Supporting Information

Continuous flow synthesis of N,N-dimethyltryptamine (DMT) analogues with therapeutic potential

*Andreas Simoensa, Andreas Dejaegerea, Marthe Vandeveldea, Christian V. Stevensa,**

Department of Green Chemistry and Technology
Synthesis, Bioresources and Bioorganic Chemistry Research Group
Ghent University
Coupure Links 653, 9000 Ghent, Belgium
E-mail: chris.stevens@ugent.be

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Materials and methods

The synthetic procedures made use of commercially available reagents and solvents primarily purchased from Sigma-Aldrich®, Acros Organics®, Apollo scientific® and TCI®. Distilled water was obtained by the demineralization of tap water by an Aquadem ion exchanger from the 22DF type. The melting point of compounds was determined by a Büchi Melting Point M-560. 1-[(4-Hydrazinophenyl)methyl]-1H-1,2,4-triazole hydrochloride (CAS: 154748-67-1) was purchased from BLD Pharmatech GmbH.

Liquid Chromatography coupled with Mass Spectrometry (LC-MS)

LC-MS analyses were performed on an Agilent 1200 Series HPLC equipped with a Supelco Ascentis® Express C18 column (3 cm x 4.6 mm, 2.7 µm fused-core particles, 90 Å), a Phenomenex Guard column (SecurityGuard Standard) and a UV-DAD detector. The liquid chromatography system is coupled to an Agilent 1100 Series MS with electrospray ionization (4000 V, 70 eV) and a single quadrupole detector.

Nuclear Magnetic Resonance spectrometry (NMR)

^{1}H-NMR, ^{13}C-NMR and 2D spectra were obtained from a Bruker Avance III HD Nanobay spectrometer, equipped with a 1H/BB z-gradient probe (BBO, 5 mm). Measurements were taken at 400 MHz and 100.6 MHz respectively. Chemical shifts were reported as δ-values (ppm) and coupling constants (J) were expressed in Hertz (Hz). Deuterated solvents ($CDCl_3$, MeOD, DMSO, acetone-d_6, D_2O) containing TMS as an internal standard were used to dissolve samples. Additional two-dimensional spectra were obtained as well to assign signals with certainty. Spectra could be consulted and processed *via* TOPSPIN 4.3.0 software.

Infrared spectroscopy (IR)

Infrared spectra were obtained from solid or dissolved samples with a signal-to-noise ratio (S/N) of 30 000:1 using a Shimadzu IRAffinity-1S Fourier Transform Infrared Spectrophotometer with a (FTIR)Quest ATR (Attenuated Total Reflectance) accessory with diamond crystal pucks. The infrared spectra were accessed and processed with LabSolutions IR software.

High Resolution Mass Spectrometry (HRMS)

HRMS analysis was conducted on a Vanquish UPLC (with a Kinetex C18 50mm x 2.1mm x 2.6µm Phenomenex column) coupled to a Q-Exactive Plus Orbitrap Mass Spectrometer with a resolution of 140000, using electron spray ionization.

Safety

Caution! *The synthesised molecules are potentially highly toxic. It is important to comply with personal protective equipment directives and general laboratory regulations. The experimental work takes place in hoods; crude reaction mixtures, or purified substances will be kept in closed recipients.*

Caution! *Sulfuric acid is considered highly corrosive and can cause severe skin irritation and eye damage.*

Experimental setup

A ReaXus 6010R Reciprocating Pump was used to flow the substrate solution consisting of the starting materials, water/acetonitrile and sulfuric acid (5%) into a heated GC oven. This pump is capable of operating with accurate flow rate up to 10 ml/min and has a pressure capability up to 414 bar (6000 psi). This model of pump was manufactured by Teledyne ISCO. To quickly and accurately heat the reactor to the desired temperature, an empty GC-oven was used as a hot air heating chamber. This was done with an Agilent 6890 Series GC system, from which the GC column had been removed. The tubing used to create the reactor was obtained from Bohlender™, and consists of PTFE which guaranteed its temperature and chemical resistance. The internal volume of the reactor is 10 ml and the internal and external diameter of these tubes is 1 and 1.6 mm respectively. An exact same model of pump was used to combine the base solution (25% NaOH) with this mixture after it exits the GC-oven and is briefly cooled in an ice bath. To administer the organic phase (ethyl acetate), a Knauer AZURA P 4.1S pump with pressure sensor and stainless steel pump head with a maximum flow rate of 10 ml/min and maximum pressure of 200 bar is used. These combined streams are mixed in 20 cm of PTFE tubing with 2.6 mm internal diameter containing static mixers, which is subsequently connected to a continuous extraction (Zaiput Flow Technologies, SEP-10) device. The permeate consists of the organic fraction containing our desired freebase product. In order to work at the required temperatures, a back pressure regulator is installed after the ice bath cooling but before mixing of the substrate stream with the base solution and organic solvent. This is done with a Bronkhorst Dual

Valve Pressure Controller P800, with a maximum pressure of 200 bar and temperature limit of 70 °C. The instrument communicates both analog ((0)4…20 mA or 0..5(10Vdc)) and digital (RS-232) and can be fitted with bus communication like EtherCAT, ProfiNet, Profibus, Modbus, DeviceNet, FlowBus, Canopen.

Reactor design

The overall setup remained largely the same for all experiments as shown in figure S1.

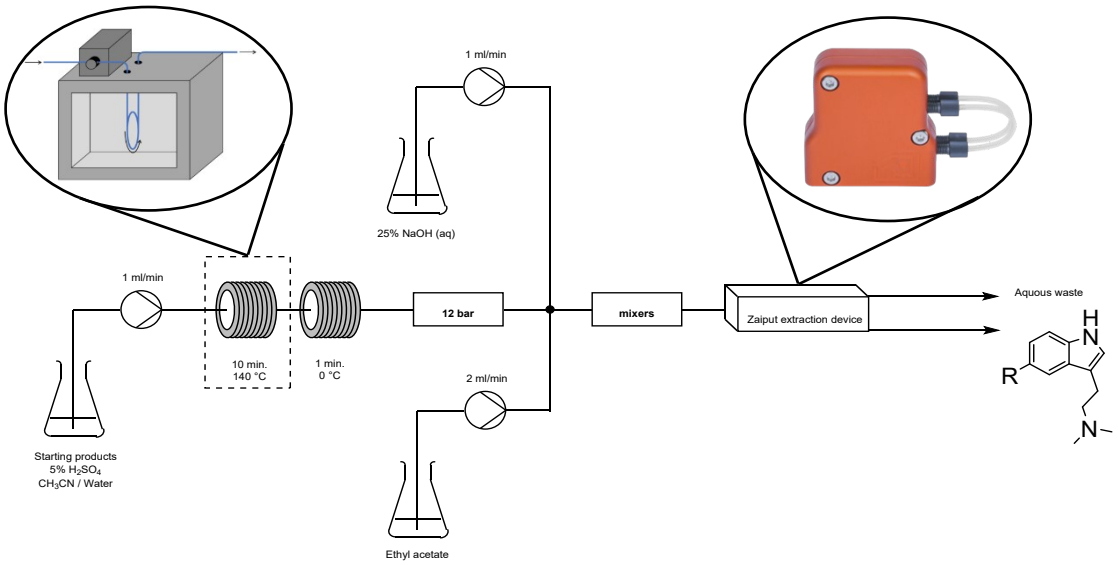
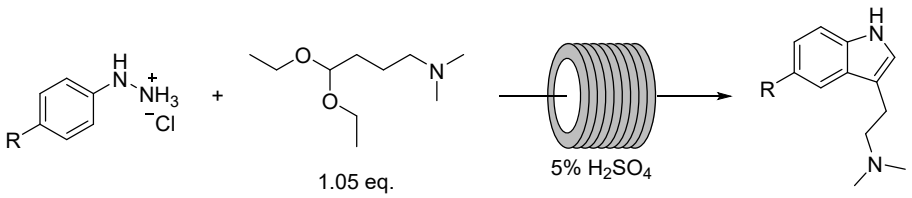


Figure S1. Schematic overview of the complete setup.

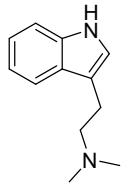
Experimental procedure

<u>Synthesis of freebase tryptamine derivatives in flow</u>



To synthesize the tryptamine derivatives as their freebase in flow, three solution had to be made. The first solution contains the respective phenylhydrazine hydrochloride (0.5 g, 0.01 g/ml), 1.05 equivalents of 4-(dimethylamino)butyraldehyde diethyl acetal, 1.35 ml H_2SO_4 and 50 ml of solvent (25 ml water : 25 ml acetonitrile or 50 ml water for **4** & **14**). The second solution contains 25 g of sodium hydroxide in 100 ml water and the last solution consists of pure ethyl acetate. The substrate stream is pumped at 1 ml/min through a 10 ml volume tubing to ensure a residence time of 10 minutes inside the reactor, which is kept at 140 °C (for **4**, **11**, **12**, **14**), 100 °C (for **8**) or 160 °C (for **10**). The reaction mixture is subsequently cooled by passing the tubing through an ice bath before entering the back pressure regulator which applies a 12 bar pressure on the reactor. Upon exiting the pressure control unit, the ethyl acetate (2 ml/min) and NaOH (aq, 1 ml/min) streams are both merged with our substrate and proper mixing is ensured by means of static mixers placed within the tubing. The combined mixture of organic and aqueous solvents is brought into the Zaiput® continuous extraction device and the organic permeate stream is collected in a clean Erlenmeyer. After evaporation of the solvent under reduced pressure, the pure tryptamine products are obtained (86-99%). To remove small traces of dimerization product, the obtained products can be dissolved in a 1:10 mixture of MeOH: acetone and filtered through a small pad of silica.

N,N-dimethyltryptamine (4)

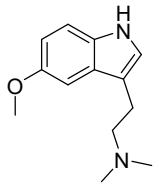


97-99%

^{1}H NMR (400 MHz, DMSO, 298 K) δ: 10.77 (br s, 1H, N*H*), 7.51 (d, J_{H-H} = 7.9 Hz, 1H, NH-Cq-CH-CH-CH-C*H*), 7.34 (d, J_{H-H} = 7.9 Hz, 1H, NH-Cq-C*H*), 7.14 (br s, 1H, NH-C*H*), 7.06 (txd, J_{H-H} = 7.9 Hz, 1.0 Hz, 1H, NH-Cq-CH-C*H*), 6.97 (txd, J_{H-H} = 7.9 Hz, 1.0 Hz, 1H, NH-Cq-CH-CH-C*H*), 2.79-2.85 (m, 2H, N-CH_2), 2.48-2.56 (m, 2H, CH_2-Cq), 2.22 (s, 6H, 2xCH_3-N)

Spectral data is in accordance with literature [1]

5-MeO-N,N-dimethyltryptamine (8)



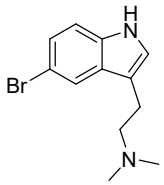
98%

^{1}H NMR (400 MHz, DMSO, 298 K) δ: 10.60 (br s, 1H, N*H*), 7.22 (d, J_{H-H} = 8.7 Hz, 1H, NH-Cq-C*H*), 7.10 (br s, 1H, NH-C*H*), 6.97 (d, J_{H-H} = 2.4 Hz, 1H, O-Cq-C*H*-Cq), 6.71 (dxd, J_{H-H} = 8.7 Hz, 2.4 Hz, 1H, NH-Cq-CH-C*H*), 3.76 (s, 3H, CH_3-O), 2.74-2.81 (m, 2H, N-CH_2), 2.47-2.55 (m, 2H, CH_2-Cq), 2.22 (s, 6H, 2xCH_3-N)

^{13}C NMR (100 MHz, DMSO, 298 K) δ: 153.3 (1C, O-*Cq*), 131.8 (1C, NH-*Cq*), 128.0 (1C, NH-Cq-*Cq*), 123.6 (1C, NH-*CH*), 112.8 (1C, NH-CH-*Cq*), 112.4 (1C, NH-Cq-*C*H), 111.3 (1C, NH-Cq-CH-*C*H), 100.6 (1C, O-Cq-*C*H-Cq), 60.4 (1C, *C*H_2-Cq), 55.8 (1C, *C*H_3-O), 45.7 (2C, 2x*C*H_3-N), 23.6 (1C, N-*C*H_2)

Spectral data is in accordance with literature [2]

5-Br-N,N-dimethyltryptamine (10)



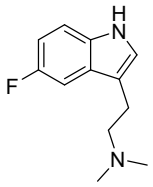
94%

^{1}H NMR (400 MHz, DMSO, 298 K) δ: 11.00 (br s, 1H, N*H*), 7.67 (d, J_{H-H} = 1.9 Hz, 1H, Br-Cq-C*H*-Cq), 7.30 (d, J_{H-H} = 8.6 Hz, 1H, NH-Cq-C*H*), 7.22 (d, J_{H-H} = 2.2 Hz, 1H, NH-C*H*), 7.16 (dxd, J_{H-H} = 8.6 Hz, 1.9 Hz, 1H, NH-Cq-CH-C*H*), 2.75-2.82 (m, 2H, N-CH_2), 2.48-2.53 (m, 2H, CH_2-Cq), 2.21 (s, 6H, 2xCH_3-N)

^{13}C NMR (100 MHz, DMSO, 298 K) δ: 135.3 (1C, NH-*Cq*), 129.6 (1C, NH-Cq-*Cq*), 124.7 (1C, NH-*C*H), 123.7 (1C, NH-Cq-CH-*C*H), 121.0 (1C, Br-Cq-*C*H-Cq), 113.8 (1C, NH-Cq-*C*H), 113.1 (1C, Br-*Cq*), 111.3 (1C, NH-CH-*Cq*), 60.4 (1C, *C*H_2-Cq), 45.6 (2C, 2x*C*H_3-N), 23.3 (1C, N-*C*H_2)

Spectral data is in accordance with literature [3]

5-F-N,N-dimethyltryptamine (11)



86%

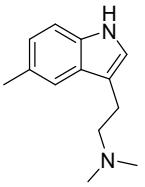
^{1}H NMR (400 MHz, DMSO, 298 K) δ: 10.89 (br s, 1H, N*H*), 7.32 (dxd, J_{H-H} = 8.9 Hz, J_{F-H} = 4.6 Hz, 1H, NH-Cq-C*H*), 7.25 (dxd, J_{F-H} = 10.1 Hz, J_{H-H} = 2.5 Hz, 1H, F-Cq-C*H*-Cq), 7.23 (~d, J_{H-H} = 2.5 Hz, 1H, NH-C*H*), 6.90 (txd, $J_{H-H/F-H}$ = 9.2 Hz, J_{H-H} = 2.5 Hz, 1H, NH-Cq-CH-C*H*), 2.74-2.82 (m, 2H, N-CH_2), 2.46-2.53 (m, 2H, CH_2-Cq), 2.21 (s, 6H, 2xCH_3-N)

^{13}C NMR (100 MHz, DMSO, 298 K) δ: 157.1 (d, J_{C-F} = 230.6 Hz, 1C, F-*Cq*), 133.3 (1C, NH-*Cq*), 127.9 (d, J_{C-F} = 9.8 Hz, 1C, NH-Cq-*Cq*), 125.1 (1C, NH-*C*H), 113.5 (d, J_{C-F} = 4.7 Hz, 1C, NH-CH-*Cq*), 112.6 (d, J_{C-F} = 9.8 Hz, 1C, NH-Cq-*C*H), 109.3 (d, J_{C-F} = 26.1 Hz, 1C, NH-Cq-CH-*C*H), 103.4 (d, J_{C-F} = 22.8 Hz, 1C, F-Cq-*C*H-Cq), 60.3 (1C, *C*H_2-Cq), 45.6 (2C, 2x*C*H_3-N), 23.4 (1C, N-*C*H_2)

^{19}F NMR (376 MHz, DMSO, 298 K) δ: -125.75 (txd, J_{H-F} = 9.7 Hz, 4.6 Hz, *F*-Cq)

Spectral data is in accordance with literature [4]

5-Me-N,N-dimethyltryptamine (12)



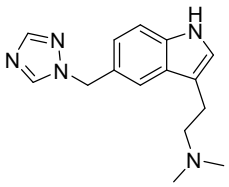
88%

^{1}H NMR (400 MHz, DMSO, 298 K) δ: 10.63 (br s, 1H, N*H*), 7.28 (br s, 1H, CH_3-Cq-C*H*-Cq), 7.22 (d, J_{H-H} = 8.2 Hz, 1H, NH-Cq-C*H*), 7.08 (~d, J_{H-H} = 2.2 Hz, 1H, NH-C*H*), 6.89 (dxd, J_{H-H} = 8.3 Hz, 1.4 Hz, 1H, NH-Cq-CH-C*H*), 2.75-2.83 (m, 2H, N-CH_2), 2.48-2.54 (m, 2H, CH_2-Cq), 2.39 (s, 3H, CH_3-Cq), 2.22 (s, 6H, 2xCH_3-N)

^{13}C NMR (100 MHz, DMSO, 298 K) δ: 135.1 (1C, NH-*Cq*), 127.9 (1C, CH_3-*Cq*), 126.9 (1C, NH-Cq-*Cq*), 123.0 (1C, NH-*C*H), 122.9 (1C, NH-Cq-CH-*C*H), 118.3 (1C, CH_3-Cq-*C*H-Cq), 112.5 (1C, CH_2-*Cq*), 111.5 (1C, NH-Cq-*C*H), 60.6 (1C, *C*H_2-Cq), 45.6 (2C, 2x*C*H_3-N), 23.6 (1C, N-*C*H_2), 21.7 (1C, *C*H_3-Cq)

Spectral data is in accordance with literature [5]

Rizatriptan (14)



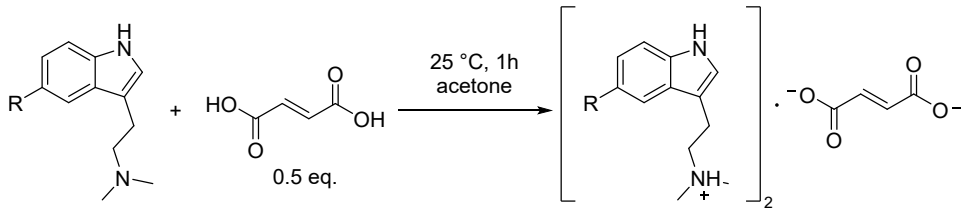
22%

^{1}H NMR (400 MHz, DMSO, 298 K) δ: 10.87 (br s, 1H, N*H*), 8.63 (s, 1H, N-C*H*-N-CH_2), 7.95 (s, 1H, N-C*H*-N-N-CH_2), 7.51 (br s, 1H, N-CH_2-Cq-C*H*-Cq), 7.31 (d, J_{H-H} = 8.4 Hz, 1H, NH-Cq-C*H*), 7.17 (~d, J_{H-H} = 2.1 Hz, 1H, NH-C*H*), 7.04 (dxd, J_{H-H} = 8.4 Hz, 1.5 Hz, 1H, NH-Cq-CH-C*H*), 5.44 (s, 2H, N-CH_2-Cq), 2.76-2.84 (m, 2H, N-CH_2), 2.47-2.54 (m, 2H, CH_2-Cq), 2.21 (s, 6H, 2xCH_3-N)

^{13}C NMR (100 MHz, DMSO, 298 K) δ: 151.9 (1C, N-*C*H-N-N-CH_2), 144.2 (1C, N-*C*H-N-CH_2), 136.2 (1C, NH-*Cq*), 127.7 (1C, N-CH_2-*Cq*), 126.3 (1C, NH-Cq-*Cq*), 123.8 (1C, NH-*C*H), 121.6 (1C, NH-Cq-CH-*C*H), 118.7 (1C, N-CH_2-Cq-*C*H-Cq), 113.3 (1C, CH_2-*Cq*), 112.0 (1C, NH-Cq-*C*H), 60.4 (1C, CH_2-*C*H_2-Cq), 53.5 (1C, N-*C*H_2-Cq), 45.6 (2C, 2x*C*H_3-N), 23.5 (1C, N-*C*H_2)

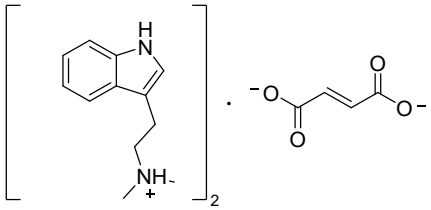
Spectral data is in accordance with literature [6]

Synthesis of 2:1 DMT derivative hemifumarate salts



The freebase tryptamine derivatives were easily transformed into their respective 2:1 hemifumarate salts by dissolving the pure freebase in a small amount of acetone (10 ml for each gram of product) and adding 0.5 equivalents of fumaric acid. This mixture is stirred vigorously for one hour after which the desired product has precipitated out of the solution and can easily be collected through filtration. After washing the desired product on the filter with fresh acetone, it is collected in a flask and put under a high vacuum in order to obtain the final product dry and in high purity (68-93% yield).

N,N-dimethyltryptamine hemifumarate (2:1) (13a)



^{1}H NMR (400 MHz, DMSO, 298 K) δ: 10.87 (br s, 1H, N*H*), 7.56 (d, J_{H-H} = 7.8 Hz, 1H, NH-Cq-CH-CH-CH-C*H*), 7.35 (d, J_{H-H} = 8.0 Hz, 1H, NH-Cq-C*H*), 7.18 (d, J_{H-H} = 2.3 Hz, 1H, NH-C*H*), 7.07 (txd, J_{H-H} = 7.9 Hz, 1.0 Hz, 1H, NH-Cq-CH-C*H*), 6.99 (txd, J_{H-H} = 7.9 Hz, 1.0 Hz, 1H, NH-Cq-CH-CH-C*H*), 6.53 (s, 1H, hemifumarate), 2.91-2.99 (m, 2H, N-CH_2), 2.83-2.91 (m, 2H, CH_2-Cq), 2.50 (s, 6H, 2xCH_3-N)

^{13}C NMR (100 MHz, DMSO, 298 K) δ: 168.0 (2C, 2x*Cq*OO$^-$), 136.7 (1C, NH-*Cq*), 135.4 (2C, 2x*C*H-CqOO$^-$), 127.5 (1C, NH-Cq-*Cq*), 123.2 (1C, NH-*C*H), 121.4 (1C, NH-Cq-CH-*C*H), 118.7 (1C, NH-Cq-CH-CH-CH-*C*H), 118.7 (1C, NH-Cq-CH-CH-*C*H), 111.9 (1C, CH_2-*Cq*), 111.8 (1C, NH-Cq-*C*H), 59.4 (1C, *C*H_2-Cq), 44.5 (2C, 2x*C*H_3-N), 22.5 (1C, N-*C*H_2)

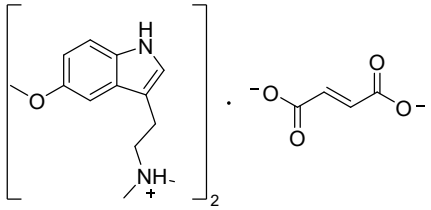
IR(cm^{-1}): 3142, 1593, 1454, 1341

$T_{m.p.}$(°C): 140

HR-MS [M+H]$^+$: 189.13818 m/z **Calc. Mass $C_{12}H_{17}N_2^+$:** 189.13862 m/z

Spectral data is in accordance with literature [7]

5-MeO-N,N-dimethyltryptamine hemifumarate (2:1) (13b)



^{1}H NMR (400 MHz, DMSO, 298 K) δ: 10.68 (br s, 1H, N*H*), 7.23 (d, J_{H-H} = 7.8 Hz, 1H, NH-Cq-C*H*), 7.12 (~d, J_{H-H} = 2.2 Hz, 1H, NH-C*H*), 7.03 (d, J_{H-H} = 2.3 Hz, 1H, O-Cq-C*H*-Cq), 6.72 (dxd, J_{H-H} = 8.8 Hz, 2.4 Hz, 1H, NH-Cq-CH-C*H*), 6.51 (s, 1H, hemifumarate), 3.77 (s, 3H, CH_3-O), 2.84-2.93 (m, 2H, N-CH_2), 2.75-2.84 (m, 2H, CH_2-Cq), 2.45 (s, 6H, 2xCH_3-N)

^{13}C NMR (100 MHz, DMSO, 298 K) δ: 168.4 (2C, 2x*Cq*OO$^-$), 153.5 (1C, *Cq*-O), 135.5 (2C, 2x*C*H-CqOO$^-$), 131.8 (1C, NH-*Cq*), 127.8 (1C, NH-Cq-*Cq*), 123.8 (1C, NH-*C*H), 112.5 (1C, NH-Cq-*C*H), 111.5 (2C, NH-Cq-CH-*C*H & NH-CH-*Cq*), 100.7 (1C, O-Cq-*C*H-Cq), 59.0 (1C, *C*H_2-Cq), 55.8 (1C, *C*H_3-O), 44.2 (2C, 2x*C*H_3-N), 22.4 (1C, N-*C*H_2)

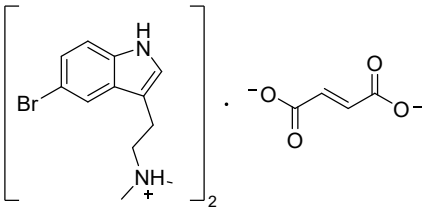
IR(cm^{-1}): 3154, 1566, 1460, 1354

$T_{m.p.}$(°C): 176

HR-MS $[M+H]^+$: 219.14871 m/z **Calc. Mass $C_{13}H_{19}N_2O^+$:** 219.14919 m/z

Spectral data is in accordance with literature [8]

5-Br-N,N-dimethyltryptamine hemifumarate (2:1) (13c)



^{1}H NMR (400 MHz, DMSO, 298 K) δ: 11.13 (br s, 1H, N*H*), 7.75 (s, 1H, Br-Cq-C*H*-Cq), 7.32 (d, J_{H-H} = 8.7 Hz, 1H, NH-Cq-C*H*), 7.25 (s, 1H, NH-C*H*), 7.18 (d, J_{H-H} = 8.6 Hz, 1H, NH-Cq-CH-C*H*), 6.53 (s, 1H, hemifumarate), 2.86-2.99 (m, 2H, N-CH_2), 2.75-2.86 (m, 2H, CH_2-Cq), 2.46 (s, 6H, 2xCH_3-N)

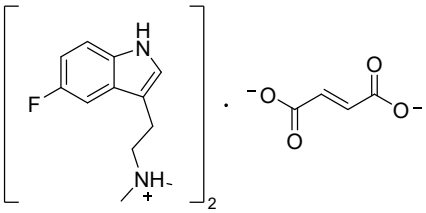
^{13}C NMR (100 MHz, DMSO, 298 K) δ: 168.5 (2C, 2x*Cq*OO^-), 135.5 (2C, 2x*C*H-CqOO^-), 135.3 (1C, NH-*Cq*), 129.4 (1C, NH-Cq-*Cq*), 125.0 (1C, NH-*C*H), 123.9 (1C, NH-Cq-CH-*C*H), 121.1 (1C, Br-Cq-*C*H-Cq), 113.9 (1C, NH-Cq-*C*H), 111.6 (1C, Br-*Cq*), 111.5 (1C, NH-CH-*Cq*), 58.8 (1C, *C*H_2-Cq), 44.0 (2C, 2x*C*H_3-N), 21.9 (1C, N-*C*H_2)

IR(cm^{-1}): 3148, 1564, 1456, 1348

$T_{m.p.}$(°C): 196.5

HR-MS $[M+H]^+$: 267.04874 m/z **Calc. Mass $C_{12}H_{16}N_2Br^+$:** 267.04914 m/z

5-F-N,N-dimethyltryptamine hemifumarate (2:1) (13d)



^{1}H NMR (400 MHz, DMSO, 298 K) δ: 11.05 (br s, 1H, N*H*), 7.30-7.37 (m, 2H, F-Cq-C*H*-Cq & NH-Cq-C*H*), 7.26 (d, J_{H-H} = 2.2 Hz, 1H, NH-C*H*), 6.91 (txd, $J_{H-H/F-H}$ = 9.2 Hz, J_{H-H} = 2.5 Hz, 1H, NH-Cq-CH-C*H*), 6.53 (s, 1H, hemifumarate), 2.90-2.98 (m, 2H, N-CH_2), 2.82-2.90 (m, 2H, CH_2-Cq), 2.50 (s, 6H, 2xCH_3-N)

^{13}C NMR (100 MHz, DMSO, 298 K) δ: 168.8 (2C, 2x*Cq*OO^-), 157.1 (d, J_{C-F} = 231.6 Hz, 1C, F-*Cq*), 135.7 (2C, 2x*C*H-CqOO^-), 133.3 (1C, NH-*Cq*), 127.7 (d, J_{C-F} = 10.2 Hz, 1C, NH-Cq-*Cq*), 125.5 (1C, NH-*C*H), 112.8 (d, J_{C-F} = 10.0 Hz, 1C, NH-Cq-*C*H), 111.8 (d, J_{C-F} = 4.8 Hz, 1C, NH-CH-*Cq*), 109.5 (d, J_{C-F} = 26.2 Hz, 1C, NH-Cq-CH-*C*H), 103.5 (d, J_{C-F} = 23.1 Hz, 1C, F-Cq-*C*H-Cq), 58.5 (1C, *C*H_2-Cq), 43.8 (2C, 2x*C*H_3-N), 21.9 (1C, N-*C*H_2)

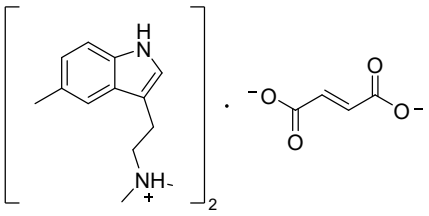
^{19}F NMR (376 MHz, DMSO, 298 K) δ: -125.48 (txd, J_{H-F} = 9.7 Hz, 4.6 Hz, *F*-Cq)

IR(cm^{-1}): 3125, 1580, 1458, 1348

$T_{m.p.}$(°C): 185.5

HR-MS $[M+H]^+$: 207.12878 m/z **Calc. Mass $C_{12}H_{16}N_2F^+$:** 207.12920 m/z

5-Me-N,N-dimethyltryptamine hemifumarate (2:1) (13e)



^{1}H NMR (400 MHz, DMSO, 298 K) δ: 10.79 (br s, 1H, N*H*), 7.36 (br s, 1H, CH_3-Cq-C*H*-Cq), 7.24 (d, J_{H-H} = 8.2 Hz, 1H, NH-Cq-C*H*), 7.14 (~d, J_{H-H} = 1.9 Hz, 1H, NH-C*H*), 6.91 (d, J_{H-H} = 8.2 Hz, 1H, NH-Cq-CH-C*H*), 6.56 (s, 1H, hemifumarate), 3.02-3.10 (m, 2H, N-CH_2), 2.95-3.02 (m, 2H, CH_2-Cq), 2.65 (s, 6H, 2xCH_3-N), 2.38 (s, 3H, CH_3-Cq)

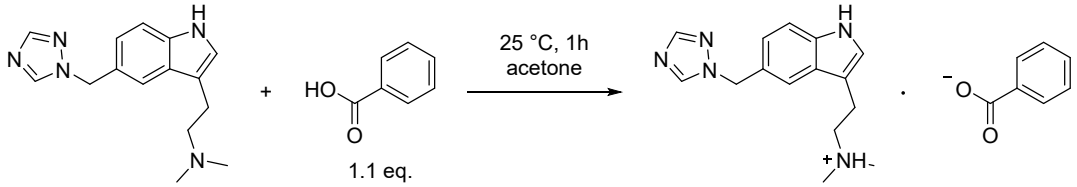
^{13}C NMR (100 MHz, DMSO, 298 K) δ: 168.4 (2C, 2x*Cq*OO^-), 135.5 (2C, 2xCH-CqOO^-), 135.1 (1C, NH-*Cq*), 127.6 (1C, CH_3-*Cq*), 127.2 (1C, NH-Cq-*Cq*), 123.5 (1C, NH-CH), 123.2 (1C, NH-Cq-CH-CH), 118.3 (1C, CH_3-Cq-CH-Cq), 111.6 (1C, NH-Cq-CH), 110.1 (1C, NH-CH-*Cq*), 57.8 (1C, CH_2-Cq), 43.0 (2C, 2xCH_3-N), 21.7 (1C, CH_3-Cq), 21.2 (1C, N-CH_2)

IR(cm^{-1}): 3123, 1564, 1341

$T_{m.p.}$(°C): 162

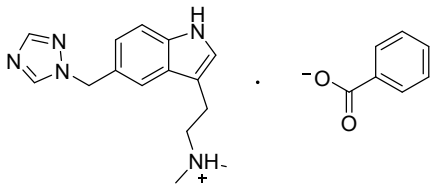
HR-MS [M+H]$^+$: 203.15395 m/z **Calc. Mass $C_{13}H_{19}N_2^+$:** 203.15428 m/z

Synthesis of Rizatriptan benzoate (1:1) (15)



The freebase rizatriptan is easily transformed into the respective 1:1 benzoate salt by dissolving the pure freebase in a small amount of acetone (10 ml for each gram of product) and adding 1.1 equivalents of benzoic acid. This mixture is stirred vigorously for one hour after which the desired product has precipitated out of the solution and can easily be collected through filtration. After washing the desired product on the filter with fresh acetone, it is collected in a flask and put under a high vacuum in order to obtain the final product dry and in high purity (87% yield).

Rizatriptan benzoate (1:1) / Maxalt® / MK462 (15)



^{1}H NMR (400 MHz, DMSO, 298 K) δ: 10.88 (br s, 1H, N*H*), 8.62 (s, 1H, N-C*H*-N-CH_2), 7.95 (s, 1H, N-C*H*-N-N-CH_2), 7.92-7.97 (m, 2H, 2xC$H_{benzoic,\ ortho}$), 7.55-7.61 (m, 1H, C$H_{benzoic,\ para}$), 7.53 (br s, 1H, Cq-C*H*-Cq), 7.44-7.50 (m, 2H, 2xC$H_{benzoic,\ meta}$), 7.31 (d, J_{H-H} = 8.3 Hz, 1H, NH-Cq-C*H*), 7.18 (~d, J_{H-H} = 2.2 Hz, 1H, NH-C*H*), 7.04 (dxd, J_{H-H} = 8.3 Hz, 1.6 Hz, 1H, NH-Cq-CH-C*H*), 5.43 (s, 2H, N-CH_2-Cq), 2.81-2.88 (m, 2H, N-CH_2), 2.60-2.67 (m, 2H, CH_2-Cq), 2.32 (s, 6H, 2xCH_3-N)

^{13}C NMR (100 MHz, DMSO, 298 K) δ: 168.3 (1C, *Cq*OO^-), 151.9 (1C, N-CH-N-N-CH_2), 144.2 (1C, N-CH-N-CH_2), 136.2 (1C, NH-*Cq*), 132.7 (1C, CH$_{benzoic,\ para}$), 132.6 (1C, *Cq*CqOO^-), 129.7 (2C, 2xCH$_{benzoic,\ ortho}$), 128.8 (2C, 2xCH$_{benzoic,\ meta}$), 127.6 (1C, N-CH_2-*Cq*), 126.4 (1C, NH-Cq-*Cq*), 123.9 (1C, NH-CH), 121.7 (1C, NH-Cq-CH-CH), 118.8 (1C, Cq-CH-Cq), 112.8 (1C, CH_2-CH_2-*Cq*), 112.0 (1C, NH-Cq-CH), 59.8 (1C, CH_2-Cq), 53.5 (1C, N-CH_2-Cq), 45.1 (2C, 2xCH_3-N), 23.0 (1C, N-CH_2)

IR(cm^{-1}): 3122, 1339, 1138

$T_{m.p.}$(°C): 180.5

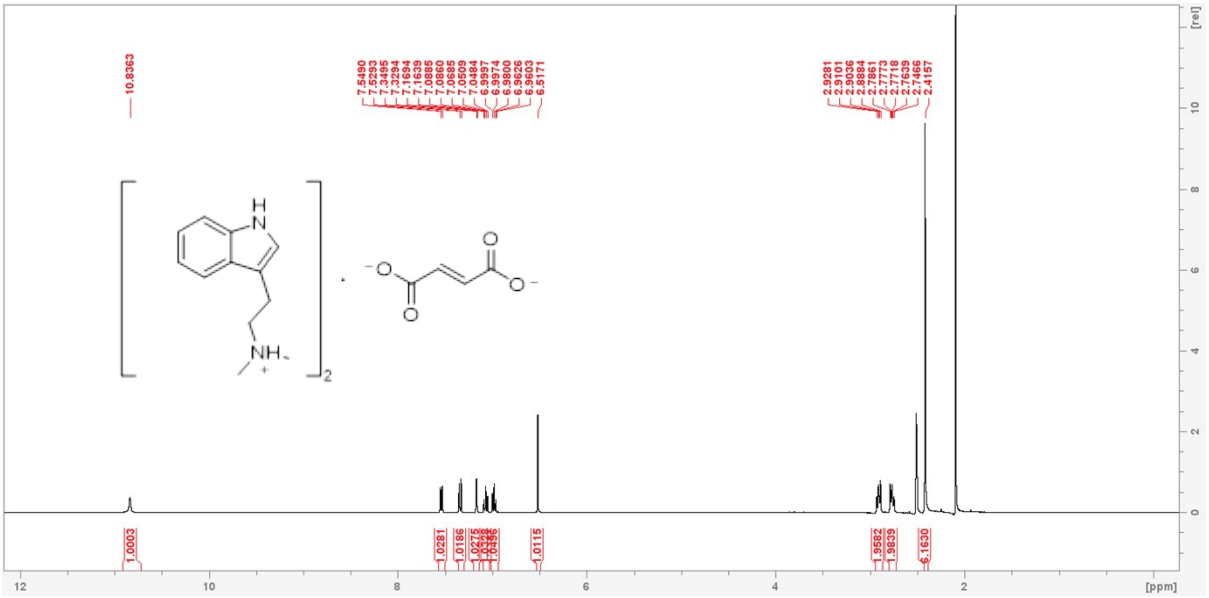
HR-MS [M+H]$^+$: 270.17067 m/z **Calc. Mass $C_{15}H_{20}N_5^+$:** 270.17132 m/z

NMR Spectra

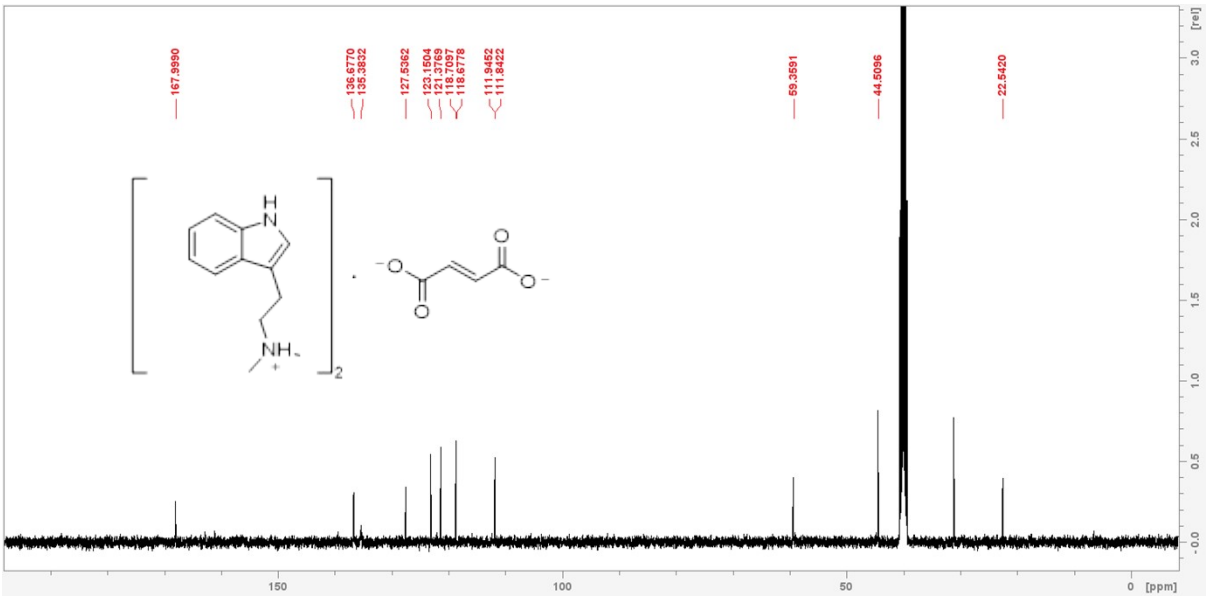
(Peak labels for residual solvents such as acetone and DMSO are omitted)

N,N-dimethyltryptamine hemifumarate (2:1) (13a)

^{1}H NMR

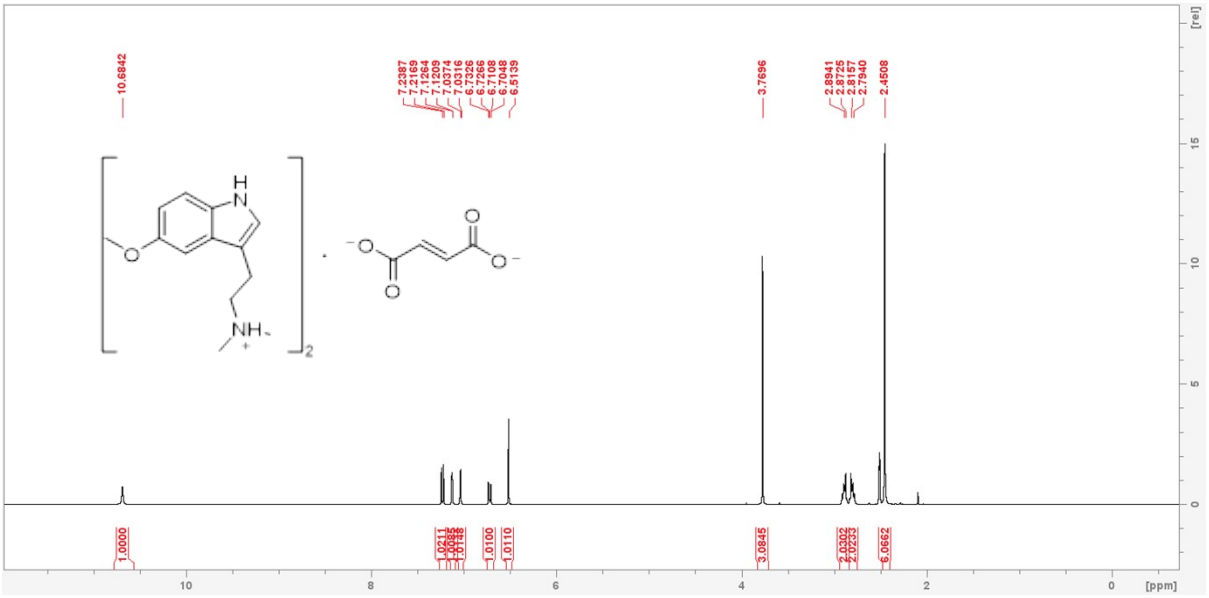


^{13}C NMR

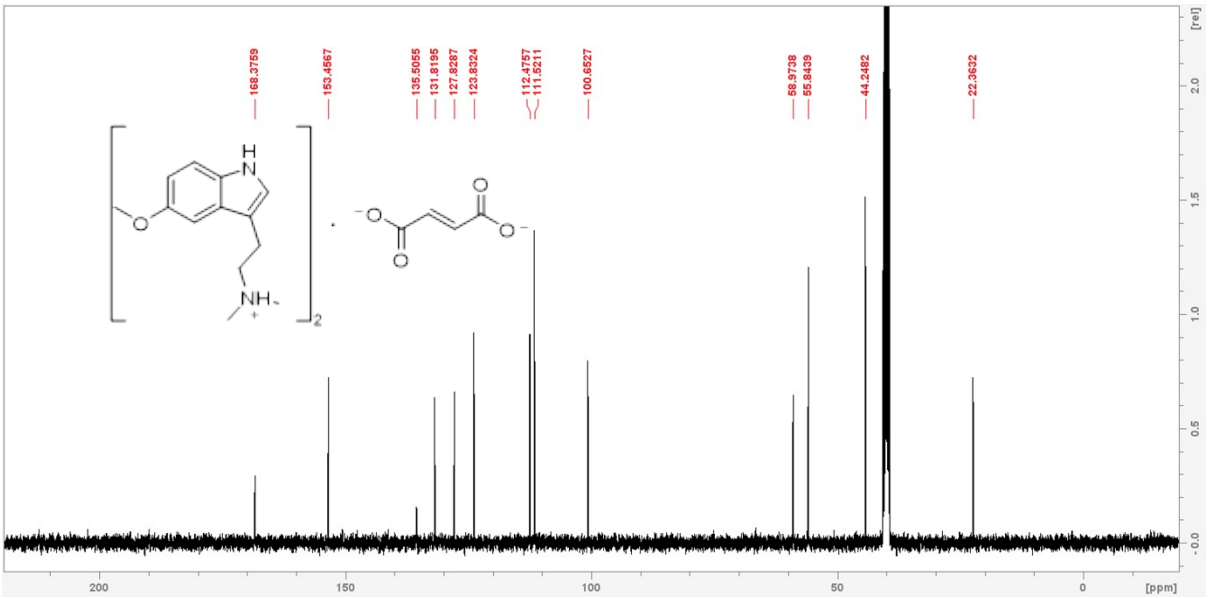


5-MeO-N,N-dimethyltryptamine hemifumarate (2:1) (13b)

^{1}H NMR

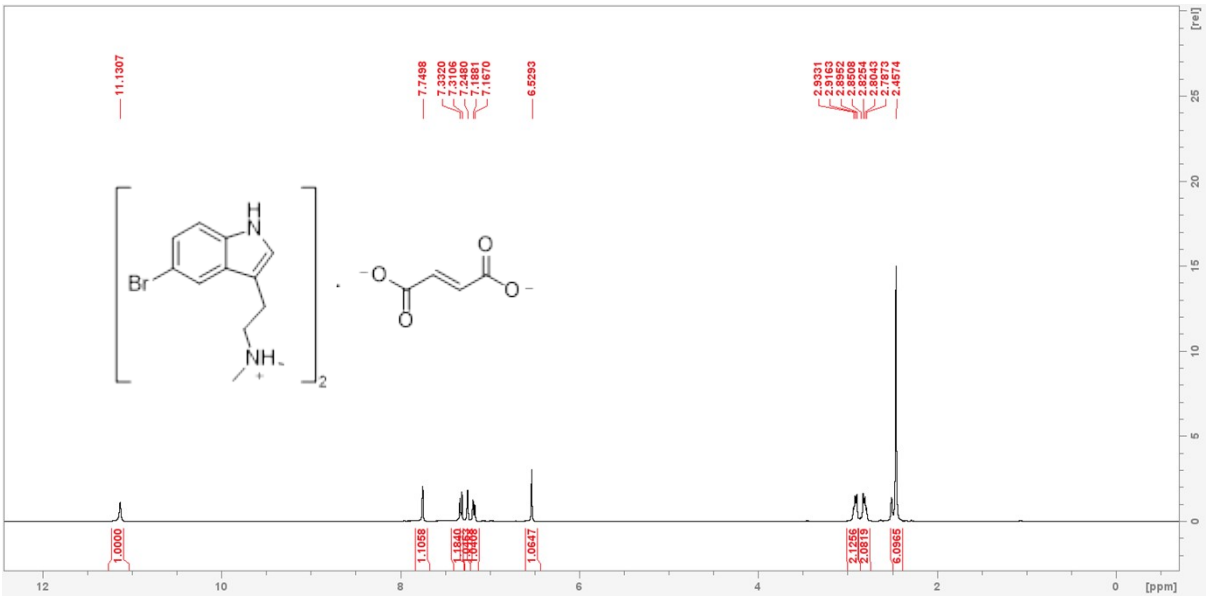


^{13}C NMR

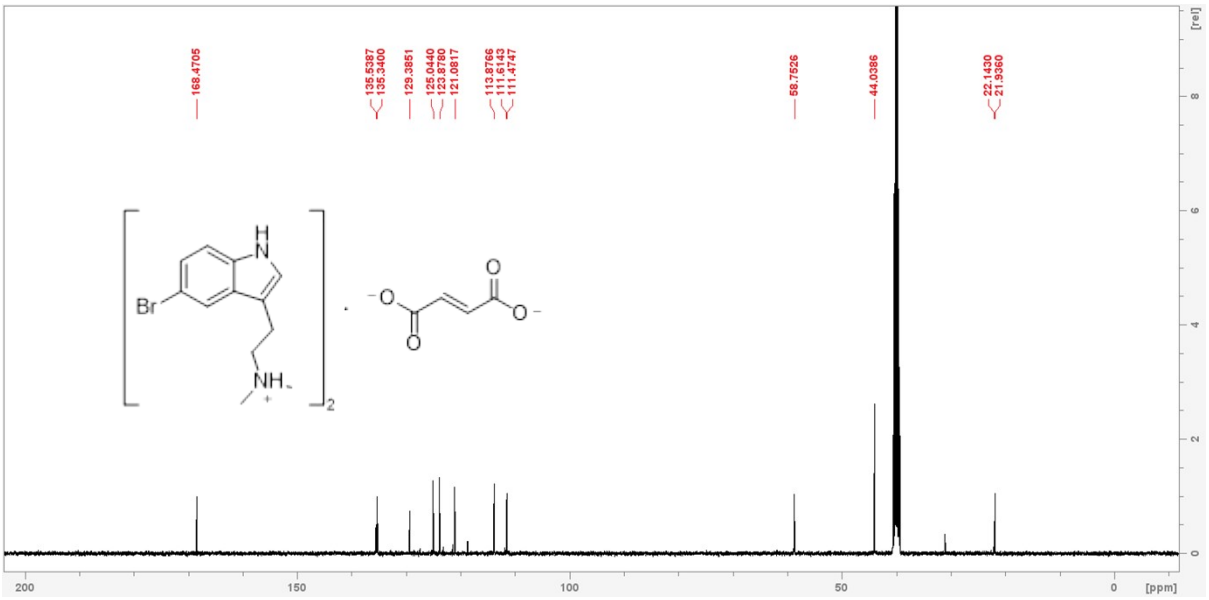


5-Br-N,N-dimethyltryptamine hemifumarate (2:1) (13c)

^{1}H NMR

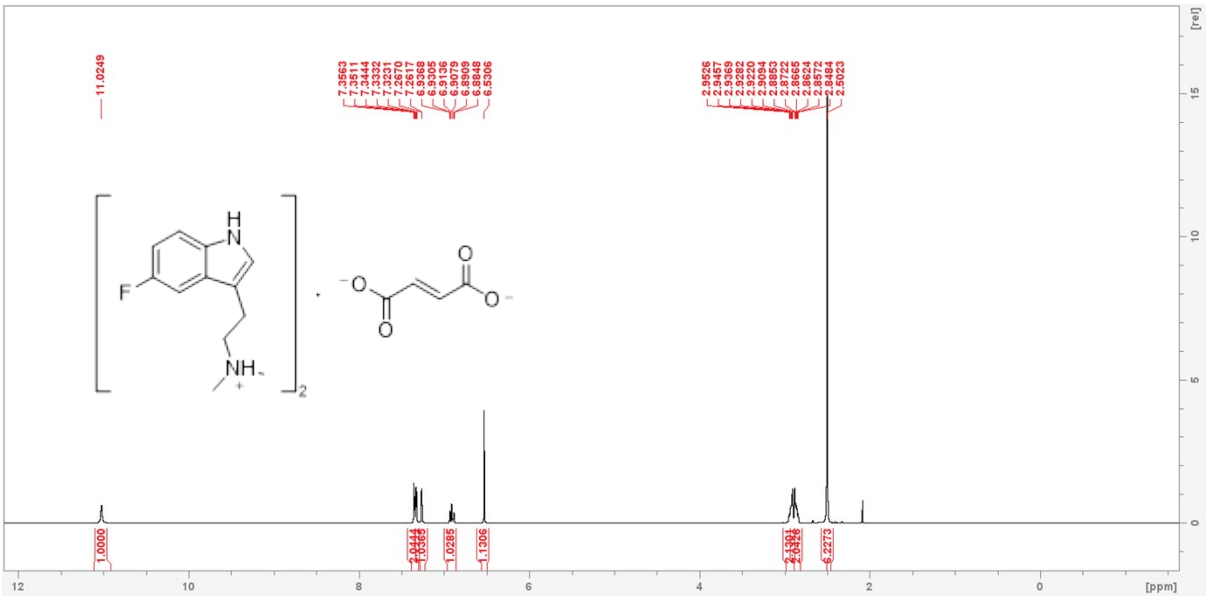


^{13}C NMR

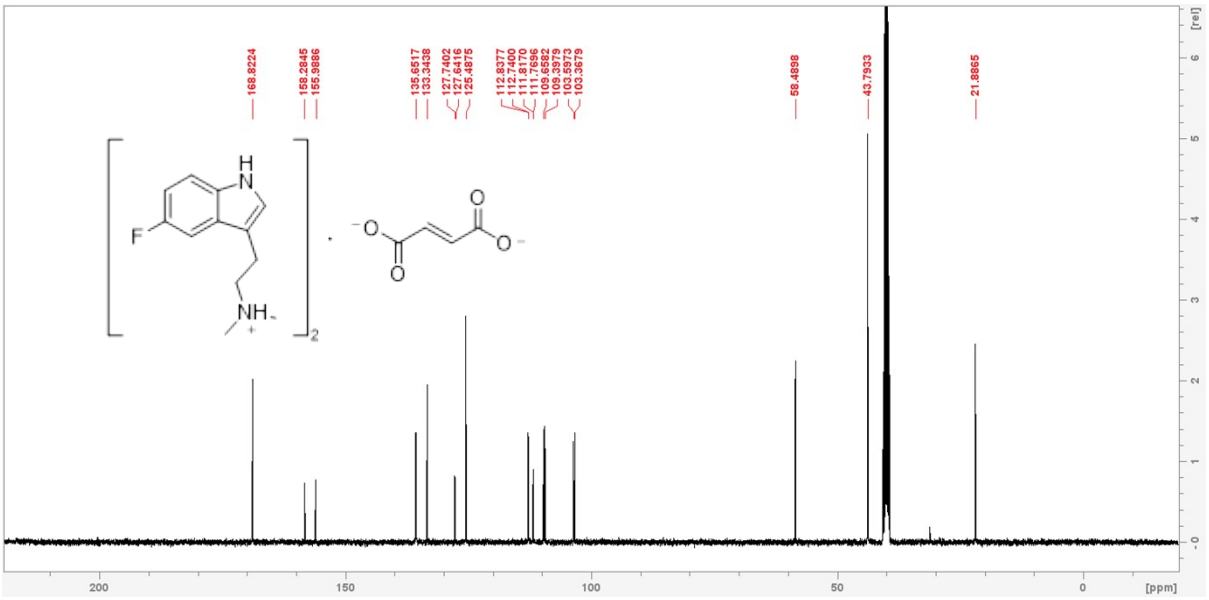


5-F-N,N-dimethyltryptamine hemifumarate (2:1) (13d)

^{1}H NMR



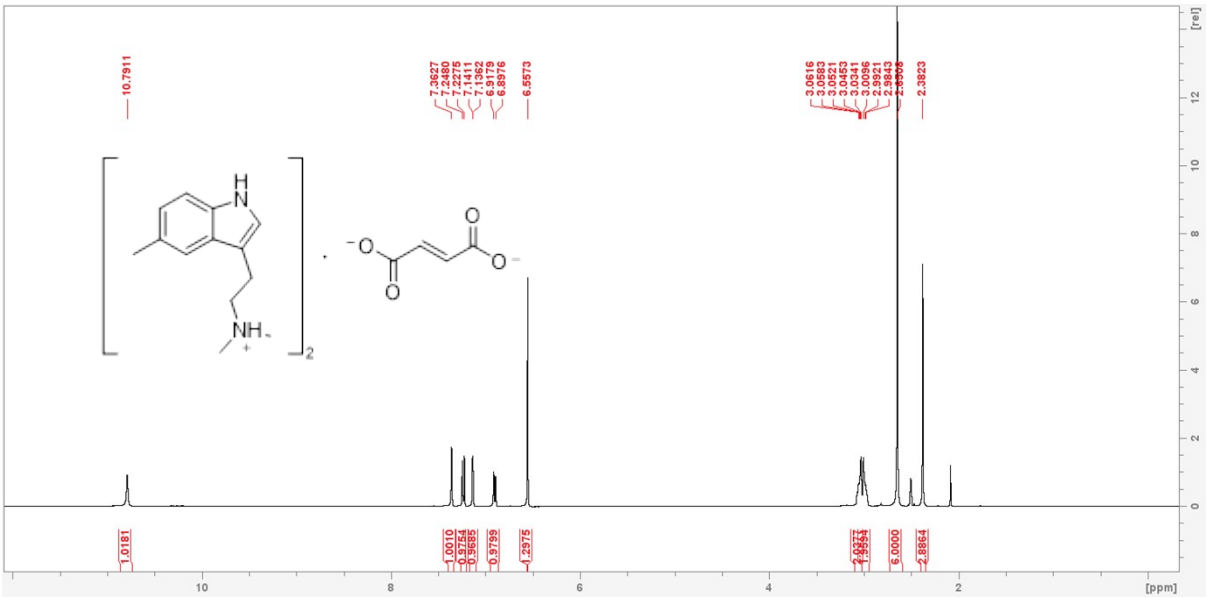
^{13}C NMR



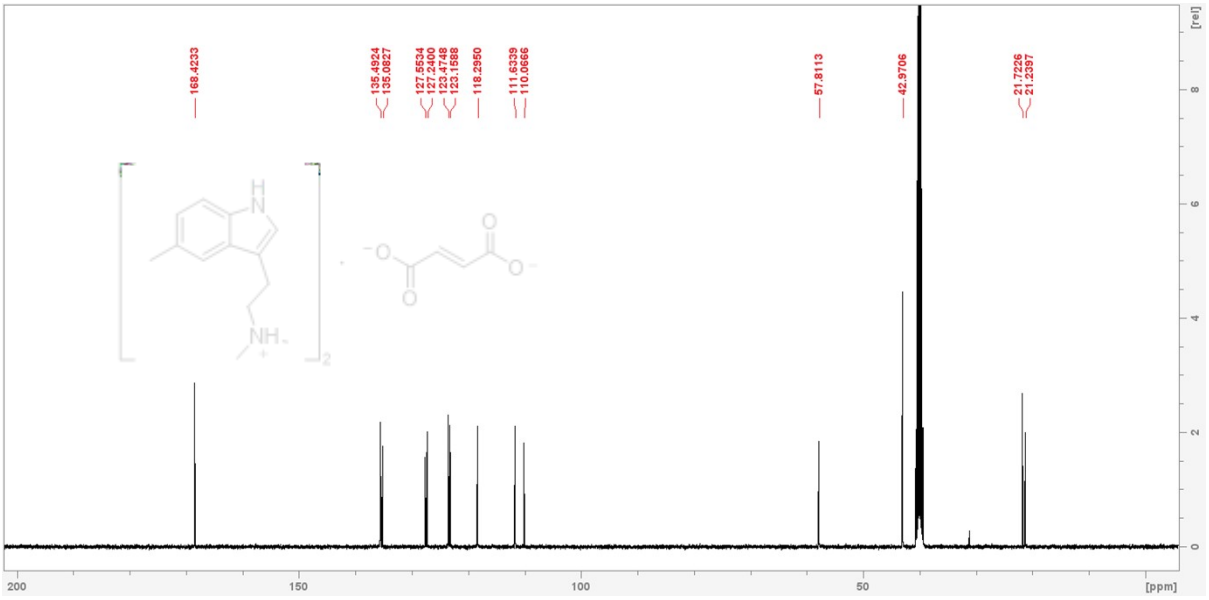
^{19}F NMR

5-Me-N,N-dimethyltryptamine hemifumarate (2:1) (13e)

^{1}H NMR

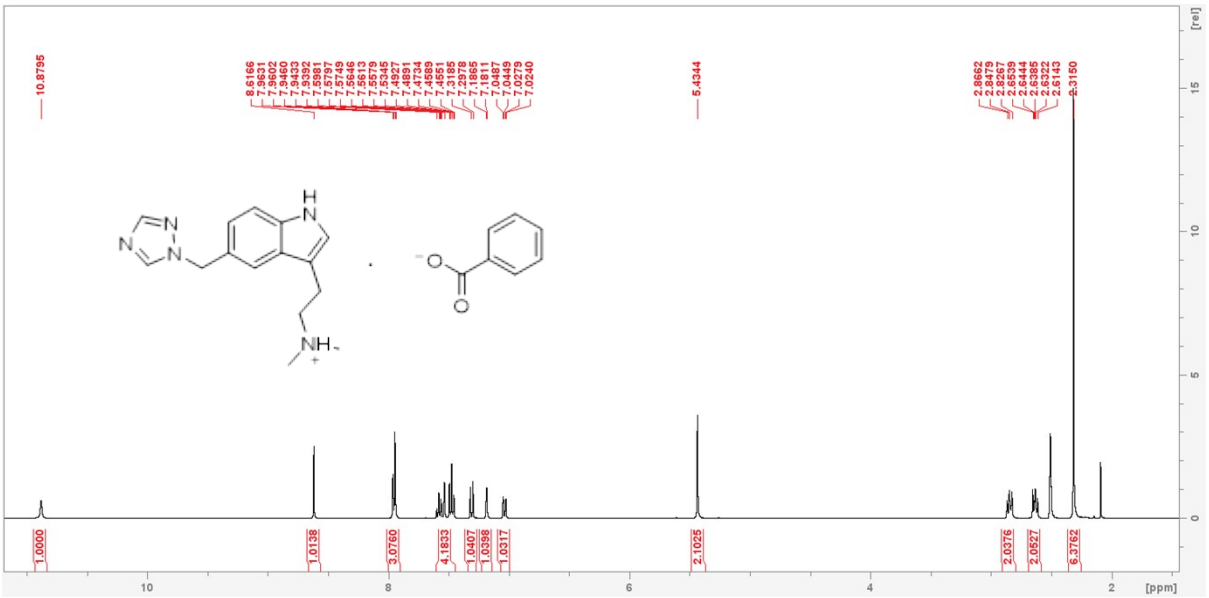


^{13}C NMR

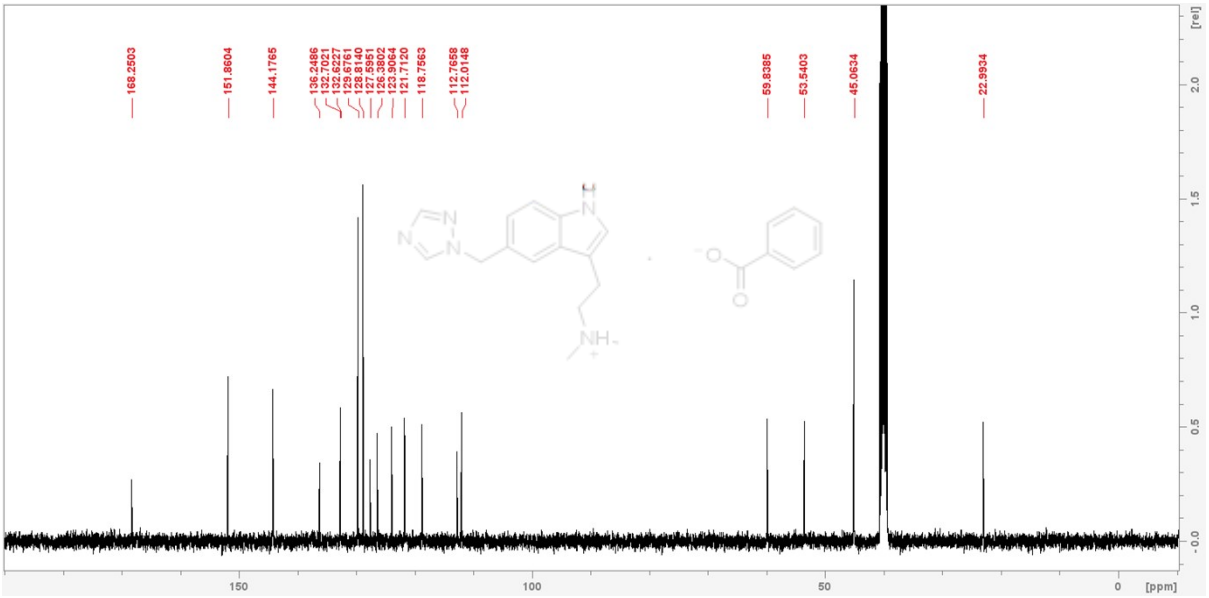


Rizatriptan benzoate (1:1) / Maxalt® / MK462 (15)

^{1}H NMR

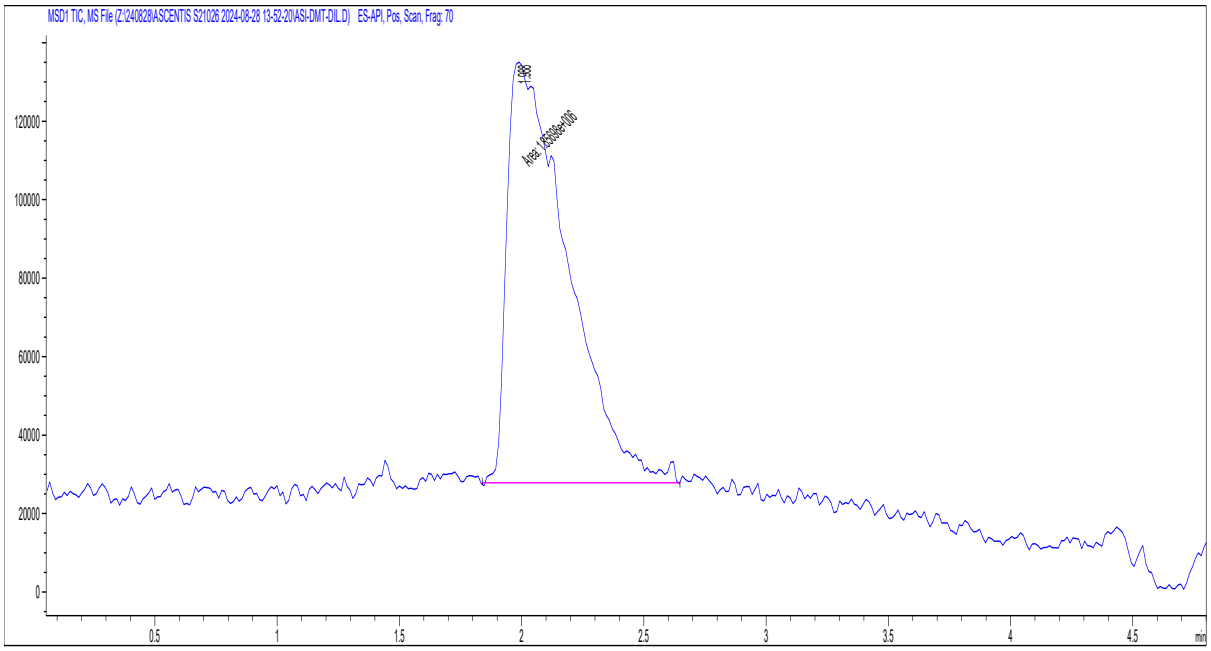


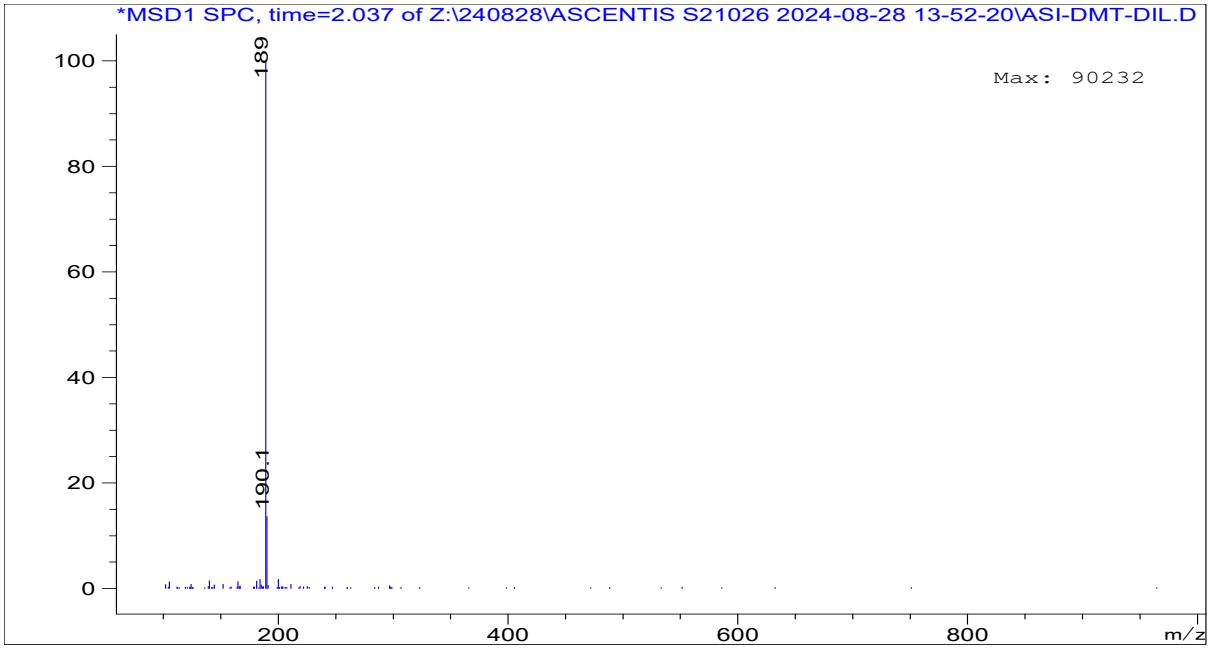
^{13}C NMR



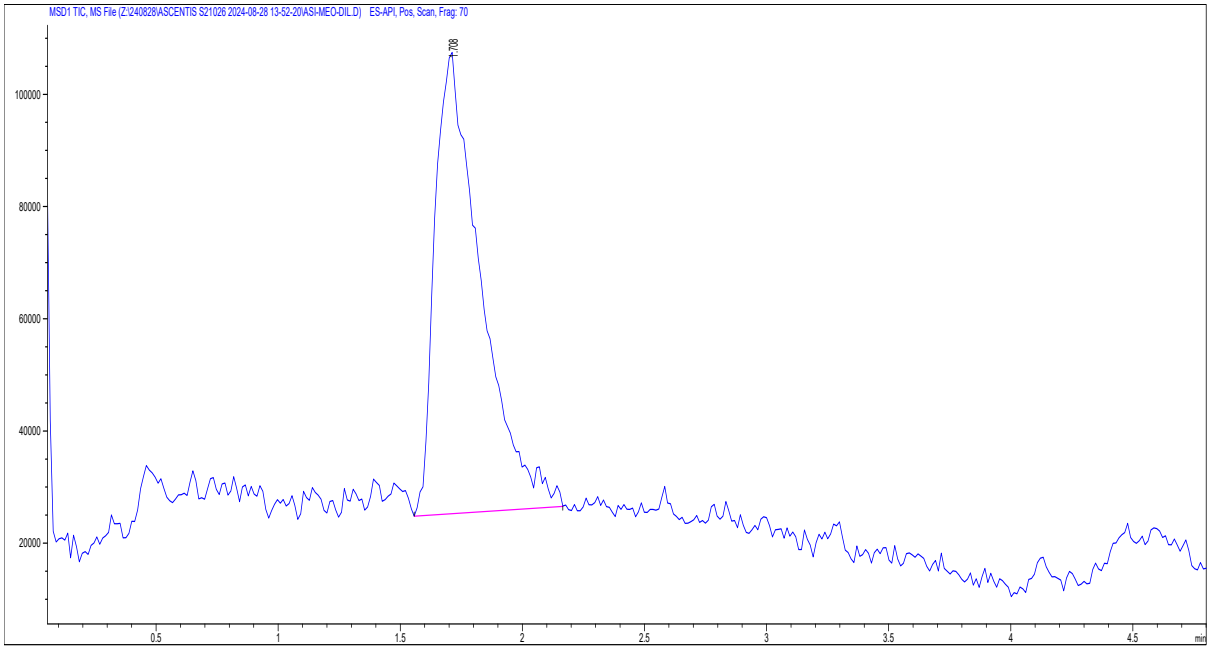
HPLC-MS

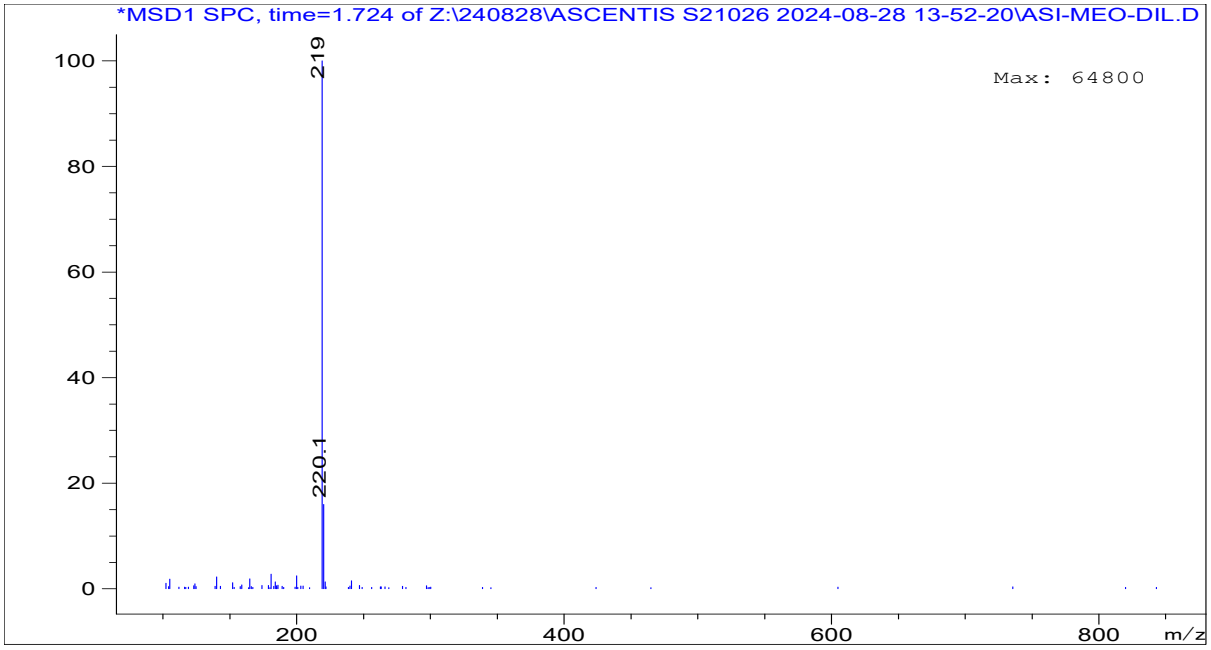
N,N-dimethyltryptamine hemifumarate (2:1) (13a)



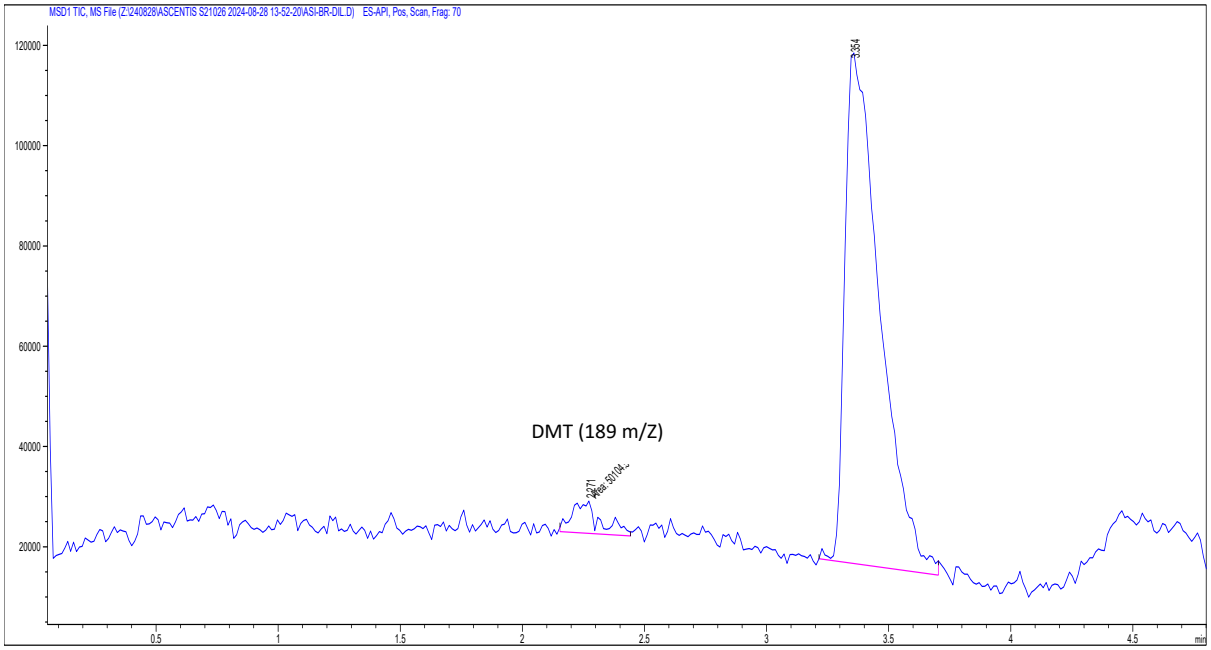


5-MeO-N,N-dimethyltryptamine hemifumarate (2:1) (13b)





5-Br-N,N-dimethyltryptamine hemifumarate (2:1) (13c)



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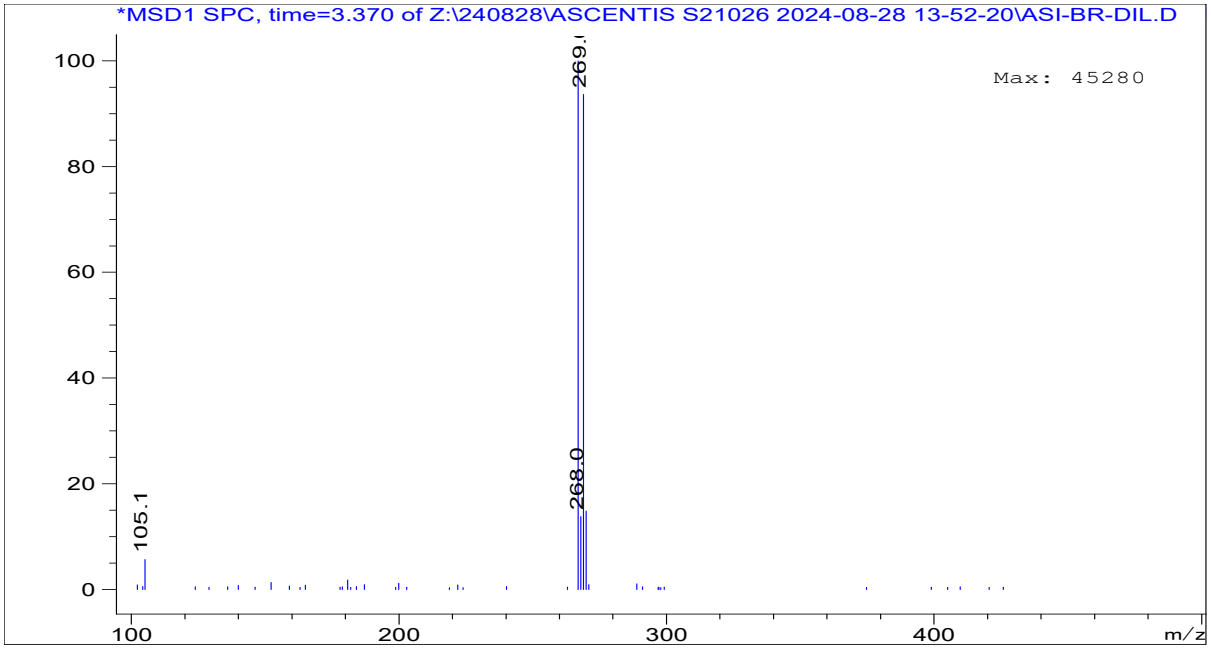
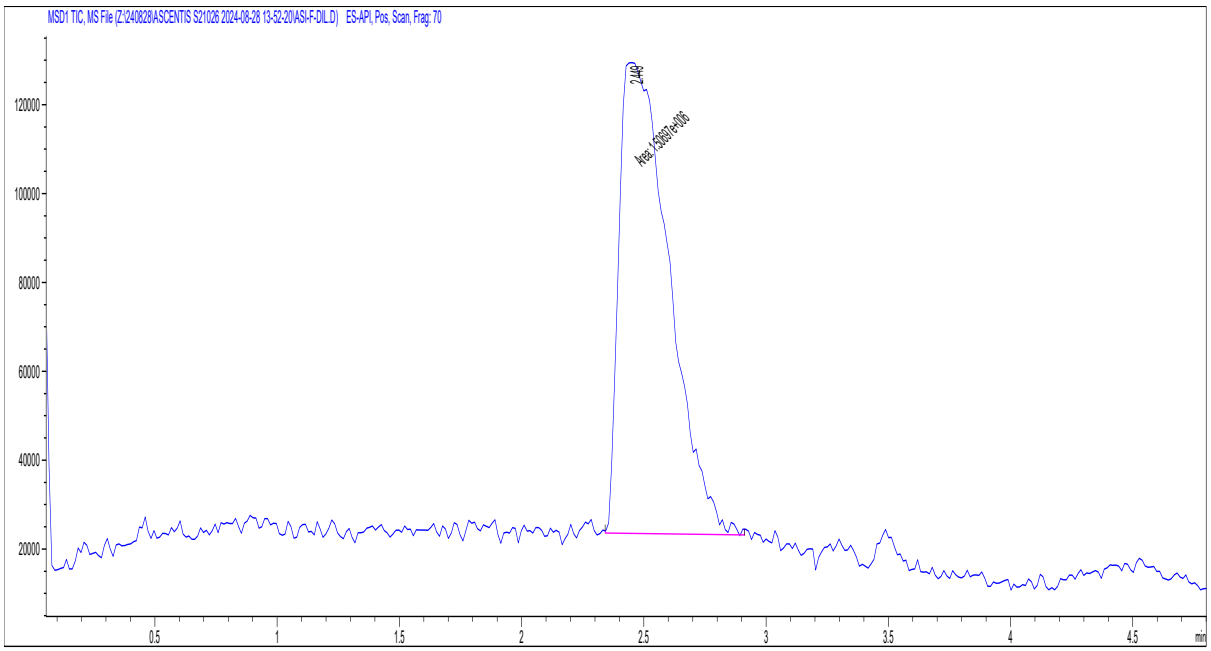
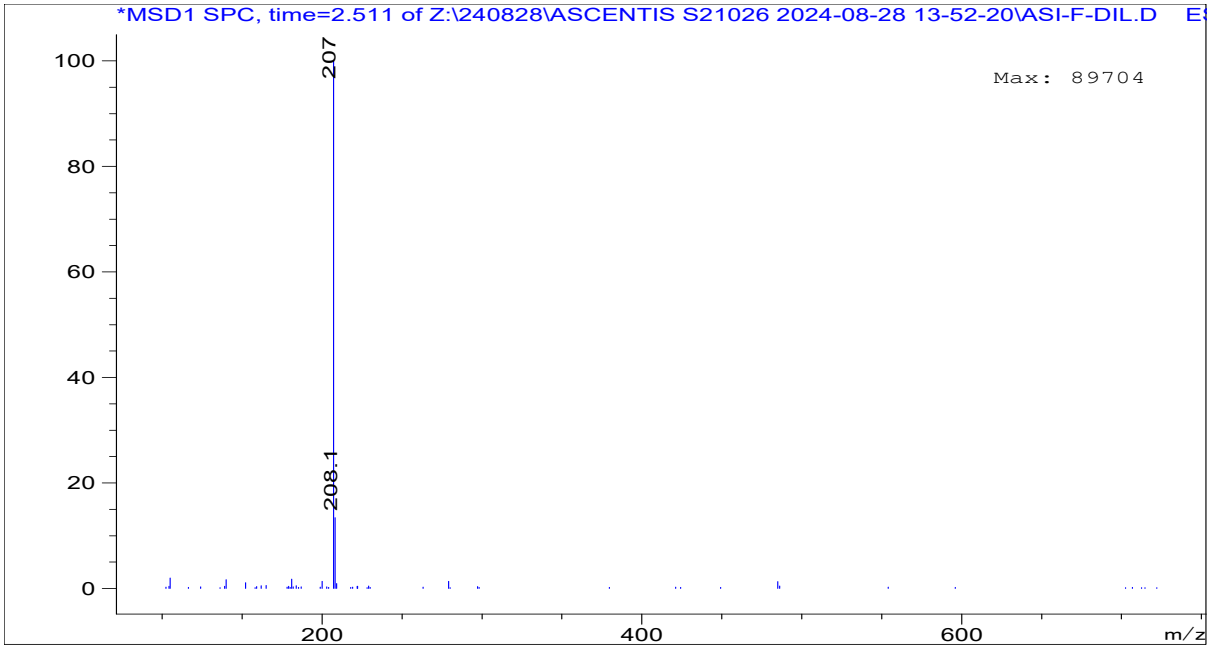
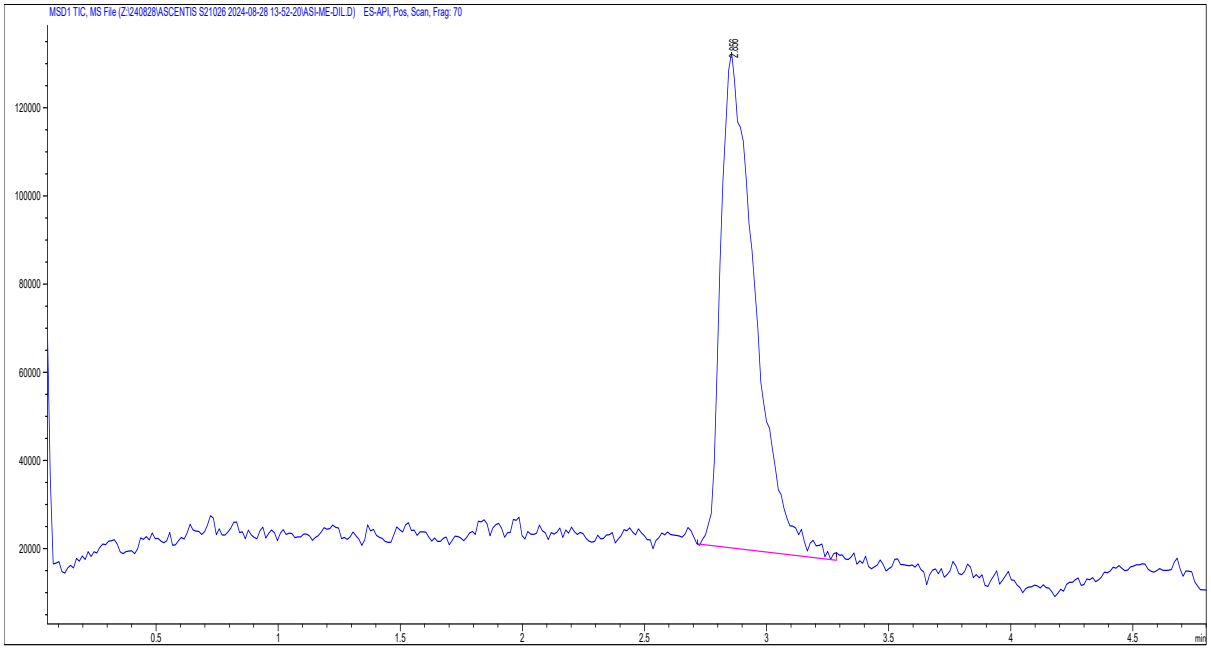


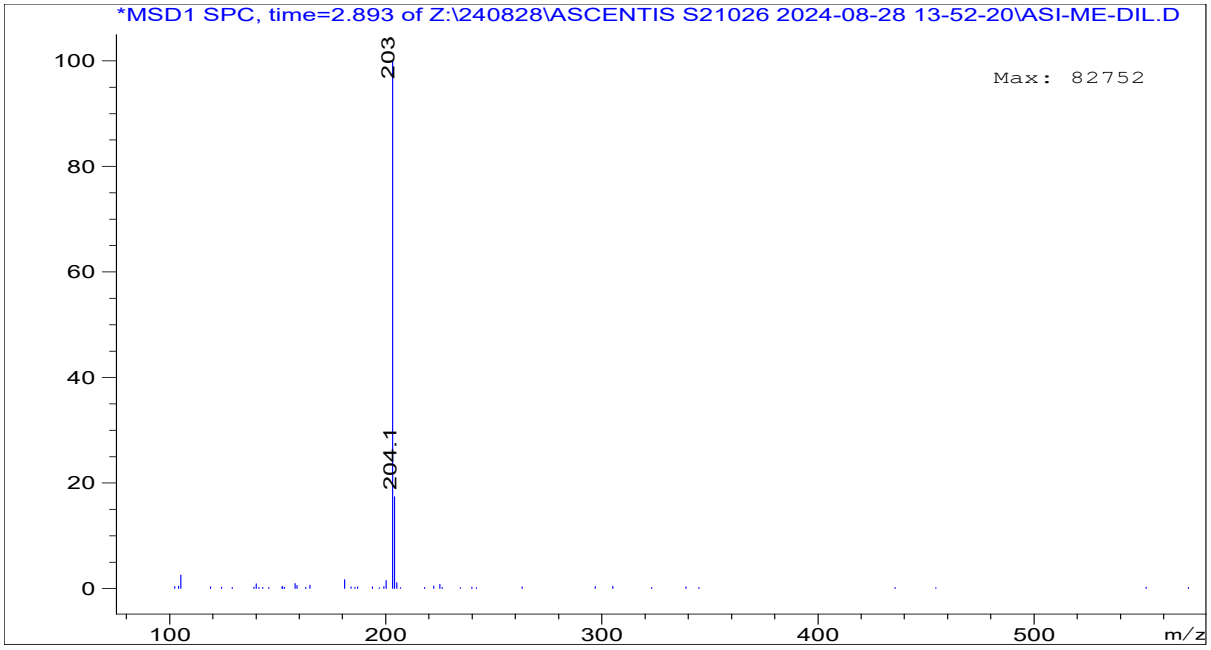
5-F-N,N-dimethyltryptamine hemifumarate (2:1) (13d)



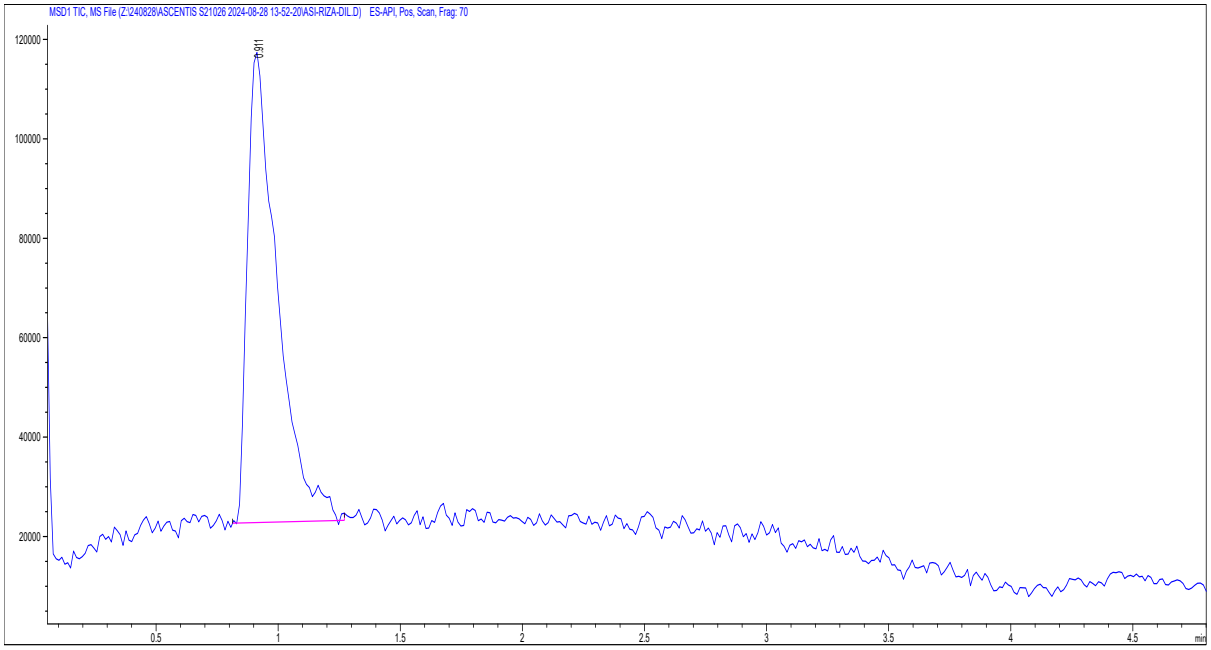


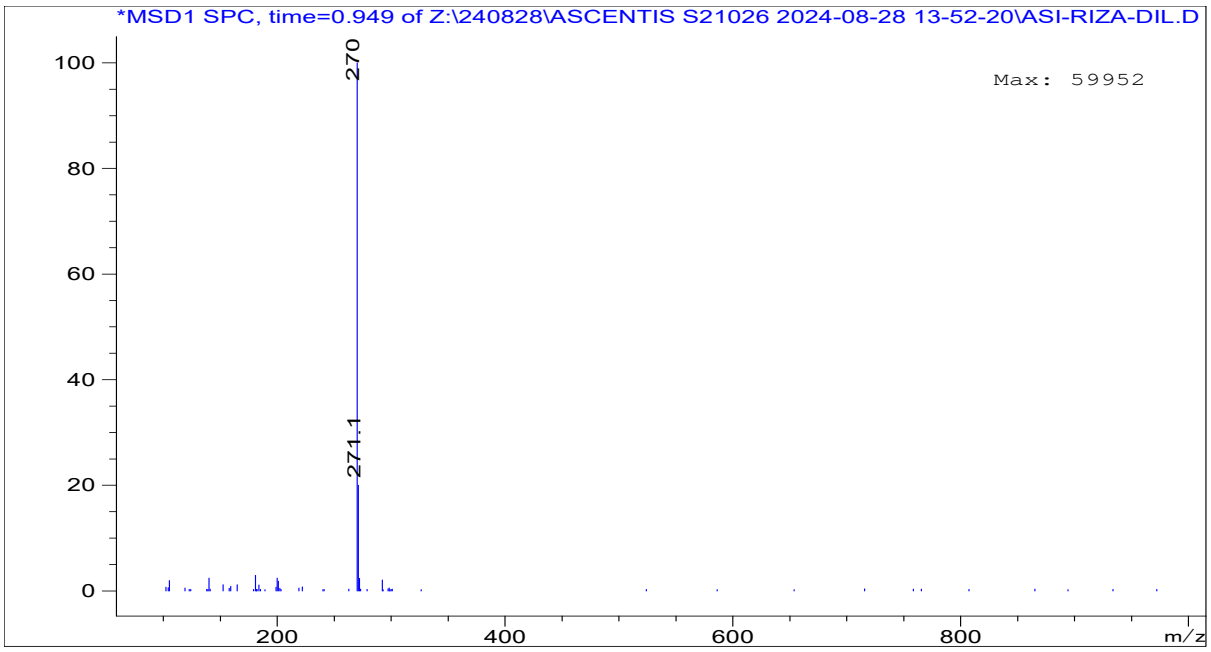
5-Me-N,N-dimethyltryptamine hemifumarate (2:1) (13e)





Rizatriptan benzoate (1:1) / Maxalt® / MK462 (15)

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m/z

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