Electronic Supplementary Material (ESI) for ChemComm.

Biomimetic synthesis of tramadol

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1. General experimental procedures

Chemistry

Electrospray ionization (ESI) mass spectra were acquired at the Analytical Department of Grenoble University on an Esquire 300 Plus instrument (Bruker Daltonics) with a nanospray inlet. Combustion analyses were performed at the Analytical Department of Grenoble University; Silica gel F-254 plates (0.25 mm; Merck) were used for thin-layer chromatography (TLC), and silica gel 60 (200–400 mesh; Merck) was used for flash chromatography. Unless otherwise stated, reagents were obtained from commercial sources and were used without further purification.

NMR spectroscopy

NMR spectroscopic data were recorded on Brüker AC-400 instrument (400 MHz) and at 400 and 500 MHz Varian Inova spectrometer. Chemical shifts are reported in parts per million (δ), with use of the residual $CDCl_3$ signal (δH 7.26, δC 77.2) and CD_3OD signal (δH 3.31, δC 49.0) as internal standards for ^1H and ^{13}C NMR. Coupling constants (*J*) are given in Hz.

UHPLC-PDA-ESI-MS

UHPLC-TOF-MS analyses were performed on a Waters Acquity UPLC system coupled to a Waters Micromass-LCT Premier Time of Flight Mass spectrometer (Milford, MA, USA), equipped with an electrospray interface (ESI). Compound separation were performed on a C_{18} column (Waters Acquity UPLC BEH C_{18}, 150 mm x 2.1 mm i.d.; 1.7 µm, Waters, Milford, MA, USA). The mobile phase consisted of H_2O (A) and acetonitrile (B), each containing 0.1% formic acid (v/v). For high resolution detection, the following gradient was used: from 5-95% B in 30 min at a flow rate of 460 µL. The auto sampler and the column oven were set at 10 and 40°C, respectively. Injection volume was 2 µL. Detection was performed in positive

ionization mode in the 100-1300 Da range with acquisition times of 0.3 sec in W-mode. The ESI conditions were set as follows: capillary voltage 2400 V, cone voltage 40 V, source temperature 120°C, desolvation temperature 300°C, cone gas flow 20 L/h, desolvation gas flow 800 L/h, and MCP (micro channel plate) detector voltage 2500 V.

HPLC-PDA-ESI-MS analysis of the crude reaction mixture containing the Tramadol isomers (11 and **12)**

HPLC-PDA-ESIMS analyses were conducted on an HP 1100 system equipped with a photodiode array detector (Agilent Technologies, Santa Clara, CA, USA) connected to a Finnigan MAT LCQ ion-trap mass spectrometer (Finnigan, San Jose, CA, USA), equipped with a Finnigan electrospray interface (ESI). The HPLC conditions were as follows: X-Bridge C18 column (5 µm, 250 x 4.6 mm i.d.; Waters); solvent system: CH_3CN-H_2O, both containing 0.1% formic acid; gradient mode: 5% to 100% CH_3CN in 60 min, 100% CH_3CN for 5 min; flow rate: 1 mL/min; injection volume: 20 µL; sample concentration: 10 mg/mL in MeOH. The UV absorbance was measured at 210 nm, and the UV-PDA spectra were recorded between 190 and 600 nm (step 2 nm). The ESIMS conditions were as follows: capillary voltage: 30 V; capillary temperature: 200 °C; source voltage: 4.5 kV; source current: 80 µA; nitrogen was used as the sheath gas; positive and negative ion modes. The spectra (180-1200 Da) were recorded every 3 seconds.

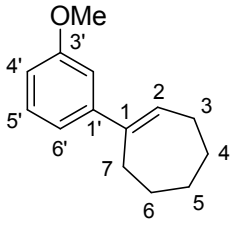
Semi-preparative HPLC-UV isolation of Tramadol from the crude reaction mixture

HPLC-UV preparative analysis was performed with an Armen modular spot prep II (Saint-Avé, France), equipped with a UV detector. The HPLC conditions were as follows: X-Bridge

C_{18} column (5 µm, 250 x 19 mm i.d.; Waters); solvent system: CH_3CN-H_2O, both containing 0.1% formic acid; gradient mode: 5% to 30% CH_3CN in 40 min, 40% to 100% CH_3CN in 5 min and 100% CH_3CN in 5 min; flow rate: 15 mL/min; injection volume: 200 µL; sample concentration: 20 mg/mL in MeOH. The UV absorbance was measured at 210 and 254 nm. 13 fractions were collected in the zone supposed to contain Tramadol.

2. Synthesis of intermediates

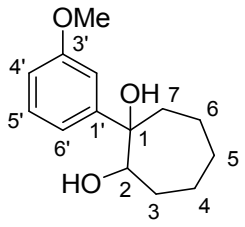
1-(3-Methoxyphenyl)cyclohept-1-ene (6):



To a solution of bromoanisole (1.0 g, 5.35 mmol) in anhydrous THF (10 mL) was added a 2.5 M solution of *n*-BuLi in hexanes (2.15 mL, 5.35 mmol) at -78 °C, and the mixture was stirred at -78 °C for 45 min. A solution of cycloheptanone (545 mg, 4.86 mmol) in anhydrous THF (5 mL) was then added and the mixture was stirred at -78 °C for a further 2 h. The solvents were removed under reduced pressure then the residue was diluted into distilled water and the mixture extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure to afford a yellow oil, which was purified by flash chromatography on silica gel (eluent CH_2Cl_2) to afford 1-(3-methoxyphenyl)cycloheptanol (984 mg, 92%) as a pure colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (t, 1H, J = 8.0 Hz, $H_{5'}$), 7.07-7.13 (m, 2H, $H_{2',6'}$), 6.80 (dd, 1H, J = 8.0 Hz, 2.5 Hz, $H_{4'}$), 3.83 (s, 3H, OCH_3), 1.55-2.10 (m, 12H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7 ($C_{3'}$), 152.9 ($C_{1'}$), 129.4 ($C_{5'}$), 117.1 ($C_{6'}$), 111.7, 110.9

($C_{2'}$, $C_{4'}$), 77.2 (C_1), 55.4 (O*C*H$_3$), 43.4 ($C_{2,7}$), 29.3 ($C_{4,5}$), 22.8 ($C_{3,6}$). MS (ESI) *m/z* 219 (M–H)$^-$. The obtained alcohol was dehydrated to **6** as follows. To a solution of 1-(3-methoxyphenyl)cyclo-heptanol (964 mg, 4.38 mmol) in CH_2Cl_2 (20 mL) was added trifluoroacetic acid (336 μL, 4.38 mmol) and the mixture was stirred at 25 °C for 1 h. Water was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated under reduced pressure to afford **6** (750 mg, 100%) as a yellow oil which was analytically pure and used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, 1H, *J* = 8.0 Hz, $H_{5'}$), 7.00 (ddd, 1H, *J* = 8.0 Hz, 1.6 Hz, 1.0 Hz, $H_{6'}$), 6.95 (dd, 1H, *J* = 2.5 Hz, 1.6 Hz, $H_{2'}$), 6.83 (ddd, 1H, *J* = 8.0 Hz, 2.5 Hz, 1.0 Hz, $H_{4'}$), 6.19 (t, 1H, *J* = 6.8 Hz, H_2), 3.87 (s, 3H, OC*H*$_3$), 2.68 (m, 2H, C*H*$_2$), 2.36 (m, 2H, C*H*$_2$), 1.91 (m, 2H, C*H*$_2$), 1.60-1.75 (m, 4H, C*H*$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6 ($C_{3'}$), 146.6 (C_1), 145.0 ($C_{1'}$), 130.6, 129.1 (C_2, $C_{5'}$), 118.3 ($C_{6'}$), 111.6, 111.6 ($C_{2'}$, $C_{4'}$), 55.2 (O*C*H$_3$), 32.9 (*C*H$_2$), 32.8 (*C*H$_2$), 28.9 (*C*H$_2$), 27.0 (*C*H$_2$), 26.9 (*C*H$_2$).

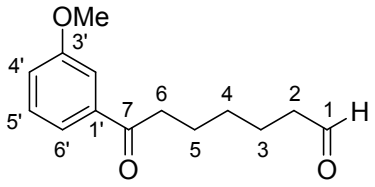
1-(3-Methoxyphenyl)cycloheptane-1,2-diol (7):



To a solution of **6** (7.28 g, 36.0 mmol) in a mixture of THF (150 mL) and water (50 mL) were added a 4% (w/v) aqueous solution of osmium tetroxide OsO_4 (11.5 mL) and a 50% aqueous solution of *N*-methylmorpholine *N*-oxide (NMO, 14 mL) and the mixture was stirred at 25 °C for 96 h. A saturated aqueous solution of $NaHSO_3$ (50 mL) was added and the mixture was stirred at 25 °C for 30 min, then extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and the filtrate was

concentrated under reduced pressure to afford **7** (8.00 g, 94%) as a brown oil which was analytically pure and used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, 1H, J = 8.0 Hz, $H_{5'}$), 7.10 (dd, 1H, J = 2.5 Hz, 1.6 Hz, $H_{2'}$), 7.04 (ddd, 1H, J = 8.0 Hz, 1.6 Hz, 0.8 Hz, $H_{6'}$), 6.79 (ddd, 1H, J = 8.0 Hz, 2.5 Hz, 0.8 Hz, $H_{4'}$), 3.96 (dd, 1H, J = 10.5 Hz, 2.6 Hz, H_2), 3.82 (s, 3H, OCH_3), 1.45-2.05 (m, 10H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8 ($C_{3'}$), 150.3 ($C_{1'}$), 129.5 ($C_{5'}$), 117.0 ($C_{6'}$), 112.0, 111.1 ($C_{2'}$, $C_{4'}$), 78.9 (C_1), 55.3 (OCH$_3$), 39.0 (CH$_2$), 29.8 (CH$_2$), 26.7 (CH$_2$), 22.8 (CH$_2$), 20.1 (CH$_2$).

7-(3-Methoxyphenyl)-7-oxoheptanal (8):



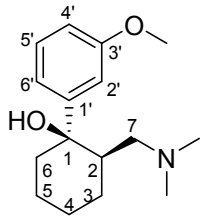
To a solution of **7** (8.00 g, 33.9 mmol) in a mixture of THF (200 mL) and water (50 mL) was added sodium periodate ($NaIO_4$, 9.90 g, 46.3 mmol) and the mixture was stirred at 25°C for 48 h. The suspension was filtered and the solid was washed three times with ethyl acetate. The filtrate was then extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated under reduced pressure to afford a black oil which was purified by flash chromatography on silica gel (eluent CH_2Cl_2/MeOH 99/1) to afford **8** (6.64 g, 84%) as a pure brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (t, 1H, J = 1.7 Hz, H_1), 7.53 (ddd, 1H, J = 7.9 Hz, 1.5 Hz, 0.9 Hz, $H_{6'}$), 7.48 (dd, 1H, J = 2.6 Hz, 1.5 Hz, $H_{2'}$), 7.37 (t, 1H, J =7.9 Hz, $H_{5'}$), 7.10 (ddd, 1H, J = 7.9 Hz, 2.6 Hz, 0.9 Hz, $H_{4'}$), 3.86 (s, 3H, OCH_3), 2.97 (t, 2H, J = 7.3 Hz, H_6), 2.47 (td, 2H, J = 7.3 Hz, 1.7 Hz, H_2), 1.76 (p, 2H, J = 7.3 Hz, CH_2), 1.69 (p, 2H, J = 7.3 Hz, CH_2), 1.40-1.47 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8 (C_1), 200.1 (C_7),

160.0 ($C_{3'}$), 138.5 ($C_{1'}$), 129.8 ($C_{5'}$), 120.9 ($C_{6'}$), 119.6 ($C_{4'}$), 112.5 ($C_{2'}$), 55.6 (OCH_3), 43.9 (C_2), 38.5 (C_6), 29.0 (C_4), 24.2 (C_5), 22.1 (C_3). MS (ESI) *m/z* 215 $[M–H_3O]^-$, 233 $[M–H]^-$.

3. Synthesis of (±)-(*1R,2R*)-2-(dimethylaminomethyl)-1-(3-methoxyphenyl)cyclohexanol (9) and (±)-(*1R,2S*)-2-(dimethylaminomethyl)-1-(3-methoxyphenyl)cyclohexanol (10).

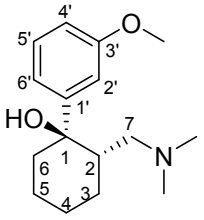
A solution of dicarbonyl **8** (262 mg, 1.15 mmol) and dimethylamine (2 M in THF, 103.7 mg, 2.30 mmol) in anhydrous THF (86 mL) was refluxed for 24 h. Then, $NaBH_3CN$ (108 mg, 2.85 mmol) was added and the mixture was stirred at room temperature for 24 h. Water was added and the mixture was extracted with CH_2Cl_2. The organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure to afford 239 mg of crude material. The later was subjected to purification by semi-preparative HPLC. In order to localize the Tramadol in the reaction mixture the crude material was analyzed by HPLC-PDA-ELSD-ESI-MS with an X-Bridge C_{18} column (5 µm, 250 x 4.6 mm i.d.; Waters). Two peaks, both with $[M+H]^+$ ions at *m/*z 264, and eluting between 16-22 min were attributed to the presence of different stereoisomers of Tramadol. This deduction was confirmed by the HPLC-PDA-ESI-MS analysis of a Tramadol standard in the same conditions. The analytical HPLC conditions were scaled-up for semi-preparative HPLC using a gradient transfer method [Guillarme et al., *Eur. J. Pharma. and Biopharma*. 2008, 68, 430-440]. Four injections were made from a solution at 20 mg/200 µL. A total of 13 fractions (F1-F13) were obtained from the region considered to contain the Tramadol isomers based on the LC-MS results. Fractions 1–3 yielded pure (±)-(*1R,2S*)-Tramadol (**10**) and fraction 9 afforded pure (±)-(*1R,2R*)-Tramadol (**9**). Beside isomers of tramadol, compounds **11**, **12** and **13** were detected.

(±)-(*1R,2R*)-2-(Dimethylaminomethyl)-1-(3-methoxyphenyl)cyclohexanol (9):



^{1}H NMR (CD_3OD, 500 MHz) δ 1.50 (qt, 1H, J_1 = 12.5 Hz, J_2 = 3.7 Hz, H_{4ax}), 1.61 (dt, 1H, J_1 = 12.8 Hz, J_2 = 3.4 Hz, H_{5eq}), 1.70 (m, 1H, H_{6eq}), 1.72 (m, 1H, H_{3ax}), 1.81 (m, 1H, H_{3eq}), 1.82 (m, 1H, H_{5ax}), 1.87 (m, 1H, H_{4eq}), 1.88 (m, 1H, H_{6ax}), 2.10 (ddt, 1H, J_1 = 12.0 Hz, J_2 = 9.0 Hz, J_3 = 3.4 Hz, H_2), 2.32 (d, 1H, J_1 = 13.4 Hz, H_{7b}), 2.40 (s, 6H, $N(CH_3)_2$), 2.70 (dd, 1H, J_1 = 13.4 Hz, J_2 = 9.1 Hz, H_{7a}), 3.80 (s, 3H, OCH_3), 6.81 (dd, 1H, J_1 = 7.9 Hz, J_1 = 2.5 Hz, $H_{4'}$), 7.05 (d, 1H, J_1 = 7.9 Hz, $H_{6'}$), 7.09 (d, 1H, J_1 = 2.5 Hz, $H_{2'}$), 7.28 (t, 1H, J_1 = 7.9 Hz, $H_{5'}$). ^{13}C NMR (CD_3OD, 126 MHz) δ 22.7 (C_5), 26.6 (C_4), 27.6 (C_3), 41.9 (C_6), 43.8 (C_2), 45.3 ($N(CH_3)_2$), 55.6 (OCH_3), 62.1 (C_7), 76.4 (C_1), 112.3 ($C_{2'}$), 112.7 ($C_{4'}$), 118.3 ($C_{6'}$), 130.4 ($C_{5'}$), 151.1 ($C_{1'}$), 161.3 ($C_{3'}$). ESI-HRMS *m/z* 264.1951 $[M+H]^+$ (calculated for $C_{16}H_{26}NO_2$, 264.1964, Δppm = 4.9).

(±)-(*1R,2S*)-2-(Dimethylaminomethyl)-1-(3-methoxyphenyl)cyclohexanol (10):

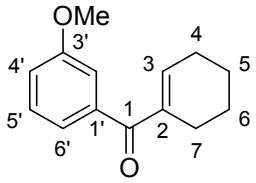


^{1}H NMR (CD_3OD, 500 MHz) δ 1.60 (m, 1H, H_{4eq}), 1.63 (m, 1H, H_{3eq}), 1.66 (m, 1H, H_{4ax}), 1.69 (m, 1H, H_{5eq}), 1.82 (m, 1H, H_{6eq}), 1.86 (m, 1H, H_{5ax}), 2.05 (m, 1H, H_{3ax}), 2.07 (m, 1H,

H_{6ax}), 2.19 (dq, 1H, J_1 = 9.0 Hz, J_2 = 5.0 Hz, H_2), 2.42 (dd, 1H, J_1 = 13.1 Hz, J_2 = 5.0 Hz, H_{7b}), 2.58 (s, 6H, $N(CH_3)_2$), 3.04 (dd, 1H, J_1 = 13.1 Hz, J_2 = 9.0 Hz, H_{7a}), 3.81 (s, 3H, OCH_3), 6.88 (ddd, 1H, J_1 = 8.1 Hz, J_2 = 2.5 Hz, J_3 = 0.9 Hz, $H_{4'}$), 7.12 (m, 1H, $H_{6'}$), 7.15 (m, 1H, $H_{2'}$), 7.31 (t, 1H, J_1 = 8.1 Hz, $H_{5'}$). ^{13}C NMR (CD_3OD, 126 MHz) δ 22.2 (C_4), 22.3 (C_5), 25.3 (C_3), 35.8 (C_6), 43.3 (C_2), 44.1 ($N(CH_3)_2$), 55.5 (OCH_3), 59.9 (C_7), 74.9 (C_1), 113.2 ($C_{4'}$), 113.4 ($C_{2'}$), 119.3 ($C_{6'}$), 130.3 ($C_{5'}$), 148.9 ($C_{1'}$), 161.2 ($C_{3'}$). ESI-HRMS *m/z* 264.1951 $[M+H]^+$ (calculated for $C_{16}H_{26}NO_2$, 264.1964, Δppm = 4.9).

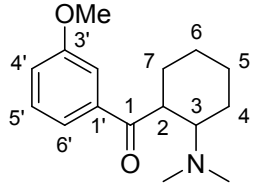
4. Spectral characterization of by-products 11, 12 and 13

Cyclohexen-1-yl-(3-methoxyphenyl)methanone (11):



^{1}H NMR (500 MHz, CD_3OD) δ 7.35 (t, 1H, J = 7.8 Hz, $H_{5'}$), 7.15 (dt, 1H, J = 7.8 Hz, 1.1 Hz, $H_{6'}$), 7.12 (d, 1H, J = 2.5 Hz, $H_{2'}$), 7.10 (ddd, 1H, J = 7.8 Hz, 2.5 Hz, 1.1 Hz, $H_{4'}$), 6.63 (tt, 1H, J = 3.8 Hz, 1.7 Hz, H_3), 3.83 (s, 3H, OCH_3), 2.37 (m, 2H, H_7), 2.30 (m, 2H, H_4), 1.75 (m, 2H, H_6), 1.69 (m, 2H, H_5). ^{13}C NMR (126 MHz, CD_3OD) δ 199.8 (C_1), 160.8 ($C_{3'}$), 146.1 (C_3), 141.0 ($C_{1'}$), 139.5 (C_2), 130.1 ($C_{5'}$), 122.3 ($C_{6'}$), 118.2 ($C_{4'}$), 114.8 ($C_{2'}$), 55.7 (OCH_3), 26.8 (C_4), 24.7 (C_7), 22.9 (C_6), 22.5 (C_5). HRMS (ESI) *m/z* 217.1220 $(M+H)^+$ (calcd for $C_{14}H_{17}O_2$, 217.1229, Δppm = 4.2).

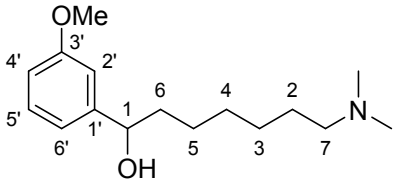
[2-(Dimethylamino)cyclohexyl)](3-methoxyphenyl)methanone (12):



^{1}H NMR (500 MHz, CD_3OD) δ 7.64 (dt, 1H, J = 8.0 Hz, 1.2 Hz, $H_{6'}$), 7.52 (dd, 1H, J = 2.6 Hz, 1.2 Hz, $H_{2'}$), 7.43 (t, 1H, J = 8.0 Hz, $H_{5'}$), 7.19 (ddd, 1H, J = 8.0 Hz, 2.6 Hz, 1.2 Hz, $H_{4'}$), 3.85 (s, 3H, OCH_3), 3.71 (td, 1H, J_1 = 11.0 Hz, 3.9 Hz, H_2), 3.16 (td, 1H, J = 11.0 Hz, 3.0 Hz, H_3), 2.31 (s, 6H, N(CH_3)$_2$), 2.00 (m, 1H, H_{7a}), 1.96 (m, 1H, H_{4a}), 1.91 (m, 1H, H_{5a}), 1.77 (m, 1H, H_{6a}), 1.45 (m, 1H, H_{7b}), 1.39 (m, 1H, H_{6b}), 1.38 (m, 1H, H_{4b}), 1.37 (m, 1H, H_{5b}). ^{13}C NMR (126 MHz, CD_3OD) δ 204.8 (C_1), 161.4 ($C_{3'}$), 139.1 ($C_{1'}$), 130.7 ($C_{5'}$), 121.7 ($C_{6'}$), 120.2 ($C_{4'}$), 113.8 ($C_{2'}$), 65.8 (C_3), 55.7 (OCH$_3$), 48.6 (C_2), 40.8 (N(CH$_3$)$_2$), 32.4 (C_4), 26.2 (C_6), 26.0 (C_5), 23.6 (C_3). HRMS (ESI) *m/z* 262.1797 $(M+H)^+$ (calcd for $C_{16}H_{24}NO_2$, 262.1807, Δppm = 3.8).

7-Dimethylamino-1-(3-methoxyphenyl)heptan-1-ol (Open form of Tramadol (13):*

The numbering of the compound below is not the one followed for nomenclature. It was chosen to be in line with the numbering adopted for Tramadol (structures above)



^{1}H NMR (CD_3OD, 500 MHz) δ 1.29 (m, 1H, $H_{5''}$), 1.34 (m, 2H, H_3), 1.37 (m, 2H, H_4), 1.41 (m, 1H, $H_{5'}$), 1.61 (m, 2H, H_2), 1.68 (m, 1H, $H_{6''}$), 1.75 (m, 1H, $H_{6'}$), 2.66 (s, 6H, N(CH_3)$_2$), 2.84 (t, 2H, J_1 = 8.2 Hz, H_7), 3.79 (s, 3H, OCH_3), 4.57 (t, 1H, J_1 = 7.1 Hz, H_1), 6.80 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.2 Hz, $H_{4'}$), 6.89 (d, 1H, J_1 = 8.3 Hz, $H_{6'}$), 6.90 (d, 1H, J_1 = 2.2 Hz, $H_{2'}$), 7.28 (t, 1H, J = 8.3 Hz, $H_{5'}$). ^{13}C NMR (CD_3OD, 126 MHz) δ 26.3 (C_2), 26.6 (C_5), 27.7 (C_3), 30.2 (C_4), 40.0 (C_6), 44.0 (N(CH$_3$)$_2$), 55.6 (OCH$_3$), 59.5 (C_7), 75.0 (C_1), 112.7 ($C_{2'}$), 113.5 ($C_{4'}$), 119.4 ($C_{6'}$), 130.3 ($C_{5'}$), 148.3 ($C_{1'}$), 161.1 ($C_{3'}$). HRMS (ESI) *m/z* 266.2137 $[M+H]^+$, (calculated for $C_{16}H_{28}NO_2$, 266.2120, Δppm = 6.4).

5. NMR spectra of the synthesized compounds

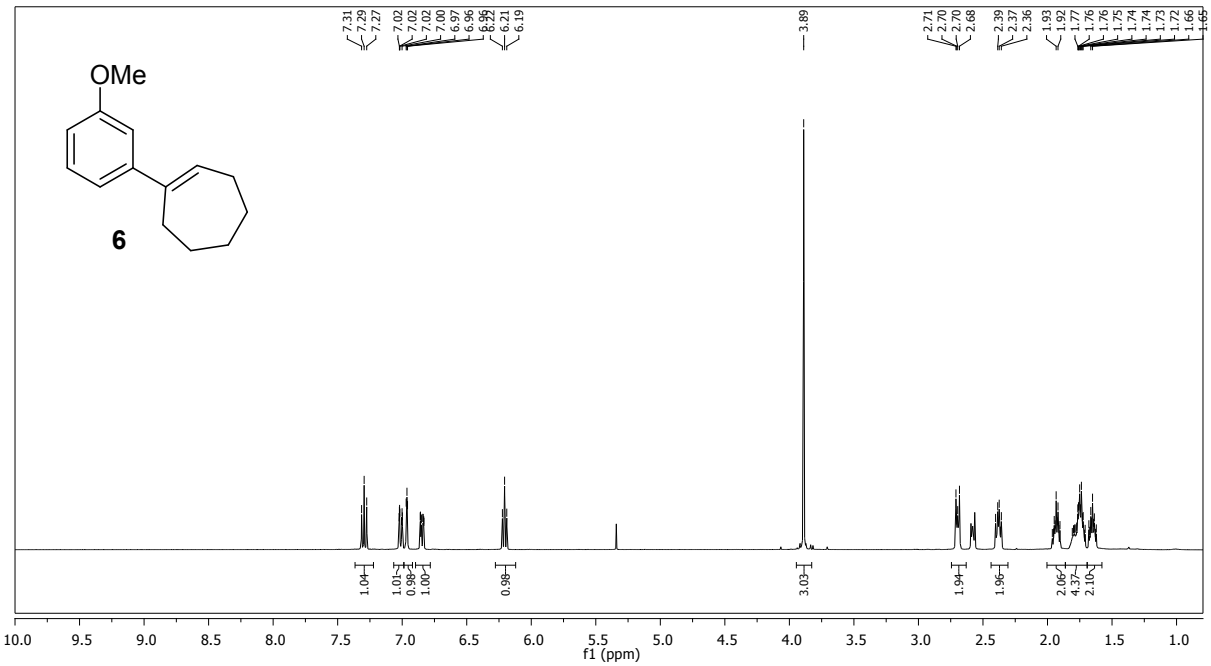


Figure 1S. ^{1}H NMR of compound **6** (400 MHz, $CDCl_3$).

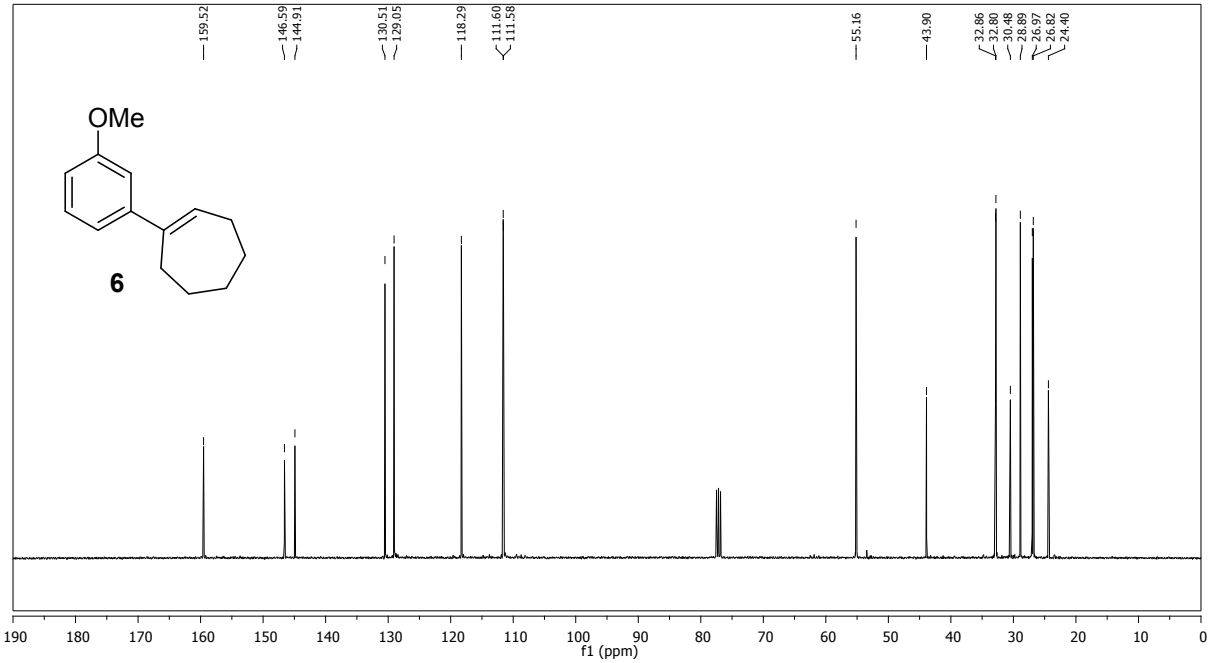


Figure 2S. ^{13}C NMR of compound **6** (125 MHz, $CDCl_3$).

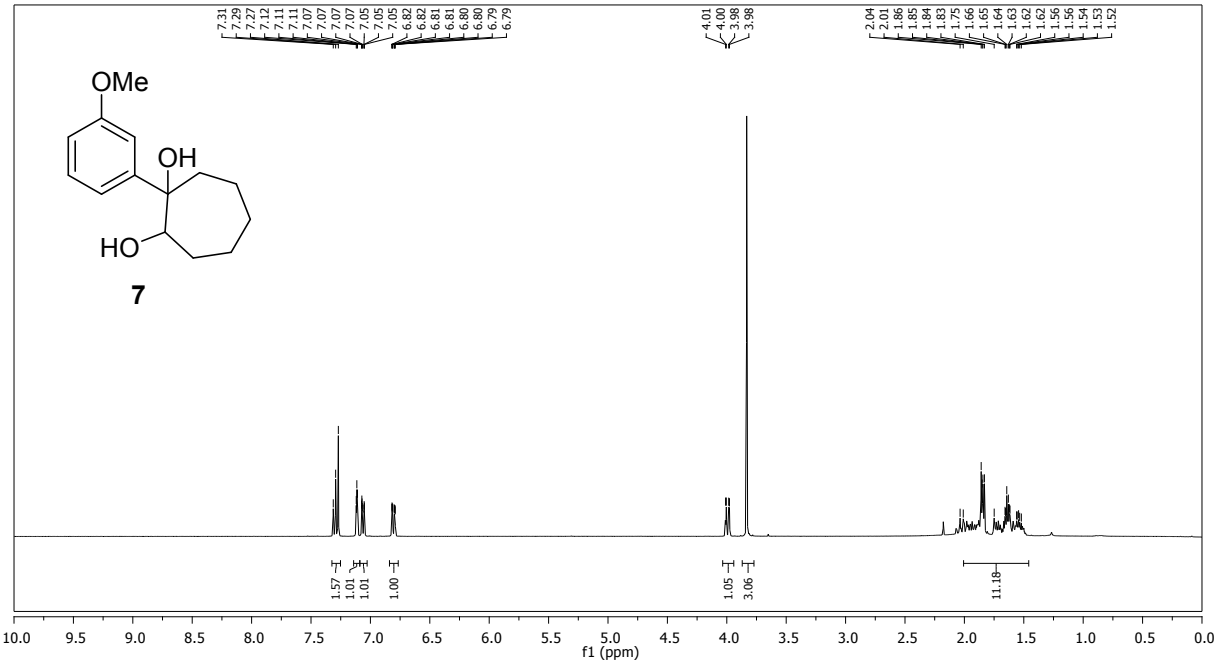


Figure 3S. ^{1}H NMR of compound **7** (400 MHz, $CDCl_3$).

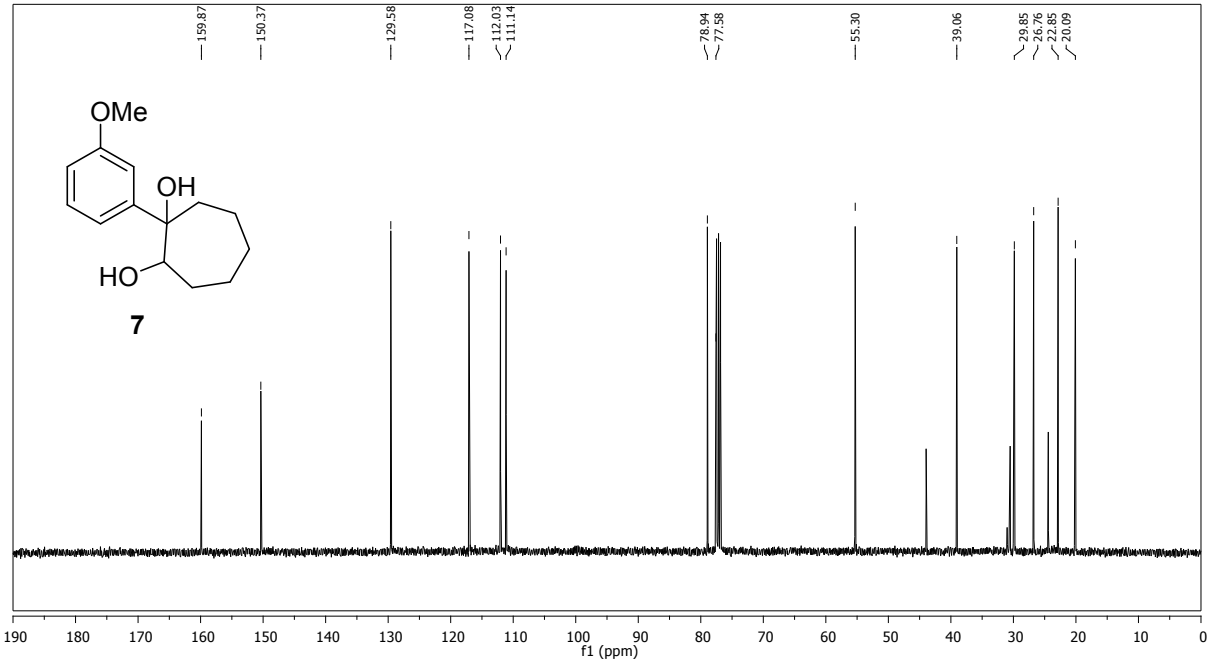


Figure 4S. ^{1}H NMR of compound **7** (125 MHz, $CDCl_3$).

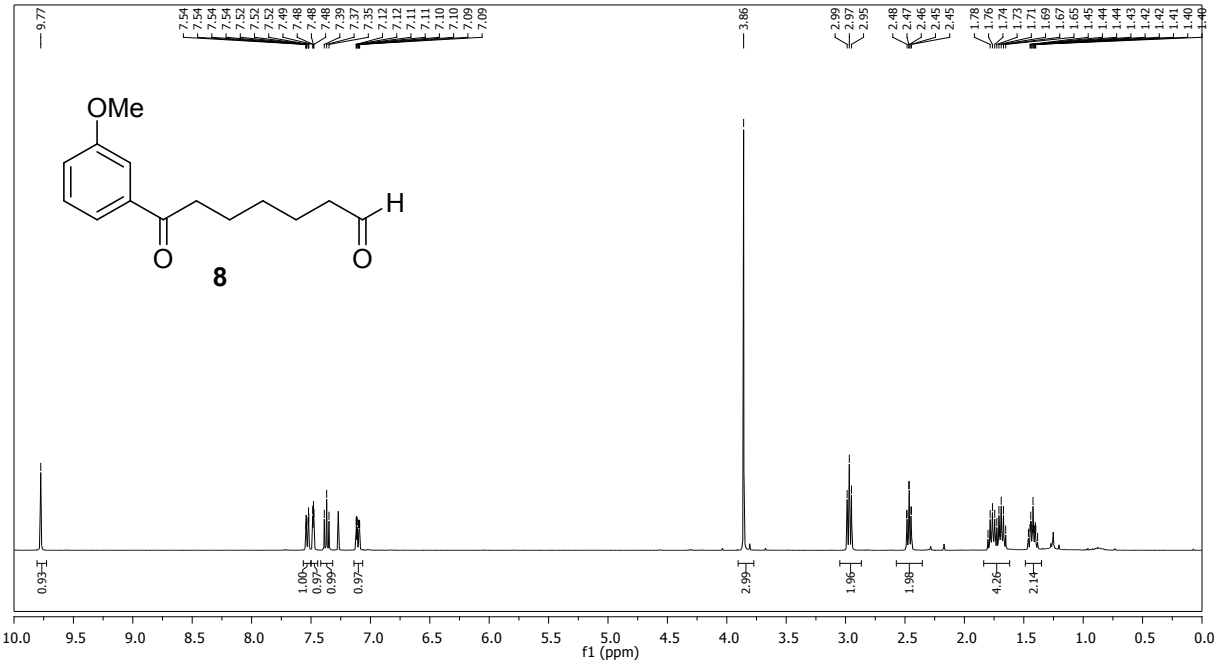


Figure 5S. ^{1}H NMR of compound **8** (400 MHz, $CDCl_3$).

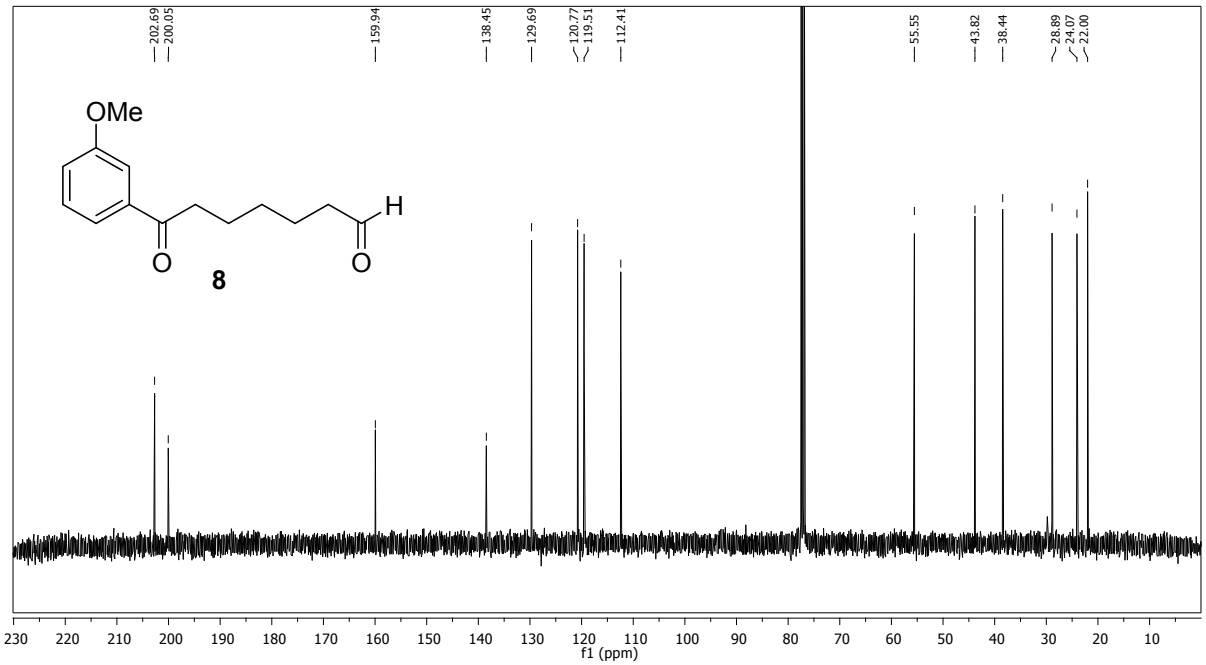


Figure 6S. ^{13}C NMR of compound **8** (125 MHz, $CDCl_3$).

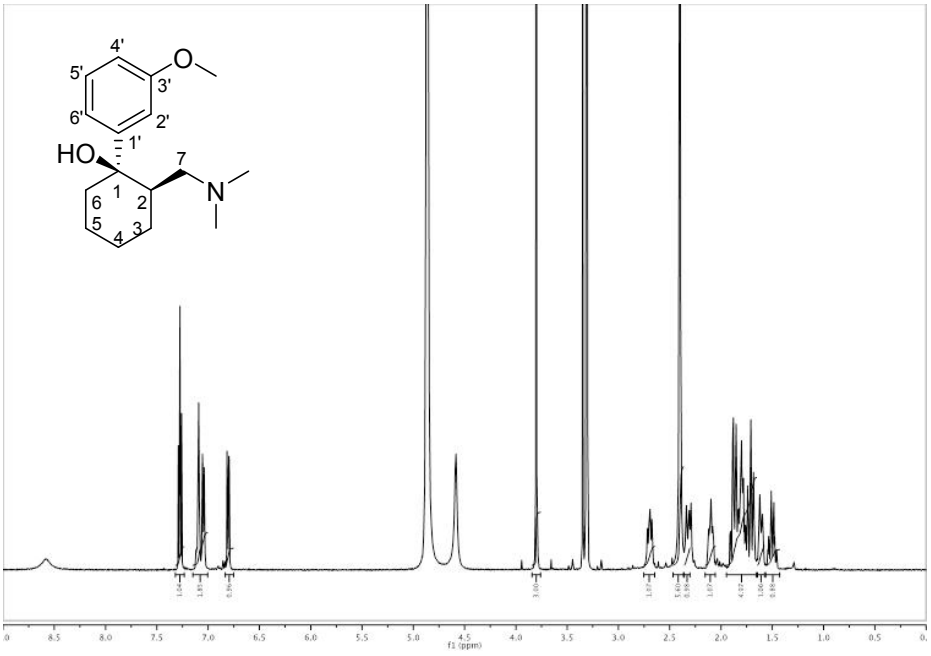


Figure 7S. ^{1}H NMR of compound **9** (±)-(*1R, 2R*)-Tramadol (500 MHz, CD_3OD).

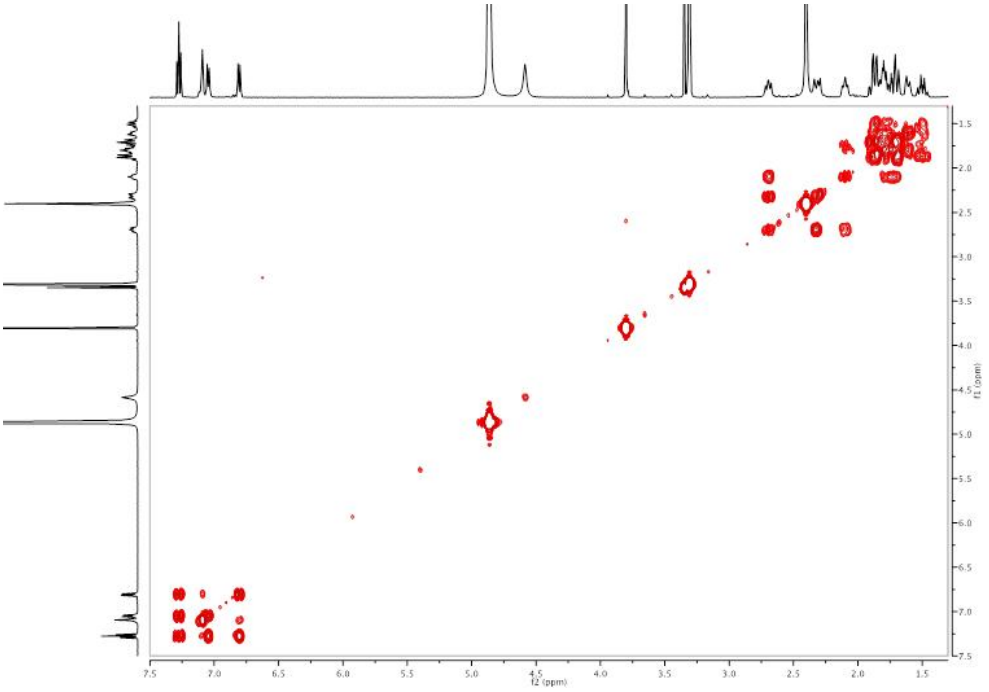


Figure 8S. ^{1}H-^{1}H COSY NMR of compound **9** (±)-(*1R,2R*)-Tramadol (500 MHz, CD_3OD).

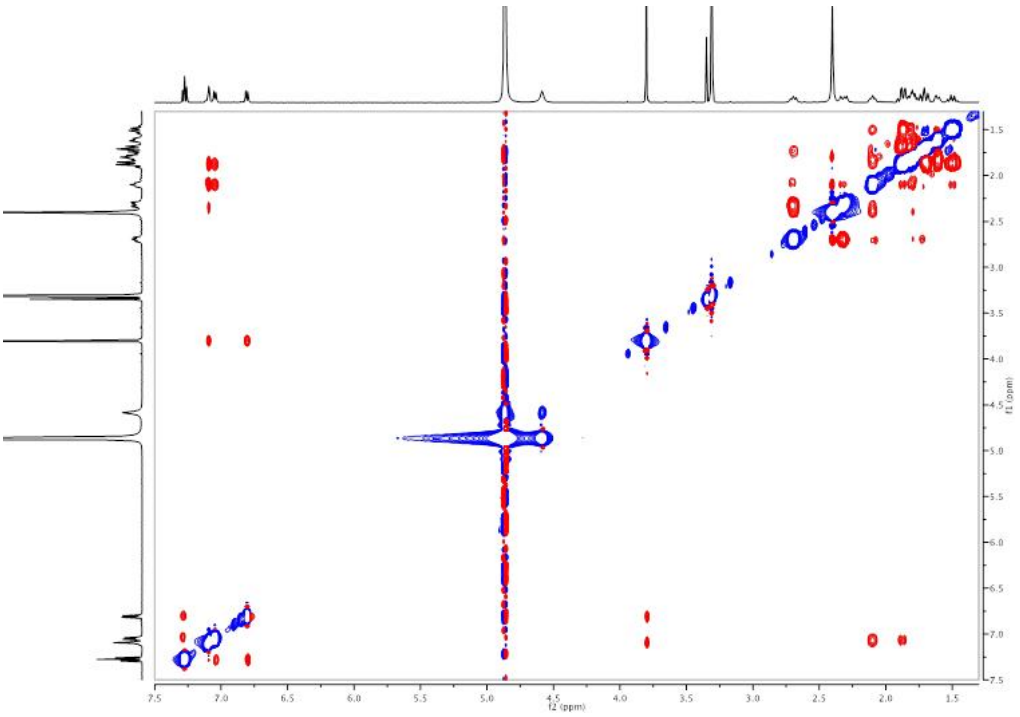


Figure 9S. ^{1}H-^{1}H NOESY NMR of compound **9** (±)-(*1R,2R*)-Tramadol (500 MHz, CD_3OD).

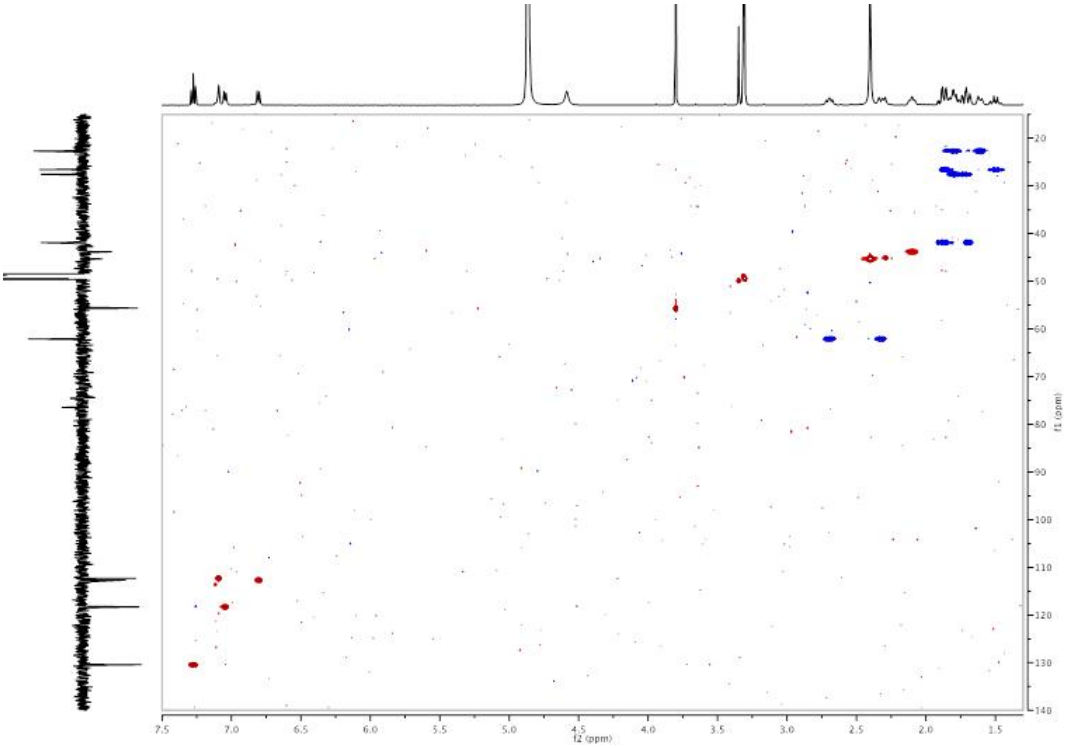


Figure 10S. ^{1}H-^{13}C HSQC NMR of compound **9** (±)-(*1R,2R*)-Tramadol (500 MHz, CD_3OD).

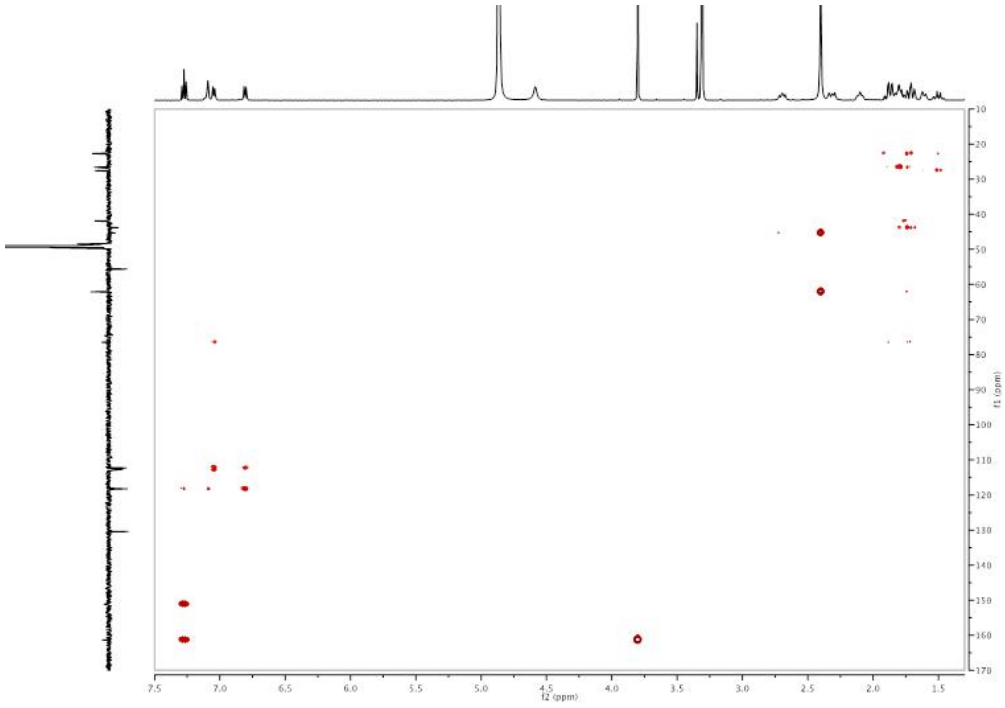


Figure 11S. ^{1}H-^{13}C HMBC NMR of compound **9** (±)-(*1R,2R*)-Tramadol (500 MHz, CD_3OD).

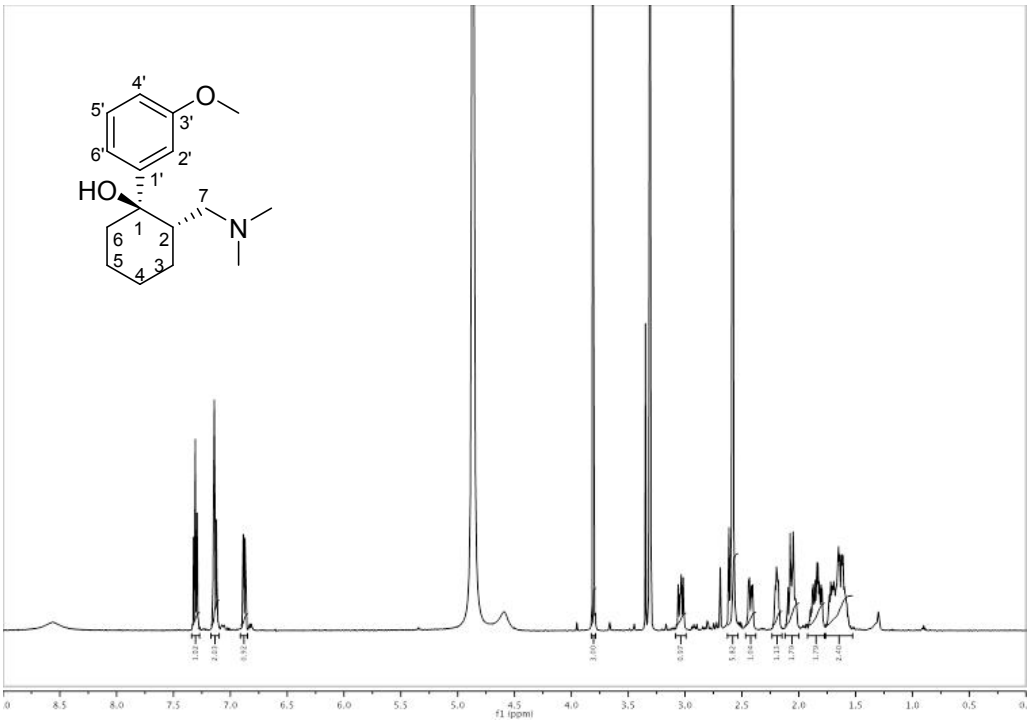


Figure 12S. ^{1}H NMR of compound **10** (±)-(*1R,2S*)-Tramadol (500 MHz, CD_3OD).

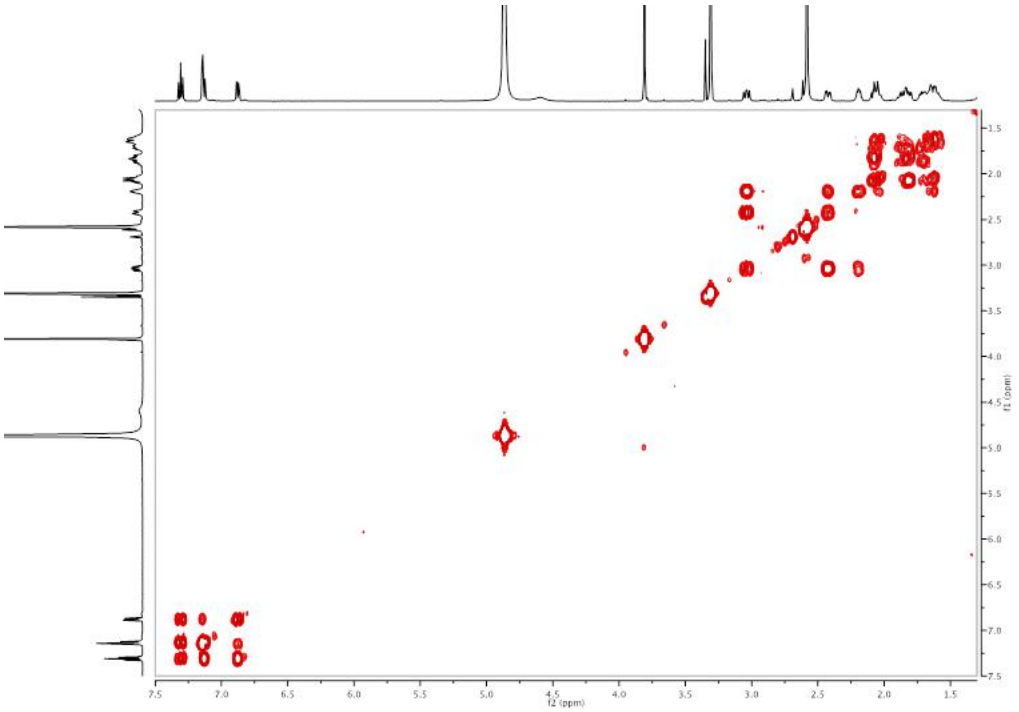


Figure 13S. ^{1}H-^{1}H COSY NMR of compound **10** (±)-(*1R,2S*)-Tramadol (500 MHz, CD_3OD).

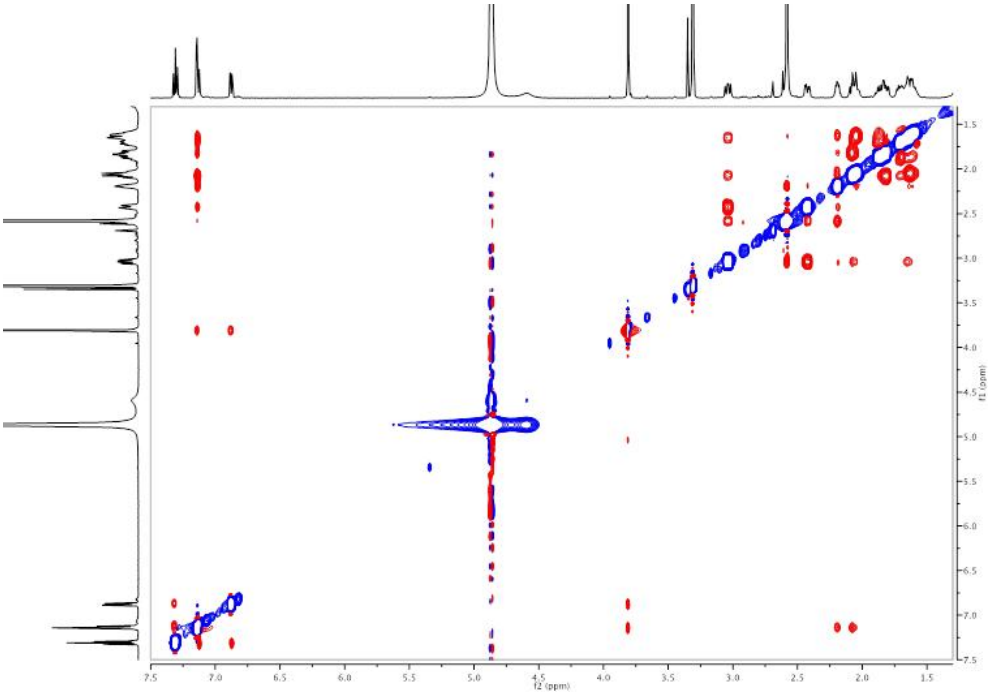


Figure 14S. ^{1}H-^{1}H NOESY NMR of compound **10** (±)-(*1R,2S*)-Tramadol (500 MHz, CD_3OD).

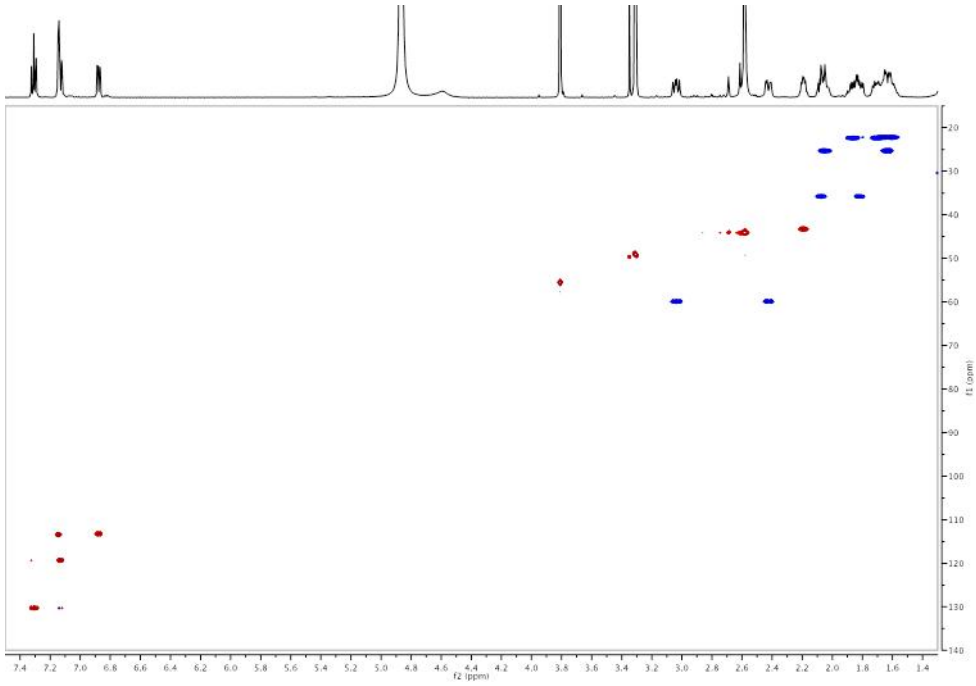


Figure 15S. ^{1}H-^{13}C HSQC NMR of compound **10** (±)-(*1R,2S*)-Tramadol (500 MHz, CD_3OD).

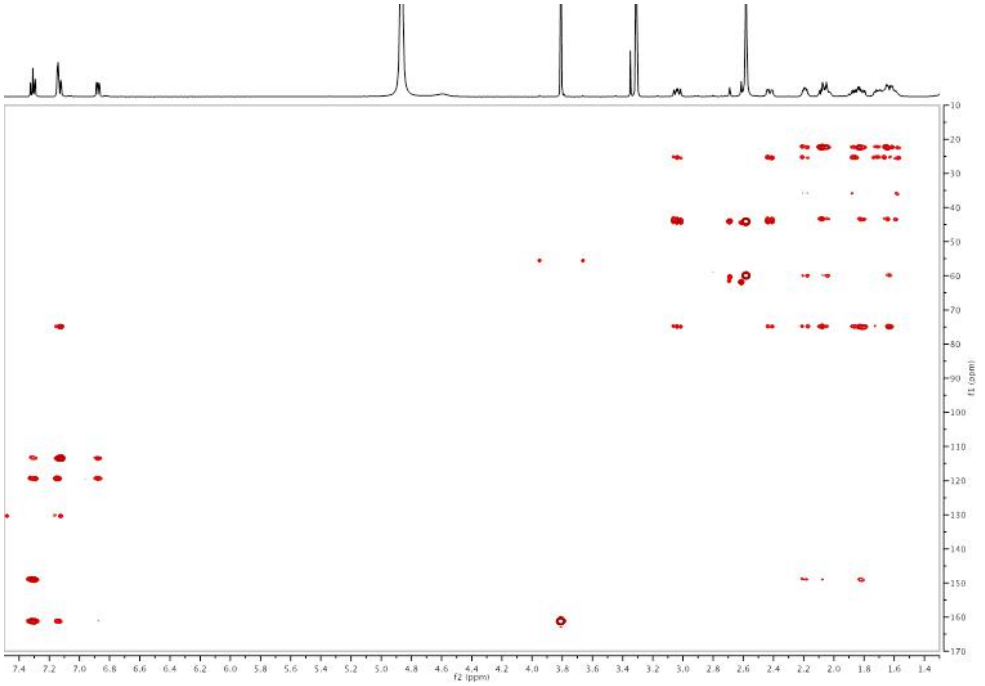


Figure 16S. ^{1}H-^{13}C HMBC NMR of compound **10** (±)-(*1R,2S*)-Tramadol (500 MHz, CD_3OD).

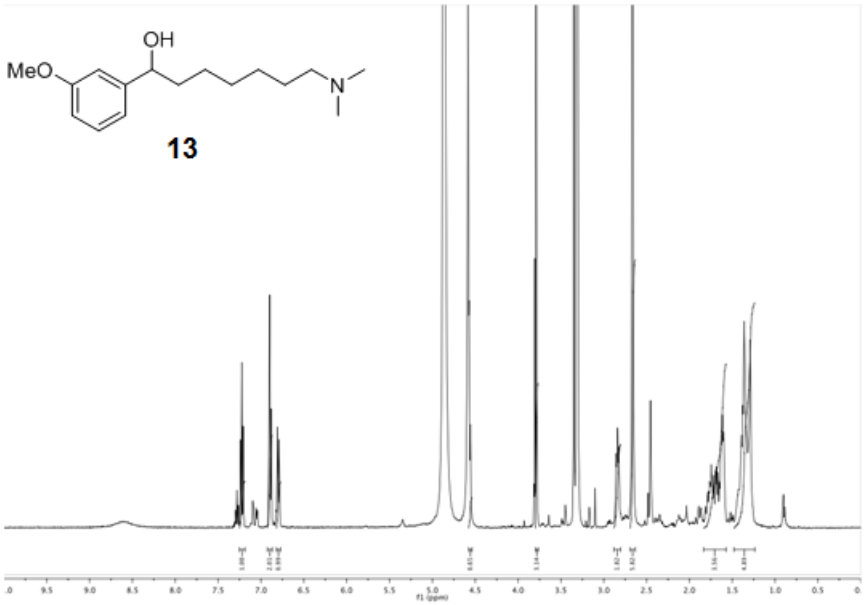


Figure 17S. ^{1}H NMR of compound **13** corresponding to the open form of Tramadol.

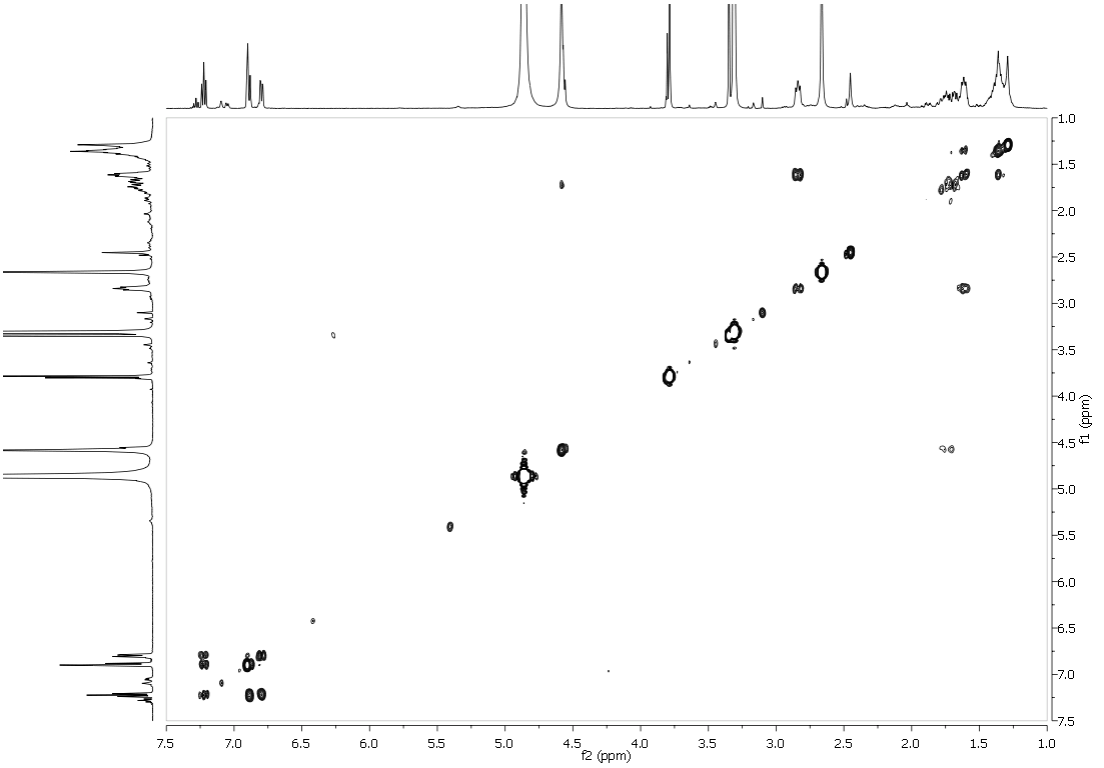


Figure 18S. ^{1}H-^{1}H COSY NMR of compound **13** corresponding to the open form of Tramadol.

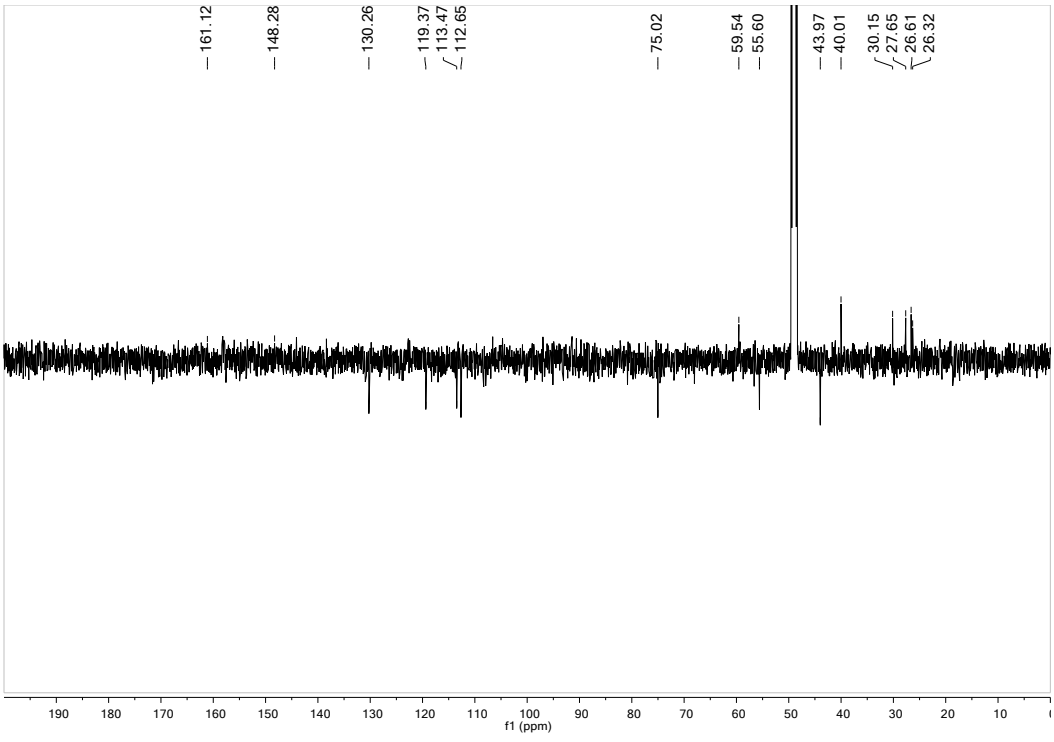


Figure 19S. ^{13}C NMR of compound **13** corresponding to the open form of Tramadol.

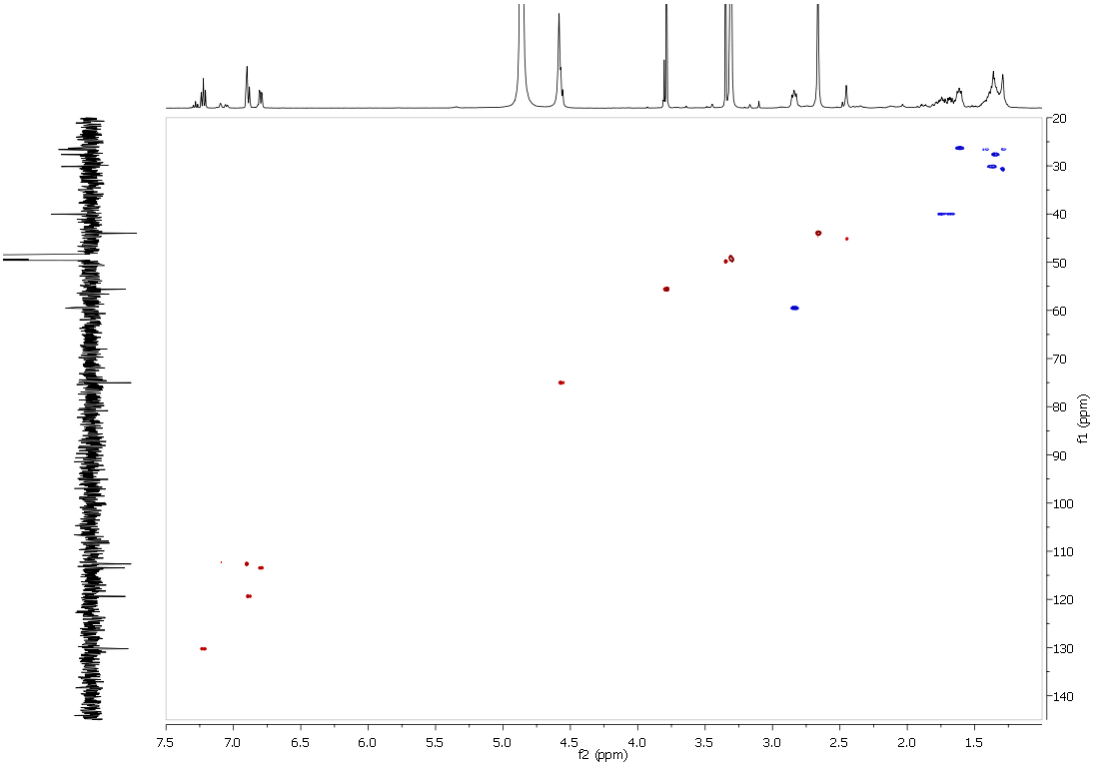


Figure 20S. ^{1}H-^{13}C HSQC NMR of compound **13** corresponding to the open form of Tramadol.

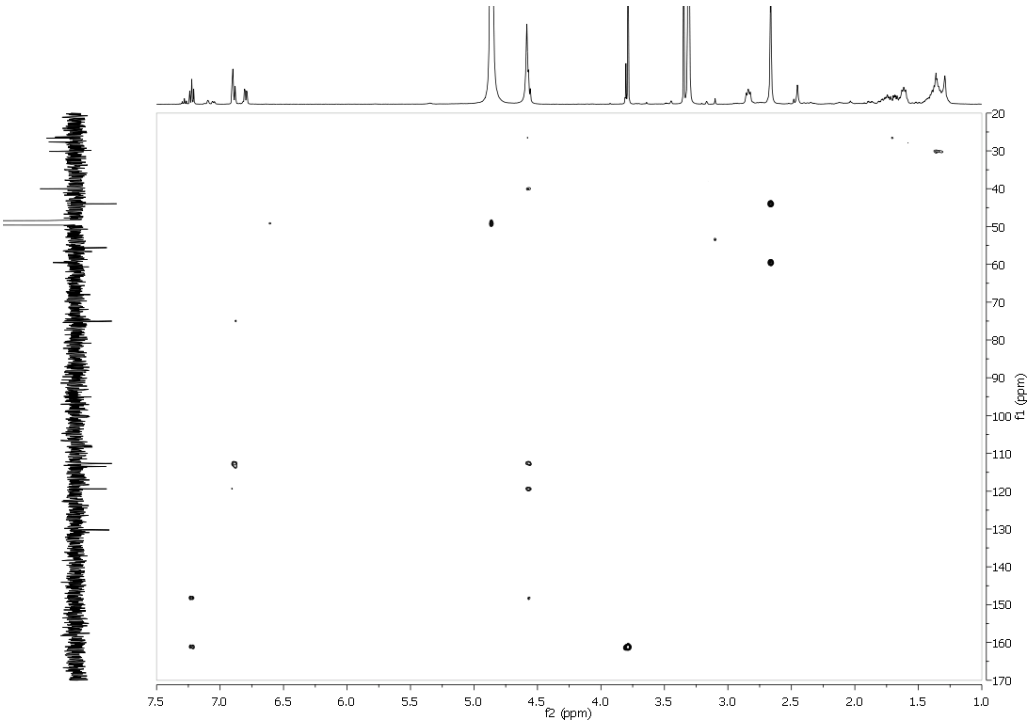


Figure 21S. ^{1}H-^{13}C HMBC NMR of compound **13** corresponding to the open form of Tramadol.

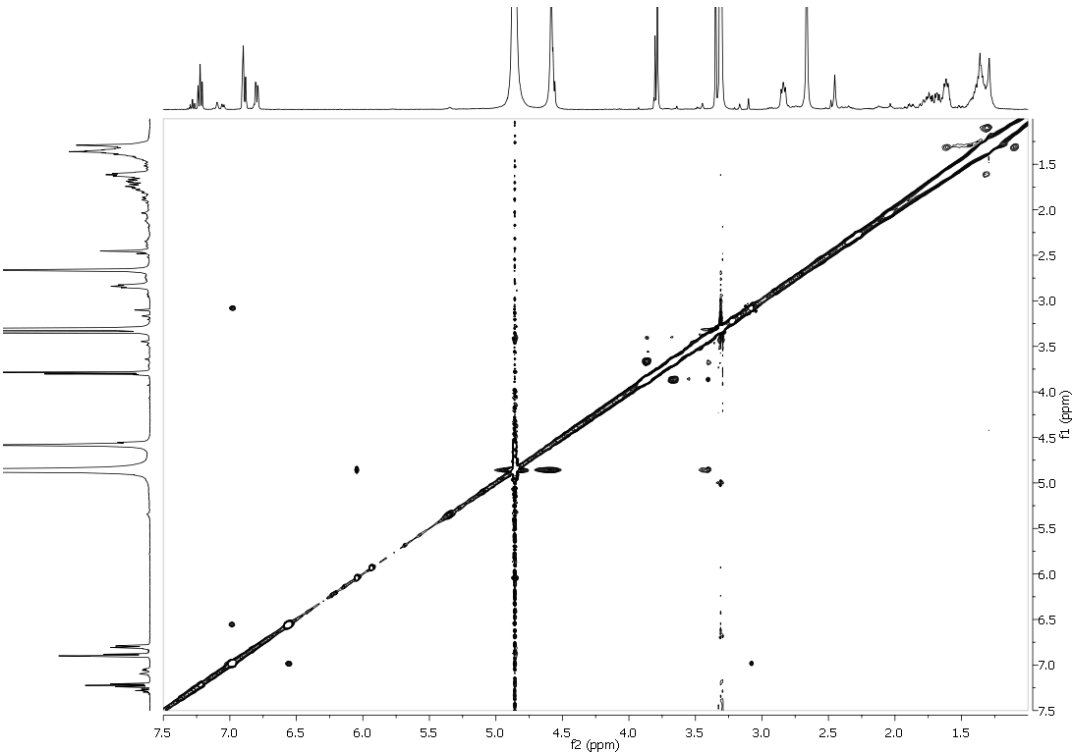


Figure 22S. ^{1}H-^{1}H NOESY NMR of compound **13** corresponding to the open form of Tramadol.