Supporting Information

First scale-up: problems and resolutions on the synthesis of WAY-253752, a novel, dual-acting SSRI/5HT$_{1A}$ antagonist.

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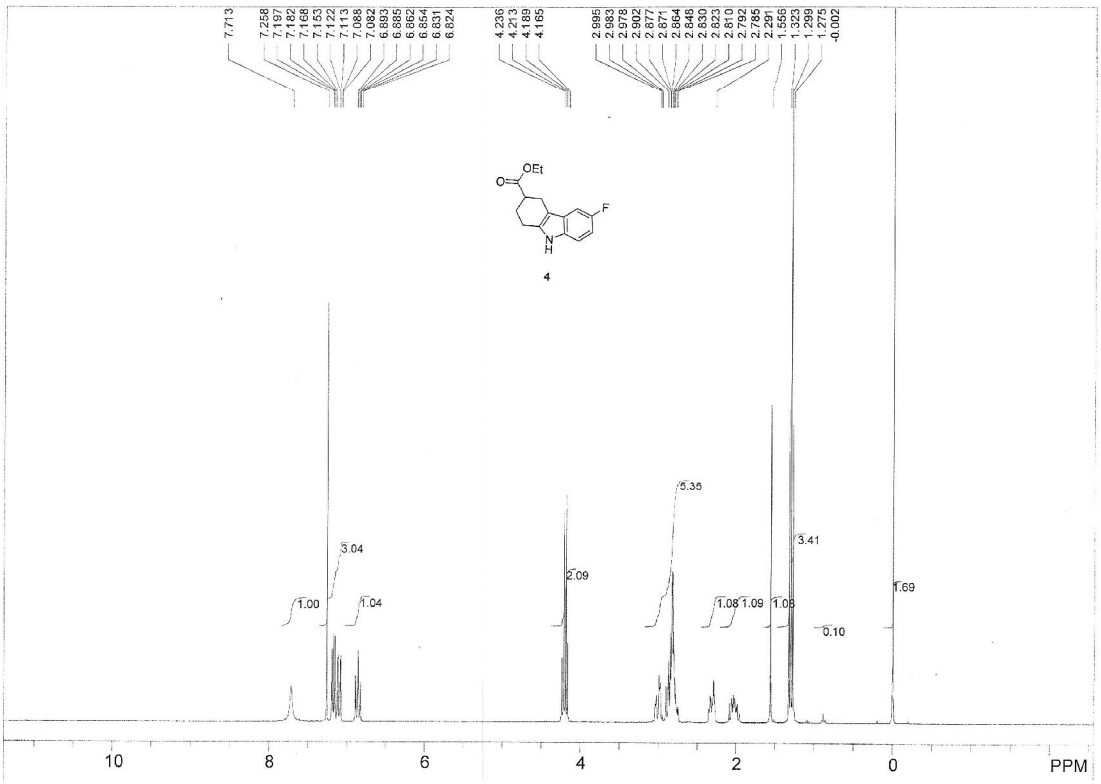
General Experimental Methods

^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ (compounds 4, 11) and DMSO-d6 (compounds 14, 16, 17, 1) using tetramethylsilane as a standard. Chiral HPLC analysis was performed on HP 1100-6 liquid chromatograph equipped with a Whelk O1 RR 4.6 x 250 mm column. Mobile phase composition: 60% heptane containing 0.02% TFA, 40% isopropyl alcohol, flow rate 1 mL/min.

NMR Spectra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7.197
7.182
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7.113
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6.862
6.854
6.831
6.824
4.236
4.213
4.189
4.165
2.995
2.983
2.978
2.902
2.877
2.871
2.864
2.848
2.830
2.823
2.810
2.792
2.785
2.291
1.556
1.323
1.299
1.275
-0.002
OEt
O
F
N
H
4
1.00
3.04
1.04
2.09
5.35
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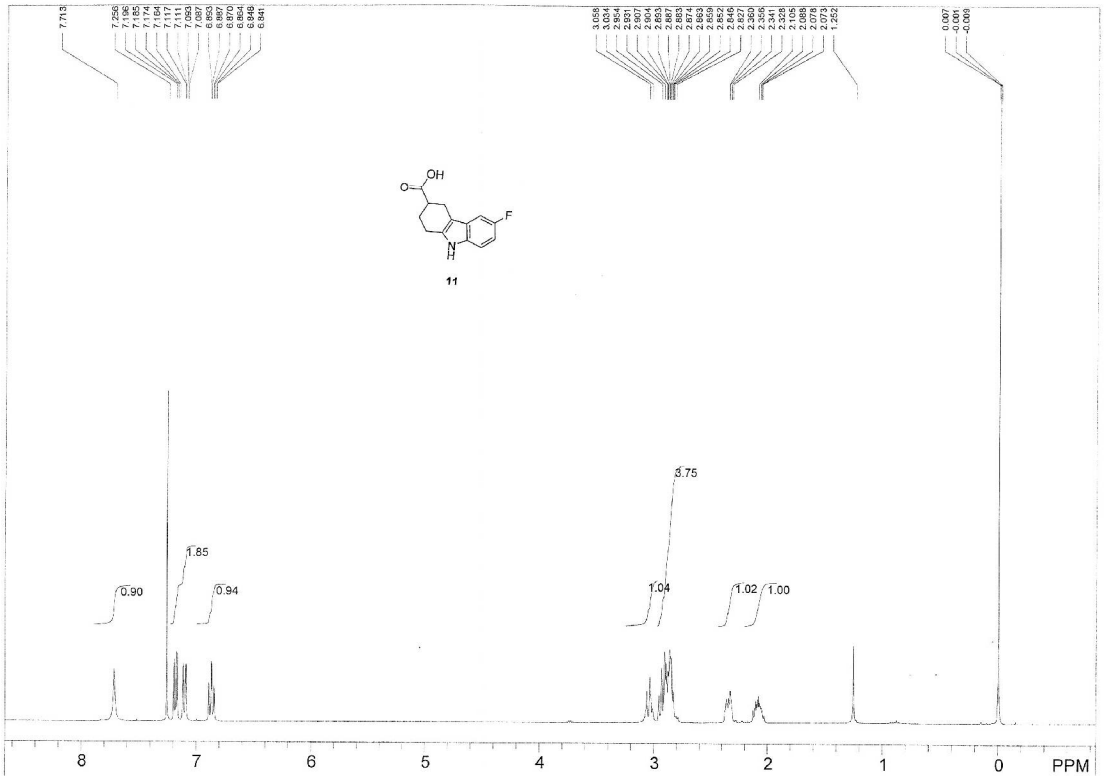
1.09
1.08
3.41
0.10
1.69
10
8
6
4
2
0
PPM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7.087
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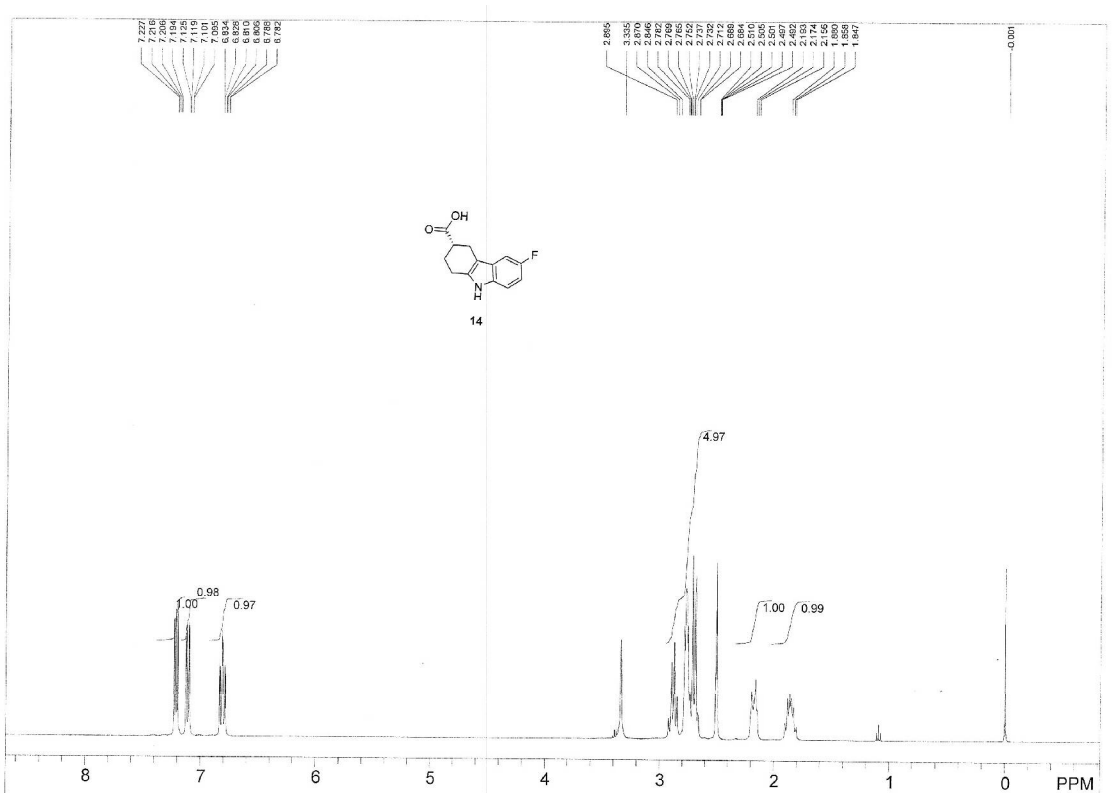
6.870
6.864
6.848
6.841
3.059
3.034
2.954
2.931
2.907
2.901
2.893
2.887
2.874
2.693
2.659
2.652
2.646
2.627
2.350
2.345
2.341
2.328
2.185
2.165
2.078
2.073
1.252
0.007
-0.001
-0.009
OH
O
F
N
H
11
0.90
1.85
0.94
3.75
1.04
1.02
1.00
8
7
6
5
4
3
2
1
0
PPM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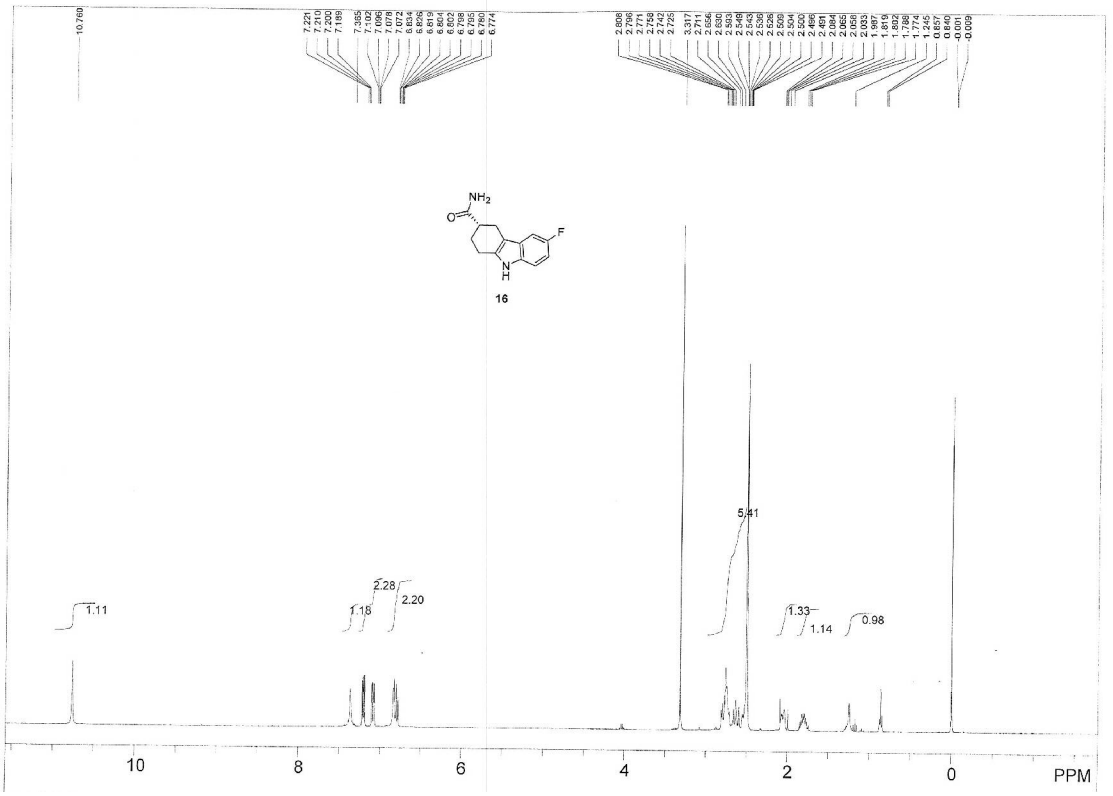
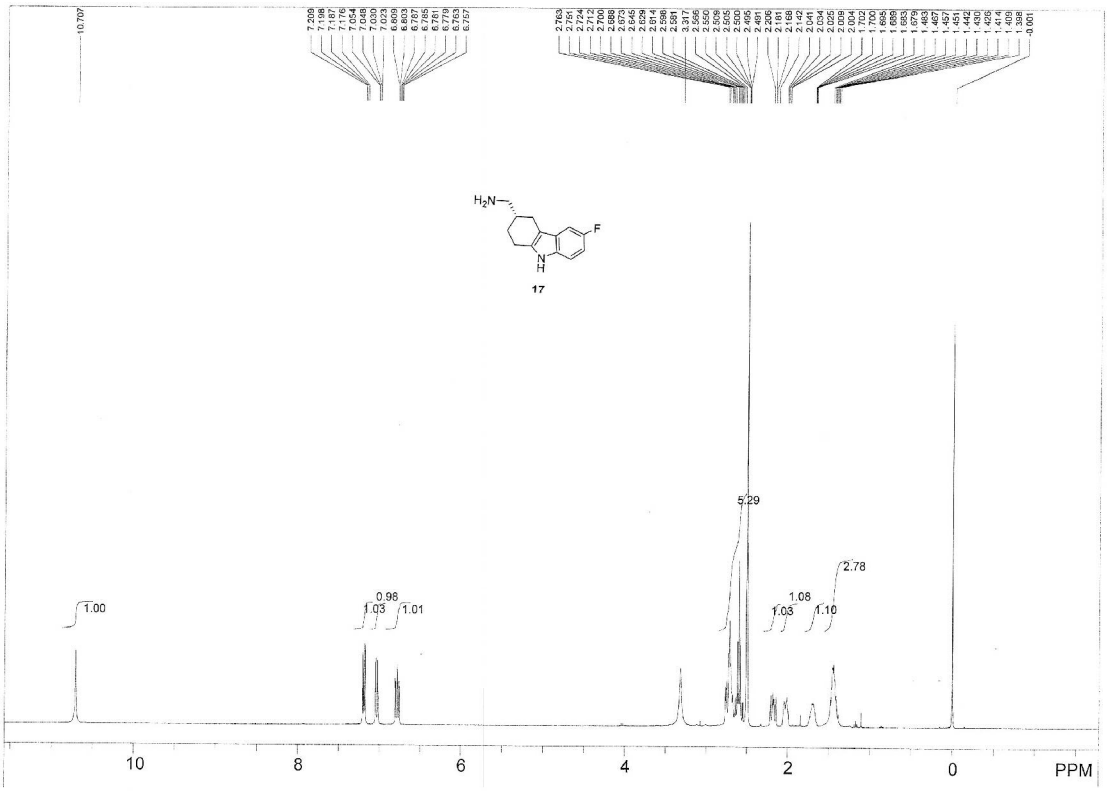
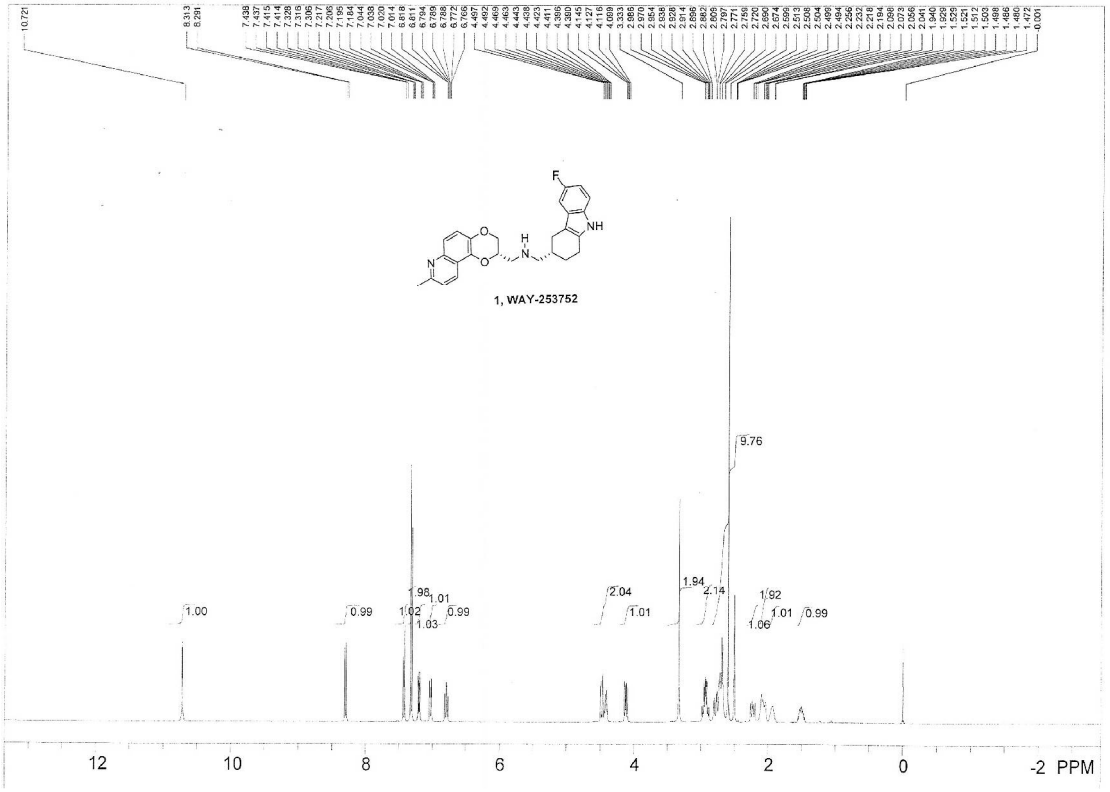
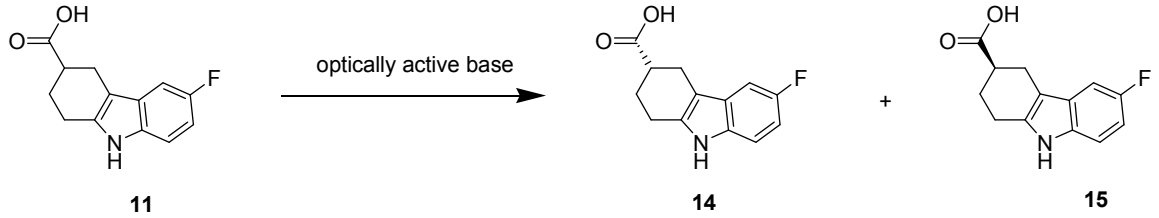
O
F
N
H
14
4.97
1.00
0.98
0.97
1.00
0.99
PPM


NH2
O
F
N
H
16
5.41
1.11
2.28
1.18
2.20
1.33
1.14
0.98
PPM


17
1.00
0.98
1.03
1.01
5.29
1.08
1.03
1.10
2.78
10
8
6
4
2
0
PPM


1, WAY-253752
1.00
0.99
1.02
1.98
1.01
1.03
0.99
2.04
1.01
1.94
2.14
9.76
1.92
1.01
1.06
0.99
12
10
8
6
4
2
0
-2 PPM

First resolution of the racemic acid 11

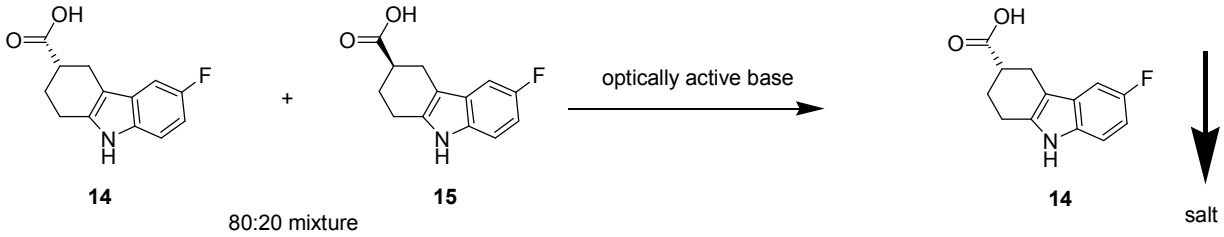


11 **14** **15**

0.1M Solutions of the racemic acid, 8, and the optically active bases in acetonitrile were made, mixed up in 1:1 ratio, and left in open vials.

Base	Results
(-)-ψ−ephedrine	No crystals
(+)-dehydroabietyl amine	Fast precipitation, amorphous
D-(+)-2-aminobutanol	No crystals
(-)-N-benzylphenetylamine	No crystals
(-)-Cinchonidine	Slow crystallization, **14/15** ratio 2:98 Mother liquor **14/15** ratio 80:20

Second resolution of the acid, enriched with the right enantiomer



14 80:20 mixture **15** **14**

Base	**Results**	**S:R ratio in the salt**
(+)-ephedrine	No crystals	
(-)-ephedrine	Crystals, forming slowly	80:20
(+)-norephedrine	No crystals	
(+)-pseudoephedrine	Crystals, forming slowly	98:2
(+)-naphthylethylamine	Crystals, forming very fast	80:20
(-)-naphthylethylamine	Crystals, forming very fast	80:20
(-)-methylbenzylamine	Crystals, forming slowly	80:20