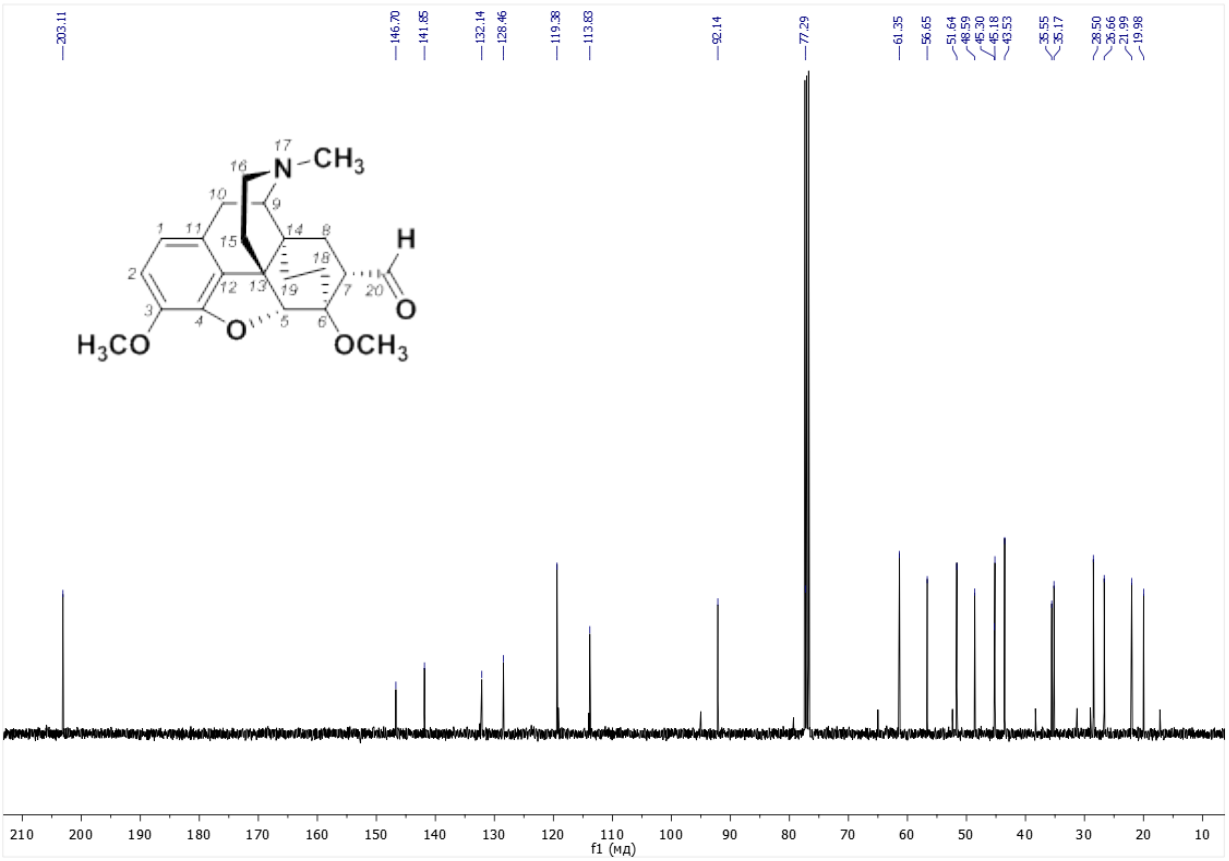


Figure S18. ^{13}C NMR spectra of compound **18**.

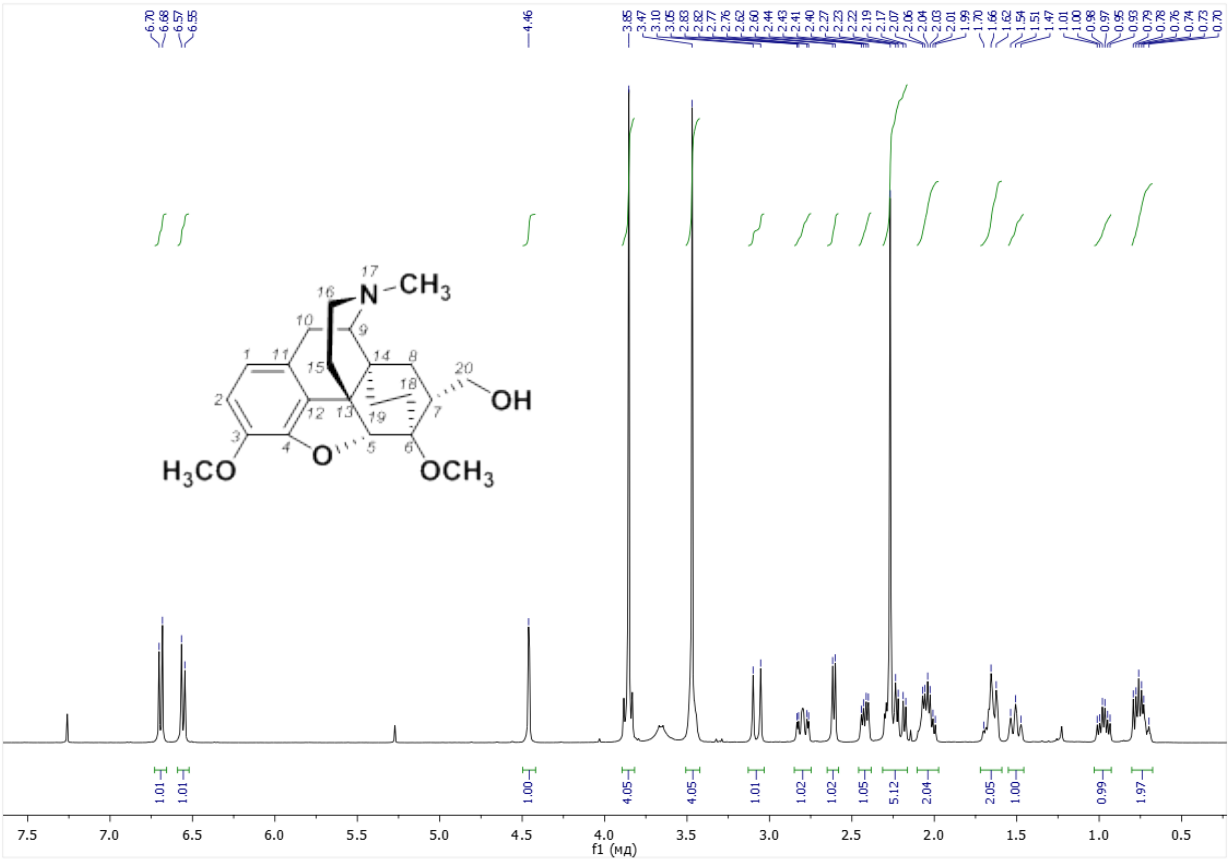


Figure S19. ^{1}H NMR spectra of compound **19**.

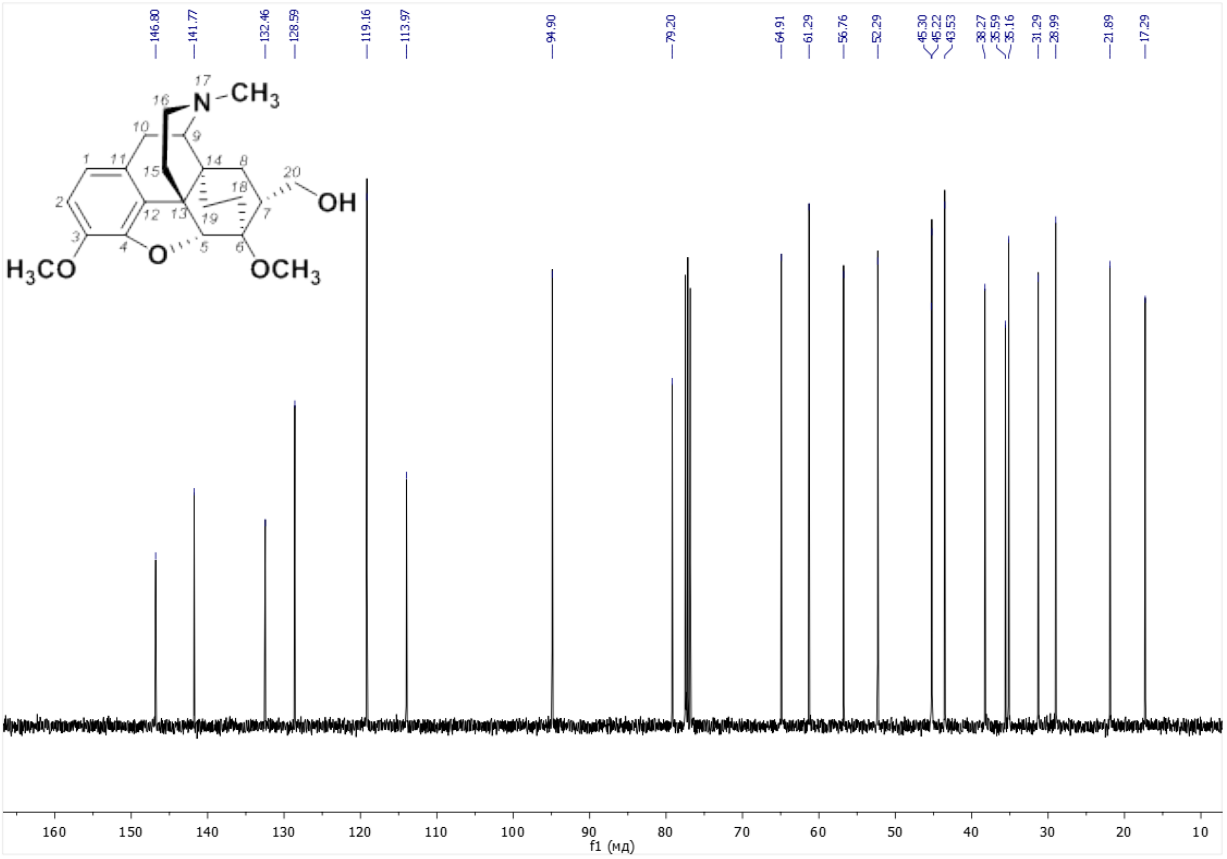


Figure S20. ^{13}C NMR spectra of compound **19**.

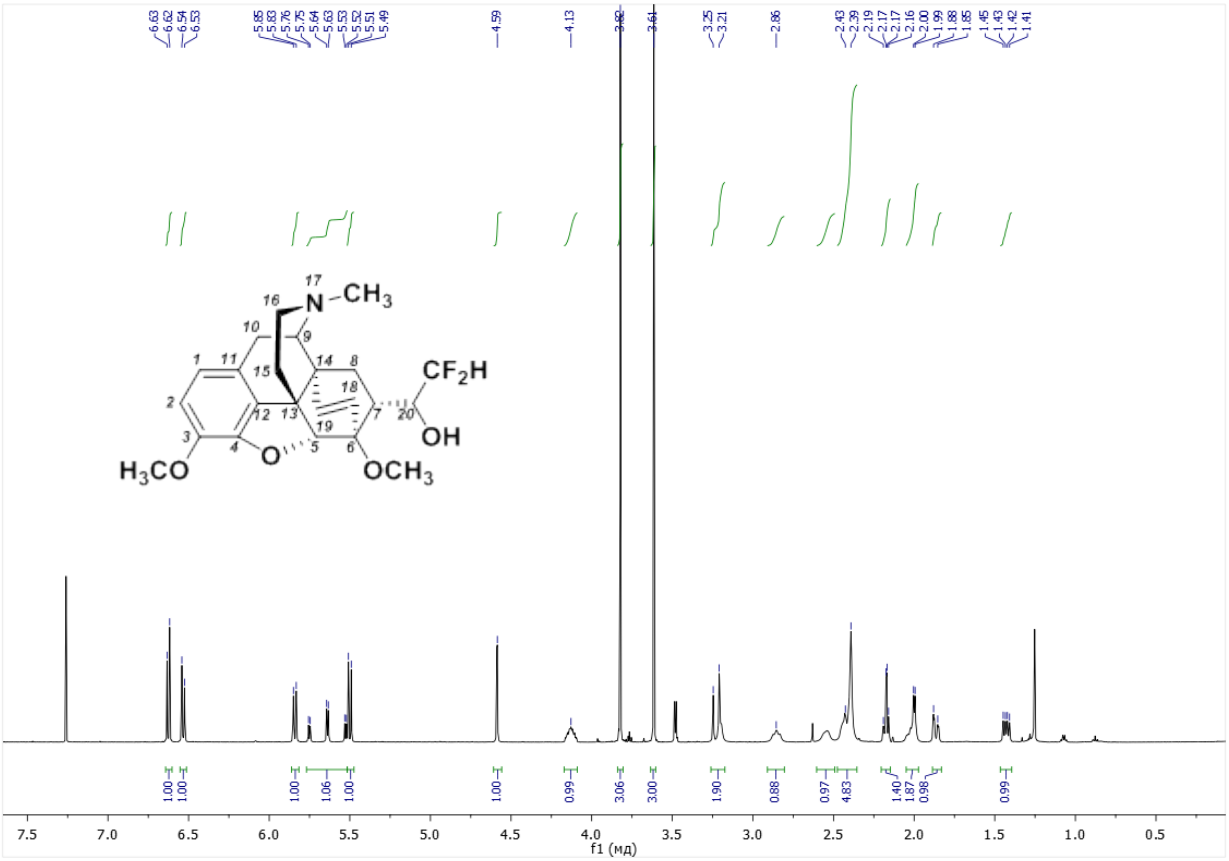


Figure S21. [1]H NMR spectra of compound **26 (1st epimer)**.

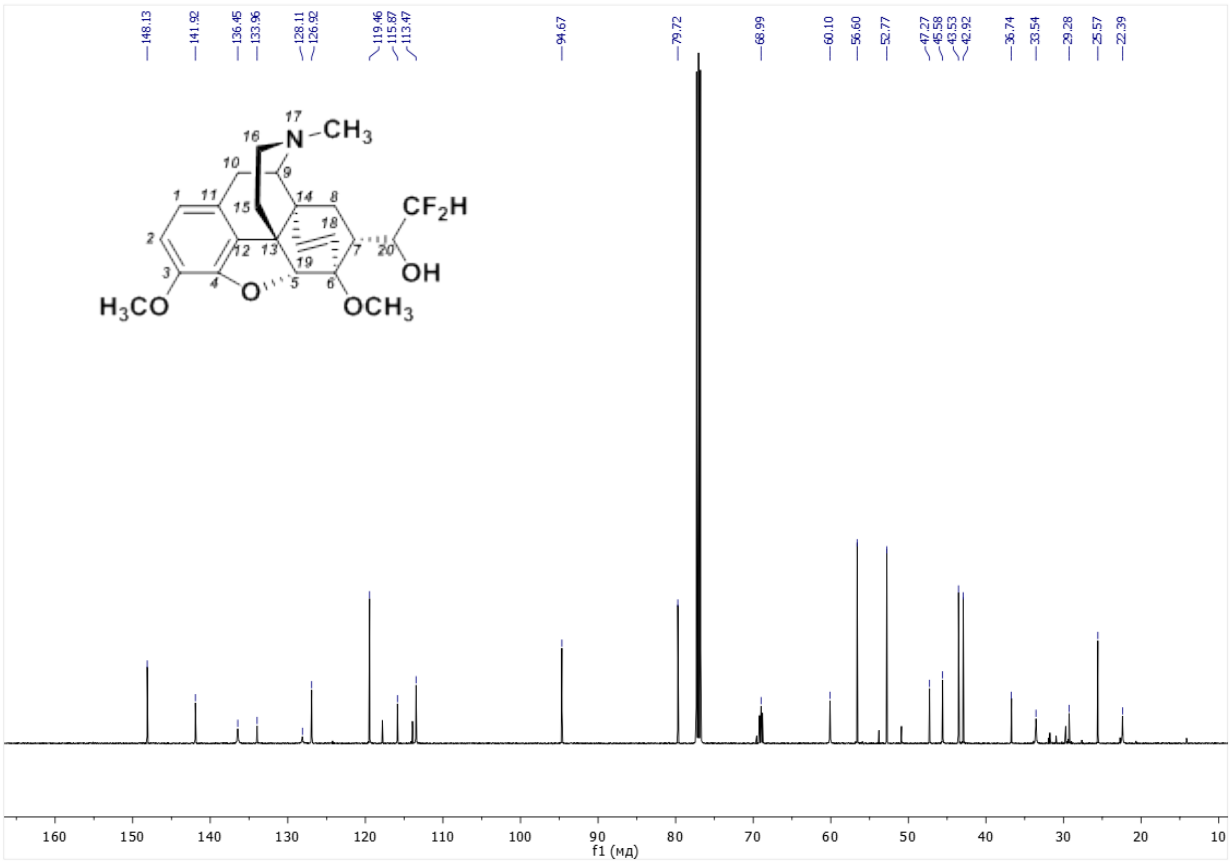


Figure S22. [13]C NMR spectra of compound **26 (1st epimer)**.

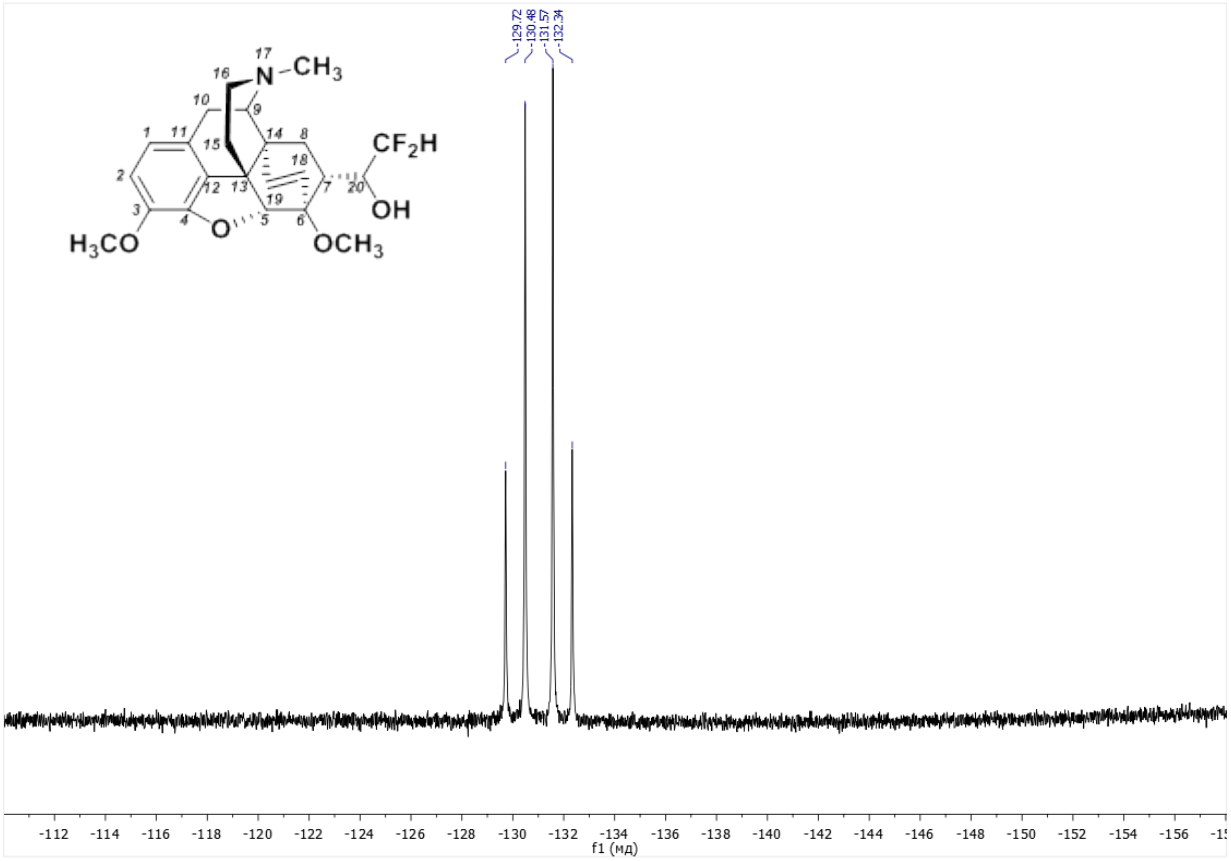


Figure S23. $^{19}F\{^{1}H\}$ NMR spectra of compound **26 (1st epimer)**.

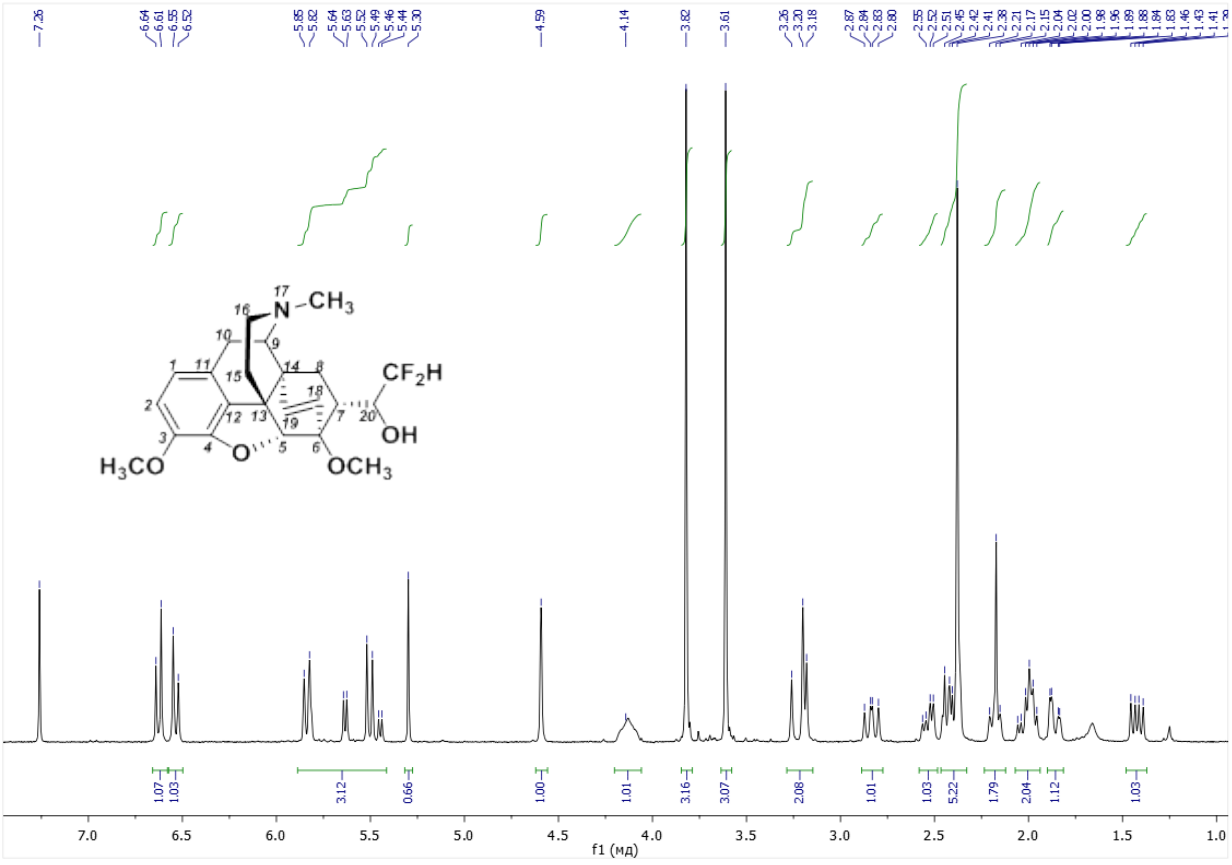


Figure S24. ^{1}H NMR spectra of compound **26 (2nd epimer)**.

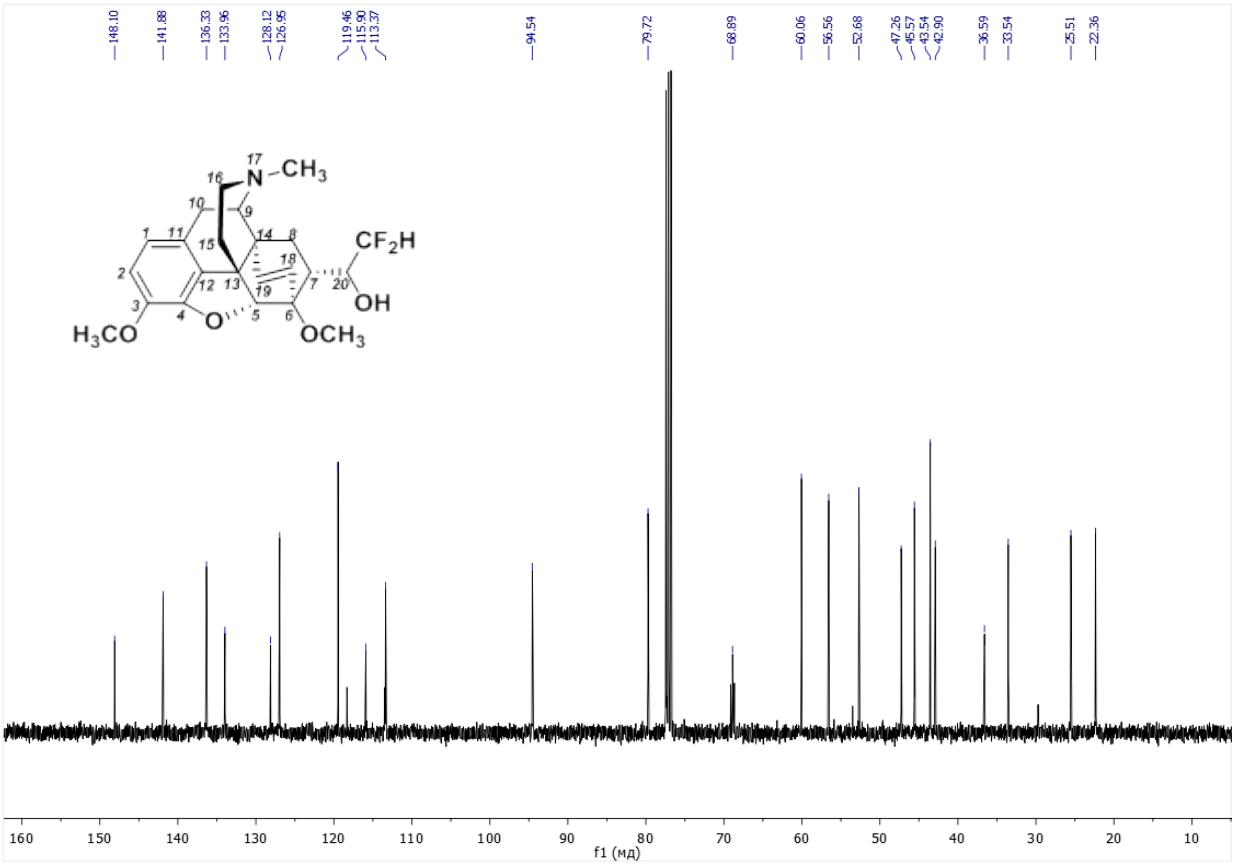


Figure S25. ^{13}C NMR spectra of compound **26 (2nd epimer)**.

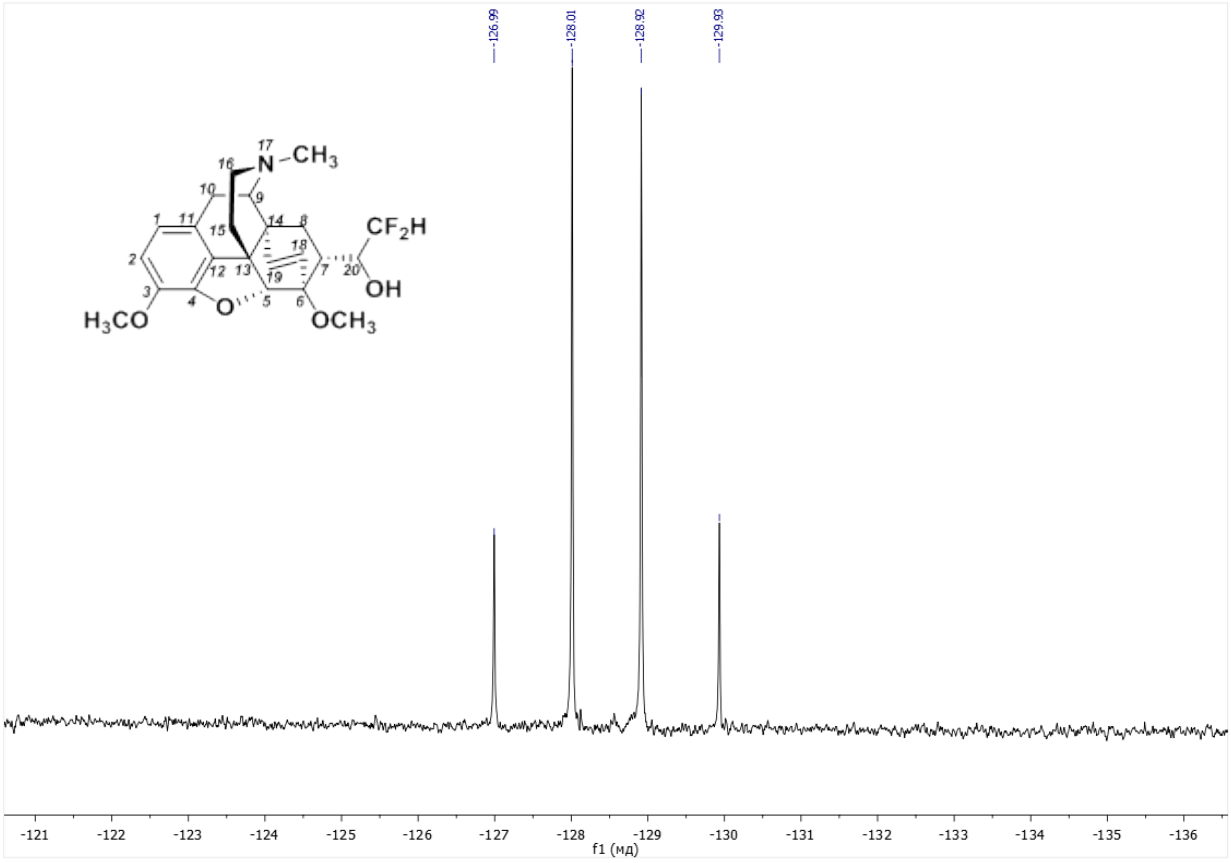


Figure S26. $^{19}F\{^{1}H\}$ NMR spectra of compound **26 (2nd epimer)**.

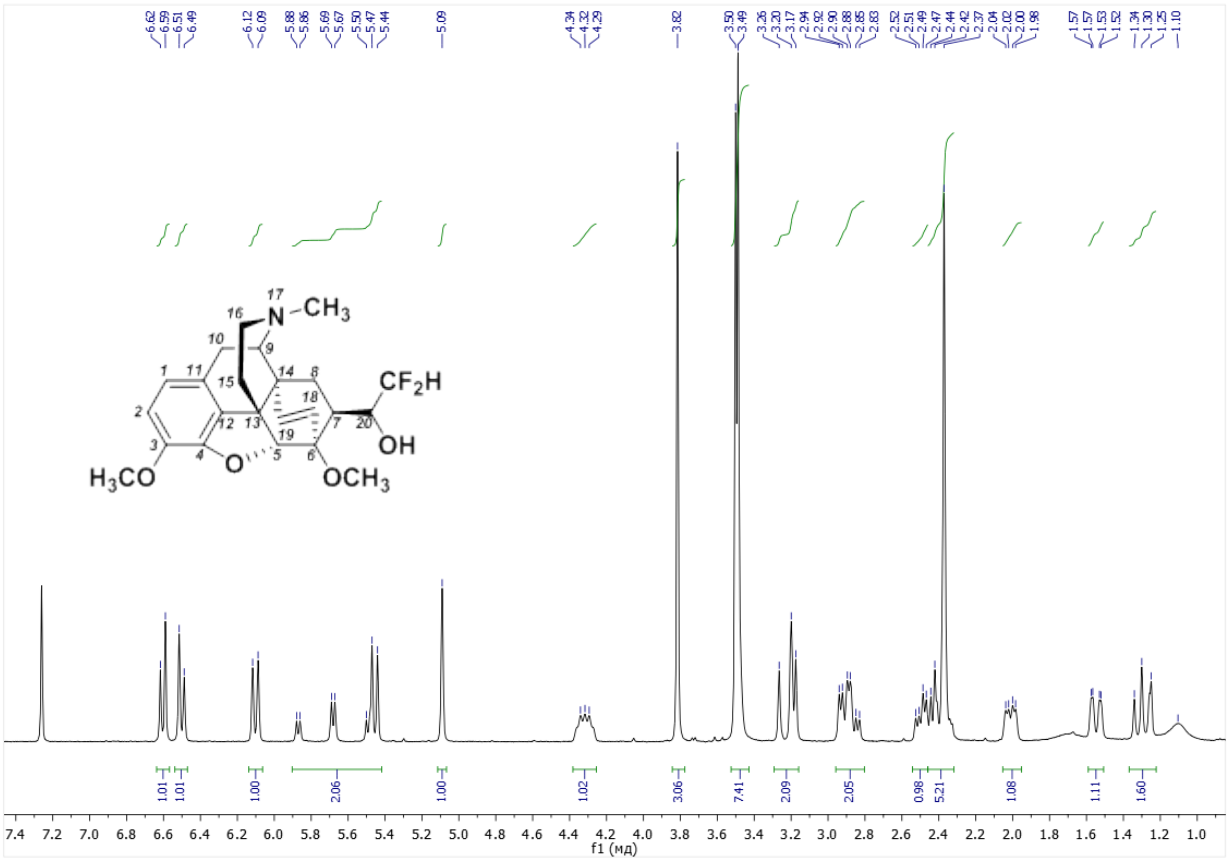


Figure S27. ^{1}H NMR spectra of compound **27**.

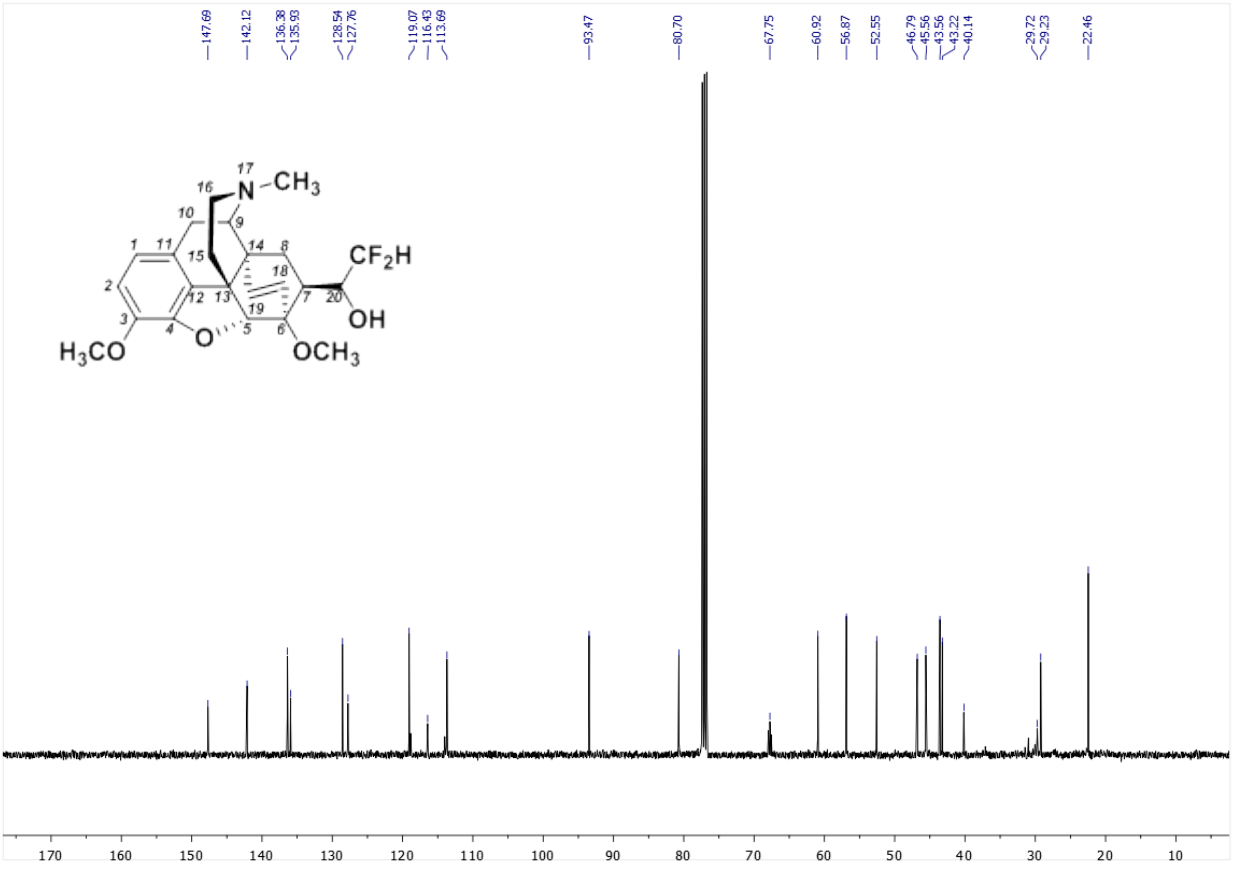


Figure S28. ^{13}C NMR spectra of compound **27**.

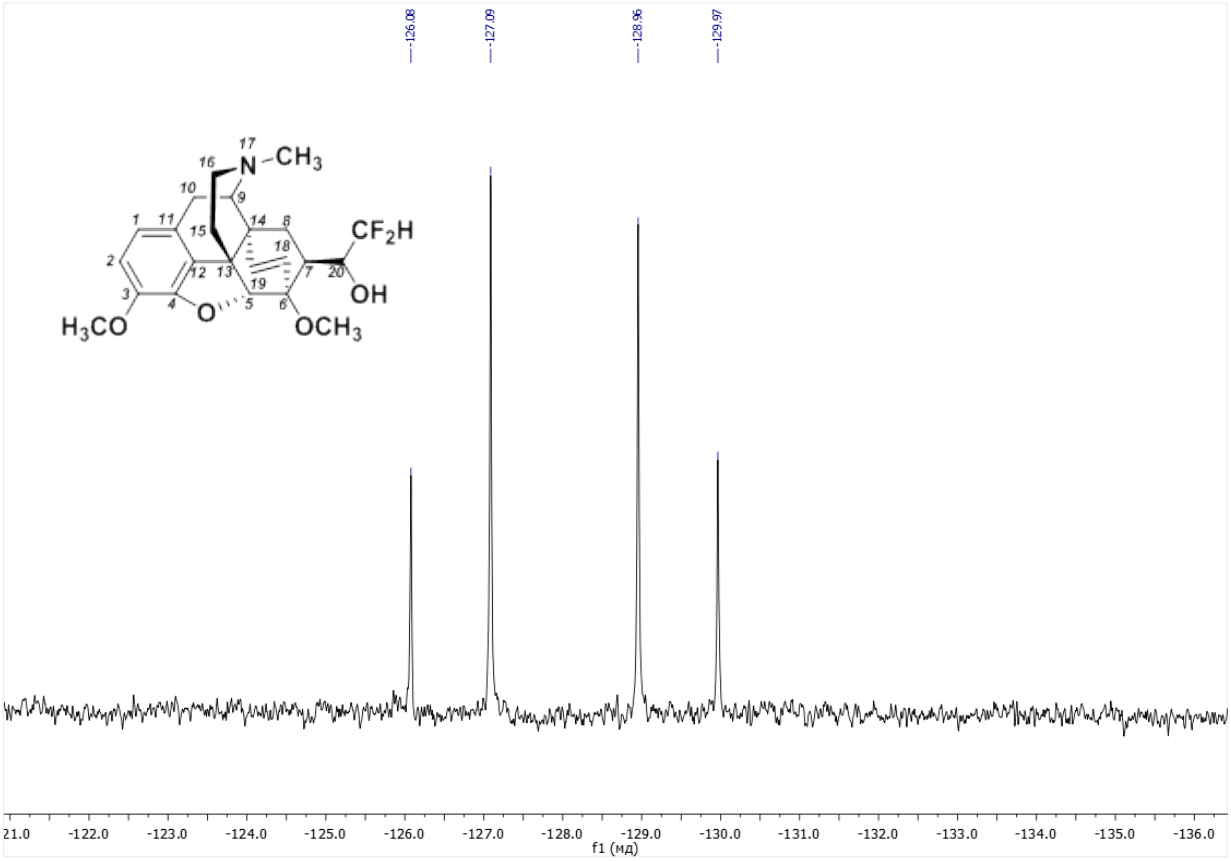


Figure S29. $^{19}F\{^{1}H\}$ NMR spectra of compound **27**.

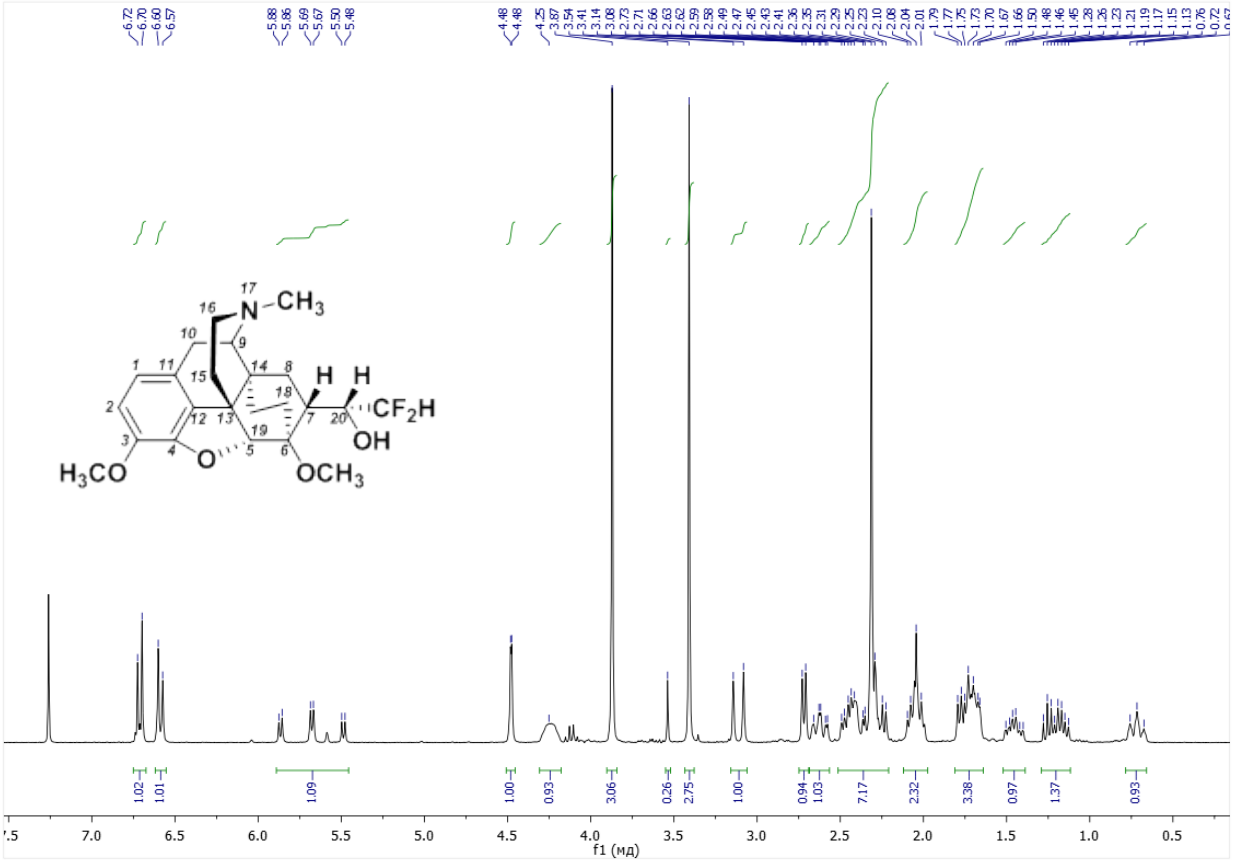


Figure S30. ^{1}H NMR spectra of compound **24**.

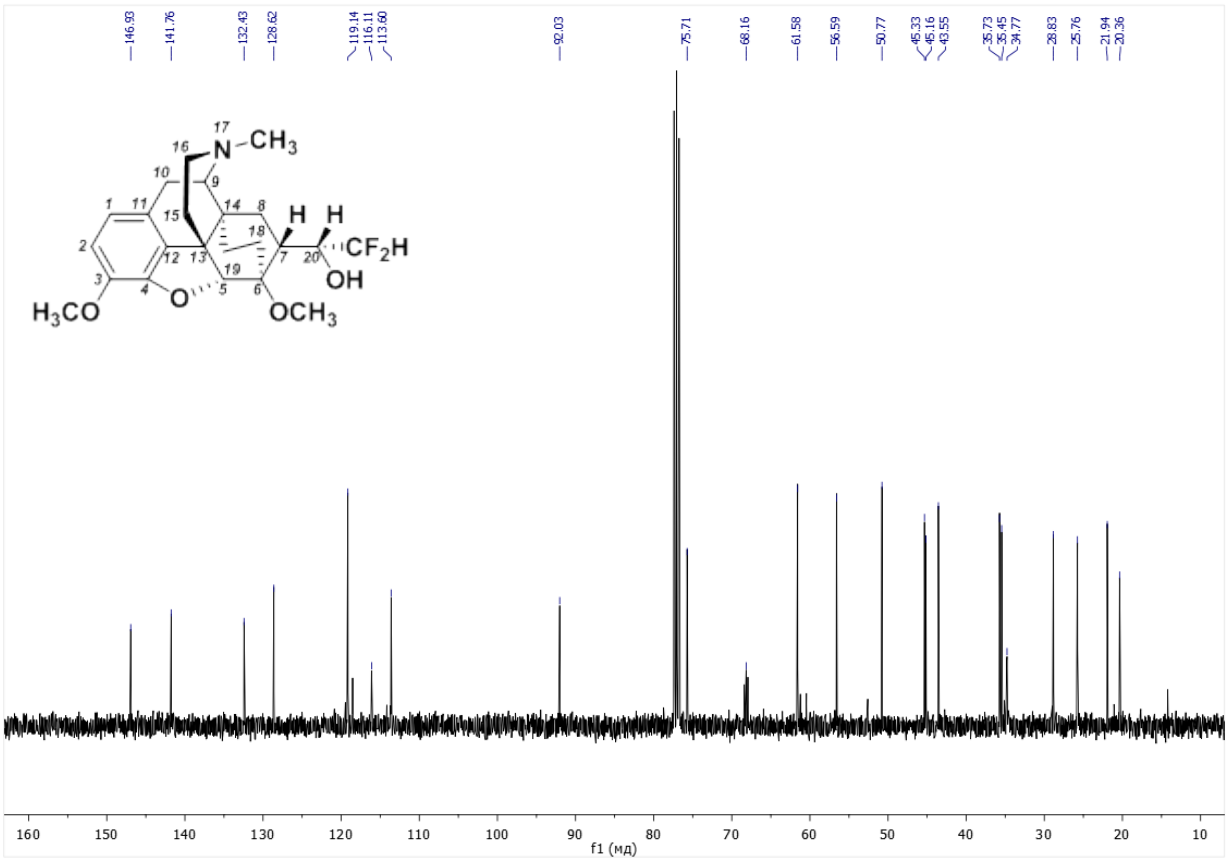


Figure S31. ^{13}C NMR spectra of compound **24**.

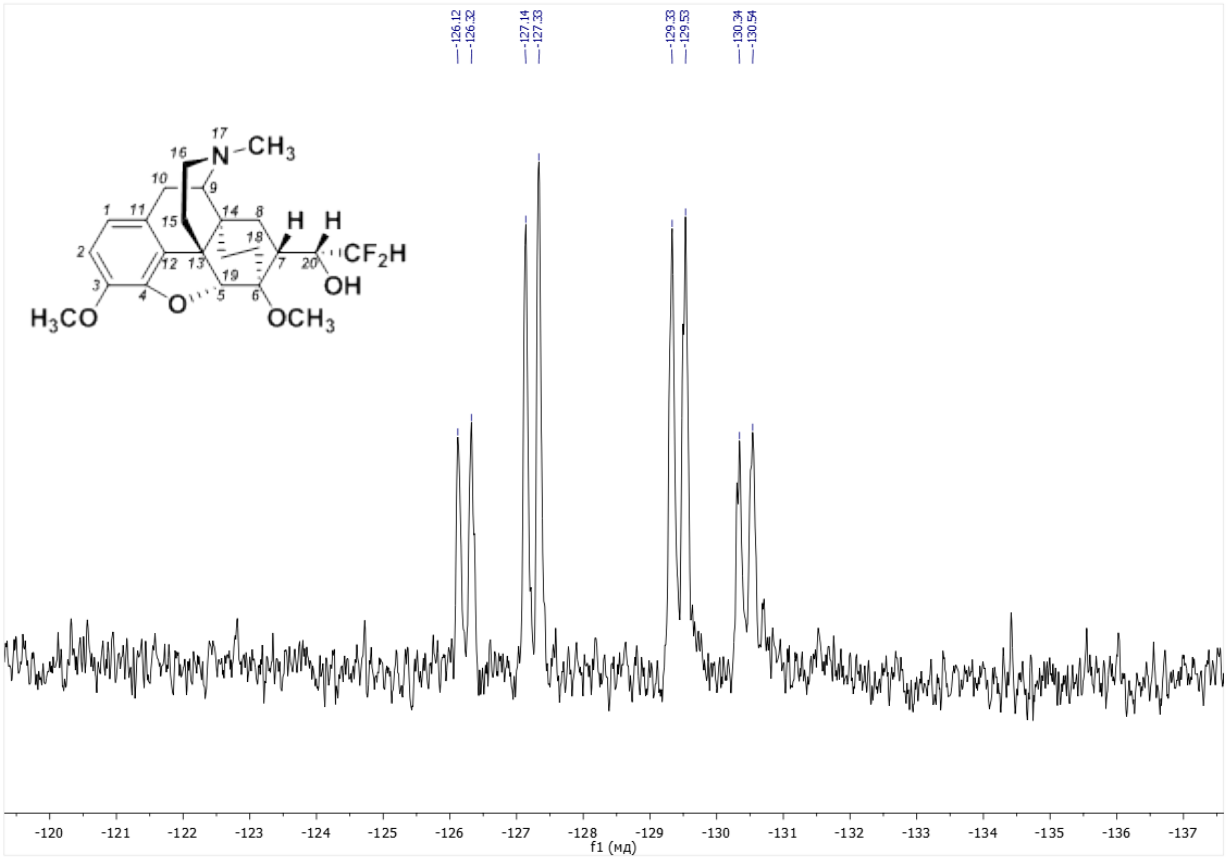


Figure S32. ^{19}F NMR spectra of compound **24**.

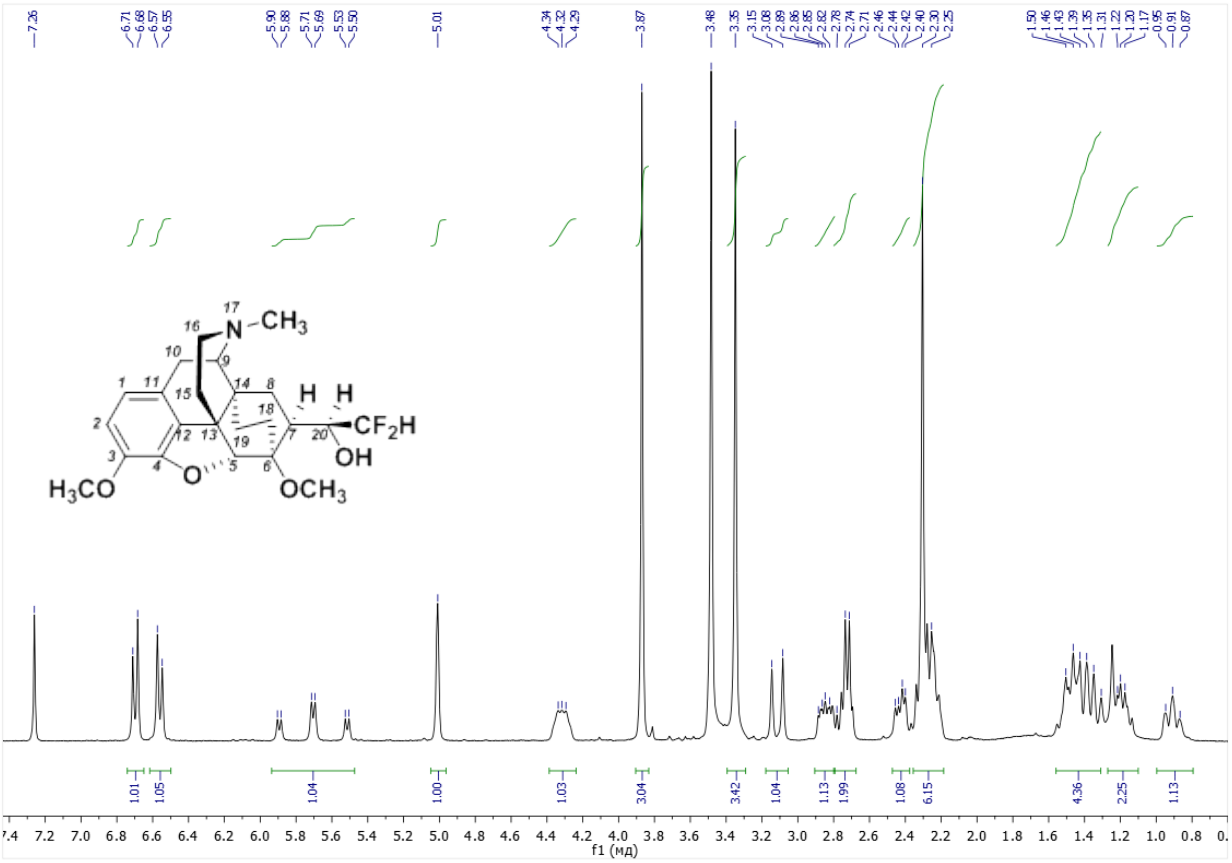


Figure S33. ^{1}H NMR spectra of compound **25**.

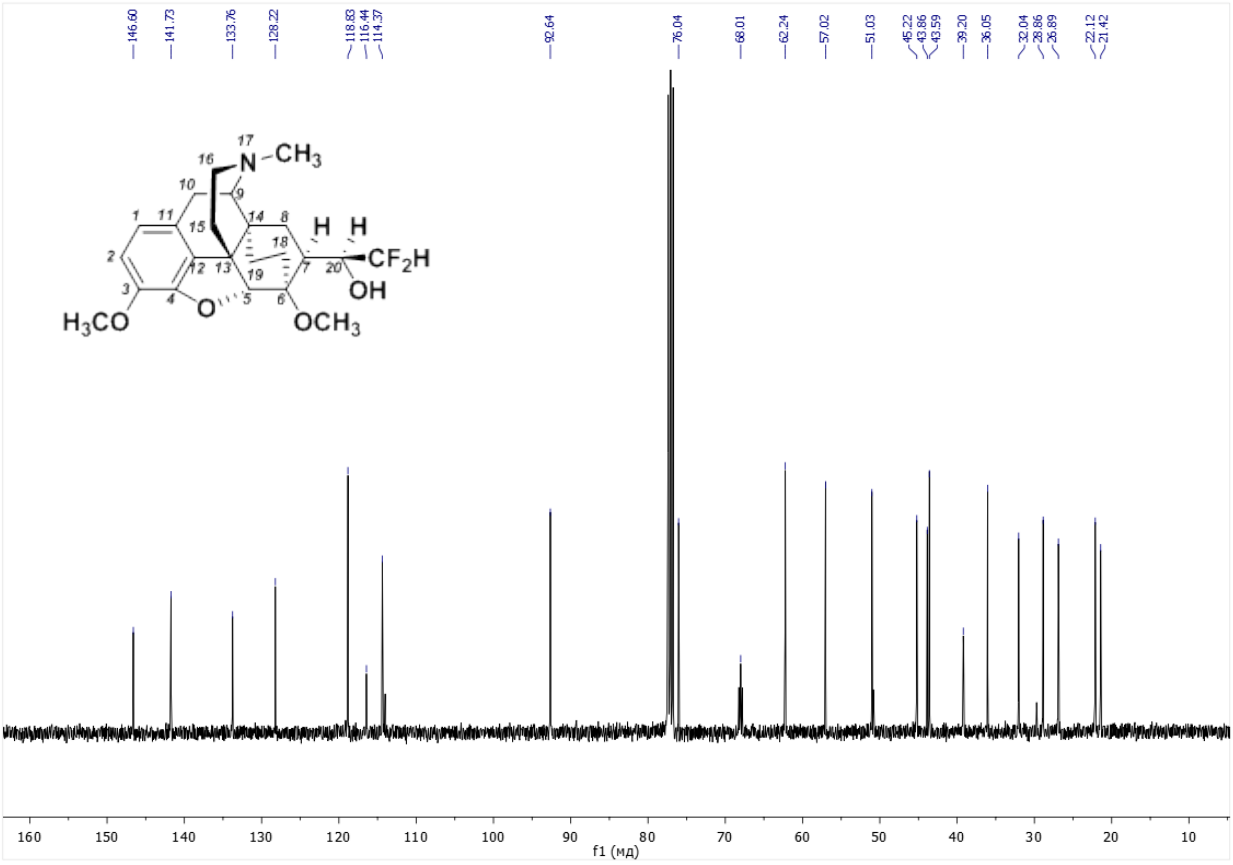


Figure S34. ^{13}C NMR spectra of compound **25**.

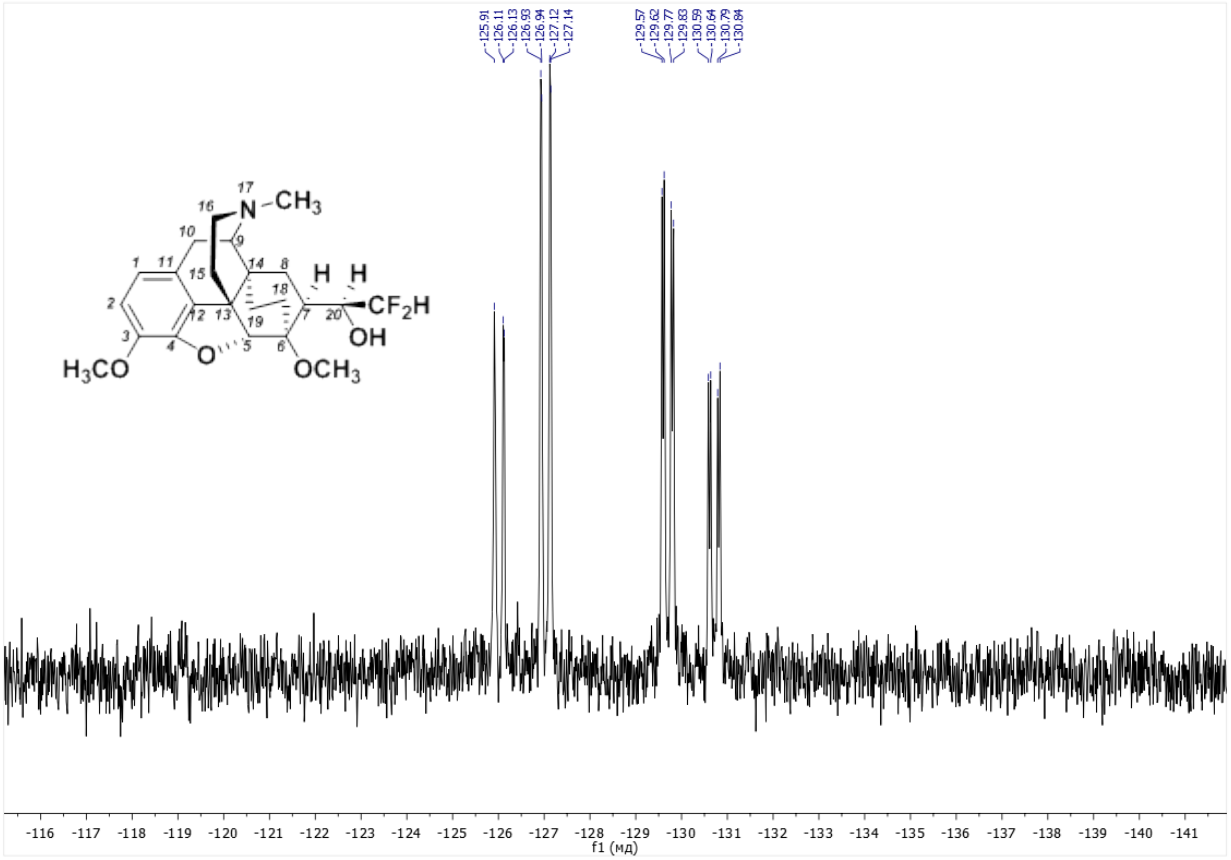


Figure S35. ^{19}F NMR spectra of compound **25**.

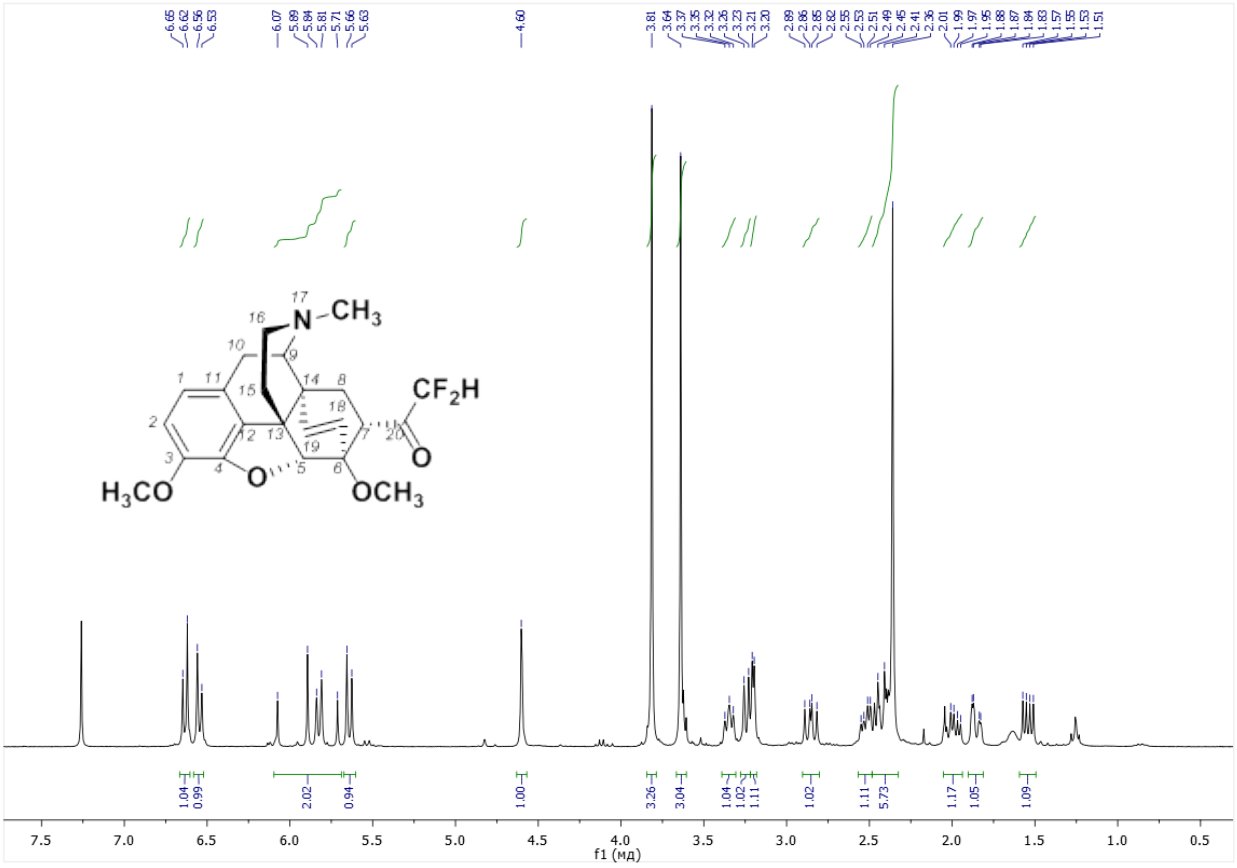


Figure S36. ^{1}H NMR spectra of compound **10**.

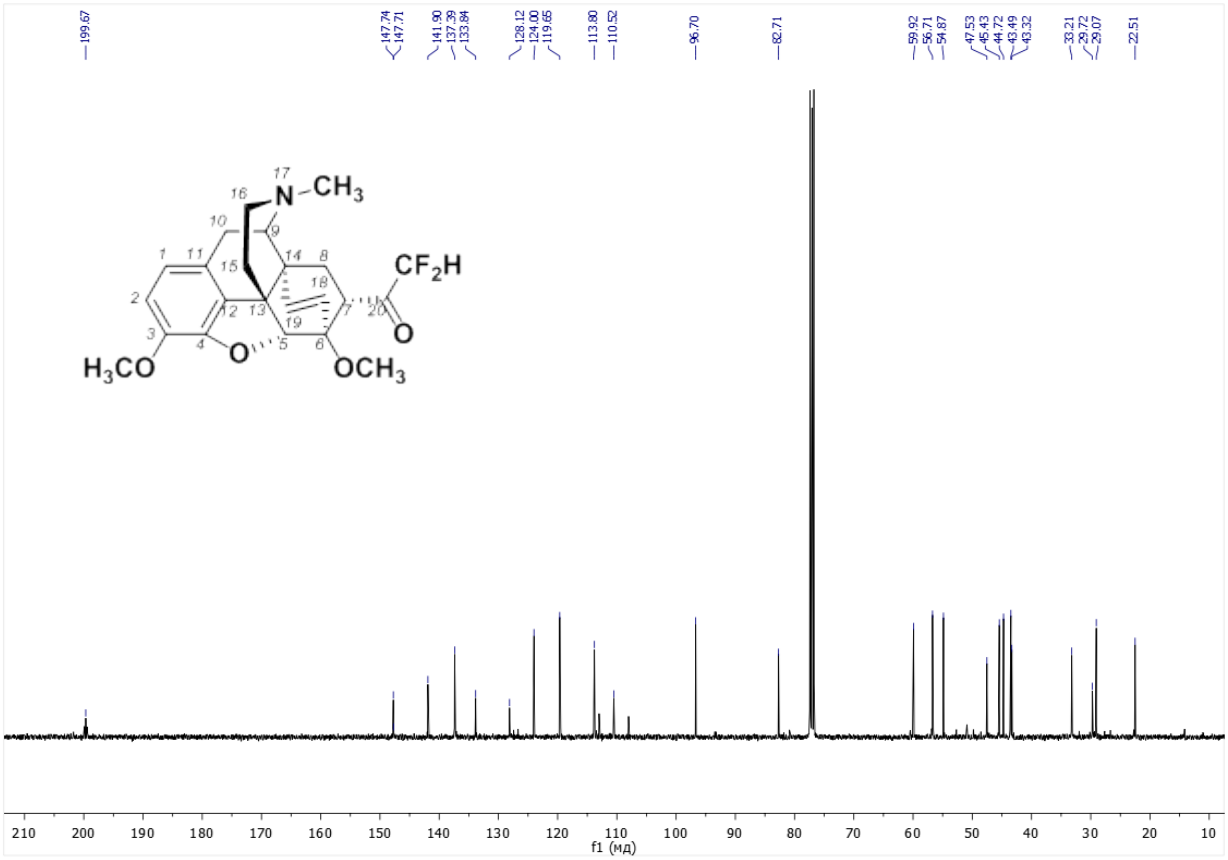


Figure S37. ^{13}C NMR spectra of compound **10**.

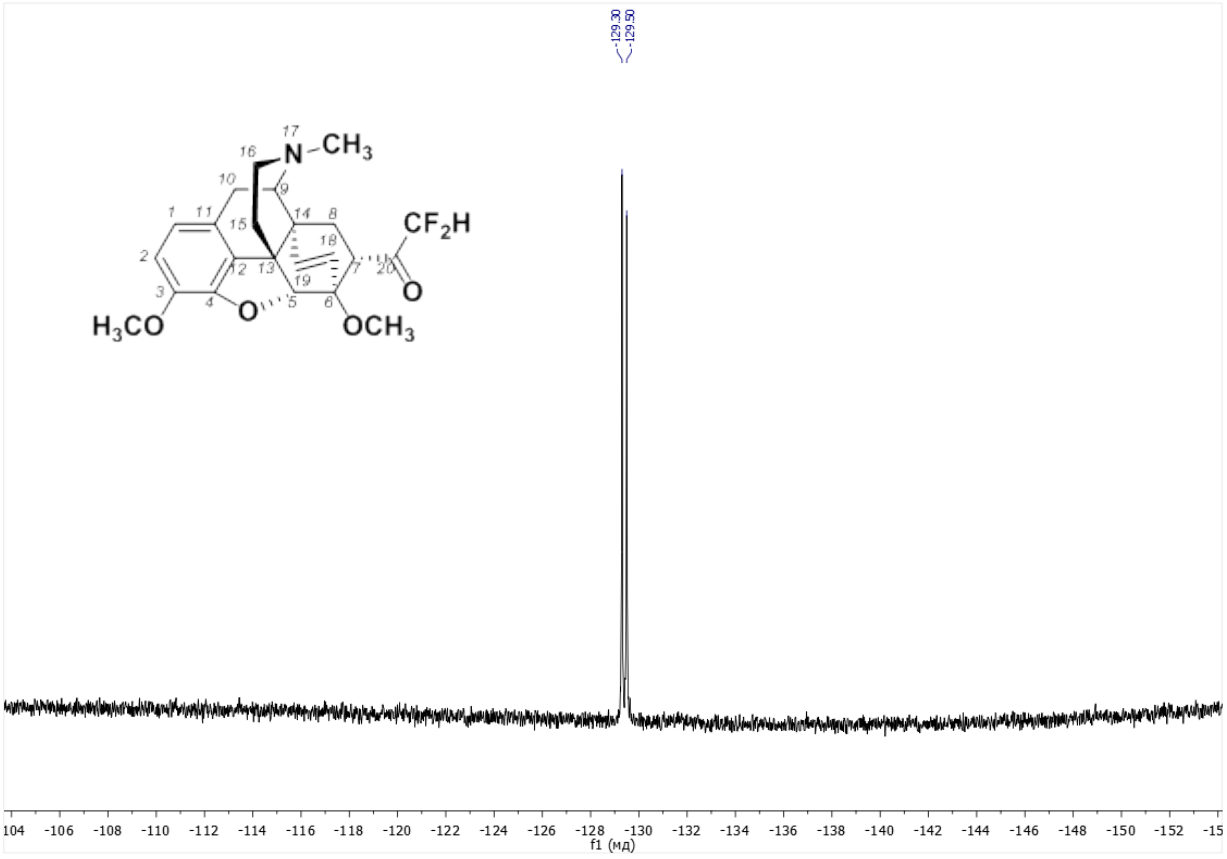


Figure S38. ^{19}F NMR spectra of compound **10**.

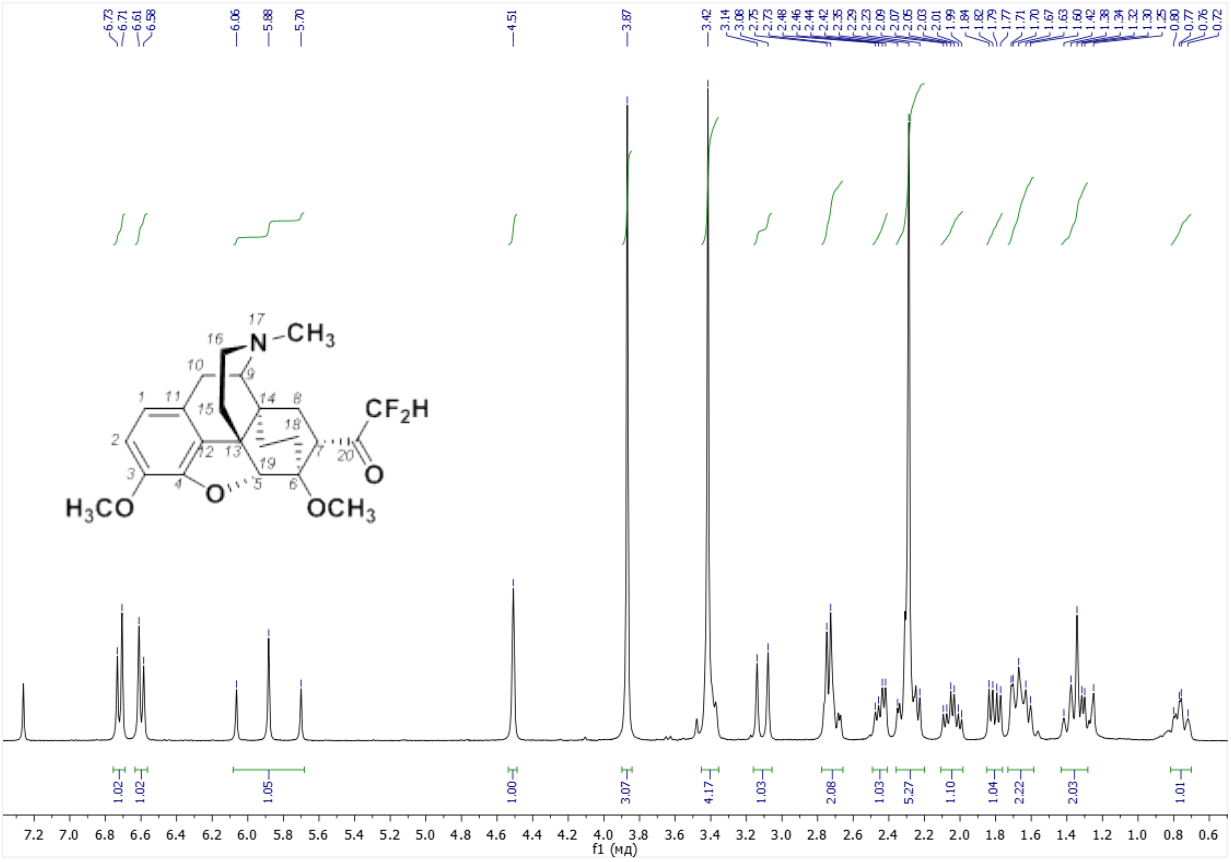


Figure S39. ^{1}H NMR spectra of compound **13**.

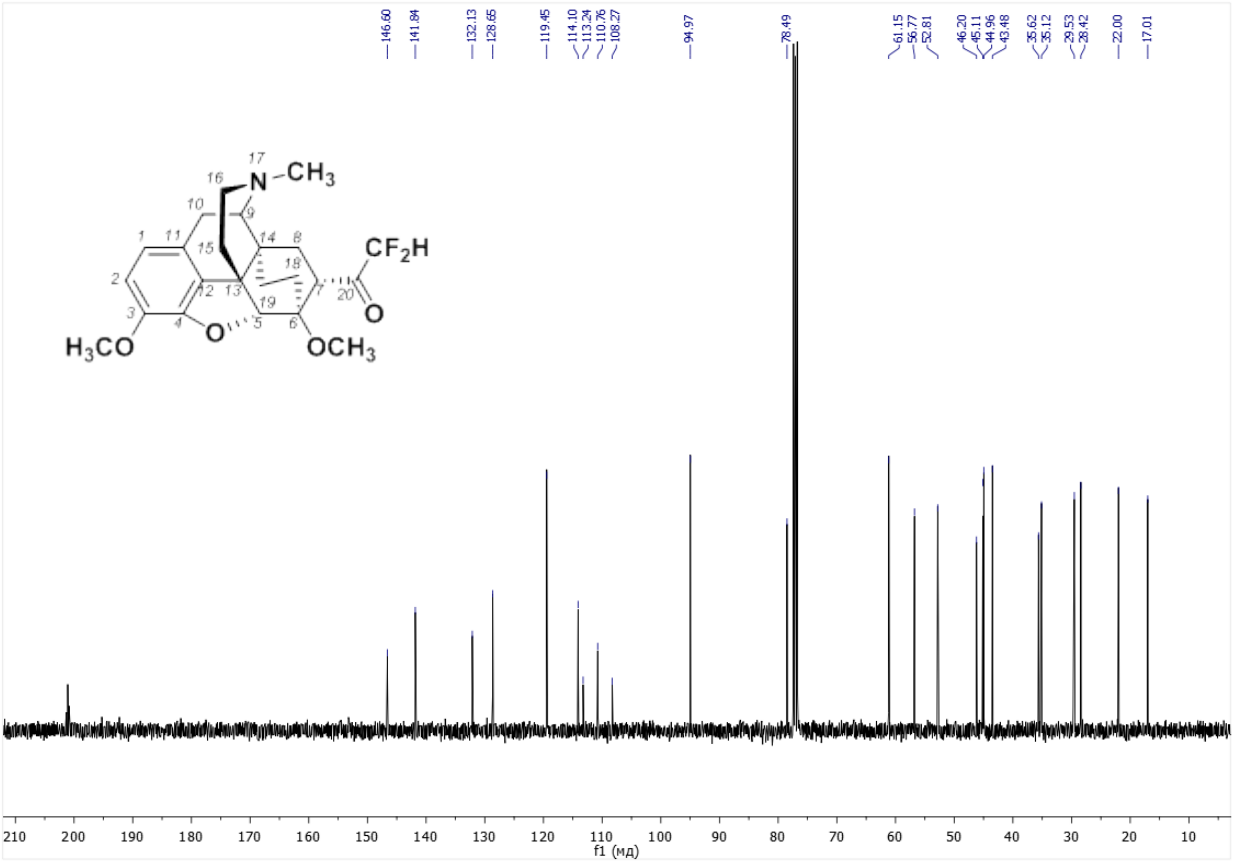


Figure S40. ^{13}C NMR spectra of compound **13**.

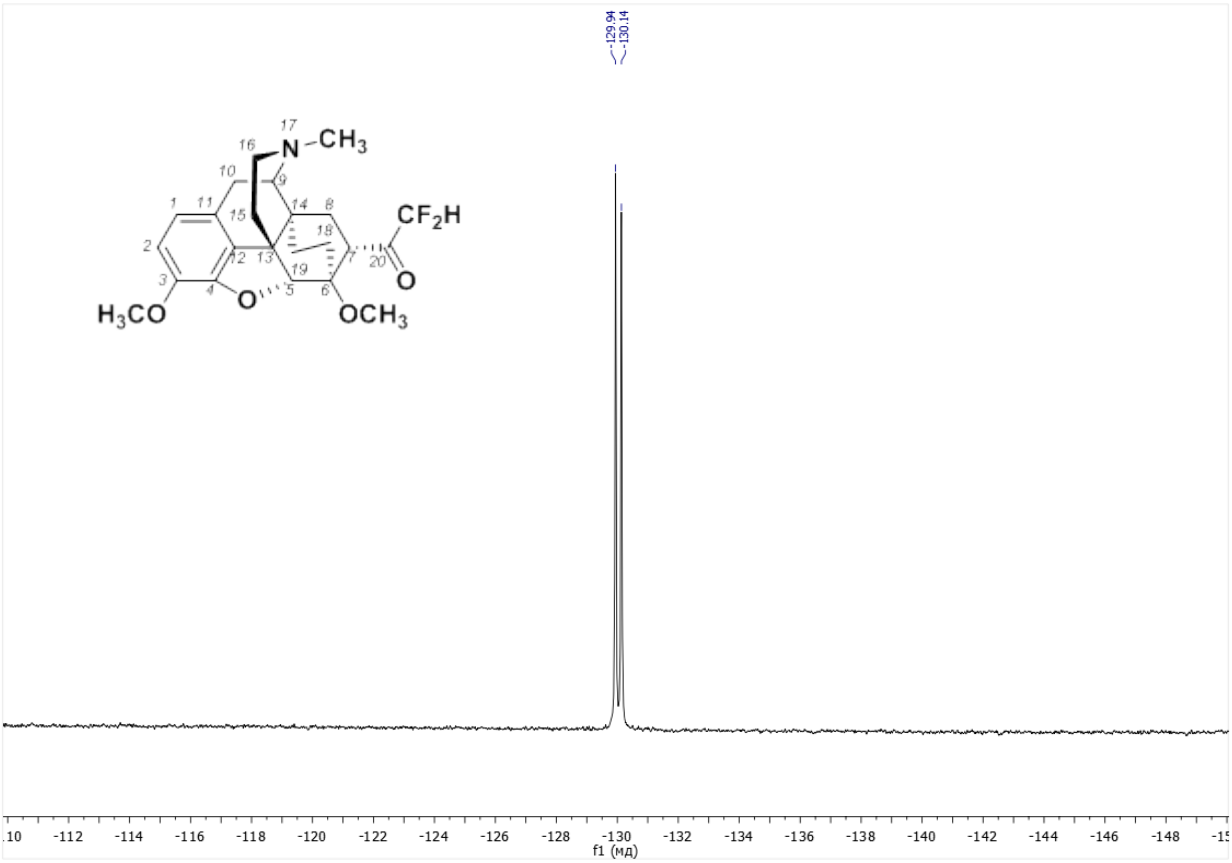


Figure S41. ^{19}F NMR spectra of compound **13**.

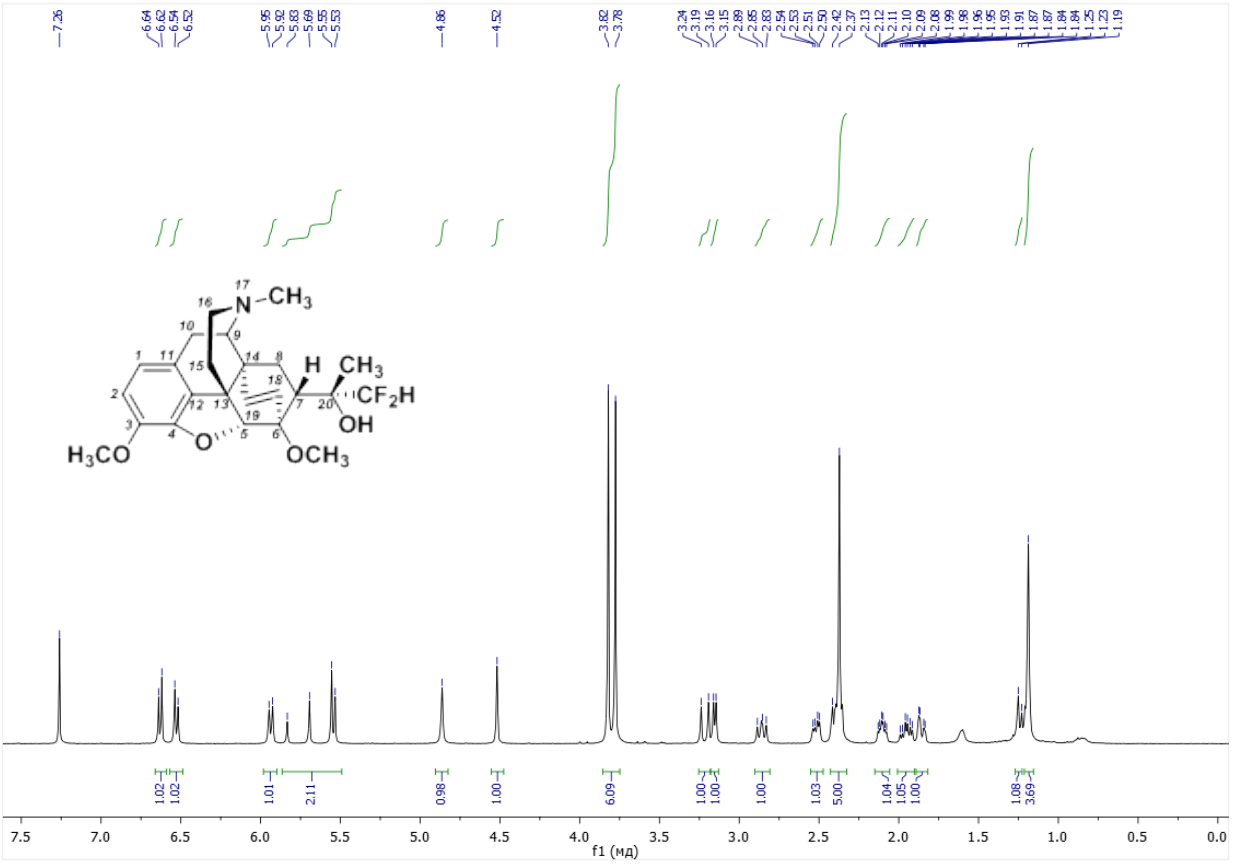


Figure S42. ^{1}H NMR spectra of compound 20*R*-**31**.

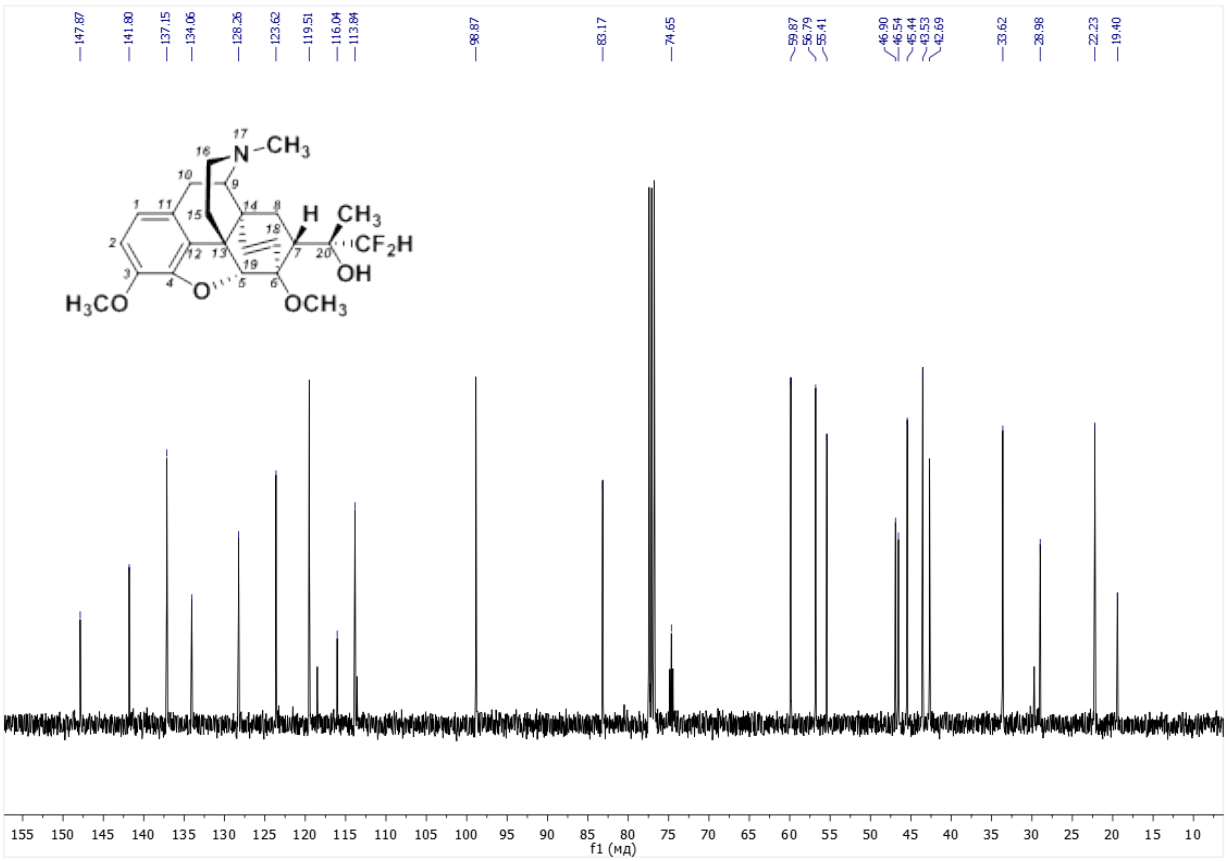


Figure S43. ^{13}C NMR spectra of compound 20*R*-**31**.

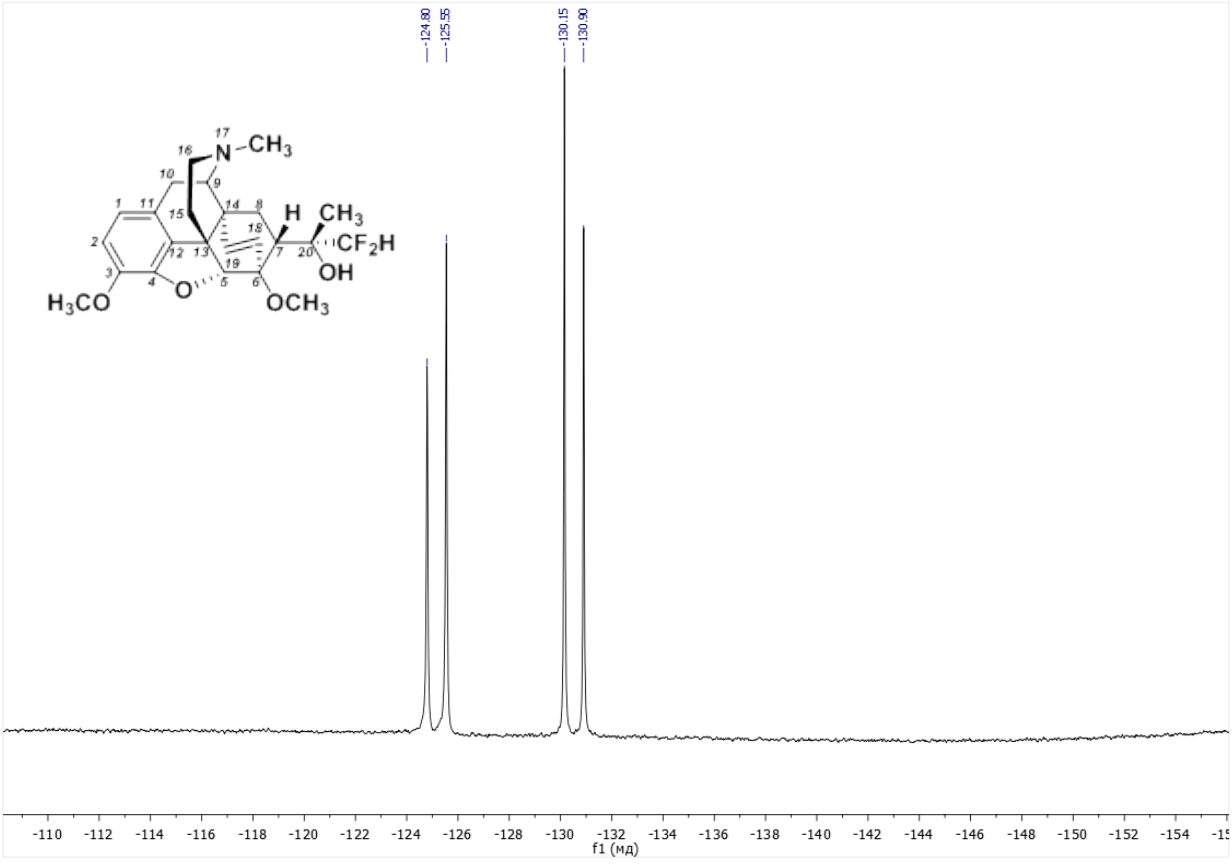


Figure S44. $^{19}F\{^{1}H\}$ NMR spectra of compound 20*R*-**31**.

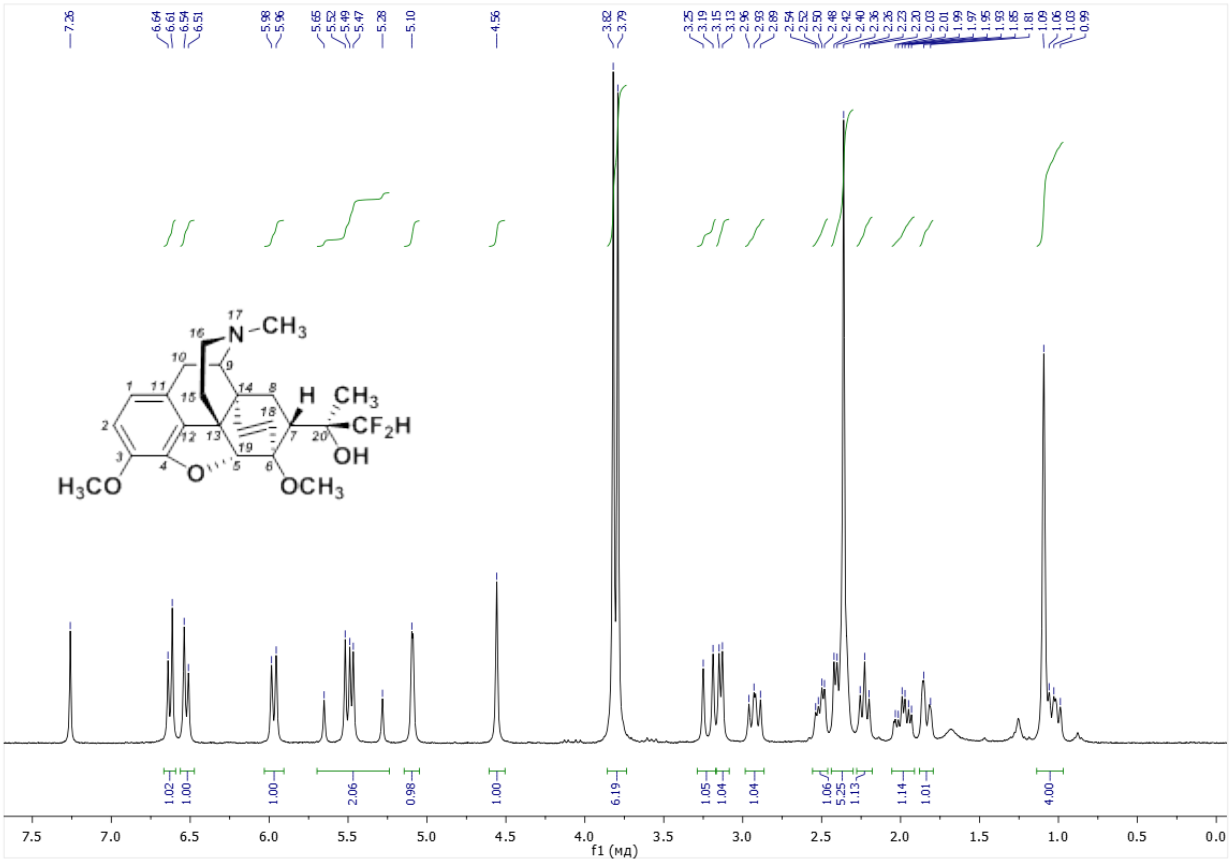


Figure S45. ^{1}H NMR spectra of compound 20*S*-**31**.

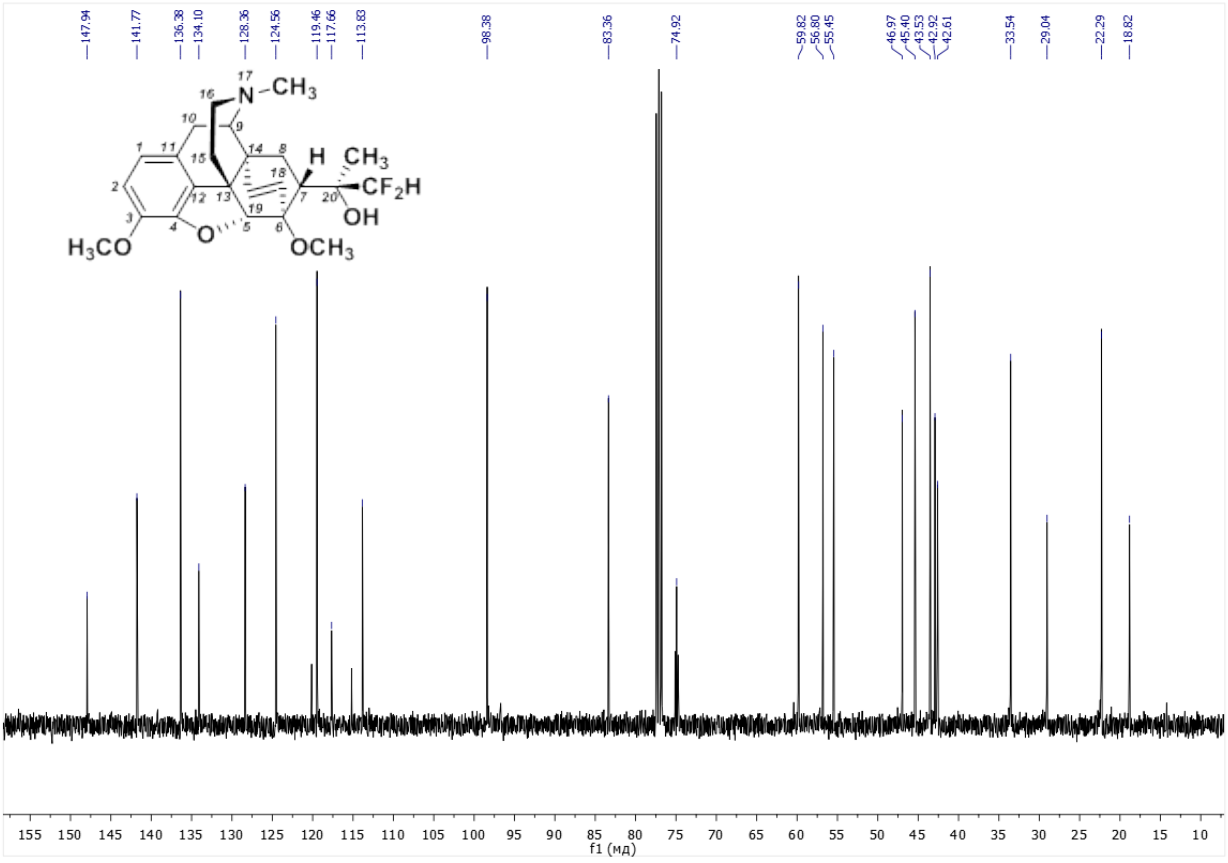


Figure S46. ^{13}C NMR spectra of compound 20*S*-**31**.

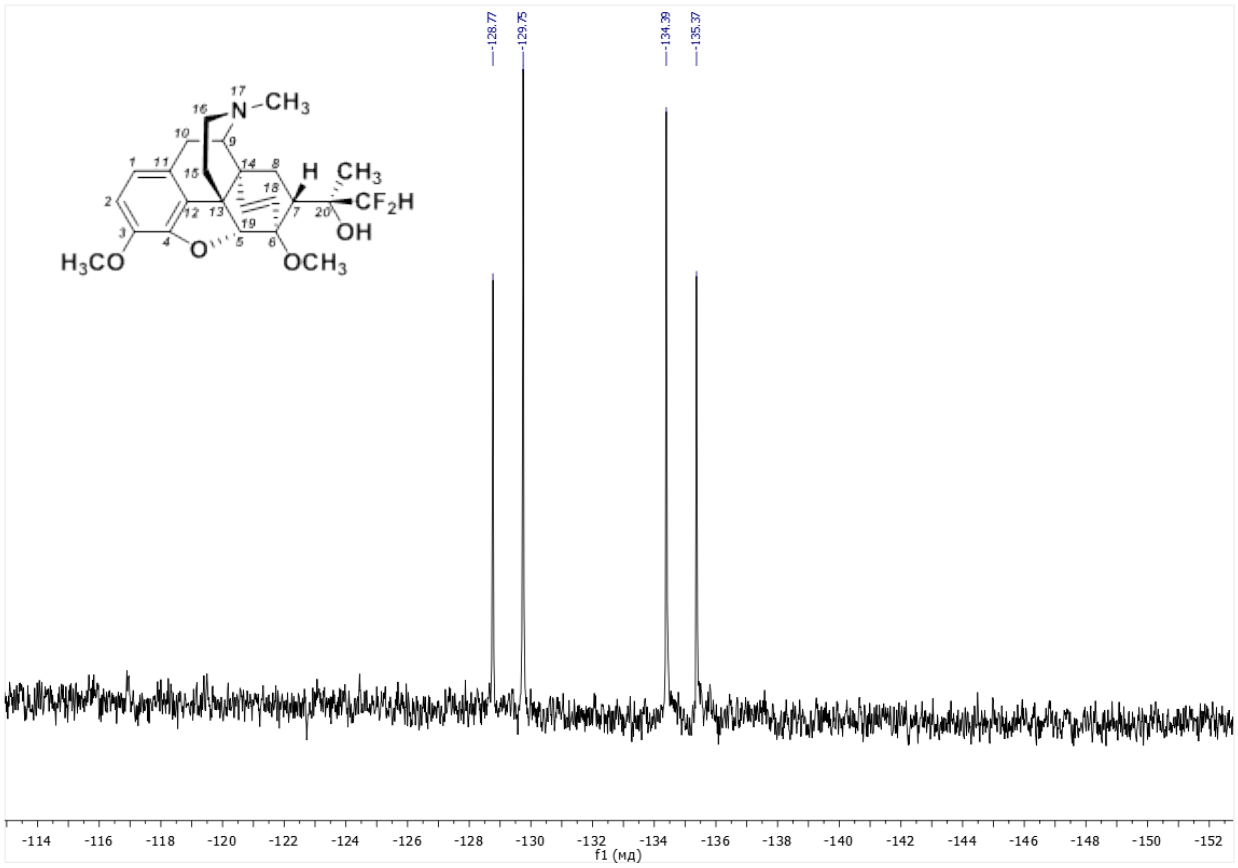


Figure S47. $^{19}F\{^{1}H\}$ NMR spectra of compound 20*S*-**31**.

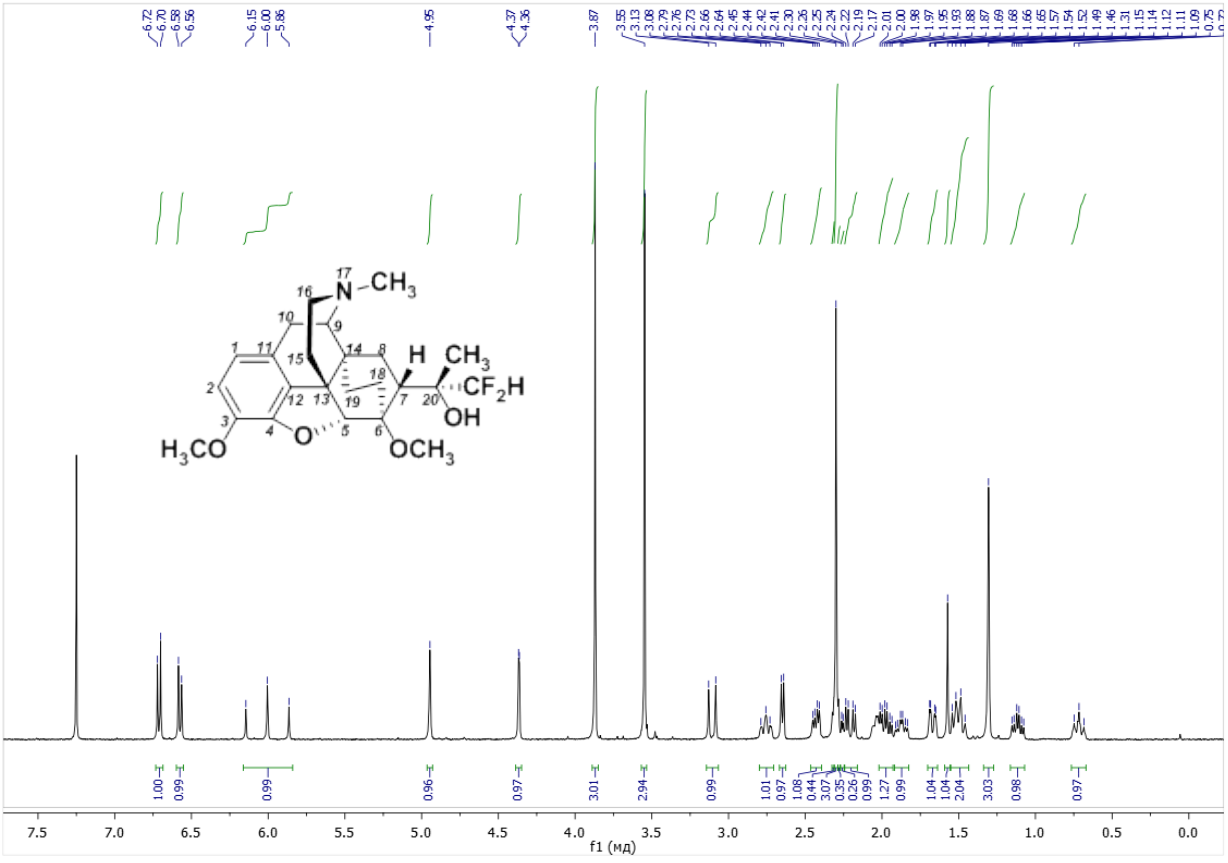


Figure S48. ^{1}H NMR spectra of compound **33**.

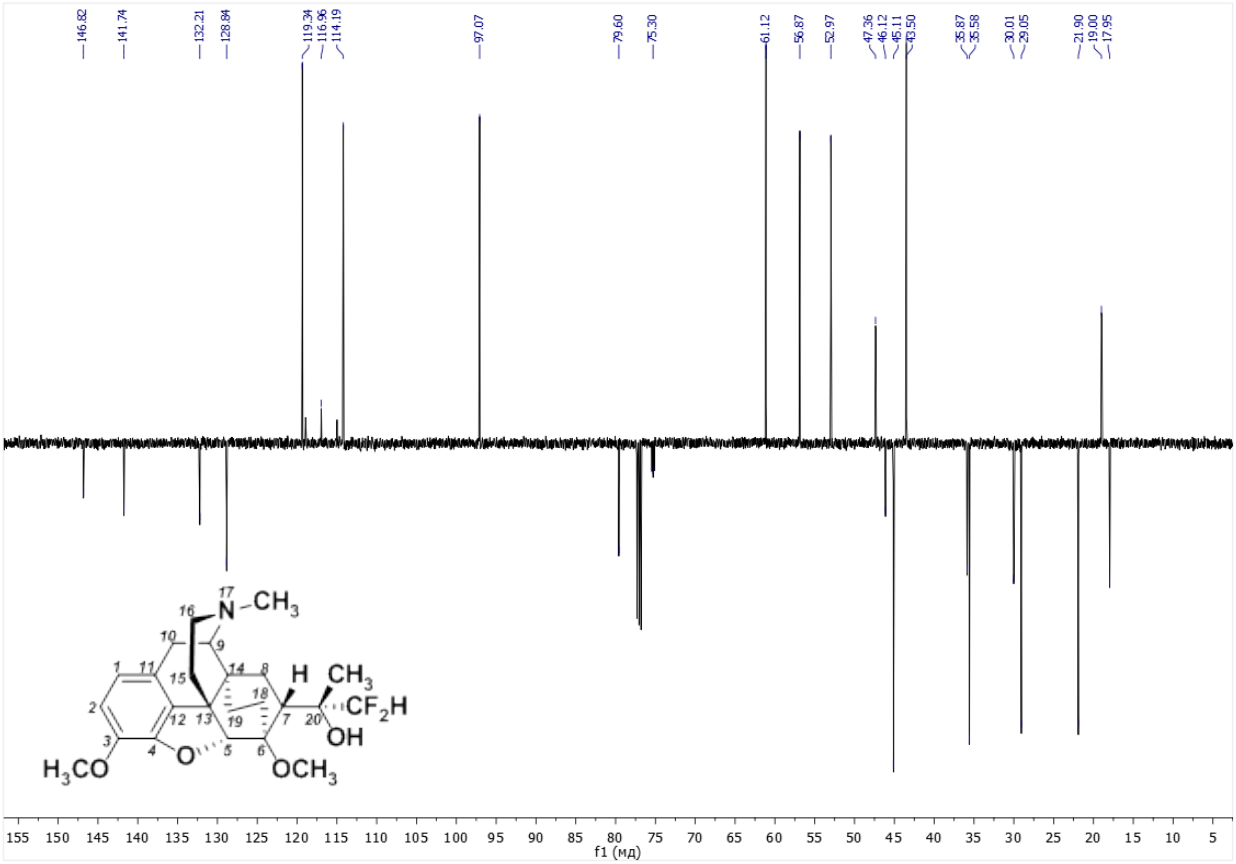


Figure S49. ^{13}C NMR spectra of compound **33**.

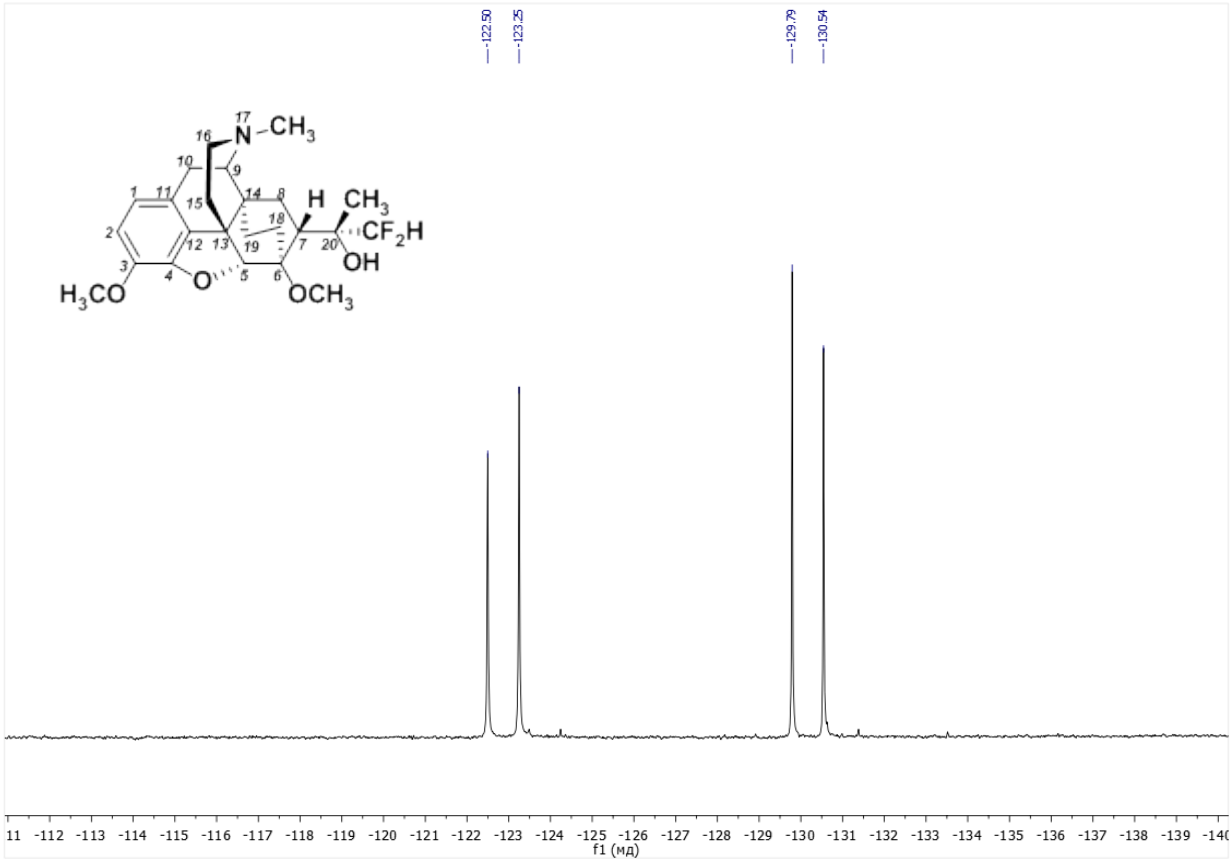


Figure S50. $^{19}F\{^{1}H\}$ NMR spectra of compound **33**.

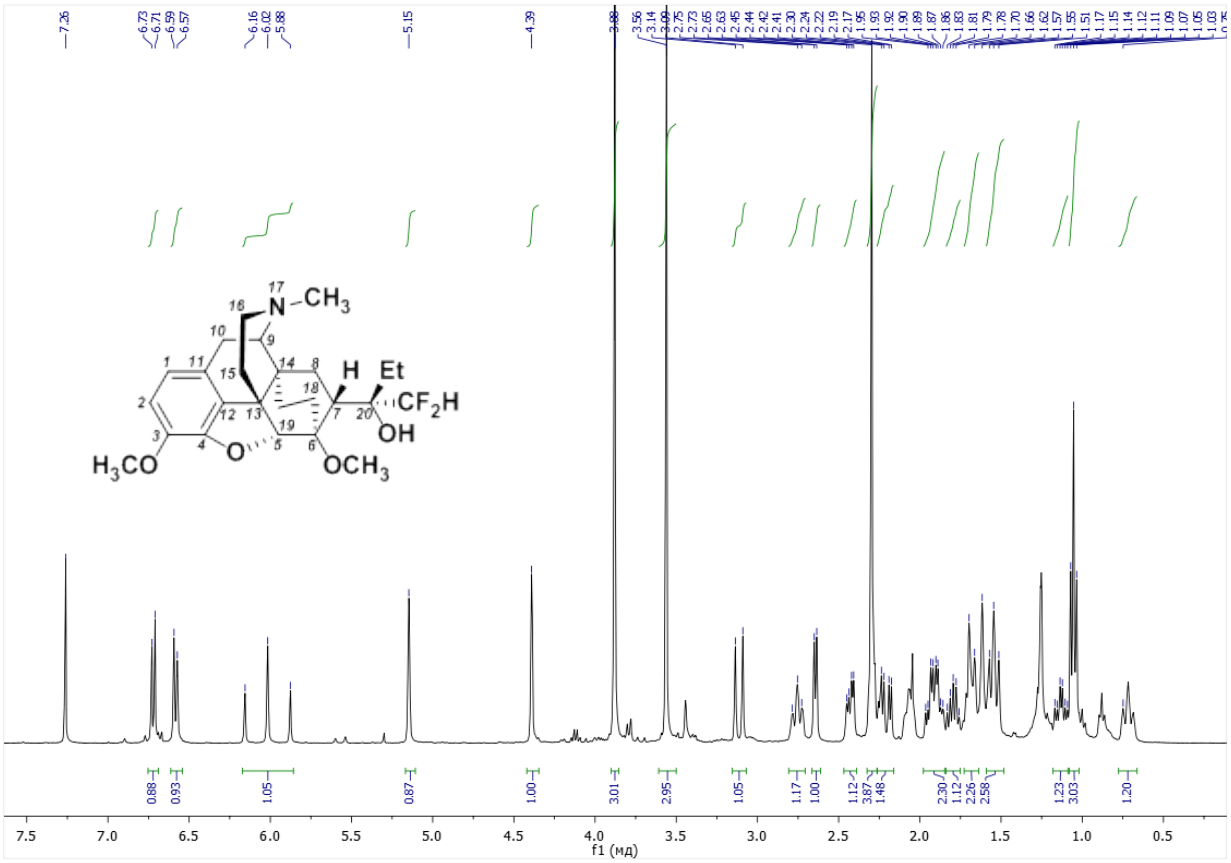


Figure S51. ^{1}H NMR spectra of compound **35**.

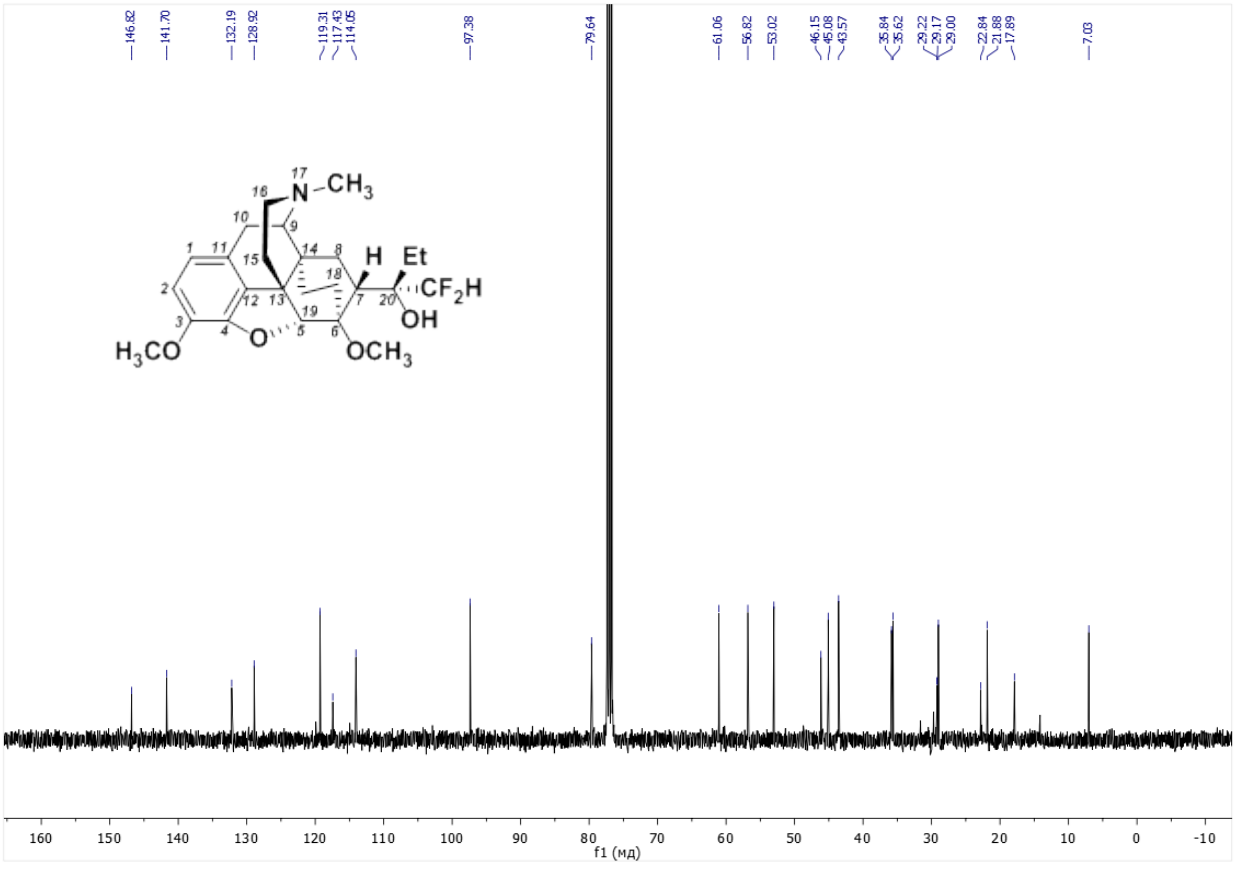


Figure S52. ^{13}C NMR spectra of compound **35**.

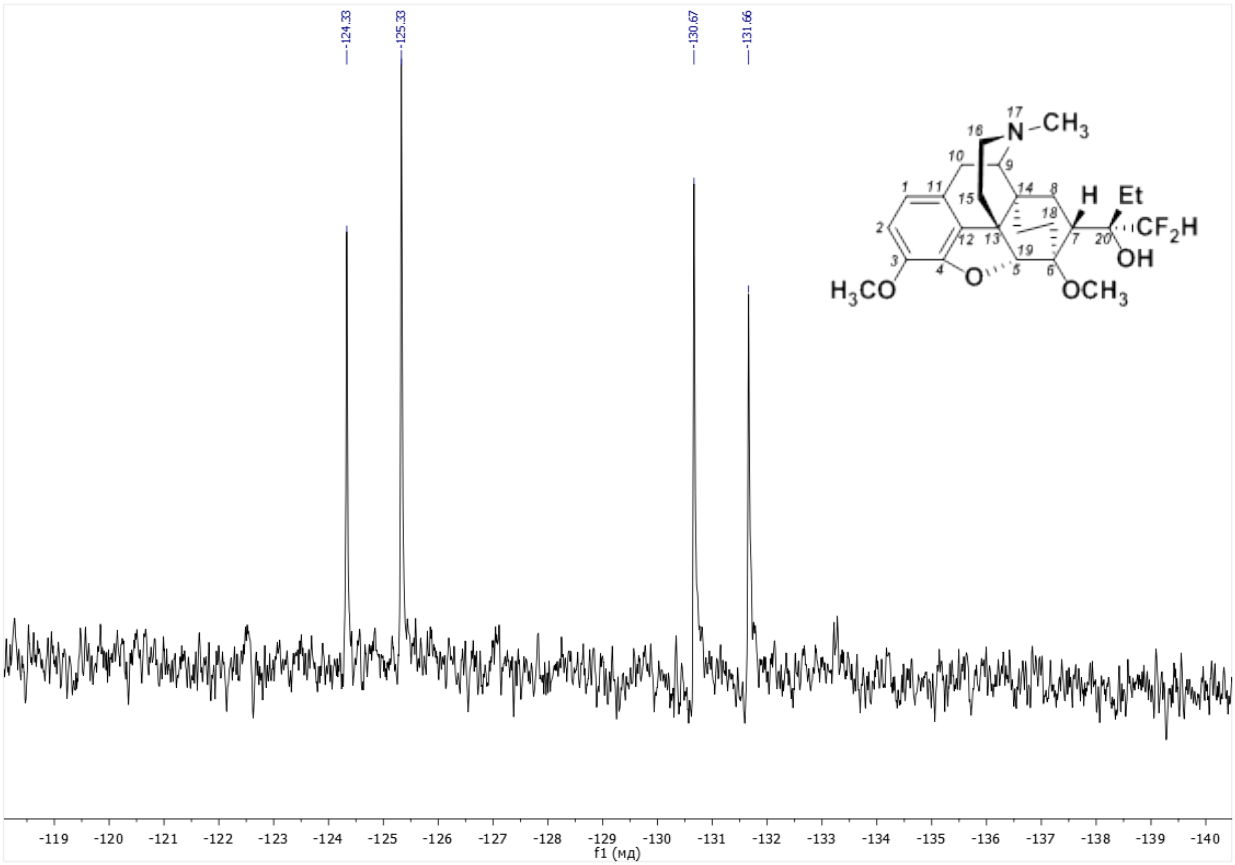


Figure S53. $^{19}F\{^{1}H\}$ NMR spectra of compound **35**.

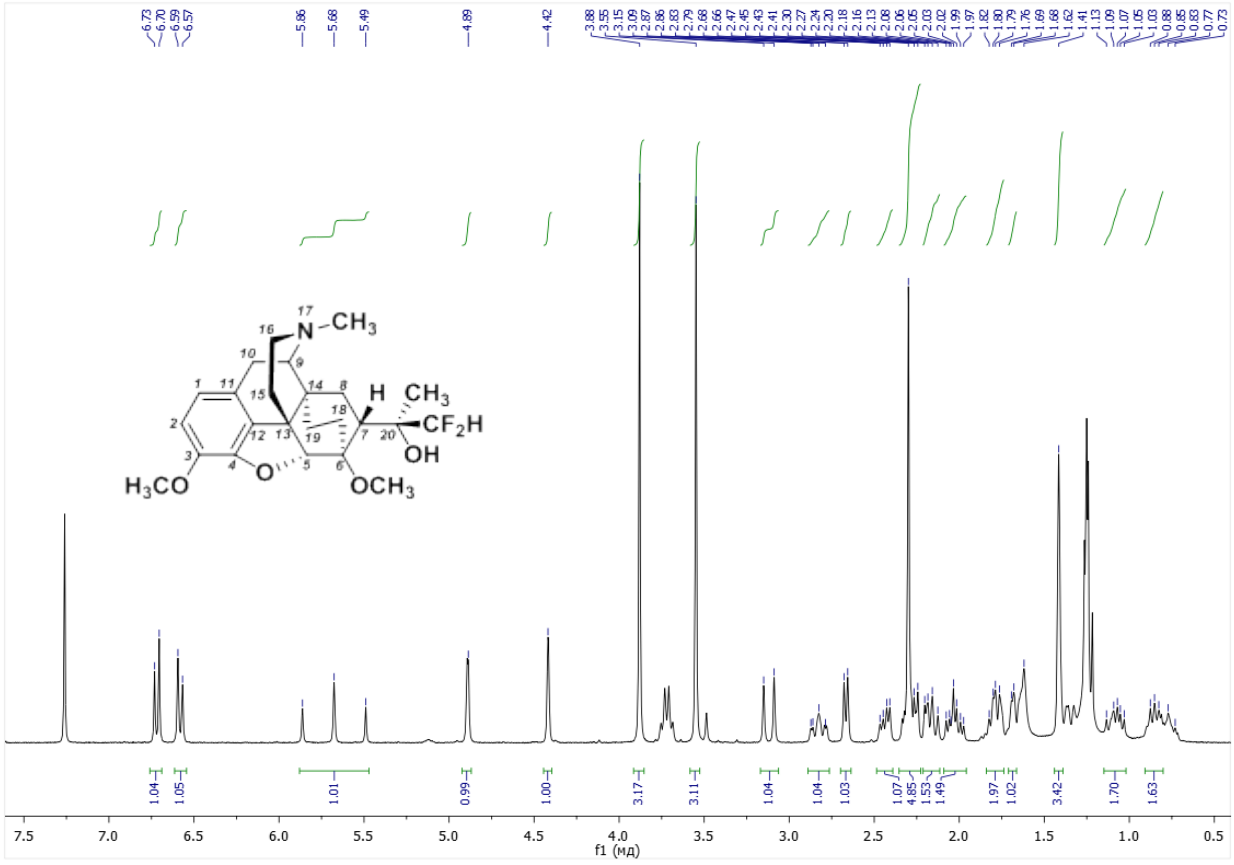


Figure S54. ^{1}H NMR spectra of compound 20*S*-**36**.

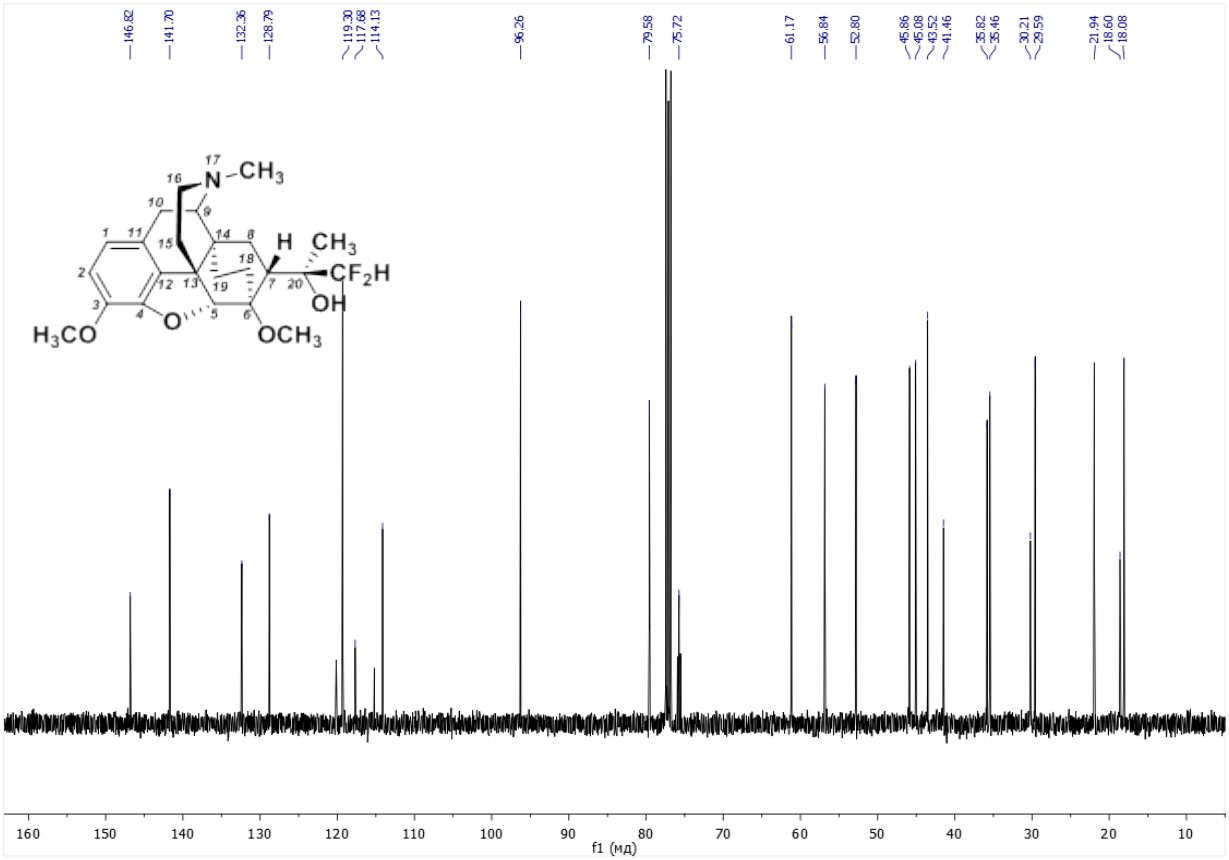


Figure S55. ^{13}C NMR spectra of compound 20*S*-**36**.

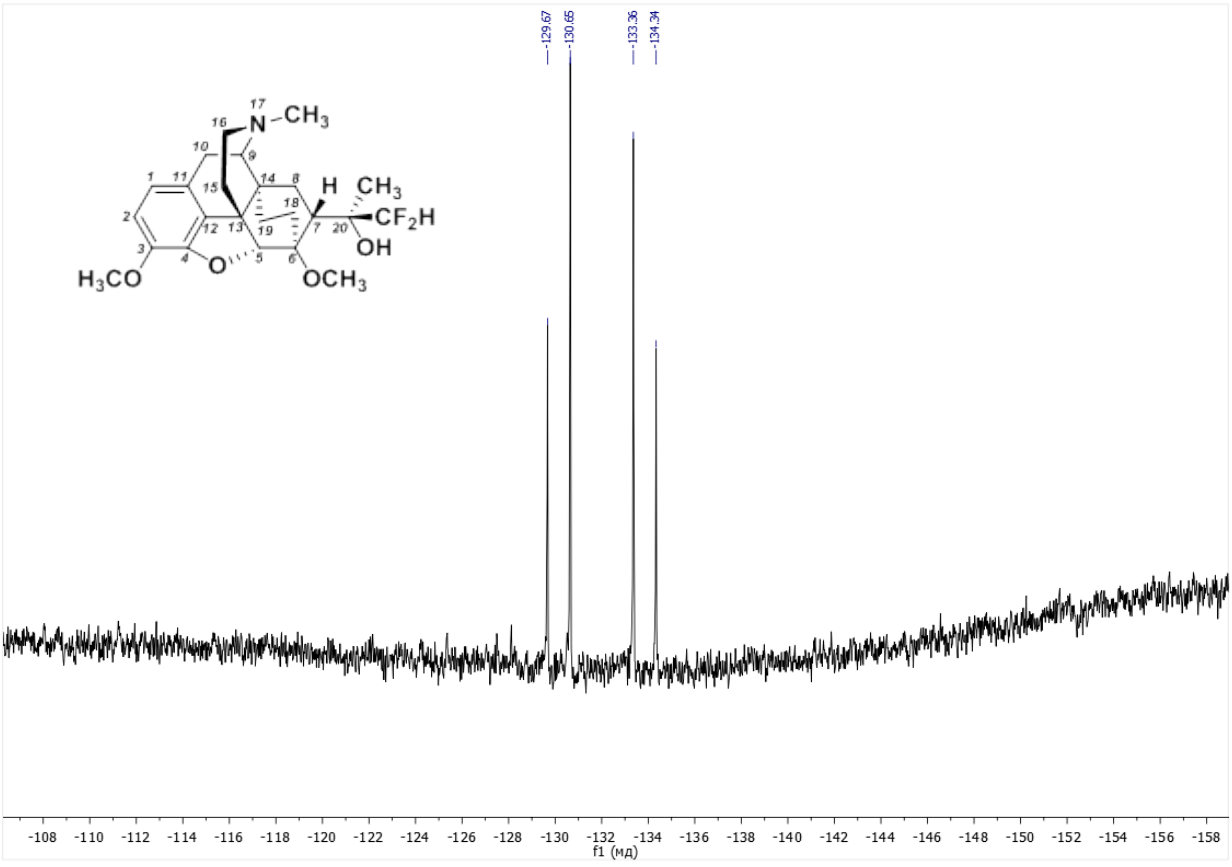


Figure S56. $^{19}F\{^{1}H\}$ NMR spectra of compound 20*S*-**36**.

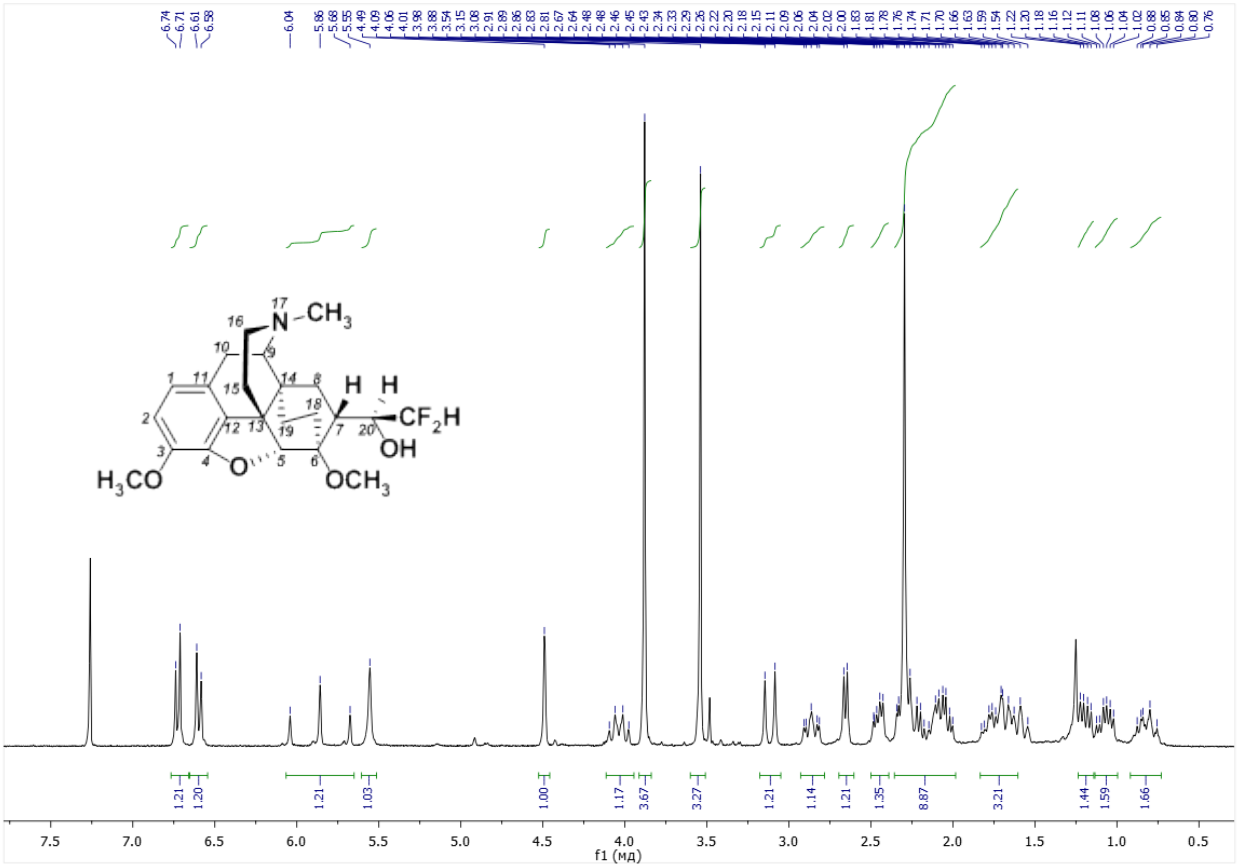


Figure S57. ^{1}H NMR spectra of compound **37**.

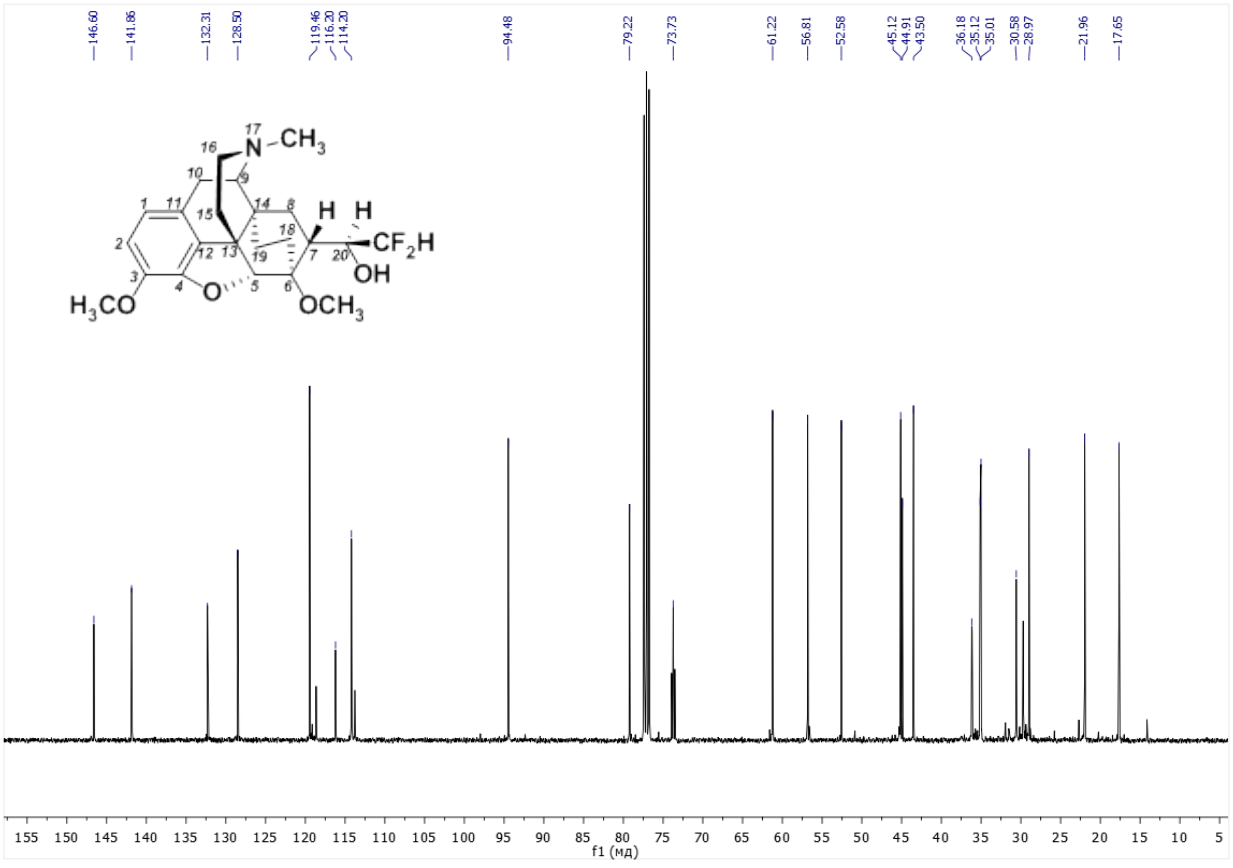


Figure S58. ^{13}C NMR spectra of compound **37**.

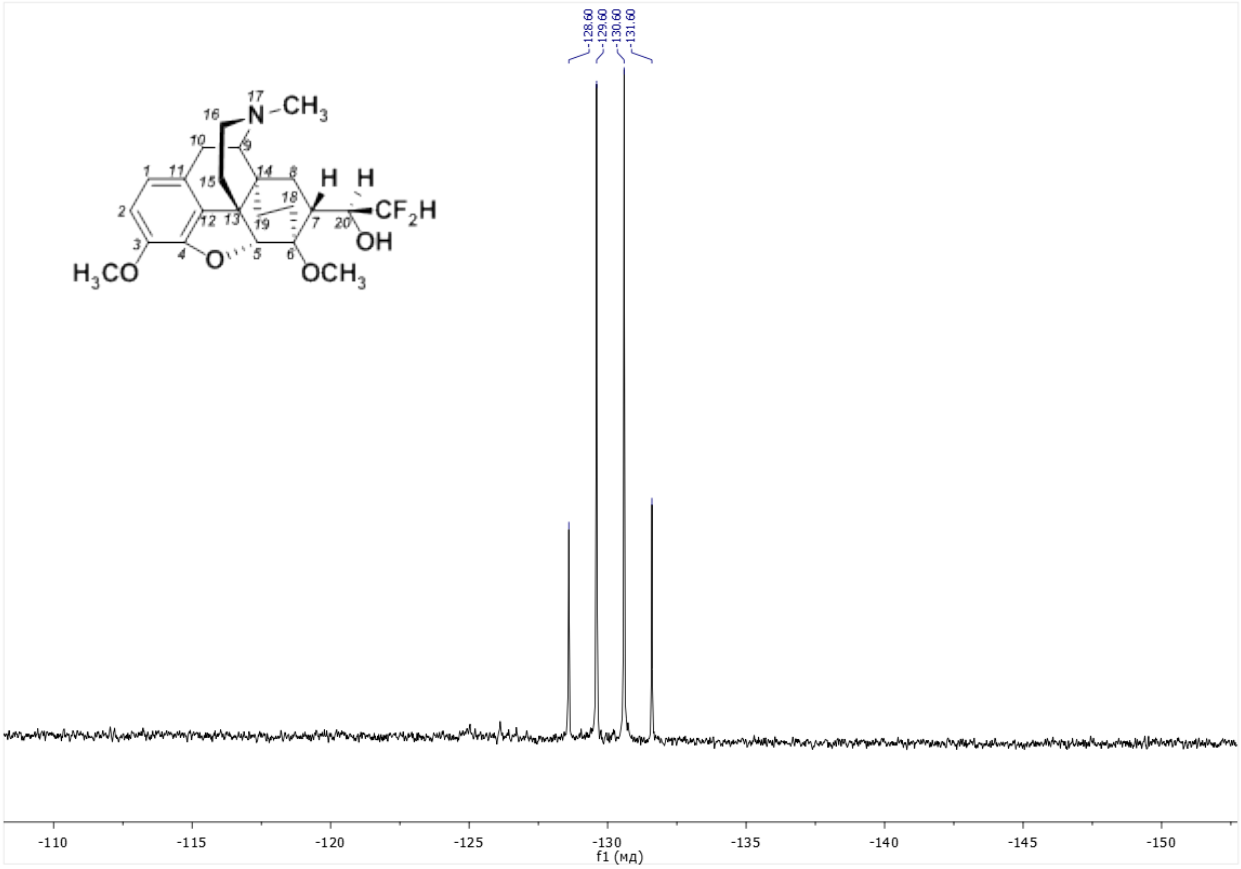


Figure S59. ^{19}F NMR spectra of compound **37**.

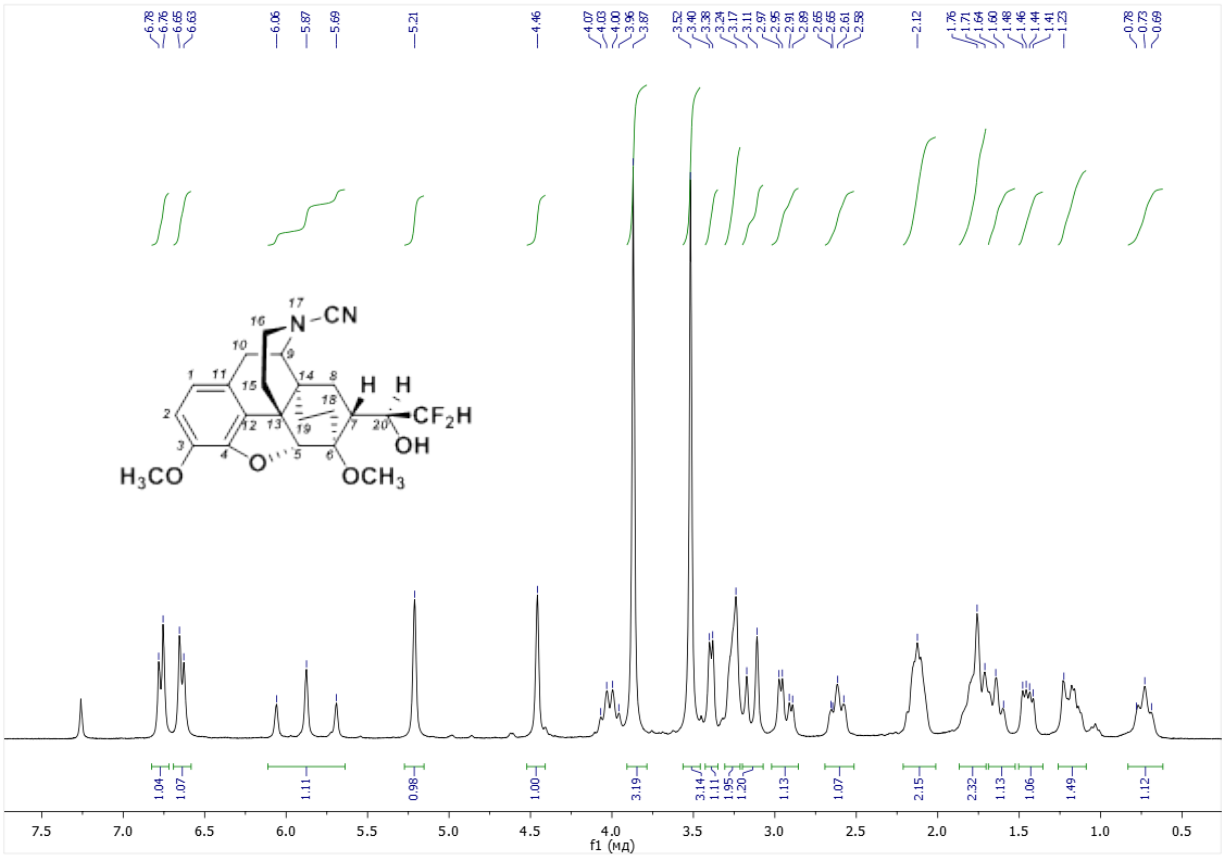


Figure S60. ^{1}H NMR spectra of compound **38**.

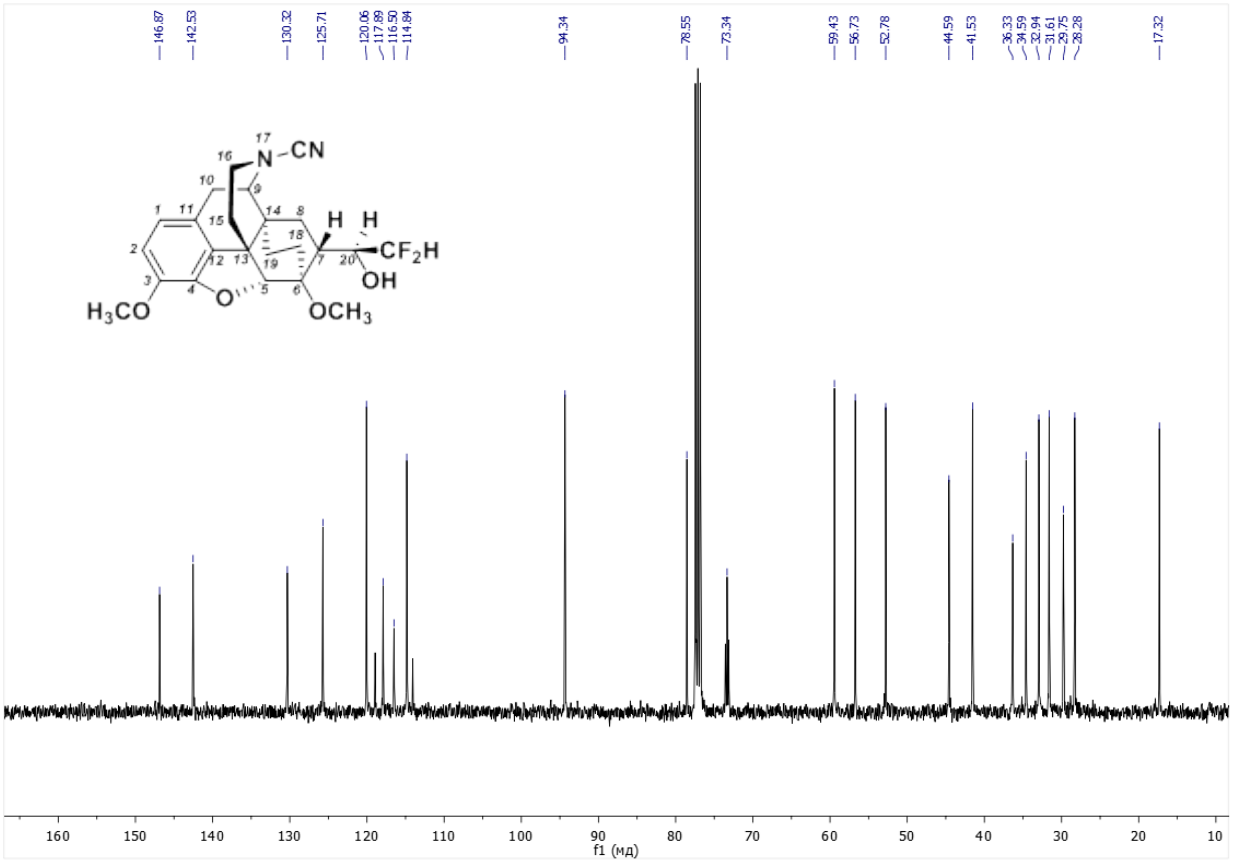


Figure S61. ^{13}C NMR spectra of compound **38**.

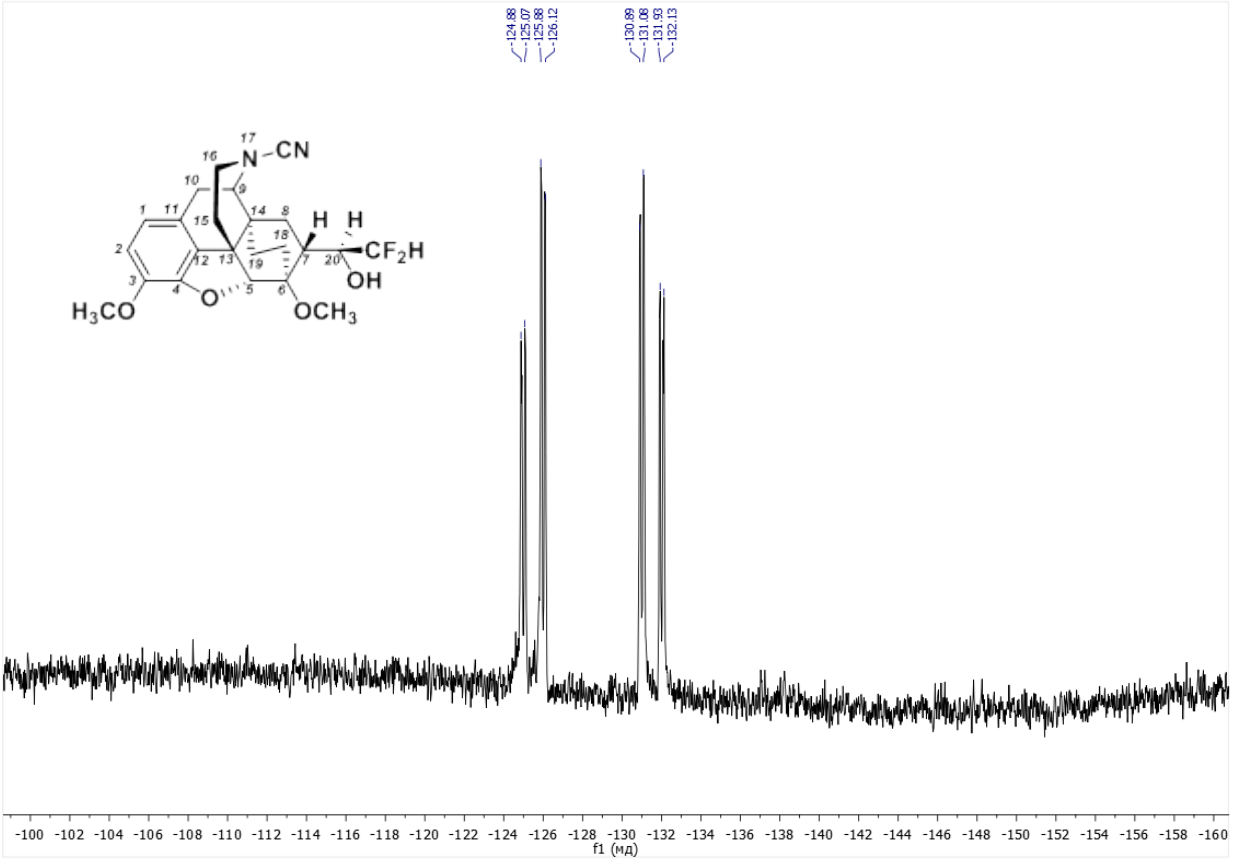


Figure S62. ^{19}F NMR spectra of compound **38**.

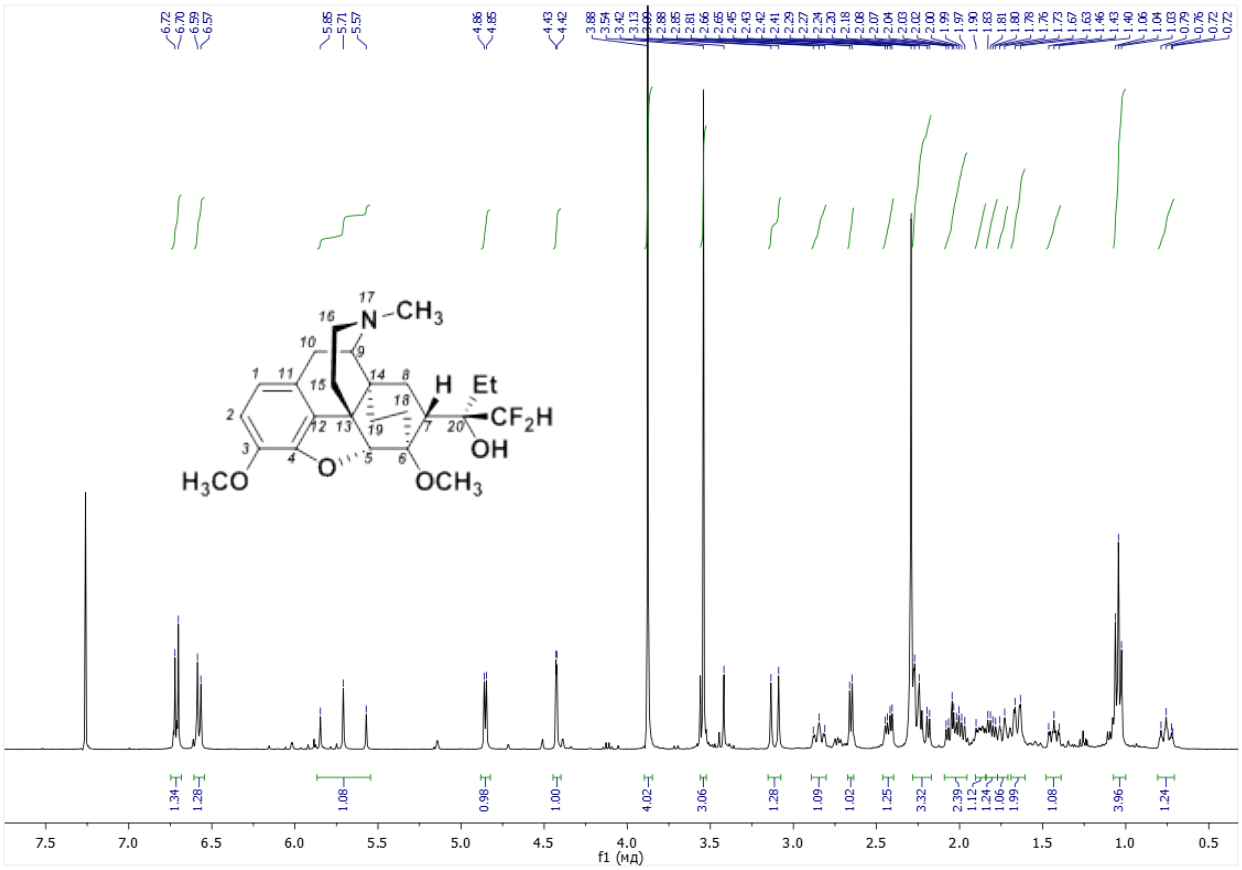


Figure S63. ^{1}H NMR spectra of compound **39a**.

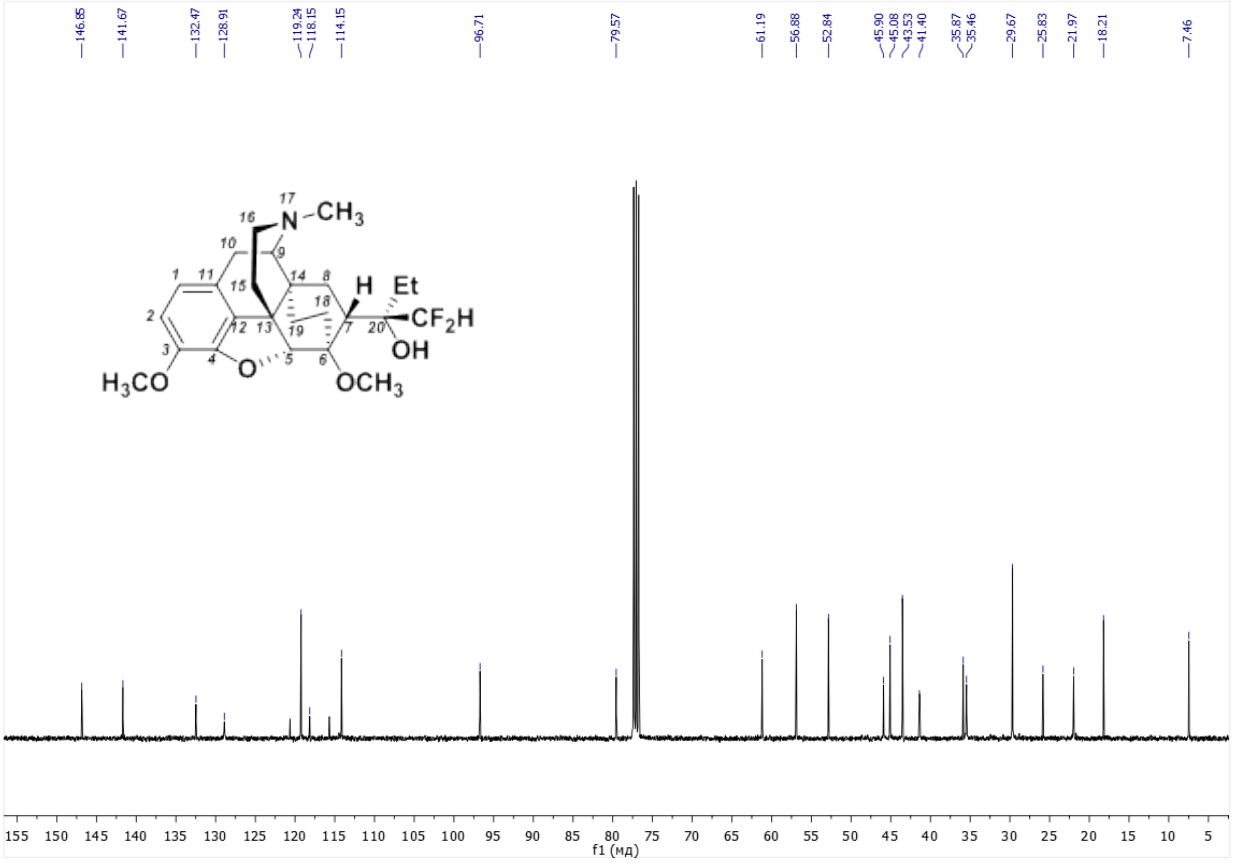


Figure S64. ^{13}C NMR spectra of compound **39a**.

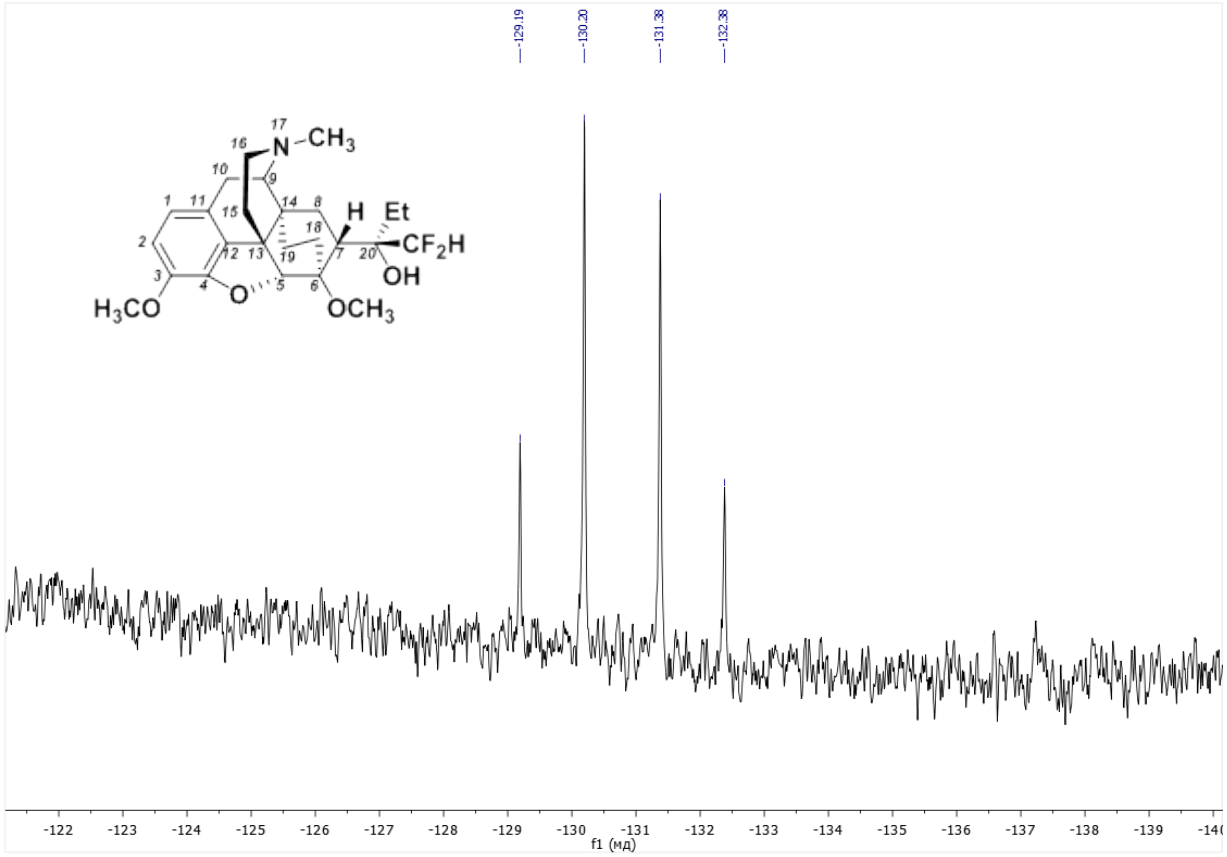


Figure S65. $^{19}F\{^{1}H\}$ NMR spectra of compound **39a**.

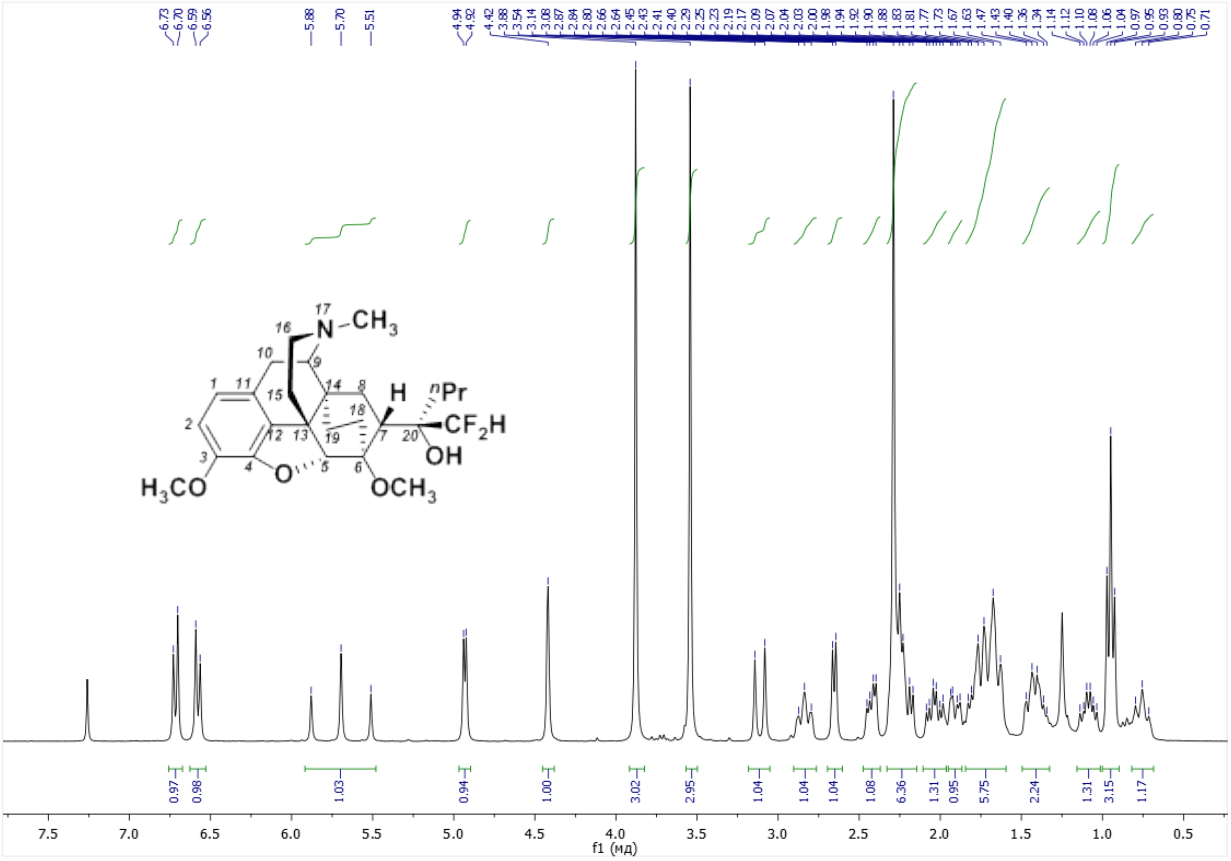


Figure S66. ^{1}H NMR spectra of compound **39b**.

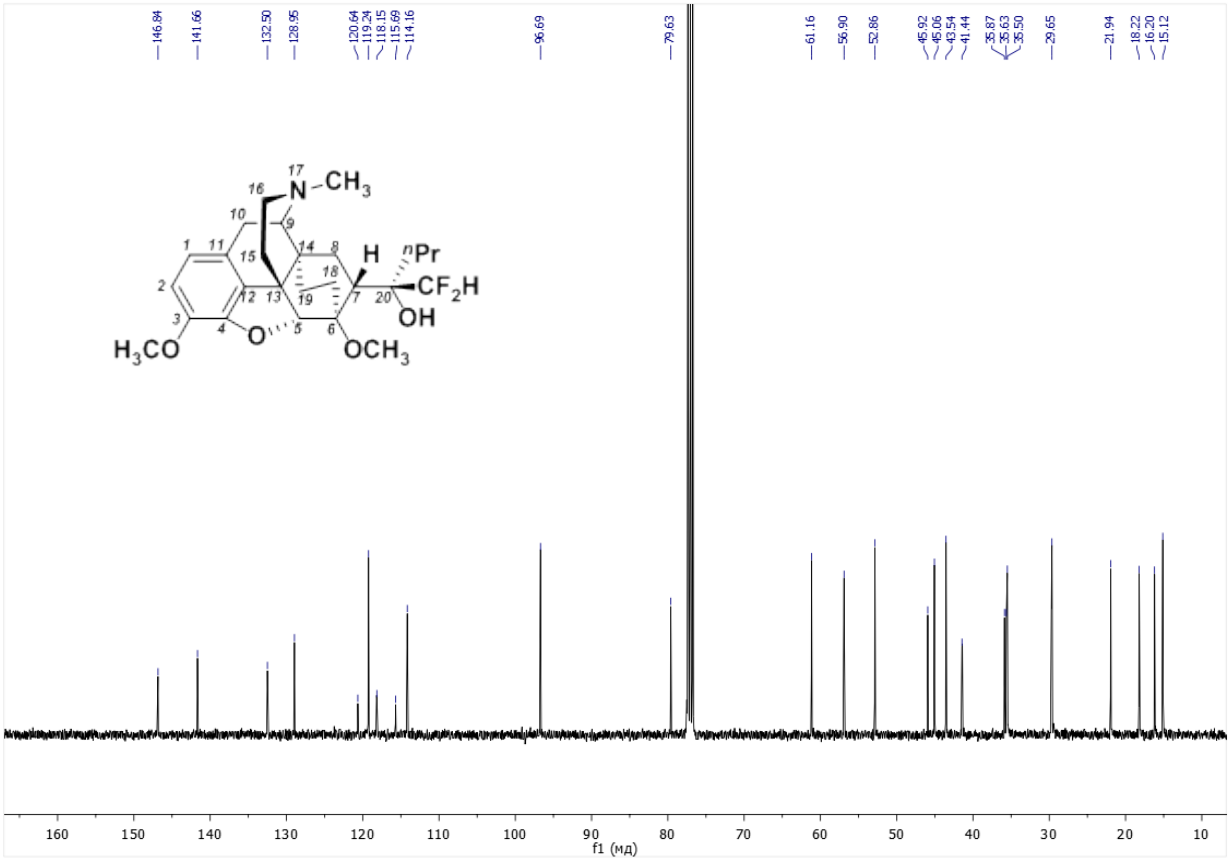


Figure S67. ^{13}C NMR spectra of compound **39b**.

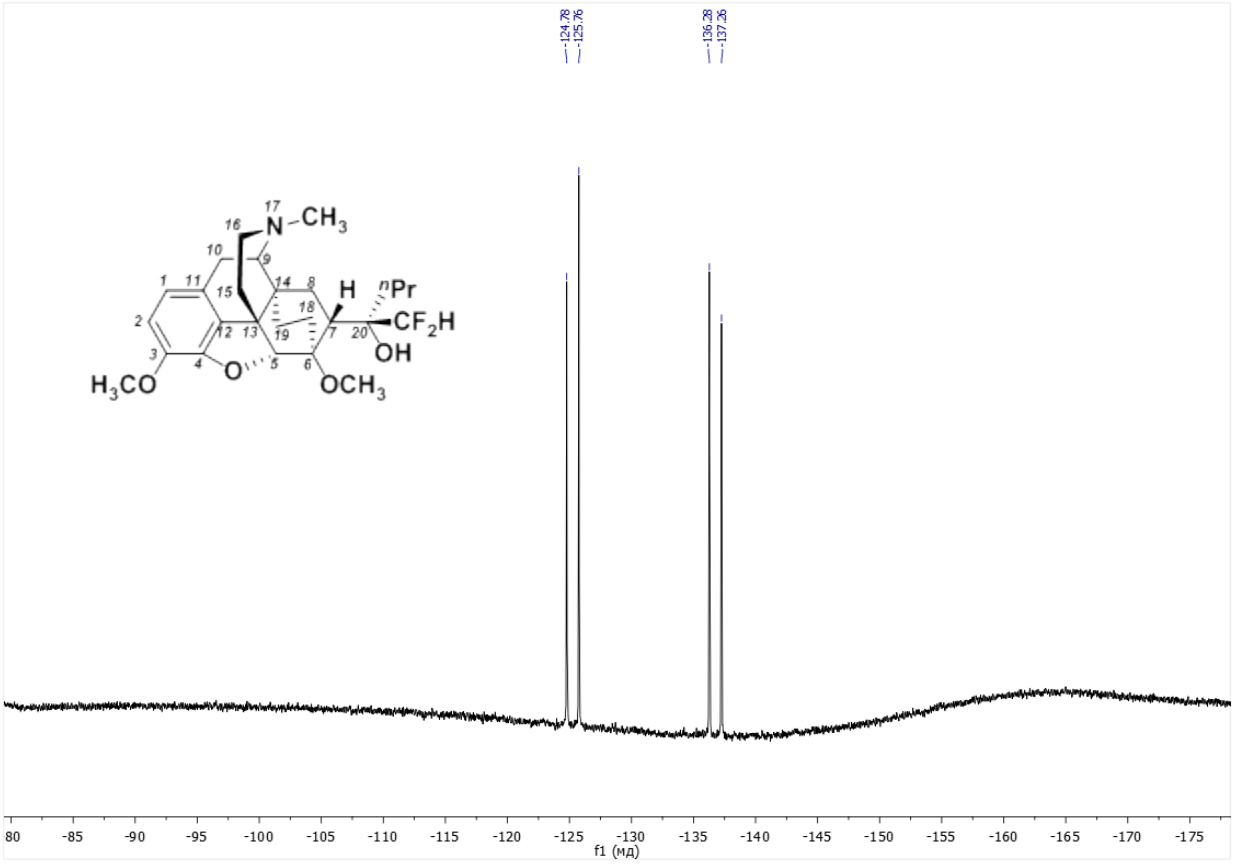


Figure S68. $^{19}F\{^{1}H\}$ NMR spectra of compound **39b**.

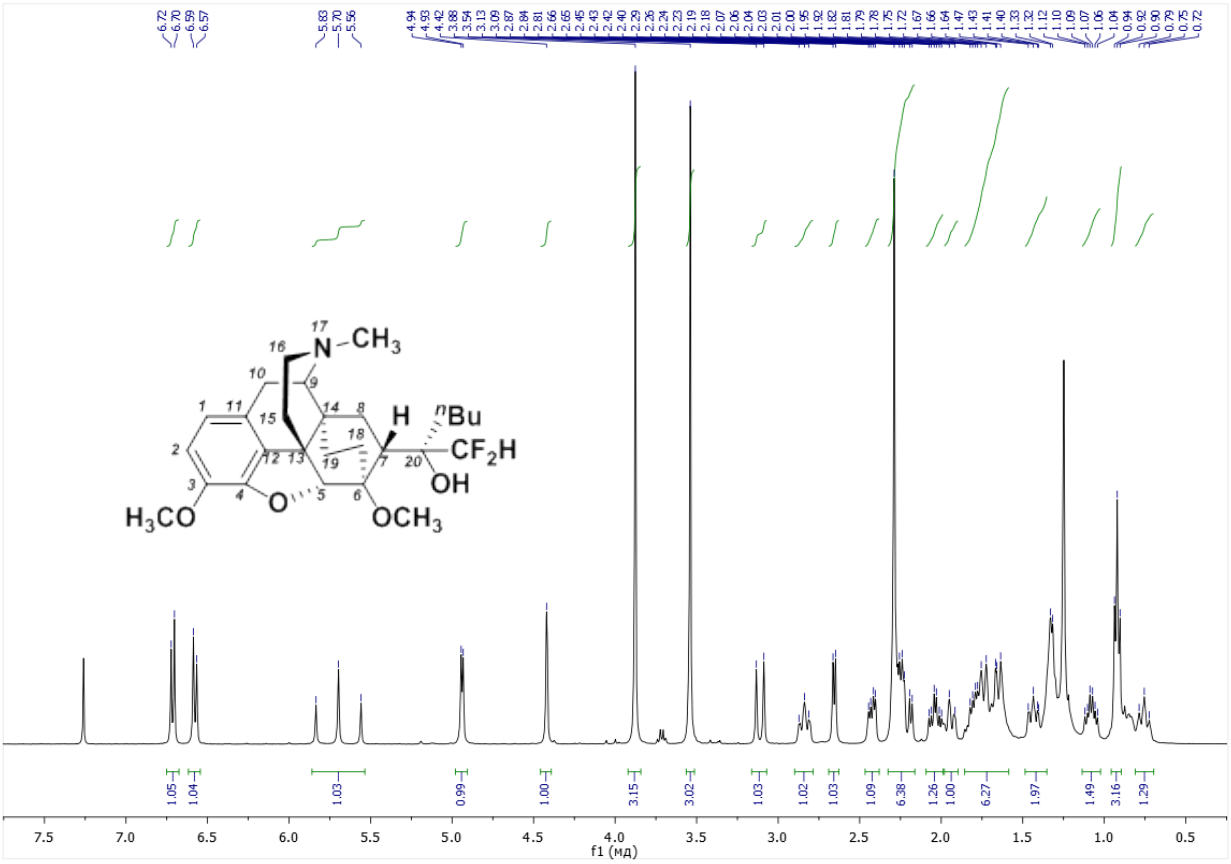


Figure S69. ^{1}H NMR spectra of compound **39c**.

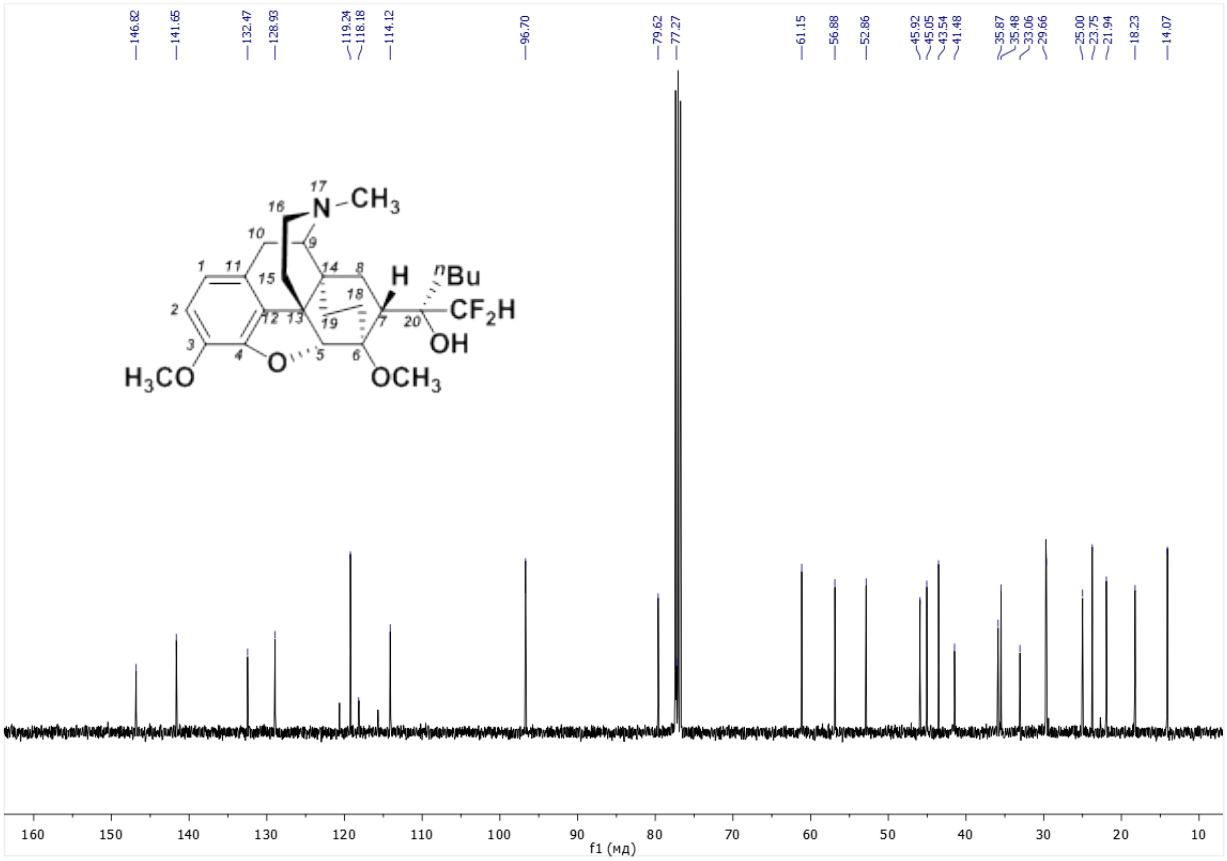


Figure S70. ^{13}C NMR spectra of compound **39c**.

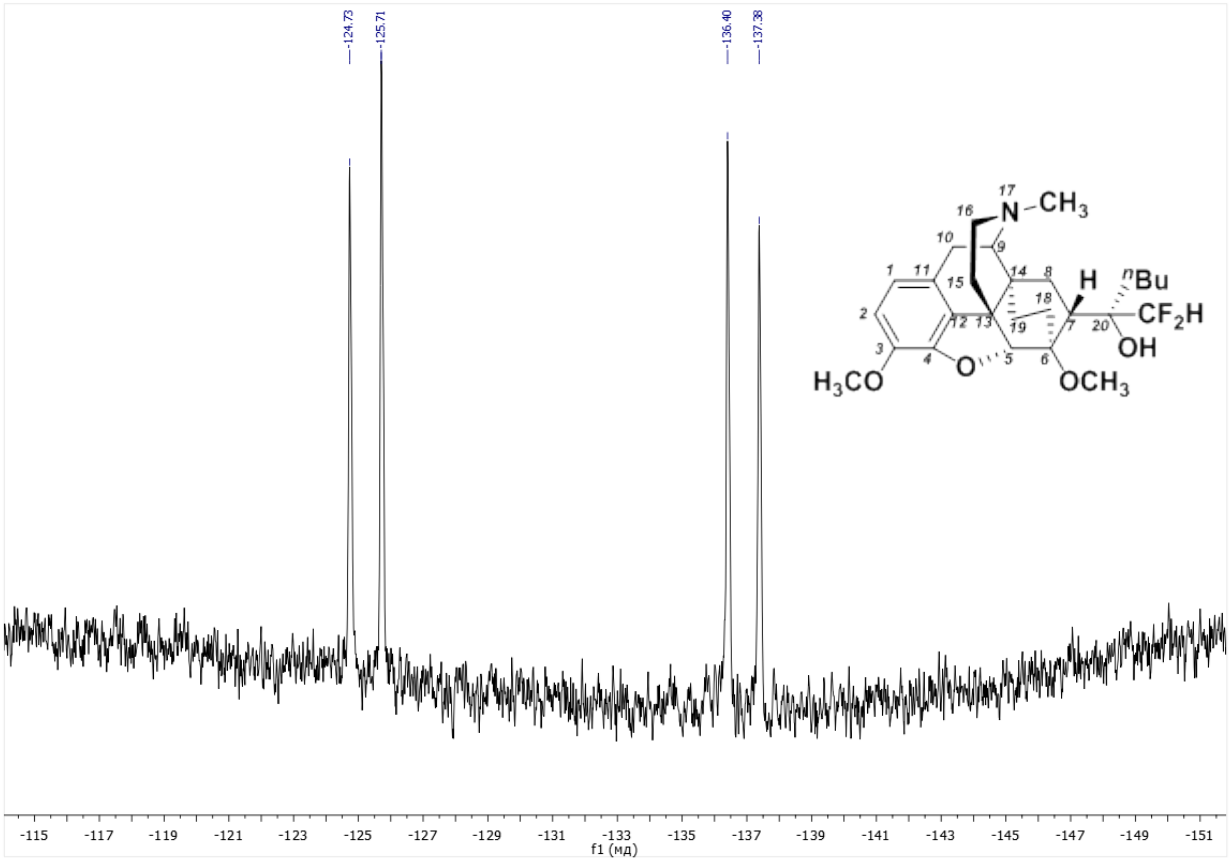


Figure S71. $^{19}F\{^{1}H\}$ NMR spectra of compound **39c**.

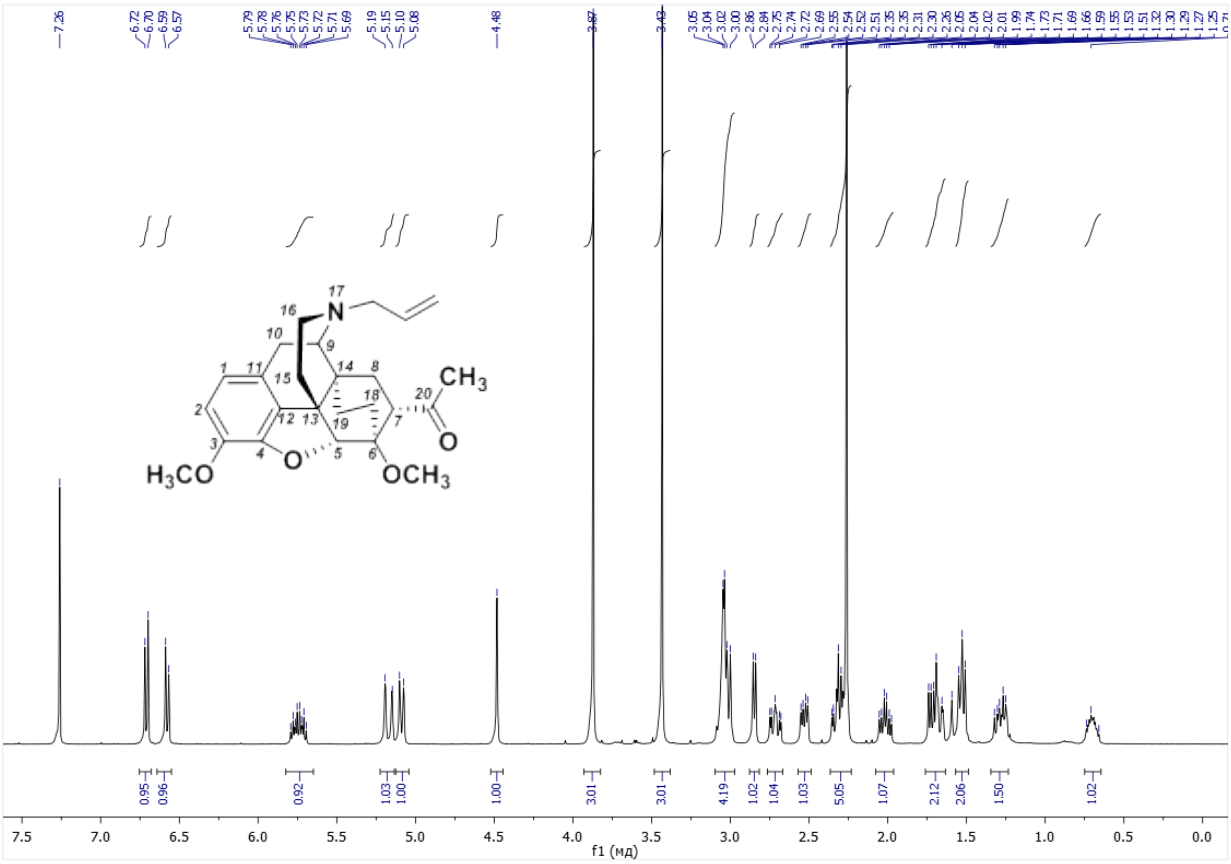


Figure S72. ^{1}H NMR spectra of compound **46**.

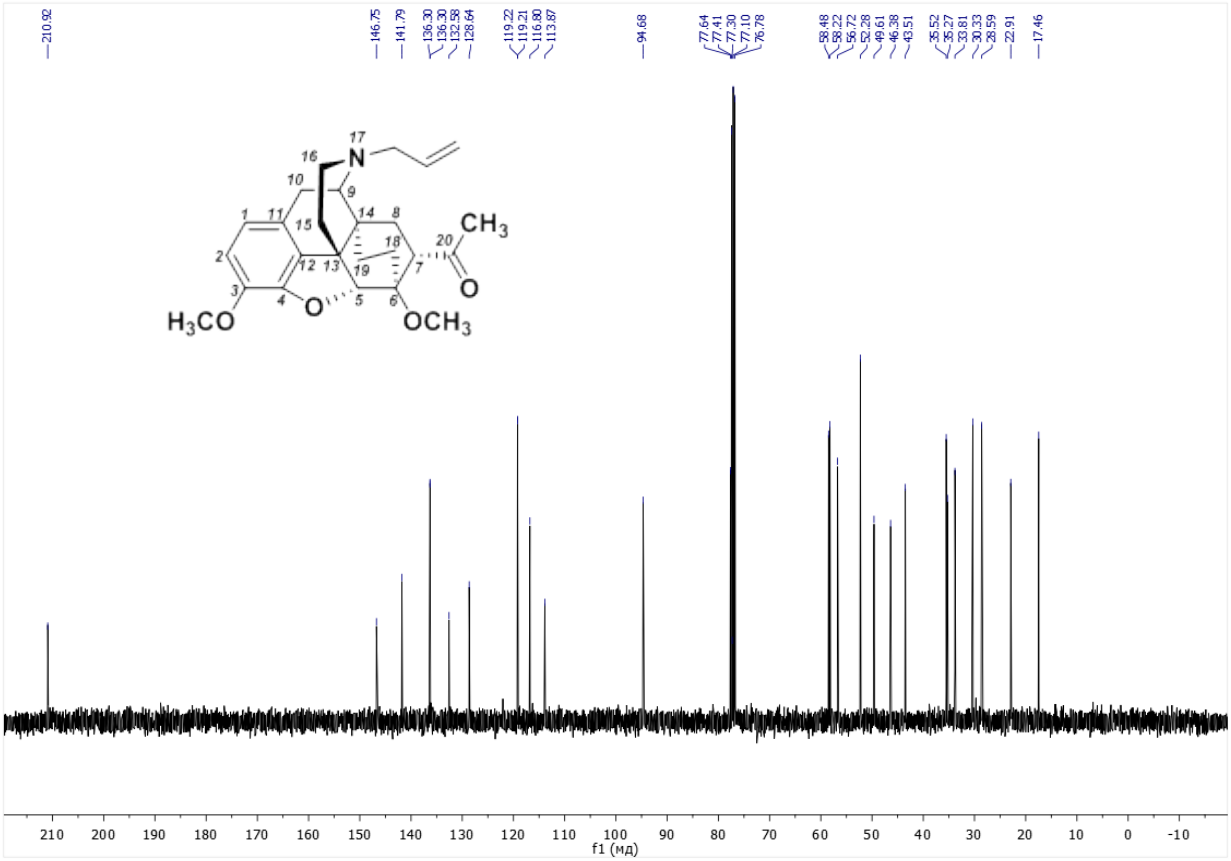


Figure S73. ^{13}C NMR spectra of compound **46**.

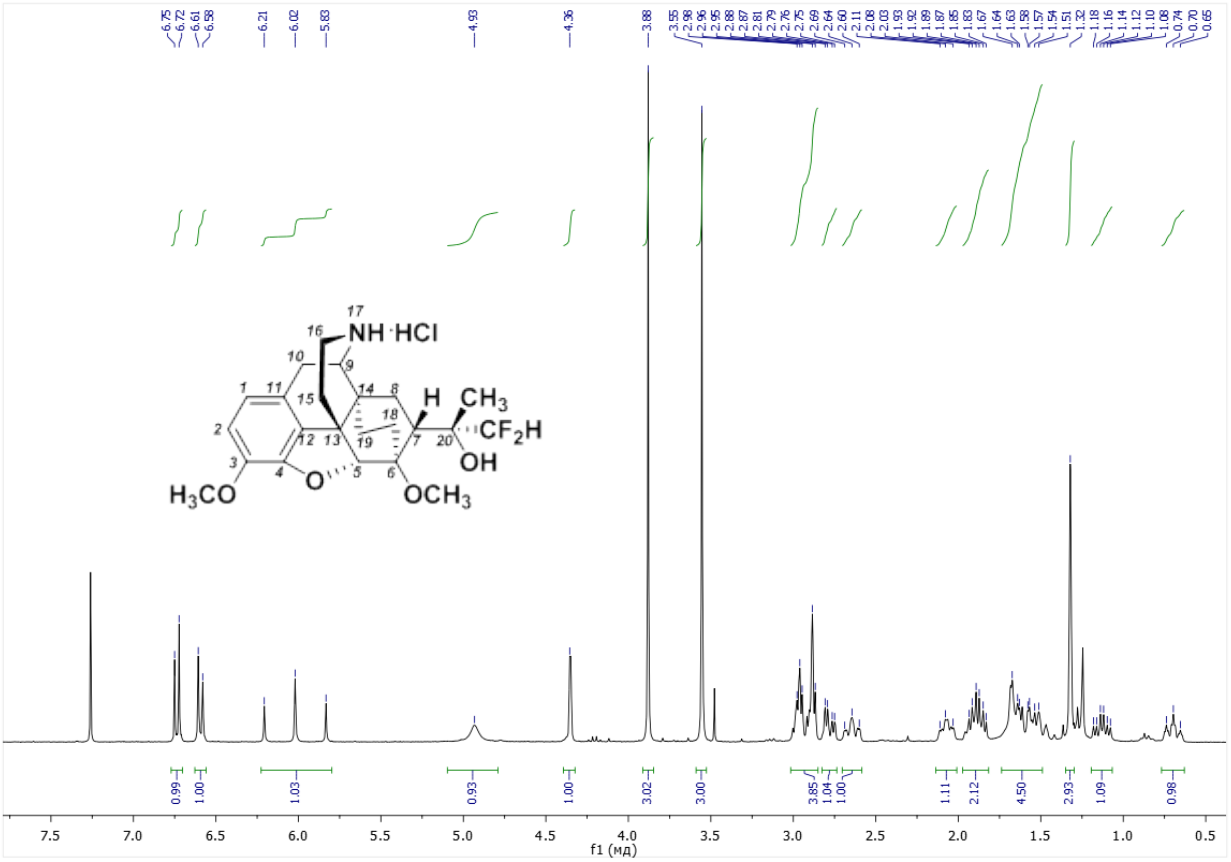


Figure S74. ^{1}H NMR spectra of compound **41**.

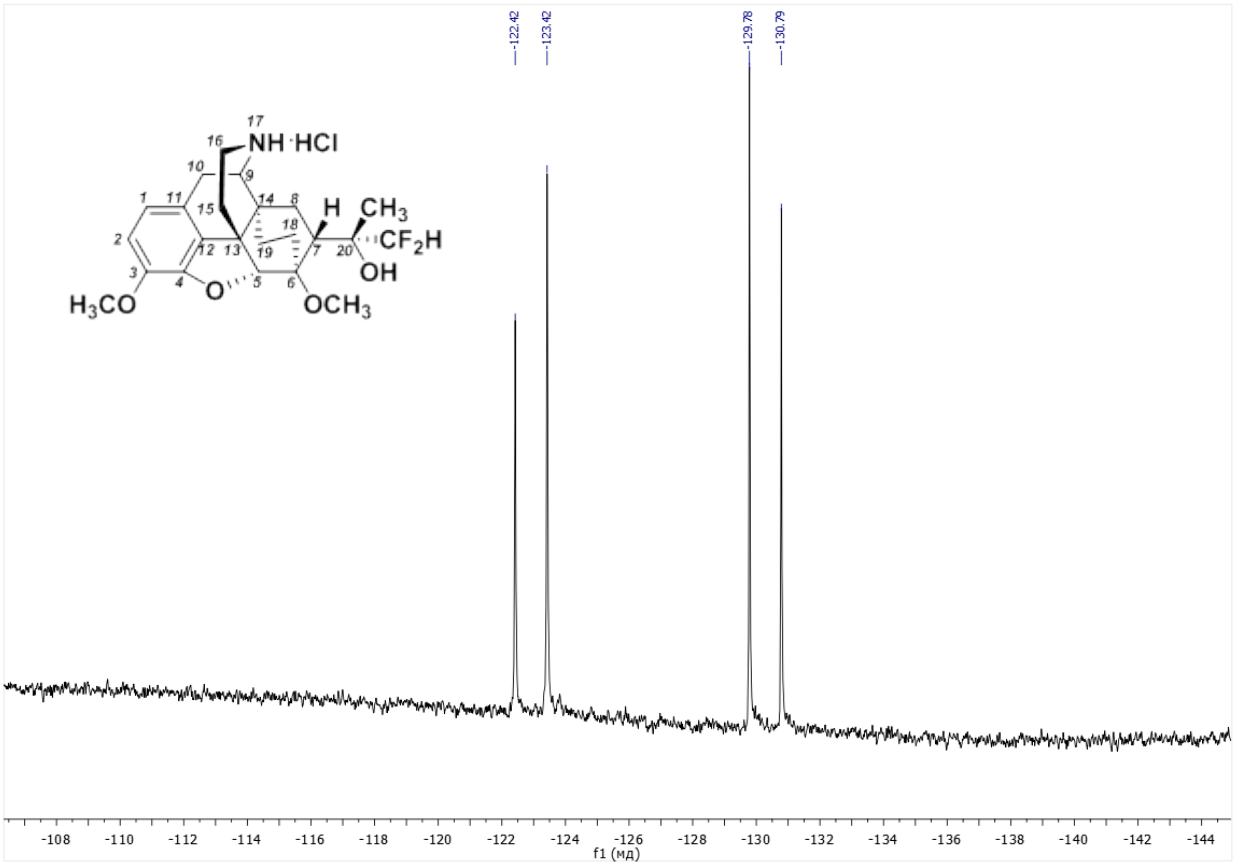


Figure S75. $^{19}F\{^{1}H\}$ NMR spectra of compound **41**.

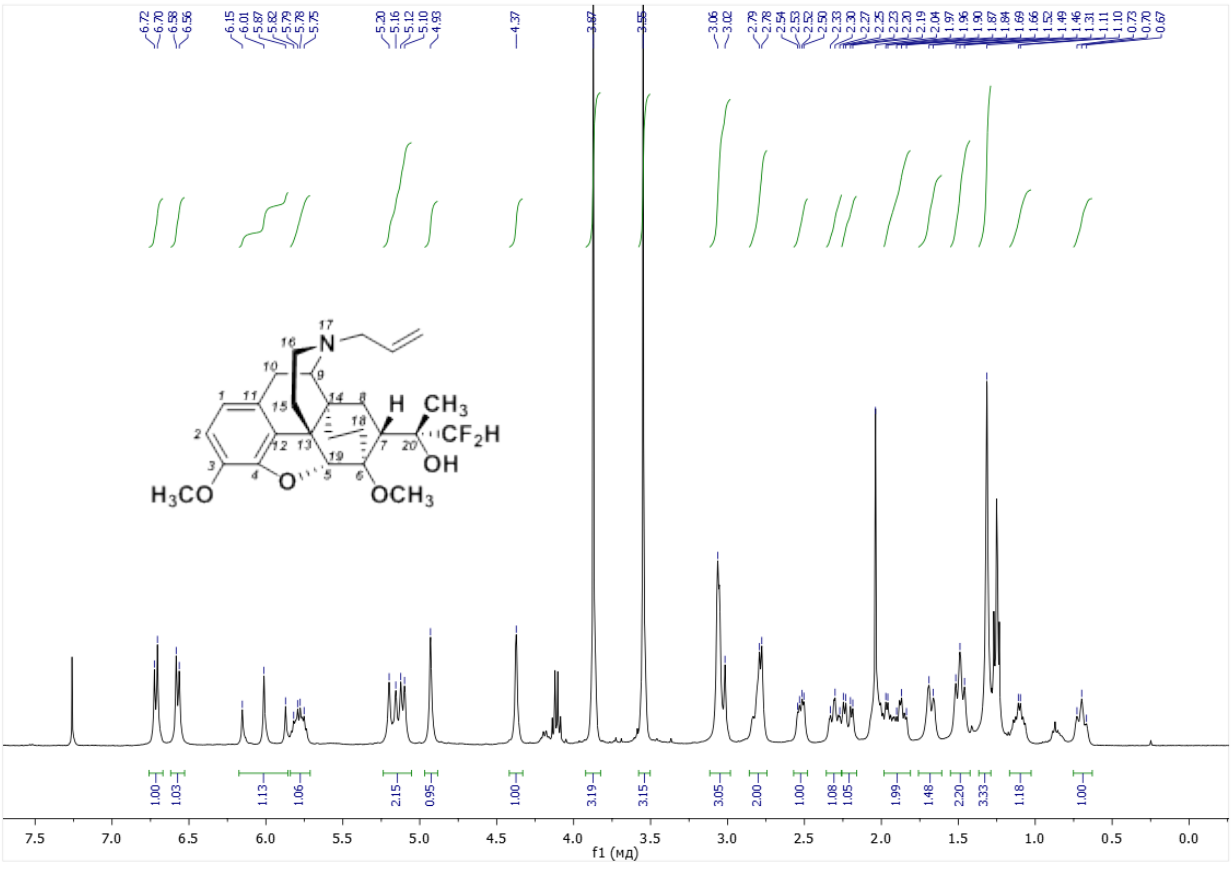


Figure S76. ^{1}H NMR spectra of compound **42**.

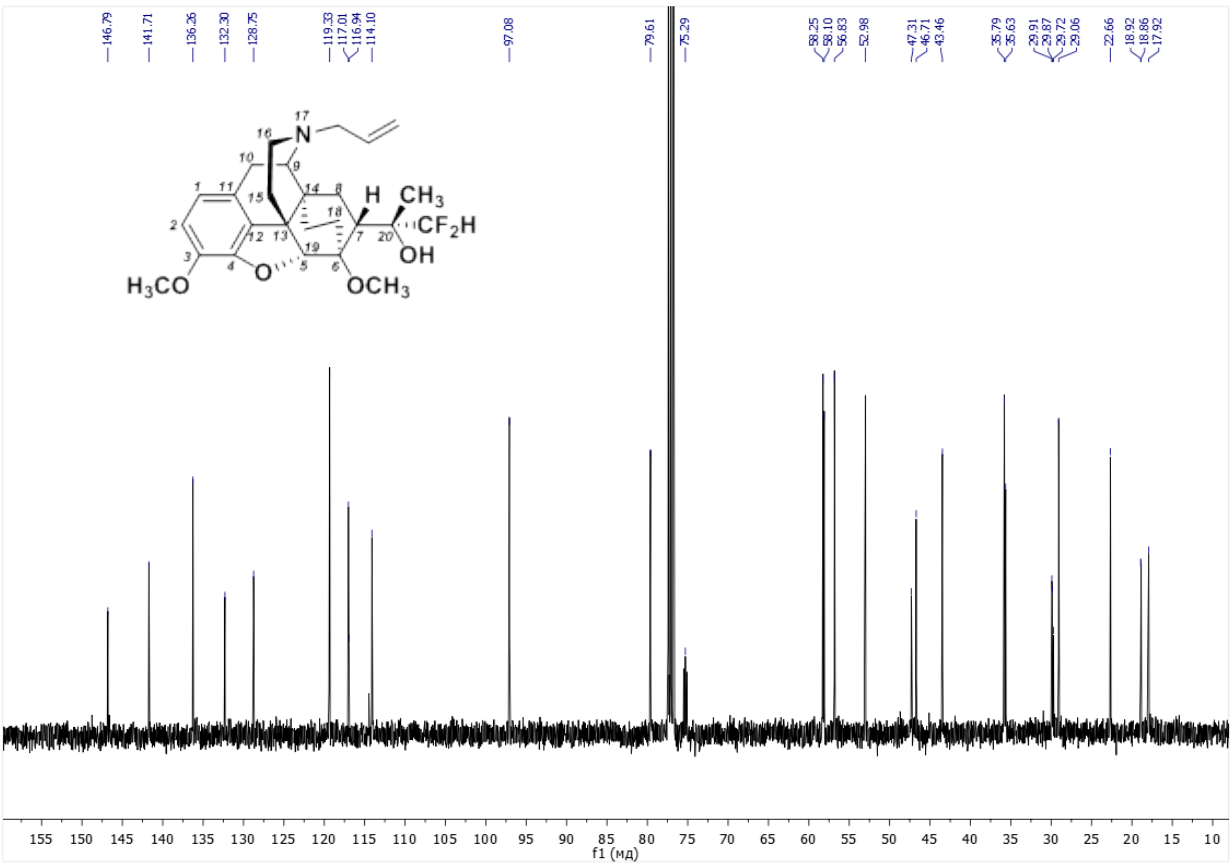


Figure S77. ^{13}C NMR spectra of compound **42**.

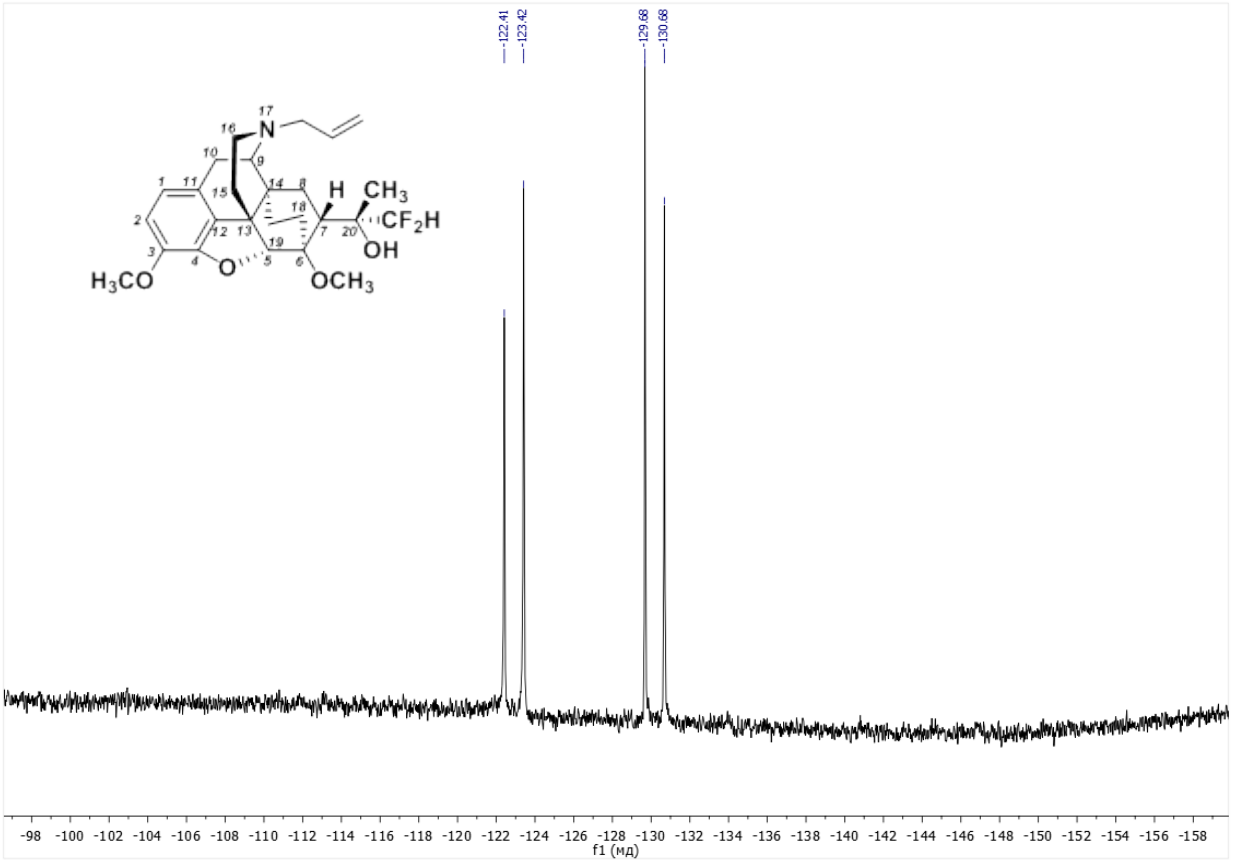


Figure S78. $^{19}F\{^{1}H\}$ NMR spectra of compound **42**.

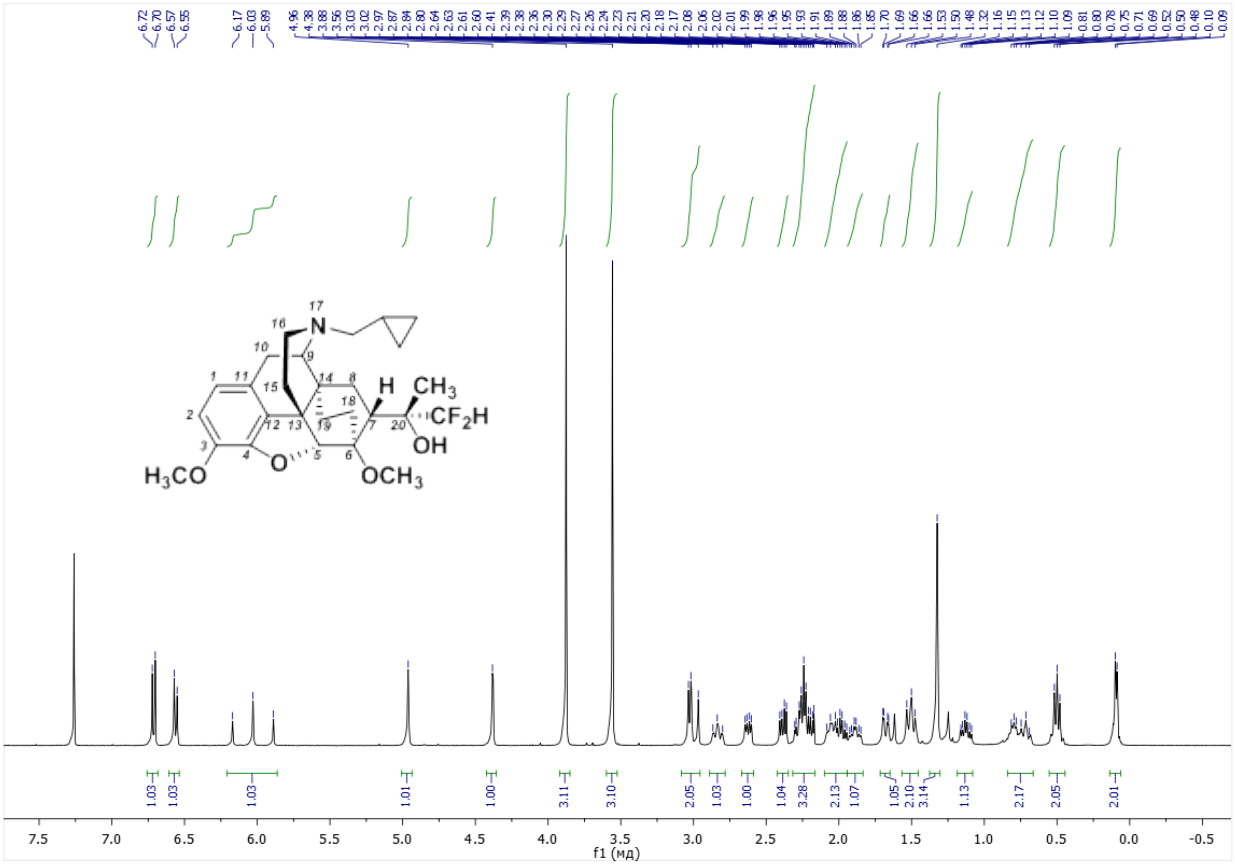


Figure S79. ^{1}H NMR spectra of compound **43**.

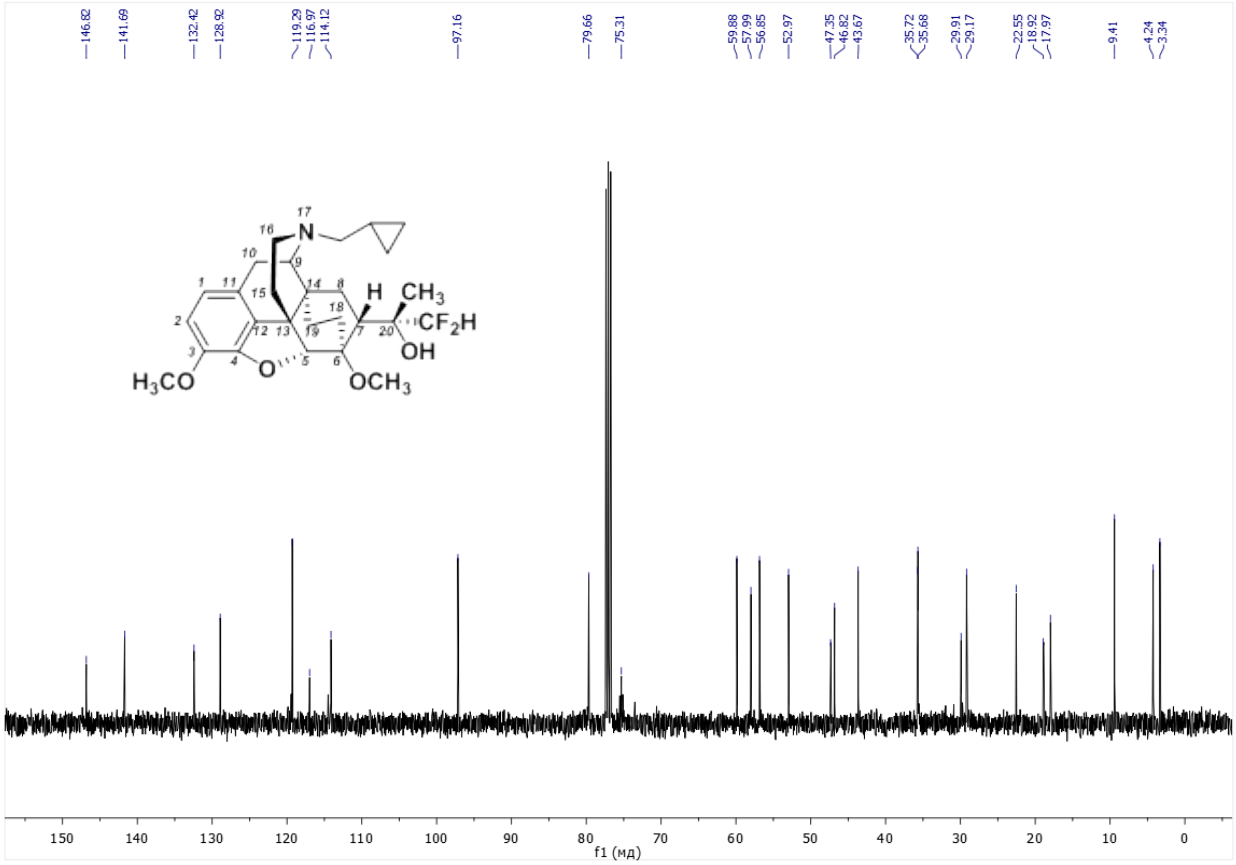


Figure S80. ^{13}C NMR spectra of compound **43**.

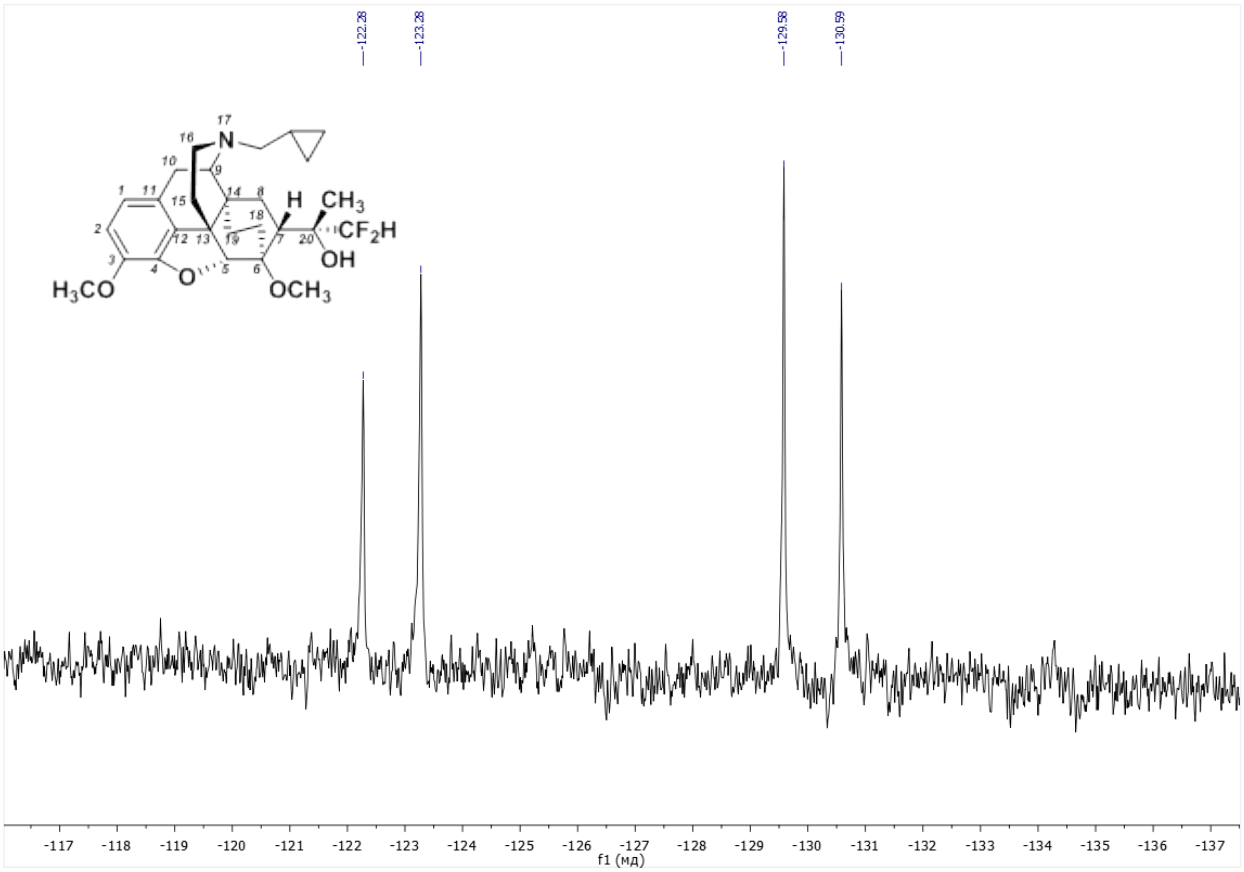


Figure S81. $^{19}F\{^{1}H\}$ NMR spectra of compound **43**.

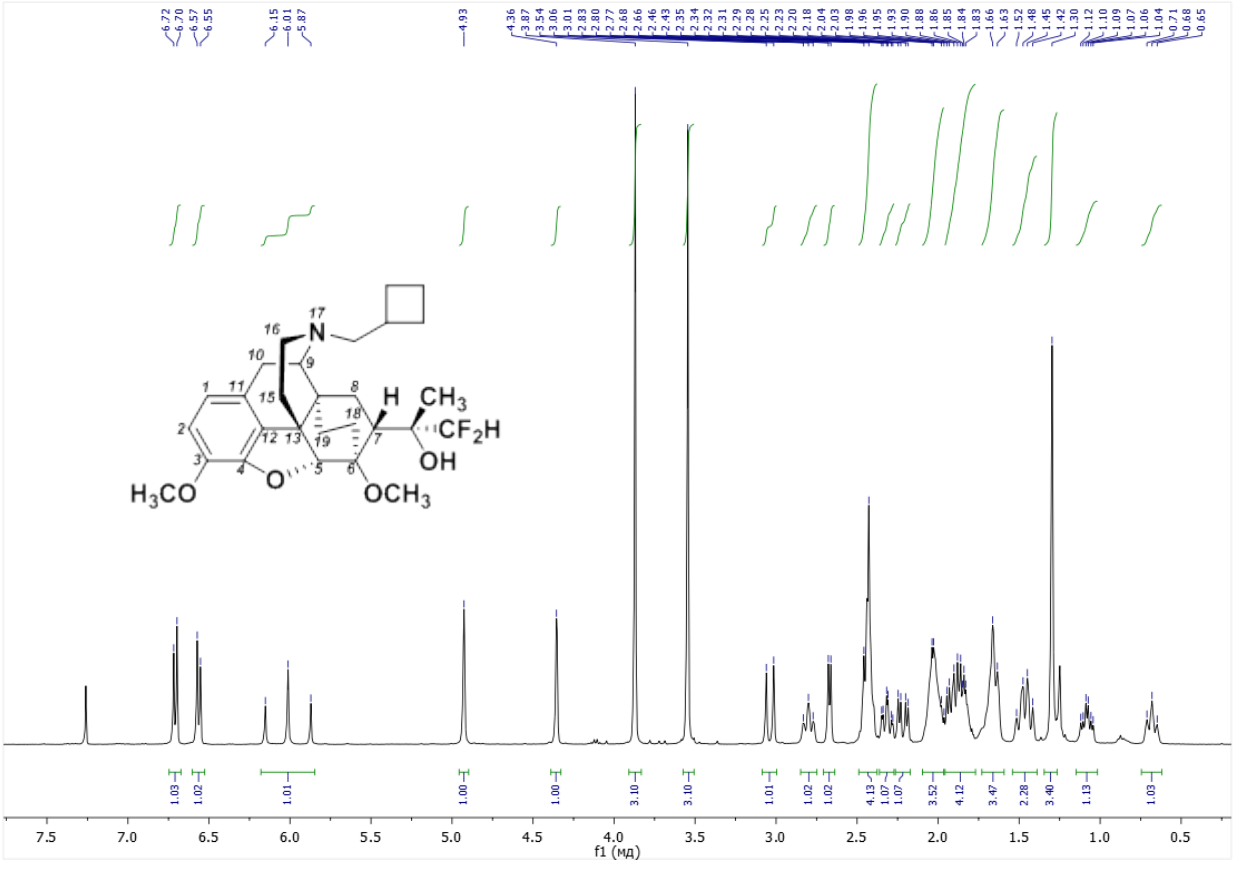


Figure S82. ^{1}H NMR spectra of compound **44**.

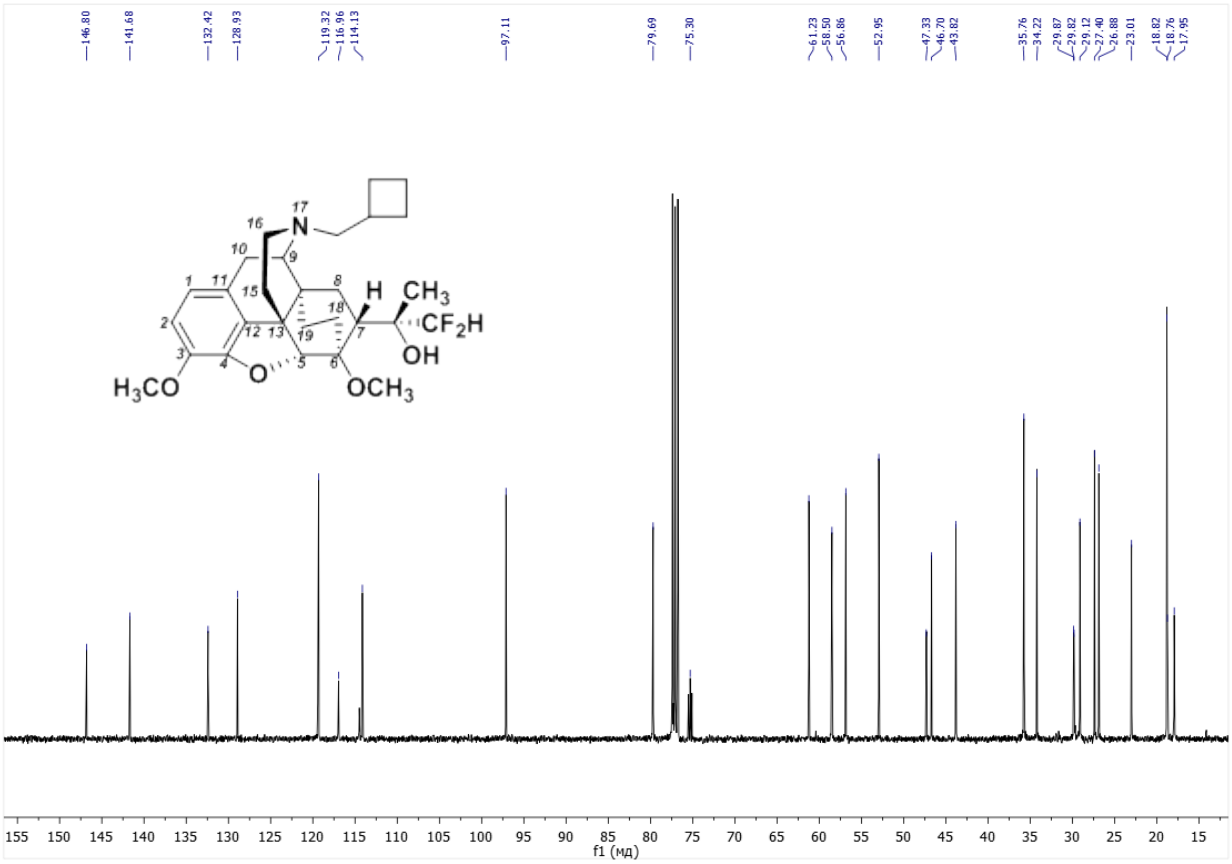


Figure S83. ^{13}C NMR spectra of compound **44**.

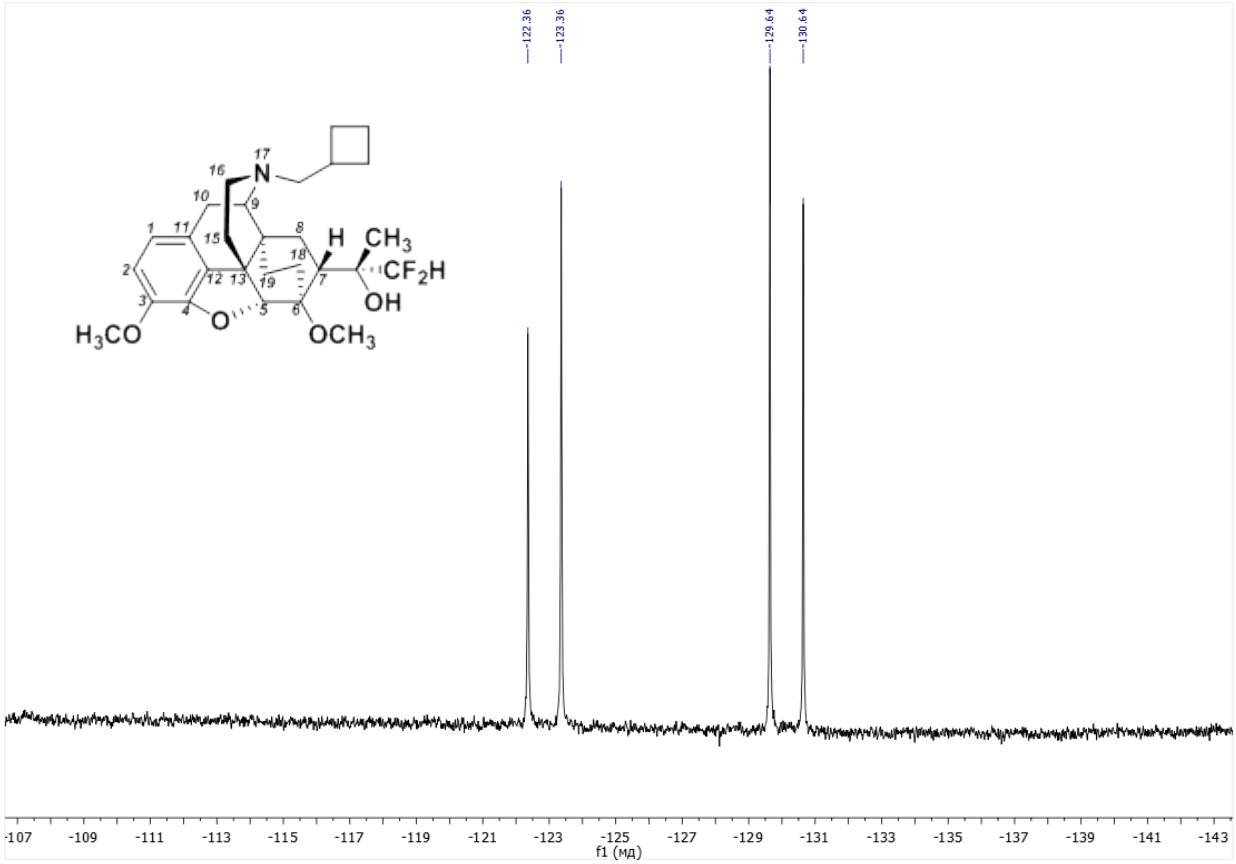


Figure S84. $^{19}F\{^{1}H\}$ NMR spectra of compound **44**.

5. References

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[2] I. V. Sandulenko, E. S. Kovaleva, A. S. Peregudov, V. N. Kalinin, S. K. Moiseev, *ChemistrySelect*, 2016, **1**, 1004-1005.

[3] O.V. Dolomanov, L.J. Bourhis, R.J. Gildea, J.A.K. Howard and H. Puschmann, *J. Appl. Cryst.* 2009, **42**, 339-341.

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