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Articles

Structure−Activity Studies for a Novel Series of *N*-(Arylethyl)-*N*-(1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-*N*-methylamines Possessing Dual 5-HT Uptake Inhibiting and α_2-Antagonistic Activities

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In search of an α_2-antagonist/5-HT uptake inhibitor as a potential new class of antidepressant with a more rapid onset of action, compound **3** was prepared and observed to possess high affinity for the α_2-receptor (K_i = 6.71 nM) and the 5-HT uptake site (20.6 nM). A series of tertiary amine analogs of **3** were synthesized and assayed for their affinity at both the α_2-receptor and the 5-HT uptake site. The structure−activity relationship reveals that a variety of structural modifications to the arylethyl fragment are possible with retention of this dual activity. On the tetralin portion, 5-OMe substitution and the (*R*) stereochemistry at C-1 are optimal with alternate substitutions producing compounds retaining high affinity for the α_2-receptor but lacking affinity for the 5-HT uptake site. Data for several rigidified 5-*O*-alkyl analogs suggests that the favored orientation of the oxygen lone pairs may be away from the 6-position of the tetralin.

Introduction

The major pharmacological approach to the treatment of depression currently consists of the chronic administration of agents that interfere with the primary mechanisms of removal from the synapse of one or both of the neurotransmitters norepinephrine (NE) and serotonin (5-HT). Mechanistically, this occurs via inhibition of monoamine metabolism or neuronal reuptake.[1] It is theorized that the resultant therapeutic response is due to the facilitation of neurotransmission caused by the increased synaptic availability of NE and/or 5-HT, and the subsequent adaptive biochemical changes that take place at the receptor or postreceptor level.[1,2,4b] The period of several weeks typically required for the onset of antidepressant action with such agents has been attributed to a feedback inhibition, via presynaptic autoreceptors,[3,4] of further NE and/or 5-HT release caused by an acute rise in synaptic neurotransmitter concentrations following inhibition of metabolism or reuptake. This has given rise to the concept that blockade of these inhibitory receptors in conjunction with monoamine reuptake inhibition might bring about a more rapid onset of antidepressant action.[5,7,8]

The role of the α_2-autoreceptor in inhibiting the release of NE has been well documented,[6] and considerable evidence now exists implicating the desensitization of α_2-receptors as a key component in the onset of efficacy of certain antidepressants.[3,7−10] Indeed, the coadministration of α_2-antagonists with various antidepressants in animal studies has been shown to accelerate β-[5,7] and 5-HT_2-receptor[8] downregulation, biochemical changes suggestive of an early onset of action. The release of 5-HT, on the other hand, is inhibited not only by activation of presynaptic 5-HT_1-autoreceptors[4,11] but also α_2-heteroreceptors.[12] Moreover, the α_2-antagonists yohimbine and idazoxan have been shown to potentiate 5-HT release.[12c,13] However, contrary to the inhibitory effect of NE on 5-HT release,

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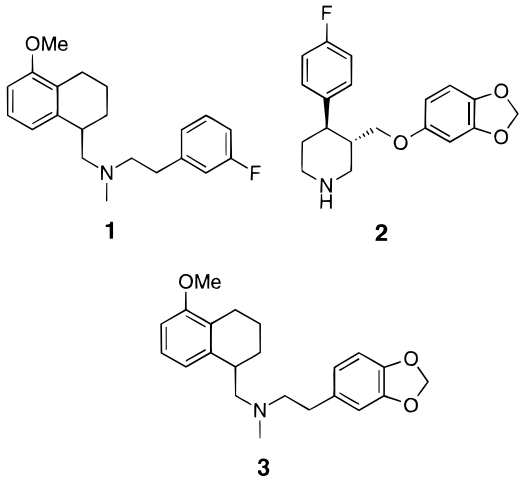


Figure 1.

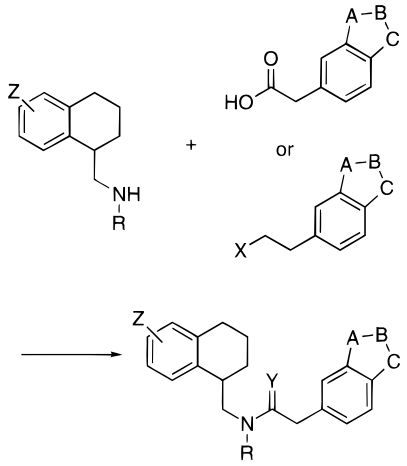
evidence suggests that hippocampal release of NE is actually stimulated by 5-HT.[14] Thus, 5-HT reuptake inhibition may, by acutely increasing 5-HT concentrations, activate not only 5-HT$_1$-autoreceptors but also α_2-heteroreceptors indirectly by enhancing NE release. Therefore, an agent with the dual profile of a 5-HT reuptake inhibitor and an α_2-antagonist[15] might serve to enhance synaptic concentrations of 5-HT relative to that achievable through 5-HT uptake inhibition alone and in turn produce a more effective antidepressant response.

Our search for a 5-HT uptake inhibitor/α_2-antagonist began with the phenethyl-1-(aminomethyl)tetralin (**1**, Figure 1), identified through screening as possessing high affinity for the α_2-receptor (K_i = 3.2 nM) with modest potency at inhibiting 5-HT uptake (IC_{50} = 160 nM). In an effort to enhance the potency of **1** at inhibition of 5-HT uptake, consideration was given to incorporating into **1** structural features common to other 5-HT uptake inhibitors from the literature. Indeed, the class of compounds potent at inhibiting 5-HT uptake encompasses a wide variety of structural types.[16] Inspection of molecular models, however, indicated that good overlap could be achieved between the nitrogen and the (methylenedioxy)phenyl of the potent uptake inhibitor paroxetine **2** and the nitrogen and fluorophenyl of **1**. Thus, preparation of the methylenedioxy analog of **1** resulted in compound **3**, which possessed 8-fold greater potency at inhibiting 5-HT uptake (IC_{50} = 21 nM) and nearly equivalent α_2 binding affinity (K_i = 6.7 nM). At this point, an extensive SAR investigation was initiated in an effort to explore in greater depth the structural requirements for this dual activity. This study has resulted in the development of a novel series of structural analogs of **3** possessing high affinity for the α_2-receptor that also potently inhibit 5-HT uptake. A preliminary account describing the in vitro pharmacological profile and putative antidepressant effects in vivo of one member of this series, **40** (A-80426), has recently appeared.[17]

Chemistry

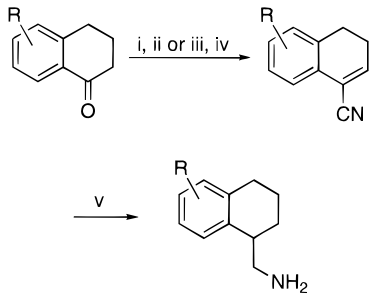
Structure−activity relationship (SAR) studies on the parent structure **3** entailed investigation of the aromatic tetralin substitution pattern and absolute stereochemistry at C-1, alkyl substitution of the basic nitrogen, and modification of the appended (methylenedioxy)phenethyl fragment. The tertiary amines described in this report were assembled by one of three different methods (Scheme 1). Method A consisted simply of alkylation of an [(*N*-methylamino)methyl]tetralin with the appropriate arylethylhalide or mesylate. In method B, an [(*N*-methylamino)methyl]tetralin was coupled to an arylacetic acid fragment and the amide reduced. An alternative method C entailed reaction of a primary (aminomethyl)tetralin (R = H) with an arylacetic acid fragment, followed by reduction and alkylation of the secondary amine.

Scheme 1. Methods A−C[a]



[a] Method A: R = Me; X = Cl, Br, OMs: i. Method B: R = Me: ii, iv. Method C: R = H: iii, iv, v. Conditions: (i) Li_2CO_3, MeCN, Δ; (ii) EDCI, HOBt, THF; (iii) $(COCl)_2$, CH_2Cl_2; (iv) BH_3, THF; (v) CH_2O, $NaCNBH_3$.

Scheme 2. Methods D−F[a]

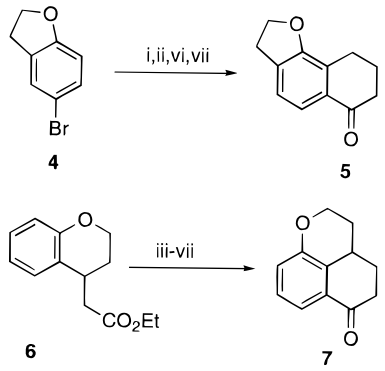


[a] Method D: i,ii. Method E: iii, i. v. Method F: v. Conditions: (i) TMSCN, ZnI_2; (ii) EtOH, HCl; (iii) DECNP, LiCN; (iv) *p*-TsOH, benzene; (v) H_2, RaNi.

1-(Aminomethyl)tetralin fragments were prepared from the corresponding tetralones by either trimethylsilyl cyanide (TMSCN) or diethyl cyanophosphonate (DECNP) addition, followed by elimination and reduction of the resulting dihydronaphthalene-1-carbonitrile (Scheme 2). The choice of cyanide equivalent was dictated by the propensity of the intermediate cyanohydrin to undergo elimination, with TMSCN being favored for tetralones possessing an electron-donating group para to the carbonyl, and DECNP being favored for all other cases. Two previously undescribed tetralones **5**, and **7**, were prepared via the elaboration of known precursors **4**[18] and **6**[19] to the appropriate carboxylic acids followed by Friedel−Crafts cyclization (Scheme 3).

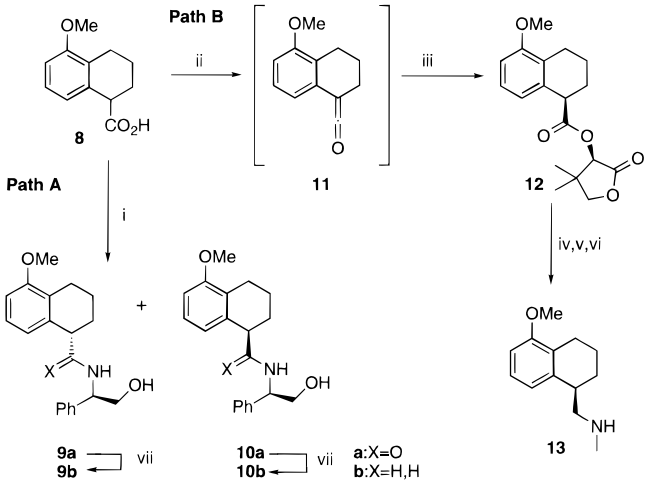
The separate enantiomers with respect to the C-1 position of the tetralin ring were obtained by reaction of racemic 5-OMe-tetralin-1-carboxylic acid **8** with (*R*)-

Scheme 3[a]



[a] Conditions: (i) $ClCO(CH_2)_2CO_2Et$, $AlCl_3$; (ii) H_2, 10% Pd/C; (iii) $LiAlH_4$; (iv) MsCl, Et_3N; (v) KCN, EtOH; (vi) KOH, EtOH/H_2O; (vii) PPA, 100 °C.

Scheme 4[a]

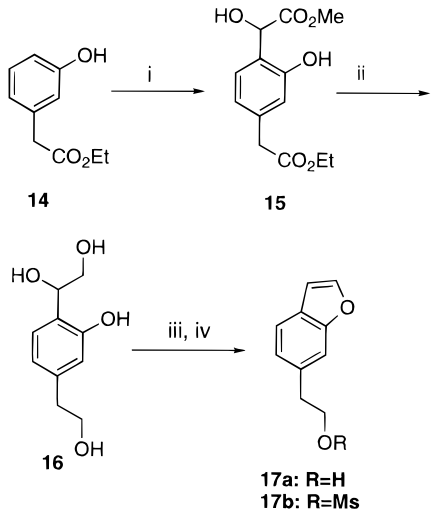


[a] Conditions: (i) $(COCl)_2$; (*R*)-phenylglycinol; (ii) $(COCl)_2$; Et-NMe_2; (iii) (*R*)-pantolactone; (iv) $LiAlH_4$; (v) MsCl, Et_3N; (vi) $MeNH_2$; (vii) BH_3, THF.

phenylglycinol (Scheme 4, path A) and chromatographic separation of the resultant diastereomeric amides **9a** and **10a**. The amides were reduced to the secondary amines **9b** and **10b**, and the absolute stereochemistry was determined by X-ray analysis of a crystal of the HCl salt of **10b**, the secondary amine possessing the (*R*) stereochemistry at the C-1 position. Removal of the chiral auxiliary by catalytic hydrogenation yielded the resolved primary amines. Once it was established that the required absolute stereochemistry at C-1 was (*R*), an enantioselective synthesis was developed (Scheme 4, path B). Racemic tetralin-1-carboxylic acid was converted to its acid chloride, and treatment of the acid chloride with dimethylethylamine provided the ketene **11** in situ. Addition of (*R*)-pantolactone[20] then resulted in a highly diastereoselective addition to yield exclusively (>95%) the (*R*,*R*) diastereomer **12**. Reduction of the resulting ester−lactone intermediate ($LiAlH_4$) followed by activation of the alcohol as its mesylate ester[21] and displacement with anhydrous methylamine yielded the resolved [(*N*-methylamino)methyl]tetralin intermediate **13** in excellent chemical yield and enantiomeric purity.

The arylacetic acids and arylethyl halides and mesylates used in this study were either known compounds or prepared using well-established methodologies. For one compound of particular interest from this study, **40**

Scheme 5[a]



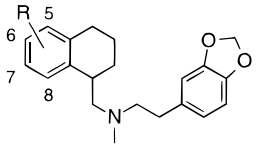
[a] Conditions: (i) $HCOCO_2Me$, $TiCl_4$; (ii) BH_3, THF; (iii) C_6H_5NHCl, $HO(CH_2)_2OH$, 120 °C; (iv) MsCl, Et_3N.

(A-80426), a new, efficient synthesis of the benzofuran ring was developed. The existing methodology of Barker,[22] involving cyclization of an (aryloxy)acetaldehyde acetal, was initially investigated; however, poor regioselectivity in the cyclization prompted us to develop improved methodology. Condensation of the ethyl ester of *m*-hydroxyphenylacetic acid **14** with methyl glyoxylate (Scheme 5) in the presence of titanium tetrachloride[23,24] at 0 °C provided regioselectively in 80% yield the desired 1,3,4-substituted hydroxy ester adduct **15**. Reduction with excess borane in tetrahydrofuran at reflux provided in 99% yield a triol intermediate **16** that upon heating in ethylene glycol at 120 °C with pyridine hydrochloride cyclized to the desired benzofuran alcohol **17a** in 40% yield,[25] which was then activated as the methanesulfonate **17b** for coupling.

Results and Discussion

The tertiary amine analogs of **3** were assayed for their affinity at the α_2-receptor as well as for the ability to inhibit 5-HT uptake in vitro. The SAR study reported herein is broken into three parts: (1) substitution on the tetralin ring; (2) modifications of the methylenedioxy portion of the (methylenedioxy)phenethyl fragment; and (3) nitrogen substitution. On the tetralin portion, methoxy substitution was investigated at positions 5−8, and the 5-position was further probed with a variety of substituents differing in size and hydrogen-bonding capacity. The results are summarized in Table 1. In general, deviation from the 5-methoxy substitution resulted in a loss of activity at inhibiting 5-HT uptake ranging from 5.5−69 fold, whereas α_2 binding was only moderately affected. Interestingly, the 8-methoxy analog **20** displayed slightly improved α_2 affinity with respect to **3**, however it was nearly 2 orders of magnitude less active at inhibiting 5-HT uptake. The data obtained on the hydrogen bond donating 5-hydroxy and 5-sulfonamido analogs **23** and **26** exemplify the importance of a Lewis basic functional group at this position for potent 5-HT uptake inhibition. Also, increasing the steric bulk at this position, as in the 5-ethoxy compound **24**, exerts an adverse affect on 5-HT uptake inhibition. The failure of the 5,6-dimethoxy analog **22** to demonstrate potent 5-HT uptake inhibition could be due to an

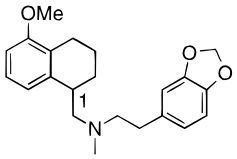
Table 1. SAR of Aromatic Tetralin Ring



no.	R	α-2 binding affinity K_i (nM)[a] (95% confidence limits)	5-HT uptake inhibition IC_{50} (nM)[a] (95% confidence limits)
3	5-OMe	6.71 (3.05, 14.7)	20.6 (10.4, 41.0)
18	6-OMe	23.5[b]	469[c]
19	7-OMe	57.5 (35.5, 93.0)	1420[c]
20	8-OMe	2.88 (0.786, 10.6)	1430[c]
21	H	8.19 (3.99, 16.8)	1090[c]
22	5,6-di OMe (*R*)	15.5[c]	757[c]
23	5-OH	7.54 (2.59, 22.0)	1240 (212, 7250)
24	5-OEt (*R*)	1.86 (0.907, 3.81)	198 (57.6, 681)
25	5-SMe	21.0[c]	117[c]
26	5-$NHSO_{2Me}$	19.0 (0.424, 7.31)	658[c]
2	paroxetine	6310 (3850, 10300)	6.43 (2.29, 18.0)
	rauwolscine	2.89 (2.10, 3.98)	>10,000[c]
	napamezole	4.17 (1.59, 11.0)	887 (454, 1730)

[a] Number of determinations ≥ 3. [b] Number of determinations = 2. [c] Number of determinations = 1.

Table 2. SAR of C-1 Stereochemistry



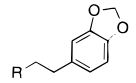
no.	C-1 stereochemistry	α-2 binding affinity K_i (nM)[a] (95% confidence limits)	5-HT uptake inhibition IC_{50} (nM)[a] (95% confidence limits)
3	racemic	6.71 (3.05, 14.7)	20.6 (10.4, 41.0)
27	(*R*)	1.70 (0.333, 8.63)	12.7 (2.52, 64.3)
28	(*S*) (49.7, 158)	88.6 (410, 4170)	1310

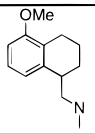
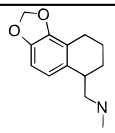
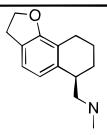
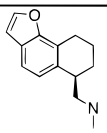
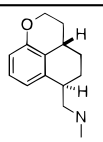
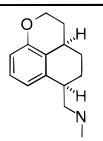
[a] Number of determinations ≥ 3.

unfavorable influence of the 6-methoxy group on the orientation of the adjacent 5-methoxy substituent (vide infra) and vice versa since 6-methoxy substitution is not detrimental to activity when compared with the unsubstituted compound **21**. From these results, 5-methoxy substitution clearly provided the optimal combination of activities on the tetralin portion. Evaluation of the stereochemistry at C-1 of the tetralin for **3** (Table 2) indicates that the majority of the activities at the α_2-receptor and the 5-HT uptake site resides in the (*R*) enantiomer **27**.

In order to examine the potential importance of the binding orientation of the oxygen lone pairs of **3**, several rigidified 5-alkoxytetralins were prepared (Table 3). The dihydrobenzofuran analog **30**, where the alkyl group is

Table 3. SAR of Rotationally Locked 5-Alkoxytetralins



no.	R	α-2 binding affinity Ki(nM)[a] (95% confidence limits)	5-HT Uptake Inhibition IC_{50}(nM)[a] (95% confidence limits)
3		6.71 (3.05, 14.7)	20.6 (10.4, 41.0)
29		11.0[b] (8.64, 14.1)	60.3[b]
30		5.57 (3.28, 9.48)	26.7 (9.40, 75.9)
31		4.88 (1.18, 20.1)	101[b]
32		94.1 (89.1, 99.3)	436 (129, 1480)
33		113 (50.2, 254)	862[c]

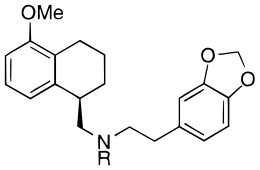
[a] Number of determinations ≥ 3. [b] Number of determinations = 2. [c] Number of determinations = 1.

tethered back onto the 6-position of the tetralin, had activity comparable to that of the more potent enantiomer **27**. The corresponding benzofuran **31** was significantly weaker at 5-HT uptake inhibition, indicative of the importance of the Lewis basicity of the oxygen. The methylenedioxy analog **29** displayed activity equivalent to that of **30**, bearing in mind that **29** was tested as a racemate. In contrast to these findings, it is interesting to note that the two compounds having the tether to the 4-position, **32** and **33**, were well over an order of magnitude less potent at both the α_2-receptor and the 5-HT uptake site. These results suggest that the oxygen lone pairs of the 5-methoxy may be oriented away from the 6-position in binding to both of these sites.

A brief examination into the importance of the *N*-alkyl group was undertaken (Table 4). Although replacement of methyl with ethyl led to only a slight drop in α_2 affinity, 5-HT uptake inhibition was at least 10-fold weaker. Larger groups such as cyclopropyl, methylenecyclopropyl, and propargyl were dramatically weaker even at the α_2 site and hence were not evaluated for 5-HT uptake inhibition. The presence of a tertiary amine, however, appears essential as the corresponding secondary amine **34** displayed poor activity in both assays.

Modifications of the phenethyl appendage consisted primarily of replacement of the methylenedioxy ring with other heterocycles containing one or two hetero-

Table 4. SAR of Nitrogen Substitution



no.	R	α-2 binding affinity K_i (nM)[a] (95% confidence limits)	5-HT uptake inhibition IC_{50} (nM)[a] (95% confidence limits)
27	Me	1.70 (0.333, 8.63)	12.7 (2.52, 64.3)
34	H[b]	88.2[c]	414[d]
35	Et[b]	5.73[c]	158[d]
36	cyclopropyl	266[d]	NA
37	methylene cyclopropyl	54.3[d]	NA
38	propargyl	184[d]	NA

[a] Number of determinations ≥ 3. [b] Racemate. [c] Number of determinations = 2. [d] Number of determinations = 1.

atoms in various positions (Tables 5−7). The point of attachment of the connecting ethyl chain to the phenyl ring was held constant. In contrast to the sensitivity of 5-HT uptake inhibitory activity to substitution changes on the tetralin portion, modifications of both the position and nature of the heteroatom were well tolerated. Nitrogen, oxygen, and sulfur atoms were generally interchangeable with only minor perturbations in activity. Indeed, even the indan **44** (Table 5) lacking a heteroatom was quite active at 5-HT uptake inhibition. Typically, the range in activity at 5-HT uptake inhibition spanned from approximately 2-fold more potent than **27** for **54** and **60** to around 5-fold less active for a variety of analogs of differing structure. Likewise, with just a few exceptions nearly all compounds in this series possessed high affinity for the α_2-receptor, in the nanomolar range. Some interesting exceptions to these observations, however, did manifest themselves. The isobenzofuran **43**, for example, was nearly 20-fold less active at 5-HT uptake inhibition than either of the isomeric dihydrobenzofurans **39** and **41**. Also, the related analogs **49**, **53**, and **54** with other atoms at this position showed high affinity for the 5-HT uptake site. Also noteworthy was the marked inactivity at the 5-HT site of the two isomeric indoline trifluoromethanesulfonamides **52** and **58**. These compounds were substantially weaker than the unsubstituted indolines **50** and **56** or methanesulfonamide derivatives **51** and **57**. All three trifluoromethanesulfonamides displayed poor affinity for the α_2-receptor, ranging between 25 and 35 times less potent than the corresponding methanesulfonamides.

Structure−activity studies on this series are best summarized by division of the generic structure into a left-hand (aminomethyl)tetralin fragment and a right-hand arylethyl appendage. The left-hand substructure is not at all tolerant of structural manipulation. 5-OMe substitution is optimal, and only very modest changes are at all tolerated. (*R*) stereochemistry at the one stereocenter is required for both of the described activities. *N*-Methyl substitution of the basic amine is required. By contrast, a significant degree of structural modification is permitted on the pendant arylethyl substructure. A large variety of fused heterocycles are well tolerated. The presence of heteroatoms is not an absolute requirement; the indan derivative **44** retains good affinity for both the 5-HT uptake site and the α_2 binding site. The structural diversity tolerated in this portion of the molecule allows for potential adjustment of physiochemical parameters such as lipophilicity, aqueous solubility, and the like; which in turn allows for optimization of pharmaceutical properties such as oral absorption and metabolic stability. Optimization of these parameters resulted in the selection of **40** (A-80426) for more in-depth pharmacological evaluation, the results of which have been presented elsewhere.[26,27]

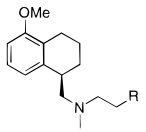
Experimental Section

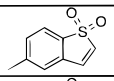
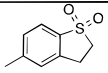
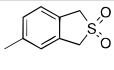
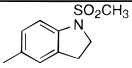
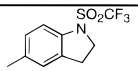
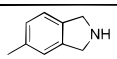
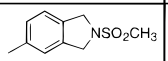
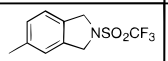
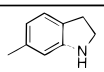
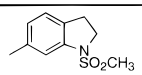
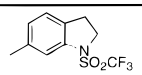
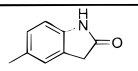
Chemistry. Proton NMR spectra were obtained on a General Electric QE 300 or QZ 300 MHz instrument with chemical shifts (δ) reported relative to tetramethylsilane as internal standard. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed either by Oneida Research Services, Robertson Microlit Laboratories, or the Analytical Department at Abbott Laboratories. Column chromatography was carried out on silica gel 60 (230−400 mesh). Thin-layer chromatography (TLC) was performed using 250 μm silica gel 60 glass-backed plates with F_{254} as indicator. HPLC separations were done using a Waters Associates Prep LC/System 500 liquid chromatograph. Optical rotations were measured with a Perkin-Elmer 541 polarimeter. X-ray crystal structures were obtained on a Rigaku AFC5R diffractometer. All physical data and yields for final compounds correspond to the indicated salt form unless otherwise noted.

Method A. *N*-[2-(Benzofuran-6-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate (40, A-80426). Benzofuran-6-ethanol methanesulfonate ester (1.20 g, 5.0 mmol) and *N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine (for preparation, see method G) (1.03 g, 5.0 mmol) were combined in CH_3CN (10 mL) with Li_2CO_3 (0.554 g, 7.5 mmol), and the reaction was heated to reflux for 48 h. The reaction was quenched in H_2O and extracted with Et_2O (2 × 100 mL). The organic phase was washed with water and brine and dried (K_2CO_3). The solvent was evaporated, and the resulting oily product was dissolved in EtOAc and treated with 1.1 equiv of $MeSO_3H$. The product was collected and dried to yield 1.70 g of **40** (76%): mp 191−193 °C; ^{1}H NMR ($CDCl_3$) of the free base δ 1.6−2.0 (m, 4H), 2.4 (s, 3H), 2.3−3.0 (m, 9H), 3.81 (s, 3H), 6.67 (d, 1H), 6.72 (dd, 1H), 6.80 (d, 1H), 7.09 (m, 2H), 7.36 (s, 1H), 7.49 (d, 1H), 7.57 (d, 1H). Anal. ($C_{24}H_{31}NO_5S$) C, H, N.

Benzofuran-6-ethanol Methanesulfonate Ester (17b). 3-Hydroxyphenylacetic acid (347 g, 2.28 mol) was esterified by heating to reflux in EtOH (1.2 L) with concentrated H_2SO_4 (10 mL) for 5 h. The crude product was distilled at 160 °C (1 mm) to yield 391.7 g (95%) of 3-hydroxyphenylacetic acid ethyl ester as a clear oil. To a mixture of 3-hydroxyphenylacetic acid ethyl ester (225 g, 1.25 mol) and methyl glyoxalate (160 g) in CH_2Cl_2 (2 L) at 0 °C was added with vigorous stirring a solution of $TiCl_4$ (142 mL, 1.29 mol) in CH_2Cl_2 (800 mL). After 4 h at 0 °C the reaction was quenched by the addition of ice (800 mL) to the flask followed by stirring for 30 min. The layers were then separated, and the organic layer was dried ($MgSO_4$) and filtered through a short plug of silica gel, eluting first with CH_2Cl_2 and then EtOAc. The EtOAc fraction was washed through a fresh plug of silica gel and the solvent evaporated to yield 265 g of **15** (80%) as a light clear oil. A solution of 1.0 M BH_3·THF (2.66 L) was heated to reflux, the heat source was removed, and compound **15** (254 g, 0.95 mol) in THF (350 mL) was added at such a rate as to maintain a gentle reflux (1.5 h). After the addition was complete, the reaction was continued at reflux for 2.5 h, cooled in an ice bath, and quenched by slow addition of MeOH (1 L). The solvent was evaporated to yield 188 g of **16** (99%) as a colorless thick oil. A solution of compound **16** (104 g) in ethylene glycol (800 mL) was heated to 120 °C and treated with pyridine hydro-

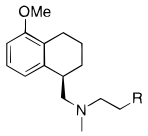
Table 5. SAR of Arylethyl Side Chain

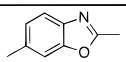
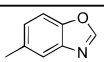
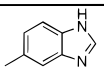
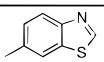
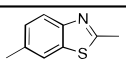
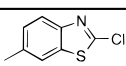
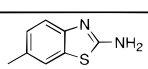
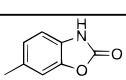
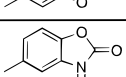
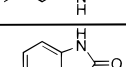


no.	R	α-2 binding affinity Ki(nM)[a] (95% confidence limits)	5-HT Uptake Inhibition IC_{50}(nM)[a] (95% confidence limits)
27		1.70 (0.333, 8.63)	12.7 (2.52, 64.3)
39		1.88 (0.413, 14.1)	18.1 (9.69, 33.8)
40		2.01 (1.07, 3.78)	13.1 (8.10, 21.1)
41		1.76 (0.424, 7.31)	14.6 (11.9, 18.0)
42		2.78 (1.56, 4.97)	17.6 (8.06, 38.5)
43		2.64 (0.815, 8.55)	229 (38.0, 1370)
44		8.99 (4.02, 20.1)	20.5 (4.70, 89.1)
45		2.65 (0.550, 12.8)	24.3 (11.1, 53.3)
46		17.9 (11.0, 29.0)	52.8 (20.9, 133)
47		4.82 (3.78, 6.14)	51.0 (25.1, 104)
48		4.67 (1.10, 19.9)	33.7 (1.65, 689)
49		1.78 (1.15, 2.77)	6.67 (1.78, 25.0)
50		3.42 (1.45, 8.08)	31.8 (15.8, 63.8)
51		4.62 (0.830, 25.7)	35.0 (13.1, 93.7)
52		158 (115, 218)	132 (102, 170)
53		5.99 (2.98, 12.0)	11.6 (3.40, 39.8)
54		5.33 (1.42, 20.0)	5.81 (1.34, 25.3)
55		142 (103, 196)	59.8 (57.2, 62.6)
56		11.7 (7.32, 18.7)	79.1 (29.8, 210)
57		5.35 (2.06, 13.9)	38.9 (8.60, 176)
58		125 (72.6, 213)	183 (10.7, 3110)
59		4.91 (1.51, 16.0)	22.2 (4.90, 100)

[a] Number of determinations ≥ 3.

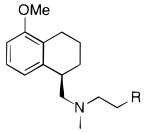
Table 6. SAR of Arylethyl Side Chain

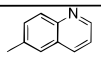


no.	R	α-2 binding affinity Ki(nM)[a] (95% confidence limits)	5-HT Uptake Inhibition IC_{50}(nM)[a] (95% confidence limits)
27		1.70 (0.333, 8.63)	12.7 (2.52, 64.3)
60		1.22 (0.401, 3.73)	5.25 (0.913, 30.2)
61		9.27[b]	42.8 (14.3, 128)
62		1.77 (0.694, 4.51)	16.7 (8.59, 32.4)
63		5.21 (0.979, 27.7)	11.3 (6.70, 19.1)
64		2.73 (1.31, 5.69)	8.94[b] (3.51, 22.8)
65		2.12[b] (0.792, 5.66)	86.7[b] (18.6, 405)
66		5.45 (1.09, 27.3)	38.2 (13.5, 108)
67		5.67 (1.43, 22.5)	9.47 (2.52, 35.6)
68		4.51 (1.75, 11.7)	19.4 (9.52, 39.4)
69		7.50 (1.52, 37.0)	68.3 (34.9, 134)
70		10.8 (8.71, 13.4)	16.3 (9.37, 28.4)

[a] Number of determinations ≥ 3. [b] Number of determinations = 2.

Table 7. SAR of Arylethyl Side Chain



no.	R	α-2 binding affinity Ki(nM)[a] (95% confidence limits)	5-HT Uptake Inhibition IC_{50}(nM)[a] (95% confidence limits)
71		6.79 (2.27, 20.3)	18.1 (10.1, 32.4)
72		6.07[b] (2.77, 13.3)	53.9[b] (5.23, 556)
73		3.91 (2.06, 7.40)	46.7 (15.9, 137)
74		1.81 (0.227, 14.4)	44.4 (14.3, 138)

[a] Number of determinations ≥ 3. [b] Number of determinations = 2.

chloride (80 g), and the solution was heated to reflux for 30 min. The reaction was cooled, quenched on ice, and extracted with ether (4 × 450 mL). The extracts were washed with 1 N

HCl, 1 N NaOH, and brine, dried ($MgSO_4$), filtered, and evaporated to yield 37.9 g of an oil that was distilled at 105−110 °C (0.5 mm) to give 34.5 g of **17a** (40%) as a colorless oil. To a solution of **17a** (6.74 g, 41.5 mmol) in CH_2Cl_2 (40 mL) with NEt_3 (6.37 mL, 45.7 mmol) at 0 °C was added a solution of MsCl (3.38 mL, 43.6 mmol) in CH_2Cl_2 (10 mL), and the reaction was stirred for 2 h at 0 °C to provide upon workup 10.0 g of **17b** (100%) as a colorless oil.

Method B. *N*-[2-[3,4-(Methylenedioxy)phenyl]ethyl]-*N*-(1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-*N*-methylamine Methanesulfonate (21). Step 1. *N*-(1,2,3,4-Tetrahydronaphthalen-1-ylmethyl)-*N*-methylamine hydrochloride (prepared by methods D and F) (2.10 g, 10 mmol), 3,4-(methylenedioxy)phenylacetic acid (2.0 g, 11 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.30 g, 12 mmol), and 1-hydroxybenzotriazole (2.97 g, 22 mmol) were combined in THF (30 mL) and stirred at room temperature for 18 h. The reaction was quenched in water, extracted with EtOAc (2 × 50 mL), washed successively with 10% aqueous HCl, 5% $NaHCO_3$, brine, and dried ($MgSO_4$), and evaporated to dryness to yield 3.2 g (95%) of the intermediate amide. **Step 2**. The amide was treated with 1.0 M BH_3·THF (38 mL) in THF (30 mL) at reflux for 5 h. The reaction was quenched by addition of MeOH, evaporated to dryness, and then treated at reflux for 1 h with MeOH (30 mL) and iPrOH saturated with anhydrous HCl (15 mL). After evaporation, basification, and extraction, the free base was converted to its methanesulfonate salt and recrystallized from Et_2O and EtOH to yield 1.89 g of **21**: mp 140−1 °C; ^{1}H NMR (DMSO-d_6) δ 1.6−1.9 (m, 4H), 2.28 (s, 3H), 2.6−3.4 (m, 9H), 5.95 (s, 2H), 6.7−7.3 (m, 7H), 9.0 (br s, 1H). Anal. ($C_{22}H_{29}NO_5S$) C, H, N.

Method C. *N*-[2-[3,4-(Methylenedioxy)phenyl]ethyl]-*N*-[(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-methyl]amine Hydrochloride (34). Step 1. Oxalyl chloride (1.3 mL, 15 mmol) was added to a solution of 3,4-(methylenedioxy)phenylacetic acid (1.80 g, 10 mmol) in 40 mL of CH_2Cl_2 and 3 drops of DMF. After 45 min at 25 °C, the solvent was evaporated. The resulting acid chloride was added to a solution of *N*-[(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]amine hydrochloride (prepared by methods E and F) (2.28 g, 10 mmol) in 40 mL of CH_2Cl_2 and 4.18 mL of NEt_3. After 2 h, the reaction was quenched in 100 mL 5% aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated to dryness to provide the intermediate amide. **Step 2.** The amide was dissolved in 20 mL of THF and 22 mL of 1.0 M BH_3·THF was added. The reaction was refluxed for 4 h, cooled to room temperature, and quenched by the addition of 5 mL of MeOH. The solvent was evaporated, and the residue was dissolved in 20 mL of MeOH and 10 mL of saturated iPrOH/HCl. The reaction was refluxed for 30 min and then evaporated to dryness. The product was recrystallized from EtOH to yield 2.60 g of **34**: mp 178−80 °C; ^{1}H NMR (DMSO-d_6) δ 1.6−1.9 (m, 4H), 2.34 (s, 3H), 2.4−3.6 (m, 7H), 3.88 (s, 3H), 3.9−4.1 (m, 2H), 5.99 (s, 2H), 6.73 (dd, 1H), 6.78−6.92 (m, 4H), 7.17 (t, 1H), 8.4 (br s, 2H). Anal. ($C_{22}H_{29}NO_6S\cdot{}^1/_2H_2O$) C, H, N. **Step 3. *N*-[2-[3,4-(Methylenedioxy)phenyl]-ethyl]-*N*-[(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-methyl]-*N*-methylamine Methanesulfonate (3).** The secondary amine **34** (as the hydrochloride salt) (0.940 g, 2.50 mmol) was dissolved in MeOH (25 mL) and 37% aqueous formaldehyde (6.9 mL). To the above solution was added 1.2 g of $NaCNBH_3$, and the reaction was stirred at 25 °C for 2 h. The reaction was quenched in 5% aqueous $NaHCO_3$ solution (100 mL), extracted with ether, dried (K_2CO_3), and evaporated to dryness. The resulting oil was converted to its methanesulfonic acid salt, and the product recrystallized from EtOH and Et_2O to yield 0.830 g of **3**: mp 159−61 °C; ^{1}H NMR ($CDCl_3$) δ 1.7−2.2 (m, 4H), 2.5−3.5 (m, 9H), 2.85 (s, 3H), 3.00 (d, 3H), 3.82 (s, 3H), 5.94 (s, 2H), 6.7 (m, 5H), 7.15 (t, 1H), 10.9 (br s, 1H). Anal. ($C_{23}H_{31}NO_6S$) C, H, N.

Method D. The trimethylsilyl cyanide additions were conducted as previously described.[28]

Method E. 5-Methoxy-3,4-dihydronaphthalene-1-carbonitrile. To a solution of 5-methoxy-1-tetralone (8.80g, 50 mmol) in anhydrous THF (50 mL) at 5 °C was added first LiCN (0.50 g, 6.6 mmol) and then diethyl cyanophosphonate (9.1 mL, 60 mmol) over 10 min and the reaction allowed to proceed for 45 min at 5 °C. After workup and isolation, the resultant cyanohydrin was heated in benzene (100 mL) to reflux with *p*-TsOH (0.50 g, 2.6 mmol) for 2 h to give 7.81 g (84%) of the title compound.

Method F. *N*-[(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]amine Hydrochloride. 5-Methoxy-3,4-dihydronaphthalene-1-carbonitrile (16.7 g) was reduced under 4 atm of H_2 with RaNi (34 g) in MeOH (225 mL) with NH_3 (25 mL) at room temperature. Solvents were evaporated, and the crude product was converted to the hydrochloride salt to provide 7.15 g of the title compound.

Resolution Methods: Step 1. (1*S*)- and (1*R*)-5-Methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic (*R*)-(−)-Phenylglycinol Amides (9a and 10a). 5-Methoxytetralin-1-carboxylic acid (1.03 g, 5.00 mmol) was dissolved in CH_2Cl_2 (50 mL), and oxalyl chloride (0.65 mL) and DMF (2 drops) were added. After 1 h at reflux, solvent and excess reagent were evaporated. The resulting acid chloride was added to a solution of (*R*)-(−)-2-phenylglycinol (0.823 g, 6.00 mmol) and 1.4 mL of NEt_3 in CH_2Cl_2 (50 mL). After 1 h, the reaction was quenched in dilute HCl, extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated to dryness. The resulting solid was purified by chromatography over silica gel to yield 0.70 g of (1*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic (*R*)-(−)-phenylglycinol amide (**10a**): mp 179−80 °C; ^{1}H NMR ($CDCl_3$) δ 1.75−2.0 (m, 3H), 2.3 (m, 1H), 2.39 (dd, 1H), 2.6 (m, 1H), 2.80 (dt, 1H), 3.70 (t, 1H), 3.79 (m, 2H), 3.84 (s, 3H), 5.1 (m, 1H), 6.05 (m, 1H), 6.75 (d, 1H), 6.77 (d, 1H), 7.13 (m, 3H), 7.3 (m, 3H). Further elution yielded 0.65 g of (1*S*)-5-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic (*R*)-(−)-phenylglycinol amide (**9a**): mp 181−3°C; NMR ($CDCl_3$) δ 1.6−2.0 (m, 3H), 2.3 (m, 1H), 2.57 (t, 1H), 2.6 (m, 1H), 2.76 (dt, 1H), 3.73 (t, 1H), 3.7 (m, 2H), 3.83 (s, 3H), 5.07 (m, 1H), 6.08 (m, 1H), 6.76 (d, 1H), 6.81 (d, 1H), 7.13 (m, 3H), 7.3 (m, 3H). **Step 2. [(*R*)-2-Phenyl-2-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]amino]ethanol Hydrochloride (10b).** The (*R*,*R*) product **10a** (7.18 g, 22 mmol) was dissolved in 100 mL of THF, 110 mL of 1.0 M BH_3·THF was added, and the reaction was refluxed for 3.5 h. MeOH (50 mL) was then added and the solvent evaporated. The residual product was dissolved in methanol (50 mL) and iPrOH saturated with HCl(g) (25 mL) and refluxed for 30 min. Solvent was evaporated to yield 5.96 g of the desired product **10b** as a white solid: mp 157−8 °C; ^{1}H NMR ($CDCl_3$) δ 1.4 (m, 1H), 1.76 (m, 1H), 2.25 (m, 1H), 2.4 (m, 1H), 2.62 (m, 1H), 2.97 (m, 1H), 3.1 (m, 1H), 3.52 (m, 1H), 3.75 (s, 3H), 4.08 (m, 1H), 4.5 (m, 2H), 5.62 (m, 1H), 6.62 (d, 1H), 6.73 (d, 1H), 7.03 (t, 1H), 7.43 (m, 3H), 7.7 (m, 2H), 9.5 (br s, 1H), 9.7 (br s, 1H).

[(*R*)-2-Phenyl-2-[((*S*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]amino]ethanol Hydrochloride (9b). The (*S*,*R*) product **9a** (4.6 g, 14 mmol) was treated as described in the preceding example to yield 4.0 g of **9b** as a white solid: mp 190−1 °C; ^{1}H NMR ($CDCl_3$) δ 1.6−2.0 (m, 3H), 2.25 (m, 1H), 2.43 (m, 1H), 2.7 (m, 1H), 3.07 (m, 1H), 3.5 (m, 1H), 3.77 (s, 3H), 4.02 (m, 1H), 4.4 (m, 2H), 5.5 (m, 1H), 6.62 (d, 1H), 6.63 (d, 1H), 7.03 (t, 1H), 7.43 (m, 3H), 7.68 (m, 2H), 9.1 (m, 1H), 10.1 (m, 1H).

[(*R*)-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-methyl]amine Hydrochloride (10c). The amine **10b** (3.22 g, 9.3 mmol) was dissolved in MeOH (100 mL) and treated with H_2 in the presence of Pd/C at 25 °C for 24 h. The reaction was filtered and evaporated to yield 1.65 g of the title compound **10c** as a white solid: mp 266−7 °C; ^{1}H NMR (DMSO-d_6) δ 1.6−1.9 (m, 4H), 2.45 (m, 1H), 2.62 (dt, 1H), 2.92 (dd, 1H), 3.04 (m, 2H), 3.77 (s, 3H), 6.80 (d, 1H), 6.86 (d, 1H), 7.13 (t, 1H), 8.07 (br s, 3H); $[\alpha]^{25}_D = +26.7°$.

[(*S*)-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-methyl]amine Hydrochloride (9c). The amine **9b** (3.89 g, 11.2 mmol) was dissolved in MeOH (100 mL), treated with H_2 in the presence of Pd/C at 25 °C for 24 h, filtered, and evaporated to dryness to yield 2.39 g of the title compound **9c** as a white solid, mp 267−9 °C; ^{1}H NMR (DMSO-d_6) δ 1.6−1.9 (m, 4H), 2.45 (m, 1H), 2.62 (dt, 1H), 2.92 (dd, 1H), 3.04 (m, 2H), 3.77 (s, 3H), 6.80 (d, 1H), 6.86 (d, 1H), 7.13 (t, 1H), 8.07 (br s, 3H); $[\alpha]^{25}_D = -25.6°$.

Method G, Step 1: (*R*)-5-Methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic Acid (*R*)-Dihydro-3-hydroxy-4,4-dimethyl-2(3*H*)-furanone Ester (12). 3,4-Dihydro-5-methoxynaphthalene-1-carbonitrile (prepared by method E) (54.8 g) was reduced with $NaBH_4$ (22.4 g) in EtOH (600 mL) at reflux for 1 h. After cooling, the reaction was poured onto ice/HCl and extracted with CH_2Cl_2 (3×), and the organics were washed with brine, dried ($MgSO_4$), and evaporated to give 56 g of the saturated nitrile (99%). This nitrile was heated to reflux for 20 h in 45% KOH (275 mL) and ethylene glycol (225 mL), cooled, poured onto ice/HCl, and extracted with CH_2Cl_2. The organics were washed with brine and dried ($MgSO_4$), and solvents were evaporated to give 5-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (48 g, 78%). This acid (46.31 g, 224.6 mmol) was dissolved in toluene (1 L), and to the solution was added oxalyl chloride (21.6 mL, 247 mmol) and DMF (0.5 mL). After 1.5 h at 50 °C, the solution was cooled to 10 °C and dimethylethylamine (73 mL, 674 mmol) was added. The reaction was stirred at ambient temperature for 3 h and then cooled to −70 °C. (*R*)-Dihydro-3-hydroxy-4,4-dimethyl-2(3*H*)-furanone (35.1 g, 269.5 mmol) was added, and the reaction was stirred for 2 h, warming slowly to −30 °C. The reaction was then poured into water and extracted with Et_2O. The combined organic extracts were washed with 5% $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated to dryness under reduced pressure. Trituration with 1:1 Et_2O/hexane yielded 61.68 g (86%) of **12** as a white solid: mp 74−77 °C; ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 3H), 1.17 (s, 3H), 1.7−2.2 (m, 4H), 2.7 (m, 2H), 3.80 (s, 3H), 3.98 (t, 1H), 4.01 (s, 2H), 4.40 (s, 1H), 6.72 (d, 1H), 6.83 (d, 1H), 7.12 (t, 1H). **Step 2. *N*-[((*R*)-5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Hydrochloride (13).** To $LiAlH_4$ (14.7 g, 387.2 mmol) suspended in THF (400 mL) was added 61.65 g (196.6 mmol) of furanone ester **12** dissolved in THF (200 mL) over 30 min. After an additional 1 h, the reaction was quenched using the Fieser workup conditions, filtered through Celite, and evaporated to dryness to yield 36.98 g (98%) of alcohol as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.54 (bs, 1H), 1.7−2.0 (m, 4H), 2.5−2.7 (m, 2H), 2.97 (m, 1H), 3.80 (d, 2H), 3.81 (s, 3H), 6.70 (d, 1H), 6.86 (d, 1H), 7.12 (t, 1H). The above alcohol (36.98 g, 192.3 mmol) was dissolved in CH_2Cl_2 (600 mL) and NEt_3 (53.6 mL, 385 mmol). The solution was cooled to 0 °C, and MsCl (17.85 mL, 230.7 mmol) was added over 15 min. After 1 h at 0 °C, the reaction was poured into water and extracted with CH_2Cl_2. The combined organic extracts were washed with 5% $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated to dryness to yield 49.05 g (94%) of the title compound as a light yellow solid: mp 55−56 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.7−2.0 (m, 4H), 2.56 (m, 1H), 2.75 (dt, 1H), 2.98 (s, 3H), 3.22 (m, 1H), 3.81 (s, 3H), 4.28 (t, 1H), 4.40 (dd, 1H), 6.71 (d, 1H), 6.81 (d, 1H), 7.12 (t, 1H). The mesylate (49.0 g, 181 mmol) was dissolved in anhydrous methylamine (125 mL) and allowed to stand in a tightly stoppered container at 25 °C for 48 h. The vessel was cooled on ice, and the stopper was removed. The reaction was warmed to ambient temperature, and excess methylamine was allowed to evaporate. The product was suspended in 2 N NaOH and extracted with Et_2O (2 × 150 mL). The ethereal solution was extracted with 10% HCl (2 × 100 mL), and the aqueous extracts were then basified to pH 12 with aqueous NaOH. The aqueous suspension was extracted with CH_2Cl_2 (2 × 100 mL), and the organic phase was dried over K_2CO_3 and evaporated to yield 34.5 g of a colorless oil (93%). The oil was dissolved in Et_2O (500 mL) and treated with a saturated solution of anhydrous HCl in EtOH. The resulting white solid was collected and recrystallized from ethanol to yield 38.0 g of **13**: mp 214−215 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.65−1.9 (m, 4H), 2.4−2.7 (m, 2H), 2.59 (s, 3H), 3.0−3.3 (m, 3H), 3.76 (s, 3H), 6.81 (d, 1H), 6.87 (d, 1H), 7.14 (t, 1H), 8.7 (bs, 2H).

***N*-[(6-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenyl]ethyl]-amine Methanesulfonate (18).** [(6-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]amine hydrochloride (prepared from 6-methoxytetralone via methods D and F) (1.5 g, 6.2 mmol) was reacted with 3,4-(methylenedioxy)phenylacetic acid (1.80 g, 10 mmol) as described in method C to yield 0.85 g of **18**: mp 135-6 °C; ^{1}H NMR (DMSO-d_6) δ 1.6−1.9 (m, 4H), 2.3 (s, 3H), 2.4−3.4 (m, 9H), 2.95 (d, 3H), 3.72 (s, 3H), 6.0 (s, 2H), 6.6−7.0 (m, 5H), 7.08 (t, 1H), 9.0 (br s, 1H). Anal. ($C_{23}H_{31}NO_6S$) C, H, N.

***N*-[(7-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenyl]ethyl]-amine Methanesulfonate (19).** [(7-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]amine hydrochloride (prepared from 7-methoxytetralone using methods E and F) (1.6 g, 7.0 mmol) was reacted with 3,4-(methylenedioxy)phenylacetic acid (1.80 g, 10 mmol) as described in method C to yield 0.65 g of **19**: mp 115−6 °C; ^{1}H NMR (DMSO-d_6) δ 1.6−1.9 (m, 4H), 2.3 (s, 3H), 2.4−3.4 (m, 9H), 2.95 (d, 3H), 3.74 (s, 3H), 6.0 (s, 2H), 6.6−7.0 (m, 5H), 7.0 (m, 1H), 9.0 (br s, 1H). Anal. ($C_{23}H_{31}NO_6S$) C, H, N.

***N*-[(8-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenyl]ethyl]amine Methanesulfonate (20).** [(8-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]amine hydrochloride (prepared according to methods D and F from 8-methoxytetralone[29]) (0.53 g, 1.4 mmol) was reacted with 3,4-(methylenedioxy)-phenylacetic acid (0.36 g, 2.0 mmol) as described in method C to yield 0.44 g of **20**: mp 113−5 °C; ^{1}H NMR (free base, $CDCl_3$) δ 1.5−1.8 (m, 3H), 2.13 (m, 1H), 2.39 (s, 3H), 2.45−2.80 (m, 8H), 3.21 (m, 1H), 3.80 (s, 3H), 5.92 (s, 2H), 6.6−6.8 (m, 5H), 7.08 (t, 1H). Anal. ($C_{23}H_{31}NO_6S\cdot 1/4\ H_2O$) C, H, N.

***N*-[((*R*)-5,6-Dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenyl]-ethyl]amine Methanesulfonate (22).** *N*-[((*R*)-5,6-Dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]amine (prepared via methods D and G) (0.70 g) was reacted with 3,4-(methylenedioxy)phenylacetic acid (0.80 g) by method C to yield 0.28 g of **22**: mp 150−1 °C; ^{1}H NMR (DMSO-d_6) δ 11.68−1.90 (m, 5H), 2.32 (s, 3H), 2.5−2.8 (m, 2H), 2.85 (s, 3H), 3.1−3.5 (m, 5H), 3.68 (s, 3H), 3.79 (s, 3H), 6.00 (s, 2H), 6.70−7.05 (m, 6H), 9.0 (br s, 1H). Anal. ($C_{24}H_{33}NO_7S\cdot 1/4H_2O$) C, H, N.

***N*-[(5-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenyl]ethyl]amine Hydrochloride (23).** *N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-methylamine hydrochloride (prepared by methods E and F) (1.21 g, 5.0 mmol) was treated with 4.0 g of BBr_3 (20 mmol) in CH_2Cl_2 (50 mL) at 0 °C to yield after isolation 1.13 g of the phenol intermediate. This compound was then treated as described in method B to yield 0.88 g of **23** as a white solid: mp 235−7 °C; ^{1}H NMR (DMSO-d_6) δ 1.7−2.1 (m, 4H), 2.4−3.5 (m, 9H), 2.93 (d, 3H), 6.00 (s, 2H), 6.6−7.0 (m, 6H), 9.37 (s, 1H), 9.8 (br s, 1H). Anal. ($C_{21}H_{26}ClNO_3$) C, H, N.

***N*-[((*R*)-5-Ethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenyl]ethyl]amine Methanesulfonate (24).** From 3,4-(methylenedioxy)phenylacetic acid (0.42 g) and *N*-[((*R*)-5-ethoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-*N*-methylamine (0.50 g) by method B, 0.49 g of **24**: mp 162−3 °C; ^{1}H NMR (DMSO-d_6) δ 1.32 (t, 3H), 1.7−1.9 (m, 4H), 2.31 (s, 3H), 2.4−3.4 (m, 9H), 2.93 (d, 3H), 4.0 (m, 2H), 6.0 (s, 2H), 6.7−7.0 (m, 5H), 7.13 (m, 1H), 9.1 (br s, 1H). Anal. ($C_{24}H_{33}NO_6S$) C, H, N.

***N*-Methyl-*N*-[2-[3,4-(methylenedioxy)phenyl]ethyl]-*N*-[[5-(methylthio)-1,2,3,4-tetrahydronaphthalen-1-yl]methyl]-amine Hydrochloride (25).** 5-Hydroxy-1-tetralone (20 g) was added to NaH (3.7 g) in DMF (200 mL), followed by dimethylthiocarbamyl chloride (18.3 g), and the reaction was heated at 85 °C for 16 h to give 9.66 g of the thiocarbamate. Upon 2 h of heating in mineral oil (100 mL) at 270 °C the thiocarbamate underwent the Newmann−Kwart rearrangement to give, after cooling and precipitation with cyclohexane, 8.44 g of 5-thiotetralone. The thiolate anion, prepared from NaOH (6 g) in MeOH (90 mL), was alkylated with MeI (6 g) to give 4.47 g of 5-(methylthio)tetralone. 5-(Methylthio)-tetralone (0.38 g) was converted to 3,4-dihydro-5-(methylthio)-naphthalene-1-carbonitrile (0.4 g) via method E, reduced to the saturated nitrile with $NaBH_4$ (0.23 g) in 1:1 EtOH/dimethoxyethane (20 mL) for 17 h at room temperature, and hydrolyzed by heating to reflux with 45% KOH (15 mL) in ethylene glycol (12 mL) for 12 h to give 5-(methylthio)-1,2,3,4-

tetrahydronaphthalene-1-carboxylic acid (0.35 g). In a modification of method B, reaction of 3,4-(methylenedioxy)-*N*-methylphenethylamine (0.86 g) and 5-(methylthio)-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (1.0 g) yielded 0.685 g of **25**: mp 169−70 °C; ^{1}H NMR (DMSO-d_6) δ 1.7−2.0 (m, 6H), 2.30 (s, 3H), 2.44 (s, 3H), 2.4−3.5 (m, 8H), 5.98 (s, 2H), 6.7-6.9 (m, 3H), 7.1 (m, 2H), 7.20 (t, 1H), 9.1 (br s, 1H). Anal. ($C_{23}H_{31}NO_5S_2$) C, H, N.

***N*-[(5-Methanesulfonamido-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methyl-*N*-[2-[3,4-(methylenedioxy)-phenyl]ethyl]amine Hydrochloride (26).** 5-Amino-1-tetralone[30] (1.02 g) was reacted with MsCl (0.80 g) and pyridine (13 mL) to give 1.48 g (98%) of 5-methanesulfonamido-1-tetralone that was benzylated with NaH and benzyl bromide in DMF and elaborated onto the corresponding aminomethyltetralin via methods E and F. 3,4-(Methylenedioxy)phenylacetic acid (0.568 g) and 1-(aminomethyl)-5-(*N*-benzylmethanesulfonamido)-1,2,3,4-tetrahydronaphthalene hydrochloride (1.14 g) were reacted by method C. The resulting N-benzylated product was treated with 20% Pd/C (1.05 g) and H_2 (4 atm) in methanol for 4 h to yield 0.378 g of **26**: mp 153−5 °C; ^{1}H NMR (DMSO-d_6) δ 1.65−2.1 (m, 6H), 2.55−3.55 (m, 7H), 2.91 (d, 3H), 3.37 (s, 3H), 5.93 (s, 2H), 6.7−7.0 (m, 3H), 7.2 (m, 3H), 9.0 (s, 1H), 9.9 (br s, 1H). Anal. ($C_{22}H_{29}N_2O_4SCl$) C, H, N.

***N*-[((R)-5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-methyl]-*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenyl]ethyl]amine Methanesulfonate (27).** From 0.313 g (1.74 mmol) 3,4-(methylenedioxy)phenylacetic acid and 0.330 g of [(*R*)-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]amine hydrochloride **10c** (1.45 mmol) as described in method C to yield 0.382 g od **27**: mp 169−70 °C; ^{1}H NMR ($CDCl_3$) δ 1.7−2.2 (m, 4H), 2.5−3.5 (m, 9H), 2.85 (s, 3H), 3.00 (d, 3H), 3.82 (s, 3H), 5.94 (s, 2H), 6.7 (m, 5H), 7.15 (t, 1H), 10.9 (br s, 1H). Anal. ($C_{23}H_{31}NO_6S$) C, H, N.

***N*-[((S)-5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-methyl]-*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenyl]ethyl]amine Methanesulfonate (28).** From 0.275 g (1.2 mmol) of [(*S*)-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-amine hydrochloride and 0.264 g (1.50 mmol) of 3,4-(methylenedioxy)phenylacetic acid by method C to yield 0.280 g of **28**: mp 169−70 °C; ^{1}H NMR ($CDCl_3$) δ 1.7−2.2 (m, 4H), 2.5−3.5 (m, 9H), 2.85 (s, 3H), 3.00 (d, 3H), 3.82 (s, 3H), 5.94 (s, 2H), 6.7 (m, 5H), 7.15 (t, 1H), 10.9 (br s, 1H). Anal. ($C_{23}H_{31}NO_6S$) C, H, N.

***N*-Methyl-*N*-[[5,6-(methylenedioxy)-1,2,3,4-tetrahydronaphthalen-1-yl]methyl]-*N*-[2-[3,4-(methylenedioxy)-phenyl]ethyl]amine Methanesulfonate (29).** From 1.5 g of [[5,6-(methylenedioxy)-1,2,3,4-tetrahydronaphthalen-1-yl]-methyl]amine (prepared by methods D and F) and 1.45 g of 3,4-(methylenedioxy)phenylacetic acid by method C to yield 1.15 g of **29**: mp 144−5 °C; ^{1}H NMR (DMSO-d_6) δ 1.6−1.9 (m, 4H), 2.3 (s, 3H), 2.5−3.4 (m, 9H), 2.92 (d, 3H), 6.0 (d, 2H), 6.7−7.0 (m, 5H), 9.1 (br s, 1H). Anal. ($C_{23}H_{29}NO_7S$) C, H, N.

(*R*)-6-[(*N*-Methylamino)methyl]-*N*-[2-[3,4-(methylenedioxy)phenyl]ethyl]-2,3,6,7,8,9-hexahydronaphtho[1,2-*b*]-furan Methanesulfonate (30). Acylation of 5-bromo-2,3-dihydrobenzofuran (**4**)[18] (41.4 g) with ethylsuccinyl chloride (43 mL) in the presence of $AlCl_3$ (53.3 g) in dichloroethane (500 mL) at room temperature for 16 h gave 19.5 g of the keto−ester as a white solid after workup. This solid was then reduced under 4 atm of H_2 with 10%Pd/C catalyst (3.9 g) in EtOH (500 mL) to provide 12.4 g of an oil that was reacted for 3 h at room temperature with KOH (14 g) in 1:1 EtOH/H_2O (250 mL) to give 10.9 g of carboxylic acid upon acidification with 12 N HCl. This acid was then cyclized with PPA (100 mL) by heating to 100 °C for 20 min to yield 7.6 g of 2,3,6,7,8,9-hexahydronaphtho[1,2-*b*]furan-6-one (**5**). Compound **5** was then elaborated to (*R*)-(+)-6-[(*N*-methylamino)methyl]-2,3,6,7,8,9-hexahydronaphtho[1,2-b]furan using methods E and G, and the resultant amine (0.80 g) and 3,4-(methylenedioxy)phenylacetic acid (0.64 g) were reacted by method B to yield 0.33 g of **30**: mp 185−6 °C; ^{1}H NMR (DMSO-d_6) δ 1.65−1.9 (m, 4H), 2.29 (s, 3H), 2.85−3.0 (m, 5H), 3.05−3.6 (m, 9H), 4.50 (t, 2H), 5.99 (s, 2H), 6.7−7.1 (m, 5H), 9.0 (br s, 1H). Anal. ($C_{24}H_{31}NO_7S$) C, H, N.

(*R*)-6-[(*N*-Methylamino)methyl]-*N*-[2-[3,4-(methylenedioxy)phenyl]ethyl]-6,7,8,9-tetrahydronaphtho[1,2-*b*]-furan Hydrochloride (31). (*R*)-(+)-6-[(*N*-Methylamino)-methyl]-2,3,6,7,8,9-hexahydronaphtho[1,2-*b*]furan (0.50 g) and 3,4-(methylenedioxy)phenylacetic acid (0.38 g) were coupled as in method B, step 1. The intermediate amide (0.52 g) and DDQ (0.41 g) were heated at reflux in dioxane for 4 h to yield, after column purification, 0.31 g of dehydrogenated intermediate. The amide was treated as in method B, step 2 with BH_3·THF at reflux for 3 h to yield 0.23 g of **31**: mp 240−2 °C; ^{1}H NMR (CD_3OD) δ 1.85−2.1 (m, 5H), 2.9−3.6 (m, 8H), 3.05 (s, 3H), 5.94 (s, 2H), 6.73−6.90 (m, 3H), 6.78 (d, 1H), 7.13 (m, 1H), 7.43 (d, 1H), 7.74 (d, 1H). Anal. ($C_{23}H_{26}ClNO_3\cdot{}^1/_4H_2O$) C, H, N.

***trans*-6-[(*N*-Methylamino)methyl]-*N*-[2-[3,4-(methylenedioxy)phenyl]ethyl]-2,3,3a,4,5,6-hexahydronaphtho-[1,8-*bc*]pyran Methanesulfonate (32) and *cis*-6-[(*N*-Methylamino)methyl]-*N*-[2-[3,4-(methylenedioxy)phenyl]-ethyl]-2,3,3a,4,5,6-hexahydronaphtho[1,8-*bc*]pyran Methanesulfonate (33).** Ethyl (chroman-4-yl)acetate (**6**)[19] (11.0 g) was reduced with $LiAlH_4$ (3.6 g) in THF (500 mL) to give 9.83 g of an alcohol that was reacted with MsCl (4.6 mL) and NEt_3 (8.3 mL) in CH_2Cl_2 (250 mL) to yield 12 g of crude mesylate. The mesylate was diplaced with KCN (5.87 g) by heating to reflux in EtOH (250 mL) for 8 h, and then the nitrile was hydrolyzed using 45% KOH (150 mL) in ethanol (200 mL) to give upon acidification 5.51 g of the carboxylic acid in 57% overall yield from **6**. The carboxylic acid was cyclized with PPA (140 mL) at 100 °C for 20 min to provide **7** (4.29 g) in 85% yield. Compound **7** was then elaborated according to methods E and F to 6-(aminomethyl)-2,3,3a,4,5,6-hexahydronaphtho[1,8-*bc*]pyran (0.524 g) that was reacted with 3,4-(methylenedioxy)phenylacetic acid (0.470 g) by method C, step 1. The intermediate amides were separated by HPLC (55:45 hexane:EtOAc) into the *cis* (less polar) (0.210 g) and *trans* (more polar) (0.340 g) products. The purified *trans* amide (0.44 g) was reduced and alkylated according to method C to yield 0.16 g of **32**, mp 128−9 °C. The *trans* stereochemistry was assigned by single-crystal X-ray analysis of **32**. ^{1}H NMR (free base, $CDCl_3$) δ 1.25−1.45 (m, 2H), 1.5−1.9 (m, 3H), 1.96 (m, 1H), 2.12 (m, 1H), 2.25−2.85 (m, 6H), 2.37 (s, 3H), 2.95 (m, 1H), 4.18 (m, 1H), 4.38 (m, 1H), 5.92 (s, 2H), 6.55−6.8 (m, 5H), 7.02 (t, 1H). Anal. ($C_{24}H_{31}NO_7S$) C, H, N. The purified *cis* amide (0.44 g) was elaborated according to method C to yield, after chromatography and several recrystallizations from EtOAc, 0.023 g of **33**: mp 105−6 °C; ^{1}H NMR (free base, $CDCl_3$) δ 1.15−1.35 (m, 2H), 1.67 (ddd, 1H), 1.95 (m, 2H), 2.13 (m, 1H), 2.34 (s, 3H), 2.4−2.8 (m, 7H), 3.03 (m, 1H), 4.14 (m, 1H), 4.38 (m, 1H), 5.92 (s, 2H), 6.58−6.75 (m, 4H), 6.85 (d, 1H), 7.03 (t, 1H). Anal. ($C_{24}H_{31}NO_7S\cdot0.75H_2O$) C, H, N.

***N*-Ethyl-*N*-[(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-[2-[3,4-(methylenedioxy)phenyl]ethyl]-amine Hydrochloride (35).** From 3,4-(methylenedioxy)-phenylacetic acid (1.20 g) and *N*-ethyl-*N*-[(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]amine (1.50 g) by method B to yield, 1.50 g of **35**: mp 140−1 °C; ^{1}H NMR (DMSO-d_6) δ 1.30 (t, 3H), 1.75 (m, 4H), 2.07 (m, 1H), 2.45 (m, 1H), 2.65 (m, 1H), 3.0 (m, 2H), 3.1−3.7 (m, 7H), 3.78 (s, 3H), 6.0 (s, 2H), 6.7−7.0 (m, 5H), 7.15 (t, 1H), 10.0 (br s, 1H). Anal. ($C_{23}H_{30}ClNO_3$) C, H, N.

***N*-Cyclopropyl-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-[2-[3,4-(methylenedioxy)phenyl]ethyl]amine Hydrochloride (36).** From 3,4-(methylenedioxy)phenylacetic acid (0.63 g, 3.5 mmol) and *N*-cyclopropyl-*N*-[(*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]amine (0.80 g, 3.5 mmol) (prepared using method G from cyclopropylamine and (*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalene-1-methanol methanesulfonate ester) by method B to yield, 0.87 g of **36**: mp 100−103 °C; ^{1}H NMR (DMSO-d_6) δ 0.8−1.2 (m, 4H), 1.7−1.9 (m, 3H), 2.05 (m, 1H), 2.42 (m, 1H), 2.70 (m, 1H), 2.95−3.20 (m, 3H), 3.25−3.70 (m, 4H), 3.78 (s, 3H), 6.00 (s, 2H), 6.70−7.00 (m, 5H), 7.17 (t, 1H), 9.85 (br s, 1H). Anal. ($C_{24}H_{30}ClNO_3$) C, H, N.

***N*-(Cyclopropylmethyl)-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-[2-[3,4-(methylenedioxy)phenyl]ethyl]amine Hydrochloride (37).** From 3,4-

(methylenedioxy)phenylacetic acid (0.59 g, 3.3 mmol) and *N*-(cyclopropylmethyl)-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]amine (0.80 g, 3.3 mmol) (prepared using method G from (cyclopropylmethyl)amine and (*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalene-1-methanol methanesulfonate ester) by method B to yield, 0.60 g of **37**: mp 110−111 °C ^{1}H NMR ($CDCl_3$) δ 0.50 (m, 2H), 0.82 (m, 2H), 1.30 (m, 1H), 1.90 (m, 1H), 2.00 (m, 1H), 2.42 (m, 1H), 2.58 (m, 1H), 2.80 (dt, 1H), 3.00−3.40 (m, 9H), 3.83 (s, 3H), 5.95 (d, 2H), 6.73 (m, 4H), 6.80 (d, 1H), 7.15 (t, 1H). Anal. ($C_{25}H_{32}ClNO_3$) C, H, N.

***N*-[((*R*)-5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-methyl]-*N*-[2-[3,4-(methylenedioxy)phenyl]ethyl]-*N*-propargylamine Hydrochloride (38).** From 3,4-(methylenedioxy)phenylacetic acid (0.48 g, 2.7 mmol) and *N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-propargylamine (0.61 g, 2.7 mmol) (prepared using method G from propargylamine and (*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalene-1-methanol methanesulfonate ester) by method B to yield, 0.35 g of **38**: mp 88−90 °C; ^{1}H NMR (DMSO-d_6) δ 1.65−1.8 (m, 4H), 2.03 (m, 1H), 2.35−2.8 (m, 2H), 2.92−3.04 (m, 2H), 3.20−3.70 (m, 4H), 3.78 (s, 3H), 4.02 (m, 1H), 4.23−4.38 (m, 2H), 5.98 (s, 2H), 6.70−7.00 (m, 5H), 7.15 (t, 1H), 10.5 (br s, 1H). Anal. ($C_{24}H_{28}ClNO_3 \cdot {}^3/_4H_2O$) C, H, N.

***N*-[2-(2,3-Dihydrobenzofuran-6-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Hydrochloride (39).** Reaction of 3-hydroxyphenylacetic acid (40 g) with EtOH/H_2SO_4 gave the corresponding ethyl ester (36.9 g) that was converted to the sodium salt with 80% NaH (7.4 g) in DMF (250 mL) and alkylated with bromoacetaldehyde diethyl acetal (37 mL) to give 49.6 g of product after column chromatography. This acetal (20 g) was then cyclized at 110 °C in PPA (5 g) and toluene (200 mL) for 12 h to give after column chromatography 7.66 g (56%) of a mixture of benzofuran-6-acetic acid ethyl ester and benzofuran-4-acetic acid ethyl ester in a 3:1 ratio. This mixture was then hydrolyzed with aqueous 1 M NaOH. The crude mixture of acids was recrystallized several times from hexane to provide in 98% purity benzofuran-6-acetic acid (3.5 g) that was reduced under 1 atm of H_2 at room temperature using 10% Pd/C to 2,3-dihydrobenzofuran-6-acetic acid. From 2,3-dihydrobenzofuran-6-acetic acid (0.31 g) and **13** (0.40 g) by method B to yield, 0.31 g of **39**: mp 227−229 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.6−2.0 (m, 4H), 2.38 (s, 3H), 2.4−3.0 (m, 9H), 3.17 (t, 2H), 3.81 (s, 3H), 4.54 (t, 2H), 6.68 (m, 3H), 6.80 (d, 1H), 7.10 (m, 2H). Anal. ($C_{23}H_{30}NO_2Cl$) C, H, N.

***N*-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate (41).** 2,3-Dihydrobenzofuran-5-acetic acid[31] (0.98 g, 5.5 mmol) and **13** (1.21 g, 5.0 mmol) were reacted according to method B to yield 1.29 g of **41**: mp 161−163 °C; ^{1}H NMR ($CDCl_3$) δ 1.7−2.2 (m, 4H), 2.5−3.5 (m, 9H), 2.86 (s, 3H), 3.00 (d, 3H), 3.18 (t, 2H), 3.81 (s, 3H), 4.55 (t, 2H), 6.71 (m, 3H), 6.94 (dd, 1H), 7.15 (m, 2H), 10.8 (bs, 1H). Anal. ($C_{24}H_{33}NO_5S$) C, H, N.

***N*-[2-(Benzofuran-5-yl)ethyl]-*N*-[(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate (42).** 2,3-Dihydrobenzofuran-5-acetic acid was oxidized with NBS and benzoyl peroxide in CCl_4 to give benzofuran-5-acetic acid. This acid (0.54 g) and **13** (0.57 g) were reacted by method B to yield, 0.52 g of **42**: mp 156−157 °C; ^{1}H NMR ($CDCl_3$) of the free base δ 1.6−1.8 (m, 3H), 1.95 (m, 1H), 2.40 (s, 3H), 2.4−3.0 (m, 9H), 3.81 (s, 3H), 6.66 (d, 1H), 6.70 (d, 1H), 6.81 (d, 1H), 7.08 (t, 1H), 7.12 (dd, 1H), 7.4 (d, 1H), 7.41 (s, 1H), 7.59 (d, 1H). Anal. ($C_{24}H_{31}NO_6S$) C, H, N.

***N*-[2-(1,3-Dihydroisobenzofuran-5-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate (43).** Treatment of 1,3-dihydroisobenzofuran-6-methanol[32] (1.74 g) with PPh_3 (3.23 g) and CBr_4 (5.58 g) gave 2.1 g of the bromide that was then diplaced with NaCN (0.97 g) in DMSO (10 mL) at room temperature to yield 0.8 g of nitrile that was hydrolyzed with 2.5 M NaOH to provide 0.58 g of 1,3-dihydroisobenzofuran-5-acetic acid. From 1,3-dihydroisobenzofuran-5-acetic acid (1.00 g) and **13** (0.95 g) by method B, substituting $LiAlH_4$ for borane, yielded 0.77 g of **43**: mp 162−164 °C; ^{1}H NMR (DMSO-d_6) δ 1.6−2.0 (m, 4H), 2.99 (d, 3H), 2.5−3.5 (m, 9H), 3.73 (s, 3H), 5.0 (m, 4H), 6.8-7.3 (m, 6H). Anal. ($C_{24}H_{33}NO_5S$) C, H, N.

***N*-[2-(Indan-5-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate (44).** From indan-5-acetic acid[33] (1.0 g) and **13** (0.96 g) by method B to yield, 1.18 g of **44**: mp 170−172 °C; ^{1}H NMR (DMSO-d_6), δ 1.7−2.1 (m, 6H), 2.31 (s, 3H), 2.4−3.5 (m, 13H), 2.96 (d, 3H), 3.77 (s, 3H), 6.82 (d, 1H), 6.87 (d, 1H), 7.0−7.3 (m, 4H), 9.1 (bs, 1H). Anal. ($C_{25}H_{35}NO_4S$) C, H, N.

***N*-[2-(2,3-Dihydrobenzo[*b*]thien-5-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate (45).** From 2,3-dihydrobenzothiophene-5-acetic acid[31] (0.80 g) and **13** (0.72 g) by method B to yield, 0.33 g of **45**: mp 158−159 °C; ^{1}H NMR ($CDCl_3$) of the free base δ 1.6−1.8 (m, 3H), 1.94 (m, 1H), 2.38 (s, 3H), 2.3−3.0 (m, 9H), 3.2−3.4 (m, 4H), 3.82 (s, 3H), 6.67 (d, 1H), 6.80 (d, 1H), 6.94 (dd, 1H), 7.1 (m, 3H). Anal. ($C_{24}H_{33}NO_4S_2$) C, H, N.

***N*-[2-(Benzo[*b*]thien-5-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate (46).** Reaction of 5-(bromomethyl)benzothiophene[34] with LiCN/DMF for 4 h at room temperature gave a nitrile that was directly hydrolyzed with 1:1 45% KOH:EtOH at reflux to form benzothiophene-5-acetic acid. This acid (0.90 g) and **13** (1.03 g) were coupled by method B, substituting $LiAlH_4$ for borane to yield 0.95 g of **46**: mp 181−182 °C; ^{1}H NMR ($CDCl_3$) δ 1.75−2.25 (m, 5H), 2.55 (m, 1H), 2.78 (m, 1H), 2.88 (s, 3H), 3.04 (d, 3H), 3.20-3.65 (m, 6H), 3.81 (s, 3H), 6.70 (m, 2H), 7.13 (t, 1H), 7.30 (m, 2H), 7.47 (d, 1H), 7.73 (d, 1H), 7.82 (d, 1H), 11.0 (bs, 1H). Anal. ($C_{24}H_{31}NO_4S_2$) C, H, N.

***N*-[2-(1,1-Dioxobenzo[*b*]thien-5-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Hydrochloride (47).** Benzothiophene-5-acetic acid (see previous expermimental) was reduced with 1.0 M BH_3·THF at 0 °C for 2 h and the resultant alcohol (0.6 g) oxidized with *m*-CPBA (1.45 g) in CH_2Cl_2 (50 mL) for 4 h at room temperature to give 0.66 g of a sulfone that was reacted with methanesulfonyl chloride (0.26 mL) and NEt_3 (0.48 mL) in CH_2Cl_2 (4 mL) to provide 0.74 g of 1,1-dioxobenzothiophene-5-ethanol methanesulfonate ester. From 1,1-dioxobenzothiophene-5-ethanol methanesulfonate ester (0.37 g) and **13** (0.29) by method A to yield, 0.10 g of **47**: mp 191−194 °C; ^{1}H NMR (DMSO-d_6) δ 1.65−2.05 (m, 5H), 2.3−3.6 (m, 9H), 2.95 (d, 3H), 3.78 (s, 3H), 6.80 (d, 1H), 6.90 (d, 1H), 7.15 (t, 1H), 7.4 (d, 1H), 7.5−7.65 (m, 2H), 7.83 (d, 1H), 9.8 (br s, 1H). Anal. ($C_{23}H_{28}NO_3SCl \cdot H_2O$) C, H, N.

***N*-[2-(1,1-Dioxo-2,3-dihydrobenzo[*b*]thien-5-yl)ethyl]-*N*-[((*R*)-5-methoxy1,2,3,4-tetrahydronaphthalen-1-yl)-methyl]-*N*-methylamine Hydrochloride (48).** 2,3-Dihydrobenzothiophene-5-acetic acid[31] was reduced with 2.0 equiv of BH_3·THF at 0 °C for 2 h, and the resultant alcohol was converted to the bromide using CBr_4/PPh_3 and then oxidized to the sulfone with *m*-CPBA. From 5-(2-bromoethyl)-1,1-dioxo-2,3-dihydrobenzo[b]thiophene (0.315 g) and **13** (0.332 g) by method A to yield, 0.147 g of **48**: mp 225−226 °C; ^{1}H NMR (CD_3OD) δ 1.8−2.0 (m, 4H), 2.5−2.9 (m, 2H), 3.0−3.6 (m, 14H), 3.81 (s, 3H), 6.8 (m, 2H), 7.15 (t, 1H), 7.4−7.5 (m, 2H), 7.7 (m, 1H). Anal. ($C_{23}H_{30}ClNO_3S$) C, H, N.

***N*-[2-(2,2-Dioxo-1,3-dihydrobenzo[*c*]thien-5-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-methyl]-*N*-methylamine Methanesulfonate (49).** 5-(2-Hydroxyethyl)-2,2-dioxo-1,3-dihydrobenzo[*c*]thiophene (prepared by the method of Grigg[32] substituting 3-butyn-1-ol for propargyl alcohol) was reacted with CBr_4 and PPh_3 to provide 5-(2-bromoethyl)-2,2-dioxo-1,3-dihydrobenzo[*c*]thiophene (0.275 g) that was coupled with **13** (0.242 g) by method A to give 0.237 g of **49**: mp 169−71 °C; ^{1}H NMR (DMSO-d_6) δ 1.7−2.0 (m, 4H), 2.3 (s, 3H), 2.4−2.7 (m, 4H), 3.0 (s, 3H), 3.0−3.6 (m, 7H), 3.78 (s, 3H), 4.5 (m, 4H), 6.85 (m, 2H), 7.15 (m, 1H), 7.3 (m, 3H). Anal. ($C_{24}H_{33}NO_6S_2$) C, H, N.

***N*-[(2,3-Dihydroindol-5-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Bis(methanesulfonate) (50).** Indoline was N-benzoylated with PhCOCl/NEt_3 and then subjected to Friedel-

Crafts acetylation using AcCl and $AlCl_3$ in CH_2Cl_2 at reflux. 6-Acetyl-*N*-benzoylindoline (1.33 g, 5.00 mmol) was then added to a solution of thallium trinitrate (2.45 g, 5.50 mmol) in MeOH (12.5 mL) with 60% $HClO_4$ (2.5 mL) and the reaction allowed to proceed for 4 h at room temperature to provide *N*-benzoyl-2,3-dihydroindolyl-5-acetic acid methyl ester (1.36 g, 93%). This ester was hydrolyzed with LiOH in THF/H_2O to give *N*-benzoyl-2,3-dihydroindolyl-5-acetic acid and this acid (0.98 g) reacted with **13** (0.85 g) by method B to yield the intermediate *N*-benzyl analog of the title compound as its dihydrochloride salt. Hydrogenation of this intermediate using a palladium catalyst in MeOH afforded 0.60 g of **50**: mp 207−208 °C; ^{1}H NMR (DMSO-d_6) δ 1.7−2.0 (m, 4H), 2.3 (s, 6H), 2.4−2.7 (m, 2H), 2.96 (d, 3H), 3.0−3.7 (m, 12H), 3.77 (s, 3H), 6.82 (d, 1H), 6.88 (d, 1H), 7.1−7.4 (m, 4H), 9.2 (bs, 2H). Anal. ($C_{25}H_{38}N_2O_7S_2$) C, H, N.

***N*-[2-(*N*-Methanesulfonamido-2,3-dihydroindol-5-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate (51).** From *N*-methanesulfonamido-2,3-dihydroindole-5-acetic acid (prepared by the same sequence as outlined for example **50**) (1.14 g) and **13** (0.90 g) by method B to yield 0.98 g of **51**: mp 202−203 °C; ^{1}H NMR (DMSO-d_6) δ 1.7−1.9 (m, 4H), 2.7 (s, 3H), 2.4−2.6 (m, 2H), 2.93 (d, 3H), 2.95 (s, 3H), 2.9-3.6 (m, 9H), 3.78 (s, 3H), 3.92 (m, 2H), 6.81 (d, 1H), 6.87 (d, 1H), 7.07−7.3 (m, 4H), 9.1 (bs, 1H). Anal. ($C_{25}H_{36}N_2O_6S_2$) C, H, N.

***N*-[2-[*N*-(Trifluoromethanesulfonamido)-2,3-dihydroindol-5-yl]ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate (52).** From *N*-(trifluoromethanesulfonamido)-2,3-dihydroindole-5-acetic acid (prepared by the same sequence as example **50**) (1.00 g, 3.2 mmol) and **13** (0.78 g, 3.2 mmol) by method B gave 0.47 g of **52**: mp 83 °C; ^{1}H NMR (DMSO-d_6) δ 11.65−1.9 (m, 4H), 2.32 (s, 3H), 2.38−2.8 (m, 2H), 2.97 (s, 3H), 3.10−3.80 (m, 7H), 3.78 (s, 3H), 3.90−4.10 (m, 2H), 4.20−4.28 (m, 2H), 6.81 (d, 1H), 6.87 (d, 1H), 7.10−7.40 (m, 4H), 9.0 (br s, 1H). Anal. ($C_{25}H_{33}N_2O_6S_2F_3$) C, H, N.

***N*-[2-(1,3-Dihydroisoindol-5-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine dihydrochloride (53).** 5-Methoxycarbonylisoindoline hydrochloride[35] (5.0 g) was reacted with benzoyl chloride (3.96 g) and NEt_3 (9.9 mL) in CH_2Cl_2 (150 mL) to give 5.89 g of benzamide (89%) that was subjected to ester hydrolysis with LiOH·H_2O (2.6 g) in 2:1 THF/H_2O (120 mL) to give 5.1 g (92%) of the corresponding carboxylic acid. This acid (2.6 g) was converted to the acid chloride with oxalyl chloride (1.48 g) in CH_2Cl_2 (75 mL) and then reacted with diazomethane to give 2.64 g of diazo ketone (94%) that was rearranged by the addition of Ag_2O (1 g) in portions over 3 h to a solution of the diazo ketone in EtOH (60 mL) at reflux to provide 2.0 g of *N*-benzoyl-1,3-dihydroisoindol-5-yl acetic acid ethyl ester (73%). Hydrolysis of this ester (2.6 g) with LiOH·H_2O (1.1 g) in 2:1 THF/H_2O (60 mL) gave *N*-benzoyl-1,3-dihydroisoindol-5-ylacetic acid (2.00 g, 7.1 mmol) that was coupled with **13** (1.55 g) by method B to yield the intermediate *N*-benzyl analog (2.62 g). Hydrogenation of this intermediate using a palladium catalyst in MeOH afforded 0.83 g of **53**: mp 188 °C; ^{1}H NMR (CD_3OD) δ 1.88 (m, 5H), 3.05−3.30 (m, 5H), 3.45 (m, 5H), 3.80 (s, 3H), 4.62 (m, 4H), 6.83 (m, 2H), 7.16 (t, 1H), 7.40 (m, 3H). Anal. ($C_{23}H_{30}N_2O$·2HCl·0.5H_2O) C, H, N.

***N*-[2-(*N*-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate Hemihydrate (54).** 5-(Methoxycarbonyl)isoindoline hydrochloride[35] (3.93 g) was reacted with MsCl (2.54 g) and NEt_3 (7.8 mL) in CH_2Cl_2 (150 mL) to give 4.47 g of the sulfonamide (95%) that was reduced with $LiAlH_4$ (1.3 g) in THF (60 mL) at room temperature over 75 min to provide 3.52 g (94%) of the corresponding alcohol. The alcohol was then converted to the mesylate with MsCl (2.1 g) and NEt_3 (4.3 mL) in CH_2Cl_2 and the mesylate displaced with 0.5 M LiCN/DMF (30 mL) at room temperature for 1 h to give 2.47 g of the nitrile. This nitrile was then hydrolyzed with 45% KOH (20 mL) in EtOH (50 mL) at reflux for 1 h to yield *N*-methanesulfonamido-1,3-dihydroisoindole-5-acetic acid (2.25 g, 75%). This acid (1.0 g) was reacted with **13** (1.05 g) by method B to yield 0.77 g of **54**: mp 209 °C; ^{1}H NMR ($CDCl_3$) of the free base δ 1.5−2.0 (m, 6H), 2.38 (s, 3H), 2.4−3.0 (m, 7H), 2.88 (s, 3H), 3.81 (s, 3H), 4.68 (s, 4H), 6.67 (d, 1H), 6.80 (d, 1H), 7.1 (m, 4H). Anal. ($C_{25}H_{36}N_2O_6S_2$·0.5H_2O) C, H, N.

***N*-[2-(*N*-Trifluoromethanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate (55).** *N*-[2-(1,3-Dihydroisoindol-5-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine (**53**) (0.340 g) was dissolved in CH_2Cl_2 (10 mL) and treated with NEt_3 (0.68 mL, 5 mmol) and trifluoromethanesulfonic anhydride (0.85 g) to yield 0.158 g of **55**: mp 210 °C; ^{1}H NMR ($CDCl_3$) of the free base δ 1.5−2.0 (m, 6H), 2.38 (s, 3H), 2.4−3.0 (m, 7H), 3.81 (s, 3H), 4.88 (s, 4H), 6.67 (d, 1H), 6.79 (d, 1H), 7.05−7.20 (m, 4H). Anal. ($C_{24}H_{29}N_2F_3O_3S$) C, H, N.

***N*-[2-(2,3-Dihydroindol-6-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Dihydrochloride (56).** From (2-oxoindolin-6-yl)acetic acid[36] (700 mg) and **13** (800 mg) by method B to yield, 360 mg of **56**: ^{1}H NMR ($CDCl_3$) δ 1.50−2.25 (m, 8H), 2.50 (m, 4H), 2.76 (m, 4H), 2.99 (t, 2H), 3.54 (t, 2H), 3.81 (m, 3H), 6.54 (m, 1.5H), 6.68 (m, 1H), 6.80 (m, 1H), 7.05 (m, 1.5H). Anal. ($C_{23}H_{30}N_2O$·2HCl·0.5H_2O) C, H, N.

***N*-[2-(*N*-Methanesulfonamido-2,3-dihydroindol-6-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate (57).** Methanesulfonamido-2,3-dihydroindole-6-methanol[37] was converted to *N*-methanesulfonamido-2,3-dihydroindole-6-acetic acid via the method used in example **54**, and the acid (0.983 g) and **13** (0.846 g) were reacted by method B to yield 1.12 g of **57**: mp 163−165 °C; ^{1}H NMR (DMSO-d_6) δ 1.7−1.9 (m, 5H), 2.4−3.6 (m, 16H), 3.35 (s, 3H), 3.77 (s, 3H), 3.93 (m, 2H), 6.82 (d, 2H), 6.86 (d, 2H), 6.95 (t, 1H), 7.1−7.3 (m, 3H), 9.0 (br s, 1H). Anal. ($C_{25}H_{36}N_2O_6S_2$) C, H, N.

***N*-[2-[*N*-(Trifluoromethanesulfonamido)-2,3-dihydroindol-6-yl]ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate (58).** Indole-6-carboxylic acid methyl ester[38] (5.39 g, 30 mmol) in acetic acid (75 mL) at 15 °C was reduced with $NaCNBH_3$ (5.39 g, 90 mmol) to give 3.69 g of the indoline. This indoline was converted to the trifluoromethanesulfonamide with triflic anhydride and NEt_3, elaborated on as in example **53** to *N*-(trifluoromethanesulfonamido)-2,3-dihydroindole-6-acetic acid (0.928 g) and reacted with **13** (0.725 g) by method B to yield 0.654 g of **58**: mp 140−141 °C; ^{1}H NMR (DMSO-d_6) δ 1.8 (m, 4H), 2.4−2.7 (m, 2H), 2.95 (s, 3H), 3.0−3.5 (m, 7H), 3.3 (s, 3H), 3.78 (s, 3H), 4.2 (m, 2H), 6.8 (d, 1H), 6.87 (d, 1H), 7.15 (m, 2H), 7.3 (m, 2H). Anal. ($C_{25}H_{33}F_3N_2O_6S_2$) C, H, N.

5-[2-[[(*R*)-5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]methyl]amino]ethyl]-1,3-dihydroindol-2-one Methanesulfonate (59). From 5-(2-chloroethyl)-2,3-dihydroindol-2-one[39] (1.4 g) and **13** (1.2 g) by method A to yield, 0.44 g of **59**: mp 133−134 °C; ^{1}H NMR (DMSO-d_6) δ 1.6−2.0 (m, 5H), 2.4−3.5 (m, 8H), 2.31 (s, 3H), 2.97 (d, 3H), 3.48 (s, 2H), 3.78 (s, 3H), 6.7−7.2 (m, 6H), 9.1 (bs, 1H), 9.87 (s, 1H). Anal. ($C_{24}H_{32}N_2O_5S$·H_2O) C, H, N.

***N*-[2-(Benzoxazol-6-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate (60).** 3-Hydroxy-4-nitrobenzyl alcohol[40] was converted to 3-hydroxy-4-nitrophenylacetic acid using the method employed in example **43**, and the acid (0.711 g) and **13** (0.725 g) were reacted by method B. The intermediate product was hydrogenated using a palladium catalyst in EtOH to yield an intermediate aminophenol. Treatment of this intermediate with triethyl orthoformate at reflux for 18 h yielded 0.54 g of **60**: mp 139−141 °C; ^{1}H NMR ($CDCl_3$) δ 1.7−2.3 (m, 5H), 2.5−3.6 (m, 8H), 2.89 (s, 3H), 3.06 (d, 3H), 3.82 (s, 3H), 6.7 (m, 2H), 7.13 (t, 1H), 7.27 (dd, 1H), 7.55 (bs, 1H), 7.72 (d, 1H), 8.09 (s, 1H), 11.0 (bs, 1H). Anal. ($C_{23}H_{30}N_2O_5S$) C, H, N.

***N*-[2-(2-Methylbenzoxazol-6-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate (61).** 3-Hydroxy-4-nitrophenylacetic acid (see example **60** for preparation) (1.70 g) and **13** (2.00 g) were reacted by method B. The product was reduced

with H_2 over a palladium catalyst in EtOH to yield an aminophenol that was heated in triethyl orthoacetate at reflux for 1 h to yield 1.15 g of **61**: mp 159−161 °C; ^{1}H NMR ($CDCl_3$) of the free base δ 1.6−2.0 (m, 5H), 2.39 (s, 3H), 2.4−3.0 (m, 8H), 2.61 (s, 3H), 3.80 (s, 3H), 6.66 (d, 1H), 6.80 (d, 1H), 7.08 (d, 1H), 7.12 (dd, 1H), 7.31 (d, 1H), 7.52 (d, 1H). Anal. ($C_{24}H_{32}N_2O_5S$) C, H, N.

***N*-[2-(Benzoxazol-5-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate (62).** 4-Hydroxy-3-nitrophenylacetic acid[41] (1.17 g) and **13** (1.20 g) were reacted by method B. The product was hydrogenated using a palladium catalyst in EtOH to yield an aminophenol that was treated with triethyl orthoformate at reflux for 1 h to yield 1.24 g of **62**: mp 175−177 °C; ^{1}H NMR ($CDCl_3$) of the free base δ 1.6−1.8 (m, 3H), 1.93 (m, 1H), 2.39 (s, 3H), 2.4−3.0 (m, 9H), 3.81 (s, 3H), 6.67 (d, 1H), 6.80 (d, 1H), 7.09 (t, 1H), 7.22 (dd, 1H), 7.47 (d, 1H), 7.62 (d, 1H), 8.08 (s, 1H). Anal. ($C_{23}H_{30}N_2O_5S$) C, H, N.

***N*-[2-(Benzimidazol-5-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Bis(methanesulfonate) (63).** 4-Aminophenylacetic acid was esterified with H_2SO_4/MeOH and then converted to the amide using Ac_2O/pyridine. 4-*N*-Acetamidophenylacetic acid methyl ester (12.4 g) was nitrated by addition to a chilled mixture of 70% HNO_3 (19 mL) and Ac_2O (210 mL) prepared at −10 °C to give 15 g of yellow solid that was exhaustively hydrolyzed with 5 N HCl to provide 4-amino-3-nitrophenylacetic acid. This acid (0.97 g) and **13** (1.0 g) were reacted by method B. The product was hydrogenated using a palladium catalyst in EtOH to give a dianiline that was refluxed with formic acid (1.2 equiv) in 10% aqueous HCl for 1 h to yield 0.61 g of **63**: mp 162−164 °C; ^{1}H NMR ($CDCl_3$) of the free base δ 1.6−1.8 (m, 3H), 1.94 (m, 1H), 2.39 (s, 3H), 2.4−3.0 (m, 9H), 3.80 (s, 3H), 6.67 (d, 1H), 6.81 (d, 1H), 7.08 (t, 1H), 7.13 (dd, 1H), 7.47 (bs, 1H), 7.59 (bs, 1H), 8.01 (s, 1H), 9.5 (bs, 1H). Anal. ($C_{24}H_{35}N_3O_7S_2$) C, H, N.

***N*-[2-(Benzothiazol-6-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate (64).** Compound **66** (0.70 g) was reduced under 4 atm H_2 using 10% Pd/C in MeOH with NaOAc to provide 0.44 g **64**, mp 165−167 °C. ^{1}H NMR ($CDCl_3$) of the free base δ 1.4−2.0 (m, 6H), 2.47 (s, 3H), 2.4−3.1 (m, 7H), 3.80 (s, 3H), 6.67 (d, 1H), 6.80 (d, 1H), 7.09 (t, 1H), 7.35 (m, 2H), 7.80 (s, 1H), 8.04 (d, 1H), 8.91 (s, 1H). Anal. ($C_{23}H_{30}N_2O_4S_2 \cdot {}^1/_4H_2O$) C, H, N.

***N*-[2-(2-Methylbenzothiazol-6-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate (65).** 4-Aminophenylacetic acid (2.88 g) was iodinated with ICl (2.83 g) in CH_2Cl_2 (20 mL) to give 2.82 g (56%) of 4-amino-3-iodophenylacetic acid. This iodo compound (1.46 g) was reacted with 1,1′-bis(diphenylphosphino)ferrocene (55 mg), CuO (0.28 g), thioacetamide (0.38 g), and tris(dibenzylideneacetone)dipalladium(0) (0.46 mg) in DMF (5 mL)[42] at 60 °C for 6 h to provide 0.51 g of 2-methylbenzothiazole-6-acetic acid methyl ester that was hydrolyzed with LiOH in THF/H_2O to the corresponding acid. 2-Methylbenzothiazole-6-acetic acid (0.62 g) and **13** (0.78 g) were reacted by method B. The crude borane reduction product, in lieu of treatment with HCl, was evaporated, suspended in ether, and treated with TMEDA (tetramethylethylenediamine) (1.2 equiv) at reflux for 4 h to yield 0.56 g of **65**: mp 164−167 °C; ^{1}H NMR (DMSO-d_6) δ 1.7−1.9 (m, 6H), 2.55−3.65 (m, 6H), 2.31 (s, 3H), 3.0 (d, 3H), 3.78 (s, 3H), 6.8−6.9 (m, 2H), 7.15 (t, 1H), 7.43 (dd, 1H), 7.95 (d, 1H), 8.0 (d, 1H), 9.1 (br s, 1H). Anal. ($C_{24}H_{32}N_2O_4S_2$) C, H, N.

***N*-[2-(2-Chlorobenzothiazol-6-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate (66).** To 2-aminobenzothiazole-6-acetic acid (see example **67** for preparation) was added formic acid (16.5 mL) and then AcOH (6.3 mL) and 12 N HCl (12.3 mL), and the mixture was cooled to 0 °C. An aqueous solution of $NaNO_2$ (2.16 g) was added over 10 min and stirred for 30 min, and then this mixture was added to a solution of CuCl (4.02 g) in 12 N HCl (18.6 mL) and water (42.5 mL) at 10 °C followed by heating to 60 °C for 10 min. Following workup, 2.17 g of 2-chlorobenzothiazole-6-acetic acid (32%) was obtained. This acid (0.33 g) and **13** (0.31 g) were reacted by method B. The crude borane reduction product, in lieu of treatment with HCl, was evaporated, suspended in Et_2O, and treated with TMEDA (1.2 equiv) at reflux for 4 h to yield 0.23 g of **66**: mp 153−154 °C; ^{1}H NMR (DMSO-d_6) δ 1.7−1.9 (m, 4H), 2.3 (s, 3H), 3.0 (d, 3H), 3.1−3.5 (m, 9H), 3.77 (s, 3H), 6.83 (d, 1H), 6.87 (d, 1H), 7.15 (t, 1H), 7.5 (dd, 1H), 7.97 (d, 1H), 8.04 (d, 1H), 9.3 (bs, 1H). Anal. ($C_{23}H_{29}ClN_2O_4S_2$) C, H, N.

***N*-[2-(2-Aminobenzothiazol-5-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Bis(methanesulfonate) (67).** 4-Aminophenylacetic acid (20 g) and ammonium thiocyanate (20 g) were dissolved in AcOH (300 mL), and the mixture was cooled to 15 °C, treated with Br_2 (6.8 mL) in AcOH (10 mL), and then stirred at room temperature for 4 h to give 23.4 g of 2-aminobenzothiazole-5-acetic acid. This acid (1.15 g) and **13** (1.30 g) were reacted by method B, substituting 4 equiv of TMEDA for the HCl treatment to decompose the intermediate borane complex to give 0.97 g of **67**: mp 200−202 °C; ^{1}H NMR (DMSO-d_6) δ 1.4−2.0 (m, 6H), 2.47 (s, 3H), 2.4−3.0 (m, 7H), 3.81 (s, 3H), 5.1 (bs, 2H), 6.65 (d, 1H), 6.80 (d, 1H), 7.09 (t, 1H), 7.14 (dd, 1H), 7.44 (bs, 1H), 7.47 (d, 1H). Anal. ($C_{24}H_{35}N_3O_7S_3$) C, H, N.

6-[2-[[((*R*)-5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]methylamino]ethyl]-3*H*-benzoxazol-2-one Hydrochloride (68). 3-Hydroxy-4-nitrophenylacetic acid (see example **60** for preparation) (0.91 g) and **13** (1.0 g) were reacted by method B. The product was reduced with H_2/Pd in EtOH to give an aminophenol that was reacted with 1,1′-carbonyldiimidazole in THF at reflux for 2 h to yield 0.49 g of **68**: mp 147−149 °C; ^{1}H NMR ($CDCl_3$) of the free base δ 1.55−2.0 (m, 4H), 2.39 (s, 3H), 2.4−3.0 (m, 9H), 3.81 (s, 3H), 6.67 (d, 1H), 6.80 (d, 1H), 6.97 (m, 2H), 7.1 (m, 2H), 8.7 (bs, 1H). Anal. ($C_{22}H_{27}ClN_2O_3$) C, H, N.

***N*-[2-(2-Methylbenzoxazol-5-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate (69).** 4-Hydroxy-3-nitrophenylacetic acid[41] (1.70 g) and **13** (2.00 g) were reacted by method B. The product was treated with H_2/Pd in EtOH to yield an amino-phenol that was heated in triethyl orthoacetate at reflux for 1 h to yield 1.36 g of **69**: mp 178−179 °C; ^{1}H NMR (DMSO-d_6) δ 1.7−1.9 (m, 4H), 2.31 (s, 3H), 2.60 (s, 3H), 2.96 (d, 3H), 2.9−3.6 (m, 9H), 3.79 (s, 3H), 6.81 (d, 1H), 6.89 (d, 1H), 7.16 (t, 1H), 7.29 (dd, 1H), 7.65 (m, 2H), 9.2 (bs, 1H). Anal. ($C_{24}H_{32}N_2O_5S$) C, H, N.

5-[2-[[((*R*)-5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]methylamino]ethyl]-3*H*-imidazol-2-one Hydrochloride (70). 4-Amino-3-nitrophenylacetic acid (see example **63** for preparation) (1.34 g) and **13** (1.50 g) were reacted by method B. The product was treated with H_2/Pd in EtOH to give a dianiline that was reacted with 1,1′-carbonyldiimidazole in THF at reflux for 2 h to yield 0.33 g of **70**: mp 192−196 °C; ^{1}H NMR (DMSO-d_6) δ 1.6−1.9 (m, 4H), 2.4−3.5 (m, 9H), 2.9 (d, 3H), 3.77 (s, 3H), 6.85 (m, 5H), 7.12 (t, 1H), 9.8 (bs, 1H), 10.08 (s, 1H), 10.17 (s, 1H). Anal. ($C_{22}H_{28}ClN_3O_2 \cdot 0.75H_2O$) C, H, N.

***N*-[2-(Quinolin-7-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Dihydrochloride (71).** From 7-acetylquinoline[43] was obtained quinoline-7-acetic acid by the method of Jones.[44] Quinoline-7-acetic acid (1.84 g, 11 mmol) and **13** (2.42 g, 10.0 mmol) were reacted by method B to yield 0.91 g of **71**: mp 87−90 °C; ^{1}H NMR (DMSO-d_6) δ 1.8 (m, 4H), 2.4−2.7 (m, 2H), 3.0 (s, 3H), 3.2−3.8 (m, 7H), 3.8 (s, 3H), 6.8 (d, 1H), 6.9 (d, 1H), 7.15 (t, 1H), 7.9 (m, 2H), 8.2 (m, 2H), 8.95 (d, 1H), 9.17 (d, 1H). Anal. ($C_{24}H_{30}Cl_2N_2O \cdot 0.75H_2O$) C, H, N.

***N*-[2-(Isoquinolin-7-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate (72).** From 7-acetylisoquinoline[45] was obtained isoquinoline-7-acetic acid by the method of Jones.[44] isoquinoline-7-acetic acid (0.56 g) and **13** (0.72 g) reacted by method B was obtained 0.45 g of **72**: ^{1}H NMR ($CDCl_3$) of the free base δ 1.55−2.0 (m, 5H), 2.4−3.1 (m, 11H), 3.81 (s, 3H), 6.67 (d, 1H), 6.80 (d, 1H), 7.07 (t, 1H), 7.6 (m, 2H), 7.77 (m, 2H), 8.48 (d, 1H), 9.2 (s, 1H). Anal. ($C_{24}H_{30}Cl_2N_2O \cdot H_2O$) C, H, N.

***N*-[2-(Quinolin-6-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Hydrochloride Dihydrate (73).** Quinoline-6-acetic acid[44] (1.0 g) and **13** (0.95 g) were reacted by method B to yield 0.79 g of **73**: mp 137−139 °C; ^{1}H NMR (DMSO-d_6) δ 1.6−2.7 (m, 7H), 2.95 (d, 3H), 3.2−3.7 (m, 6H), 3.79 (s, 3H), 6.80 (d, 1H), 6.92 (d, 1H), 7.15 (t, 1H), 7.85−8.3 (m, 4H), 8.82 (m, 1H), 9.14 (m, 1H). Anal. ($C_{24}H_{30}ClN_2O\cdot 2H_2O$) C, H, N).

***N*-[2-(Quinoxalin-6-yl)ethyl]-*N*-[((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-*N*-methylamine Methanesulfonate (74).** 4-Amino-3-nitrophenylacetic acid (see example **63** for preparation) (0.97 g) and **13** (1.0 g) were reacted by method B. The product was hydrogenated over palladium in EtOH to yield a dianiline that was reacted with 2,3-dihydroxy-1,4-dioxane to yield 0.88 g of **74**: mp 192 °C; ^{1}H NMR (DMSO-d_6) δ 1.7−2.0 (m, 4H), 2.3 (s, 3H), 2.4−3.6 (m, 9H), 3.03 (d, 3H), 3.79 (s, 3H), 6.84 (d, 1H), 6.90 (d, 1H), 7.16 (t, 1H), 7.85 (dd, 1H), 8.1 (m, 2H), 8.96 (m, 2H), 9.1 (bs, 1H). Anal. ($C_{24}H_{31}N_3O_4S$) C, H, N.

Biology. Binding to α_2-receptors obtained from rat cortical membranes was determined by displacement of [^{3}H]rauwolscine as previously described.[46] Likewise, assay conditions to determine the inhibition of uptake of [^{3}H]serotonin in synaptosomes from rat cortex followed our published procedure.[46]

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Supporting Information Available: X-ray report data for compounds **10b** and **32** (35 pages). Ordering information is given on any current masthead page.

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