Electronic Supplementary Material (ESI) for RSC Advances.

Accelerating Preclinical PET-Screening: Reductive Amination with [^{11}C]Methoxybenzaldehydes

Matthias M. Herth*[a,b,c], Sebastian Leth-Petersen[b], Szabolcs Lehel[a], Martin Hansen[b], Gitte M. Knudsen[c], Nic Gillings[a], Jacob Madsen[a] and Jesper L. Kristensen[b]

a) *PET and Cyclotron Unit, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark*

b) *Department of Drug Design and Pharmacology, The Faculty of Health and Medical Sciences, University of Copenhagen. Universitetsparken 2, DK-2100 Copenhagen, Denmark*

c) *Center for Integrated Molecular Brain Imaging, Rigshospitalet and University of Copenhagen, Blegdamsvej 9, DK-2100 Copenhagen, Denmark*

CORRESPONDING AUTHOR
Matthias M. Herth
Phone: (+45) 353 36487
Fax: (+45) 35 33 60 41
matthias.herth@nru.dk

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1. Experimental Section

General. Chemicals were purchased from Acros, Fluka, Sigma, Tocris, or Merck. Unless otherwise stated, all chemicals were used without further purification. Flash chromatography was performed on silica gel 60 (35-70 μm).. Thin layer chromatography (TLC) was performed using plates from Merck (silica gel 60 F_{254} and aluminium oxide 60 F_{254}). Compounds were visualized by heating after dipping in ninhydrin solution (1 g Ninhydrin, 2.5 mL AcOH, 500 mL *n*-BuOH, 22.5 mL water). ^{1}H-NMR and ^{13}C-NMR spectra were recorded using a 300 Mhz Varian Mercury 300 BB, 400 MHz Bruker Avance III or 600 MHz, Bruker Avance III HD spectrometers. Chemical shifts are quoted as δ values (ppm) relative to tetramethylsilane (TMS) as internal standard for ^{1}H-NMR and solvent residual peaks as internal standard for ^{13}C-NMR. Analytical high performance liquid chromatography (HPLC) measurements were performed on a Dionex system consisting of a P680A pump, a UVD 170U detector and a Scansys radiodetector. Chemical purity was checked either by HPLC. [^{11}C]Methane was produced via the ^{14}N(p,α)^{11}C reaction by bombardment of an [^{14}N]N2 containing 10% H_2 target with a 17 MeV proton beam in a Scanditronix MC32NI cyclotron. Full spectral data of previously published compounds can be found in the indicated references.

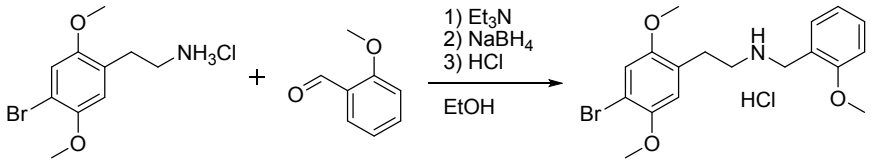
Organic syntheses

2C-B, 2C-D, 2C-E, 2C-T and 2C-T7 were synthesized as described before [1].

General procedure A - for the synthesis of secondary amine hydrochlorides

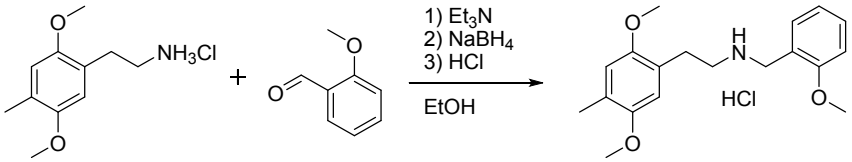
To a suspension of the amine hydrochloride (or hydrobromide) (1.0 mmol) and aldehyde (1.1 mmol) in EtOH (10 mL) was added Et_3N (1.0 mmol) and the reaction was stirred until formation of the imine was complete according to TLC or GC (30 mins to 3 hrs). $NaBH_4$ (2.0 mmol) was added to the reaction which was stirred for another 30 minutes. The reaction mixture was evaporated under reduced pressure and redissolved in EtOAc/H_2O (30 mL, 1:1). The organic layer was isolated and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH/NH_3 98:2:0.04). The purified free base was dissolved in EtOH (2 mL) and there was added ethanolic HCl (1M, 2 mL) and the solution was diluted with Et_2O until crystals formed. The crystals were collected by filtration and dried under reduced pressure.

2-(4-bromo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine hydrochloride (Cimbi 36)



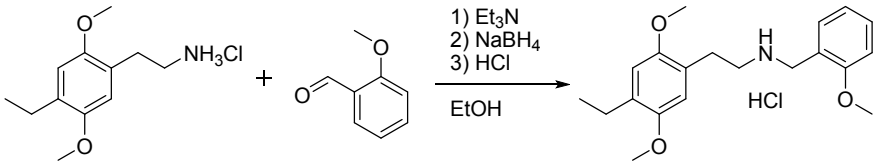
Obtained from 2C-B·HCl and 2-methoxybenzaldehyde by general procedure A in 85% yield as a colorless solid. mp. 179 – 181 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.34 (2H, br s) , 7.50 (1H, d, J = 7.4 Hz), 7.39 (1H, t, J = 8,3 Hz), 7.17 (1H, s), 7.06 (1H, d, J = 8.3 Hz), 7.01 (1H, s), 6.98 (1H, t, J = 7.4 Hz), 4.10 (2H, s), 3.79 (3H, s), 3.73 (3H, s), 2.93 – 3.11 (4H, m). ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.3, 151.3, 149.2, 131.3, 130.6, 125.4, 120.2, 119.6, 115.7, 114.8, 110.9, 108.7, 56.6, 56.2, 55.6, 45.6, 44.7, 26.3.

2-(2,5-dimethoxy-4-methylphenyl)-*N*-(2-methoxybenzyl)ethanamine hydrochloride (Cimbi 98)



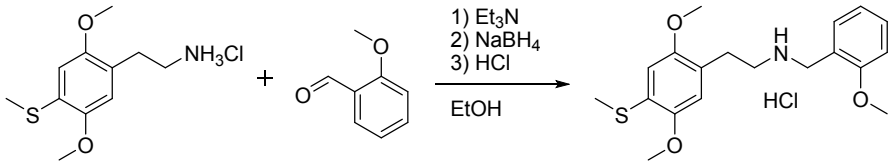
Obtained from 2C-D·HCl and 2-methoxybenzaldehyde by general procedure A in 90% yield as a colorless solid. mp. 166 – 168 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.36 (2H, br s), 7.48 – 7.53 (1H, m), 7.35 – 7.42 (1H, m), 7.04 – 7.08 (1H, m), 6.94 – 7.01 (1H, m), 6.80 (1H, s), 6.76 (1H, s), 4.10 (2H, t, J = 5.3 Hz), 3.82 (3H, s), 3.72 (3H, s), 3.69 (3H, s), 2.90 – 3.07 (4H, m), 2.12 (3H, s) ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.3, 150.9, 150.4, 131.4, 130.5, 124.7, 122.5, 120.2, 119.6, 113.8, 112.6, 110.9, 55.8, 55.6, 55.6, 46.1, 44.6, 26.4, 16.1.

2-(4-ethyl-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine (Cimbi 148)



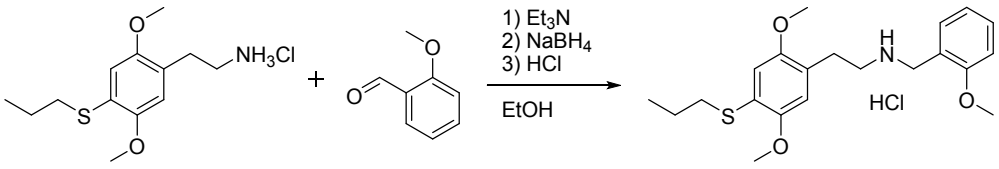
Obtained from 2C-E·HCl and 2-methoxybenzaldehyde by general procedure A in 74% yield as a colorless solid. mp. 160 – 161 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.08 (2H, br s), 7.48 (1H, dd, J = 7.5, 1.6 Hz), 7.40 (1H, ddd, J = 8.3, 7.6, 1.7 Hz), 7.09 (1H, dd, J = 8.3, 0.8 Hz), 7.00 (1H, ddd, J = 7.5, 7.6, 0.8 Hz), 6.81 (1H, s), 6.78 (1H, s), 4.13 (2H, br s), 3.83 (3H, s), 3.73 (3H, s), 3.72 (3H, s), 3.08 – 3.02 (2H, m), 2.96 – 2.91 (2H, m), 2.54 (2H, q, J = 7.4 Hz), 1.10 (3H, t, J = 7.5 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ 157.5, 150.9, 150.7, 131.4, 131.1, 130.8, 122.6, 120.4, 119.7, 113.2, 112.5, 111.1, 55.9, 55.8, 55.6, 46.2, 44.9, 26.3, 22.8, 14.5.

2-(2,5-dimethoxy-4-(methylthio)phenyl)-*N*-(2-methoxybenzyl)ethanamine hydrochloride (Cimbi 168)



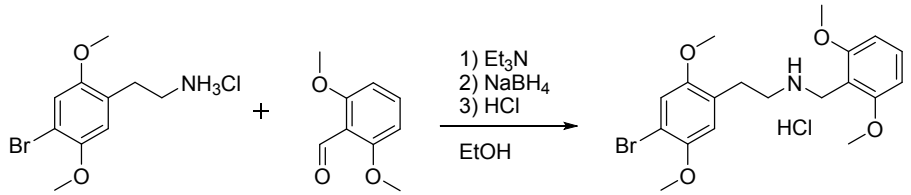
Obtained from 2C-T·HCl and 2-methoxybenzaldehyde by general procedure A in 76% yield as a colorless solid. mp. 147 – 153 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.06 (2H, br s), 7.47 (1H, dd, J = 7.5, 1.7 Hz), 7.41 (1H, ddd, J = 8.3, 7.5, 1.7 Hz), 7.09 (1H, dd, J = 8.3, 1.0 Hz), 7.00 (1H, td, J = 7.5, 1.0 Hz), 6.83 (1H, s), 6.76 (1H, s), 4.13 (2H, s), 3.84 (3H, s), 3.78 (3H, s), 3.76 (3H, s), 3.08 – 3.02 (2H, m), 2.97 – 2.91 (2H, m), 2.41 (3H, s). ^{13}C NMR (150 MHz, DMSO-d_6) δ 157.5, 151.6, 149.5, 131.4, 130.8, 125.8, 121.6, 120.4, 119.7, 113.2, 111.1, 109.3, 56.2, 56.1, 55.6, 46.1, 44.9, 26.1, 13.7.

2-(2,5-dimethoxy-4-(propylthio)phenyl)-*N*-(2-methoxybenzyl)ethanamine hydrochloride (Cimbi 188)



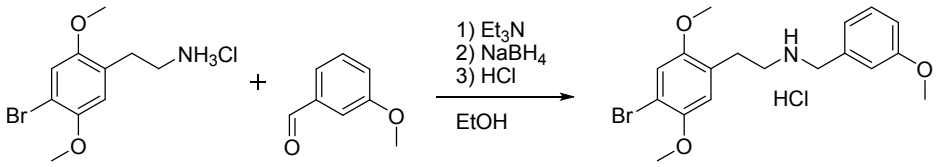
Obtained from 2C-T7·HCl and 2-methoxybenzaldehyde by general procedure A in 49% yield as a colorless solid. mp. 121 – 123 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.03 (2H, br s), 7.47 (1H, dd, J = 7.5, 1.7 Hz), 7.42 (1H, ddd, J = 8.3, 7.5, 1.7 Hz), 7.09 (1H, dd, J = 8.3, 1.0 Hz), 7.00 (1H, td, J = 7,5, 1.0 Hz), 6.84 (1H, s), 6.82 (1H, s), 4.13 (2H, s), 3.84 (3H, s), 3.76 (6H, s), 3.09 – 3.03 (2H, m), 2.96 – 2.92 (2H, m), 2.89 (2H, t, J = 7.2 Hz), 1.58 (2H, sextuplet, J = 7.2 Hz), 0.98 (3H, t, J = 7.2 Hz). ^{13}C NMR (150 MHz, DMSO-d_6) δ 157.5, 151.3, 150.5, 131.4, 130.8, 123.8, 122.6, 120.4, 119.7, 113.6, 111.4, 111.1, 56.2, 56.1, 55.6, 46.1, 44.9, 32.7, 26.2, 21.8, 13.3.

2-(4-bromo-2,5-dimethoxyphenyl)-*N*-(2,6-dimethoxybenzyl)ethanamine hydrochloride (Cimbi 218)



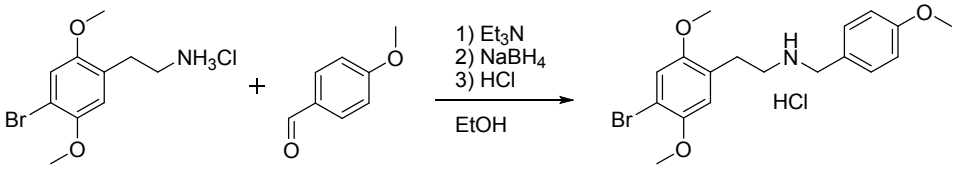
Obtained from 2C-B·HCl and 2,6-dimethoxybenzaldehyde by general procedure A in 56% yield as a colorless solid. mp. 193-194 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.07 (2H, br s), 7.36 (1H, t, J = 8.4 Hz), 7.16 (1H, s), 6.97 (1H, s), 6.71 (2H, d, J = 8.4 Hz), 4.08 (2H, s), 3.81 (6H, s), 3.78 (3H, s), 3.73 (3H, s), 2.97 (4H, s). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.4 (2C), 151.2, 149.2, 131.1, 125.4, 115.7, 114.7, 108.7, 106.9, 103.8 (2C), 56.6, 56.2, 55.9 (2C), 45.5, 38.6, 26.3

2-(4-bromo-2,5-dimethoxyphneyl)-*N*-(3-methoxybenzyl)ethanamine hydrochloride (Cimbi 340)



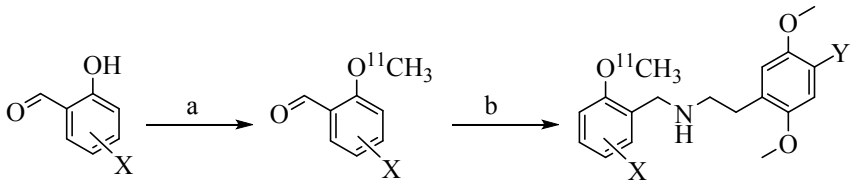
Obtained from 2C-B·HCl and 3-methoxybenzaldehyde by general procedure A in 64% yield as a colorless solid. mp. 156 – 157 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.61 (2H, br s), 7.36 – 7.30 (1H, m), 7.29 – 7.25 (1H, m), 7.19 (1H, s), 7.14 – 7.11 (1H, m), 6.96 (1H, ddd, J = 8.3, 2.6, 0.7 Hz), 4.11 (2H, app t, J = 5.6 Hz), 3.79 (3H, s), 3.78 (3H, s), 3.74 (3H, s), 3.09 – 2.96 (4H, m). ^{13}C NMR (150 MHz, DMSO-d_6) δ 159.3, 151.5, 149.4, 133.4, 129.7, 125.5, 122.1, 115.9, 115.5, 115.0, 114.4, 108.9, 56.6, 56.2, 55.2, 49.7, 45.5, 26.3.

2-(4-bromo-2,5-dimethoxyphneyl)-*N*-(4-methoxybenzyl)ethanamine hydrochloride (Cimbi 388)



Obtained from 2C-B·HCl and 4-methoxybenzaldehyde by general procedure A in 64 % yield as a colorless solid. mp. 189 – 190 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.35 (2H, br s), 7.53 – 7.43 (2H, m), 7.19 (1H, s), 7.01 (1H, s), 6.99 – 6.96 (2H, m), 4.07 (2H, app t, J = 5.1 Hz), 3.79 (3H, s), 3.77 (3H, s), 3.74 (3H, s), 3.08 – 2.99 (2H, m), 2.98 – 2.92 (2H, m). ^{13}C NMR (150 MHz, DMSO-d_6) δ 159.6, 151.5, 149.4, 131.7, 125.5, 123.7, 115.9, 115.0, 113.9, 108.9, 56.6, 56.2, 55.2, 49.2, 45.3, 26.4.

General radiosynthesis conditions for the 2-step, one-pot reductive model kit amination



Precursor **[^{11}C]product**

Supplementary Scheme 1: a) appropriate hydroxybenzaldehyde (HBA), [^{11}C]CH_3OTf, NaOH, DMSO, RT, 60 s b) appropriate phenethylamine, $NaBH_3CN$, AcOH, MeOH, 130 °C, 5 min

[^{11}C]MeOTf produced using a fully automated system was transferred in a stream of helium to a 1.1-mL vial containing the appropriate labelling precursor (HBA, 0.1µmol), 2N NaOH (2 equiv.) and DMSO (300 µL). The resulting mixture was stirred at room temperature for 120 s. Afterwards the appropriate phenethylamine (15 µmol) and $NaBH_3CN$ (63 µmol) dissolved in 0.6 mL MeOH and 5 µL AcOH were added, then heated to 130 °C for 5 min and finally purified by HPLC on an Onyx Monolithic C18 column (Phenomenex Inc.) (100 x 10 mm; 25:75 EtOH: 0.1% phosphoric acid at a flow rate of 9 mL/min). The fraction corresponding to the labeled product (6 mL) was collected into a 20-mL vial containing phosphate buffer (9 mL, 100 mM, pH 7), giving a 15 mL solution of the ^{11}C-labelled final product with a pH of approximately 7. All compounds were produced with a 40 min beam.

Retention times and reaction parameters:

1) [^{11}C]Cimbi-36 = 550 s; Cimbi-94 = 250 s; 2-[^{11}C]MB-CHO = 280 s; isolated yield = 1.6 GBq; A_s = 146 GBq/µmol
2) [^{11}C]Cimbi-218 = 800 s; isolated yield = 1.1 GBq; A_s= 145 GBq/µmol
3) [^{11}C]Cimbi-188 = 1500 s; 2-[^{11}C]MB-CHO = 280 s; isolated yield = 0.54 GBq; A_s = 168 GBq/µmol
4) [^{11}C]Cimbi-168 = 300 s; 2-[^{11}C]MB-CHO = 280 s; isolated yield = 1.1 GBq; A_s = 125 GBq/µmol
5) [^{11}C]Cimbi-148 = 1100 s; 2-[^{11}C]MB-CHO = 280 s; isolated yield = 0.4 GBq; A_s = 77 GBq/µmol
6) [^{11}C]Cimbi-98 = 419 s; 2-[^{11}C]MB-CHO = 280 s; isolated yield = 1.1 GBq; A_s = 122 GBq/µmol
7) [^{11}C]Cimbi-388 = 500 s; 4-[^{11}C]MB-CHO = 250 s; isolated yield = 1.1 GBq; A_s = 61 GBq/µmol
8) [^{11}C]Cimbi-340 = 500 s; 3-[^{11}C]MB-CHO = 280 s; isolated yield = 2.3 GBq; A_s = 68 GBq/µmol

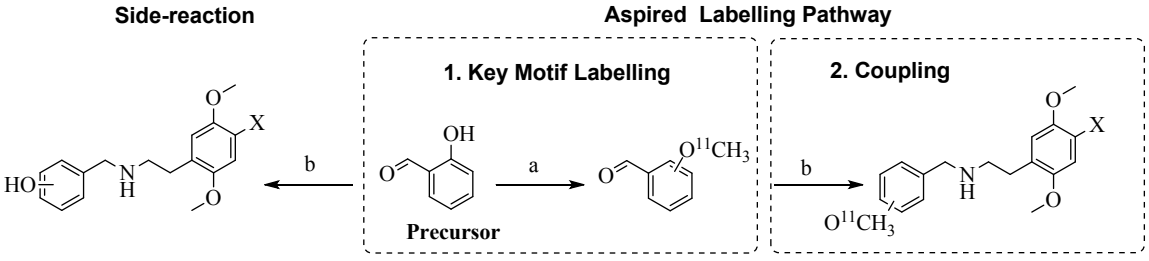
Determination of specific activity and purity

The radiotracer preparation was visually inspected for clarity, and absence of colour and particles. Chemical and radiochemical purities were assessed on the same aliquot by HPLC analysis. Specific activity (A_s) of the radiotracers were calculated from three consecutive HPLC analyses (average) and determined by the area of the UV absorbance peak corresponding to the radiolabeled product on the HPLC chromatogram and compared to a standard curve relating mass to UV absorbance (λ = 296 μm). Column used: Kinetex 2.6μm C18 100Å column (Phenomenex Inc.) (50 x 4.6 mm (33:67 acetonitrile: 0.1% phosphoric acid; and flow rate: 1.5 mL/min.

Retention times:

1) [^{11}C]Cimbi-36 = 1.3 min; Cimbi-94 = 0.9 min, 2) [^{11}C]Cimbi-218 = 1.8 min, 3) [^{11}C]Cimbi-188 = 2.4 min , 4) [^{11}C]Cimbi-168 = 1.1 min, 5) [^{11}C]Cimbi-148 = 1.8 min, 6) [^{11}C]Cimbi-98 = 1.2 min, 7) [^{11}C]Cimbi-388 = 1.2 min, 8) [^{11}C]Cimbi-340 = 1.1 min, 9) 2-[^{11}C]MB-CHO = 1.0 min

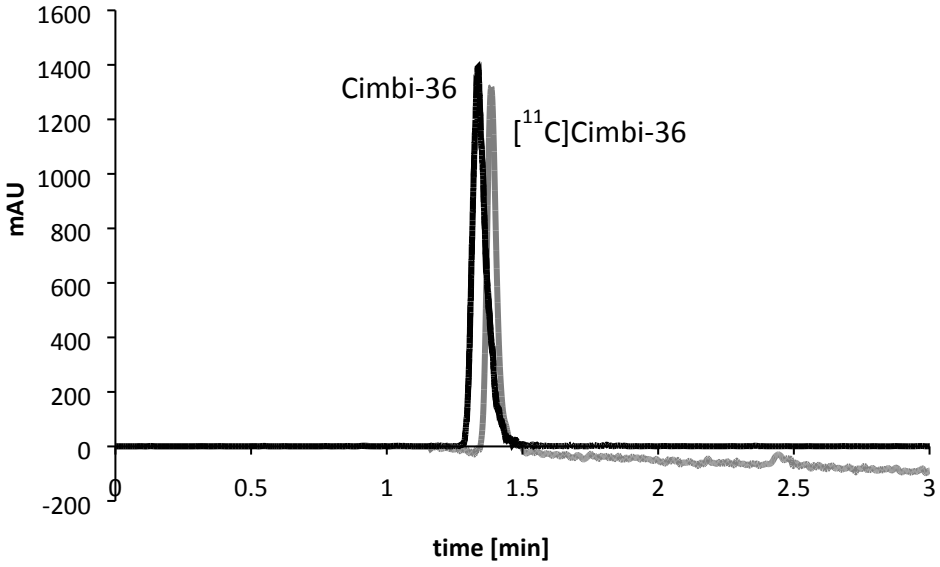
All analyzed final product solutions contained < 15% EtOH and an acceptable contamination of the phenolic side-product (< 0.038 μg/mL). This amount is ~ 3 times lower than the accepted one by the Danish authorities for human [^{11}C]Cimbi-36 productions and in the same order compared to that achieved with the previous [^{11}C]Cimbi-36 labelling method. No imine, 2-HBA and 2C-B were detected in the final formulation.



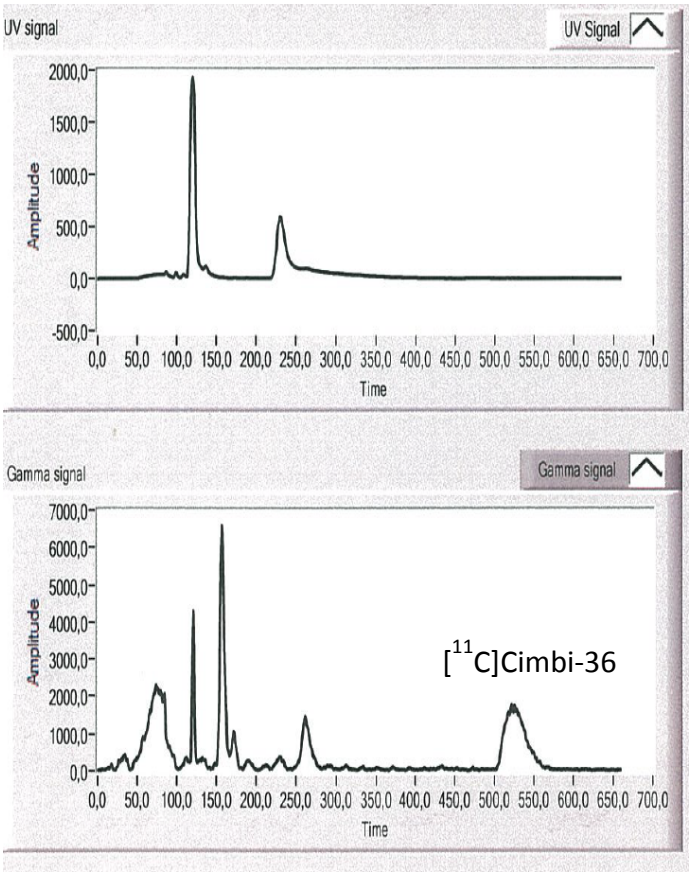
Supplementary Scheme 2: Novel one-pot, 2-step reductive ^{11}C-amination strategy to label phenethylamines; a) 2-HBA, [^{11}C]CH_3OTf, NaOH, DMSO, 25 °C, 60 sec b) Appropriate phenethylamine, $NaBH_3CN$, CH_3COOH, MeOH, 130 °C, 5 min

2. Analytical and semi-prep chromatograms

a)

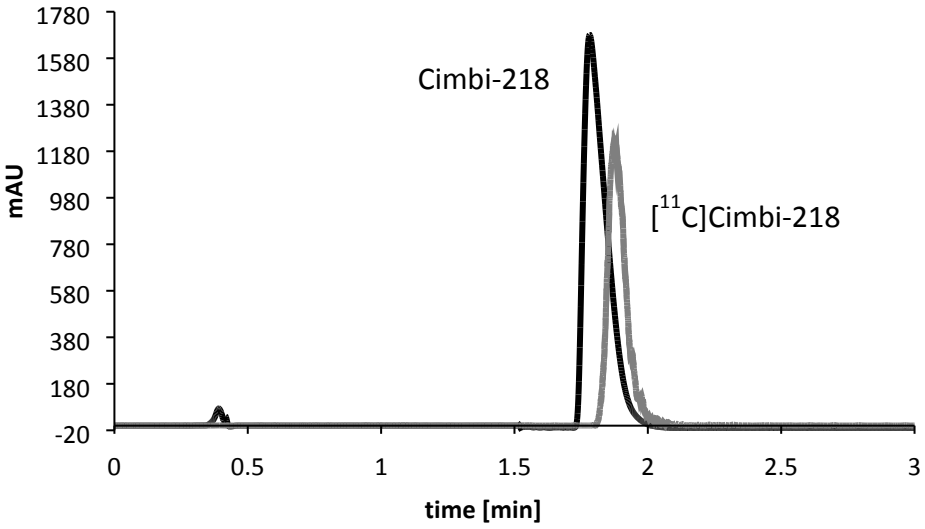


b)

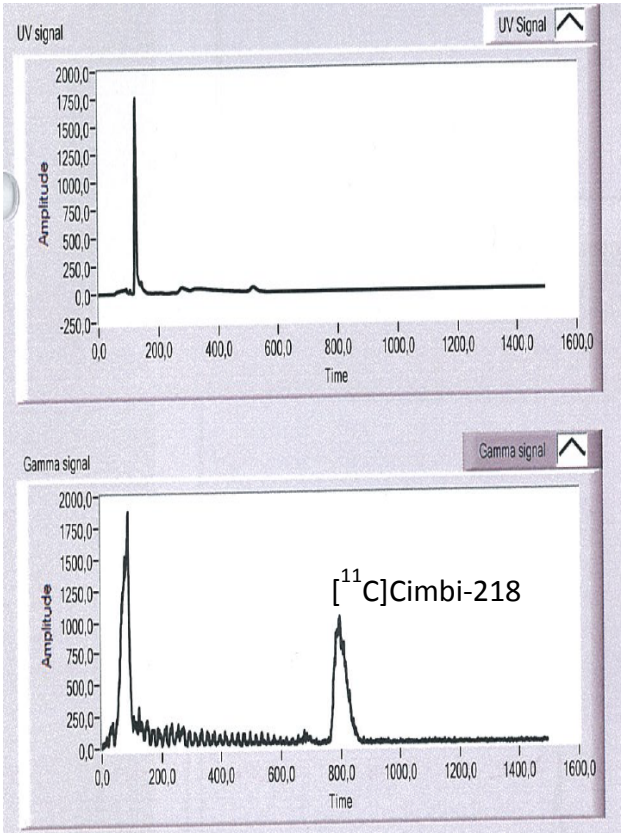


Supplementary Scheme 3: Analytical (UV: black; radio grey) (a) and semi-preparative (b) HPLC chromatograms of [^{11}C]Cimbi-36

a)

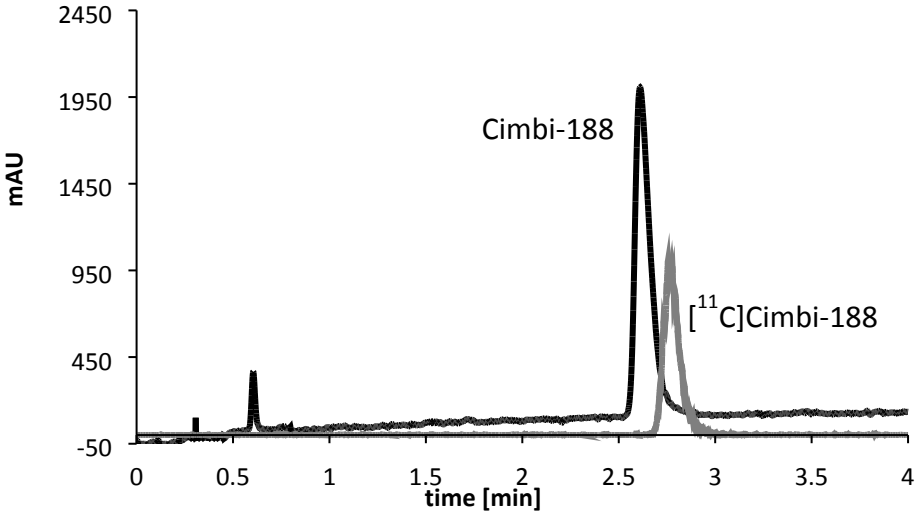


b)

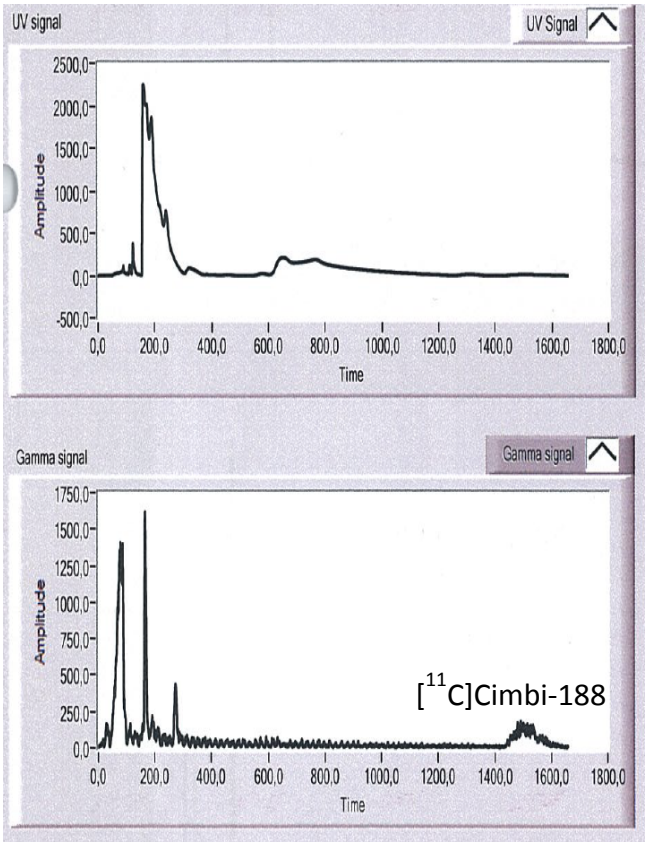


Supplementary Scheme 4: Analytical (UV: black; radio grey) (a) and semi-preparative (b) HPLC chromatograms of [^{11}C]Cimbi-218

a)

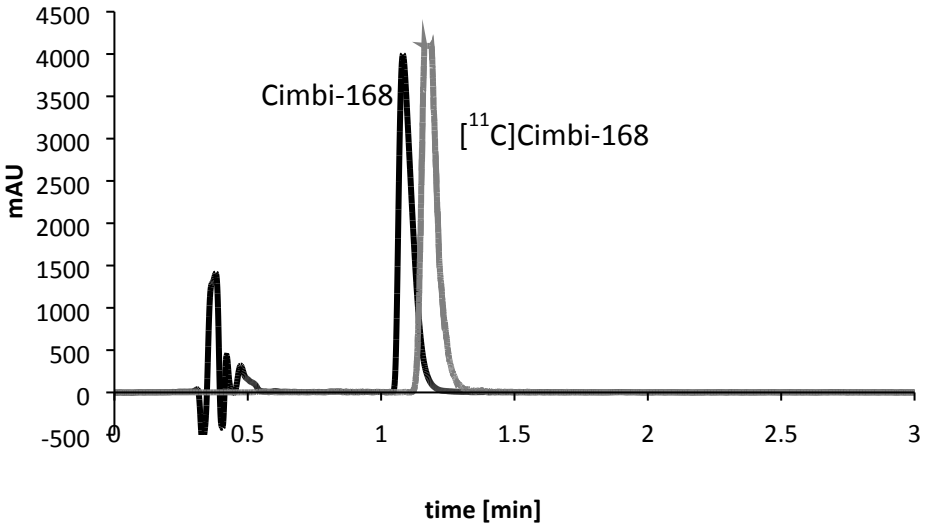


b)

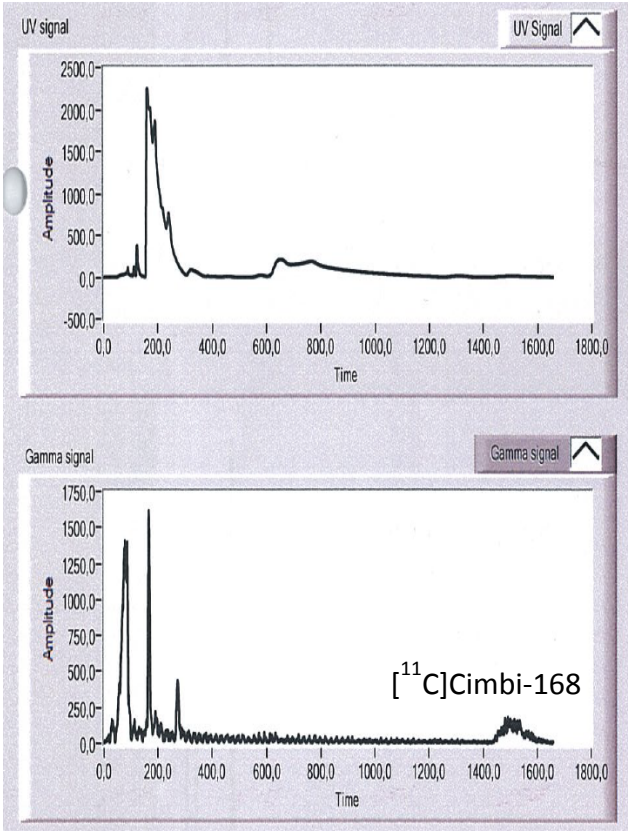


Supplementary Scheme 5: Analytical (UV: black; radio grey) (a) and semi-preparative (b) HPLC chromatograms of [^{11}C]Cimbi-188

a)

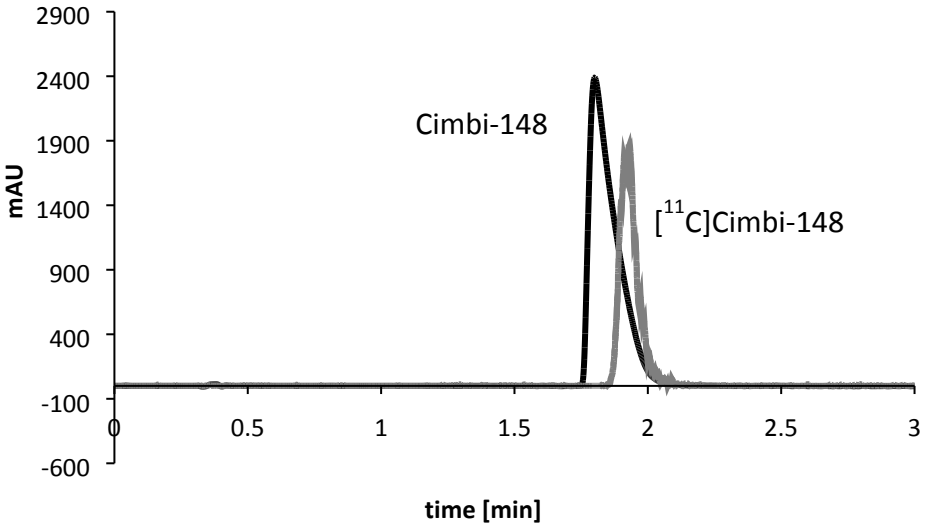


b)

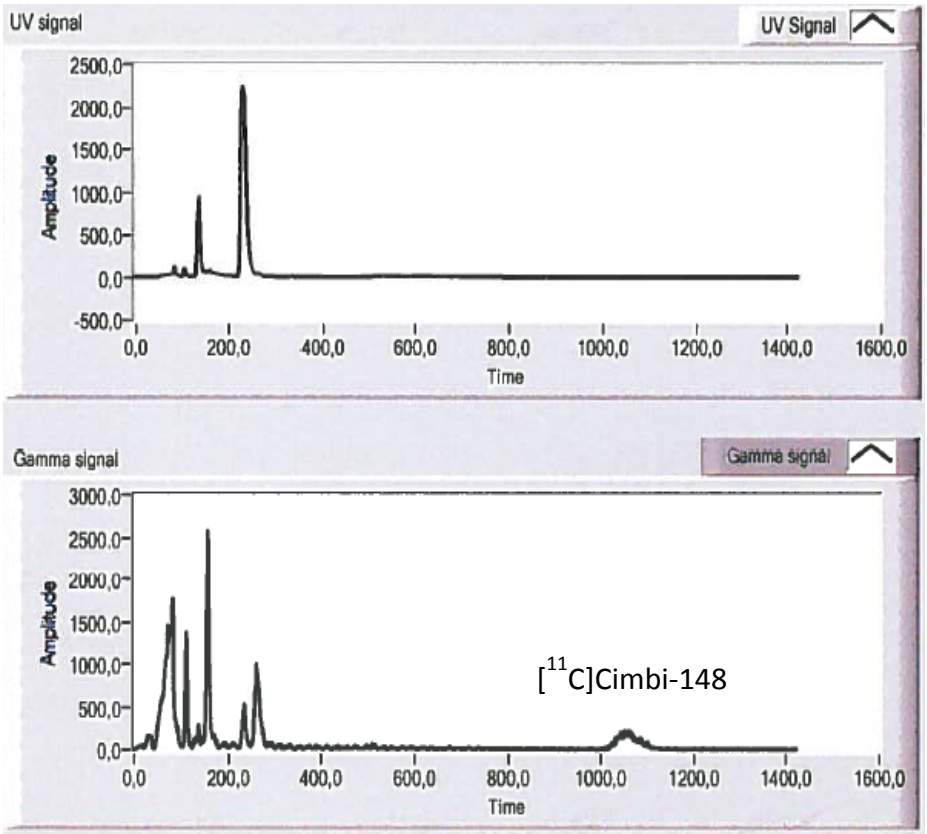


Supplementary Scheme 6: Analytical (UV: black; radio grey) (a) and semi-preparative (b) HPLC chromatograms of [^{11}C]Cimbi-168

a)

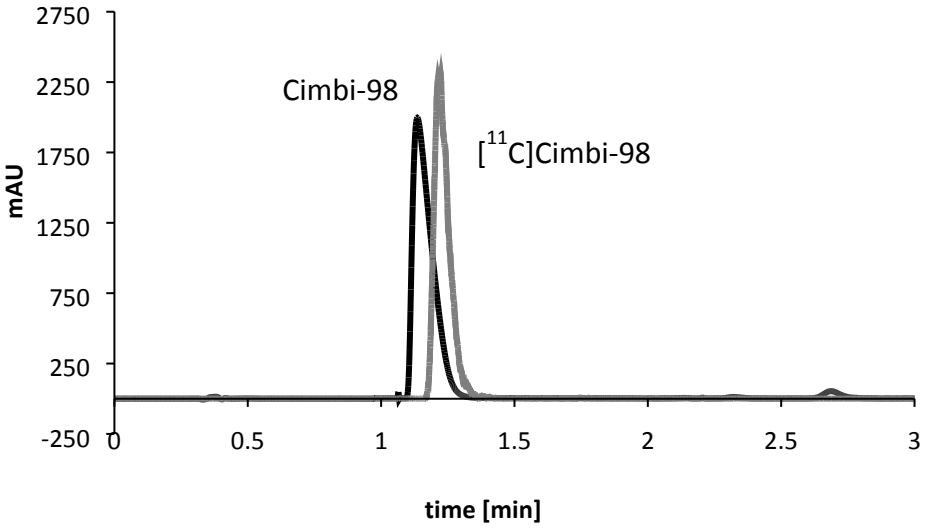


b)

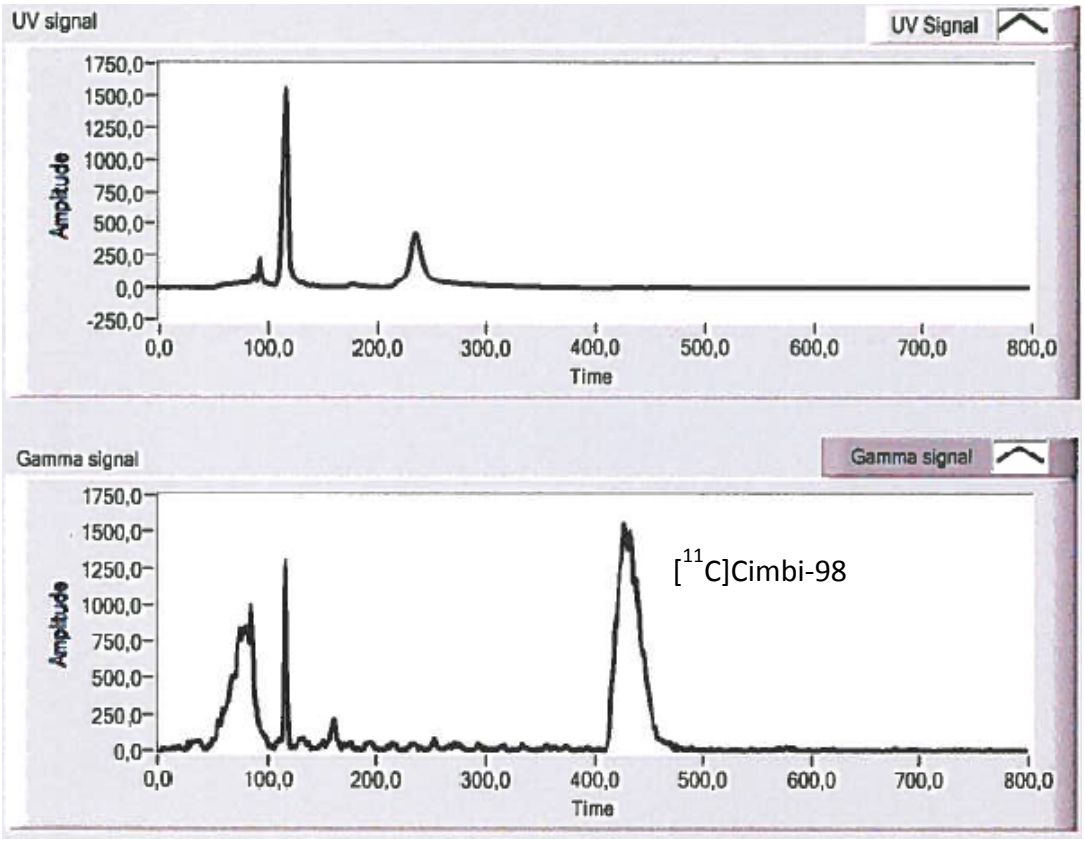


Supplementary Scheme 7: Analytical (UV: black; radio grey) (a) and semi-preparative (b) HPLC chromatograms of [^{11}C]Cimbi-148

a)

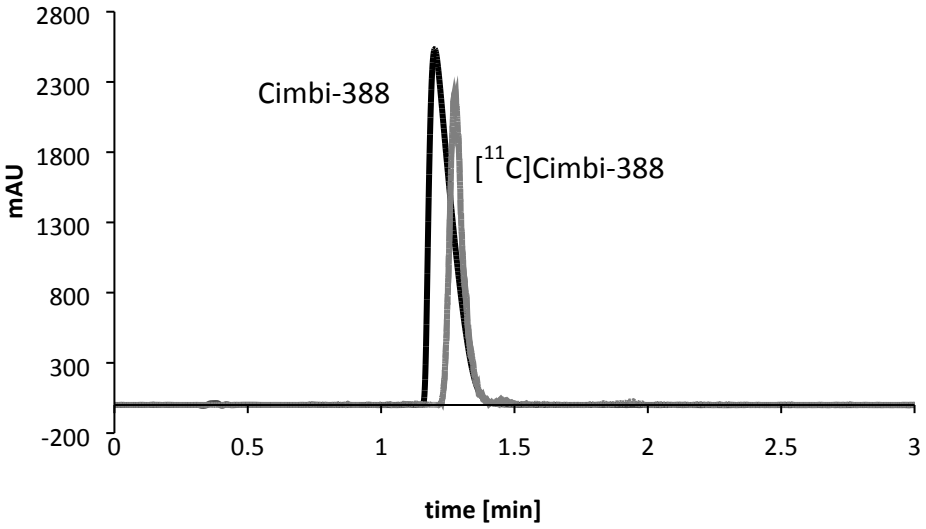


b)

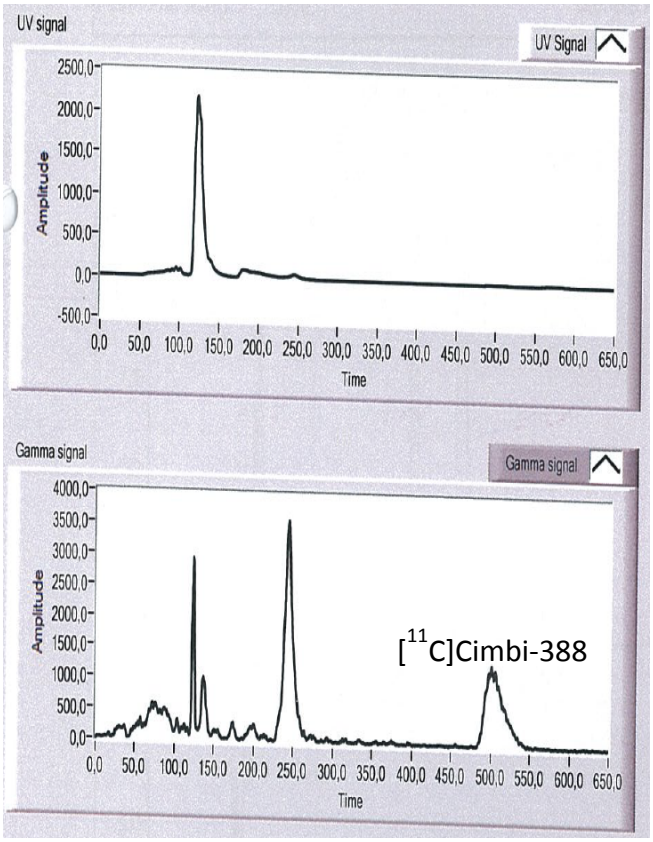


Supplementary Scheme 8: Analytical (UV: black; radio grey) (a) and semi-preparative (b) HPLC chromatograms of [^{11}C]Cimbi-98

a)

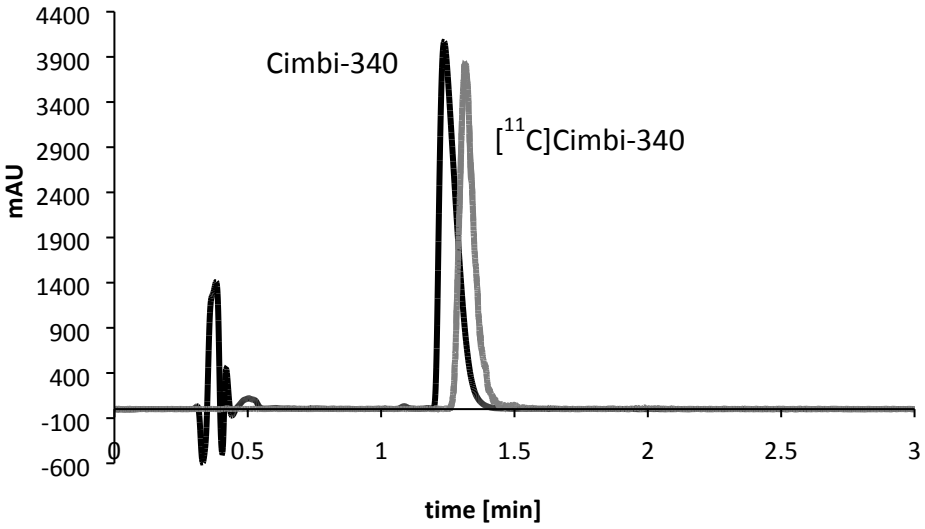


b)

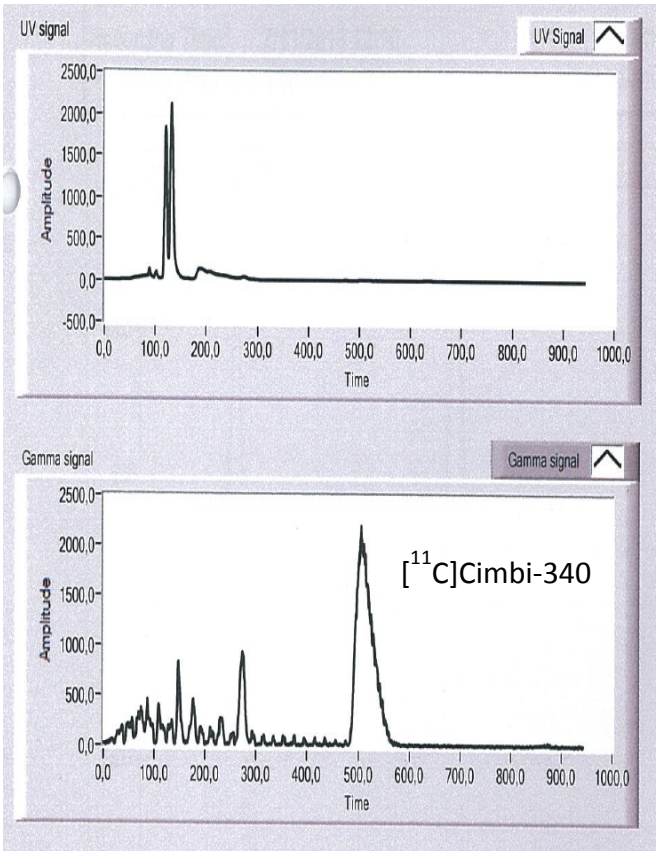


Supplementary Scheme 9: Analytical (UV: black; radio grey) (a) and semi-preparative (b) HPLC chromatograms of [^{11}C]Cimbi-388

a)



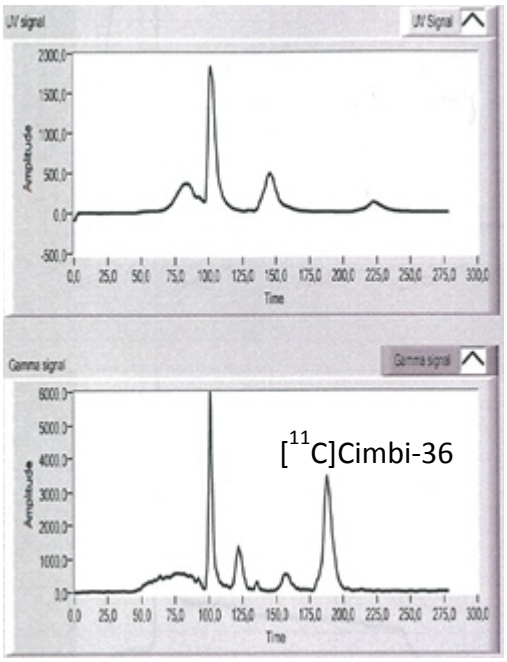
b)



Supplementary Scheme 10: Analytical (UV: black; radio grey) (a) and semi-preparative (b) HPLC chromatograms of [^{11}C]Cimbi-340

3. GMP compliant radiosynthesis for Cimbi-36

[^{11}C]methyl triflate was transferred in a stream of helium to a 1.1 ml vial containing 0.1-0.2 mg of the labelling precursor (tert-butyl 4-bromo-2,5-dimethoxyphenethyl(2-hydroxybenzyl)carbamate) and 2 µl 2M NaOH in 300 ul acetone and the resulting mixture was heated at 40 °C for 30 seconds. Subsequently, 250 µl TFA/acetone (1:1) was added and the mixture heated at 80 °C for 5 min. After neutralization with a mixture of 750 µl 2M NaOH and 3.7 ml 0.1 % phosphoric acid, the reaction mixture was purified by HPLC (Waters Xterra C18, 2.5 µm, 50 x 10 mm; eluent 25/75 ethanol/0.1 % phosphoric acid; flow rate 9 ml/min. The fraction corresponding to the labelled product (ca. 3.5 min) was collected by allowing the HPLC eluent to flow directly through a 0.22 µm sterile filter (Millex GV, Millipore) into a 20 ml glas vial containing 9 ml sterile phosphate buffered saline solution (pH 7), giving a 14 ml sterile solution of [^{11}C]Cimbi-36 containing around 7 % w/v ethanol. The total synthesis time following end of bombardment was 30 min, yielding 1-2 GBq of [^{11}C]Cimbi-36 with radiochemical purity of >95% and specific radioactivity in the range of 240-1400 GBq/µmol at end of synthesis.



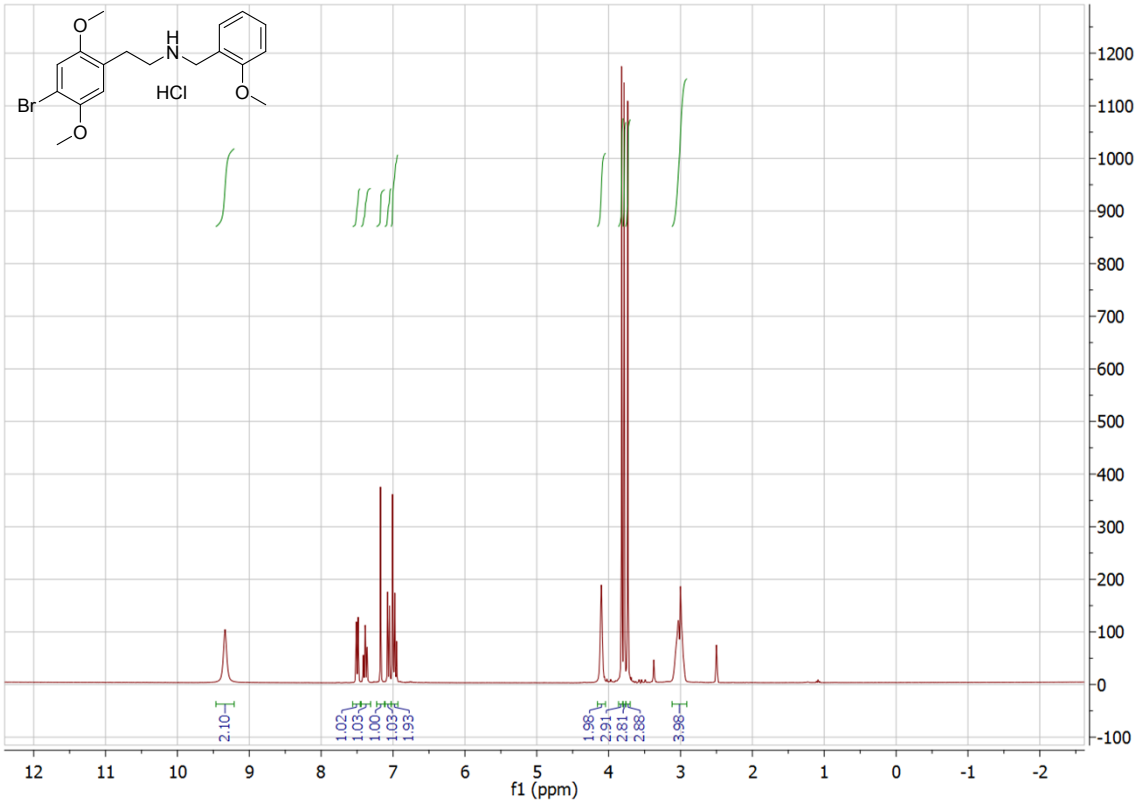
Supplementary Scheme 11: Semi-preparative HPLC chromatograms of [^{11}C]Cimbi-36

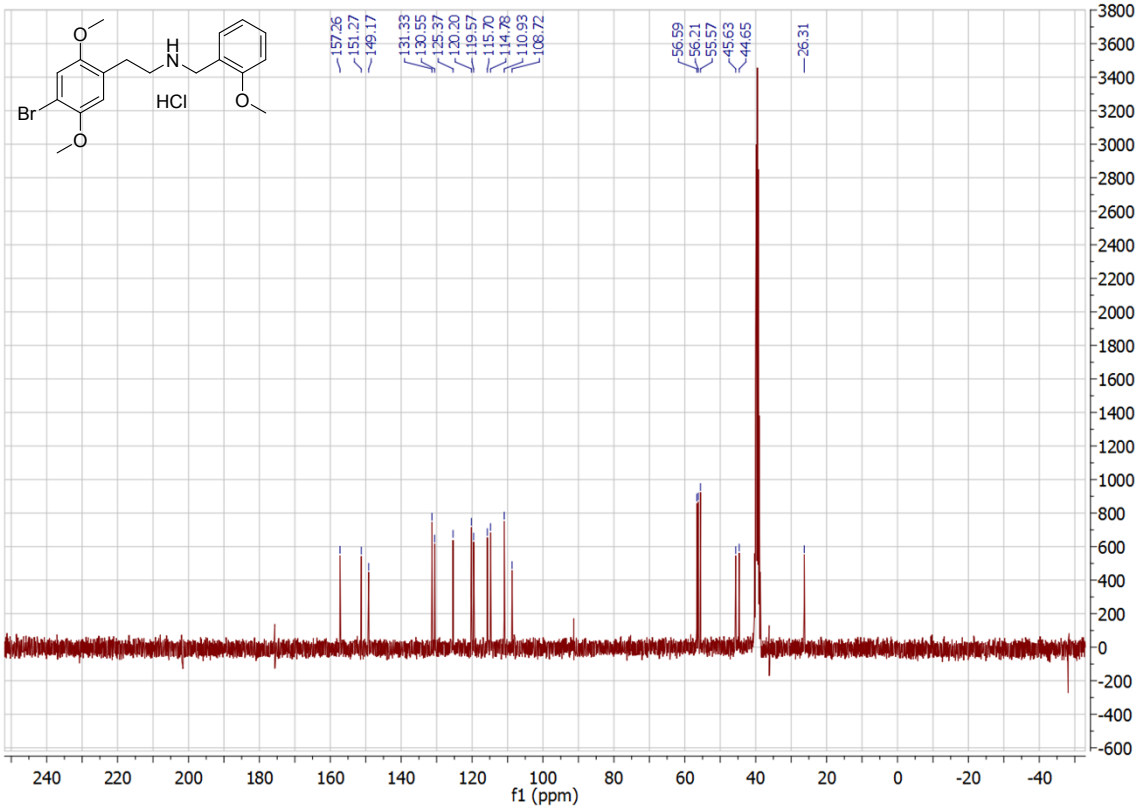
4. References

[1] Shulgin, A. and Shulgin, A.; PiHKAL: A Chemical Love Story, *Transform Press*, 1991, ISBN 0-9630096-0-5.

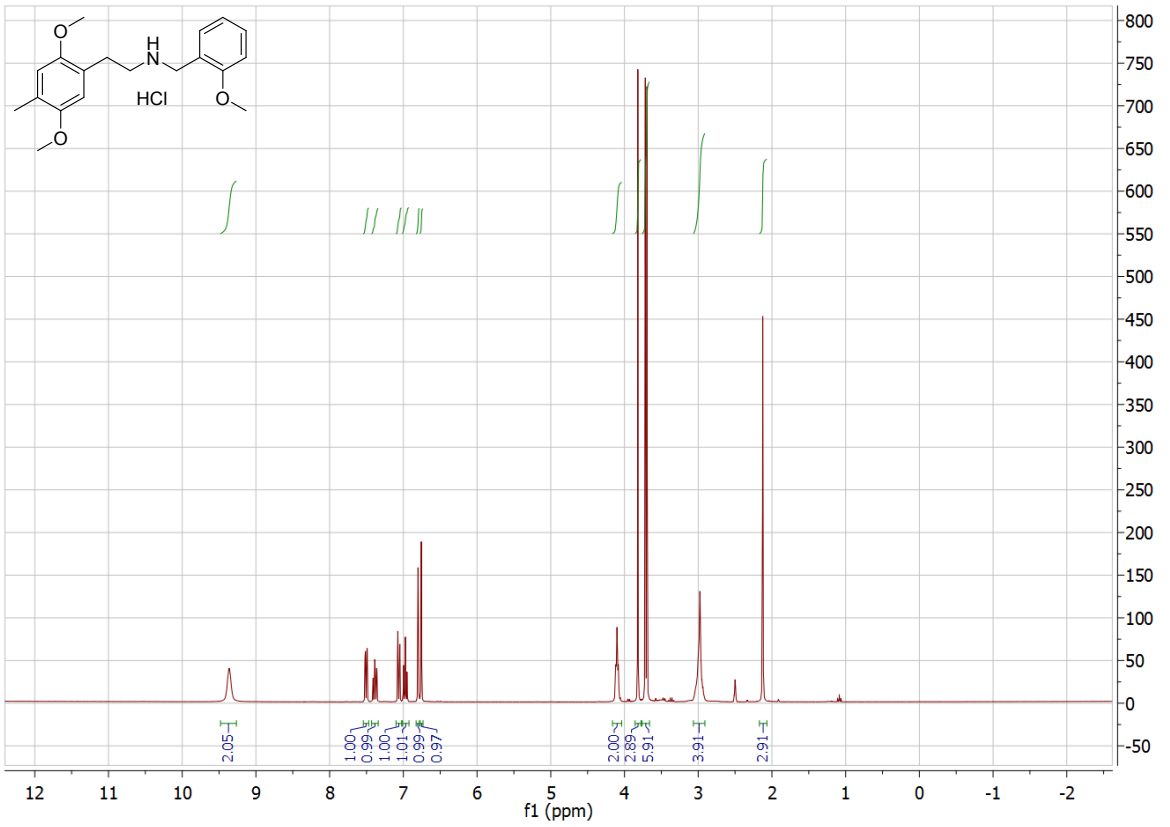
5. Spectroscopic data for selected compounds

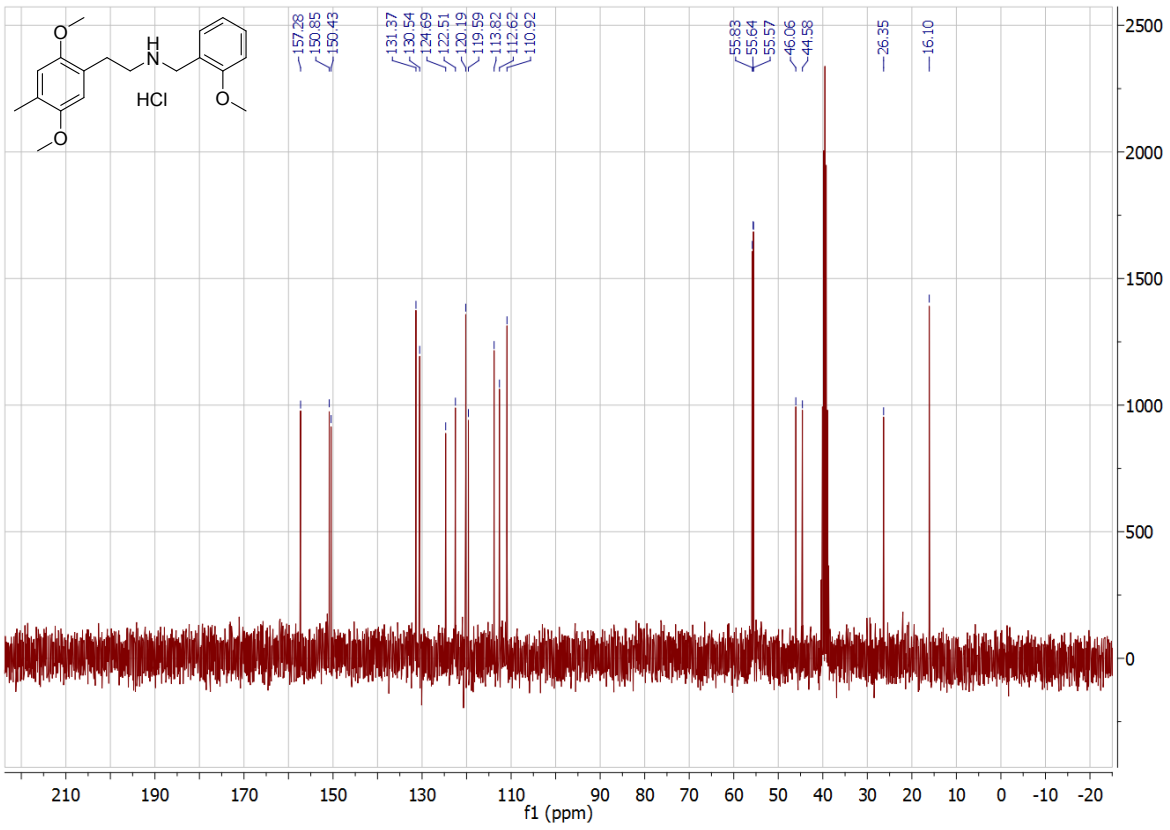
Cimbi 36



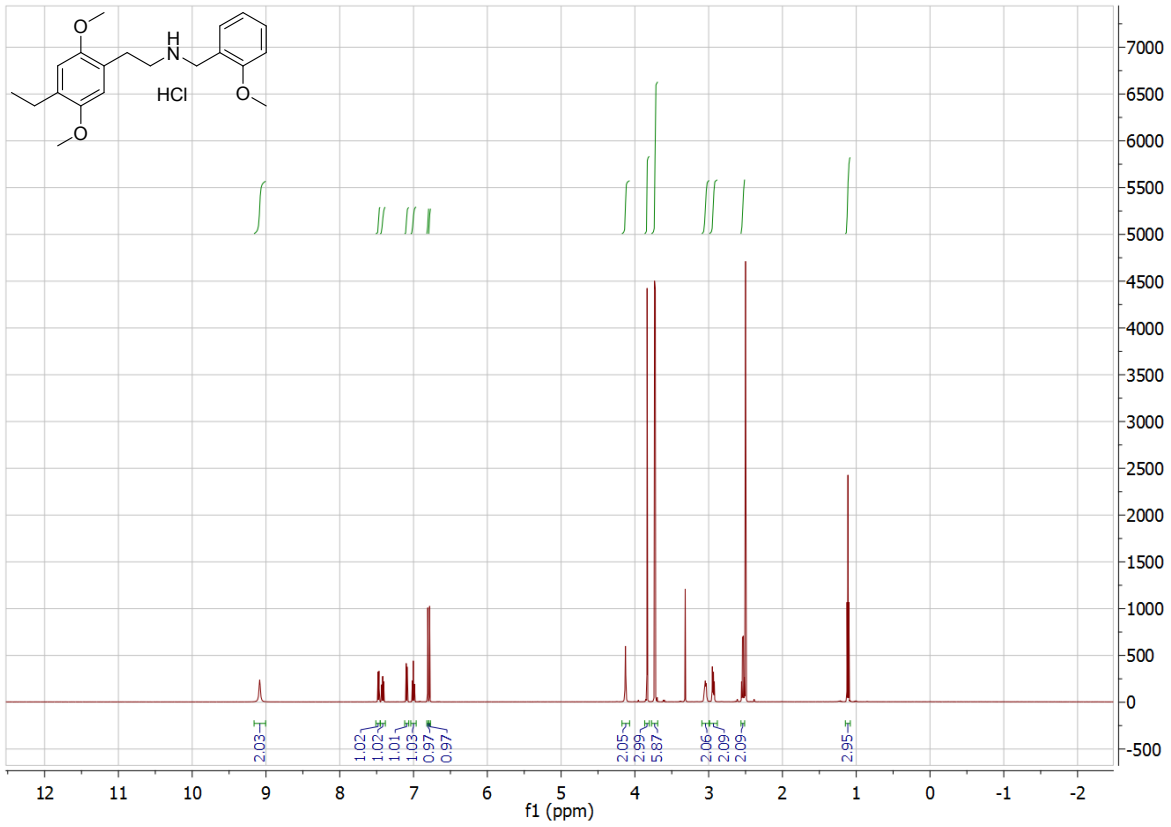


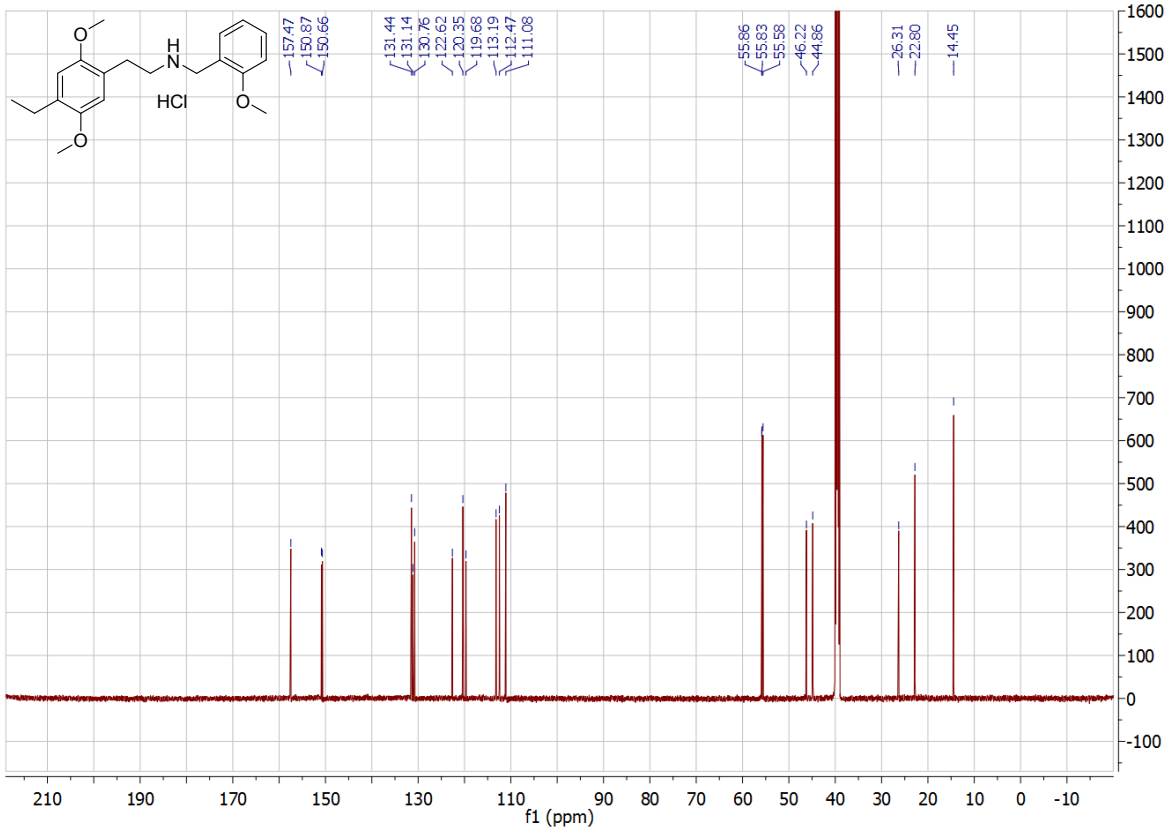
Cimbi 98


HCl
2.05
1.00
0.99
1.00
1.01
0.99
0.97
2.00
2.89
5.91
3.91
2.91
f1 (ppm)

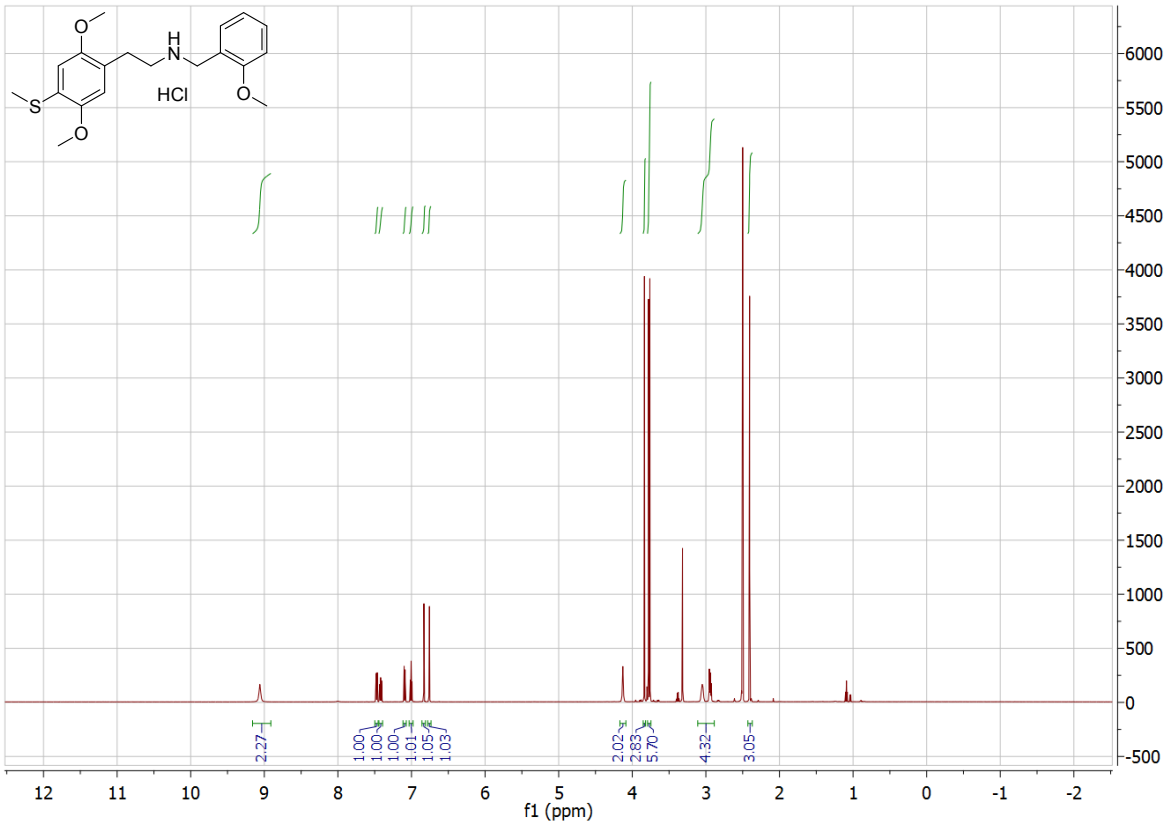

HCl
157.28
150.85
150.43
131.37
130.54
124.69
122.51
120.19
119.59
113.82
112.62
110.92
55.83
55.64
55.57
46.06
44.58
26.35
16.10
f1 (ppm)

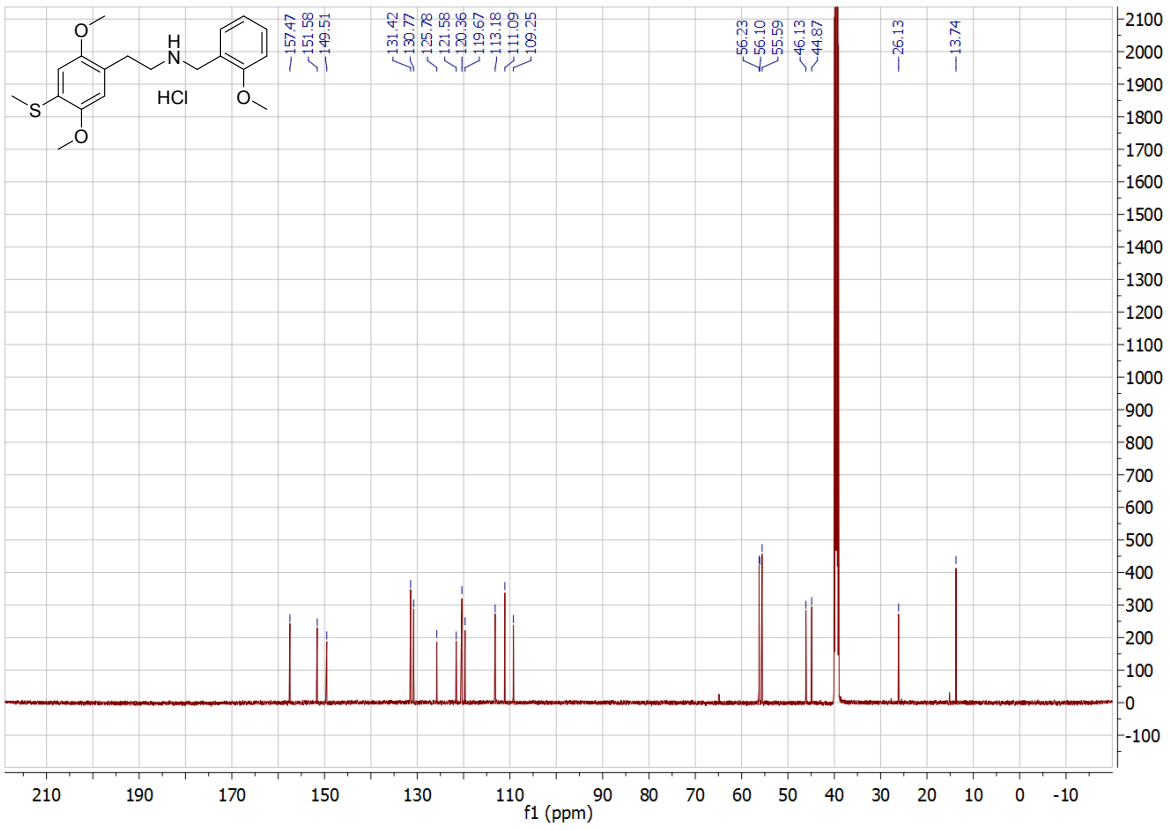
Cimbi 148


HCl
2.03
1.02
1.02
1.01
1.03
0.97
0.97
2.05
2.99
5.87
2.06
2.09
2.09
2.95
f1 (ppm)

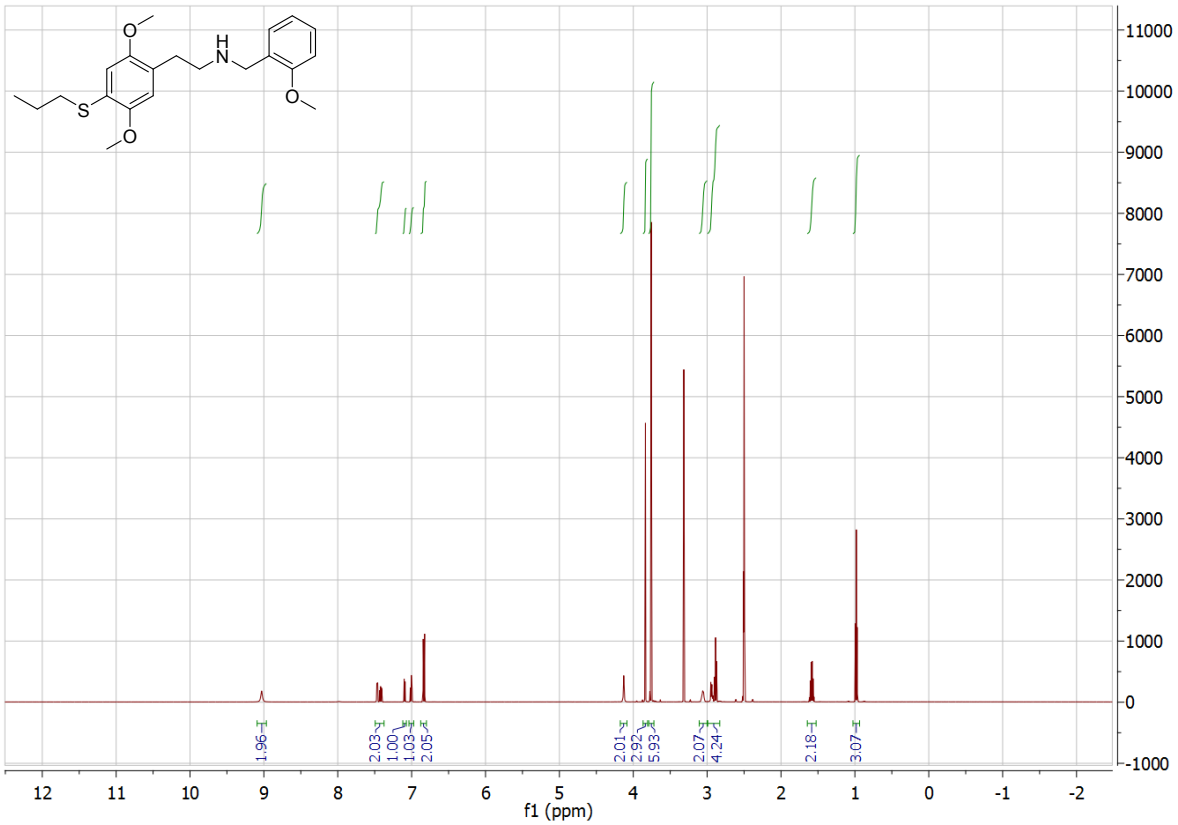

HCl
157.47
150.87
150.66
131.44
131.14
130.76
122.62
120.35
119.68
113.19
112.47
111.08
55.86
55.83
55.58
46.22
44.86
26.31
22.80
14.45
f1 (ppm)

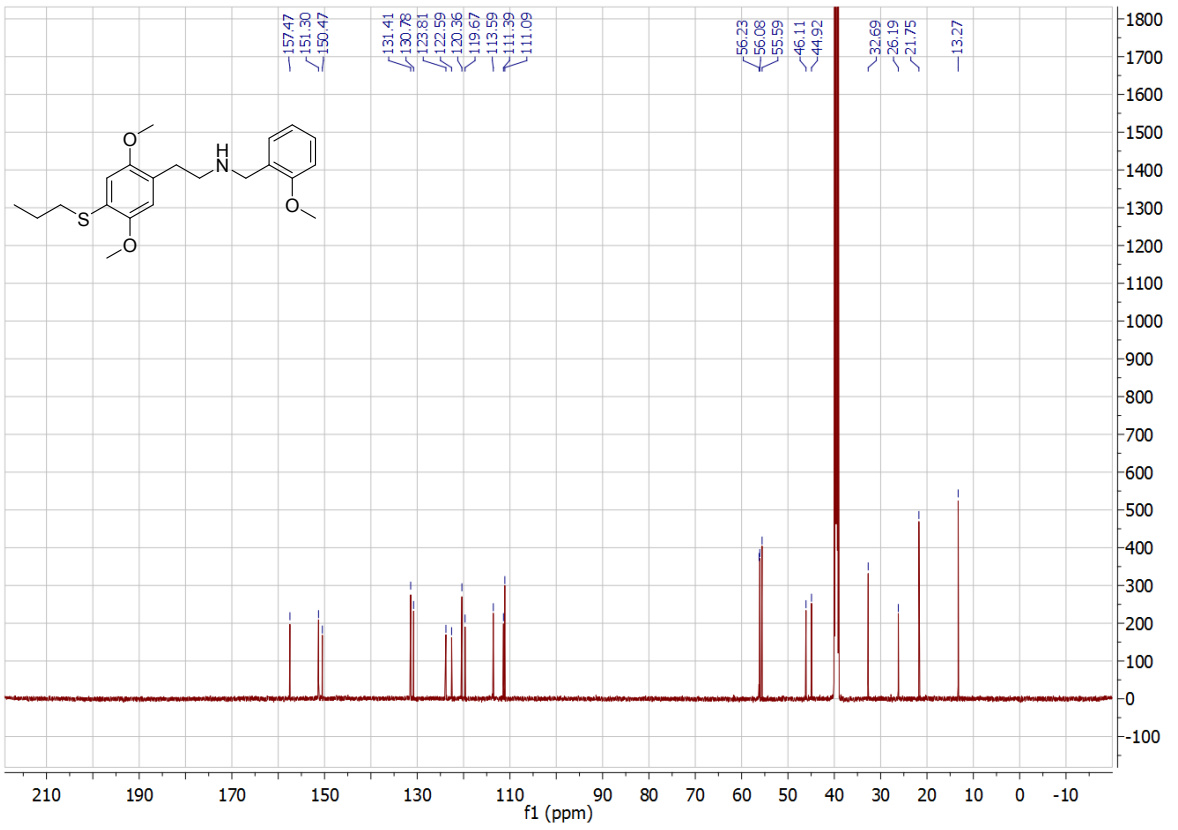
Cimbi 168


HCl
2.27
1.00
1.00
1.00
1.01
1.05
1.03
2.02
2.83
5.70
4.32
3.05
f1 (ppm)

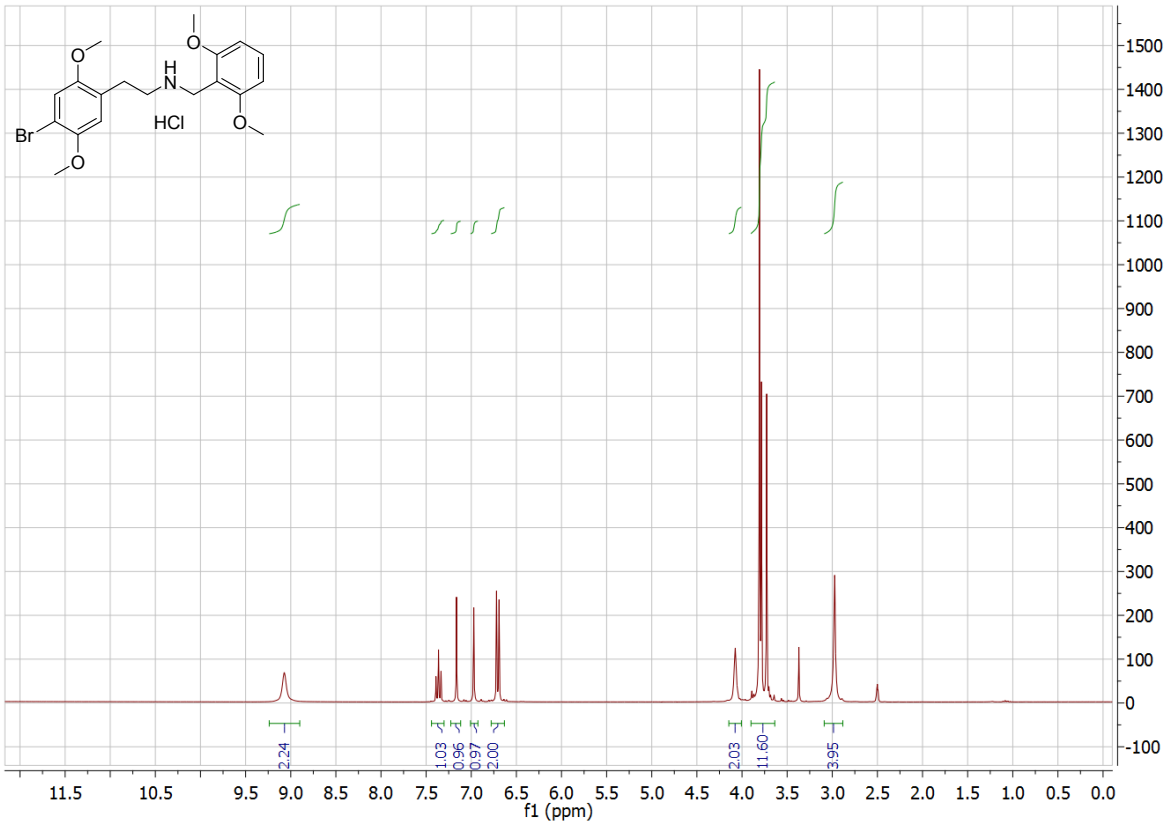

HCl
157.47
151.58
149.51
131.42
130.77
125.78
121.58
120.36
119.67
113.18
111.09
109.25
56.23
56.10
55.59
46.13
44.87
26.13
13.74
f1 (ppm)

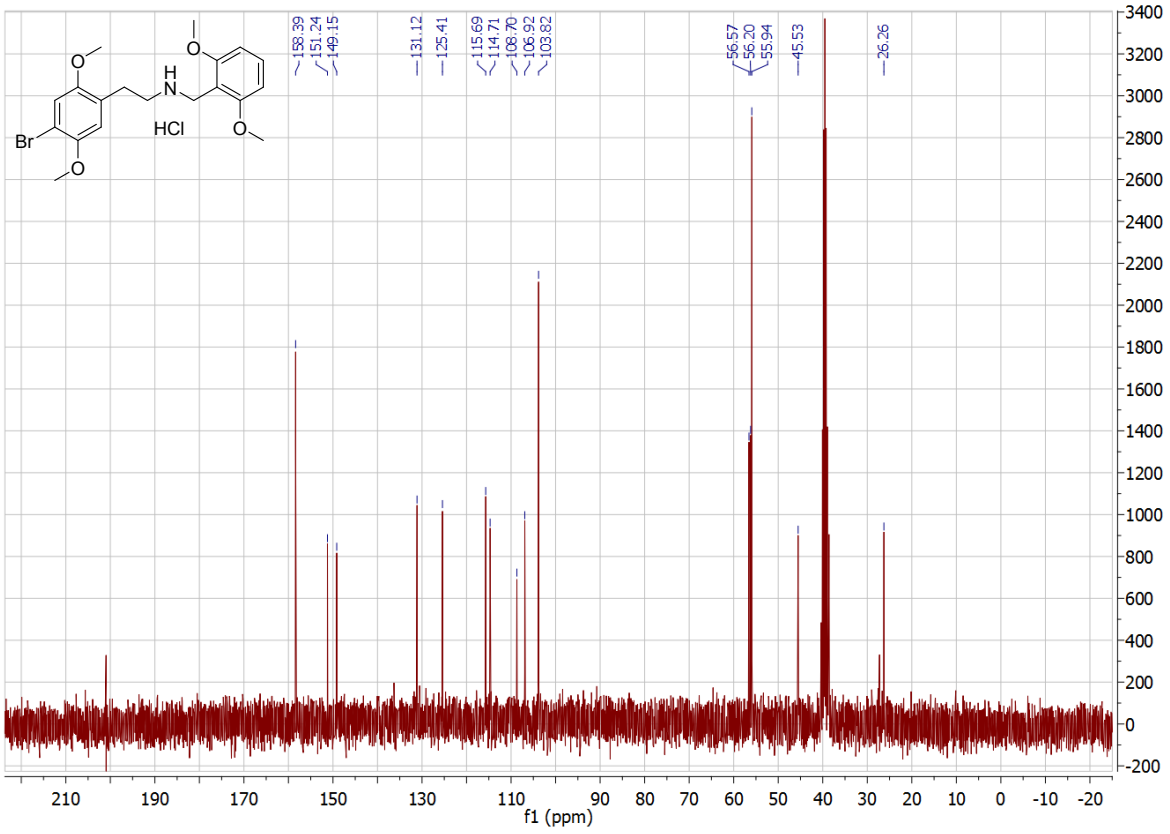
Cimbi 188


1.96
2.03
1.00
1.03
2.05
2.01
2.92
5.93
2.07
4.24
2.18
3.07
f1 (ppm)

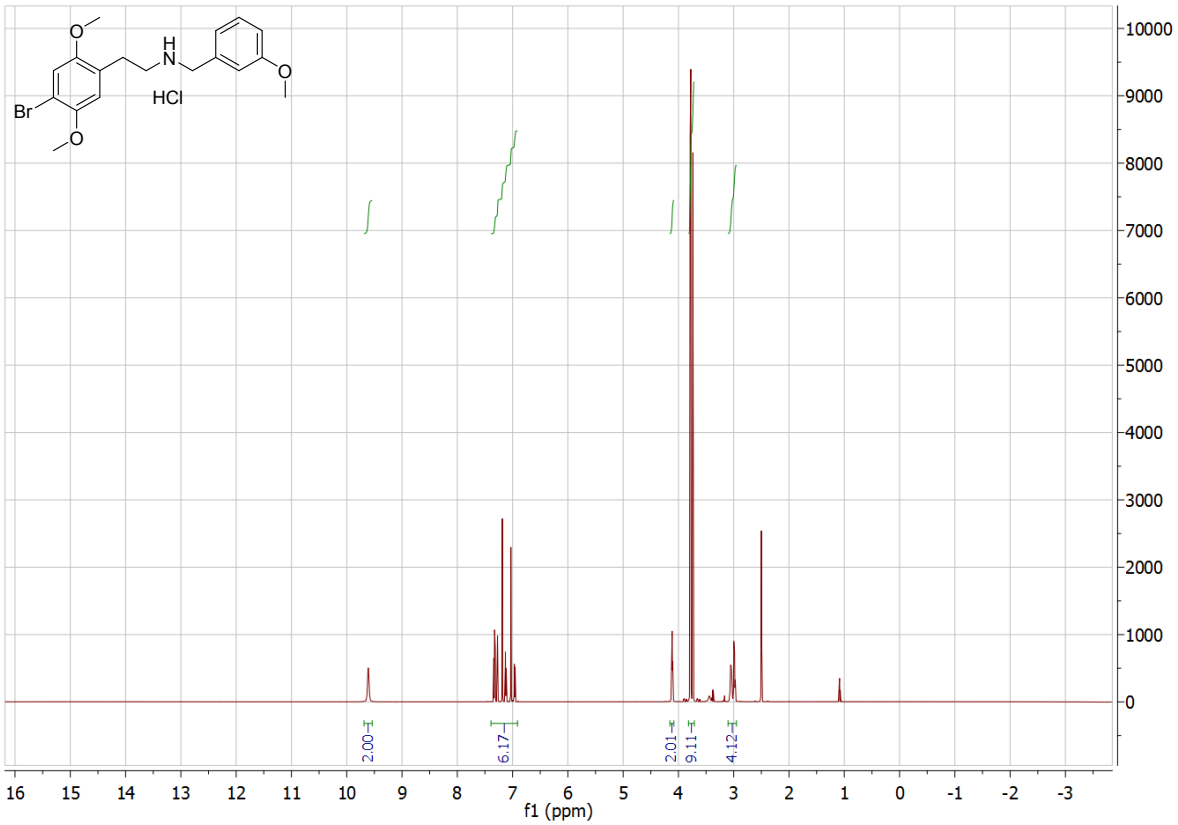

157.47
151.30
150.47
131.41
130.78
123.81
122.59
120.36
119.67
113.59
111.39
111.09
56.23
56.08
55.59
46.11
44.92
32.69
26.19
21.75
13.27
f1 (ppm)

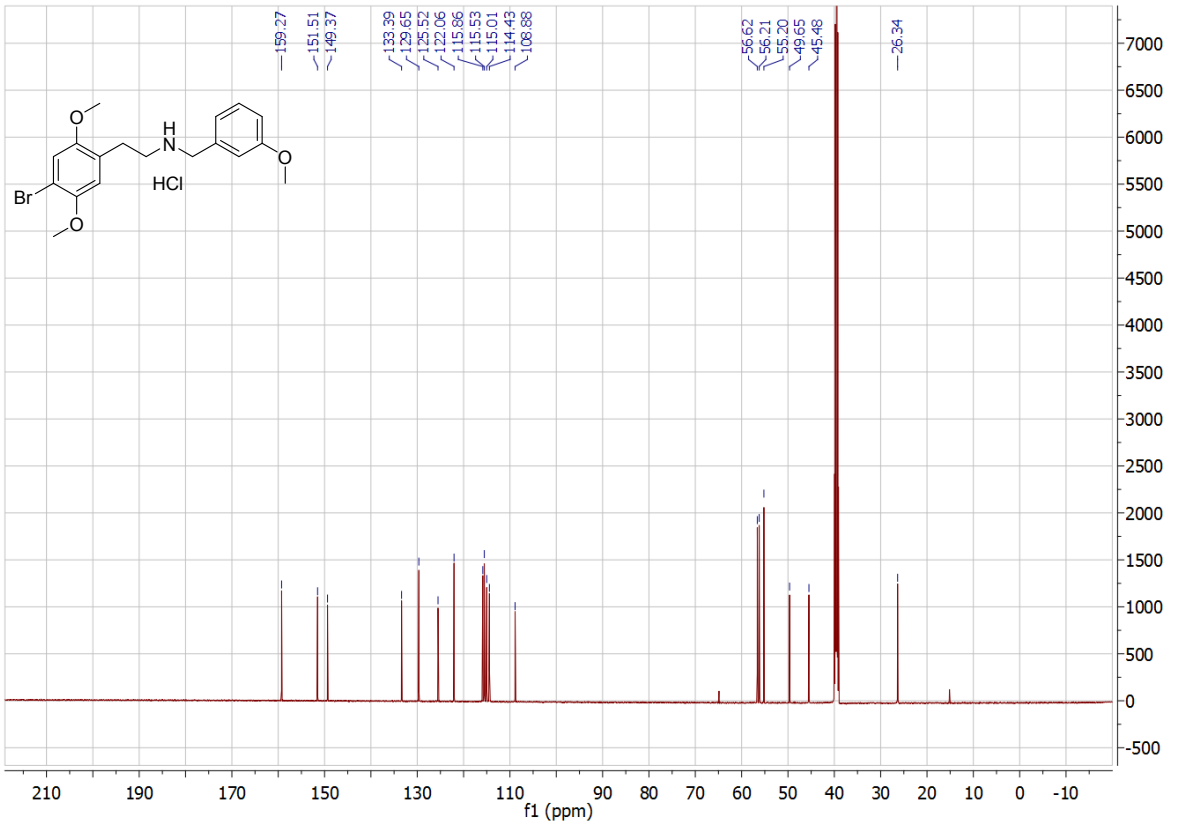
Cimbi 218


Br
O
O
H
N
HCl
O
O
2.24
1.03
0.96
0.97
2.00
2.03
11.60
3.95
f1 (ppm)

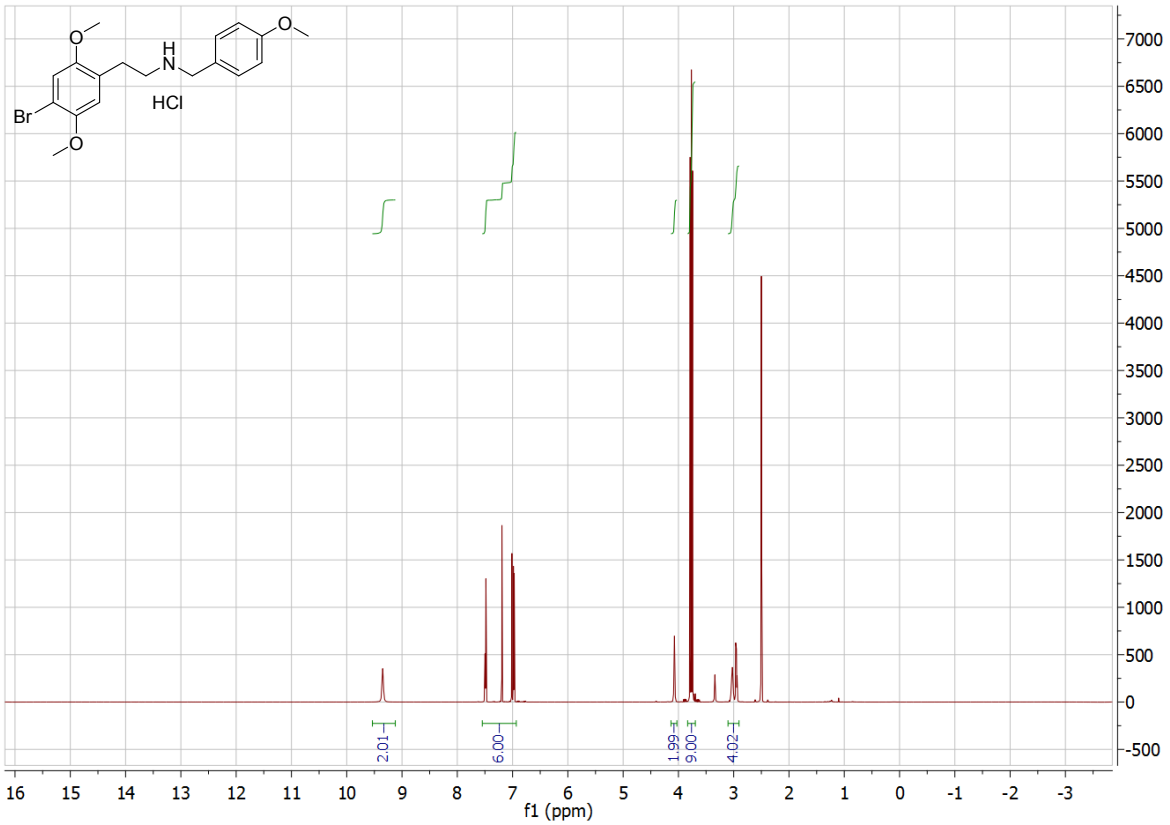

Br
O
O
H
N
HCl
O
O
158.39
151.24
149.15
131.12
125.41
115.69
114.71
108.70
106.92
103.82
56.57
56.20
55.94
45.53
26.26
f1 (ppm)

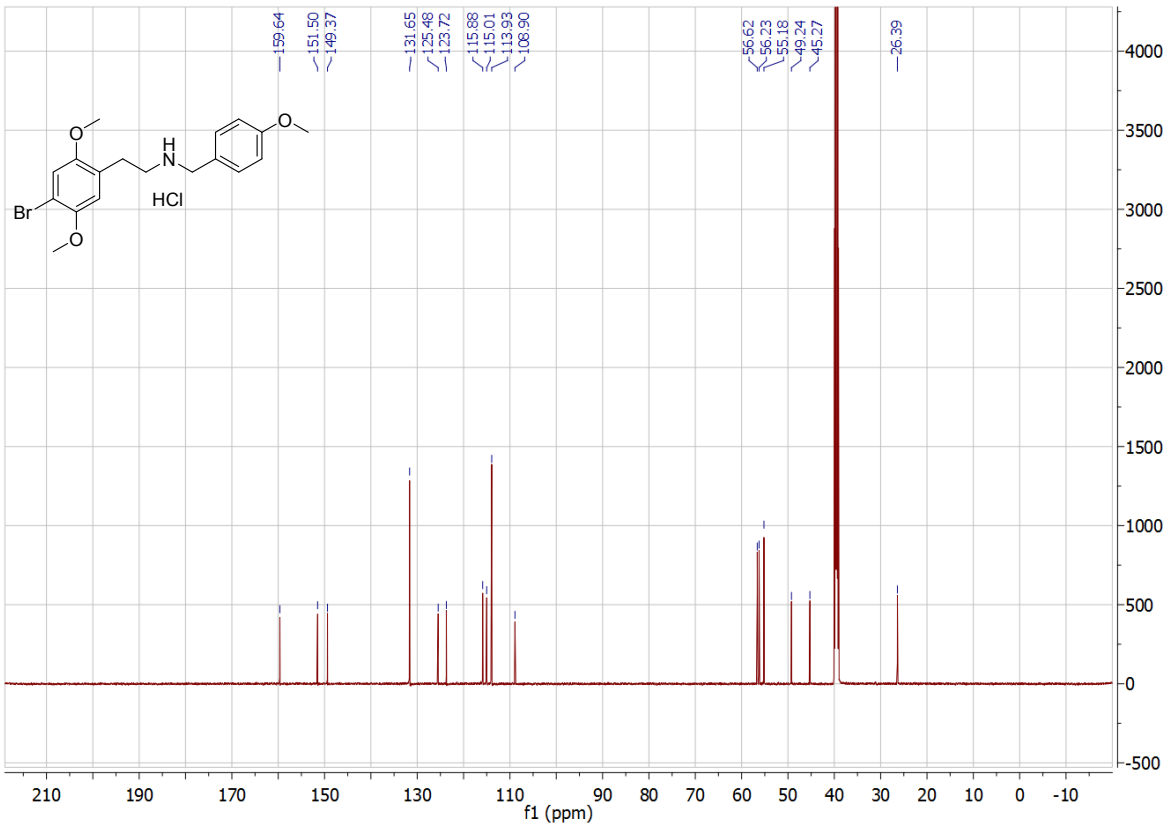
Cimbi 340


Br
O
O
H
N
HCl
O
2.00
6.17
2.01
9.11
4.12
f1 (ppm)


159.27
151.51
149.37
133.39
129.65
125.52
122.06
115.86
115.53
115.01
114.43
108.88
56.62
56.21
55.20
49.65
45.48
26.34
Br
O
O
H
N
HCl
O
f1 (ppm)

Cimbi 388


HCl
Br
2.01
6.00
1.99
9.00
4.02
f1 (ppm)


159.64
151.50
149.37
131.65
125.48
123.72
115.88
115.01
113.93
108.90
56.62
56.23
55.18
49.24
45.27
26.39
HCl
Br
f1 (ppm)