SUPPLEMENTARY INFORMATION

Identification of tris-(phenylalkyl)amines as new selective 5-HT_{2B} receptor ligands

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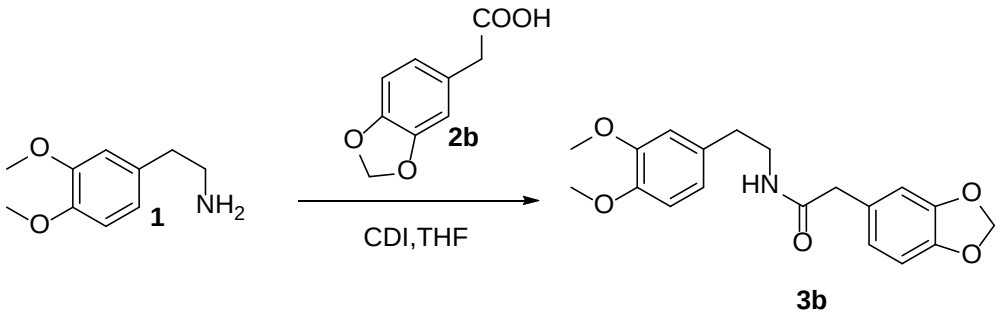
General Experimental Procedures

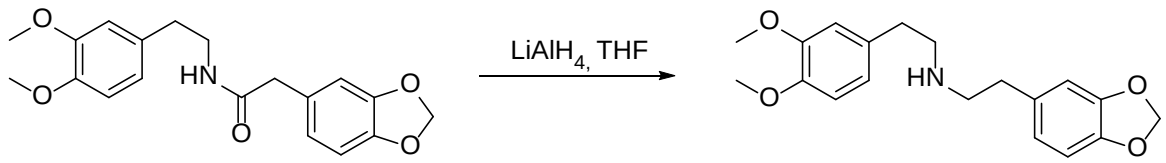
All reactions were carried out in oven-dried glassware under a nitrogen atmosphere. Reagents were purchased at the highest commercial quality and used without further purification. HRESIMS data were obtained using an Agilent 6520 QTOF instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker DPX-500 spectrometer (operating at 500 MHz for ^{1}H; 125 MHz, respectively, for ^{13}C) using $CDCl_3$ as solvent. Tetramethylsilane (δ 0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (δ 77.0 ppm) in ^{13}C NMR as solvent. Reactions were monitored by TLC with Whatman Flexible TLC silica gel G/UV 254 precoated plates (0.25 mm). TLC plates were visualized by UV (254 nm) and by staining with vanillin spraying reagent (2 gm vanillin in 1 L of 10% H_2SO_4) followed by heating. Flash column chromatography was performed with silica gel 60 (EMD Chemicals, 230-400 mesh, 0.063 mm particle size).

Typical procedure for amide coupling – synthesis of compound 3b



To a solution 3, 4-methylenedioxyphenylacetic acid (**2b**, 4.93 g, 27.3 mmol) in THF (30 mL) was added CDI (5.30 g, 32.7 mmol) in portions at 0 ^{O}C. The reaction mixture was warmed to rt and stirred for 30 min and was then cooled to 0 ^{O}C. 3,4-dimethoxyphenylethylamine (**1**, 5.07 g, 28.0 mmol) was added in THF (20 mL) drop-wise to the reaction mixture at the same temperature and left at rt for 12 h. The solid that separated from the reaction mixture was filtered and washed with diethyl ether. The filtrate was evaporated to give a solid which was again suspended in diethyl ether and filtered to give second crop of the product. This was used in the next step without further purification.

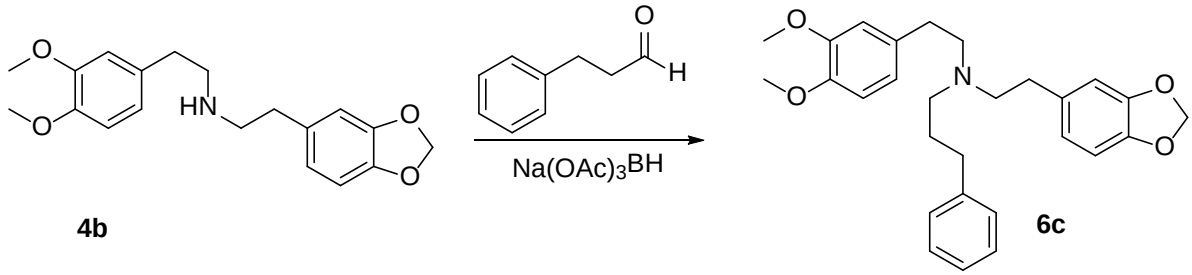
Typical procedure for amide reduction - synthesis of compound 4b



3b **4b**

To a suspension of $LiAlH_4$ (1.17 g, 15.35 mmol) in THF (40 mL) was added compound **3b** (1.05 g, 3.07 mmol) in THF (20 mL) at 0 ^{O}C. The reaction mixture was warmed to rt and stirred at reflux for 6 h. The reaction mixture was cooled to rt then to 0 ^{O}C and aqueous 10% NaOH was added drop-wise carefully. The organic layer was separated and to the remaining suspension was added ethyl acetate (20 mL) and the mixture stirred vigorously at rt for 30 min. The ethyl acetate layer was separated and combined with the THF layer and the combined organic layers evaporated under reduced pressure to produce a residue. This residue was dissolved in DCM and washed with brine, dried over Na_2SO_4 and evaporated to give the crude amine. The crude amine was used in the next step without further purification.

Typical procedure for reductive amination - synthesis of compound 6c



4b **6c**

To a solution amine **4b** (0.98 g, 2.97 mmol) and hydrocinnamaldehyde (0.797 g, 5.94 mmol) in DCM was added $Na(OAc)_3BH$ (2 .5 eq) in portions. The resulting reaction mixture was stirred overnight at rt. The reaction mixture was quenched with aqueous 10% $NaHCO_3$ (15 mL) and the DCM layer was separated. The aqueous phase was extracted with DCM. The combined organic

layers were dried over Na_2SO_4 and evaporated to give the crude product. The crude compound was purified by column chromatography on silica gel (60-120) in 20-40% ethyl acetate/hexanes as eluent.

Compound 6a: Colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (s, 1H), 7.21-7.20 (m, 3H), 7.17 (m, 1H), 6.69 (d, *J*=8.5, 1H), 6.35-6.58 (m, 2H), 6.56 (s, 1H), 6.52 (s, 1H), 6.49 (m, 1H), 5.82 (s, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 3.63 (s, 2H), 2.67-2.62 (m, 8H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 148.7, 147.4, 147.2, 145.6 134.3, 133.2, 128.8, 128.5, 128.2, 127.6, 127.0, 126.9, 121.5, 120.6, 100.7, 65.3, 58.4, 55.9, 55.8, 33.5, 33.2; HRESIMS calculated for $C_{26}H_{30}NO_4$ ($[M+H]^+$), 420.2175, found 420.2168.

Compound 6b: Colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 7.21-7.13 (m, 3H), 6.80-6.60 (m, 6H), 5.91 (s, 2H), 3.86 (2s, 6H), 2.92-2.64 (m, 12H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 148.8, 147.5, 147.5, 145.8 136.9, 133.5, 128.7, 128.4, 126.0, 121.4, 120.5, 119.1, 112.0, 111.1, 109.1, 108.2, 106.4, 100.8, 56.0, 55.94, 55.90, 55.87, 55.85, 33.7, 33.6; HRESIMS calculated for $C_{27}H_{32}NO_4$ ($[M+H]^+$), 434.2331, found 434.2329.

Compound 6c: Colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.19 (m, 6H), 7.21-7.20 (m, 3H), 6.84-6.62 (m, 5H), 5.96 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 2.91-2.50 (m, 12H), 1.87-1.83 (m, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 148.9, 148.8, 147.6, 147.5, 147.4, 146.8, 145.7, 136.7, 136.1, 133.0, 132.4, 128.6, 128.5, 127.6, 126.3, 126.2, 121.4, 120.5, 199.1, 112.0, 111.8, 111.2, 109.1, 108.1, 108.0, 106.4, 100.9, 100.7, 69.3, 62.5, 56.5, 56.2, 55.9, 55.8, 55.7, 55.5, 33.4, 33.2, 29.6; HRESIMS calculated for $C_{28}H_{34}NO_4$ ($[M+H]^+$), 448.2488, found 448.2483.

Compound 6d: Colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (m, 1H), 7.21-7.20 (dd, *J1=J2*=1.5, 1H), 6.86 (m, 2H), 6.81 (m, 1H), 6.70 (m, 3H), 6.66 (m, 1H), 6.67 (dd, *J1=J2*=1.5, 1H), 5.89 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 2.74-2.60 (m, 12H), 1.77 (t, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 157.4, 148.7, 147.5, 147.2, 145.6 134.5, 133.3, 130.6, 129.7, 126.9, 121.4, 120.5, 120.3, 112.0, 111.2, 110.1, 109.1, 108.1,100.7, 56.2, 56.1, 55.9, 55.8, 55.1, 53.6, 33.4, 33.3, 28.2, 27.1; HRESIMS calculated for $C_{29}H_{36}NO_5$ ($[M+H]^+$), 478.2593, found 478.2588.

Compound 6e: Colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (m, 1H), 6.78 (m, 2H), 6.81 (m, 1H), 6.73-6.70 (m, 5H), 6.66-6.59 (m, 2H), 5.90 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.79 (s, 3H), 2.73-2.63 (m, 8H), 2.60-2.56 (m, 4), 1.82-1.76 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 159.6, 148.8, 147.5, 147.3, 143.9 134.4, 133.2, 129.2, 121.4, 120.8, 120.5, 114.2, 112.0, 111.2, 110.9, 109.2, 108.1,100.7, 56.2, 56.1, 55.9, 55.8, 55.1, 53.3, 33.7, 33.4, 33.3, 28.2; HRESIMS calculated for $C_{29}H_{36}NO_5$ ($[M+H]^+$), 478.2593, found 478.2593.

Compound 6f: Colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09-7.05 (m, 2H), 6.80-6.59 (m, 8H), 5.91 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.78 (s, 3H), 2.79-2.49 (m, 12H), 1.83-1.75 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 157.8, 148.9, 147.8, 147.7, 147.5, 129.2, 121.5, 120.5, 119.1, 113.8, 111.9, 111.3, 109.0, 108.1, 106.4, 100.9, 57.1, 55.95, 55.93, 55.90, 55.2, 53.3, 33.4, 32.5, 32.0, 29.1; HRESIMS calculated for $C_{29}H_{35}NO_5$ ($[M+H]^+$), 478.2593, found 478.2586.

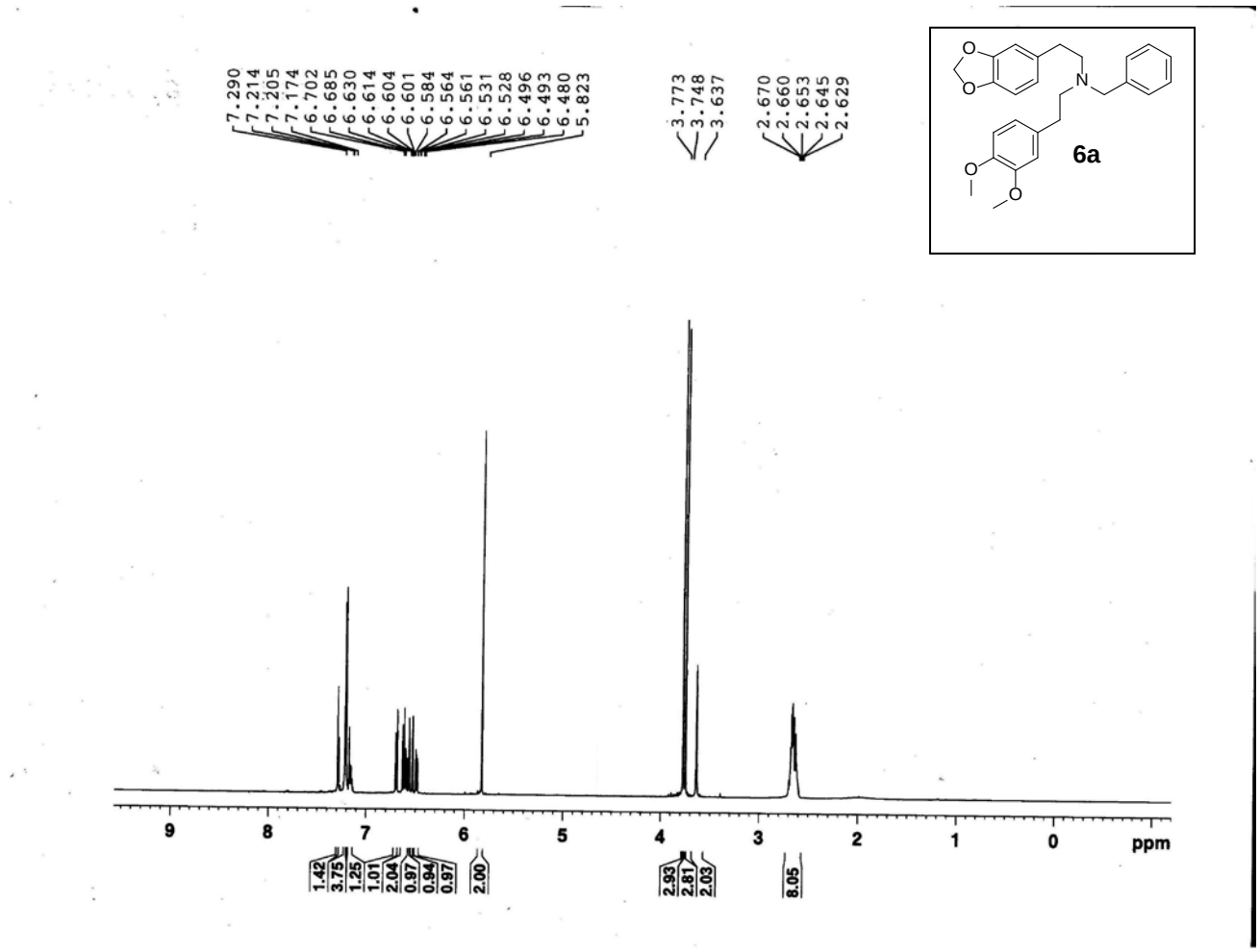
Compound 6g: Colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 (m, 1H), 6.72-6.71 (m, 3H), 6.67 (m, 1H), 6.62 (m, 1H), 6.40 (m, 2H), 5.89 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 2.75-2.67 (m, 8H), 2.60-2.53 (m, 4H), 1.81-1.78 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 153.0, 148.8, 147.5, 147.3, 145.7, 138.0, 136.0, 134.3, 133.1, 121.4, 120.5, 119.3, 112.0, 111.2, 110.4, 109.1, 108.1, 105.2, 100.7, 60.8, 56.1, 56.0, 55.9, 55.8, 53.3, 34.3,34.0, 33.4, 33.3, 32.5, 29.0; HRESIMS calculated for $C_{30}H_{38}NO_5$ ($[M+H]^+$), 508.2699, found 508.2693.

Compound 6h: Colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79-6.62 (m, 8H), 5.90 (s, 2H), 3.86 (3s, 9H), 3.76 (2s, 6H), 2.74-2.57 (m, 12H), 1.79-1.77 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 153.4, 151.7, 148.8, 147.5, 147.2, 145.6, 134.4, 133.2, 131.9, 121.4, 120.5, 116.3, 112.0, 111.3, 111.2, 110.7, 109.1, 108.1, 56.1, 56.0, 55.9, 55.8, 55.6, 33.3, 33.2, 28.3, 27.0; HRESIMS calculated for $C_{31}H_{40}NO_7$ ($[M+H]^+$), 538.2805, found 538.2801.

Compound 6i: Colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (t, *J*=7.5 Hz, 1H), 6.90-6.67 (m, 9H), 5.98 (s, 2H), 4.61 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 2.71-2.58 (m, 8H), 1.82-1.70 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 159.6, 148.7, 147.8, 147.6, 144.1, 135.0, 133.8, 129.3, 120.8, 120.5, 114.2, 112.0, 111.1, 110.9, 108.2, 107.9, 107.7, 101.0, 65.3, 55.9, 55.7, 55.5, 55.1, 53.1, 133.6, 133.0, 128.8; HRESIMS calculated for $C_{28}H_{34}NO_5$ ($[M+H]^+$), 464.2437, found 464.2431 .

Compound 6j: Colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.72 (d, *J*=8, 1H), 6.72 (s, 2H), 6.65 (m, 2H), 6.36 (s, 2H), 6.49 (m, 1H), 5.92 (s, 2H), 3.83 (5s, 15H), 3.55 (s, 2H), 2.69 (m, 4H), 2.53 (m, 4H), 1.78 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 153.0, 148.7, 147.6, 147.2, 146.3, 138.2, 136.0, 133.8, 133.3, 121.6, 120.5, 112.0, 111.1, 109.1, 107.7, 105.2, 100.8, 60.8, 58.3, 56.0, 55.9, 55.7, 55.6, 53.2, 34.0, 33.1, 29.0; HRESIMS calculated for $C_{30}H_{38}NO_7$ ($[M+H]^+$), 524.2648, found 524.2640.

Compound 6k: Colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.31 (m, 4H), 7.25 (m, 1H), 6.88-6.74 (m, 6H), 6.72 (m, 1H), 6.67 (m, 1H), 5.99 (s, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 3.50-3.49 (m, 2H), 2.81-2.58 (m, 8H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 148.9, 148.8, 147.6, 147.5, 147.4, 146.8, 145.7, 136.7, 136.1, 133.0, 132.4, 128.5, 127.6, 126.3, 126.2, 121.4, 120.5, 119.1, 112.0, 111.8, 111.2, 109.1, 108.1, 108.0, 106.4, 100.9, 100.7, 69.3, 62.5, 56.5, 56.2, 55.9, 55.8, 55.7, 55.5, 33.46, 33.40, 33.31, 29.6 ; HRESIMS calculated for $C_{28}H_{32}NO_4$ ($[M+H]^+$), 446.2331, found 446.2324.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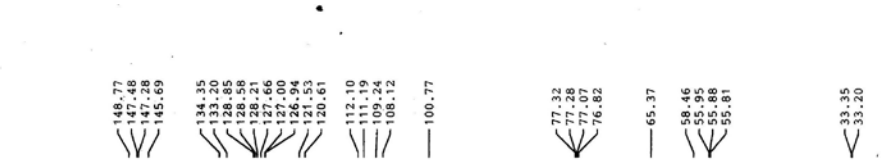
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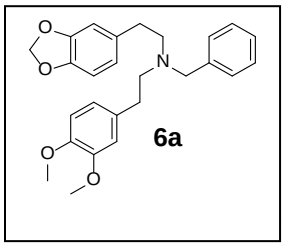
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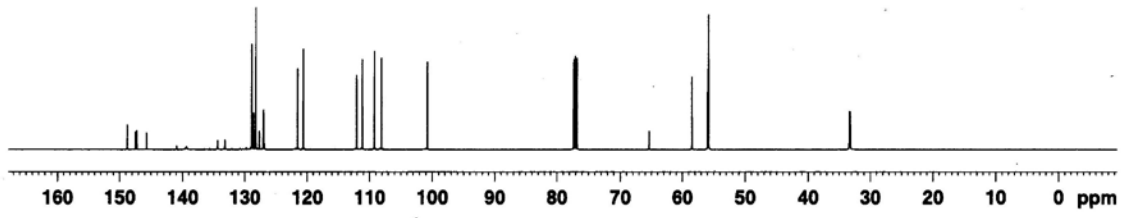
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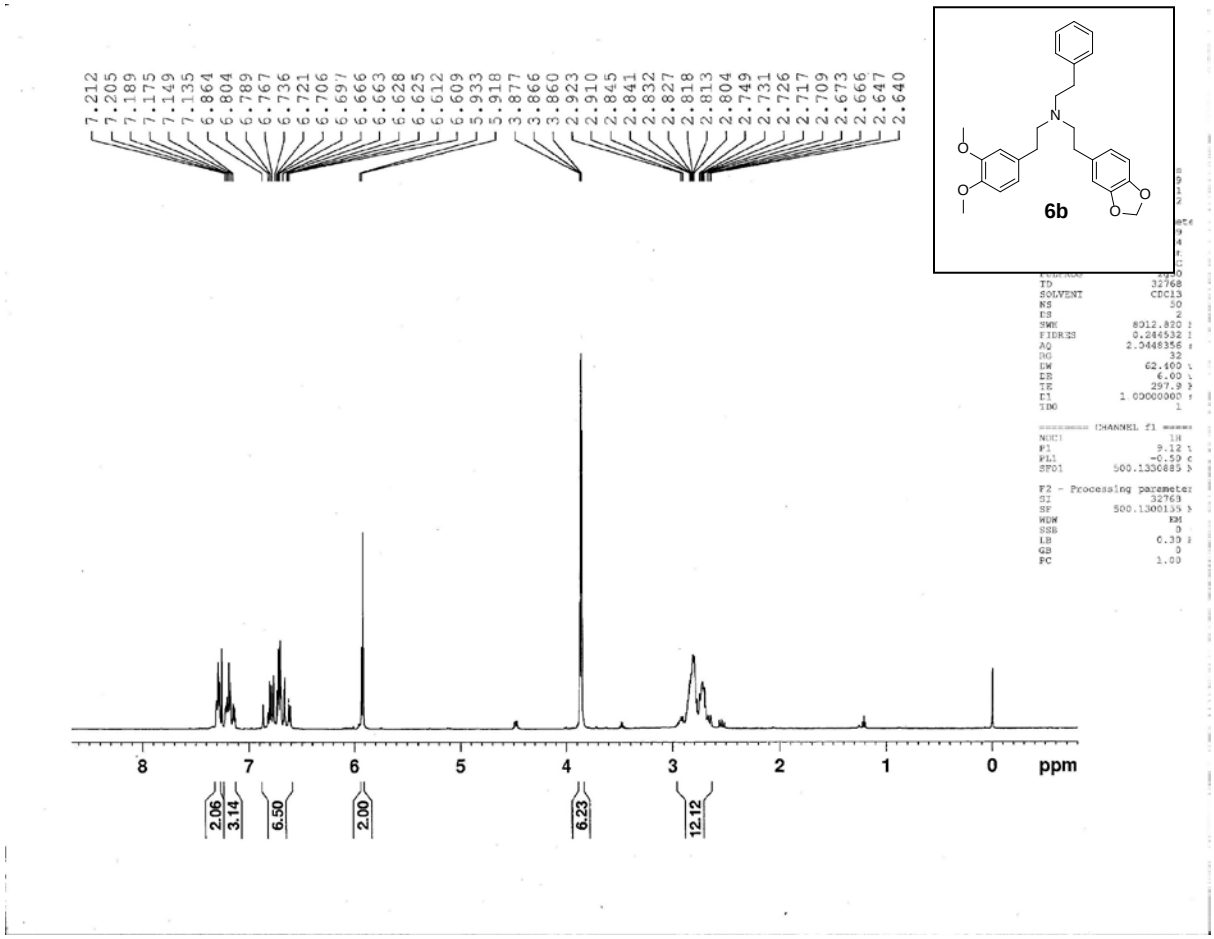
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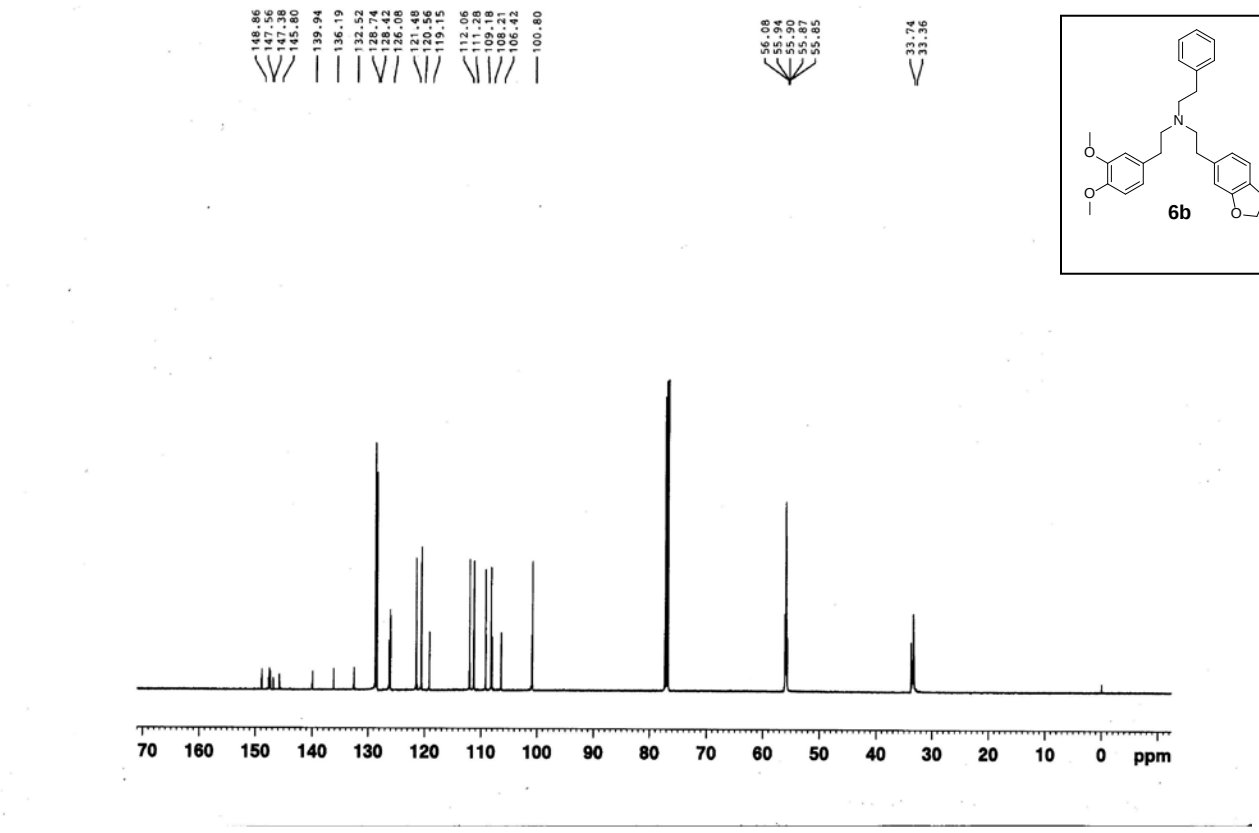
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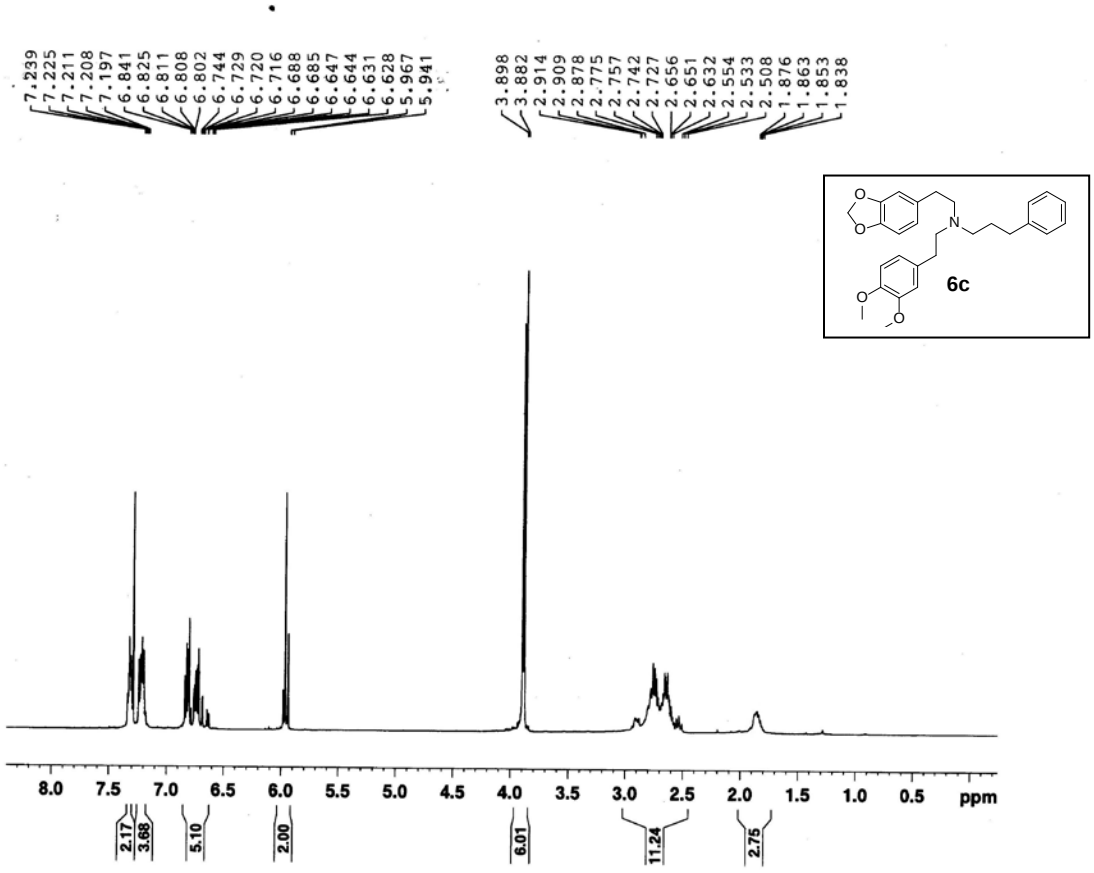
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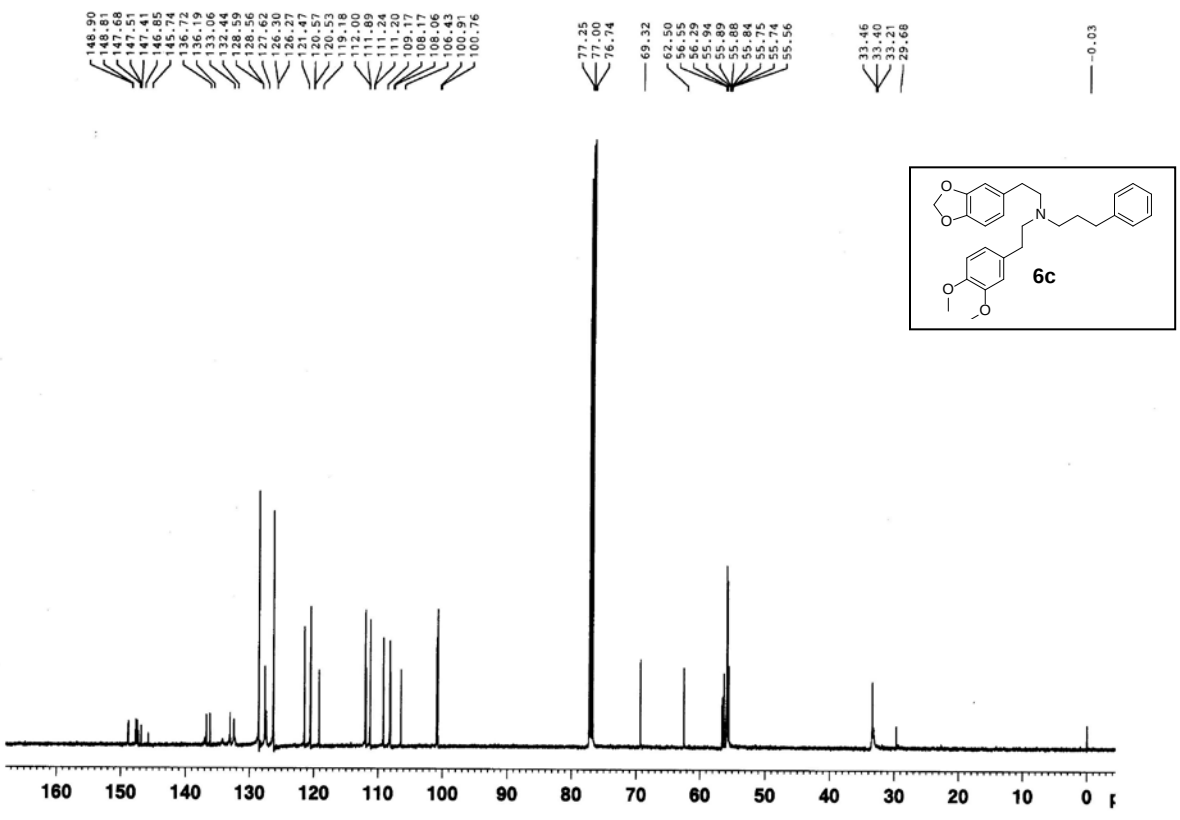
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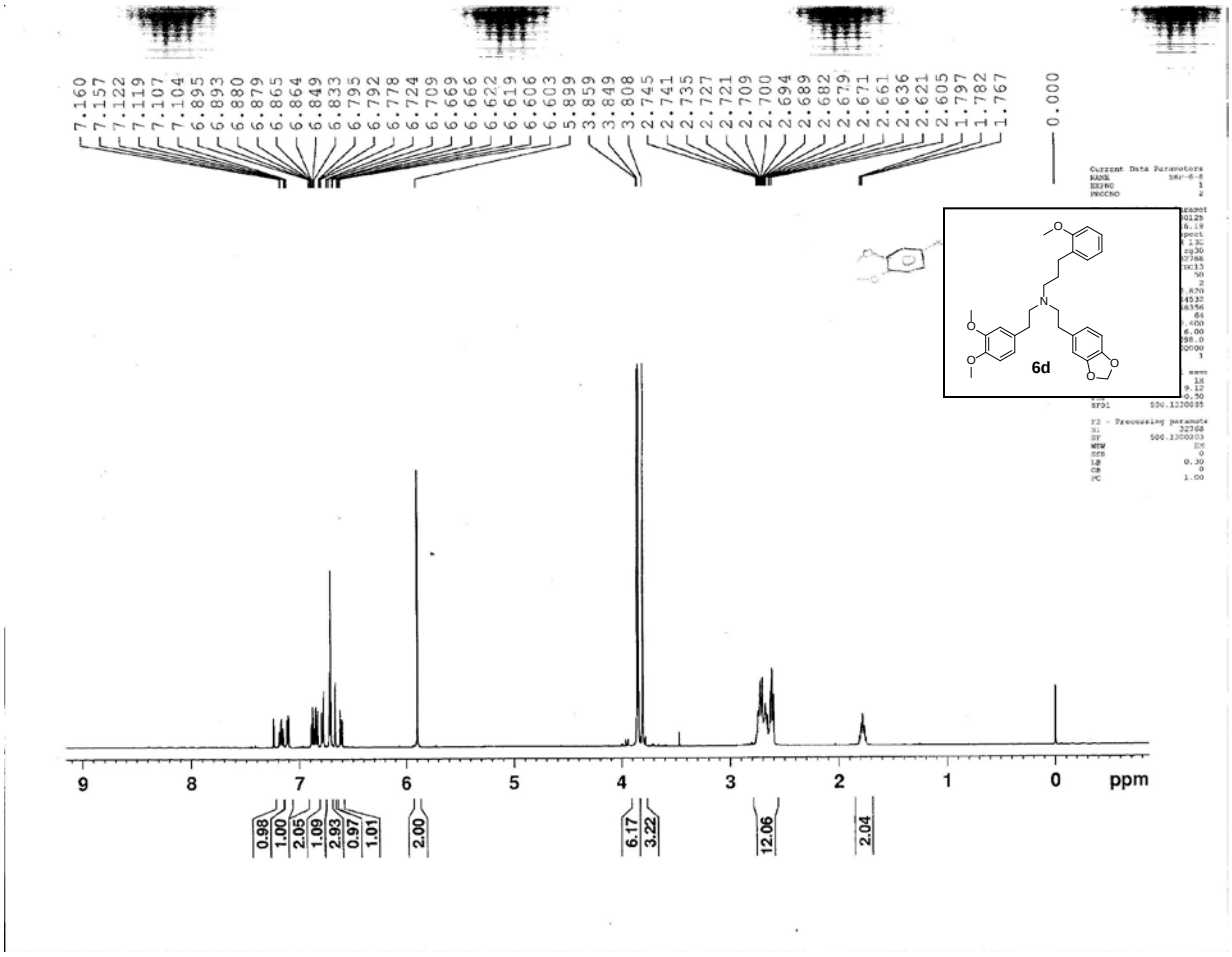
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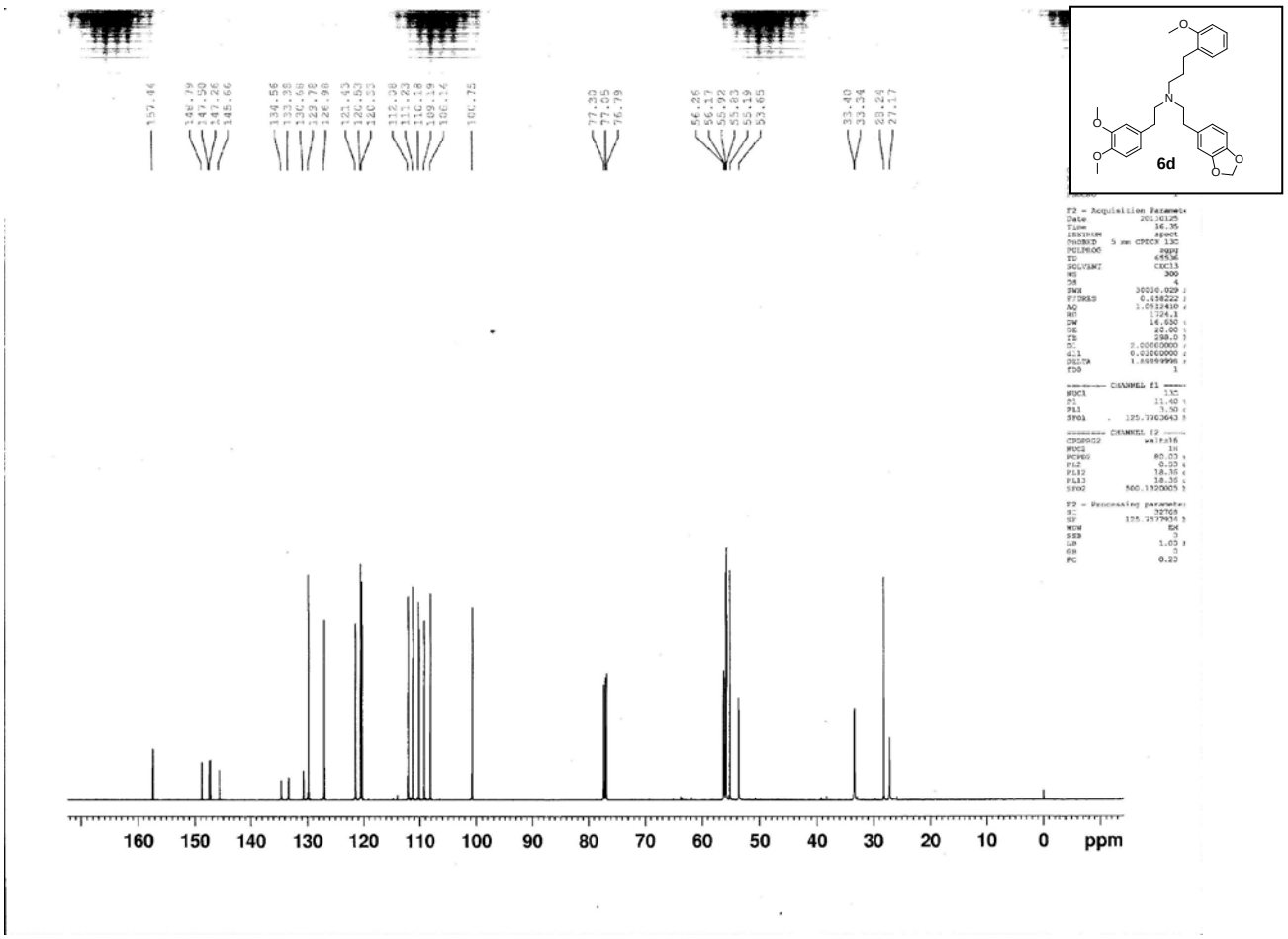
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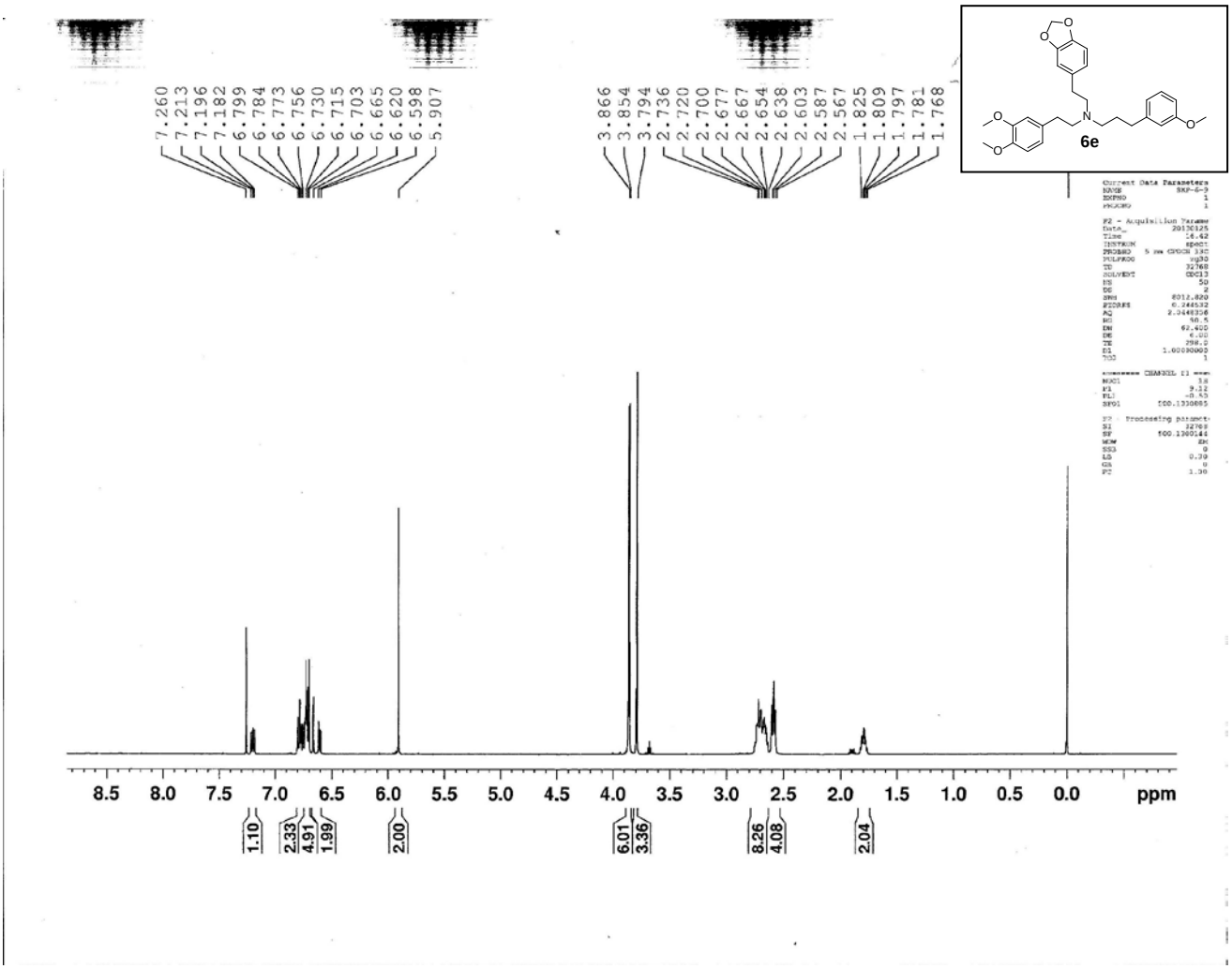
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6.784
6.773
6.756
6.730
6.715
6.703
6.665
6.620
6.598
5.907
3.866
3.854
3.794
2.736
2.720
2.700
2.677
2.667
2.654
2.638
2.603
2.587
2.567
1.825
1.809
1.797
1.781
1.768
6e
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
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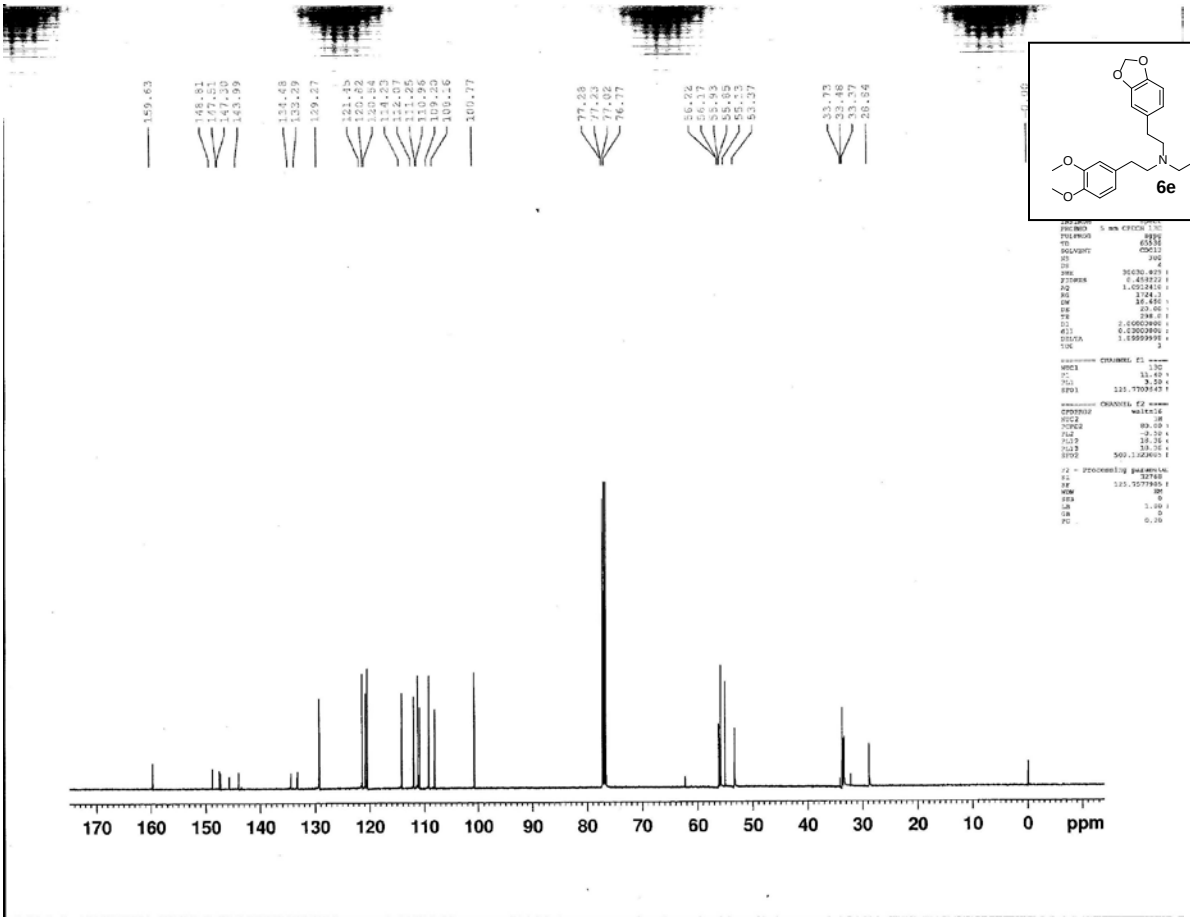
2.33
4.91
1.99
2.00
6.01
3.36
8.26
4.08
2.04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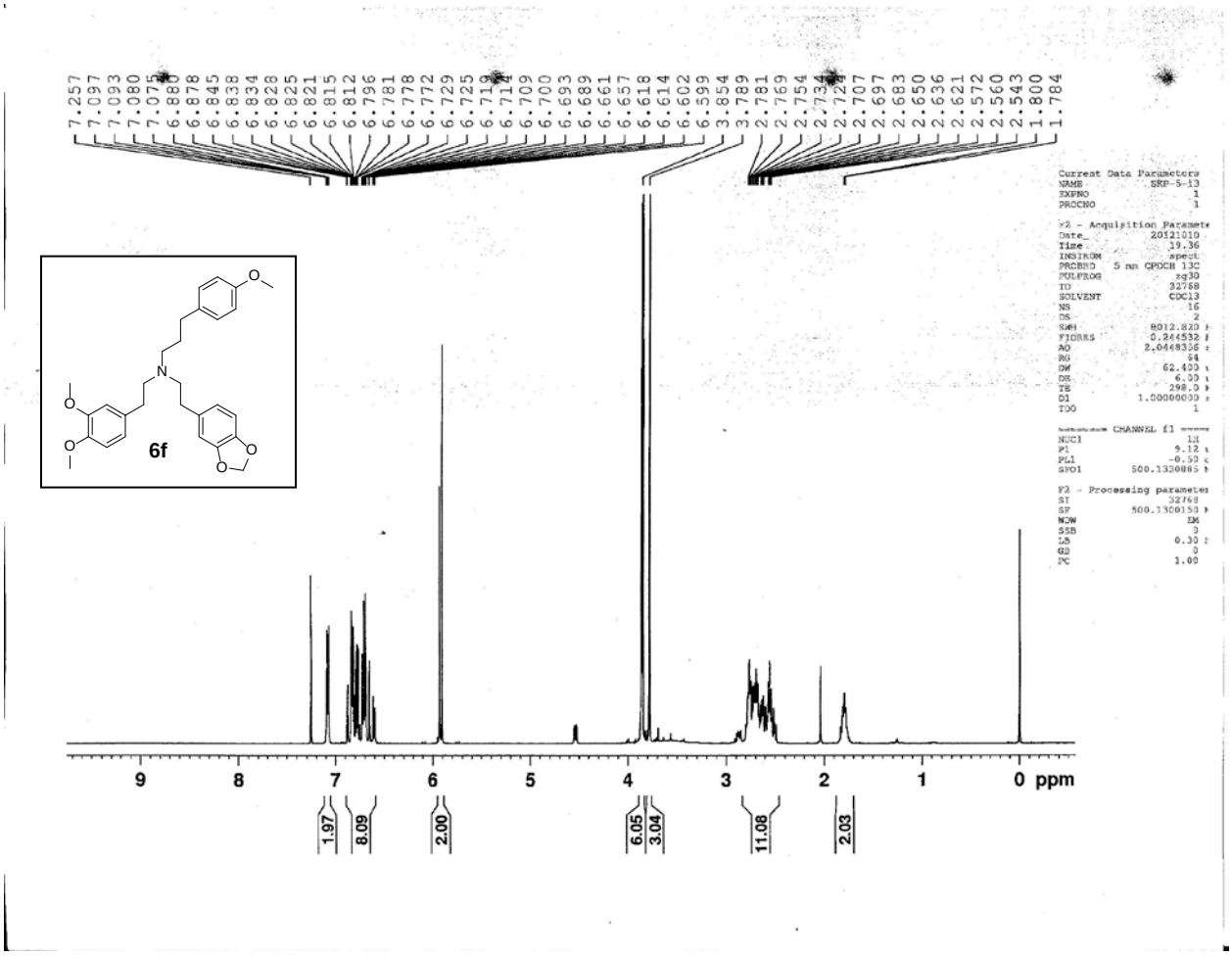
147.51
147.40
143.99
134.48
133.39
129.27
121.35
120.82
120.54
114.03
112.07
111.25
110.96
109.20
100.16
100.77
77.28
77.23
77.02
76.77
56.22
56.17
55.95
55.85
55.15
53.97
33.73
33.48
33.17
28.64
6e
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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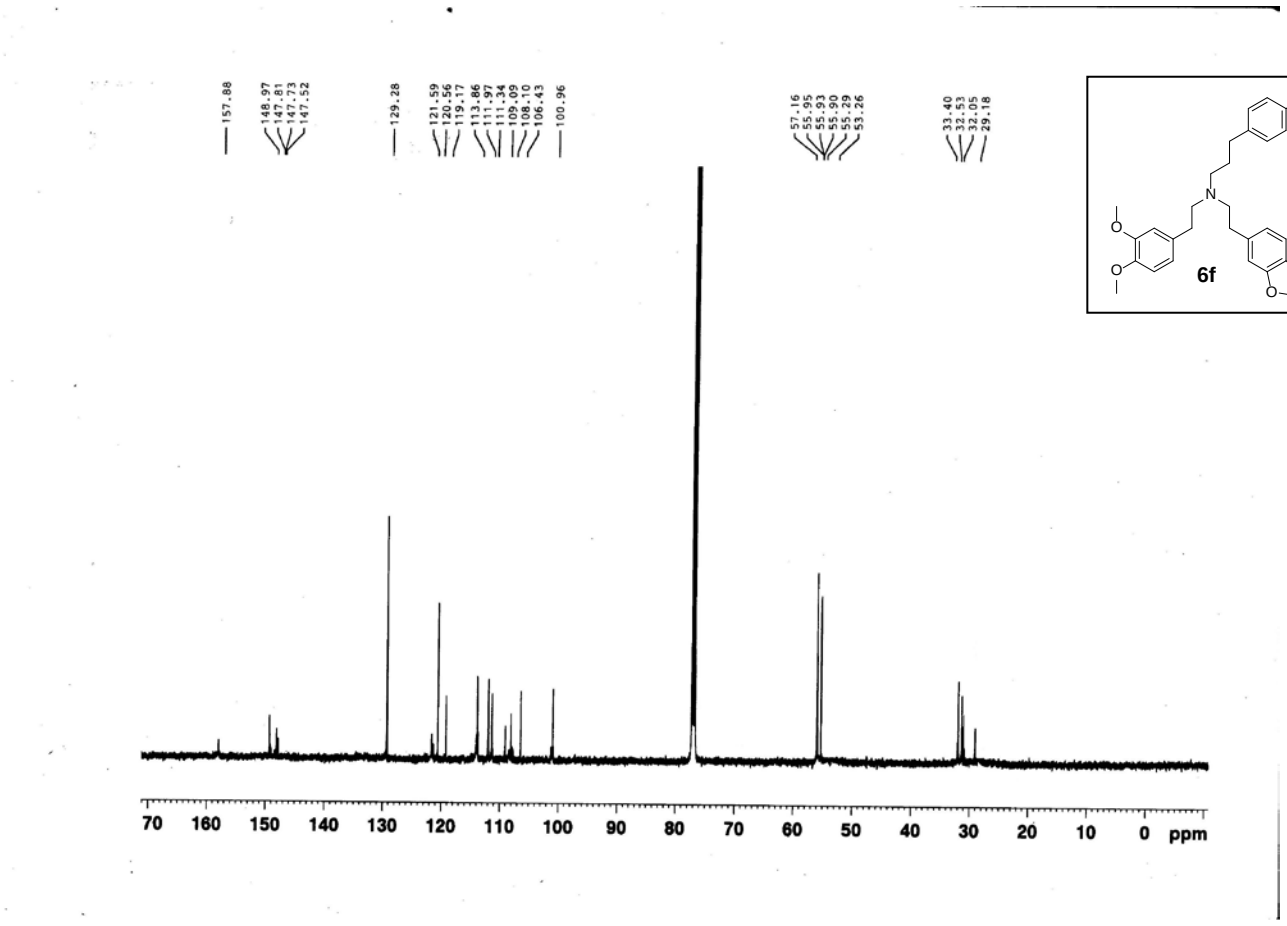
7.093
7.080
7.075
6.880
6.878
6.845
6.838
6.834
6.828
6.825
6.821
6.815
6.812
6.796
6.781
6.778
6.772
6.729
6.725
6.709
6.700
6.693
6.689
6.661
6.657
6.618
6.614
6.602
6.599
3.854
3.789
2.781
2.769
2.754
2.734
2.724
2.707
2.697
2.683
2.650
2.636
2.621
2.572
2.560
2.543
1.800
1.784
6f
9
8
7
6
5
4
3
2
1
0 ppm
1.97
8.09
2.00
6.05
3.04
11.08
2.03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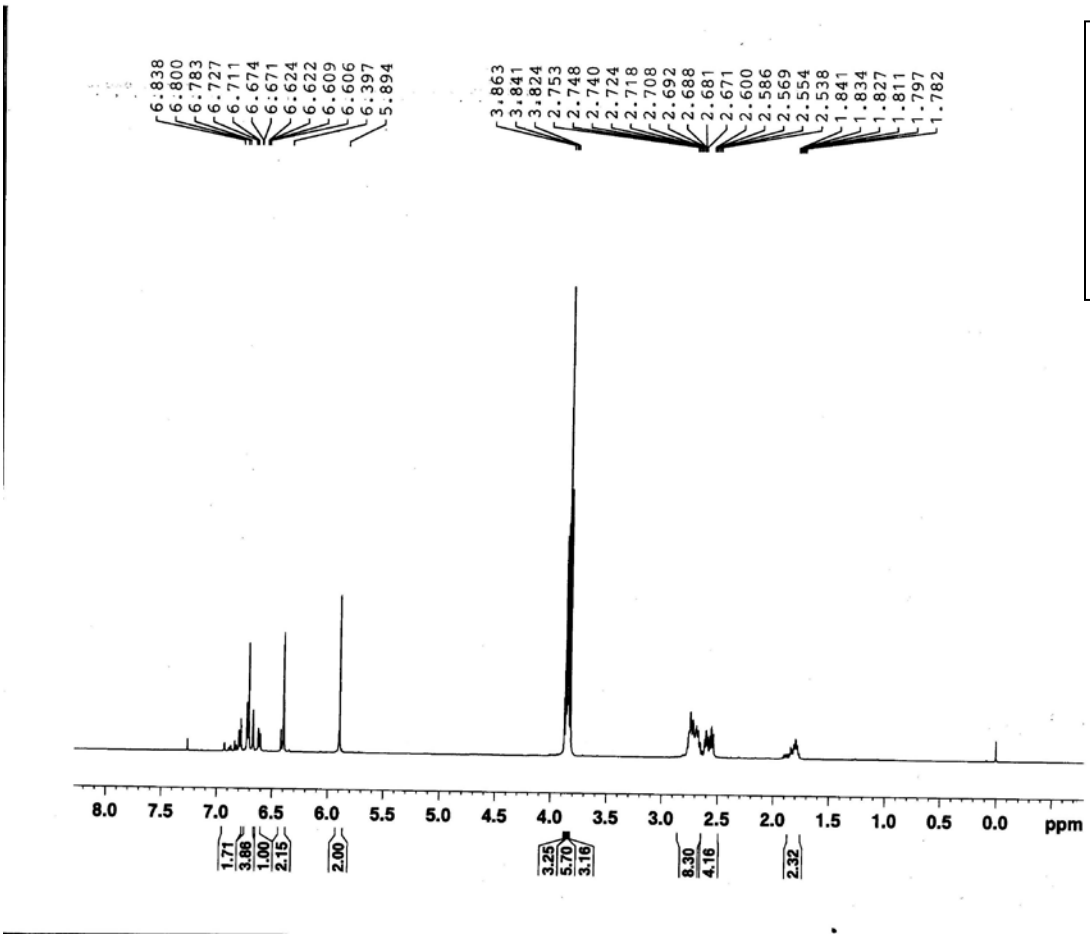
129.28
121.59
120.56
119.17
113.86
111.97
111.34
109.09
108.10
106.43
100.96
57.16
55.95
55.93
55.90
55.29
53.26
33.40
32.53
32.05
29.18
6f
70 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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6.711
6.674
6.671
6.624
6.622
6.609
6.606
6.397
5.894
3.863
3.841
3.824
2.753
2.748
2.740
2.724
2.718
2.708
2.692
2.688
2.681
2.671
2.600
2.586
2.569
2.554
2.538
1.841
1.834
1.827
1.811
1.797
1.782
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
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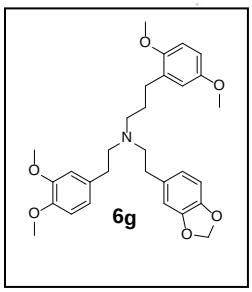
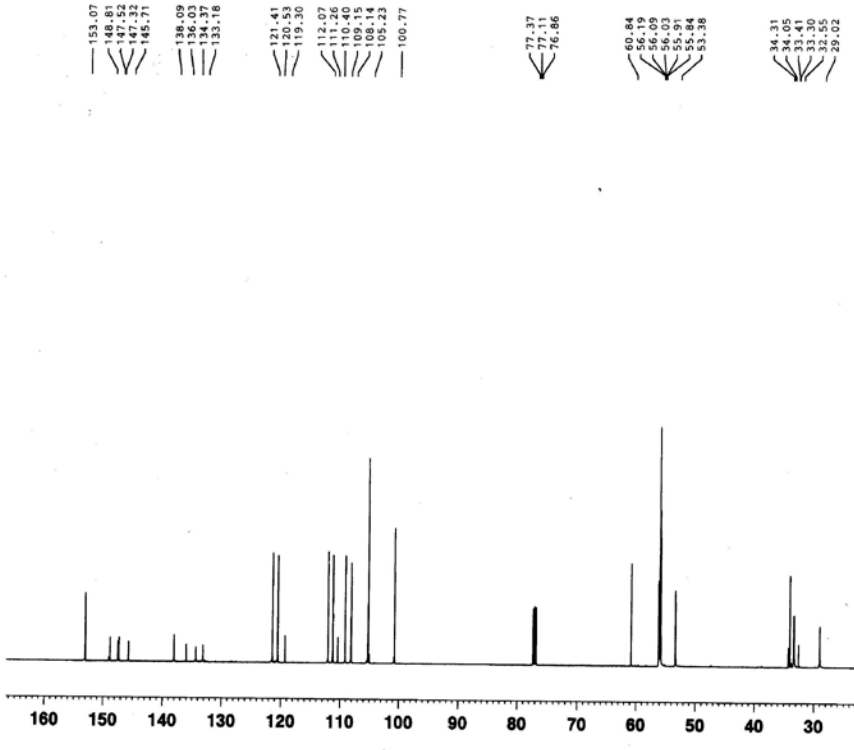
3.86
1.00
2.15
2.00
3.25
5.70
3.16
8.30
4.16
2.32


6g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145.71
138.09
136.03
134.37
133.18
121.41
120.53
119.30
112.07
111.26
110.40
109.15
108.14
105.23
100.77
77.37
77.11
76.86
60.84
56.19
56.09
56.03
55.91
55.84
53.38
34.31
34.05
33.41
33.30
32.55
29.02
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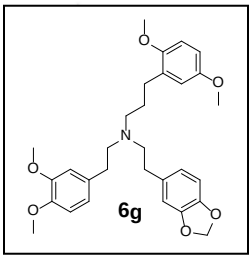
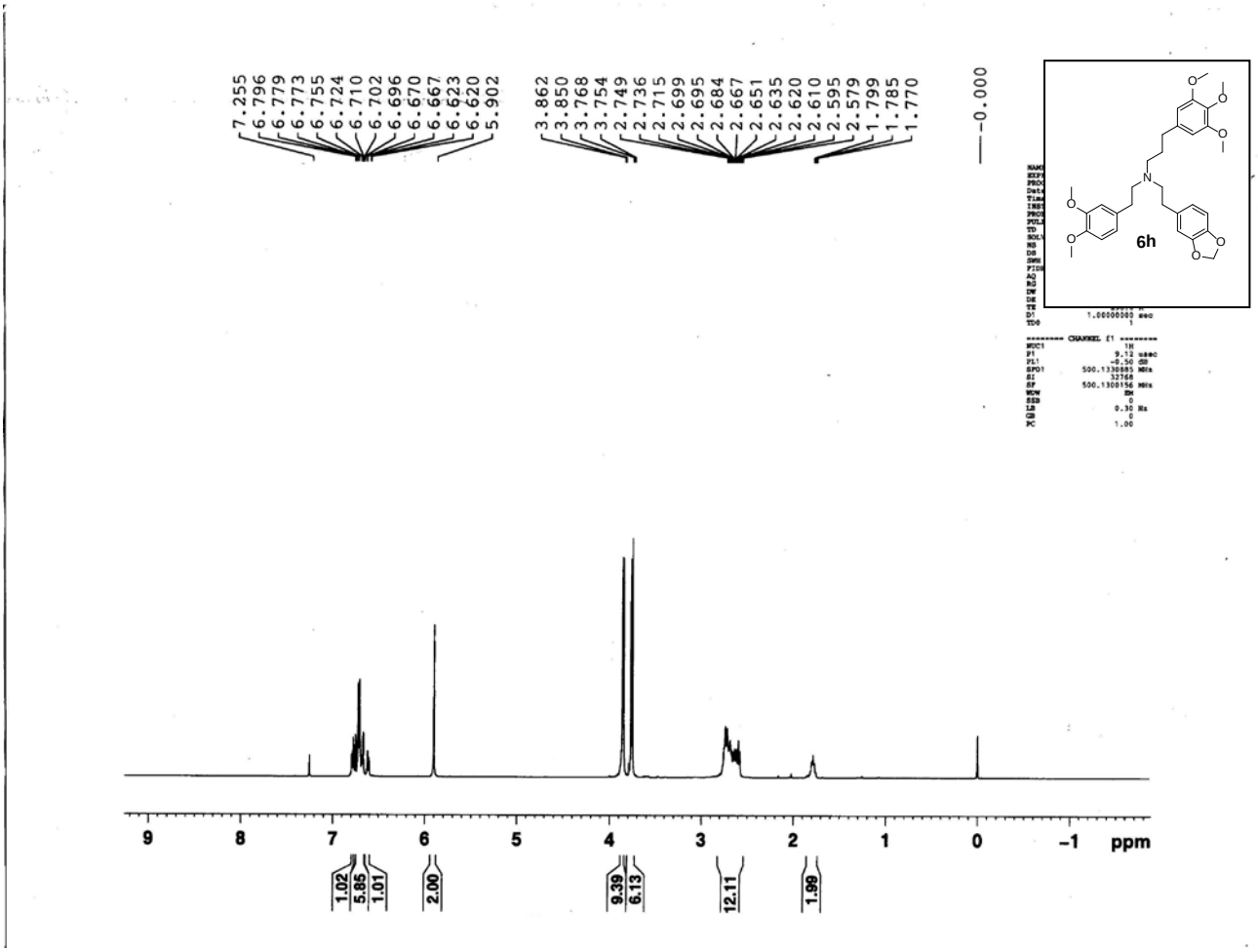
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


6g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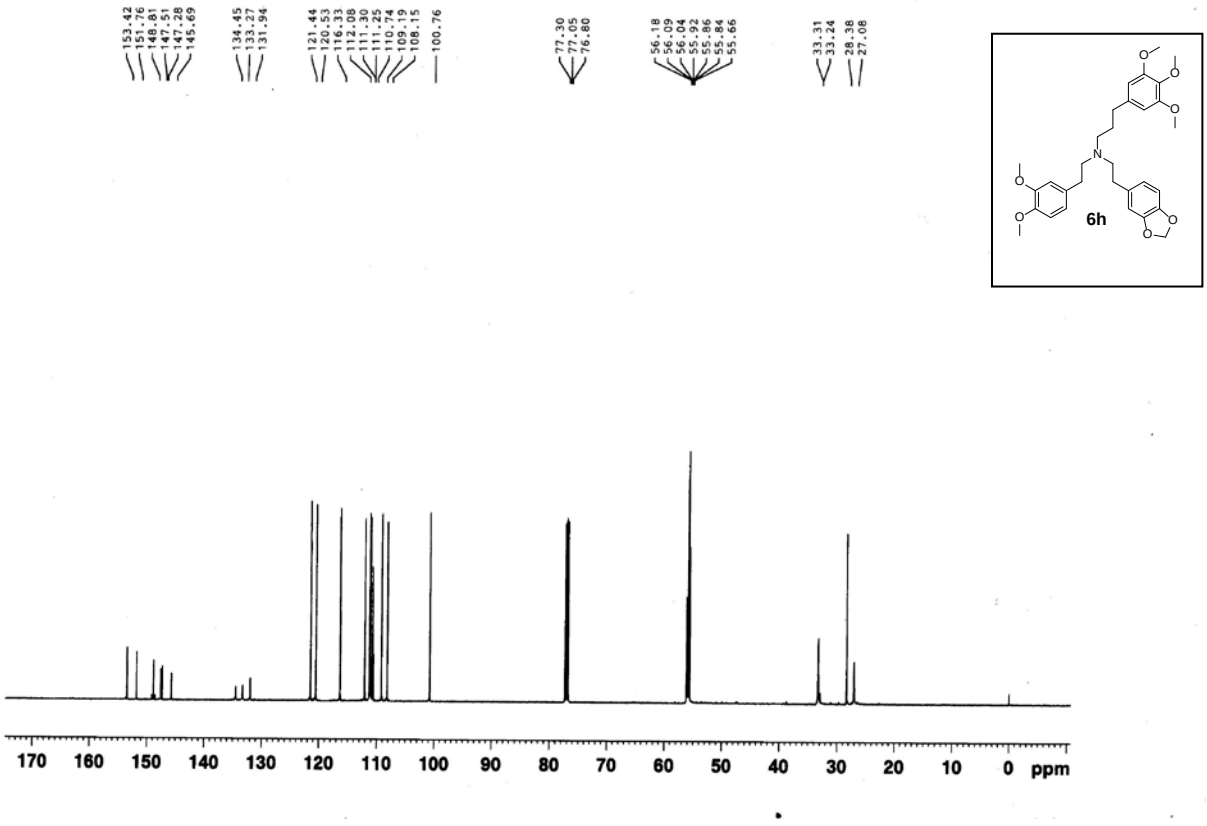
6.779
6.773
6.755
6.724
6.710
6.702
6.696
6.670
6.667
6.623
6.620
5.902
3.862
3.850
3.768
3.754
2.749
2.736
2.715
2.699
2.695
2.684
2.667
2.651
2.635
2.620
2.610
2.595
2.579
1.799
1.785
1.770
0.000
6h
9
8
7
6
5
4
3
2
1
0
−1
ppm
1.02
5.85
1.01
2.00
9.39
6.13
12.11
1.99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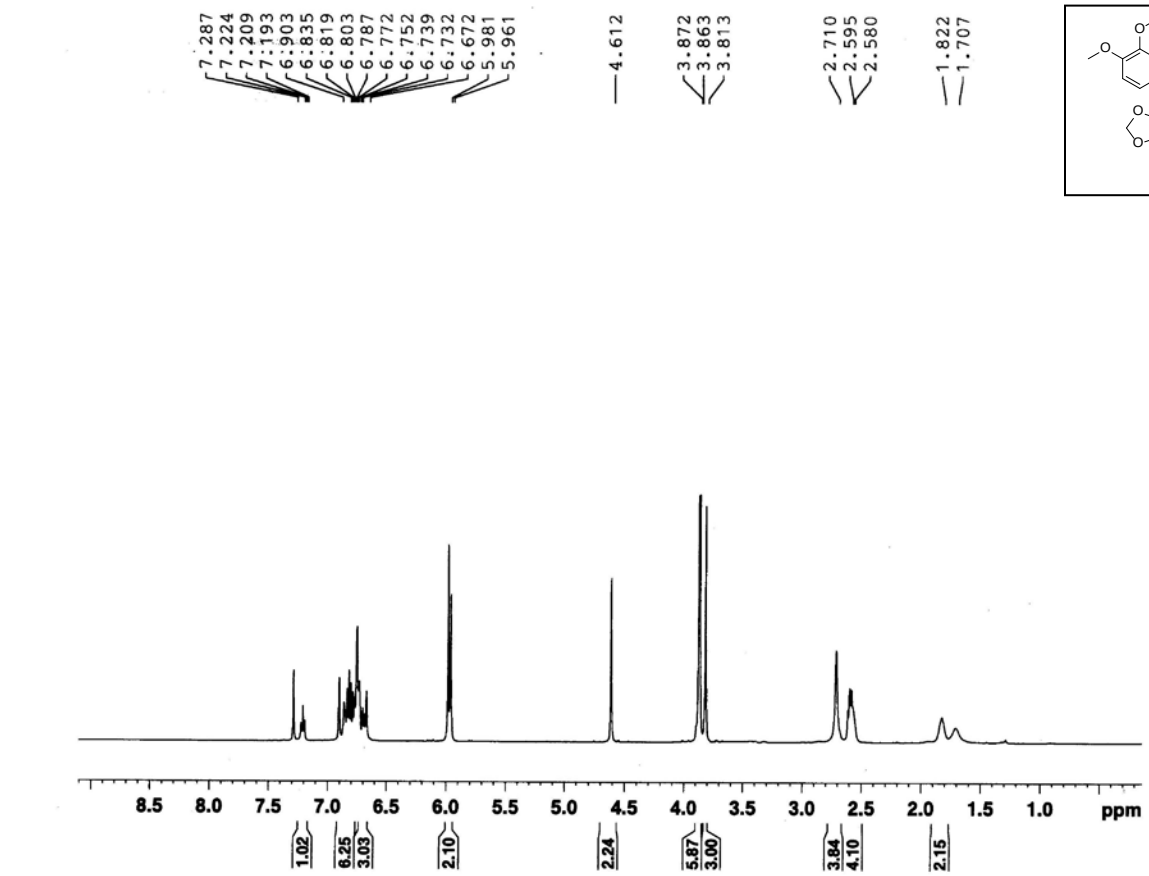
151.76
148.81
147.51
147.28
145.69
134.45
133.27
131.94
121.44
120.53
116.33
112.08
111.30
111.25
110.74
109.19
108.15
100.76
77.30
77.05
76.80
56.18
56.09
56.04
55.92
55.86
55.84
55.66
33.31
33.24
28.38
27.08
6h
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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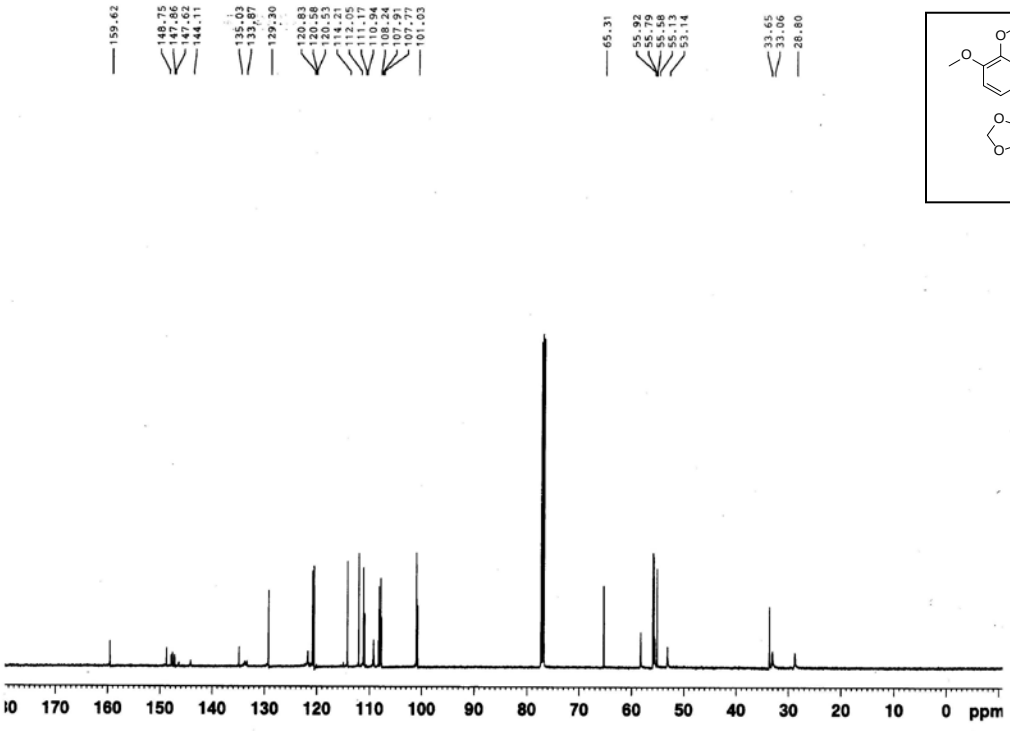
7.209
7.193
6.903
6.835
6.819
6.803
6.787
6.772
6.752
6.739
6.732
6.672
5.981
5.961
4.612
3.872
3.863
3.813
2.710
2.595
2.580
1.822
1.707
6i
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.02
6.25
3.03
2.10
2.24
5.87
3.00
3.84
4.10
2.15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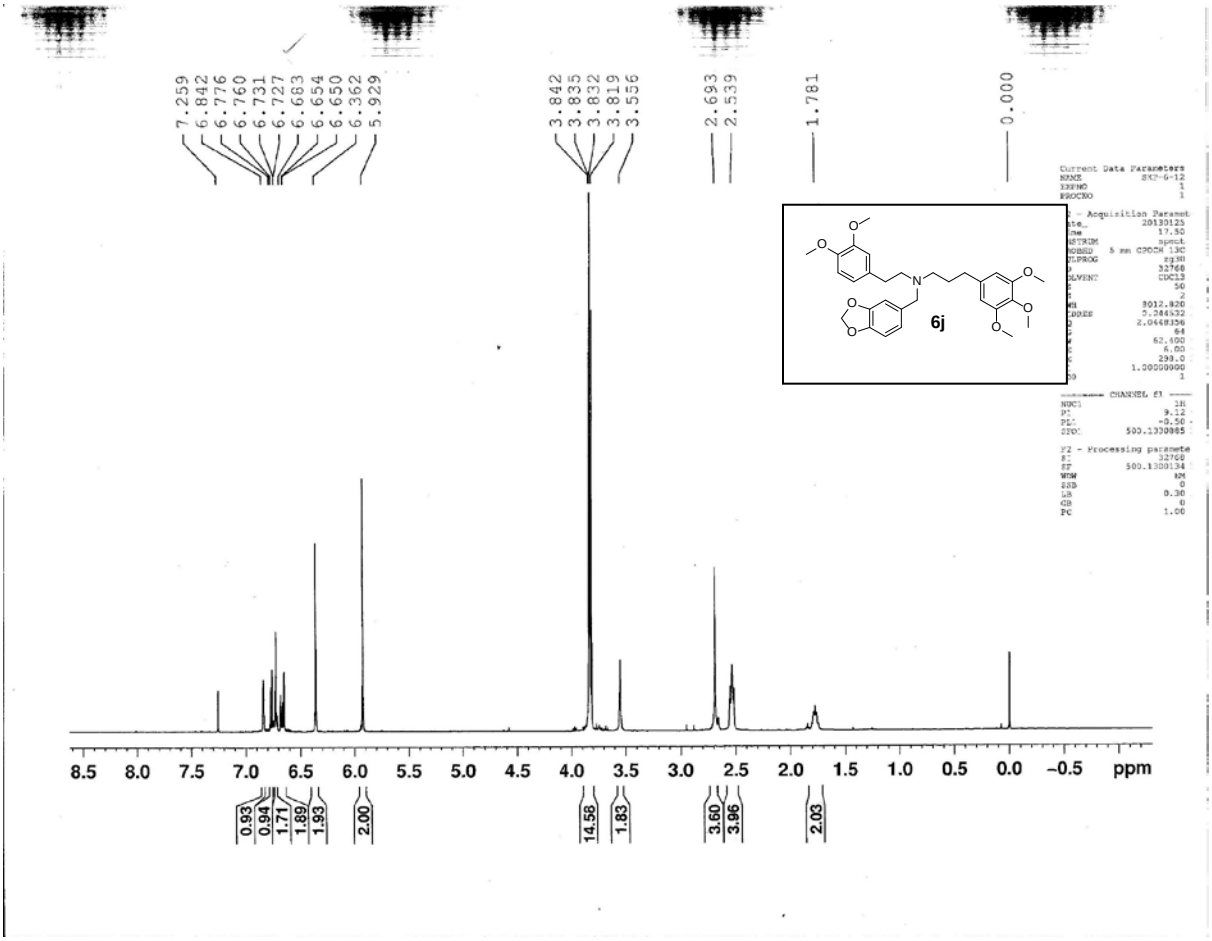
148.75
147.86
147.62
144.11
135.03
133.87
129.30
120.83
120.58
120.53
114.21
112.05
111.17
110.94
108.24
107.91
107.77
101.03
65.31
55.92
55.79
55.58
55.13
53.14
33.65
33.06
28.80
6i
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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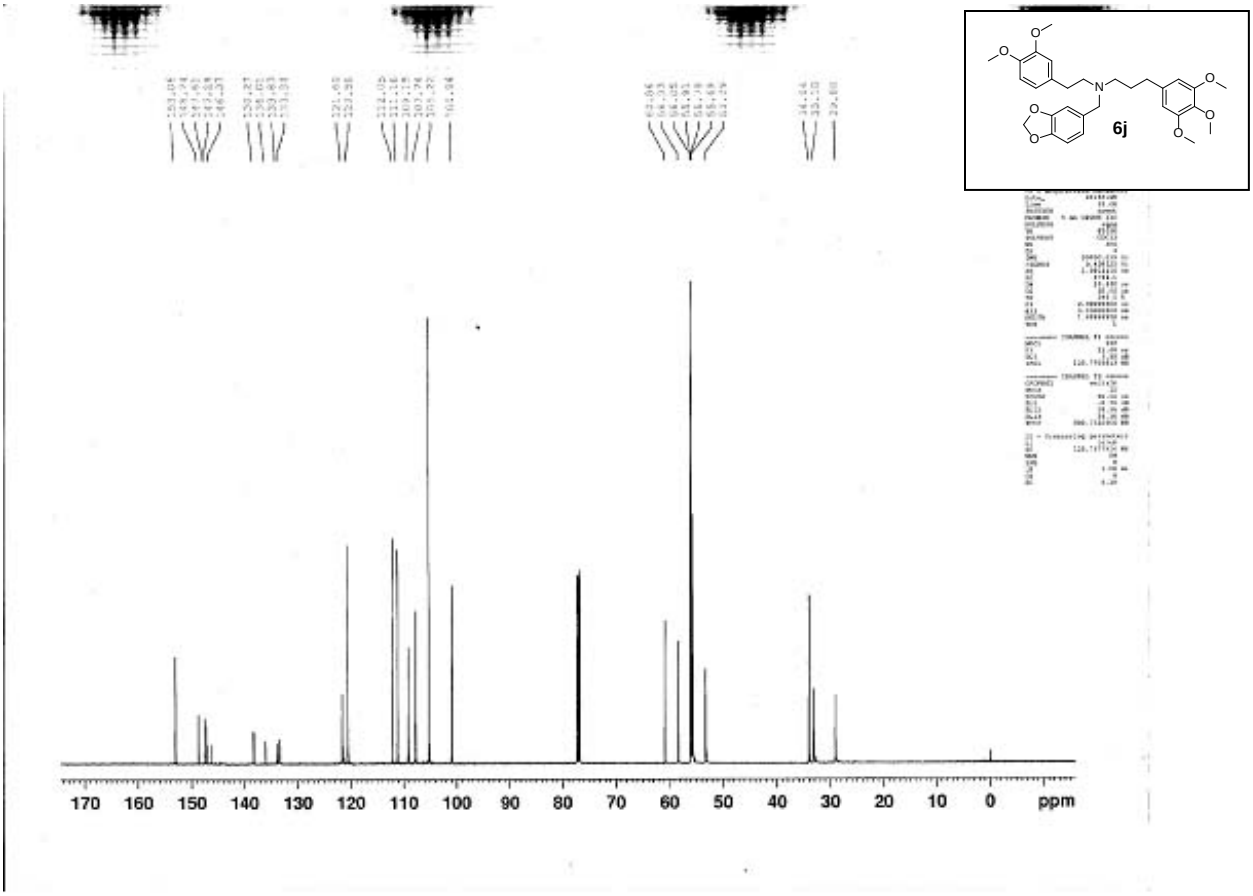
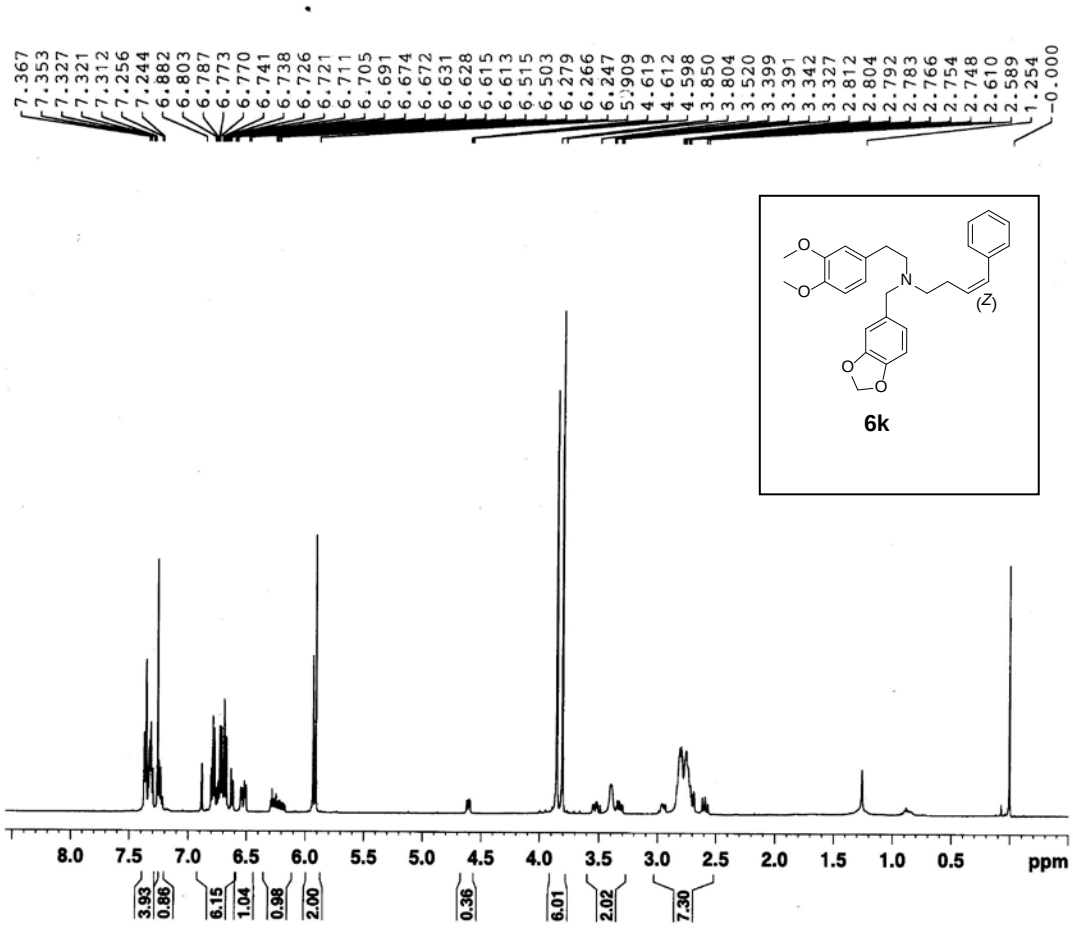
6.842
6.776
6.760
6.731
6.727
6.663
6.654
6.650
6.362
5.929
3.842
3.835
3.832
3.819
3.556
2.693
2.539
1.781
0.000
6j
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 ppm
0.93
0.94
1.71
1.89
1.93
2.00
14.58
1.83
3.60
3.96
2.03


6j
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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7.321
7.312
7.256
7.244
6.882
6.803
6.787
6.773
6.770
6.741
6.738
6.726
6.721
6.711
6.705
6.691
6.674
6.672
6.631
6.628
6.615
6.613
6.515
6.503
6.279
6.266
6.247
5.909
4.619
4.612
4.598
3.850
3.804
3.520
3.399
3.391
3.342
3.327
2.812
2.804
2.792
2.783
2.766
2.754
2.748
2.610
2.589
1.254
-0.000
O
O
N
(Z)
O
O
6k
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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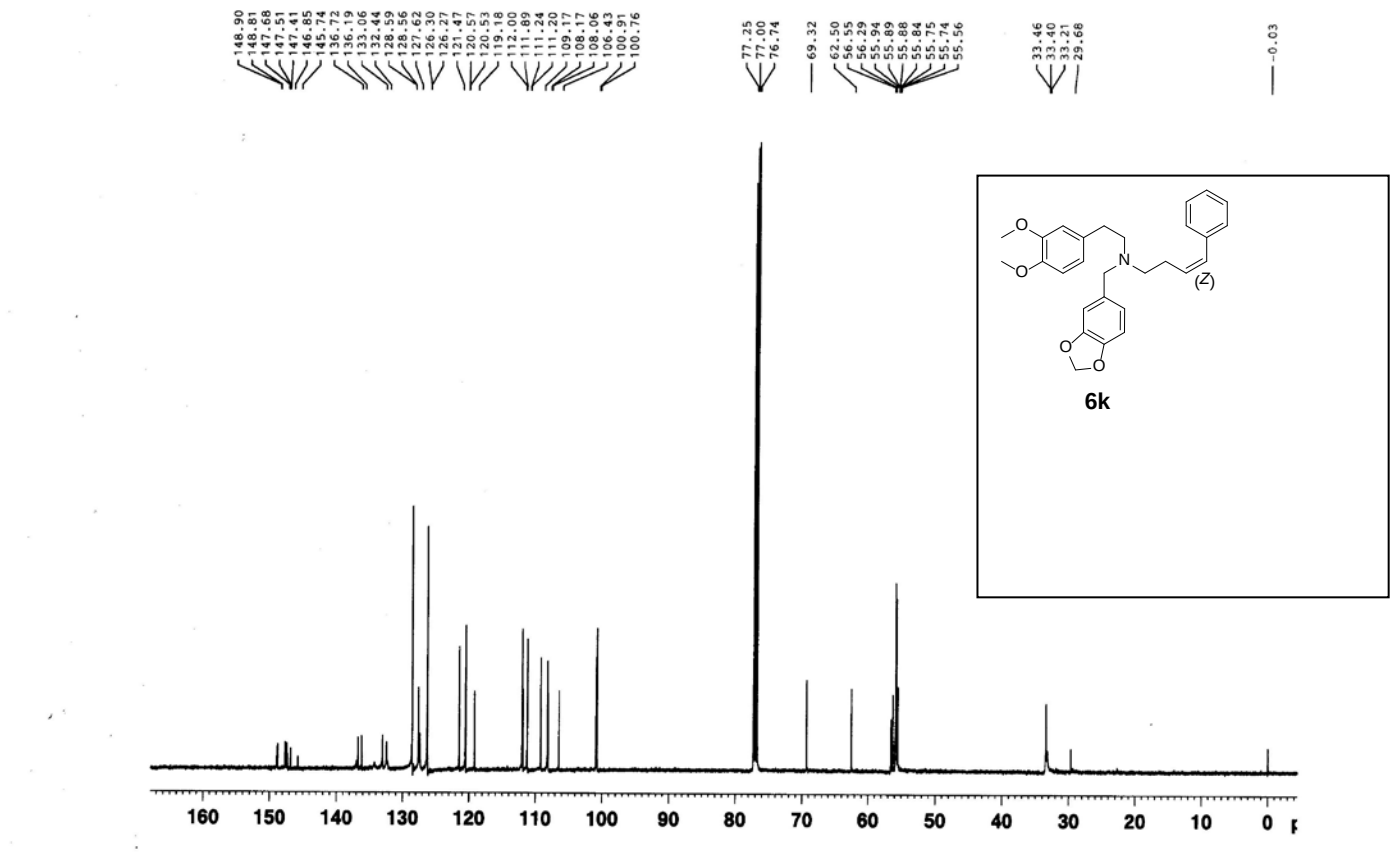
0.86
6.15
1.04
0.98
2.00
0.36
6.01
2.02
7.30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147.41
146.85
145.74
136.72
136.19
133.06
132.44
128.59
128.56
127.62
126.30
126.27
121.47
120.57
120.53
119.18
112.00
111.89
111.24
111.20
109.17
108.17
108.06
106.43
100.91
100.76
77.25
77.00
76.74
69.32
62.50
56.55
56.29
55.94
55.89
55.88
55.84
55.75
55.74
55.56
33.46
33.40
33.21
29.68
-0.03
(Z)
6k
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

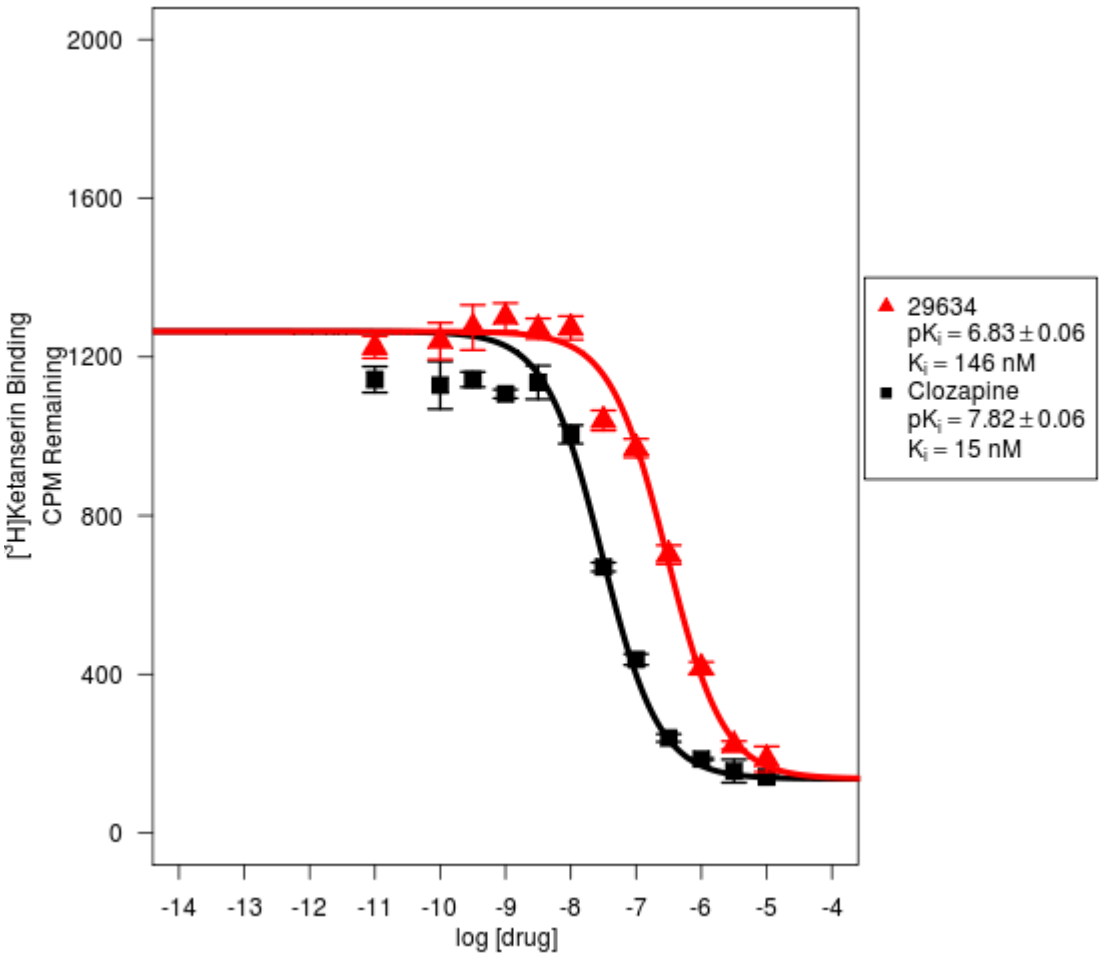

Figure 1. Inhibition of [^{3}H]ketanserin binding to human cloned 5-HT$_{2a}$ receptors by compound **6h** (PDSP code 29634, red triangle) and clozapine (black square)

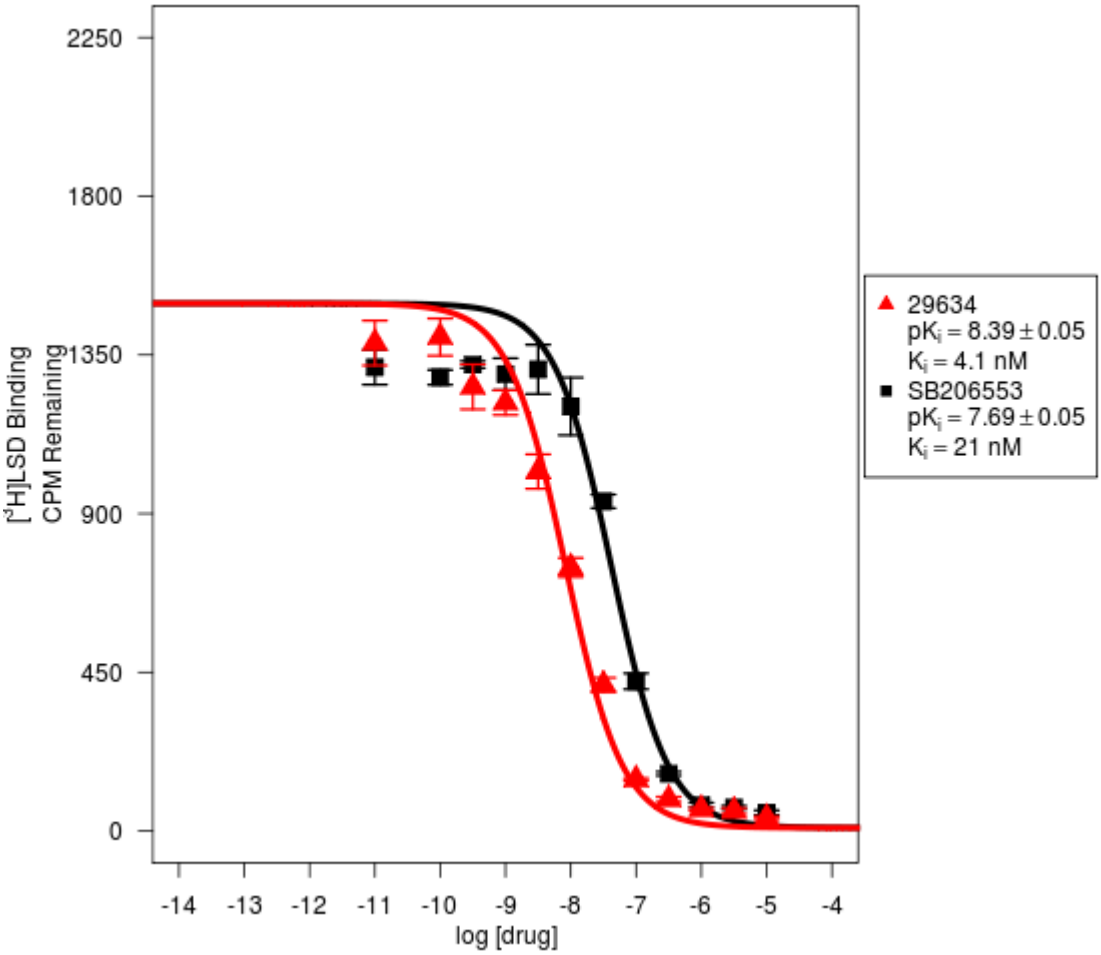

Figure 2. Inhibition of [^{3}H]LSD binding to human cloned 5-HT$_{2B}$ receptors by compound **6h** (PDSP code 29634, red triangle) and SB206553 (black square)

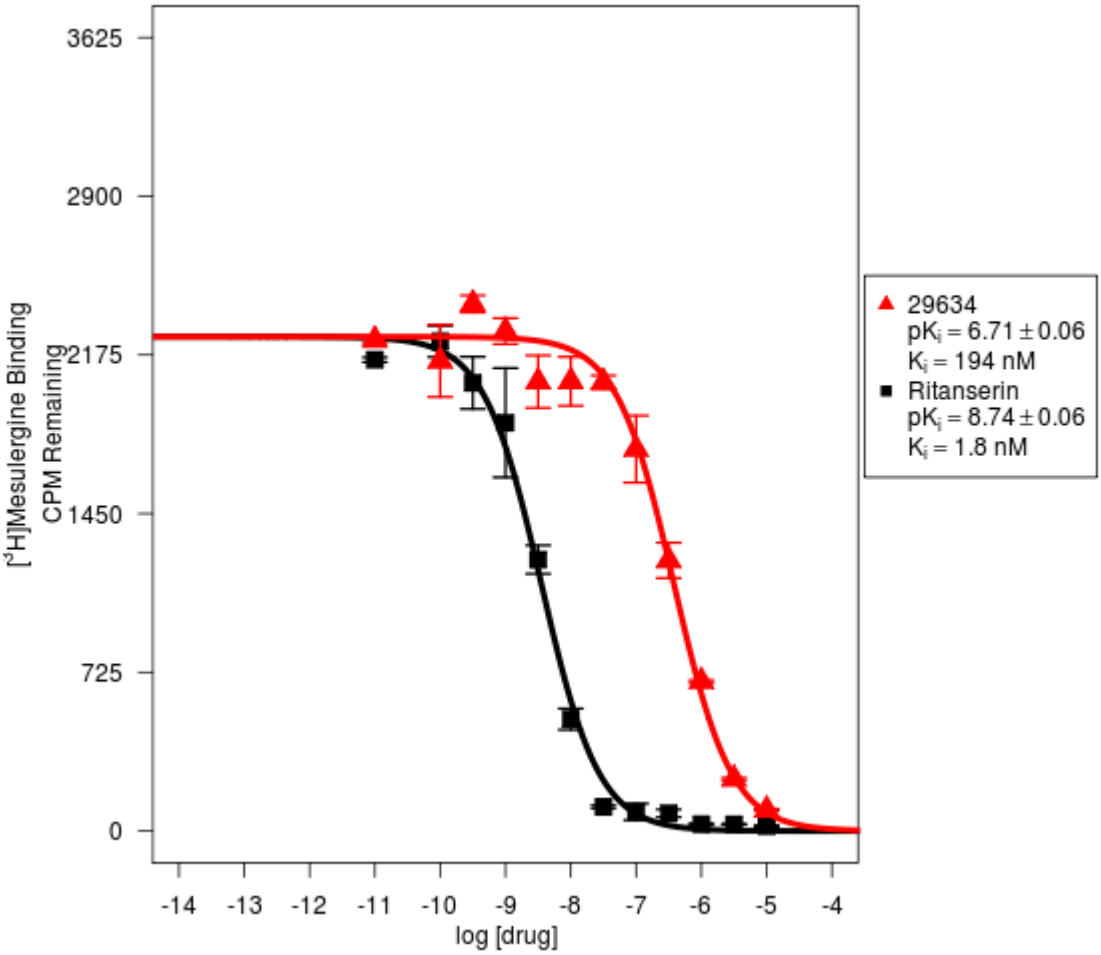

Figure 3. Inhibition of [^{3}H]mesulergine binding to human cloned 5-HT$_{2c}$ receptors by compound **6h** (PDSP code 29634, red triangle) and ritanserin (black square)