Syntheses and Binding Studies of New [(Aryl)(aryloxy)methyl]piperidine Derivatives and Related Compounds as Potential Antidepressant Drugs with High Affinity for Serotonin (5-HT) and Norepinephrine (NE) Transporters

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In a wide search program toward new, efficient, and fast-acting antidepressant drugs, we have prepared series of new compounds having an (aryl)(aryloxy)methyl moiety linked directly or through a methylene chain to different substituted and unsubstituted cycles (isoquinoline, piperazine, piperidine, tetrahydropyran, or cyclopentane). These compounds have been evaluated for their affinities for serotonin (5-HT) transporter (SERT) and 5-HT_{1A} and 5-HT_{2A} receptors. Racemic mixtures of 4-[(aryl)(aryloxy)methyl]piperidine derivatives showed much higher affinity values for SERT than fluoxetine and resulted in lack of affinity for 5-HT_{1A} and 5-HT_{2A} receptors. Some of these racemic mixtures were resolved to their enantiomers and tested for binding to norepinephrine (NE) transporter (NET), dopamine (DA) transporter (DAT), and α_2 receptor. Several of these enantiomers [**(−)-15b**, **(−)-15j**, **(−)-15t**, **(+)-15u**] displayed a dual binding profile with affinities for SERT and NET with K_i < 25 nM and a NET/SERT ratio <10. Compound **(−)-15j** (coded as F-98214-TA for development studies) showed a dual binding profile with very high affinity values for SERT and NET (K_i = 1.9 and 13.5 nM, respectively), and further pharmacological characterization is in progress for its evaluation as a antidepressant.

Introduction

Depression is a common psychiatric disorder and one of the most frequent illnesses in the world affecting people of all gender, ages, and backgrounds. The causes of depression are complex and differ widely among individuals, but they are thought to involve brain biochemistry, inherited genes, social environment, and upbringing. In studying brain, the dysfunction of the norepinephrine (NE), serotonin (5-HT), and dopamine (DA) neurotransmitter systems known as monoamine hypothesis[1] is the most widely accepted basis for depression. In the past, tricyclic antidepressant (TCA) compounds and monoamine oxidase inhibitors (MAOIs) represented the major pharmacological treatments for this illness. These classical antidepressants are thought to act by increasing 5-HT and NE levels at neuronal synapses. The down side with the use of these drugs is their low selectivity and interaction with several other types of receptors, inside as well as outside the brain, causing unwanted side effects. Furthermore, the monoamine hypothesis does not fully explain the therapeutic action of antidepressants nor does it clarify the pathophysiology of depression and cannot justify the slow onset of action, because 4−6 weeks are required to establish therapeutic efficacy.[2] Despite these shortcomings, the monoamine hypothesis has provided the rationale for the development of new generations of antidepressants with a broader range of efficacy and safety in depression treatment. In this regard, one of the major advances has been the introduction of the selective serotonin reuptake inhibitors[3] (SSRIs, Chart 1) which have a lower side-effect profile and ease of clinical management. Unfortunately, SSRIs do not improve the slow onset of action, a behavior which is in sharp contrast with their fast inhibition of 5-HT uptake after acute treatment. Over the past decade a third generation of antidepressants has been developed. Thus, one approach to the treatment of depression has involved the development of selective NE reuptake inhibitors (NARIs) such as nisoxetine[4] and reboxetine[5,6] (Chart 1). The last one has recently been marketed and has refocused attention on the role of the NE system in depression. Neuroanatomical connections among NE, 5-HT, and DA systems support the hypothesis that these functional interactions could be an important anatomical substrate for the therapeutic action of antidepressants.[7] Dual action antidepressants that modify only both central serotonergic and noradrenergic functions may be superior to treat depression.[8] The new generation of 5-HT and NE reuptake inhibitors (SNRIs) is an example of such agents. One of them, venlafaxine[9,10] (Chart 1), shows a faster onset of action and increased efficacy.[11] Another approach is the use of the noradrenergic and specific serotonergic antidepressant (NSSA) mirtazapine[12] (Chart 1), which increases noradrenergic and serotonergic transmission through blockade of central α_2-adrenoceptors as well as some 5-HT receptor subtypes (5-HT_2 and 5-HT_3). Compared with SSRIs, mirtazapine is reported to have a slightly faster onset of action and fewer side effects.[12] To date, a complete and convincing proof of early onset of action has not been demostrated for any single antidepressant drug.[13]

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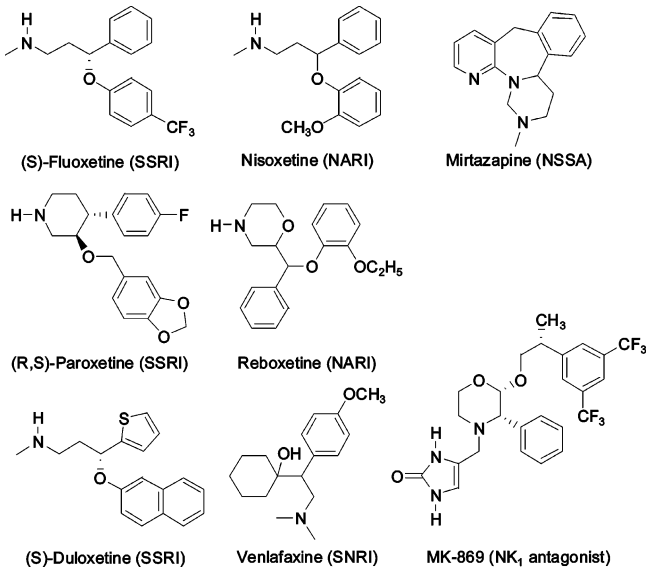
Chart 1. Antidepressant Structures



More recently, nonmonoaminergic approaches such as corticotropin-releasing factor (CRF)[14,15] and neurokinin 1 (NK_1) receptors[16] have been involved in the pathophysiology of depression.

As mentioned above, the common problem in current antidepressant therapies is their slow onset of action. It has been suggested that the delayed onset in the clinical action of SSRIs might be explained by the time required for desensitization of somatodendritic 5-HT_{1A} autoreceptors,[17] which are located on the cell bodies and dendrites of 5-HT neurons in the dorsal raphe nucleus (DRN). The 5-HT excess in the extracellular space of the DRN, obtained after acute treatment with a SSRI antidepressant, activates 5-HT_{1A} autoreceptors and reduces the neuronal activity releasing 5-HT by nerve terminals in forebrain. However, chronic administration of SSRIs for 3−4 weeks leads to functional desensitization of somatodendritic 5-HT_{1A} autoreceptors, with the result that 5-HT release is increased in the prefrontal cortex. The time necessary to obtain these adaptive changes is consistent with the delayed onset of action of SSRIs in major depression.[18] Given the lack of selective 5-HT_{1A} receptor antagonists for human use, early attempts to prove this hypothesis were carried out using the β-adrenoceptor and 5-HT_{1A} receptor ligand (±)-pindolol,[19] which enhances the clinical action of antidepressant drugs, although it appears to have more limited effect in treating resistant depression.[20] On the basis of the experimental evidence that 5-HT_{1A} receptor ligands increase the neurochemical and behavioral effects of SSRIs, there has been considerable interest to find compounds with both properties to bring a more inmediate and complete antidepressant effect.[21]

Our research program toward new, efficient, and fast-acting antidepressant drugs has been aimed at the discovery of compounds with a dual binding profile showing 5-HT and/or NE reuptake inhibition and affinity for different 5-HT receptor subtypes (5-HT_{1A} or 5-HT_{2A}). With this aim, we have designed the series of compounds showed in Chart 2 based on coupling structural moieties related to serotonin transporter (SERT) and norepinephrine transporter (NET) inhibition to different fragments that may provide 5-HT receptor affinity (5-HT_{1A} or 5-HT_{2A} antagonism). We have considered the chemical structures of fluoxetine[22] (SSRI, Chart 1), nisoxetine[4] (NARI, Chart 1), and reboxetine[5,6] (NARI, Chart 1) as a starting point for our design.

Chemistry

We have prepared new compounds of general formula **1** (Chart 2) having an (aryl)(aryloxy)methyl moiety linked directly or through a methylene chain to different substituted and unsubstituted cycles (isoquinoline, piperazine, piperidine, cyclopentane, or tetrahydropyran) that could provide affinity for different 5-HT receptor subtypes. As some marketed antidepressants (Chart 1), compounds of series **I**−**V** (Chart 2) have a nitrogen atom while compounds **18** and **21** (series **VI**) lack it. In series **IV**, **V**, and **VI** (Chart 2) the (aryl)(aryloxy)methyl moiety is linked directly or through one methylene group to piperidine, cyclopentane, or tetrahydropyran cycles, resulting in compounds with a more rigid structure. We herein report the synthesis of these compounds and the determination of their binding affinities for SERT, NET, DAT (dopamine transporter), and 5-HT receptors (5-HT_{1A}, 5-HT_{2A}).

Compounds of series **I** and **II** (Table 1) were synthesized by following the routes depicted in Scheme 1. Reduction of halo ketones **2a** and **2b** with sodium borohydride followed by reaction with different phenols under Mitsunobu conditions[23] yielded **3a**−**e**. Alkylation of (4-fluorophenyl)piperidin-4-ylmethanone,[24] 3-(piperazin-1-yl)benzo[*d*]isoxazole,[25] and 3-(piperazin-1-yl)-benzo[*d*]isothiazole[25] with properly substituted halides **3a**−**e** afforded **4a**−**l**. Compounds **4m,n** were prepared by reaction of **3f** with conveniently substituted phenols. Halide **3f** was obtained by alkylation of 3-(piperazin-1-yl)benzo[*d*]isothiazole[25] with halo ketone **2a**, reduction of resulting ketone with sodium borohydride, and treatment of corresponding alcohol with thionyl chloride.

Compounds of series **III** (Table 2) were prepared according to procedures described in Scheme 2. Thus, **7a**−**h** (R_3 = H, OCH_3) were synthesized by alkylation of conveniently substituted isoquinolines **5a,b** with 3-chloropropiophenone and later reduction of the ketone with sodium borohydride to give alcohols **6a,b**, which reacted with thionyl chloride, affording the corresponding chlorides. Reaction of these chlorides with adequately substituted phenols yielded compounds **7a**−**h**. Alternatively, **7i**−**l** (R_3 = OH) were prepared by demethylation of **5b** to give 5,6-dihydroxyisoquinoline, which was alkylated with 3-chloropropiophenone. Protection of hydroxyl groups with acetyl chloride followed by hydrogenation gave alcohol **6c**. Finally, reaction of alcohol **6c** with properly substituted phenols under Mitsunobu conditions[23] and deprotection provided compounds **7i**−**l**.

Compounds **10a**−**j** (Series **IV**, Table 3) were prepared from commercially available piperidine-3-carboxylic acid ethyl ester (Scheme 3). Thus, protection of nitrogen atom with benzyl bromide and hydrolysis of the ester group followed by treatment with thionyl chloride afforded the acyl chloride, which reacted with 4-fluorobenzene under Friedel−Crafts acylation conditions.[26] The nitrogen atom of the resulting ketone was deprotected by treatment with ethyl chloroformate followed

Chart 2. General Formula and Series of Synthesized Compounds

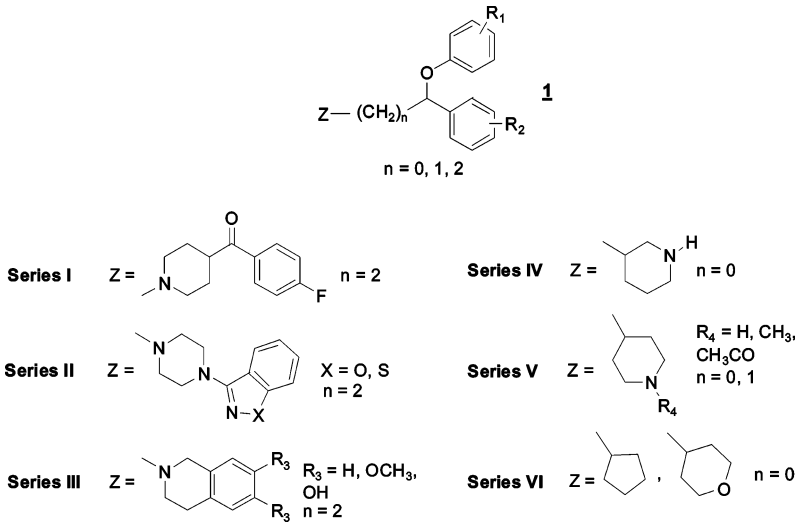
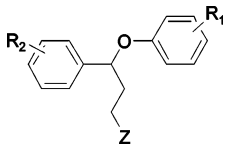


Table 1. Compounds of Series **I** and **II** (**4a**−**n**)



				K_i (nM)[a]		
compd	R_1	R_2	Z[b]	5-HT_{1A}	5-HT_{2A}	SERT
4a	2-F	H	C	70.2	5.3	>1000[c]
4b	2-F	H	B	117.7	17.2	>1000[c]
4c	3-CF_3	H	C	>1000[c]	28.2	>1000[c]
4d	4-OCH_3	H	C	69.7	10.2	>1000[c]
4e	4-OCH_3	H	B	182.0	18.9	>1000[c]
4f	4-NO_2	H	B	254.3	53.3	>1000[c]
4 g	2-F	H	A	37.8	8.0	>1000[c]
4h	4-OCH_3	H	A	93.6	53.8	>1000[c]
4i	4-NO_2	H	A	>1000[c]	23.0	>1000[c]
4j	4-NO_2	4-F	A	>1000[c]	55.1	>1000[c]
4k	4-NH_2	4-F	A	>1000[c]	14.4	>1000[c]
4l	4-NH_2	H	A	107.8	16.4	>1000[c]
4m	2-CF_3	H	C	445.6	24.1	>1000[c]
4n	4-CF_3	H	C	33.7	40.2	>1000[c]
8-OH-DPAT				1.2	>1000[c]	>1000[c]
mirtazapine				>1000[c]	14.8	>1000[c]
fluoxetine				>1000[c]	>1000[c]	30.8
paroxetine				>1000[c]	>1000[c]	0.7

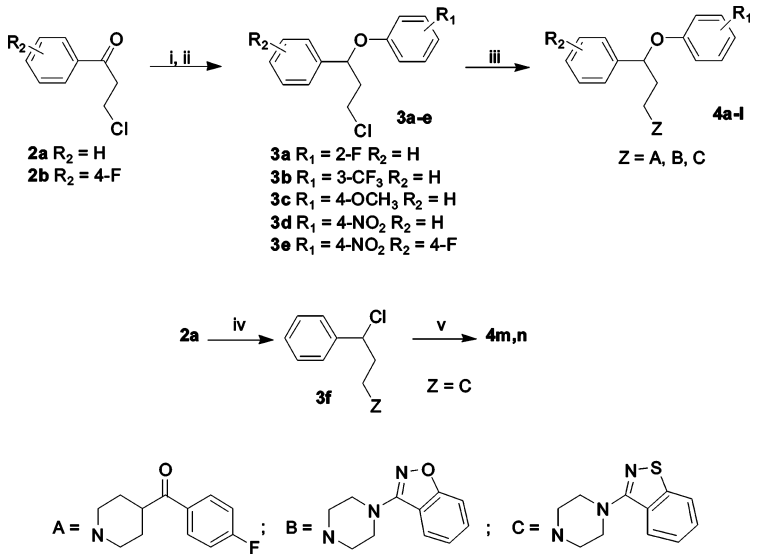
[a] SEM less than 15%. [b] Z: A, (4-fluorophenyl)piperidin-4-yl-methanone;[25] B, 3-(piperazin-1-yl)benzo[*d*]isoxazole;[26] C, 3-(piperazin-1-yl)benzo[*d*]isothiazole.[26] [c] IC_{50} (nM).

by glacial acetic acid and aqueous HBr to give **8**. Reaction with $(Boc)_2O$ followed by reduction with sodium borohydride afforded alcohols **9**, which underwent Mitsunobu reaction[23] with conveniently substituted phenols, yielding compounds **10a**−**j** as a mixture of diastereomers.

Alcohols **14a**−**k** were the key intermediates in the synthesis of racemic mixtures of compounds **15a-au**[27] (series **V**, Table 4), as shown in Scheme 4. Thus, alcohols **14a**−**k** were prepared from 1-acetylpiperidine-4-carboxylic acid,[24] 4-cyanopiperidine-1-carboxylic acid *tert*-butyl ester **12**,[28] or (1-acetylpiperidin-4-yl)acetic acid **13** by following known procedures. Treatment of 1-acetylpiperidine-4-carboxylic acid[24] with thionyl chloride gave the corresponding acyl chloride that after Friedel−Crafts acylation with conveniently substituted benzenes and deprotection with aqueous HCl solution afforded ketones **11a**−**c**. Protection of ketones **11a**−**c,f** as *tert*-butyl carbamate and reduction with sodium borohydride yielded alcohols **14a**−**c,f**. Reduction of ketone **11a** with sodium borohydride gave alcohol **14j**. Reaction of **11a** with formic acid/formaldehyde afforded ketone **11i**, which by reduction with sodium borohydride yielded alcohol **14h**. Isonipecotamide was treated with thionyl chloride followed by $(Boc)_2O$ to afford **12**,[28] which by reaction with the conveniently substituted Grignard reagents[24] gave ketones **11f,g**. Reduction of ketones **11f,g** with sodium borohydride yielded alcohols **14i** and **14k**. Treatment of 1-acetylpiperidine-4-carboxylic acid[24] with thionyl chloride gave corresponding acyl chloride that reacted under Friedel−Crafts acylation conditions with fluorobenzene to afford ketone **11h**, which was treated with sodium borohydride to yield alcohol **14g**. Alcohols **14d,e** were prepared from ketones **11d,e** by reduction with sodium borohydride, and these ketones were obtained from (1-acetylpiperidin-4-yl)acetic acid **13** as is shown in Scheme 4. Preparation of **13** started from 1-benzylpiperidin-4-one that was subjected to Wittig−Horner−Emmons reaction, reduction of the conjugated double bond, and deprotection of the nitrogen atom to give an intermediate compound which after protection of the amine group and hydrolysis of the ester afforded **13**. Racemic mixtures of compounds **15a-au**[27] (series **V**, Table 4) were obtained from racemic alcohols **14a**−**k** by standard procedures, either Mitsunobu[23] (method A) or aromatic nucleophilic substitution (method B) reactions,[29] followed if necessary by deprotection of the amine group. Enantiomers **15**[27] (series **V**, Table 6) were obtained either by fractional crystallization of diastereomeric dibenzoyltartrates (method C) or from enantioenriched alcohols **(+)-** or **(−)-14j,k** (method D). These alcohols **(+)-** or **(−)-14j,k** were prepared from ketones **11a,f** by reduction with (+) or (−)-*B*-chlorodiisopinocampheylborane[30] ((+) or (−)-DIPCl).

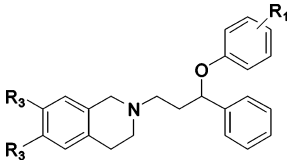
As is shown in Scheme 5, compounds **18** and **21** (series **VI**, Table 5) were obtained by aromatic nucleophilic substitution[29] from corresponding secondary alcohols **17** and **20**. Thus, **17** was prepared from commercially available cyclopentanecarboxylic acid following known procedures, and **20** was prepared from acid **19**[31] by treatment with thionyl chloride followed by Friedel−

Scheme 1. [a] General Synthesis of Series **I** and **II**



[a] Reagents: (i) $NaBH_4$, methanol; (ii) $R_1C_6H_4OH$, DEAD, Ph_3P, THF; (iii) A-H or B-H or C-H, K_2CO_3, CH_3CN; (iv) (a) C-H, K_2CO_3, CH_3CN, (b) $NaBH_4$, methanol, (c) $SOCl_2$, $CHCl_3$; (v) $R_1C_6H_4OH$, K_2CO_3, DMF.

Table 2. Compounds of Series **III** (**7a**−**l**)



			K_i (nM)[a]		
compd	R_1	R_3	5-HT_{1A}	5-HT_{2A}	SERT
7a	2-F	H	>1000[b]	>1000[b]	>1000[b]
7b	2-CF_3	H	>1000[b]	>1000[b]	>1000[b]
7c	4-Cl	H	>1000[b]	>1000[b]	>1000[b]
7d	4-CH_3	H	>1000[b]	>1000[b]	>1000[b]
7e	2-F	OCH_3	>1000[b]	>1000[b]	207.1
7f	2-CF_3	OCH_3	>1000[b]	>1000[b]	134.3
7g	4-Cl	OCH_3	>1000[b]	>1000[b]	>1000[b]
7h	4-CH_3	OCH_3	>1000[b]	>1000[b]	324.7
7i	2-F	OH	>1000[b]	>1000[b]	>1000[b]
7j	2-CF_3	OH	>1000[b]	>1000[b]	>1000[b]
7k	4-CH_3	OH	>1000[b]	>1000[b]	>1000[b]
7l	4-Cl	OH	>1000[b]	>1000[b]	>1000[b]
8-OH-DPAT			1.2	>1000[b]	>1000[b]
mirtazapine			>1000[b]	14.8	>1000[b]
fluoxetine			>1000[b]	>1000[b]	30.8
paroxetine			>1000[b]	>1000[b]	0.7

[a] SEM less than 15%. [b] IC_{50} (nM).

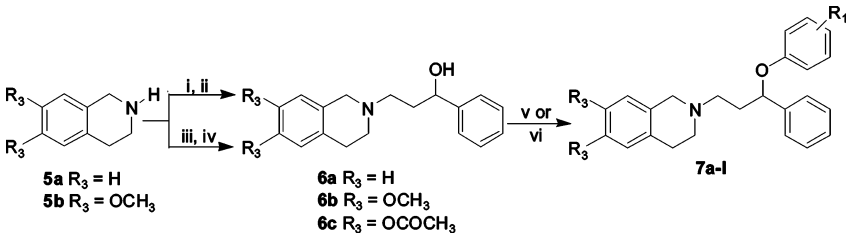
Crafts acylation conditions and reduction of the resulting ketone.

Biological Results and Discussion

Compounds of series **I**−**VI** were evaluated for their affinities for 5-HT_{1A} and 5-HT_{2A} receptors and SERT from rat brain using radioligand binding assays. Compounds that displayed good affinity for SERT were evaluated for their affinities for NET, DAT, and α_2 receptor to complete their binding profiles as potential antidepressants. Details of the performed binding assays are described in the Experimental Section. Structure and binding data of the compounds are shown in Tables 1−6.

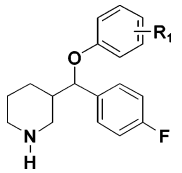
(4-Fluorophenyl)piperidin-4-ylmethanone, 3-(piperazin-1-yl)benzo[*d*]isoxazole, and 3-(piperazin-1-yl)benzo[*d*]-isothiazole derivatives **4a**−**n** (series **I** and **II**, Table 1) have shown low to moderate affinity values for 5-HT_{1A} (IC_{50} > 1000 nM to K_i = 33.7 nM) and moderate to high values for 5-HT_{2A} (K_i = 55.1−5.3 nM) receptors but neither of them exhibited significant affinity for SERT (IC_{50} > 1000 nM). The affinities for the 5-HT_{2A} receptor showed by compounds **4a**−**n** seem to be independent of the aryloxy substituents and could be associated with the heterocyclic moieties (4-fluorophenyl)piperidin-4-ylmethanone, 3-(piperazin-1-yl)benzo[*d*]isoxazole, and 3-(piperazin-1-yl)benzo[*d*]isothiazole present in several compounds described as 5-HT_{2A} receptor ligands.[25,32] Tetrahydroisoquinoline derivatives **7a**−**l** (series **III**, Table 2) lack significant affinities for 5-HT_{1A} and 5-HT_{2A} (IC_{50} > 1000 nM) receptors and 6,7-dimethoxy-substituted derivatives **7e**, **7f**, and **7h** displayed low affinity values for SERT (K_i = 207.1, 134.3, and 324.7 nM, respectively) that are much lower than that of fluoxetine (K_i = 30.8 nM). The common structural feature of all these compounds (series **I**, **II** and **III**, Chart 2) was the (aryl)(aryloxy)methyl moiety linked through a chain of two methylene groups to different substituted heterocycles, piperidine, piperazine, or isoquinoline, with a tertiary amine group instead of the secondary amine group present in fluoxetine and reboxetine. Since neither of the previously tested compounds showed good affinity for SERT, series **I**−**III** were not further pursued and our interest was focused on the synthesis of compounds of series **IV**−**VI**. In series **IV**, the (aryl)-(aryloxy)methyl moiety was linked directly to a piperidine ring at the 3-position while in series **V** that moiety was attached directly or through a methylene group to the 4-position of a piperidine ring. Thus, most compounds of both series have a secondary amine group as in fluoxetine and reboxetine. However, in series **VI** the (aryl)(aryloxy)methyl moiety was linked to cycles without any amine group. 3-Piperidine derivatives **10a**−**j** (series **IV**, Table 3), synthesized as diastereomeric mixtures and with an aryl group substituted at the 4-position with a fluoro atom, showed high affinity values for SERT (K_i = 40.6 to 4.2 nM) and lack of

Scheme 2. [a] General Synthesis of Series **III**



[a] Reagents: (i) 3-chloropropiophenone, K_2CO_3, CH_3CN; (ii) $NaBH_4$, methanol; (iii) (a) 45% HBr, (b) 3-chloropropiophenone, K_2CO_3, CH_3CN; (iv) (a) CH_3COCl, CH_3CO_2H, (b) H_2, 10% Pd/C, ethanol; (v) (a) $SOCl_2$, $CHCl_3$, (b) $R_1C_6H_4OH$, K_2CO_3, DMF; (vi) (a) $R_1C_6H_4OH$, DEAD, Ph_3P, THF, (b) 3 N HCl, methanol.

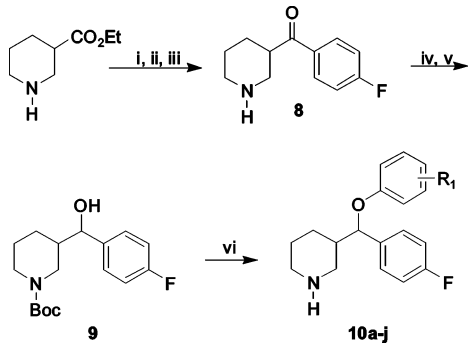
Table 3. Compounds of Series **IV** (**10a**−**j**)



compd	R_1	K_i (nM)[a] 5-HT_{1A}	5-HT_{2A}	SERT
10a	H	>1000[b]	>1000[b]	40.6
10b	4-F	>1000[b]	>1000[b]	23.4
10c	4-Cl	>1000[b]	>1000[b]	13.9
10d	4-CF_3	>1000[b]	>1000[b]	26.2
10e	4-CH_3	>1000[b]	>1000[b]	22.6
10f	4-OCH_3	>1000[b]	>1000[b]	20.8
10g	4-CN	>1000[b]	>1000[b]	40.0
10h	3,4-Cl	>1000[b]	>1000[b]	32.2
10i	OCH_2CH_2O	>1000[b]	>1000[b]	4.2
10j[c]		>1000[b]	>1000[b]	21.5
8-OH-DPAT		1.2	>1000[b]	>1000[b]
mirtazapine		>1000[b]	14.8	>1000[b]
fluoxetine		>1000[b]	>1000[b]	30.8
paroxetine		>1000[b]	>1000[b]	0.7

[a] SEM less than 15%. [b] IC_{50} (nM). [c] **10j**: the aryloxy group is 1-naphthyloxy.

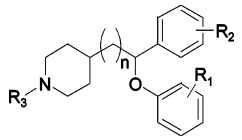
Scheme 3. [a] General Synthesis of Series **IV**



[a] Reagents: (i) (a) benzyl bromide, Na_2CO_3, CH_3CN, (b) 20% aq HCl; (ii) (a) $SOCl_2$, (b) 4-fluorobenzene, $AlCl_3$, dichloroethane; (iii) (a) $ClCO_2Et$, benzene, (b) glacial acetic acid, 48% aq HBr; (iv) $(Boc)_2O$, $NaHCO_3$, H_2O; (v) $NaBH_4$, H_2O, methanol; (vi) (a) $R_1C_6H_4OH$ (for **10j**: 1-naphthol), DEAD, Ph_3P or Ph_2PyP, THF, (b) CF_3COOH, CH_2Cl_2.

affinity for 5-HT_{1A} and 5-HT_{2A} (IC_{50} > 1000 nM) receptors. Compounds **10a**−**j** presented affinity values for SERT lower than that showed by paroxetine (K_i = 0.7 nM) but in the same range than fluoxetine or even better. The hydrophobic, electronic, and steric effects of aryloxy substitution seem to be ineffectual as the moderate to high affinity values found at SERT binding assay for all tested compounds suggest. 4-Piperidine

Table 4. Compounds of Series **V** (racemic mixtures **15a**−**au**[27])

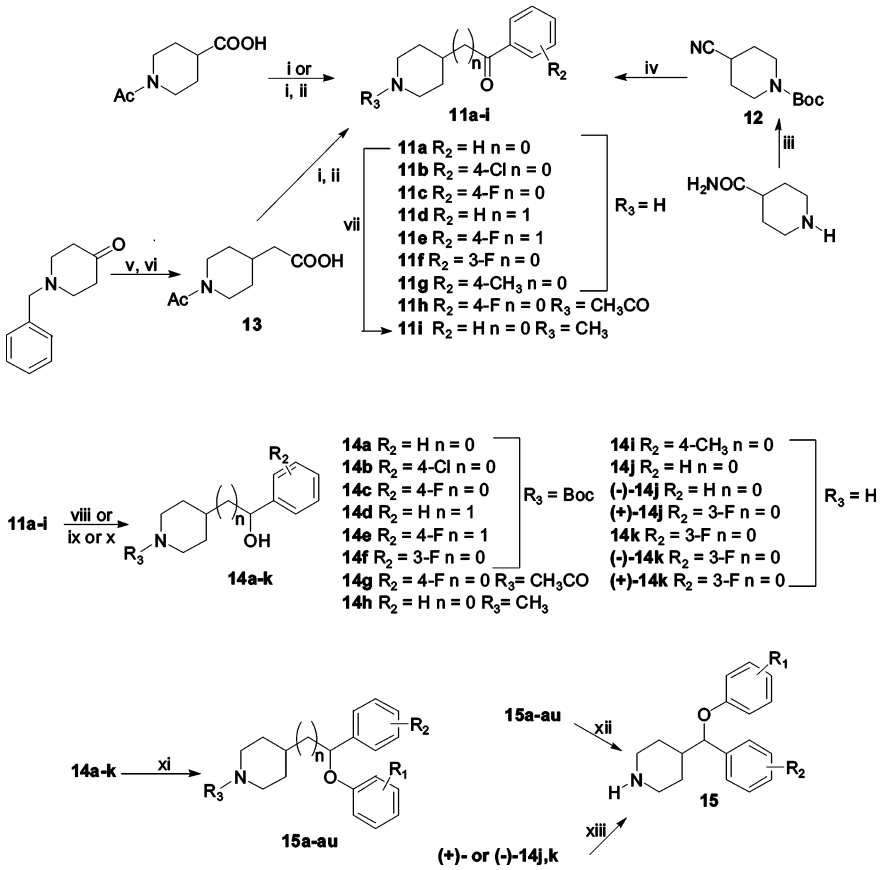


compd	R_1	R_2	R_3	n	K_i (nM)[a] 5-HT_{1A}	5-HT_{2A}	SERT
15a	H	H	H	0	>1000[b]	>1000[b]	2.3
15b	2-F	H	H	0	>1000[b]	>1000[b]	6.3
15c	2-CF_3	H	H	0	>1000[b]	>1000[b]	124.2
15d	2-CN	H	H	0	>1000[b]	>1000[b]	105.0
15e	2-phenyl	H	H	0	>1000[b]	149.1	>1000[b]
15f	2-Cl	H	H	0	>1000[b]	>1000[b]	8.2
15g	3-I	H	H	0	>1000[b]	>1000[b]	3.7
15h	3-Br	H	H	0	>1000[b]	>1000[b]	10.0
15i	3-CF_3	H	H	0	>1000[b]	>1000[b]	9.0
15j	3-F	H	H	0	>1000[b]	>1000[b]	1.0
15k	3-CN	H	H	0	>1000[b]	>1000[b]	1.0
15l	3-Cl	H	H	0	>1000[b]	>1000[b]	2.6
15m	4-NO_2	H	H	0	>1000[b]	>1000[b]	2.4
15n	4-I	H	H	0	>1000[b]	>1000[b]	20.6
15o	4-phenyl	H	H	0	>1000[b]	>1000[b]	>1000[b]
15p	4-F	H	H	0	>1000[b]	>1000[b]	1.1
15q	4-CF_3	H	H	0	>1000[b]	>1000[b]	17.1
15r	4-Br	H	H	0	>1000[b]	>1000[b]	2.0
15s	H	4-Cl	H	0	>1000[b]	>1000[b]	19.4
15t	2-F	3-F	H	0	>1000[b]	>1000[b]	9.3
15u	3-F	3-F	H	0	>1000[b]	>1000[b]	16.1
15v	3-F	4-CH_3	H	0	>1000[b]	>1000[b]	14.1
15x	4-F	3-F	H	0	>1000[b]	360.2	5.8
15y	4-F	4-Cl	H	0	>1000[b]	>1000[b]	7.5
15z	4-F	4-F	H	0	>1000[b]	>1000[b]	0.9
15ab	4-OCH_3	4-F	H	0	>1000[b]	>1000[b]	0.9
15ac	2-CH_3, 3-F	H	H	0	>1000[b]	>1000[b]	5.3
15ad	2-CH_3, 3-Cl	H	H	0	>1000[b]	>1000[b]	12.2
15ae	2-CH_3, 5-Cl	H	H	0	>1000[b]	>1000[b]	15.6
15af	3-Cl, 4-CN	H	H	0	>1000[b]	>1000[b]	3.9
15ag	3-Cl, 4-Cl	H	H	0	>1000[b]	>1000[b]	9.9
15ah	3-F, 5-OCH_3	H	H	0	>1000[b]	>1000[b]	1.9
15ai	3-F, 5-CN	H	H	0	>1000[b]	>1000[b]	2.6
15aj	3,5-diF	H	H	0	>1000[b]	>1000[b]	3.4
15ak	4-F	H	H	1	>1000[b]	139.9	78.3
15al	4-OCH_3	H	H	1	>1000[b]	>1000[b]	47.0
15am	4-F	4-F	H	1	>1000[b]	193.5	67.7
15an	4-CN	4-F	H	1	>1000[b]	>1000[b]	16.9
15ao	CH_3O	4-F	CH_3CO	0	>1000[b]	>1000[b]	>1000[b]
15ap	H	4-F	CH_3CO	0	>1000[b]	>1000[b]	>1000[b]
15aq	4-F	H	CH_3	0	>1000[b]	44.4	>1000[b]
15ar	2-OH, 3-F	H	H	0	>1000[b]	>1000[b]	15.5
15as	3-F, 4-OH	H	H	0	>1000[b]	>1000[b]	21.3
15at	3-OH, 5-F	H	H	0	>1000[b]	>1000[b]	2.0
15au[c]		H	H	0	>1000[b]	>1000[b]	8.3
8-OH-DPAT					1.2	>1000[b]	>1000[b]
mirtazapine					>1000[b]	14.8	>1000[b]
fluoxetine					>1000[b]	>1000[b]	30.8
paroxetine					>1000[b]	>1000[b]	0.7

[a] SEM less than 15%. [b] IC_{50} (nM). [c] **15au**: the aryloxy group is 1-naphthyloxy.

derivatives **15a**−**au**[27] (series **V**, Table 4) prepared as racemic mixtures displayed in most of the cases the

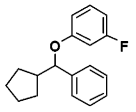
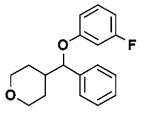
Scheme 4. [a] General Synthesis of Series **V**



[a] Reagents: (i) (a) $SOCl_2$, (b) $R_2C_6H_5$, $AlCl_3$, dichloroethane; (ii) 6 N HCl; (iii) (a) $SOCl_2$, (b) $(Boc)_2O$, $NaHCO_3$, H_2O; (iv) (a) $R_2C_6H_4MgX$, ether, (b) 10% aq HCl, methanol; (v)NaH, $(EtO)_2P(O)CH_2CO_2Et$, benzene; (vi) (a) H_2, 10% Pd/C, ethanol, (b) ammonium formate, ethanol, (c) Ac_2O; (vii) HCOOH, HCHO; (viii) (a) $(Boc)_2O$, $NaHCO_3$, H_2O, (b) $NaBH_4$, methanol; (ix) $NaBH_4$, methanol, H_2O; (x) $NaBH_4$, methanol or (+) or (-)-DIPCl, CH_2Cl_2; (xi) method A [(a) $R_1C_6H_4OH$, Ph_2PyP, DEAD, THF, (b) 10% aq HCl, methanol] or method B [(a) NaH, $R_1C_6H_4F$, potassium benzoate, DMSO, (b) 10% aq HCl, methanol] (xii) method C [(a) D- or L-dibenzoyltartaric acid, ethanol, methanol, (b) 10% aq NaOH]; (xiii) method D [(a) $(Boc)_2O$, methanol, (b) NaH, $R_1C_6H_4F$ (for **15au**, 1-fluoronaphthalene), potassium benzoate, DMSO, (c) 10% aq HCl, methanol, (d) D- or L-dibenzoyltartaric acid, ethanol, (e) 10 % aq NaOH].

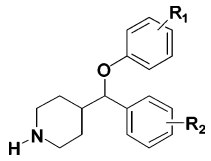
same affinity profile as compounds **10a**−**j** with moderate to very high affinity values for SERT (K_i = 124.4−0.9 nM) and lack of affinity for 5-HT_{1A} and 5-HT_{2A} receptors. Several compounds of series **V** showed much higher affinity for SERT than fluoxetine and approximately equal to paroxetine. As affinity profiles of series **IV** and **V** were similar, our interest was concentrated on compounds of series **V**, because they were racemic mixtures of enantiomers that could be resolved easier than diastereomeric mixtures of series **IV**. According to data shown in Table 4, most of the compounds **15a**−**au**[27] are potential antidepressants because they showed high affinity for SERT. However, there are some remarkable structural facts worth noting. In general, compounds having a substituent at the 2-position of the aryloxy group showed decreased affinity for SERT compared to parent compound **15a** (K_i = 2.3 nM), while substitution at the 3- or 4-position seems to maintain or even slightly increase the affinity for SERT. Thus, 3-fluoro (**15j**), 3-cyano (**15k**), 3-chloro (**15l**), 3-iodo (**15g**), 4-fluoro (**15p**), 4-nitro (**15m**), and 4-bromo (**15r**) substituted aryloxy compounds exhibited K_i values from 1.0 to 3.7 nM. The introduction of a second substituent on the aryloxy group of **15j** and **15l** did not improve and in some cases decreased the binding to SERT as showed by the more substituted compounds **15ac**−**ad**, **15af**−**aj**, **15ar**, and

Table 5. Compounds of Series **VI**

Compound	K_i (nM)[a] 5-HT_{1A}	5-HT_{2A}	SERT
 **18**	>1000[b]	>1000[b]	>1000[b]
 **21**	>1000[b]	>1000[b]	>1000[b]
8-OH-DPAT	1.2	>1000[b]	>1000[b]
mirtazapine	>1000[b]	14.8	>1000[b]
fluoxetine	>1000[b]	>1000[b]	30.8
paroxetine	>1000[b]	>1000[b]	0.7

[a] SEM less than 15%. [b] IC_{50} (nM).

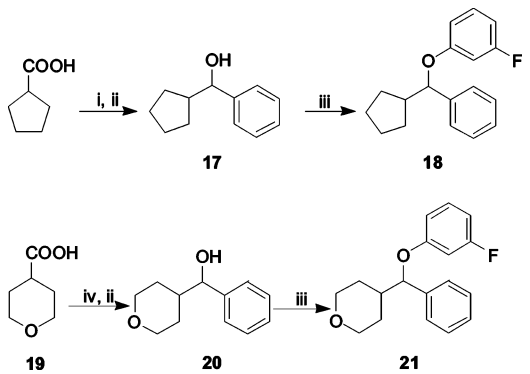
Table 6. Compounds of Series **V** (Enantiomers **15**[27])



			K_i (nM)[a]					
compd	R_1	R_2	5-HT_{1A}	5-HT_{2A}	SERT	NET	DAT	NET/SERT
(−)-**15b**	2-F	H	>1000[b]	>1000[b]	4.2	22.5	>1000[b]	5.4
(+)-**15b**	2-F	H	>1000[b]	>1000[b]	28.5	41.4	520.3	1.4
(−)-**15j**	3-F	H	>1000[b]	>1000[b]	1.9	13.5	461.3	6.9
(+)-**15j**	3-F	H	>1000[b]	>1000[b]	7.3	98.3	163.0	13.5
(−)-**15k**	3-CN	H	>1000[b]	>1000[b]	1.7	86.9	110.5	51.7
(+)-**15k**	3-CN	H	>1000[b]	>1000[b]	1.4	179.9	>1000[b]	125.8
(−)-**15l**	3-Cl	H	>1000[b]	>1000[b]	3.0	55.8	>500[b]	18.6
(+)-**15l**	3-Cl	H	>1000[b]	>1000[b]	1.5	44.0	>1000[b]	29.4
(−)-**15m**	4-NO_2	H	>1000[b]	>1000[b]	0.6	>500[b]	>1000[b]	
(+)-**15m**	4-NO_2	H	>1000[b]	>1000[b]	15.1	>1000[b]	>1000[b]	
(−)-**15p**	4-F	H	>1000[b]	>1000[b]	45.9	>1000[b]	253.4	
(+)-**15p**	4-F	H	>1000[b]	>1000[b]	0.4	111.4	821.0	247.6
(−)-**15q**	4-CF_3	H	nt[c]	nt[c]	34.8	>1000[b]	>1000[b]	
(+)-**15q**	4-CF_3	H	nt[c]	nt[c]	14.9	>1000[b]	>1000[b]	
(−)-**15r**	4-Br	H	>1000[b]	>1000[b]	5.7	>500[b]	>1000[b]	
(+)-**15r**	4-Br	H	>1000[b]	>1000[b]	23.2	>1000[b]	>1000[b]	
(−)-**15t**	2-F	3-F	>1000[b]	>1000[b]	4.3	19.1	>500[b]	4.4
(+)-**15t**	2-F	3-F	>1000[b]	>1000[b]	27.6	48.1	376.7	1.7
(−)-**15u**	3-F	3-F	>1000[b]	>1000[b]	10.0	127.8	112.8	12.8
(+)-**15u**	3-F	3-F	>1000[b]	>1000[b]	2.8	17.5	>500[b]	6.2
(−)-**15aj**	3,5-F_2	H	>1000[b]	>1000[b]	1.4	24.8	>1000[b]	17.7
(+)-**15aj**	3,5-F_2	H	>1000[b]	>1000[b]	7.1	385.9	>500[b]	54.4
(−)-**15au**[d]		H	>1000[b]	>1000[b]	28.1	>1000[b]	>1000[b]	
(+)-**15au**[d]		H	>1000[b]	>1000[b]	20.1	416.6	>1000[b]	20.7
8-OH-DPAT			1.2	>1000[b]	>1000[b]	>1000[b]	>1000[b]	
mirtazapine			>1000[b]	14.8	>1000[b]	>1000[b]	>1000[b]	
fluoxetine			>1000[b]	>1000[b]	30.8	>1000[b]	>1000[b]	
paroxetine			>1000[b]	>1000[b]	0.7	659.6	>1000[b]	942.3
reboxetine			>1000[b]	>1000[b]	>500[b]	13.7	>1000[b]	
nisoxetine			>1000[b]	>1000[b]	>500[b]	9.9	>500[b]	
venlafaxine			>1000[b]	>1000[b]	52.0	719.0	>1000[b]	15.7
mazindol			>1000[b]	>1000[b]	247.5	0.8	44.3	309.4[e]

[a] SEM less than 15%. [b] IC_{50} (nM). [c] Not tested. [d] **15au**: the aryloxy group is 1-naphthyloxy. [e] SERT/NET.

Scheme 5[a] General Synthesis of Series **VI**



[a] Reagents: (i) 85% phosphoric acid, $(CF_3SO_2)_2O$, benzene; (ii) $NaBH_4$, methanol, H_2O; (iii) (a) NaH, 1,3-difluorobenzene, potassium benzoate, DMSO, (b) 10% aq HCl; (iv) (a) $SOCl_2$, (b) $AlCl_3$, benzene

15as with K_i values ranging from 1.9 to 21.3 nM. It seems that hydrophobic, electronic, and hydrogen-bonding properties of the second substituent do not affect the affinity for SERT too much. Analogues **15ak**−**an** in which the (aryl)(aryloxy)methyl moiety was linked through a methylene to the piperidine ring exhibited moderate to high affinity values for SERT (K_i = 78.3−16.9 nM). The distance from the piperidine nitrogen to the (aryl)(aryloxy)methyl group does not seem to be critical, but affinity values were lower than those of compounds with the (aryl)(aryloxy)methyl moiety directly linked to the piperidine ring. Compounds **15s**−**ab** (K_i = 19.4 to 0.9 nM) with electron-withdrawing (−F, −Cl) or electron-donating ($-CH_3$) substituents at the aryl group displayed affinities that were in the same range as those showed by most of compounds of series **V**. Taking these findings into account it seems that binding to SERT does not depend on the electronic properties of the aryl group substitution. As is shown in Table 4, the introduction of aryloxy groups with extended conjugation leads to very divergent results of binding to SERT as in derivatives **15au** (K_i = 8.3 nM), **15e** (IC_{50} > 1000 nM), and **15o** (IC_{50} > 1000 nM). Thus, while affinity for SERT is retained in the naphthyloxy derivative **15au**, the introduction of a relatively bulky 2- or 4-phenyl substituent onto the aryloxy group (compounds **15e** and **15o**) resulted in lack of affinity. This could signify that 5-HT uptake sites are sensitive to bulky substitution at the aryloxy group. Another interesting feature to point out is that the introduction of an acetyl or a methyl group on the piperidine nitrogen has a deleterious effect to affinity for SERT. Thus, derivatives **15ao** (IC_{50} > 1000 nM), **15ap** (IC_{50} > 1000 nM), and **15aq** (IC_{50} > 1000 nM) do not bind to SERT and it seems that binding to SERT of compounds of series **V** needs the presence of a secondary amine. This

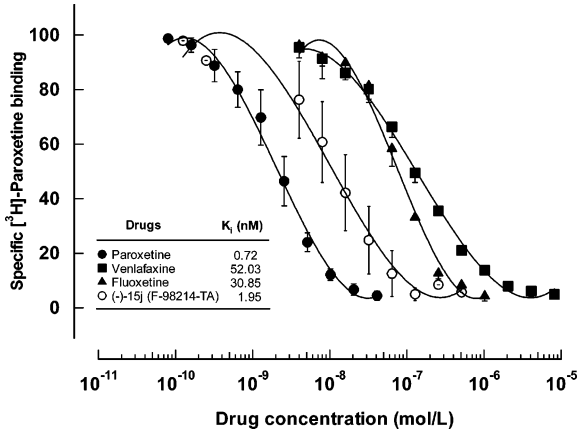


Figure 1. Competition for [^{3}H]paroxetine binding sites (SERT) in rat brain cortex by compound **(−)-15j** and antidepressant drugs.

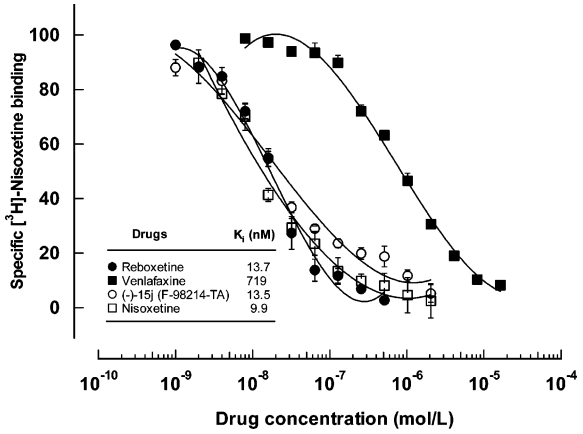


Figure 2. Competition for [^{3}H]nisoxetine binding sites (NET) in rat brain cortex by compound **(−)-15j** and antidepressant drugs.

is supported by the finding that compounds **18** and **21** (series **VI**, Table 5), which have cyclopentane or tetrahydropyran ring respectively instead of a piperidine ring, do not bind to SERT. Also, this fact could explain the low affinity for SERT of series **I, II**, and **III**. The resolution of some racemic mixtures of series **V** afforded enantiomers **15**[27] (Table 6), which were evaluated for their affinities for 5-HT_{1A} and 5-HT_{2A} receptors and SERT. These compounds displayed lack of affinity for 5-HT_{1A} and 5-HT_{2A} receptors and very high affinity for SERT with K_i values from 45.9 to 0.4 nM. Most of them bound with significant enantioselectivity to SERT, the highest ratio being (K_i **(−)-15p**/K_i **(+)-15p**) 115-fold. To extend their binding profile, enantiomers **15**[27] were tested for their affinities for NET, DAT, and α_2 receptor. As showed in Table 6, they displayed low to high affinity values for NET (IC_{50} > 1000 nM to K_i = 13.5 nM), low to moderate affinity for DAT (IC_{50} > 1000 nM to K_i = 110.5 nM) and did not exhibited affinity for the α_2 receptor (data not shown, IC_{50} > 1000 nM). Thus, several of these enantiomers [i.e., **(−)-15m**, **(−)-15q**, **(+)-15q**, **(−)-15r**, **(−)-15au**] showed binding profiles such as fluoxetine with very high affinity values for SERT and resulted in lack of affinity for NET, DAT, and α_2 receptor. Most of the compounds of Table 6 exhibited affinity values for NET lower than those of reboxetine (K_i = 13.7 nM) and nisoxetine (K_i = 9.9 nM) and higher than those of venlafaxine (K_i = 719.0 nM). Levorotatory enantiomers displayed the higher affinities. However, a group of these enantiomers, **(−)-15b** (K_i = 22.5 nM), **(−)-15j** (K_i = 13.5 nM), **(−)-15t** (K_i = 19.1 nM), and **(+)-15u** (K_i = 17.5 nM), exhibited affinities for NET in the same range as reboxetine and nisoxetine. Unlike these two compounds, which are selective for NET, this group of enantiomers showed a dual binding profile with a ratio NET/SERT < 10 and affinities with K_i < 25 nM for SERT and NET and very low for DAT. Enantiomers **(−)-15b**, **(−)-15j**, **(−)-15t**, and **(+)-15u** displayed dual binding profiles with affinity values higher than those of venlafaxine (SERT K_i = 52.0 nM, NET K_i = 719.0 nM, NET/SERT = 15.7) (Table 6). Figures 1 and 2 illustrate the dual SERT and NET binding profile of compound **(−)-15j**. Figure 1 shows competition of compound **(−)-15j** for [^{3}H]paroxetine SERT binding sites in rat brain cortex compared with those of paroxetine, venlafaxine, and fluoxetine. Figure 2 shows competition of compound **(−)-15j** for [^{3}H]nisoxetine NET binding sites in rat brain cortex compared with those of reboxetine, venlafaxine, and nisoxetine.

Conclusion

We have synthesized series of new [(aryl)(aryloxy)-methyl]piperidine, piperazine, isoquinoline, cyclopentane, and tetrahydropyran derivatives to find novel antidepressant drugs with faster onset of action and greater efficacy and safety than the current marketed antidepressants. Most of the synthesized compounds of series **IV** and **V** showed good affinity for SERT. A remarkable and common structural feature of compounds of these series is the presence of a secondary amine group, which seems to be critical for binding to SERT. This finding correlates with the fact that compounds of series **I**, **II**, **III**, and **VI** devoid of such a secondary amine lack affinity for SERT. Other factors such as the distance from the secondary amine to the (aryl)(aryloxy)methyl group and the nature of substituents on the aryl and aryloxy rings of compounds of series **IV** and **V** seem to affect slightly their affinity values for SERT. On the other hand, an important detail is that the introduction of a relatively bulky substituent onto the aryloxy group resulted in lack of affinity as occurs in compounds of series **V** and could signify that 5-HT uptake sites are sensitive to this type of substitution at the aryloxy group. Enantiomers of series **V** with high affinity for SERT were tested for their affinities for NET, DAT, and α_2 receptor. Among these compounds **(−)-15b**, **(−)-15j**, **(−)-15t**, and **(+)-15u** displayed dual SERT and NET binding profiles with values of K_i < 25 nM. From them **(−)-15j** was selected on the basis of its binding profile and antidepressant-like activity in different animal models of depression.[33] Further pharmacological characterization of **(−)-15j** (coded as F-98214-TA for these studies) as antidepressant is in progress.

Experimental Section

Chemistry. Flash column chromatography[34] was performed on silica gel, particle size 60 Å, mesh = 230−400 (Merck). Melting points were determined in open capillary tubes on a Büchi B-540 apparatus and are uncorrected. Elemental analyses are within ±0.4% of the theorical values. IR−FT spectra were taken on a Perkin-Elmer Spectrum One instrument on

KBr plates. The enantiomeric excess was determinated by HPLC using a Waters LC Module I Plus instrument with chiral columns (Chiralcel OD-R, Daicel or Lichro Cart 250-4/ Chiradex, Merck). Optical rotations were obtained on a Perkin-Elmer 341 polarimeter. ^{1}H and ^{13}C NMR were recorded on a Bruker AC-200 spectrometer; chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as an internal standard. Spectral data are consistent with assigned structures.

General Procedure for Preparation of Compounds 3a−e. 1-(3-Chloro-1-(4-fluorophenyl)propoxy)-4-nitrobenzene (3e). $NaBH_4$ (7.6 g, 0.2 mol) was added portionwise to a solution of 3-chloro-1-(4-fluorophenyl)propan-1-one (15.0 g, 80 mmol) in methanol (200 mL) over a period of 20 min at 0 °C. The mixture was stirred for 6 h until the IR carbonyl absorption band disappeared. Methanol was removed under reduced pressure and the residue partitioned between water and CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated, yielding the alcohol as an oil which was used without further purification. To a mixture of previously prepared alcohol (8.0 g, 42 mmol), 4-nitrophenol (5.9 g, 42 mmol), and Ph_3P (11.0 g, 42 mmol) in THF (anhydrous, 100 mL) at 0 °C was added dropwise a solution of diethyl azodicarboxylate (DEAD) (7.3 g, 6.6 mL, 42 mmol) in THF (anhydrous, 50 mL). The reaction was stirred at room temperature for 2 days. THF was removed and the dark residue was dissolved in CH_2Cl_2 and filtered through silica gel with CH_2Cl_2:hexane (1:1). The organic solvents were evaporated and the crude was purified by flash chromatography (CH_2Cl_2:hexane 1:1) to provide **3e** (7.9 g, 55%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.20−8.00 (m, 2H), 7.40−7.30 (m, 2H), 7.12−7.01 (m, 2H), 6.97−6.82 (m, 2H), 5.67−5.45 (m, 1H), 3.82−3.70 (m, 1H), 3.61−3.51 (m, 1H), 2.57−2.41 (m, 1H), 2.29−2.15 (m, 1H).

The following compounds were prepared analogously.

1-(3-Chloro-1-phenylpropoxy)-2-fluorobenzene (3a): oil; yield 72%; ^{1}H NMR ($CDCl_3$) δ 7.41−7.20 (m, 5H), 7.10−6.95 (m, 1H), 6.88−6.75 (m, 3H), 5.48−5.36 (m, 1H), 3.90−3.78 (m, 1H), 3.63−3.52 (m, 1H), 2.58−2.43 (m, 1H), 2.30−2.19 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 153.1 (d, J = 245.6 Hz, C−F), 145.8 (d, J = 10.5 Hz), 140.3, 128.7, 128.1, 126.0, 124.1 (d, J = 4.0 Hz), 121.6 (d, J = 6.8 Hz), 117.3, 116.2 (d, J = 18.5 Hz) 78.4, 41.2, 41.1.

1-(3-Chloro-1-phenylpropoxy)-3-trifluoromethylbenzene (3b): oil; yield 56%; ^{1}H NMR ($CDCl_3$) δ 7.39−6.92 (m, 9H), 5.46−5.37 (m, 1H), 3.82−3.71 (m, 1H), 3.60−3.49 (m, 1H), 2.5−2.4 (m, 1H), 2.22−2.10 (m,1H); ^{13}C NMR ($CDCl_3$) δ 158.0, 140.0, 131.7 (q, J = 32.2 Hz), 129.9, 128.9, 128.2, 125.9, 123.9 (q, J = 272.3 Hz), 118.8 (d, J = 1.3 Hz), 117.6 (q, J = 3.8 Hz), 113.3 (q, J = 3.9 Hz), 77.2, 41.1, 41.0.

1-(3-Chloro-1-phenylpropoxy)-4-methoxybenzene (3c): oil; yield 52%; ^{1}H NMR ($CDCl_3$) δ 7.40−7.25 (m, 5H), 6.80−6.64 (m, 4H), 5.27−5.21 (m, 1H), 3.87−3.52 (m, 2H), 3.70 (s, 3H), 2.70−2.58 (m, 1H), 2.23−2.13 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 153.9, 151.9, 141.0, 128.6, 127.7, 125.9, 117.1, 114.4, 77.7, 55.5, 41.3.

1-(3-Chloro-1-phenylpropoxy)-4-nitrobenzene (3d): colorless oil; yield 70%; ^{1}H NMR ($CDCl_3$) δ 8.07 (d, J = 9.2 Hz, 2H), 7.36−7.24 (m, 5H), 6.91 (d, J = 9.2 Hz, 2H), 5.53−5.46 (m, 1H), 3.84−3.72 (m, 1H), 3.63−3.52 (m, 1H), 2.57−2.42 (m, 1H), 2.32−2.18 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 162.5, 141.5, 138.9, 129.0, 128.4, 125.70, 125.66, 115.7, 77.5, 40.9, 40.8.

Preparation of 3-[4-[3-Chloro-3-phenylpropyl]piperazin-1-yl]benzo[*d*]isothiazole (3f). A mixture of 3-chloro-1-phenylpropan-1-one **2a** (4.1 g, 24 mmol), 3-(piperazin-1-yl)benzo[*d*]isothiazole (5.0 g, 24 mmol), and anhydrous K_2CO_3 (4.0 g, 28 mmol) in acetonitrile (200 mL) was heated overnight at 90 °C. The solvent was removed, the residue partitioned between water and CH_2Cl_2, and the organic layer washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude was purified by flash chromatography (CH_2Cl_2: methanol 98:2) and the obtained product (6.0 g, 17 mmol) dissolved in methanol (100 mL). The solution was cooled with an ice bath, treated with $NaBH_4$ (1.6 g, 43 mmol), and stirred 5 h at room temperature. The solvent was removed, the residue partitioned between water and CH_2Cl_2, and the organic layer washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude was purified by flash chromatography (CH_2Cl_2:MeOH 98:2), yielding the alcohol (5.6 g, 16 mmol) which was dissolved in Cl_3CH (25 mL) and treated dropwise with a solution of $SOCl_2$ (2.3 mL, 32 mmol) in Cl_3CH (25 mL). The mixture was stirred overnight, affording **3f** as a white solid (87% yield) after addition of Et_2O and filtration: ^{1}H NMR ($CDCl_3$ + one drop of CD_3OD) δ 7.94−7.82 (m, 2H), 7.58−7.26 (m, 7H), 5.12 (t, J = 8.3 Hz, 1H), 4.23−3.81 (m, 4H), 3.76−3.62 (m, 2H), 3.43−3.18 (m, 4H), 2.84−2.67 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 164.0, 152.1, 142.5, 139.8, 132.2, 128.5, 128.2, 127.9, 126.9, 123.8, 120.4, 61.0, 54.3, 52.9, 52.8, 50.0, 37.4.

General Procedure for Preparation of Compounds 4a−j,m,n. 3-[4-[3-(2-Fluorophenoxy)-3-phenylpropyl]piperazin-1-yl]benzo[*d*]isothiazole Hydrochloride (4a). A mixture of **3a** (1.3 g, 4.9 mmol), 3-(piperazin-1-yl)benzo[*d*]-isothiazole (1.0 g, 4.9 mmol), and anhydrous K_2CO_3 (0.8 g, 5.8 mmol) in acetonitrile (50 mL) was refluxed over 48 h. The solvent was removed, the residue partitioned between water and CH_2Cl_2, and the organic layer washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude was purified by flash chromatography (CH_2Cl_2: MeOH 99:1). The purified product was dissolved in Et_2O and treated with a saturated solution of HCl(g) in Et_2O to give the hydrochloride **4a** as a white solid (1.4 g, 58%): mp 170−172 °C; ^{1}H NMR ($CDCl_3$) δ 7.90−7.80 (m, 2H), 7.43−7.21 (m, 7H), 7.10−6.98 (m, 1H), 6.97−6.79 (m, 3H), 5.38−5.26 (m, 1H), 3.6−3.55 (m, 4H), 2.7−2.6 (m, 6H), 2.40−2.20 (m, 1H), 2.18−1.98 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 163.9, 153.2 (d, J = 245.2 Hz, C−F), 152.7, 146.1 (d, J = 10.4 Hz), 141.3, 128.5, 128.0, 127.7, 127.4, 126.1, 124.0, 123.8 (d, J = 2.4 Hz), 121.3 (d, J = 7 Hz), 120.5, 117.4 (d, J = 1.3 Hz), 116.1 (d, J = 18.5 Hz), 80.1, 54.4, 52.9, 50.1, 35.7. Anal. ($C_{26}H_{26}FN_3OS$·HCl) C, H, N.

The following compounds were prepared analogously.

3-[4-[3-(2-Fluorophenoxy)-3-phenylpropyl]piperazin-1-yl]benzo[*d*]isoxazole hydrochloride (4b): white solid; mp 183−185 °C; yield 53%; ^{1}H NMR ($CDCl_3$) δ 7.72−7.60 (d, J = 8.5 Hz, 1H), 7.50−7.10 (m, 8H), 7.10−7.0 (m, 1H), 6.92−6.77 (m, 3H), 5.37−5.23 (m, 1H), 3.63−3.52 (m, 4H), 2.70−2.58 (m, 6H), 2.39−2.28 (m, 1H), 2.15−1.98 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 163.9, 161.3, 153.2 (d, J = 245.2 Hz, C−F), 146.1 (d, J = 10.4 Hz), 141.3, 129.4, 128.6, 127.8, 126.1, 124.0 (d, J = 3.8 Hz), 122.2, 122.1, 121.3 (d, J = 7.1 Hz), 117.4, 116.17, 116.16 (d, J = 18.5 Hz), 110.4, 80.1, 54.4, 52.5, 48.3, 35.7. Anal. ($C_{26}H_{26}FN_3O_2$·HCl) C, H, N.

3-[4-[3-Phenyl-3-(3-trifluoromethylphenoxy)propyl]-piperazin-1-yl]benzo[*d*]isothiazole hydrochloride (4c): yellow solid; mp 191−194 °C; yield 37%; ^{1}H NMR (CD_3OD) δ 8.06−8.02 (d, J = 8.7 Hz, 1H), 7.93−7.89 (d, J = 8.6 Hz, 1H), 7.54−7.11 (m, 11H), 5.58−5.50 (m, 1H), 4.20−4.10 (m, 2H), 3.76−3.71 (m, 2H), 3.52−3.40 (m, 6H), 2.60−2.38 (m, 2H); ^{13}C NMR (CD_3OD) δ 163.4, 159.0, 154.2, 140.9, 132.6 (q, J = 32.1 Hz), 131.3, 130.0, 129.5, 129.3, 128.5, 127.2, 125.7, 125.3 (q, J = 271.4 Hz), 124.8, 121.7, 120.6, 118.7 (q, J = 3.8 Hz), 114.1 (q, J = 3.8 Hz), 78.7, 55.3, 52.9, 48.3, 33.9. Anal. ($C_{27}H_{26}F_3N_3OS$·HCl) C, H, N.

3-[4-[3-(4-Methoxyphenoxy)-3-phenylpropyl]piperazin-1-yl]benzo[*d*]isothiazole hydrochloride (4d): white solid; mp 135 °C (dec); yield 45%; ^{1}H NMR ($CDCl_3$) δ 7.93−7.81 (d, J = 8.3 Hz, 1H), 7.80−7.65 (d, J = 8.4 Hz, 1H), 7.40−7.20 (m, 7H), 6.80−6.68 (m, 4H), 5.20−5.10 (m, 1H), 3.65 (s, 3H), 3.55−3.45 (m, 4H), 2.64−2.50 (m, 6H), 2.30−2.20 (m, 1H), 2.10−1.90 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 163.7, 153.6, 152.5, 152.2, 141.9, 128.3, 127.8, 127.3, 125.9, 123.7, 123.68, 120.3, 116.9, 115.2, 114.3, 79.0, 55.3, 54.5, 52.8, 50.0, 35.8. Anal. ($C_{27}H_{29}N_3O_2S$·HCl) C, H, N.

3-[4-[3-(4-Methoxyphenoxy)-3-phenylpropyl]piperazin-1-yl]benzo[*d*]isoxazole hydrochloride (4e): white solid; mp 186−188 °C; yield 60%; ^{1}H NMR ($CDCl_3$) δ 7.75−7.61 (d, J = 8.7 Hz, 1H), 7.47−7.18 (m, 8H), 6.80−6.63 (m, 4H), 5.20−5.10 (m, 1H), 3.70 (s, 3H), 3.60−3.51 (m, 4H), 2.70−2.55 (m,

6H), 2.30−1.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 163.9, 161.3, 153.8, 152.3, 142.0, 129.4, 128.5, 127.5, 126.0, 122.2, 122.1, 117.0, 116.2, 114.4, 110.4, 79.2, 55.6, 54.7, 52.5, 48.3, 35.9. Anal. ($C_{27}H_{29}N_3O_3$·HCl) C, H, N.

3-[4-[3-(4-Nitrophenoxy)-3-phenylpropyl]piperazin-1-yl]benzo[*d*]isoxazole hydrochloride (4f): white solid; mp 153 °C (dec); yield 49%; ^{1}H NMR ($CDCl_3$) δ 8.07 (d, J = 8.4 Hz, 2H), 7.77−7.62 (m, 1H), 7.42−7.16 (m, 8H), 6.89 (d, J = 8.3 Hz, 2H), 5.43−5.36 (m, 1H), 3.62−3.45 (m, 4H), 2.70−2.50 (m, 6H), 2.38−2.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 163.6, 163.0, 161.0, 141.0, 140.0, 129.2, 128.6, 127.9, 125.6, 125.4, 122.0, 121.9, 115.9, 115.5, 110.1, 78.8, 54.0, 52.2, 48.0, 35.4. Anal. ($C_{26}H_{26}N_4O_4$·HCl) C, H, N.

1-[3-(2-Fluorophenoxy)-3-phenylpropyl]piperidin-4-yl]-(4-fluorophenyl)methanone hydrochloride (4g): white solid; mp 145−147 °C; yield 44%; ^{1}H NMR ($CDCl_3$) δ 8.03−7.95 (m, 2H), 7.65−7.40 (m, 11H), 5.37−5.24 (m, 1H), 3.24−2.85 (m, 3H), 2.58−1.78 (m, 10H); ^{13}C NMR ($CDCl_3$) 201.0, 165.5 (d, J = 254.4 Hz, C−F), 153.1 (d, J = 245.4 Hz, C−F), 146.1 (d, J = 10.4 Hz), 141.3, 132.4 (d, J = 2.9 Hz), 130.8 (d, J = 9.3 Hz), 128.5, 127.7, 126.0, 123.9 (d, J = 3.7 Hz), 121.2 (d, J = 6.8 Hz), 117.3 (d, J = 1.3 Hz), 116.2, 115.9, 115.4, 80.0, 54.5, 53.3, 53.0, 43.7, 35.8, 28.8. Anal. ($C_{27}H_{27}F_2NO_2$·HCl) C, H, N.

(4-Fluorophenyl)-[1-[3-(4-methoxyphenoxy)-3-phenylpropyl]piperidin-4-yl]methanone hydrochloride (4h): white solid; mp 181 °C (dec); yield 32%; ^{1}H NMR (acetone-d_6) δ 8.18−8.09 (m, 2H), 7.44−7.18 (m, 7H), 6.85−6.62 (m, 4H), 5.48−5.41 (m, 1H), 4.02−3.82 (m, 1H), 3.79−3.60 (m, 2H), 3.72 (s, 3H), 3.57−3.08 (m, 5H), 2.59−2.35 (m, 5H); ^{13}C NMR (acetone-d_6) 199.9, 168.9 (d, J = 256.0 Hz, C−F), 155.0, 152.5, 142.3, 133.0, 132.2 (d, J = 9.4 Hz), 129.3, 128.6, 127.1, 118.1, 116.5 (d, J = 21.8 Hz), 115.1, 78.9, 55.7, 54.9, 52.5, 52.0, 41.7, 33.2, 28.6, 26.6. Anal. ($C_{28}H_{30}FNO_3$·HCl) C, H, N.

(4-Fluorophenyl)-[1-[3-(4-nitrophenoxy)-3-phenylpropyl]piperidin-4-yl]methanone hydrochloride (4i): white solid; mp 117 °C (dec); yield 44%; ^{1}H NMR ($CDCl_3$) δ 8.10−7.95 (m, 4H), 7.38−7.21 (m, 5H), 7.22−7.14 (m, 2H), 6.97−6.83 (d, J = 9.0 Hz, 2H), 5.45−5.27 (m, 1H), 3.26−3.17 (m, 2H), 3.06−2.90 (m, 3H), 2.56−2.42 (m, 3H), 2.39−1.87 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 200.9, 165.4 (d, J = 254.5 Hz, C−F), 163.2, 141.1, 140.3, 132.3 (d, J = 3 Hz), 130.7 (d, J = 9.4 Hz), 128.7, 127.9, 125.8, 125.6, 115.6, 115.59 (d, J = 22 Hz), 79.1, 54.2, 53.1, 53.0, 43.5, 35.7, 28.7, 28.6. Anal. ($C_{27}H_{27}FN_2O_4$·HCl) C, H, N.

(4-Fluorophenyl)-[1-[3-(4-fluorophenyl)-3-(4-nitrophenoxy)propyl]piperidin-4-yl]methanone hydrochloride (4j): brown solid; mp 92 °C (dec); yield 49%; ^{1}H NMR ($CDCl_3$) δ 8.15−7.85 (m, 4H), 7.40−7.15 (m, 2H), 7.20−6.85 (m, 6H), 5.44−5.35 (m, 1H), 3.30−3.10 (m, 1H), 3.02−2.87 (m, 2H), 2.58−1.7 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 200.9, 165.5 (d, J = 246.5 Hz, C−F), 163.0, 162.2 (d, J = 246.5 Hz), 141.2, 136.1 (d, J = 3.2 Hz), 132.3 (d, J = 3.2 Hz), 130.7 (d, J = 9.1 Hz), 127.6 (d, J = 8.1 Hz), 125.6, 115.63, 115.64 (d, J = 21.6 Hz), 115.62 (d, J = 21.7 Hz), 78.4, 54.0, 53.1, 43.4, 35.6, 28.6. Anal. ($C_{27}H_{26}F_2N_2O_4$·HCl) C, H, N.

3-[4-[3-Phenyl-3-(2-trifluoromethylphenoxy)propyl]-piperazin-1-yl]benzo[*d*]isothiazole hydrochloride (4m): white solid; mp 170−173 °C; yield 30%; ^{1}H NMR (CD_3OD) δ 8.05 (d, J = 8 Hz, 1H), 7.97 (d, J = 8 Hz, 1H), 7.58−7.30 (m, 9H), 7.07−6.95 (m, 2H), 5.67−5.40 (m, 1H), 4.22−4.10 (m, 2H), 3.75−3.40 (m, 8H), 2.58−2.43 (m, 2H); ^{13}C NMR (Acetone-d_6) δ 162.4, 155.2, 152.8, 140.0, 133.6, 128.8, 128.4, 128.1, 128.0, 126.6 (q, J = 5.2 Hz), 126.1, 124.4, 123.9, 120.8, 120.3, 118.2 (q, J = 30.6 Hz), 114.8, 77.3, 53.6, 51.6, 50.7, 46.5, 32.2. Anal. ($C_{27}H_{26}F_3N_3OS$·HCl) C, H, N.

3-[4-[3-Phenyl-3-(4-trifluoromethylphenoxy)propyl]-piperazin-1-yl]benzo[*d*]isothiazole hydrochloride (4n): white solid; mp 195−198 °C; yield 38%; ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 7.9 Hz, 2H), 7.79 (d, J = 7.9 Hz, 2H), 7.49−7.24 (m, 7H), 6.92 (d, J = 8.7 Hz, 2H), 5.33 (dd, J = 7.9, 5.1 Hz, 1H), 3.59−3.46 (m, 4H), 2.70−2.55 (m, 6H), 2.33−2.00 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 163.9, 160.6, 152.7, 141.0, 128.7, 128.5, 128.0, 127.8, 126.8, 126.74, 126.66, 123.8, 122.5 (q, J = 30.5 Hz), 120.5, 115.7, 78.6, 54.4, 53.0, 50.1, 35.8. Anal. ($C_{27}H_{26}F_3N_3OS$·HCl) C, H, N.

General Procedure for Preparation of Compounds 4k,l. [1-[3-(4-Aminophenoxy)-3-(4-fluorophenyl)propyl]-piperidin-4-yl](4-fluorophenyl)methanone Hydrochloride (4k). A vigorously stirred solution of **4j** (2.1 g, 4.1 mmol) in ethanol (5.1 mL) was heated to reflux and treated with 10% aqueous NaOH solution (5.1 mL). Zinc dust (2.5 g) was added in portions to maintain the gentle reflux. Once the addition was completed, the reaction mixture was filtered and the filtrate poured into water and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (CH_2Cl_2: MeOH 95:5), yielding an oil (1.4 g, 79% yield) which by treatment with a saturated solution of HCl (g) in Et_2O afforded the hydrochloride **4k** as a white solid: mp 80 °C (dec); ^{1}H NMR ($CDCl_3$) δ 8.05−7.90 (m, 2H), 7.37−7.26 (m, 2H), 7.19−6.90 (m, 4H), 6.75−6.60 (d, J = 8.7 Hz, 2H), 6.57−6.47 (d, 2H), 5.15−5.02 (m, 1H), 3.60−3.10 (bs, 1H), 3.09−2.90 (m, 2H), 2.56−2.40 (m, 2H), 2.30−1.72 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 201.1, 165.6 (d, J = 254.5 Hz), 162.0 (d, J = 245.5 Hz), 151.0, 140.2, 138.0 (d, J = 3.2 Hz), 132.4 (d, J = 3 Hz), 130.8 (d, J = 9.3 Hz), 127.8 (d, J = 8.1 Hz), 117.4, 116.1, 115.7 (d, J = 22 Hz), 115.2(d, J = 22 Hz), 78.8, 54.7, 53.2, 53.1, 43.7, 35.9, 28.8. Anal. ($C_{27}H_{28}F_2N_2O_2$·HCl) C, H, N.

The following compound was prepared analogously.

[1-[3-(4-Aminophenoxy)-3-phenylpropyl]piperidin-4-yl](4-fluorophenyl)methanone hydrochloride (4l): white solid; mp 178 °C (dec); yield 50%; ^{1}H NMR ($CDCl_3$) δ 8.15−8.08 (m, 2H), 7.47−7.20 (m, 9H), 7.07−7.02 (d, J = 8.7 Hz, 2H), 5.55−5.49 (m, 1H), 3.83−3.67 (m, 3H), 3.48−3.23 (m, 5H), 2.51−2.43 (m, 2H), 2.16−1.99 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 200.9, 167.1 (d, J = 253.8 Hz), 158.8, 140.9, 132.9 (d, J = 2.7 Hz), 132.6 (d, J = 9.4 Hz), 129.8, 129.3, 127.2, 125.2, 124.7, 118.3, 116.8 (d, J = 22.1 Hz), 78.6, 55.2, 53.1, 41.5, 33.7, 27.3. Anal. ($C_{27}H_{29}FN_2O_2$·HCl) C, H, N.

General Procedure for Preparation of Compounds 6a,b. 3-(3,4-Dihydro-1*H*-isoquinolin-2-yl)-1-phenylpropanol (6a). A mixture of **5a** (6.7 g, 50 mmol), 3-chloropropiophenone (8.4 g, 50 mmol), anhydrous K_2CO_3 (14.0 g, 100 mmol), and acetonitrile (250 mL) was stirred at room temperature for 16 h and the solvent removed under reduced pressure. The residue was treated with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to give 3-(3,4-dihydro-1*H*-isoquinolin-2-yl)-1-phenylpropanone as an oil in quantitative yield. $NaBH_4$ (3.8 g, 100 mmol) was added portionwise to a well stirred solution of 3-(3,4-dihydro-1*H*-isoquinolin-2-yl)-1-phenylpropanone (11.7 g, 40 mmol) in methanol (100 mL) over a period of 20 min at 0 °C. The stirring was continued for 16 h and methanol removed under reduced pressure. The residue was partitioned between water and CH_2Cl_2 and the organic layer washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated affording in quantitative yield **6a** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.45−7.20 (m, 5H), 7.15−7.03 (m, 4H), 5.06−4.92 (m, 1H), 3.78 (d, J = 16.8 Hz, 1H), 3.64 (d, J = 16.8 Hz, 1H), 2.94−2.68 (m, 6H), 1.98−1.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 144.9, 133.9, 128.5, 128.1, 126.8, 126.4, 126.3, 125.7, 125.5, 75.3, 56.6, 56.1, 50.6, 34.0, 28.8.

Compound **6b** was prepared analogously.

3-(6,7-Dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-1-phenylpropanol (6b): oil; yield quantitative; ^{1}H NMR ($CDCl_3$) δ 7.42−7.20 (m, 5H), 6.65 (s, 1H), 6.54 (s, 1H), 5.04−4.95 (m, 1H), 3.85 (s, 6H), 3.76 (d, J = 16.9, 1H), 3.64 (d, J = 16.9, 1H), 2.94−2.62 (m, 6H), 1.95−1.87 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 147.6, 147.2, 144.9, 128.1, 126.8, 125.8, 125.6, 125.4, 111.2, 109.3, 75.4, 56.5, 55.8, 55.6, 50.7, 33.9, 28.4.

General Procedure for Preparation of Compounds 7a−h. 2-[3-(2-Fluorophenoxy)-3-phenylpropyl]-1,2,3,4-tetrahydroisoquinoline Fumarate (7a). Thionyl chloride (2.4 mL, 30 mmol) was added dropwise to a solution of **6a** (6.7 g, 25 mmol) in $CHCl_3$ (30 mL). The mixture was stirred at room temperature for 16 h. The reaction mixture was filtered,

the solid treated with 10% aqueous NaOH solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated, yielding 2-(3-chloro-3-phenylpropyl)-1,2,3,4-tetrahydroisoquinoline (4.4 g 62%). A mixture of 2-(3-chloro-3-phenylpropyl)-1,2,3,4-tetrahydroisoquinoline (1.2 g, 4 mmol), 2-fluorophenol (0.6 g, 5 mmol), anhydrous K_2CO_3 (1.1 g, 8 mmol), and DMF (20 mL) was stirred at 60 °C for 4 h and then poured into water (100 mL). The aqueous solution was extracted with Et_2O and the organic layer washed with brine and concentrated. The residue was purified by flash chromatography on silica gel (Cl_2CH_2:MeOH 98:2) to give **7a** (1.2 g, 84%) as an oil that was converted into the fumarate salt: mp 168−170 °C; ^{1}H NMR ($CDCl_3$) δ 7.40−7.25 (m, 5H), 7.15−7.05 (m, 5H), 6.92−6.75 (m, 3H), 5.35−5.25 (m, 1H), 3.65 (s, 2H), 2.95−2.85 (m, 2H), 2.75−2.60 (m, 4H), 2.45−2.30 (m, 1H), 2.15−2.00 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 153.2 (d, J = 241.2 Hz) 146.2 (d, J = 10 Hz), 141.4, 134.9, 134.4, 128.6, 127.7, 126.5, 126.1, 126.0, 125.5, 124.0 (d, J = 3.9 Hz), 121.2 (d, J = 6.5 Hz), 117.4, 116.2 (d, J = 18.4 Hz), 80.0, 56.1, 54.3, 51.0, 36.1, 29.3. Anal. ($C_{24}H_{24}FNO\cdot C_4H_4O_4$) C, H, N.

The following compounds were prepared analogously.

2-[3-Phenyl-3-(2-trifluoromethylphenoxy)propyl]-1,2,3,4-tetrahydroisoquinoline fumarate (7b): white solid; mp 145−147 °C; yield 91%; ^{1}H NMR ($CDCl_3$) δ 7.58−7.50 (m, 1H), 7.40−6.75 (m, 12 H), 5.55−5.40 (m, 1H), 3.65 (s, 2H), 2.95−2.85 (m, 2H), 2.70−2.55 (m, 4H), 2.40−2.25 (m, 1H), 2.20−2.05 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 156.2 (q, J = 1.7 Hz), 141.1, 134.8, 134.3, 132.9, 128.7, 128.6, 127.7, 126.8 (q, J = 4.8 Hz), 126.5, 126.0, 125.8, 121.1, 119.7 (q, J = 31.2 Hz), 118.6, 114.1, 78.2, 56.1, 54.0, 50.9, 36.3, 29.2. Anal. ($C_{25}H_{24}F_3NO\cdot C_4H_4O_4$) C, H, N.

2-[3-(4-Chlorophenoxy)-3-phenylpropyl]-1,2,3,4-tetrahydroisoquinoline fumarate (7c): white solid; mp 133−135 °C; yield 60%; ^{1}H NMR ($CDCl_3$) δ 7.35−7.20 (m, 5H), 7.15−6.95 (m, 6H), 6.75 (d, J = 10 Hz, 2H), 5.35−5.20 (m, 1H), 3.60 (s, 2H), 2.95−2.80 (m, 2H), 2.75−2.58 (m, 4H), 2.36−2.18 (m, 1H), 2.15−1.93 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 156.8, 141.5, 134.8, 134.3, 129.1, 128.6, 127.7, 126.5, 126.1, 126.0, 125.6, 117.3, 78.7, 56.1, 54.3, 51.1, 36.3, 29.3. Anal. ($C_{24}H_{24}ClNO\cdot C_4H_4O_4$) C, H, N.

2-[3-Phenyl-3-(4-methylphenoxy)propyl]-1,2,3,4-tetrahydroisoquinoline fumarate (7d): white solid; mp 106−108 °C; yield 56.5%; ^{1}H NMR ($CDCl_3$) δ 7.38−7.20 (m, 5H), 7.15−7.05 (m, 3H), 7.02−6.90 (m, 3H), 6.72 (d, J = 9.4 Hz, 2H), 5.33−5.15 (m, 1H), 3.65 (s, 2H), 2.95−2.78 (m, 2H), 2.68−2.55 (m, 4H), 2.36−2.00 (m, 2H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.6, 142.1, 134.8, 134.3, 129.8, 129.6, 128.5, 128.4, 127.3, 126.5, 125.9, 125.5, 115.8, 78.3, 56.1, 54.4, 51.0, 36.3, 29.2, 20.3. Anal. ($C_{25}H_{27}NO\cdot C_4H_4O_4$) C, H, N.

2-[3-(2-Fluorophenoxy)-3-phenylpropyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline fumarate (7e): white solid; mp 152−154 °C; yield 94%; ^{1}H NMR ($CDCl_3$) δ 7.40−7.25 (m, 5H), 7.15−7.00 (m, 1H), 6.92−6.75 (m, 3H), 6.60 (s, 1H), 6.52 (s, 1H), 5.45−5.35 (m, 1H), 3.83 (s, 6H), 3.57 (s, 2H), 2.82−2.67 (m, 6H), 2.52−2.38 (m, 1H), 2.18−2.07 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 153.3 (d, J = 245.4 Hz) 147.4, 147.1, 146.1 (d, J = 10.4 Hz), 141.4, 128.5, 127.7, 126.7, 126.2, 126.0, 124.0 (d, J = 3.8 Hz), 121.2 (d, J = 7 Hz), 117.3, 116.1 (d, J = 18.4 Hz), 111.3, 109.4, 79.9, 55.8, 55.6, 54.1, 51.0, 36.1, 28.8. Anal. ($C_{26}H_{28}FNO_3\cdot C_4H_4O_4$) C, H, N.

6,7-Dimethoxy-2-[3-phenyl-3-(2-trifluoromethylphenoxy)propyl]-1,2,3,4-tetrahydroisoquinoline fumarate (7f): white solid; mp 128 °C (dec); yield 80%; ^{1}H NMR ($CDCl_3$) δ 7.55 (d, J = 9.5 Hz, 1H), 7.45−7.25 (m, 6 H), 6.95−6.80 (m, 2H), 6.58 (s, 1H), 6.52 (s, 1H), 5.53−5.44 (m, 1H), 3.85 (s, 6H), 3.57 (s, 2H), 2.80−2.60 (m, 6H), 2.53−2.36 (m, 1H), 2.20−2.05 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 155.7 (q, J = 1.7 Hz), 147.4, 147.1, 141.1, 132.8, 128.6, 127.6, 126.7 (q, J = 4.7 Hz), 126.6, 126.2, 125.8, 119.5, 119.3 (q, J = 31.2 Hz), 114.0, 111.3, 109.4, 78.2, 55.8, 55.7, 53.9, 51.0, 36.3, 28.8. Anal. ($C_{27}H_{28}F_3NO_3\cdot C_4H_4O_4$) C, H, N.

2-[3-(4-Chlorophenoxy)-3-phenylpropyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline fumarate (7g): white solid; mp 129−133 °C; yield 83%; ^{1}H NMR ($CDCl_3$) δ 7.36−7.25 (m, 5H), 7.15 (d, J = 9.5 Hz, 2H), 6.76 (d, J = 9.5 Hz, 2H), 6.60 (s, 1H), 6.50 (s, 1H), 5.34−5.20 (m, 1H), 3.86 (s, 6H), 3.56 (s, 2H), 2.78−2.55 (m, 6H), 2.35−2.19 (m, 1H), 2.15−2.00 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 156.7, 147.4, 147.1, 141.4, 129.0, 128.5, 127.6, 126.5, 126.1, 125.9, 125.2, 117.2, 111.3, 109, 78.6, 55.8, 55.6, 54.1, 51.0, 36.2, 28.7. Anal. ($C_{26}H_{28}ClNO_3\cdot C_4H_4O_4$) C, H, N.

6,7-Dimethoxy-2-[3-phenyl-3-(4-methylphenoxy)propyl]-1,2,3,4-tetrahydroisoquinoline fumarate (7h): white solid; mp 172−174 °C; yield 66%; ^{1}H NMR ($CDCl_3$) δ 7.40−7.16 (m, 5H), 6.92 (d, J = 6.4 Hz, 2H), 6.80 (d, J = 6.4 Hz, 2H), 6.64 (s, 1H), 6.45 (s, 1H), 5.26−5.10 (m, 1H), 3.86 (s, 6H), 3.58 (s, 2H), 2.85−2.64 (m, 6H), 2.35−2.06 (m, 2H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.0, 147.4, 147.1, 142.1, 129.7, 129.6, 128.4, 127.3, 126.6, 126.2, 125.9, 115.8, 111.3, 109.4, 78.3, 55.8, 55.7, 54.4, 51.0, 36.4, 28.7, 20.3. Anal. ($C_{27}H_{31}NO_3\cdot C_4H_4O_4$) C, H, N.

Preparation of 2-(3-Hydroxy-3-phenylpropyl)-1,2,3,4-tetrahydroisoquinoline-6,7-diyl Diacetate (6c). A mixture of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (6.0 g, 25 mmol) and 45% HBr (75 mL) was heated at 120 °C for 2 h and then allowed to cool to room temperature. Filtration and drying afforded in quantitative yield 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrobromide as a solid. A mixture of 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrobromide (6.1 g, 25 mmol), 3-chloropropiophenone (4.2 g, 25 mmol), anhydrous K_2CO_3 (5.6 g, 40 mmol), and acetonitrile (150 mL) was stirred at room temperature for 16 h. Filtration, washing with water, and drying yielded 3-(6,7-dihydroxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-1-phenylpropanone as a yellow solid (6.3 g, 85%). Acetyl chloride (10.5 mL, 150 mmol) was added dropwise to a stirred solution of 3-(6,7-dihydroxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-1-phenylpropanone (7.5 g, 25 mmol) in acetic acid (100 mL). The reaction mixture was heated at 70 °C for 2 h and the solvent removed under reduced pressure to give 2-(3-oxophenylpropyl)-1,2,3,4-tetrahydroisoquiniline-6,7-diyl diacetate hydrochloride (10 g, 96%) as a solid which was washed with Et_2O and filtered. A solution of previously prepared ketone (10 g, 24 mmol) in methanol (200 mL) was treated with 10% palladium/carbon (0.5 g) and the reaction mixture hydrogenated at room temperature (40 psi) for 5 h. The reaction mixture was filtered to remove the palladium catalyst, the solvent distilled under reduced pressure, and the residue treated with 10% aqueous NH_4OH solution and extracted with CH_2Cl_2. The organic extracts were washed with brine and concentrated. The residue was chromatographed on silica gel (CH_2Cl_2:MeOH 98:2), affording **6c** as an oil (6.0 g, 65.3%): ^{1}H NMR ($CDCl_3$) δ 7.60−7.45 (m, 5H), 6.97 (s, 1H), 6.85 (s, 1H), 4.98−4.85 (m, 1H), 3.78 (d, J = 16.8 Hz, 1H), 3.64 (d, J = 16.8 Hz, 1H), 2.92−2.71 (m, 6H), 2.30 (s, 6H), 1.98−1.86 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 168.4, 144.7, 140.2, 139.8, 132.6, 132.5, 128.1, 126.8, 125.4, 123.0, 121.0, 75.2, 56.3, 55.4, 50.0, 34.0, 28.3, 20.5.

General Procedure for Preparation of Compounds 7i−l. 2-[3-Phenyl-3-(2-trifluoromethylphenoxy)propyl]-1,2,3,4-tetrahydroisoquinoline-6,7-diol Hydrochloride (7j). A mixture of **6c** (2.2 g, 5.9 mmol) and 2-trifluoromethylphenol (0.9 g, 5.9 mmol) in THF (40 mL) was stirred at room temperature and triphenylphosphine (1.5 g, 5.9 mmol) added. A solution of DEAD (0.9 mL, 5.9 mmol) in THF (10 mL) was added dropwise, the reaction temperature being kept below 20 °C. After stirring for 24 h, the mixture was concentrated in vacuo and the yellow oily residue extracted with Et_2O and washed with 1 N aqueous HCl solution (3 × 50 mL). The aqueous layer was treated with 10% aqueous NaOH solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to give 2-[3-phenyl-3-(2-trifluoromethylphenoxy)propyl]-1,2,3,4-tetrahydroisoquinoline-6,7-diyl diacetate (2.3 g). A mixture of previously prepared ester (1.2 g), 3 N aqueous HCl solution (2.5 mL), and MeOH (25 mL) was refluxed for 2 h. After cooling to room temperature the solvent was removed under reduced pressure and the residue chromatographed on silica gel (CH_2Cl_2:MeOH 95:5) to give 0.6 g of **7j** (mp 128−131 °C, 65%): ^{1}H NMR ($CDCl_3$) δ 7.75−7.65 (m, 1H), 7.58−7.25 (m,

6H), 7.00−6.89 (m, 1H), 6.80−6.68 (m, 1H), 6.55 (s, 1H), 6.42 (s, 1H), 5.56−5.40 (m, 1H), 3.85 (bs, 2H), 3.35−2.66 (m, 8H). Anal. ($C_{25}H_{24}F_3NO_3$·HCl) C, H, N.

The following compounds were prepared analogously.

2-[3-(2-Fluorophenoxy)-3-phenylpropyl]-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrochloride (7i): white solid; mp 117 °C (dec); yield 58%; ^{1}H NMR ($CDCl_3$) δ 7.45−7.22 (m, 5H), 7.12−6.96 (m, 1H), 6.85−6.70 (m, 3H), 6.50−6.35 (2 bs, 2H), 5.35−5.20 (m, 1H), 3.75 (bs, 2H), 3.20−2.60 (m, 8H). Anal. ($C_{24}H_{24}FNO_3$·HCl) C, H, N.

2-[3-Phenyl-3-(4-methylphenoxy)propyl]-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrochloride (7k): yellow solid; mp 152−155 °C; yield 62%; ^{1}H NMR ($CDCl_3$) δ 7.46−7.18 (m, 5H), 6.94 (d, J = 6.5 Hz, 2H), 6.75 (d, J = 6.5 Hz, 2H), 6.50 (bs, 2H), 5.35−5.10 (m, 1H), 3.76 (bs, 2H), 3.25−2.57 (m, 8H), 2.17 (s, 3H). Anal. ($C_{25}H_{27}NO_3$·HCl) C, H, N.

2-[3-Phenyl-3-(4-chlorophenoxy)-propyl]-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrochloride (7l): white solid; mp 125 °C (dec); yield 40%; ^{1}H NMR ($CDCl_3$) δ 7.36−7.21 (m, 5H), 7.10 (d, J = 9.5 Hz, 2H), 6.70 (d, J = 9,5 Hz, 2H), 6.29 (s, 1H), 6.12 (s, 1H), 5.10−4.93 (m, 1H), 3.85 (bs, 2H), 3.28−2.45 (m, 8H). Anal. ($C_{24}H_{24}ClNO_3$·HCl) C, H, N.

Preparation of (4-Fluorophenyl)piperidin-3-ylmethanone (8). A mixture of piperidine-3-carboxylic acid ethyl ester (10 g, 63.6 mmol), benzyl bromide (10.8 g, 7.5 mL, 65.9 mmol), anhydrous Na_2CO_3 (8.5 g, 80.2 mmol), and acetonitrile (80 mL) was refluxed for 15 h, then acetonitrile was removed under reduced pressure. The residue was treated with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to give 1-benzyl-piperidine-3-carboxylic acid ethyl ester as an oil in quantitative yield. Recently prepared oil (15.7 g, 63.6 mmol) was treated with 20% aqueous HCl solution (100 mL) and refluxed for 4 h. The reaction was concentrated to dryness to obtain 1-benzylpiperidine-3-carboxylic acid as a white solid. A mixture of acid (40 g, 0.16 mol) and $SOCl_2$ (50 mL) was stirred at room temperature for 1 h and then $SOCl_2$ removed under reduced pressure. The residue was dissolved in 1,2-dichloroethane (50 mL) and the solution added dropwise to a mixture of fluorobenzene (70 mL, 0.75 mol), 1,2-dichloroethane (50 mL), and $AlCl_3$ (50 g, 0.37 mol) cooled in an ice bath. The reaction mixture was refluxed for 2.5 h, cooled, and poured onto ice−water. After stirring for 30 min, the mixture was extracted with chloroform and the organic layer washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to give the hydrochloride salt of (1-benzylpiperidin-3-yl)(4-fluorophenyl)methanone as a white solid in 75% yield. To a solution of (1-benzylpiperidin-3-yl)(4-fluorophenyl)methanone (24 g, 0.08 mol) in benzene (220 mL) was added dropwise ethyl chloroformate (12 mL, 0.10 mol). The reaction mixture was refluxed for 3 h, cooled to room temperature, and washed with 10% aqueous HCl solution and brine. The organic layer was dried over anhydrous Na_2SO_4 and filtered and the solvent removed under vacuum. Purification by flash chromatography on silica gel (Cl_3CH and Cl_3CH:Et_2O 9:1) gave 3-(4-fluorobenzoyl)piperidine-1-carboxylic acid ethyl ester as an oil in 88% yield. The carbamate (8 g, 28.0 mmol) was refluxed with glacial acetic acid (347 mL) and 48% HBr (78 mL) for 1.5 h. The mixture was allowed to cool to room temperature and evaporated to dryness. The residue was treated with water, cooled in an ice bath, treated with solid sodium hydroxide (pH > 10), and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to give **8** as an oil (97% yield): ^{1}H NMR ($CDCl_3$) δ 8.04−7.96 (m, 2H), 7.19−7.09 (m, 2H), 3.51−3.38 (m, 1H), 3.25−3.19 (m, 1H), 3.10−3.02 (m, 1H), 2.91−2.80 (m, 1H), 2.74−2.62 (m, 2H), 2.06−1.98 (m, 1H), 1.86−1.57 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 200.7, 165.5 (d, J = 254.6 Hz), 132.2 (d, J = 3 Hz), 130.7 (d, J = 9.5 Hz), 115.6 (d, J = 21.7 Hz), 48.8, 46.2, 44.6, 27.8, 25.3.

Preparation of 3-[(4-Fluorophenyl)hydroxymethyl]-piperidine-1-carboxylic Acid *tert*-Butyl Ester (9). A mixture of **8** (1.1 g, 5.3 mmol), sodium bicarbonate (1.5 g, 17.7 mmol), and water (15 mL) was treated with $(Boc)_2O$ (1.5 g, 6.9 mmol) and stirred for 20 h at room temperature. The reaction mixture was extracted with $CHCl_3$ and the organic layer washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel (CH_2Cl_2 and CH_2Cl_2:Et_2O 9.5:0.5) gave 3-(4-fluorobenzoyl)piperidine-1-carboxylic acid *tert*-butyl ester as an oil (90% yield). 3-(4-Fluorobenzoyl)piperidine-1-carboxylic acid *tert*-butyl ester (5.9 g, 19.3 mmol) was dissolved in methanol (75 mL), and the solution was cooled in an ice bath and treated with $NaBH_4$ (0.5 g) in water (8.5 mL). The mixture was heated in an oil bath (50−55 °C) for 2 h and cooled, and methanol was removed under reduced pressure. The residue was treated with water/brine and extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and filtered and the solvent evaporated under vacuum to give in quantitative yield **9** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.32−7.24 (m, 2H), 7.07−6.98 (m, 2H), 4.48−4.37 (m, 1H), 3.92−3.50 (m, 2H), 3.08 (m, 1H), 2.85−2.33 (m, 2H), 1.92−1.57 (m, 4H), 1.45 and 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 162.2 (d, J = 248.4 Hz, C−F), 154.9, 138.5 (d, J = 3.2 Hz), 128.2 (d, J = 8.0 Hz) and 128.0 (d, J = 8.2 Hz), 115.2 (d, J = 21.4 Hz), 79.6 and 79.3, 75.5, 47.2, 44.6, 42.9, 28.4 and 28.3, 27.7, 23.8.

General Procedure for Preparation of Compounds 10a−j. 3-[(4-Fluorophenyl)(phenoxy)methyl]piperidine Hydrochloride (10a). A mixture of **9** (1.1 g, 3.5 mmol) and phenol (0.3 g, 3.7 mmol) in anhydrous THF (12 mL) was stirred at room temperature and Ph_3P (1.1 g, 4.1 mmol) was added. A solution of DEAD (0.8 mL, 5.0 mmol) in THF (2.5 mL) was dropwise added to keep the temperature of the reaction mixture below 20 °C. After stirring for 3 h, the mixture was concentrated in vacuo and the obtained yellow oily residue was extracted with Et_2O and the organic layer washed with cold 6 N HCl (3 × 50 mL) and 10% aqueous NaOH solution and the solvent removed under reduced pressure. The resulting yellow oil was dissolved in CH_2Cl_2 (20 mL), a solution of trifluoroacetic acid (2.0 mL) in CH_2Cl_2 (5 mL) dropwise added, and the mixture stirred for 15 h at room temperature. Then, it was washed with 10% aqueous NaOH solution and brine and the organic layer concentrated and purified by flash chromatography (CH_2Cl_2:Et_2O:isopropilamine 8:2:0.5 to 8:2:1) to yield an oil (57% yield) which was dissolved in Et_2O and treated with a saturated hydrogen chloride solution in Et_2O to obtain hydrochloride **10a**: mp 86 °C (dec); ^{1}H NMR (DMSO-d_6) δ 9.38−9.15 (m, 2H), 7.38−7.18 (m, 7H), 6.95−6.86 (m, 2H). 5.34−5.21 (m, 1H), 3.59−2.56 (m, 4H), 2.37−2.16 (m, 1H), 1.85−1.23 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 161.5 (d, J = 244.6 Hz), 157.3, 134.5 and 134.4 (d, J = 2.7 Hz), 129.5, 128.6 (d, J = 8.3 Hz) and 128.5 (d, J = 8.2 Hz), 121.3, 117.6, 117.5 and 117.4 (d, J = 21.8 Hz), 79.5 and 78.7, 44.9, 43.4, 24.1, 23.2, 20.9. Anal. ($C_{18}H_{20}FNO$·HCl) C, H, N.

The following compounds were prepared analogously.

3-[(4-Fluorophenoxy)(4-fluorophenyl)methyl]piperidine hydrochloride (10b): mp 78 °C (dec); yield 56%; ^{1}H NMR (DMSO-d_6) δ 9.60−9.20 (m, 2H), 7.45−6.85 (m, 8H), 5.36 and 5.21 (d, J = 6.6 Hz and d, J = 7.5 Hz, 1H), 3.38−2.22 (m, 5H), 1.83−1.14 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 161.7 (d, J = 244.3 Hz), 156.6 (d, J = 236.6 Hz), 153.5, 134.7 (d, J = 3.6 Hz) and 134.6 (d, J = 3.5 Hz), 128.9 (d, J = 7.9 Hz) and 128.8 (d, J = 4.6 Hz), 117.4 (d, J = 8 Hz) and 117.0 (d, J = 7.6 Hz), 115.8 (d, J = 17.9 Hz) and 115.4 (d, J = 16.3 Hz), 80.3 and 79.4, 44.7, 43.2 and 43.1, 39.3, 24.5, 23.8, 21.1. Anal. ($C_{18}H_{19}F_2NO$·HCl) C, H, N.

3-[(4-Chlorophenoxy)(4-fluorophenyl)methyl]piperidine hydrochloride (10c): mp 106 °C (dec); yield 35%; ^{1}H NMR (DMSO-d_6) δ 9.26−9.03 (m, 2H), 7.40−7.15 (m, 6H), 6.90−6.86 (m, 2H), 5.35 and 5.25 (d, J = 6.1 Hz and J = 7.4 Hz, 1H), 3.37−2.93 (m, 2H), 2.80−2.59 (m, 2H), 2.29−2.18 (m, 1H), 1.89−1.30 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 161.7 (d, J = 244.2 Hz), 156.04 and 155.98, 134.4 and 134.3 (d, J = 2.8 Hz), 129.2, 128.9 (d, J = 8.1 Hz) and 128.8 (d, J = 8.4 Hz), 124.8 and 124.7, 117.7 and 117.6, 115.5 (d, J = 21.6 Hz), 79.9 and 79.1, 44.7, 43.2, 24.5, 23.7, 21.1. Anal. ($C_{18}H_{19}ClFNO$·HCl) C, H, N.

3-[(4-Fluorophenyl)(4-trifluoromethylphenoxy)methyl]piperidine hydrochloride (10d): mp 94 °C (dec); yield

68%; ^{1}H NMR ($CDCl_3$) δ 9.75−9.51 (m, 2H), 7.55−6.82 (m, 8H), 5.20 and 5.03 (d, J = 4.6 and 6.4 Hz, 1H), 3.62−3.25 (m, 2.5H), 2.87−2.54 (m, 2.5H), 1.89−1.36 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 162.2 (d, J = 241.6 Hz), 158.7, 133.7 and 133.6 (d, J = 2.7 Hz), 128.8 (q, J = 3.1 Hz), 128.4 (d, J = 8.2 Hz) and 128.3 (d, J = 8.3 Hz), 123.6 (q, J = 36.2 Hz), 120.9, 119.4 (q, J = 261 Hz), 118.3, 118.2, 118.0, 117.9, 116.2, 80.5 and 79.7, 46.3, 45.1, 43.4, 40.1, 27.6, 24.2, 21.1, 21.0. Anal. ($C_{19}H_{19}F_4NO$·HCl) C, H, N.

3-[(4-Fluorophenyl)(4-methylphenoxy)methyl]piperidine hydrochloride (10e): mp 86 °C (dec); yield 42%; ^{1}H NMR ($CDCl_3$) δ 9.75−9.38 (m, 2H), 7.29−7.21 (m, 2H), 7.03−6.93 (m, 4H), 6.68 (d, J = 8.5 Hz, 2H), 4.81 and 4.74 (d, J = 6.5 and 7.6 Hz, 1H), 3.62−3.38 (m, 1.5 H), 2.95−2.43 (m, 1.5 H), 2.19 (s, 3H), 2.04−1.23 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 162.3 (d, J = 247.2 Hz), 155.2, 134.0 and 133.8 (d, J = 3.1 Hz), 130.7 and 130.6, 129.8, 128.1 (d, J = 16.3 Hz), 115.5 (d, J = 21.2 Hz) and 114.7 (d, J = 21.4 Hz), 80.9 and 79.5, 46.2, 45.3, 44.1, 40.2, 40.1, 25.6, 23.1, 21.8, 21.6, 20.4. Anal. ($C_{19}H_{22}FNO$·HCl) C, H, N.

3-[(4-Fluorophenyl)(4-methoxyphenoxy)methyl]piperidine hydrochloride (10f): mp 78 °C (dec); yield 39%; ^{1}H NMR ($CDCl_3$) δ 9.78−9.42 (m, 2H), 7.35−7.26 (m, 2H), 7.16−6.91 (m, 2H), 6.73 (s, 4H), 5.07 (bs) and 4.85 (d, J = 6.5 Hz, 1H), 3.72 (s, 3H), 3.4 (m, 0.5H), 2.95−2.30 (m, 1.5H), 1.95−1.23 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 162.6 (d, J = 247.5 Hz), 155.60 and 155.64, 153.5, 134.1 and 133.8 (d, J = 3.1 Hz), 128.7 (d, J = 7.5 Hz), 118.7, 118.1, 116.3 (d, J = 22.3 Hz), 114.4, 82.3 and 80.9, 57.4, 46.3, 45.6, 44.2, 40.5, 26.7, 22.6, 21.3. Anal. ($C_{19}H_{22}FNO_2$·HCl) C, H, N.

4-[(4-Fluorophenyl)(piperidin-3-yl)methoxy]benzonitrile fumarate (10g): mp 210−213 °C; yield 35%; ^{1}H NMR (DMSO-d_6 + methanol-d_4) δ 7.75−6.95 (m, 8H), 6.40 (s, 2H), 5.38 (d, J = 8.3 Hz, 1H), 3.18−2.59 (m, 4H), 2.22−1.32 (m, 5H); ^{13}C NMR (DMSO-d_6 + methanol-d_4) δ 163.4 (d, J = 250 Hz), 162.3, 159.2, 141.4, 133.7, 128.7, 128.6, 119.3, 117.6, 116.5, 116.1, 103.8, 80.6, 44.8, 42.9, 25.1, 23.2. Anal. ($C_{19}H_{19}FN_2O$·$C_4H_4O_4$) C, H, N.

3-[(3,4-Dichlorophenoxy)(4-fluorophenyl)methyl]piperidine hydrochloride (10h): mp 86 °C (dec); yield 58%; ^{1}H NMR ($CDCl_3$) δ 9.76−9.52 (m, 2H), 7.33−7.20 (m, 3H), 7.19−6.89 (m, 3H), 6.67−6.59 (m, 1H), 5.06 and 4.93 (d, J = 4.7 Hz and J = 6.9 Hz, 1H), 3.61−3.35 (m, 1.5H), 2.82−2.29 (m, 3.5H), 1.88−1.24 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 162.5 (d, J = 248.1 Hz), 156.11 and 156.08, 132.84, 132.8 (d, J = 3.2 Hz) and 132.5 (d, J = 3.2 Hz), 130.6, 128.2 (d, J = 8 Hz), 124.83, 124.80, 118.0, 117.8, 116.0 (d, J = 21.7 Hz) and 115.5 (d, J = 25.7 Hz), 81.5 and 80.1, 45.8, 45.2, 44.1, 44.0, 25.2, 23.2, 21.5, 21.3. Anal. ($C_{18}H_{18}Cl_2FNO$·HCl) C, H, N.

3-[(Benzo[1,3]dioxol-5-yloxy)(4-fluorophenyl)methyl]-piperidine hydrochloride (10i): mp 128 °C (dec); yield 40%; ^{1}H NMR ($CDCl_3$) δ 7.28−7.21 (m, 2H), 7.06−6.95 (m, 2H), 6.56 (dd, J = 8.4 Hz, J = 1.0 Hz, 1H), 6.39 (dd, J = 2.2 Hz, J = 1 0.74 Hz, 1H), 6.22−6.16 (m, 1H), 5.83 (s, 2H), 4.98 and 4.78 (d, J = 4.8 Hz and J = 7.0 Hz, 1H), 3.67−3.42 (m, 1.5H), 2.85−2.41 (m, 1.5 H), 1.98−1.28 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 162.3 (d, J = 252 Hz), 152.7 and 152.6, 148.0, 142.0 (d, J = 3.7 Hz), 133.8, 128.2 (d, J = 8.3 Hz), 115.9 and 115.5 (d, J = 26.0 Hz), 107.8 and 107.4, 101.1, 99.2 and 98.9, 82.1 and 80.6, 46.2, 45.5, 44.1, 40.2, 25.5, 23.2, 21.8, 21.6. Anal. ($C_{19}H_{20}FNO_3$·HCl) C, H, N.

3-[(4-Fluorophenyl)(naphthalen-1-yloxy)methyl]piperidine fumarate (10j): mp 70 °C (dec); yield 47%. Free base: ^{1}H NMR ($CDCl_3$) δ 8.45−8.39 (m, 1H), 7.80−7.77 (m, 1H), 7.56−7.13 (m, 6H), 7.03−6.95 (m, 2H), 6.56−6.50 (m, 1H), 5.14 and 5.06 ((d, J = 5.8 Hz and J = 7.3 Hz), 3.51−3.46 (m, 0.5H), 3.07−2.95 (m, 1.5H), 2.66−2.54 (m, 2H), 2.12−1.24 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 162.3 (d, J = 249.3 Hz), 153.4, 136.7, 136.5, 135.2, 128.7, 128.6, 128.4, 126.5, 126.3, 126.2, 125.4, 122.5, 120.7, 115.8, 115.2, 107.4, 82.3, 81.8, 49.3, 49.2, 46.3, 43.3, 28.4, 26.3, 25.1. Anal. ($C_{22}H_{22}FNO$·$C_4H_4O_4$) C, H, N.

General Procedure for Preparation of Compounds 11a−e. 1-Phenyl-2-(piperidin-4-yl)ethanone (11d). Thionyl chloride (15 mL) was stirred at room temperature and **13** (4.7 g, 25.6 mmol) was added portionwise. The mixture was stirred at room temperature for 4 h and concentrated under reduced pressure. The oily residue was dissolved in 1,2-dichloroethane and added portionwise to a stirred suspension of $AlCl_3$ (7.0 g, 52 mmol) in dry benzene (30 mL). The reaction mixture was refluxed 2 h, cooled to room temperature, and poured into crushed ice. The aqueous mixture was extracted with $CHCl_3$ and the organic layer washed with brine and concentrated to an oil. The oil was stirred and refluxed 6 h with 6 N HCl (80 mL). After cooling, the mixture was extracted with Et_2O, and the aqueous layer was treated with 10% aqueous NaOH solution and extracted with Et_2O. The organic layer was washed with brine and concentrated to afford 3.1 g (60% yield) of **11d** as a yellowish oil: ^{1}H NMR ($CDCl_3$) δ 7.96 (m, 2H), 7.57−7.42 (m, 3H), 3.06 (m, 2H), 2.88 (d, J = 6.7 Hz, 2H), 2.65 (m, 2H), 2.12 (m, 1H), 1.78−1.64 (m, 3H), 1.22 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 199.3, 137.0, 132.7, 128.3, 127.8, 46.4, 45.5, 33.4, 32.6.

The following compounds were prepared analogously.

Phenyl(piperidin-4-yl)methanone (11a): mp 49−51 °C; yield 83%; ^{1}H NMR ($CDCl_3$) δ 7.98−7.42 (m, 5H), 3.40 (m, 1H), 3.24−3.14 (m, 2H), 2.77 (m, 2H), 1.89−1.57 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 202.00, 135.5, 132.4, 128.2, 127.7, 45.7, 43.6, 29.30.

(4-Chlorophenyl)(piperidin-4-yl)methanone (11b): mp 60−63 °C; yield 48%; ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 8.6 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 3.34 (m, 1H), 3.22 (m, 1H), 3.16 (m, 1H), 2.76 (m, 2H), 1.87−1.54 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 201.0, 139.0, 134.1, 129.5, 128.7, 45.9, 43.9, 29.5.

(4-Fluorophenyl)(piperidin-4-yl)methanone hydrochloride (11c): mp 222−224 °C; yield 84%; ^{1}H NMR ($CDCl_3$) δ 7.95 (t, J = 7.3 Hz, 2H), 7.15 (t, J = 7.3 Hz, 2H), 3.48−3.15 (m, 4H), 2.78 (m, 2H), 1.90−1.58 (m, 3H); ^{13}C NMR (DMSO-d_6 + D_2O) δ 200.5, 165.6 (d, J = 251 Hz, C−F), 132.0 (d, J = 2.6 Hz), 131.9 (d, J = 9.6 Hz), 116.4 (d, J = 21.6 Hz), 42.7, 40.3, 25.3.

1-(4-Fluorophenyl)-2-(piperidin-4-yl)ethanone (11e): oil; yield 60%; ^{1}H NMR ($CDCl_3$) δ 7.99 (m, 2H), 7.13 (t, J = 8.6 Hz, 2H), 3.09−3.03 (m, 2H), 2.84 (d, J = 6.7 Hz, 2H), 2.65 (m, 2H), 2.11 (m, 1H), 1.78−1.60 (m, 2H), 1.32−1.12 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 197.7, 165.5 (d, J = 253 Hz, C−F), 133.5 (d, J = 3.2 Hz), 130.5 (d, J = 9.5 Hz), 115.4 (d, J = 21.7 Hz), 46.2, 45.4, 33.1, 32.6.

General Procedure for Preparation of Compounds 11f,g. (3-Fluorophenyl)(piperidin-4-yl)methanone (11f). A suspension of Mg turnings (0.5 g) in anhydrous Et_2O (22 mL) was prepared and treated with a 1-bromo-3-fluorobenzene (2.1 mL, 19.4 mmol) solution in anhydrous Et_2O (16 mL) and an iodine crystal. The mixture was heated until a smooth reflux was observed and the color disappeared. The reaction mixture was refluxed for 1.5 h and allowed to cool to room temperature. A solution of **12** (2.7 g, 12.8 mmol) in anhydrous Et_2O (27 mL) was added dropwise and the reaction refluxed for 3 h. A saturated aqueous NH_4Cl solution (50 mL) was added and the mixture extracted with Et_2O. The organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel (EtOAc:hexane 2:8) gave 4-(3-fluorobenzoyl)piperidine-1-carboxylic acid *tert*-butyl ester as a yellowish oil. A mixture of 4-(3-fluorobenzoyl)piperidine-1-carboxylic acid *tert*-butyl ester (7.2 g, 23.4 mmol), methanol (130 mL), and 10% aqueous HCl solution (130 mL) was refluxed for 2 h. Methanol was removed under reduced pressure and the residue was treated with water. The aqueous mixture was cooled with an ice bath, treated with solid KOH (pH >10), and extracted with Cl_3CH. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to give **11f** as an oil (57% yield): ^{1}H NMR ($CDCl_3$) δ 7.75−7.60 (m, 1H), 7.59−7.50 (m, 1H), 7.48−7.40 (m, 1H), 7.33−7.20 (m, 1H), 3.41−3.13 (m, 3H), 2.83−2.69 (m, 2H), 1.88−1.55 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 201.1 (d, J = 2.5 Hz), 162.8 (d, J = 248.2 Hz), 138.0 (d, J = 5.9 Hz), 130.2 (d, J = 8.0 Hz), 123.8 (d, J = 3.1 Hz), 119.7 (d, J = 21.7 Hz), 114.9 (d, J = 21.7 Hz), 45.9, 44.2, 29.5.

Compound **11g** was prepared analogously.

(4-Methylphenyl)(piperidin-4-yl)methanone (11g): oil; yield 60%; ^{1}H NMR ($CDCl_3$) δ 7.84 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 3.44−3.29 (m, 1H), 3.20−3.13 (m, 2H), 2.82−2.68 (m, 2H), 2.40 (s, 3H), 1.85−1.55 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 202.0, 143.4, 133.2, 129.1, 128.2, 46.0, 43.8, 29.7.

Preparation of 1-[4-(4-Fluorobenzoyl)piperidin-1-yl]-ethanone (11h). 1-Acetyl-piperidine-4-carboxylic acid[24] (6.5 g, 38.0 mmol) was added to $SOCl_2$ (40 mL) and the resulting suspension stirred for 1 h. Hexane (100 mL) was added, and the white solid filtered, dried, and added portionwise to a mixture of $AlCl_3$ (9.3 g, 70 mmol) and fluorobenzene (60 mL). The mixture was refluxed for 2 h, cooled at room temperature, treated with ice−water, and extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated, yielding 6.4 g of **11h** as a colorless oil (68% yield): ^{1}H NMR ($CDCl_3$) δ 8.01−7.94 (m, 2H), 7.20−7.11 (m, 2H), 4.58 (m, 1H), 3.91 (m, 1H), 3.46 (m, 1H), 3.22 (m, 1H), 2.82 (m, 1H), 2.12 (s, 3H), 1.94−1.54 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 199.8, 168.6, 165.4 (d, J = 254.5 Hz), 131.8 (d, J = 3.2 Hz), 130.6 (d, J = 9.6 Hz), 115.6 (d, J = 21.9 Hz), 45.4, 42.7, 40.6, 28.2, 21.2.

Preparation of (1-Methylpiperidin-4-yl)phenylmethanone (11i). To ketone **11a** (10 g, 52.8 mmol) and formic acid (9 mL) was added a 35−40% aqueous solution of formaldehyde (6.4 mL). The mixture was heated for 3 h with an oil bath at 55−60 °C, cooled to room temperature, and treated with water and NaOH to pH >10. Brine was added and the mixture extracted with Et_2O. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to afford **11i** as an oil in 89% yield: ^{1}H NMR ($CDCl_3$) δ 7.96−7.84 (m, 2H), 7.60−7.40 (m, 3H), 3.22 (m, 1H), 2.92 (m, 2H), 2.32 (s, 3H), 2.18−1.70 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 202.2, 135.8, 132.6, 128.3, 127.9, 55.0, 46.2, 42.8, 28.5.

Preparation of 4-Cyanopiperidine-1-carboxylic Acid *tert*-Butyl Ester (12).[28] Thionyl chloride (35 mL) was added dropwise to piperidine-4-carboxylic acid amide (10 g, 78.1 mmol) with stirring and cooling (ice−water bath). The heterogeneous reaction mixture was heated to reflux for 3 h. The obtained solution was cooled to 40−50 °C and the excess of thionyl chloride eliminated under vacuum. The residue was treated with ice (300 g) under vigorous stirring, and solid KOH was added until pH 9. A small amount of a brownish solid was obtained and filtered. The filtrate was extracted with $CHCl_3$ (4 × 100 mL), and the organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated to yield 7.4 g of piperidine-4-carbonitrile (86%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.15−2.98 (m, 2H), 2.84−2.70 (m, 3H), 1.98−1.70 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 121.5, 44.0, 29.1, 26.1. Piperidine-4-carbonitrile (16.4 g, 0.15 mol) was added to a stirred solution of $NaHCO_3$ (41.5 g) in 400 mL of water. Then, $(Boc)_2O$ (35.8 g) was added portionwise, and the homogeneous reaction mixture was stirred at room temperature for 20 h, extracted with $CHCl_3$, and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to afford **12** as an oil which crystallized as pale yellow needles: mp 45−48 °C; yield 25 g (79%); ^{1}H NMR ($CDCl_3$) δ 3.75−3.60 (m, 2H), 3.42−3.30 (m, 2H), 2.82 (m, 1H), 1.95−1.78 (m, 4H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 154.2, 120.8, 79.8, 41.5, 28.2, 28.1, 26.0.

Preparation of (1-Acetylpiperidin-4-yl)acetic Acid (13). A suspension of NaH (50−60%, 10.5 g) in anhydrous benzene (170 mL) was treated dropwise with triethyl phosphonoacetate (39.5 g, 176.2 mmol) and stirred for 1 h. 1-Benzylpiperidin-4-one (32.6 g, 170 mmol) was added dropwise to keep the reaction mixture temperature <15 °C. Then, the mixture was refluxed for 30 min, cooled, and treated with 20% aqueous HCl solution. A 10% aqueous solution of NaOH was added to the aqueous layer until pH >9 and extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to give an oil (41 g) which was dissolved in ethanol (300 mL), treated with 10% Pd/C (9 g), and hydrogenated at 3 atm. After 48 h ethanol (200 mL) and an aqueous solution of ammonium formate (28 g/40 mL of H_2O) were added. The mixture was gently refluxed for 2.5 h, cooled, and filtrated. The filtrate was concentrated and the residue treated with Et_2O and 10% aqueous NaOH solution until pH >12. The aqueous layer was extracted with Et_2O, the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and filtered, and the solvent was distilled at 760 mmHg to give the ester as a yellow oil (19.5 g). A solution of ester (6.5 g, 37.9 mmol) in acetic anhydride (70 mL) was stirred at 100 °C for 3 h. The mixture was evaporated under reduced pressure and the oil was stirred at room temperature for 1 h with 5% aqueous NaOH solution (50 mL). HCl (6 N) was added until pH 3 and the mixture was again concentrated under reduced pressure. The oil was extracted with refluxing THF to yield **13 (**3.5 g, 50%) as a white solid: mp 117−120 °C; ^{1}H NMR ($CDCl_3$) δ 4.59 (m, 1H), 3.79 (m, 1H), 3.05 (m, 1H), 2.59 (m, 1H), 2.29 (d, J = 6.9 Hz, 2H), 2.11 (s, 3H), 2.05 (m, 1H), 1.86 (m, 2H), 1.22 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 173.6, 168.5, 46.3, 41.3, 40.6, 32.6, 32.0, 31.3.

General Procedure for Preparation of Compounds 14a−e. 4-(2-Hydroxy-2-phenylethyl)-piperidine-1-carboxylic Acid *tert*-Butyl Ester (14d). To a stirred mixture of **11d** (3.0 g, 15 mmol) and $NaHCO_3$ (4 g) in H_2O (50 mL) was added $(Boc)_2O$ (4 g, 18.3 mmol). After stirring for 20 h at room temperature, the mixture was extracted with $CHCl_3$ and the organic layer washed with brine, dried over anhydrous Na_2SO_4, and concentrated to yield 4 g of a pale yellow oil which was dissolved in methanol (60 mL) and treated dropwise with a solution of $NaBH_4$ (0.4 g, 10.6 mmol) in H_2O (10 mL). The mixture was stirred for 1 h at 45−50 °C, cooled at room temperature, and concentrated under reduced pressure. The residue was treated with H_2O and extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford 4 g (86%) of **14d**, as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.38−7.31 (m, 5H), 4.78 (m, 1H), 4.07 (m, 2H), 2.72 (m, 2H), 1.98−1.48 (m, 6H), 1.45 (s, 9H), 1.30−1.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 154.7, 145.1, 128.3, 127.2, 126.61, 79.1, 71.3, 45.8, 43.7, 32.5, 32.4, 31.5, 28.3.

The following compounds were prepared analogously.

4-(Hydroxyphenylmethyl)piperidine-1-carboxylic acid *tert*-butyl ester (14a): mp 77−80 °C; yield 90%; ^{1}H NMR ($CDCl_3$) δ 7.39−7.28 (m, 5H), 4.38 (d, J = 7.4 Hz, 1H), 4.10 (m, 2H), 2.61 (m, 2H), 2.08−1.62 (m, 3H), 1.44 (s, 9H), 1.36−1.09 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 154.6, 143.0, 128.1, 127.4, 126.4, 79.2, 78.1, 43.3, 28.3, 28.2, 28.1.

4-[(4-Chlorophenyl)hydroxymethyl]piperidine-1-carboxylic acid *tert*-butyl ester (14b): mp 110−112 °C; yield 99%; ^{1}H NMR ($CDCl_3$) δ 7.34−7.21 (m, 4H), 4.37 (d, J = 7.2 Hz, 1H), 4.10 (m, 2H), 2.61 (m, 2H), 1.97−1.61 (m, 4H), 1.44 (s, 9H), 1.41−1.08 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 154.7, 141.5, 133.2, 128.3, 127.9, 79.3, 77.5, 43.5, 43.3, 28.4, 28.2, 28.0.

4-[(4-Fluorophenyl)hydroxymethyl]piperidine-1-carboxylic acid *tert*-butyl ester (14c): mp 84−86 °C; yield 95%; ^{1}H NMR ($CDCl_3$) δ 7.30−7.21 (m, 2H), 7.09−6.99 (m, 2H), 4.39−4.34 (m, 1H), 4.10 (m, 2H), 2.61 (m, 2H), 2.04−1.61 (m, 3H), 1.44 (s, 9H), 1.33−1.06 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 162.1 (d, J = 243.5 Hz, C−F), 154.7, 138.8 (d, J = 3.2 Hz), 128.0 (d, J = 7.9 Hz), 115.01 (d, J = 21 Hz), 79.3, 77.6, 77.2, 43.5, 43.4, 28.3, 28.1.

4-[2-(4-Fluorophenyl)-2-hydroxyethyl]piperidinecarboxylic acid *tert*-butyl ester (14e): oil; yield 98%; ^{1}H NMR ($CDCl_3$) δ 7.34−7.28 (m, 2H), 7.04 (t, J = 8.7 Hz, 2H), 4.78 (m, 1H), 4.06 (m, 2H), 2.67 (m, 2H), 1.81−1.51 (m, 6H), 1.45 (s, 9H), 1.42−1.14 (m, 2H).

Preparation of 4-[(3-Fluorophenyl)hydroxymethyl]-piperidine-1-carboxylic Acid *tert*-Butyl Ester (14f). A suspension of Mg turnings (0.5 g) in anhydrous Et_2O (22 mL) was prepared and treated with a 1-bromo-3-fluorobenzene (2.1 mL, 19.4 mmol) solution in anhydrous Et_2O (16 mL) and an iodine crystal. The mixture was heated until a smooth reflux was observed and the color disappeared. The reaction mixture was refluxed for 1.5 h and allowed to cool to room temperature. A solution of **12** (2.7 g, 12.8 mmol) in anhydrous Et_2O (27 mL) was added dropwise and the reaction refluxed for 3 h. A

saturated aqueous NH_4Cl solution (50 mL) was added and the mixture extracted with Et_2O. The organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel (EtOAc:hexane 2:8) gave 4-(3-fluorobenzoyl)piperidine-1-carboxylic acid *tert*-butyl ester as a yellowish oil. A suspension of $NaBH_4$ (0.2 g) in H_2O (3.5 mL) was added to a solution of 4-(3-fluorobenzoyl)piperidine-1-carboxylic acid *tert*-butyl ester (2.4 g, 7.8 mmol) in methanol (30 mL) and the mixture heated for 2 h in an oil bath (50−60 °C). After concentration of methanol, the residue was extracted with CH_2Cl_2 and the organic layer washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum, yielding **14f** as a very dense yellowish oil (61% yield): ^{1}H NMR ($CDCl_3$) δ 7.34−7.22 (m, 1H), 7.05−6.91 (m, 3H), 4.35 (d, J = 6.9 Hz, 1H), 4.13−3.99 (m, 2H), 2.79 (d, J = 2.7 Hz, 1H), 2.66−2.49 (m, 2H), 1.90−1.84 (m, 1H), 1.78−1.45 (m, 1H), 1.42 (s, 9H), 1.31−1.07 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 162.8 (d, J = 246.0 Hz, C−F), 154.7, 145.8 (d, J = 6.4 Hz), 129.7 (d, J = 8.0 Hz), 122.1 (d, J = 2.4 Hz), 114.3 (d, J = 20.9 Hz), 113.3 (d, J = 21.3 Hz), 79.4, 77.6, 43.4, 28.3, 28.2, 27.9.

General Procedure for Preparation of Compounds 14 g−k. (4-Methylphenyl)(piperidin-4-yl)methanol (14i). A suspension of $NaBH_4$ (0.4 g) in H_2O (8 mL) was added to a solution of **11g** (1.2 g, 5.9 mmol) in methanol (74 mL) and the mixture was heated for 2 h in an oil bath (40 °C). After concentration of methanol, the residue was extracted with CH_2Cl_2 and the organic layer washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum, yielding **14i** as a white solid: mp 139−140 °C; 95% yield; ^{1}H NMR ($CDCl_3$) δ 7.21−7.08 (m, 5H), 4.22 (d, J = 8 Hz, 1H), 3.18−2.86 (m, 2H), 2.58−2.21 (m, 5H), 2.07−1.85 (m, 1H), 1.78−1.56 (m, 1H), 1.25−1.01 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 140.5, 137.0, 128.8, 126.5, 78.5, 46.3, 43.5, 29.6. 29.5, 21.0.

The following compounds were prepared analogously.

1-[4-[(4-Fluorophenyl)hydroxymethyl]piperidin-1-yl]-ethanone (14g): colorless oil; yield 98%; ^{1}H NMR ($CDCl_3$) δ 7.30−7.23 (m, 2H), 7.08−6.99 (m, 2H), 4.64 (m, 1H), 4.38 (m, 1H), 3.81 (m, 1H), 2.96 (m, 1H), 2.43 (m, 1H), 2.07 (s, 1.5 H), 2.04 (s, 1.5 H), 2.01−1.25 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 168.7, 168.6, 161.6 (d, J = 245 Hz), 138.9 (d, J = 3.6 Hz), 138.8, 127.8 (d, J = 9 Hz), 114.6 (d, J = 21 Hz), 76.6, 46.2, 46.1, 43.1, 41.3, 41.2, 28.5, 28.2, 27.8, 27.5, 20.9.

(1-Methyl-piperidin-4-yl)phenylmethanol (14h): mp 152−154 °C; yield 90%; ^{1}H NMR ($CDCl_3$) δ 7.36−7.20 (m, 5H), 4.33 (d, J = 7.1 Hz, 1H), 2.95−2.68 (m, 2H), 2.20 (s, 3H), 2.08−1.17 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 143.8, 128.1, 127.3, 126.6, 78.4, 55.5, 55.4, 46.0, 42.5, 28.6, 28.3.

Phenyl(piperidin-4-yl)methanol (14j): white solid; mp 164−166 °C; yield 90%; ^{1}H NMR (DMSO-d_6) δ 7.36−7.16 (m, 5H), 4.18 (d, J = 7.1 Hz, 1H), 2.87 (m, 2H), 2.50 (m, 1H), 2.30 (m, 2H), 1.70 (m, 1H), 1.46 (m, 1H), 1.18−1.05 (m, 3H); ^{13}C NMR (DMSO-d_6) 144.8, 127.9, 126.8, 77.2, 46.2, 46.1, 44.0, 29.6, 29.1.

(3-Fluorophenyl)(piperidin-4-yl)methanol (14k): white solid; mp 136−138 °C; yield 95%; ^{1}H NMR ($CDCl_3$) δ 7.38−7.23 (m, 1H), 7.13−6.87 (m, 3H), 4.35 (d, J = 7.7 Hz, 1H), 3.15−2.90 (m, 2H), 2.57−2.20 (m, 4H), 1.92−1.55 (m, 2H), 1.23−1.10 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 162.8 (d, J = 245.7 Hz, C−F), 146.4 (d, J = 6.6 Hz), 129.5 (d, J = 8.1 Hz), 122.2 (d, J = 3 Hz), 114.1 (d, J = 20.9 Hz), 113.4 (d, J = 21.5 Hz), 46.2, 46.1, 43.5, 29.3, 29.1.

General Procedure for Preparation of Compounds (+)- or (−)-14j,k. (+)-Phenyl(piperidin-4-yl)methanol ((+)-14j). To a solution of (+)-DIPCl (6.8 g, 21.2 mmol) in anhydrous CH_2Cl_2 (20 mL) cooled to 3−4 °C was added **11a** (2.0 g, 10.6 mmol) and the mixture stirred for 72 h. Acetaldehyde (2.0 mL) was added dropwise, and the mixture was warmed to room temperature and stirred for 3 h. A 6 N aqueous NaOH solution (24 mL) was added and the mixture extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The dextrorotatory alcohol [84% ee, $[\alpha]_{546}$ +36 (c = 0.121, $CHCl_3$)] was obtained in a 90% yield as a white solid (mp 64−66 °C).

The following compounds were prepared analogously.

(−)-Phenyl(piperidin-4-yl)methanol ((−)-14j): white solid; mp 48−50 °C, 86% ee, $[\alpha]_{546}$ −36 (c = 0.106, $CHCl_3$); yield 85%.

(−)-(3-Fluorophenyl)(piperidin-4-yl)methanol ((−)-14k): yellow solid; mp 125−127 °C, 84.6% ee, $[\alpha]_{436}$ −62 (c = 0.05, $CHCl_3$); yield 80%.

(+)-(3-Fluorophenyl)(piperidin-4-yl)methanol ((+)-14k): yellow solid; mp 57 °C (dec), 83.6% ee, $[\alpha]_{436}$ +42 (c = 0.089, $CHCl_3$); yield 83%.

Preparation of Cyclopentylphenylmethanol (17). A mixture of cyclopentanecarboxylic acid (6.0 g, 52.6 mmol), 85% phosphoric acid (3.6 mL), and trifluoromethanesulfonic anhydride (30.6 g, 105.4 mmol) was treated with anhydrous benzene (12 mL) and heated 4 h with an oil bath at 80 °C. The reaction mixture was cooled to room temperature, treated with water, and extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to afford an oil. A solution of previously prepared oil (8.5 g) in methanol (50 mL) was treated dropwise with a solution of $NaBH_4$ (1.2 g) in H_2O (15 mL) and heated 1 h at 40 °C, then methanol was removed under reduced pressure. The residue was treated with water and brine and extracted with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated, affording **17** as a slightly colored oil in 77% yield: ^{1}H NMR ($CDCl_3$) δ 7.35−7.22 (m, 5H), 4.39 (d, J = 8.4 Hz, 1H), 2.24 (m, 1H), 1.92−1.15 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 144.4, 128.1, 127.3, 126.4, 78.5, 47.5, 29.4, 29.3, 25.4, 25.3.

Preparation of Phenyl(tetrahydropyran-4-yl)methanol (20). A solution of acid **19**[31] (6.8 g, 52.6 mmol) in $SOCl_2$ (6 mL) was refluxed for 45 min and then concentrated under reduced pressure. The resulting yellow oil was added dropwise to a mixture of anhydrous $AlCl_3$ (13 g, 97.5 mmol) in anhydrous benzene (50 mL). After 1 h at 70−75 °C the reaction mixture was cooled to room temperature, poured into ice−water, and extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel (hexane:EtOAc 8:2), affording the ketone as colorless needles (mp 48−50 °C) in 62% yield. A solution of recently prepared ketone (6.0 g, 31.5 mmol) in methanol (35 mL) was treated dropwise with a solution of $NaBH_4$ (0.8 g) in H_2O (7 mL). The mixture was heated for 1 h at 40 °C and the solvent removed under reduced pressure, yielding **20** as a yellow oil (90% yield): ^{1}H NMR ($CDCl_3$) δ 7.39−7.24 (m, 5H), 4.33 (m, 1H), 4.17 (m, 1H), 3.87 (m, 1H), 3.41−3.19 (m, 2H), 2.11−1.10 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 142.9, 128.1, 127.5, 126.5, 78.4, 67.7, 67.5, 42.2, 29.2, 29.0.

General Procedures for Preparation of Compounds 15a−au,[27] 18, and 21. Method A: 4-[2-(4-Fluorophenoxy)-2-phenylethyl]piperidine Fumarate (15ak). To a mixture of **14d** (2 g, 6.5 mmol) and 4-fluorophenol (0.7 g, 6.7 mmol) in THF (anhydrous, 40 mL) was added diphenyl-2-pyridylphosphine (1.7 g, 6.5 mmol) and the mixture stirred at room temperature. A solution of DEAD (1.0 mL, 6.6 mmol) in THF (anhydrous, 5 mL) was added dropwise to keep the reaction mixture temperature below 20 °C. After stirring for 3 h the mixture was concentrated and the yellow oily residue extracted with Et_2O and washed with cold 6 N aqueous HCl solution (3 × 50 mL). The organic layer was washed with 10% aqueous NaOH solution and the solvent removed under reduced pressure. The yellow oil was dissolved in CH_2Cl_2 (50 mL) and trifluoroacetic acid (2.1 mL) added. The mixture was stirred for 15 h at room temperature and washed with 10% aqueous NaOH solution and brine. The organic layer was concentrated to yield 1.4 g (70%) of **15ak** as a pale yellow oil. To a solution of the crude product (1.2 g) in Et_2O (60 mL) was added fumaric acid (0.5 g, 4.0 mmol) and the mixture stirred at 20 °C for 15 h, collecting a white solid which was washed with Et_2O: yield of fumarate salt, 1.1 g (70%); mp 154−156 °C; ^{1}H NMR ($CDCl_3$) δ 7.33−7.26 (m, 5H), 6.91−6.71 (m, 4H), 5.10 (m, 1H), 3.12

(m, 2H), 2.62 (m, 2H), 2.08−1.15 (m, 8H); ^{13}C NMR (DMSO-d_6, fumarate salt) δ 168.3, 156.4 (d, J = 235 Hz, C−F), 153.8 (d, J = 2.3 Hz), 141.7, 135.2, 128.6, 127.6, 126.1, 115.5 (d, J = 19.8 Hz), 111.2 (d, J = 8 Hz), 76.9, 44.5, 42.7, 30.4, 28.9, 28.1. Anal. ($C_{19}H_{22}FNO\cdot C_4H_4O_4\cdot H_2O$) C, H, N.

The following compounds were prepared analogously.

4-[(Phenyl)(phenoxy)methyl]piperidine hydrochloride (15a): hygroscopic; yield 73%; ^{1}H NMR ($CDCl_3$) δ 9.56−6.77 (m, 10H), 4.82 (d, J = 6.6 Hz, 1H), 3.44 (m, 2H), 2.82 (m, 2H), 2.26 (m, 1H), 2.10−1.24 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 158.2, 139.8, 129.1, 129.0, 128.0, 127.2, 126.5, 120.3, 115.6, 114.2, 83.9, 46.1, 43.2, 29.2, 28.9. Anal. ($C_{18}H_{21}NO\cdot HCl$) C, H, N.

4-[(4-Chlorophenyl)phenoxymethyl]piperidine hydrochloride (15s): mp 80 °C (dec); yield 72%; ^{1}H NMR ($CDCl_3$) δ 7.37−7.14 (m, 6H), 6.87−6.76 (m, 3H), 4.78 (d, J = 6.4 Hz, 1H), 3.08 (m, 2H), 2.62 (m, 2H), 2.01−1.80 (m, 2H), 1.44−1.21 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 158.0, 138.5, 133.1, 130.1, 129.2, 128.4, 128.3, 128.1, 128.0, 120.7, 115.7, 83.3, 46.2, 43.2, 29.5, 29.3. Anal. ($C_{18}H_{20}ClNO\cdot HCl$) C, H, N.

4-[(4-Chlorophenyl)(4-fluorophenoxy)methyl]piperidine hydrochloride (15y): hygroscopic; yield 54%; ^{1}H NMR ($CDCl_3$) δ 7.38−6.65 (m, 8H), 4.73 (m, 1H), 4.18 (m, 1H), 3.80 (m, 1H), 3.68−1.20 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 157.1 (d, J = 237 Hz, C−F), 154.2 (d, J = 2.2 Hz,), 138.3, 133.23, 128.5, 128.1, 116.9 (d, J = 7.9 Hz), 115.6 (d, J = 22.6 Hz), 84.5, 46.3, 43.3, 29.4, 29.1. Anal. ($C_{18}H_{19}ClFNO\cdot HCl$) C, H, N.

4-[(4-Fluorophenyl)(4-fluorophenoxy)methyl]piperidine hydrochloride (15z): mp 90 °C (dec); yield 65%; ^{1}H NMR ($CDCl_3$) δ 7.32−6.64 (m, 8H), 4.76 (d, J = 6.4 Hz, 1H), 3.63−3.05 (m, 3H), 2.97−2.62 (m, 2H), 2.40−2.26 (m, 2H), 2.05−1.45 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 162.2 (d, J = 245.4 Hz, C−F), 157.1 (d, J = 237.8 Hz, C−F), 153.5 (d, J = 2.2 Hz), 134.3 (d, J = 3.0 Hz), 128.3 (d, J = 8.15 Hz), 128.2 (d, J = 8.2 Hz), 116.9 (d, J = 18 Hz), 115.5 (d, J = 22.8 Hz), 115.2, 115.1, 115.0, 83.1, 43.6, 43.5, 41.0, 26.1, 25.8, 25.3, 25.0, 24.9. Anal. ($C_{18}H_{19}F_2NO\cdot HCl$) C, H, N.

4-[(4-Fluorophenyl)(4-methoxyphenoxy)methyl]piperidine fumarate (15ab): mp 139−142 °C; yield 60%; ^{1}H NMR ($CDCl_3$) δ 7.53−6.71 (m, 8H), 4.66 (d, J = 6.9 Hz, 1H), 3.88−3.81 (m, 1H), 3.76 (s, 3H), 3.15 (m, 2H), 2.82−2.45 (m, 4H), 2.07−1.21 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 162.0 (d, J = 244 Hz, C−F), 153.7, 152.1, 135.7 (d, J = 3.2 Hz), 128.3 (d, J = 8 Hz), 116.9, 115.2 (d, J = 21 Hz), 114.3, 84.3, 55.6, 45.7, 42.9, 28.6, 26.1. Anal. ($C_{19}H_{22}FNO_2\cdot C_4H_4O_4\cdot H_2O$) C, H, N.

4-[2-(4-Methoxyphenoxy)-2-phenylethyl]piperidine fumarate (15al): mp 124−128 °C; yield 83%; ^{1}H NMR ($CDCl_3$) δ 7.35−7.23 (m, 6H), 6.81−6.62 (m, 3H), 5.07 (m, 1H), 3.71 (s, 3H), 3.13 (m, 2H), 2.63 (m, 2H), 2.08−1.06 (m, 8H); ^{13}C NMR (DMSO-d_6) δ 168.0, 153.4, 151.5, 142.2, 135.1, 128.5, 127.4, 126.2, 116.9, 114.5, 76.9, 55.3, 44.6, 42.8, 30.4, 28.9, 28.1. Anal. ($C_{20}H_{25}NO_2.C_4H_4O_4\cdot H_2O$) C, H, N.

4-[2-(4-Fluorophenoxy)-2-(4-fluorophenyl)ethyl]piperidine fumarate (15am): mp 130−134 °C; yield 68%; ^{1}H NMR (DMSO-d_6) δ 7.48−6.84 (m, 10H), 5.38 (m, 1H), 3.25−3.15 (m, 2H), 2.86−2.65 (m, 2H), 1.92−1.24 (m, 7H); ^{13}C NMR (DMSO-d_6) δ 167.7, 161.4 (d, J = 251 Hz, C−F), 156.4 (d, J = 270 Hz, C−F), 137.8, 135.0, 131.2, 128.3 (d, J = 8.2 Hz), 117.3 (d, J = 8.1 Hz), 115.7 (d, J = 22.4 Hz), 115.3 (d, J = 18.9 Hz), 76.2, 44.3, 42.8, 30.3, 28.8, 28.1. Anal. ($C_{19}H_{21}F_2NO\cdot C_4H_4O_4\cdot H_2O$) C, H, N.

4-[1-(4-Fluorophenyl)-2-(piperidin-4-yl)ethoxy]benzonitrile fumarate (15an): mp 98 °C (dec); yield 71%; ^{1}H NMR (DMSO-d_6) δ 7.67 (d, J = 8.9 Hz, 2H), 7.50−7.29 (m, 2H), 7.17 (t, J = 8.8 Hz, 2H), 7.05 (d, J = 8.9 Hz, 2H), 6.55 (s, 2H), 5.61 (m, 1H), 3.22 (m, 2H), 2.95−2.72 (m, 2H), 1.97−1.25 (m, 7H); ^{13}C NMR (DMSO-d_6) δ 167.2, 161.6 (d, J = 242 Hz), 160.9, 137.0 (d, J = 2.5 Hz), 134.7, 134.1, 128.3 (d, J = 8.1 Hz), 119.0, 116.8, 115.5 (d, J = 21.2 Hz), 103.1, 76.0, 44.0, 42.8, 30.2, 28.7, 28.1. Anal. ($C_{20}H_{21}FN_2O\cdot C_4H_4O_4\cdot H_2O$) C, H, N.

1-[4-[(4-Fluorophenyl)(4-methoxyphenoxy)methyl]-piperidin-1-yl]ethanone (15ao): oil; yield 39%; ^{1}H NMR ($CDCl_3$) δ 7.29−6.97 (m, 4H), 6.70 (s, 4H), 4.74−4.61 (m, 2H), 3.89−3.73 (m, 1H), 3.70 (s, 3H), 3.05 (m, 1H), 2.44 (m, 1H), 2.15−1.90 (m, 4H), 1.52−1.22 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 168.5, 161.9 (d, J = 244.8 Hz), 153.7, 151.9, 135.4, 128.2 (d, J = 7.9 Hz), 116.8, 115.1 (d, J = 21.5 Hz), 114.2, 83.8, 83.5, 55.3, 46.2, 46.1, 43.1, 41.3, 41.2, 28.7, 28.5, 27.9, 27.5, 21.2. Anal.-($C_{21}H_{24}FNO_3$) C, H, N.

1-[4-[(4-Fluorophenyl)(phenoxy)methyl]piperidin-1-yl]ethanone (15ap): oil; yield 52%; ^{1}H NMR ($CDCl_3$) δ 7.30−6.75 (m, 9H), 4.83 (t, J = 10.5 Hz, 0.7H), 4.65 (m, 1H), 3.95 (t, J = 8.5 Hz, 0.3H), 3.86 (m, 1H), 3.05 (m, 1H), 2.44 (m, 1H), 2.18−1.15 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 168.6, 162.1 (d, J = 244.6 Hz), 158.8, 157.8 (d, J = 2.5 Hz), 129.2, 128.1 (d, J = 8 Hz), 120.8, 115.7, 115.3 (d, J = 20.5 Hz), 114.3, 82.8, 82.6, 68.4, 67.3, 46.3, 46.2, 43.3, 43.2, 41.4, 41.3, 28.8, 28.5, 28.1, 28.0, 27.5, 21.3. Anal.($C_{20}H_{22}FNO_2$) C, H, N.

4-[(4-Fluorophenoxy)(phenyl)methyl]-1-methylpiperidine (15aq): yellow solid, hygroscopic; yield 32%; ^{1}H NMR ($CDCl_3$) δ 7.38−7.10 (m, 5H), 6.85−6.70 (m, 4H), 4.72 (d, J = 7.1 Hz, 1H), 2.96−2.77 (m, 2H), 2.28 (s, 3H), 2.08−1.35 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 156.9 (d, J = 245 Hz), 154.6, 139.9, 128.3, 127.6, 126.7, 116.9 (d, J = 7.9 Hz), 115.5 (d, J = 23 Hz), 84.9, 55.7, 55.6, 46.3, 42.5, 28.6, 28.4. Anal.($C_{19}H_{22}FNO$) C, H, N.

Method B: 4-[(3-Fluorophenoxy)phenylmethyl]piperidine Hemisulfate (15j). Compound **14a** (2.5 g, 8.7 mmol) was added portionwise to a stirred suspension of hexane-washed NaH (0.5 g, 10.4 mmol, of a 50% oil dispersion) in 12 mL of anhydrous DMSO. The reaction was stirred at room temperature for 30 min, potassium benzoate (1.3 g) added, and stirring continued for 30 min. 1,3-Difluorobenzene (1.2 g, 10.6 mmol) was added, the reaction temperature being kept below 20 °C by means of a water bath. The reaction mixture was heated at 65 °C for 15 h and then cooled to room temperature. A mixture of water and brine was added and the oil extracted with CH_2Cl_2. The organic layer was concentrated in vacuo, stirred, and refluxed for 1 h with MeOH (30 mL) and 10% aqueous HCl solution (30 mL). After removing the solvent, the residue was partitioned between 10% aqueous HCl solution and $CHCl_3$. The aqueous acidic solution was treated with 5% NaOH until pH >8.5, the oil that separates was extracted with $CHCl_3$, and the solvent was removed under reduced pressure to yield 1.6 g (66%) of an amber oil. The crude product was stirred for 30 min with a solution of H_2SO_4 (0.20 mL) in water (10 mL). The white solid formed was filtered and washed with water to yield 1.0 g of **15j**: mp 72−76 °C; ^{1}H NMR ($CDCl_3$) δ 7.37−7.03 (m, 6H), 6.61−6.50 (m, 3H), 4.78 (d, J = 6.4 Hz, 1H), 3.08 (m, 2H), 2.55 (m, 2H), 1.98−1.86 (m, 2H), 1.43−1.27 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 163.4 (d, J = 243.4 Hz), 159.8 (d, J = 10.5 Hz), 139.4, 129.9 (d, J = 10.1 Hz), 128.3, 127.6, 126.7, 111.5 (d, J = 2.95 Hz), 107.3 (d, J = 21.5 Hz), 103.5 (d, J = 24.7 Hz), 84.6, 46.5, 46.4, 43.4, 29.6, 29.3. Anal. ($C_{18}H_{20}FNO\cdot {}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

The following compounds were prepared analogously.

4-[(2-Fluorophenoxy)phenylmethyl]piperidine hemisulfate (15b): mp 76 °C (dec); ^{1}H NMR ($CDCl_3$ + D_2O) δ 7.33−7.26 (m, 5H), 7.05−6.95 (m, 1H), 6.85−6.67 (m, 3H), 4.80 (d, J = 7.4 Hz, 1H), 3.20−3.05 (m, 2H), 2.65−2.53 (m, 2H), 2.49−1.95 (m, 2H), 1.47−1.25 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 153.1 (d, J = 243.4 Hz), 146.2(d, J = 10.4 Hz), 139.3, 128.3, 127.8, 126.8, 123.9 (d, J = 3.95 Hz), 121.1 (d, J = 6.5 Hz), 117.1 (d, J = 2 Hz), 116.1 (d, J = 18.3 Hz), 85.8, 45.9, 43.0, 28.9, 28.8. Anal. ($C_{18}H_{20}FNO\cdot {}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

4-[Phenyl(2-trifluoromethylphenoxy)methyl]piperidine hemisulfate (15c): mp 110 °C (dec); yield 72%; ^{1}H NMR ($CDCl_3$) δ 7.52 (d, J = 7.6 Hz, 1H), 7.32−7.20 (m, 6H), 6.87 (t, J = 7.4 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 4.94 (d, J = 6.1 Hz, 1H), 3.10 (m, 2H), 2.59 (m, 2H), 1.98−1.92 (m, 2H), 1.42−1.25 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 155.7 (q, J = 1.65 Hz), 139.0, 132.8, 129.2, 128.4, 127.7, 126.9 (q, J = 4.9 Hz), 126.6, 119.4, 118.8 (q, J = 30.35 Hz), 113.7, 84.0, 46.5, 46.5, 43.5, 29.6, 29.0. Anal. ($C_{19}H_{20}F_3NO\cdot {}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

4-[Phenyl(piperidin-4-yl)methoxy]benzonitrile oxalate (15d): mp 105 °C (dec); yield 75%; ^{1}H NMR ($CDCl_3$) δ 7.52 (d, J = 7.7 Hz, 1H), 7.49−7.31 (m, 6H), 6.89 (t, J = 7.6 Hz, 1H), 6.72 (d, J = 8.5 Hz, 1H), 4.89 (d, J = 6.95 Hz, 1H), 3.11

(m, 2H), 2.60 (m, 2H), 2.14−1.97 (m, 2H), 1.47−1.26 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 159.8, 138.4, 133.8, 133.4, 128.4, 127.9, 126.6, 120.5, 116.4, 113.9, 102.2, 85.4, 46.2, 46.1, 43.1, 29.2. Anal. ($C_{19}H_{20}N_2O\cdot C_2H_2O_4\cdot H_2O$) C, H, N.

4-[(Biphen-2-yloxy)phenylmethyl]piperidine hydrochloride (15e): mp 84−87 °C; yield 75%; ^{1}H NMR ($CDCl_3$) δ 7.58 (d, J = 8.4 Hz, 2H), 7.47−7.13 (m, 9H), 7.05 (t, J = 7.6 Hz, 1H), 6.91 (t, J = 7.4 Hz, 1H), 6.73 (d, J = 8.1 Hz, 1H), 4.85 (d, J = 6.1 Hz, 1H), 2.96 (m, 2H), 2.45 (m, 2H), 1.82−1.67 (m, 2H), 1.37−1.08 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 154.9, 139.7, 138.8, 131.5, 130.7, 129.7, 128.2, 128.1, 127.6, 127.4, 126.8, 126.7, 120.6, 114.1, 84.7, 46.4, 46.4, 43.4, 29.6, 29.1. Anal. ($C_{24}H_{25}NO\cdot HCl$) C, H, N.

4-[(2-Chlorophenoxy)phenylmethyl]piperidine hemisulfate (15f): mp 123−125 °C; yield 75%; ^{1}H NMR ($CDCl_3$) δ 7.33−7.26 (m, 6H), 6.97 (t, J = 5.8 Hz, 1H), 6.76 (t, J = 5.8 Hz, 1H), 6.66 (d, J = 8.2 Hz, 1H), 4.87 (d, J = 6.4 Hz, 1H), 3.10 (m, 2H), 2.60 (m, 2H), 2.02 (m, 2H), 1.48−1.25 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 153.5, 139.2, 130.0, 128.2, 127.6, 127.2, 126.6, 123.2, 120.9, 114.8, 85.0, 46.4, 46.4, 43.4, 29.5, 29.2. Anal. ($C_{18}H_{20}ClNO\cdot{}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

4-[(3-Iodophenoxy)phenylmethyl]piperidine hemisulfate (15g): mp 127 °C (dec); yield 37%; ^{1}H NMR ($CDCl_3$) δ 7.37−7.15 (m, 7H), 6.89−6.71 (m, 2H), 4.76 (d, J = 6.5 Hz, 1H), 3.08 (m, 2H), 2.54 (m, 2H), 1.97−1.92 (m, 2H), 1.35−1.25 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 158.9, 139.2, 130.4, 129.6, 128.3, 127.6, 126.6, 125.3, 114.9, 94.1, 84.4, 46.4, 46.3, 43.4, 29.5, 29.2. Anal. ($C_{18}H_{20}INO.1/\ 2H_2SO_4\cdot 2H_2O$) C, H, N, S

4-[(3-Bromophenoxy)phenylmethyl]piperidine hemisulfate (15h): mp 98 °C (dec); yield 75%; ^{1}H NMR ($CDCl_3$) δ 7.32−7.26 (m, 6H), 7.00−6.97 (m, 2H), 6.75−6.70 (m, 1H), 4.78 (d, J = 6.4 Hz, 1H), 3.08 (m, 2H), 2.52 (m, 2H), 1.92 (m, 2H), 1.42−1.25 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 158.8, 138.9, 129.8, 127.9, 127.2, 126.2, 123.2, 122.1, 118.9, 113.9, 84.2, 46.0, 43.0, 29.2, 28.9. Anal. ($C_{18}H_{20}BrNO\cdot{}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

4-[Phenyl(3-trifluoromethylphenoxy)methyl]piperidine hydrochloride (15i): mp 58 °C (dec); yield 72%; ^{1}H NMR ($CDCl_3$) δ 7.38−6.87 (m, 9H), 4.82 (d, J = 6.5 Hz, 1H), 3.10 (m, 2H), 2.58 (m, 2H), 2.05−1.85 (m, 2H), 1.50−1.22 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 158.4, 139.1, 131.5 (q, J = 32 Hz), 129.7, 128.4, 127.7, 126.6, 123.8 (q, J = 270.6 Hz), 118.6 (d, J = 1.3 Hz), 117.1 (q, J = 3.6 Hz), 113.0 (q, J = 4 Hz), 84.7, 46.4, 46.4, 43.4, 29.6, 29.5, 29.3. Anal. ($C_{19}H_{20}F_3NO\cdot HCl$) C, H, N.

3-[Phenyl(piperidin-4-yl)methoxy]benzonitrile hydrochloride (15k): mp 82 °C (dec); yield 80%; ^{1}H NMR ($CDCl_3$) δ 7.37−7.00 (m, 9H), 4.80 (d, J = 6 Hz, 1H), 3.12 (m, 2H), 2.55 (m, 2H), 1.98−1.84 (m, 2H), 1.48−1.25 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 157.8, 137.6, 130.3, 129.0, 128.7, 126.5, 124.9, 120.7, 119.1, 118.5, 113.1, 83.5, 43.9, 43.7, 41.3, 25.2, 25.1. Anal. ($C_{19}H_{20}N_2O\cdot HCl$) C, H, N.

4-[(3-Chlorophenoxy)phenylmethyl]piperidine hemisulfate (15l): mp 101−104 °C; yield 90%; ^{1}H NMR ($CDCl_3$) δ 7.38−7.22 (m, 5H), 7.08 (t, J = 7.8 Hz, 1H), 6.82 (m, 2H), 6.70 (m, 1H), 4.78 (d, J = 5 Hz, 1H), 3.15 (m, 2H), 2.58 (m, 2H), 2.05−1.80 (m, 2H), 1.55−1.25 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 159.0, 139.2, 134.4, 129.8, 128.2, 127.5, 126.5, 120.6, 116.3, 113.8, 84.4, 46.2, 46.2, 43.2, 29.33, 29.1. Anal. ($C_{18}H_{20}ClNO\cdot{}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

4-[(4-Nitrophenoxy)phenylmethyl]piperidine hydrochloride (15m): mp 80 °C (dec); yield 80%; ^{1}H NMR ($CDCl_3$) δ 8.08 (d, J = 8.2 Hz, 2H), 7.40−7.19 (m, 5H), 6.86 (d, J = 8.2 Hz, 2H), 4.90 (d, J = 6.5 Hz, 1H), 3.10 (m, 2H), 2.58 (m, 2H), 1.97 (m, 2H), 1.50−1.22 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 163.3, 141.1, 138.3, 128.5, 127.9, 126.5, 125.5, 115.5, 85.0, 46.2, 43.2, 29.3, 29.1. Anal. ($C_{18}H_{20}N_2O_3\cdot HCl$) C, H, N.

4-[(4-Iodophenoxy)phenylmethyl]piperidine hemisulfate (15n): mp 105 °C (dec); yield 57%; ^{1}H NMR ($CDCl_3$) δ 7.41 (d, J = 8.9 Hz, 2H), 7.38−7.26 (m, 5H), 6.59 (d, J = 8.9 Hz, 2H), 4.74 (d, J = 6.5 Hz, 1H), 3.08 (m, 2H), 2.54 (m, 2H), 1.97−1.80 (m, 2H), 1.42−1.25 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 158.2, 139.3, 137.9, 128.3, 127.6, 126.6, 118.2, 84.4, 82.6, 46.4, 46.4, 43.3, 29.5, 29.2. Anal. ($C_{18}H_{20}INO\cdot{}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

4-[(Biphen-4-yloxy)phenylmethyl]piperidine hydrochloride (15o): mp 130 °C (dec); yield 82%; ^{1}H NMR ($CDCl_3$) δ 7.49−7.22 (m, 12H), 6.87 (d, J = 8.7 Hz, 2H), 4.84 (d, J = 6.4 Hz, 1H), 3.10 (m, 2H), 2.58 (m, 2H), 1.96 (m, 2H), 1.41−1.25 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 157.9, 140.6, 139.9, 133.4, 128.5, 128.2, 127.8, 127.4, 126.6, 126.5, 126.4, 115.9, 84.3, 46.4, 46.4, 43.4, 29.6, 29.2. Anal. ($C_{24}H_{25}NO\cdot HCl$) C, H, N.

4-[(4-Fluorophenoxy)phenylmethyl]piperidine hemisulfate (15p): mp 108−110 °C; yield 75%; ^{1}H NMR ($CDCl_3$) δ 7.38−7.20 (m, 5H), 6.84−6.68 (m, 4H), 4.70 (d, J = 7.1 Hz, 1H), 3.22−3.06 (m, 2H), 2.70−2.54 (m, 2H), 2.08−1.22 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 156.9 (d, J = 248 Hz), 154.7, 139.6, 128.3, 127.6, 126.7, 116.9 (d, J = 8 Hz), 115.5 (d, J = 20.7 Hz), 85.0, 46.2, 46.1, 43.2, 29.1, 28.9. Anal. ($C_{18}H_{20}FNO\cdot{}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

4-[Phenyl(4-trifluoromethylphenoxy)methyl]piperidine hemisulfate (15q): mp 128 °C (dec); yield 89%; ^{1}H NMR ($CDCl_3$) δ 7.42 (d, J = 8.5 Hz, 2H), 7.38−7.22 (m, 5H), 6.85 (d, J = 8.5 Hz, 2H), 4.84 (d, J = 6 Hz, 1H), 3.24−3.02 (m, 2H), 2.72−2.54 (m, 2H), 2.08−1.86 (m, 2H), 1.56−1.32 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 160.8, 139.1, 128.4, 127.8, 126.7 (d, J = 3.95 Hz), 126.6 (d, J = 1.5 Hz), 124.3 (q, J = 269.7 Hz), 122.6 (q, J = 32 Hz), 115.6, 84.5, 46.5, 46.5, 43.5, 29.6, 29.3. Anal. ($C_{19}H_{20}F_3NO\cdot{}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

4-[(4-Bromophenoxy)phenylmethyl]piperidine hemisulfate (15r): mp 99−103 °C; yield 75%; ^{1}H NMR ($CDCl_3$) δ 7.38−7.18 (m, 7H), 6.68 (d, J = 7 Hz, 2H), 4.75 (d, J = 5.7 Hz, 1H), 3.10 (m, 2H), 2.75 (m, 2H), 2.05−1.80 (m, 2H), 1.48−1.25 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 157.4, 139.3, 131.9, 128.3, 127.6, 126.6, 117.6, 112.6, 84.5, 46.39, 46.36, 43.4, 29.5, 29.2. Anal. ($C_{18}H_{20}BrNO\cdot{}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

4-[(2-Fluorophenoxy)(3-fluorophenyl)methyl]piperidine hydrochloride (15t): mp 90 °C (dec); yield 62%; ^{1}H NMR ($CDCl_3$) δ 9.54−9.36 (bs, 2H), 7.36−7.25 (m, 1H), 7.12−6.67 (m, 7H), 4.83 (d, J = 7.8 Hz, 1H), 3.63−3.43 (m, 1H), 2.92−2.44 (m, 4H), 2.10−1.72 (m, 3H), 1.48−1.42 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 162.9 (d, J = 247.4 Hz), 153.1 (d, J = 245.8 Hz), 145.3 (d, J = 10.5 Hz), 141.1 (d, J = 6.4 Hz), 130.3 (d, J = 8.1 Hz), 124.1 (d, J = 3.9 Hz), 122.4 (d, J = 7.1 Hz), 117.5 (d, J = 1.4 Hz), 116.3 (d, J = 18.3 Hz), 115.5 (d, J = 21.0 Hz), 113.7 (d, J = 22.2 Hz), 84.3, 43.8, 43.6, 41.0, 25.5, 25.0. Anal. ($C_{18}H_{20}F_2NO\cdot HCl$) C, H, N.

4-[(3-Fluorophenoxy)(3-fluorophenyl)methyl]piperidine hemisulfate (15u): mp 158 °C (dec); yield 50%; ^{1}H NMR ($CDCl_3$) δ 9.35−8.68 (bs, 1H), 7.16−6.64 (m, 5H), 6.41−6.27 (m, 3H), 4.86 (bs, 1H), 3.15 (m, 2H), 2.86−2.43 (m, 2H), 1.98−1.42 (m, 4H), 1.35−1.22 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 162.7 (d, J = 245.1 Hz), 162.3 (d, J = 247.1 Hz), 158.6 (d, J = 11.6 Hz), 141.2 (d, J = 10.5 Hz), 129.8 (d, J = 4.0 Hz), 129.7 (d, J = 4.5 Hz), 122.2, 114.6 (d, J = 21.1 Hz), 113.1 (d, J = 21.6 Hz), 111.1 (d, J = 3.0 Hz), 107.4 (d, J = 21.1 Hz), 103.1 (d, J = 23.6 Hz), 82.1, 43.2, 43.0, 40.3, 24.7, 24.5. Anal. ($C_{18}H_{19}F_2NO\cdot{}^1/_2H_2SO_4$) C, H, N.

4-[(3-Fluorophenoxy)(4-methylphenyl)methyl]piperidine hydrochloride (15v): mp 88 °C (dec); yield 67%; ^{1}H NMR ($CDCl_3$) δ 9.51−9.38 (m, 2H), 7.20−7.01 (m, 5H), 6.60−6.49 (m, 3H), 4.77 (d, J = 6.7 Hz, 1H), 3.60−3.43 (m, 2H), 2.95−2.78 (m, 2H), 2.30 (s, 4H), 1.96−1.51 (m, 3H), 1.45−1.26 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 163.2 (d, J = 244.9 Hz), 159.2, 159.0, 138.0, 135.3, 129.9 (d, J = 10.3 Hz), 129.4, 126.4, 111.5 (d, J = 2.8 Hz), 107.7 (d, J = 21.4 Hz), 103.6 (d, J = 24.9 Hz), 83.2, 43.8, 43.7, 41.2, 25.2,25.1, 21.0. Anal. ($C_{19}H_{22}FNO\cdot HCl$) C, H, N.

4-[(4-Fluorophenoxy)(3-fluorophenyl)methyl]piperidine hydrochloride (15x): mp 65 °C (dec); yield 30%; ^{1}H NMR ($CDCl_3$) δ 7.35−6.62 (m, 8H), 4.74 (d, J = 6.5 Hz, 1H), 3.50−3.36 (m, 2H), 2.85−2.67 (m, 2H), 2.17−1.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 162.9 (d, J = 247.4 Hz), 157.3 (d, J = 239.5 Hz), 153.7 (d, J = 2.4 Hz), 141.7 (d, J = 7.1 Hz), 130.2 (d, J = 8 Hz), 122.4 (d, J = 3.0 Hz), 117.0 (d, J = 8.0 Hz), 115.7 (d, J = 23.3 Hz), 115.1 (d, J = 21.0 Hz), 113.5 (d, J = 21.8 Hz), 83.5, 44.3, 44.2, 41.6, 29.6, 26.0, 25.9. Anal. ($C_{18}H_{19}F_2NO\cdot HCl$) C, H, N.

4-[(3-Fluoro-2-methylphenoxy)phenylmethyl]piperidine hemisulfate (15ac): mp 125 °C (dec); yield 80%; ^{1}H NMR ($CDCl_3$) δ 7.35−7.23 (m, 5H), 6.86 (q, J = 6.8 Hz, 1H), 6.54 (t, J = 8 Hz, 1H), 6.36 (d, J = 8 Hz, 1H), 4.86 (d, J = 6.1 Hz, 1H), 3.10 (m, 2H), 2.59 (m, 2H), 2.24 (d, J = 1.8 Hz, 3H), 1.96−1.91 (m, 2H), 1.47−1.26 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 161.5 (d, J = 240.4 Hz), 157.1 (d, J = 8.7 Hz), 139.6, 128.2, 127.4, 126.4, 126.0 (d, J = 10.3 Hz), 114.0 (d, J = 16.6 Hz), 108.2 (d, J = 2.9 Hz), 107.1 (d, J = 23.0 Hz), 84.1, 46.4, 46.3, 43.5, 29.6, 29.0, 17.8 (d, J = 4.8 Hz). Anal. ($C_{19}H_{22}FNO\cdot{}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

4-[(3-Chloro-2-methylphenoxy)phenylmethyl]piperidine hemisulfate (15ad): mp 130 °C (dec); yield 89%; ^{1}H NMR ($CDCl_3$) δ 7.35−7.20 (m, 5H), 6.88−6.83 (m, 2H), 6.50−6.45 (m, 1H), 4.86 (d, J = 6 Hz, 1H), 3.10 (m, 2H), 2.57 (m, 2H), 2.39 (s, 3H), 1.94 (m, 2H), 1.49−1.25 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 156.4, 139.1, 134.5, 127.9, 127.2, 126.1, 125.9, 124.9, 120.5, 110.5, 83.8, 46.1, 46.0, 43.2, 29.3, 28.7, 12.5. Anal. ($C_{19}H_{22}ClNO\cdot{}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

4-[(5-Chloro-2-methylphenoxy)phenylmethyl]piperidine hemisulfate (15ae): mp 105 °C (dec); yield 77%; ^{1}H NMR ($CDCl_3$) δ 7.37−7.29 (m, 5H), 7.00 (d, J = 8.6 Hz, 1H), 6.72 (d, J = 7.9 Hz, 1H), 6.55 (d, J = 1.9 Hz, 1H), 4.83 (d, J = 6.1 Hz, 1H), 3.10 (m, 2H), 2.56 (m, 2H), 2.28 (s, 3H), 1.92 (m, 2H), 1.46−1.25 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 156.5, 139.2, 131.4, 131.0, 128.3, 127.6, 126.5, 125.4, 119.9, 112.9, 83.9, 46.4, 46.4, 43.5, 29.7, 29.0, 16.1. Anal. ($C_{19}H_{22}ClNO\cdot{}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

3-Chloro-4-[phenyl(piperidin-4-yl)methoxy]benzonitrile hydrochloride (15af): mp 125 °C (dec); yield 70%; ^{1}H NMR ($CDCl_3$) δ 7.43 (d, J = 8.7 Hz, 1H), 7.38−7.22 (m, 5H), 6.94 (d, J = 1.6 Hz, 1H), 6.76 (d, J = 8.7 Hz, 1H), 4.84 (d, J = 6.5 Hz 1H), 3.09 (m, 2H), 2.56 (m, 2H), 1.97−1.91 (m, 2H), 1.7−1.25 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 162.1, 138.0, 137.9, 134.8, 128.7, 128.2, 126.5, 117.5, 116.3, 114.7, 104.8, 85.3, 46.3, 43.3, 29.3, 29.2. Anal. ($C_{19}H_{19}ClN_2O\cdot HCl$) C, H, N.

4-[(3,4-Dichlorophenoxy)phenylmethyl]piperidine hemisulfate (15ag): mp 108 °C (dec); yield 91%; ^{1}H NMR ($CDCl_3$) δ 7.38−7.24 (m, 5H), 7.18 (d, J = 8.8 Hz, 1H), 6.92 (d, J = 2.8 Hz, 1H), 6.64 (d, J = 8.8 Hz, 1H), 4.74 (d, J = 6.6 Hz, 1H), 3.11 (m, 2H), 2.52 (m, 2H), 2.06−1.80 (m, 2H), 1.38−1.26 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 157.3, 138.7, 132.4, 130.3, 128.4, 127.8, 126.5, 123.7, 117.9, 115.4, 84.8, 46.1, 43.1, 29.1, 28.9. Anal. ($C_{18}H_{19}Cl_2NO\cdot{}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

4-[(3-Fluoro-5-methoxyphenoxy)phenylmethyl]piperidine hydrochloride (15ah): mp 200−203 °C; yield 65%; ^{1}H NMR ($CDCl_3$) δ 7.36−7.19 (m, 5H), 6.19−6.09 (m, 3H), 4.74 (d, J = 6.5 Hz, 1H), 3.68 (s, 3H), 3.08 (m, 2H), 2.54 (m, 2H), 1.97−1.81 (m, 2H), 1.41−1.25 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 163.5 (d, J = 241.1 Hz), 160.7 (d, J = 13.5 Hz), 159.8 (d, J = 13.5 Hz), 139.0, 127.9, 127.2, 126.2, 97.5 (d, J = 2.5 Hz), 95.5 (d, J = 24.9 Hz), 93.6 (d, J = 25.5 Hz), 84.2, 54.9, 46.0, 46.0, 42.9, 29.1, 28.8. Anal. ($C_{19}H_{22}FNO_2\cdot HCl$) C, H, N.

3-Fluoro-5-[phenyl(piperidin-4-yl)methoxy]benzonitrile hydrochloride (15ai): mp 70 °C (dec); yield 76%; ^{1}H NMR ($CDCl_3$) δ 7.38−7.23 (m, 5H), 6.87−6.67 (m, 3H), 4.77 (d, J = 6.7 Hz, 1H), 3.10 (m, 2H), 2.54 (m, 2H), 1.95−1.82 (m, 2H), 1.41−1.25 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 162.7 (d, J = 247.3 Hz), 159.9 (d, J = 11.7 Hz), 137.9, 128.5, 128.1, 126.5, 117.4, 115.4 (d, J = 3.1 Hz), 113.5 (d, J = 11.9 Hz), 111.1 (d, J = 24.8 Hz), 108.5 (d, J = 24.4 Hz), 85.3, 46.2, 43.1, 29.2, 29.1. Anal. ($C_{19}H_{19}FN_2O\cdot HCl$) C, H, N.

4-[(3,5-Difluorophenoxy)phenylmethyl]piperidine hemisulfate (15aj): mp 206−208 °C; yield 86%; ^{1}H NMR ($CDCl_3$) δ 7.33−7.25 (m, 5H), 6.39−6.26 (m, 3H), 4.74 (d, J = 6.5 Hz, 1H), 3.09 (m, 2H), 2.56 (m, 2H), 1.97−1.82 (m, 2H), 1.41−1.25 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 163.4 (d, J = 244.3 Hz), 160.2 (t, J = 13.5 Hz), 138.7, 128.3, 127.7, 126.5, 99.4 (d, J = 28.6 Hz), 96.0 (t, J = 25.5 Hz), 84.9, 46.3, 46.2, 43.2, 29.3, 29.1. Anal. ($C_{18}H_{19}F_2NO\cdot{}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

2-Fluoro-6-[phenyl(piperidin-4-yl)methoxy]phenol (15ar): yellow solid; mp 82 °C (d); yield 18%; ^{1}H NMR ($CDCl_3$) δ 7.35−7.22 (m, 5H), 6.67−6.34 (m, 3H), 4.98 (d, J = 7.1 Hz, 1H), 3.27−3.11 (m, 2H), 2.67 (m, 2H), 2.18−1.82 (m, 2H), 1.78−1.25 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 152.8 (d, J = 235.6 Hz), 148.4 (d, J = 5.8 Hz), 139.8, 138.0 (d, J = 14.4 Hz), 128.2, 127.7, 126.9, 116.4 (d, J = 9.1 Hz), 113.4, 109.3 (d, J = 19.2 Hz), 85.9, 45.3, 45.2, 42.4, 29.6, 27.9, 27.4. Anal. ($C_{18}H_{20}FNO_2$) C, H, N.

2-Fluoro-4-[phenyl(piperidin-4-yl)methoxy]phenol (15as): white solid; mp 85 °C (d); yield 49%; ^{1}H NMR ($CDCl_3$) δ 7.32−7.26 (m, 5H), 6.81−6.73 (m, 1H), 6.50−6.33 (m, 2H), 4.81 (d, J = 6.4 Hz, 1H), 3.12 (m, 2H), 2.63−2.45 (m, 2H), 1.98−1.92 (m, 2H), 1.52−1.25 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 156.1 (d, J = 235.3 Hz), 145.5 (d, J = 9.9 Hz), 142.4 (d, J = 2.5 Hz), 138.6, 128.6, 128.1, 126.4, 114.7 (d, J = 9.2 Hz), 107.0 (d, J = 22.5 Hz), 102.3 (d, J = 27.1 Hz), 85.4, 46.0, 42.7, 29.7, 28.8. Anal. ($C_{18}H_{20}FNO_2$) C, H, N.

3-Fluoro-5-[phenyl(piperidin-4-yl)methoxy]phenol (15at): white solid; mp 103 °C; yield 23%; ^{1}H NMR ($CDCl_3$) δ 7.32−7.24 (m, 5H), 6.09−6.03 (m, 3H), 4.71 (d, J = 6.7 Hz, 1H), 3.10 (m, 2H), 2.64−2.42 (m, 2H), 2.05−1.85 (m, 2H), 1.49−1.25 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 163.5 (d, J = 248.0 Hz), 160.0 (d, J = 14.9 Hz), 139.7, 128.3, 127.6, 126.9, 99.4 (d, J = 2.6 Hz), 95.4 (d, J = 23.8 Hz), 93.8 (d, J = 25.3 Hz), 83.1, 45.4, 42.6, 28.5. Anal. ($C_{18}H_{20}FNO_2$) C, H, N.

4-[(Naphthalen-1-yloxy)phenylmethyl]piperidine hemisulfate (15au): mp 152 °C (dec); yield 72%; ^{1}H NMR ($CDCl_3$) δ 8.50 (m, 1H), 7.68 (m, 1H), 7.55−7.12 (m, 9H), 6.56 (d, J = 7.2 Hz, 1H), 5.08 (d, J = 5.1 Hz, 1H), 3.10 (m, 2H), 2.90−1.96 (m, 2H), 2.70−2.55 (m, 2H), 1.65−1.42 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 153.6, 139.0, 134.5, 128.3, 127.5, 127.5, 126.5, 126.2, 126.0, 125.7, 125.1, 122.1, 119.8, 106.5, 83.9, 46.7, 46.7, 43.9, 30.0, 29.2. Anal. ($C_{22}H_{23}NO\cdot{}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

1-[(Cyclopentyl)phenylmethoxy]-3-fluorobenzene (18): colorless oil; yield 58%; ^{1}H NMR ($CDCl_3$) δ 7.38−7.03 (m, 5H), 6.68−6.53 (m, 4H), 4.84 (d, J = 7.4 Hz, 1H), 2.43−2.28 (m, 1H), 1.94−1.81 (m, 1H), 1.76−0.84 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 163.4 (d, J = 243.0 Hz), 159.9 (d, J = 10.5 Hz), 141.2, 129.9 (d, J = 10.3 Hz), 128.4, 127.5, 126.4, 111.7 (d, J = 3.2 Hz), 107.2 (d, J = 21.4 Hz), 103.6 (d, J = 24.6 Hz), 84.5, 47.5, 29.4, 29.2, 25.3. Anal. ($C_{18}H_{19}FO$) C, H.

4-[(3-Fluorophenoxy)phenylmethyl]tetrahydropyran (21): yellow oil; yield 75%; ^{1}H NMR ($CDCl_3$) δ 7.38−7.28 (m, 5H), 7.22−7.03 (m, 1H), 6.62−6.49 (m, 3H), 4.78 (d, J = 6.9 Hz, 1H), 3.98 (m, 2H), 3.38 (m, 2H), 2.08−1.88 (m, 2H), 1.65−1.24 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 163.23 (d, J = 243.3 Hz), 159.5 (d, J = 11.0 Hz), 139.0, 128.9 (d, J = 9.4 Hz), 128.3, 127.7, 126.5, 111.4 (d, J = 2.4 Hz), 107.3 (d, J = 21.5 Hz), 103.4 (d, J = 24.7 Hz), 84.2, 67.6, 67.4, 42.1, 29.0, 28.9. Anal. ($C_{18}H_{19}FO_2$) C, H.

General Procedure for Resolution of Racemic Mixtures: Enantiomers 15.[27] **Method C: (−)-4-[(3-Chlorophenoxy)phenylmethylpiperidine Methanesulfonate ((−)-15l) and (+)-4-[(3-Chlorophenoxy)phenylmethyl]piperidine Methanesulfonate ((+)-15l).** l-Dibenzoyltartaric acid (3.3 g, 9.1 mmol) was added to a solution of **15L** (5.5 g, 18.2 mmol) in 96% ethanol (100 mL). The white solid was filtered and washed with ethanol, taken up in methanol (300 mL), and the suspension was stirred for 2 h at room temperature and then filtered again. The solid was suspended in methanol (200 mL), stirred for 2 h at room temperature, filtered, suspended in 10% aqueous NaOH solution, and extracted with CH_2Cl_2 to give a pale yellow oil. A solution of 1.1 g of the crude product (3.6 mmol) in Et_2O (10 mL) was treated with methanesulfonic acid (0.3 g, 3.6 mmol) in Et_2O (10 mL), stirred for 15 min at room temperature, and concentrated in vacuo. The solid residue was crystallized from acetone to yield 1.1 g of **(−)-15l** as methanesulfonate: mp 200−202 °C; 99% ee; $[\alpha]^{22}_{546}$ −2° (c = 0.646, $CHCl_3$). Anal. ($C_{18}H_{20}ClNO\cdot CH_3SO_3H$) C, H, N. The ethanolic and methanolic filtrates were combined and concentrated in vacuo, and the residue was washed with 10% aqueous NaOH solution and extracted with CH_2Cl_2 to give 2.0 g of yellow oil, which was taken with 96% ethanol (50 mL) and treated with D-dibenzoyltartaric acid (1.2 g, 3.3 mmol) in one portion. The white solid precipitate was collected, washed with ethanol, stirred with 10% aqueous NaOH solution, and extracted with CH_2Cl_2, and the extract was concentrated to an

oil (1.1 g, 3.6 mmol) which was treated with methanesulfonic acid as above to yield 1.0 g of **(+)-15l** as methanesulfonate: mp 200−202 °C; 99% ee; $[\alpha]^{22}_{546}$ 1.7° (c = 0.690, $CHCl_3$). Anal. ($C_{18}H_{20}ClNO\cdot CH_3SO_3H$) C, H, N.

The following compounds were prepared analogously.

(−)-4-[(3-Fluorophenoxy)phenylmethyl]piperidine hemisulfate ((−)-15j): 99% ee; $[\alpha]^{22}_{546}$ −10.5° (c = 0.980, $CHCl_3$); mp 121−124 °C. Anal. ($C_{18}H_{20}FNO\cdot{}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

(+)-4-[(3-Fluorophenoxy)phenylmethyl]piperidine hemisulfate ((+)-15j): 98% ee; $[\alpha]^{22}_{546}$ 10.4° (c = 0.842, $CHCl_3$); mp 121−124 °C. Anal. ($C_{18}H_{20}FNO\cdot{}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

(−)-3-[Phenyl(piperidin-4-yl)methoxy]benzonitrile hydrochloride ((−)-15k): 98% ee; $[\alpha]^{22}_{546}$ −11.1° (c = 0.680, $CHCl_3$); mp 70 °C (dec). Anal. ($C_{19}H_{20}N_2O\cdot HCl$) C, H, N.

(+)-3-[Phenyl(piperidin-4-yl)methoxy]benzonitrile hydrochloride ((+)-15k): 94% ee; $[\alpha]^{22}_{546}$ 10.5° (c = 0.600, $CHCl_3$); mp 70 °C (dec). Anal. ($C_{19}H_{20}N_2O\cdot HCl$) C, H, N.

(−)-4-[(4-Fluorophenoxy)phenylmethyl]piperidine ((−)-15p): 96% ee; $[\alpha]^{22}_{546}$ −14.0° (c = 0.237, $CHCl_3$); mp 102−104 °C. Anal. ($C_{18}H_{20}FNO$) C, H, N.

(+)-4-[(4-Fluorophenoxy)methyl]piperidine ((+)-15p): 98% ee; $[\alpha]^{22}_{546}$ 14.0° (c = 0.259, $CHCl_3$); mp 100−102 °C. Anal. ($C_{18}H_{20}FNO$) C, H, N.

(−)-4-[Phenyl(4-trifluoromethylphenoxy)methyl]-piperidine hemisulfate ((−)-15q): 95% ee; $[\alpha]^{22}_{436}$ −4.0° (c = 0.508, $CHCl_3$); mp 75 °C (dec). Anal. ($C_{19}H_{20}F_3NO\cdot{}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

(+)-4-[Phenyl(4-trifluoromethylphenoxy)methyl]-piperidine hemisulfate ((+)-15q): 96% ee; $[\alpha]^{22}_{436}$ 5.7° (c = 0.556, $CHCl_3$); mp 85 °C (dec). Anal. $C_{19}H_{20}F_3NO\cdot{}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

(−)-4-[(4-Bromophenoxy)phenylmethyl]piperidine ((−)-15r): 94% ee; $[\alpha]^{22}_{546}$ −32.5° (c = 1.048, $CHCl_3$); mp 128−130 °C. Anal. ($C_{18}H_{20}BrNO$) C, H, N.

(+)-4-[(4-Bromophenoxy)phenylmethyl]piperidine ((+)-15r): 96% ee; $[\alpha]^{22}_{546}$ 32.1° (c = 1.012, $CHCl_3$); mp 129−131 °C. Anal. ($C_{18}H_{20}BrNO$) C, H, N.

(+)-4-[(3-Fluorophenoxy)(3-fluorophenyl)methyl]-piperidine hydrochloride ((+)-15u): 96% ee; $[\alpha]^{22}_{546}$ 15° (c = 0.183, $CHCl_3$); mp 75 °C (dec); yield 37%. Anal. ($C_{18}H_{19}F_2NO\cdot HCl$) C, H, N.

(−)-4-[(3-Fluorophenoxy)(3-fluorophenyl)methyl]-piperidine hydrochloride ((−)-15u): 95.4% ee; $[\alpha]^{22}_{546}$ −16° (c = 0.170, $CHCl_3$); mp 78 °C (dec); yield 32%. Anal. ($C_{18}H_{19}F_2NO\cdot HCl$) C, H, N.

(−)-4-[(3,5-Difluorophenoxy)phenylmethyl]piperidine hemisulfate ((−)-15aj): 96% ee; $[\alpha]^{22}_{546}$ −12.7° (c = 0.724, $CHCl_3$); mp 78 °C (dec). Anal. ($C_{18}H_{19}F_2NO\cdot{}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

(+)-4-[(3,5-Difluorophenoxy)phenylmethyl]piperidine hemisulfate ((+)-15aj): 98% ee; $[\alpha]^{22}_{546}$ 12.1° (c = 0.800, $CHCl_3$); mp 78 °C (dec). Anal. ($C_{18}H_{19}F_2NO\cdot{}^1/_2H_2SO_4\cdot 2H_2O$) C, H, N, S.

General Procedure for Preparation of Enantiomers 15[27] from Enantioenriched Alcohols. Method D: (+)-4-[(4-Fluorophenoxy)phenylmethyl]piperidine ((+)-15p). To a solution of (+)-**14j** (1.8 g, 9.6 mmol) in methanol (10 mL) at 0° C was added $(Boc)_2O$ (2.5 g, 11.3 mmol) dissolved in methanol (10 mL). The mixture was stirred at room temperature for 24 h and the methanol removed under reduced pressure. Water was added and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. Alcohol was obtained as a slightly colored oil in a 93% yield. A solution of previously prepared alcohol (2.7 g, 9.3 mmol) in anhydrous DMSO (25 mL) was added to a stirred suspension of NaH (60% dispersion in mineral oil, 0.6 g) in anhydrous DMSO (5 mL). After 30 min at room temperature potassium benzoate (1.5 g, 9.6 mmol) was added and the mixture stirred 30 min, then 1,4-difluorobenzene (1.3 mL, 11.9 mmol) was added. The mixture was heated (70−75 °C oil bath) for 20 h, cooled to room temperature, poured into water and brine, and extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. A solution of the resulting residue in methanol (40 mL) and 10% aqueous HCl solution (40 mL) was refluxed for 1 h and then allowed to cool to room temperature. Methanol was evaporated and the aqueous solution extracted with hexane/Et_2O and $CHCl_3$. The organic layer was washed with 10% aqueous NaOH solution and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. The product was obtained as an oil in 54% yield. The treatment of the oil (0.5 g, 1.7 mmol) prepared above with a solution of d-dibenzoyltartaric acid (0.5 equiv) in ethanol (96%, 30 mL) provided a precipitate which was filtered (mp 198−199 °C). The resulting solid was treated with 10% aqueous NaOH solution and extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to yield the free base of **(+)-15p** as a white solid: mp 102−104 °C, 96% ee; $[\alpha]^{22}_{546}$ 15 ° (c = 0.105, $CHCl_3$). Anal. ($C_{18}H_{20}FNO\cdot HCl$) C, H, N.

The following compounds were prepared analogously.

(−)-4-[(2-Fluorophenoxy)phenylmethyl]piperidine hemisulfate ((−)-15b): 97.6% ee; $[\alpha]^{22}_{546}$ −31° (c = 0.140, $CHCl_3$); mp 90 °C (dec); yield 44%. Anal. ($C_{18}H_{20}FNO\cdot{}^1/_2H_2SO_4$) C, H, N.

(+)-4-[(2-Fluorophenoxy)phenylmethyl]piperidine hemisulfate ((+)-15b): 97.6% ee; $[\alpha]^{22}_{546}$ 31° (c = 0.081, $CHCl_3$); mp 105 °C (dec); yield 38%. Anal. ($C_{18}H_{20}FNO\cdot{}^1/_2H_2SO_4$) C, H, N.

(−)-4-[(4-Nitrophenoxy)phenylmethyl]piperidine hydrochloride ((−)-15m): 98.7% ee; $[\alpha]^{22}_{436}$ −31° (c = 0.042, ethanol); mp 59 °C (dec); yield 63%. Anal. ($C_{18}H_{20}N_2O_3\cdot HCl$) C, H, N.

(+)-4-[(4-Nitrophenoxy)phenylmethyl]piperidine hydrochloride ((+)-15m): 96% ee; $[\alpha]^{22}_{436}$ 36° (c = 0.045, ethanol); mp 55 °C (dec); yield 50%. Anal. ($C_{18}H_{20}N_2O_3\cdot HCl$) C, H, N.

(−)-4-[(4-Fluorophenoxy)phenylmethyl]piperidine ((−)-15p): 96% ee; $[\alpha]^{22}_{546}$ −14° (c = 0.200, $CHCl_3$); mp 102−104 °C; yield 64%. Anal. ($C_{18}H_{20}FNO$) C, H, N.

(−)-4-[(2-Fluorophenoxy)(3-fluorophenyl)methyl]-piperidine hydrochloride ((−)-15t): 98% ee; $[\alpha]^{22}_{436}$ −43° (c = 0.082, $CHCl_3$); mp 115 °C (dec); yield 35%. Anal. ($C_{18}H_{19}F_2NO\cdot HCl$) C, H, N.

(+)-4-[(2-Fluorophenoxy)(3-Fluorophenyl)methyl]-piperidine hydrochloride ((+)-15t): 98% ee; $[\alpha]^{22}_{436}$ 44° (c = 0.121, $CHCl_3$); mp 110 °C (dec); yield 60%. Anal. ($C_{18}H_{19}F_2NO\cdot HCl$) C, H, N.

(−)-4-[(Naphthalen-1-yloxy)phenylmethyl]piperidine hydrochloride ((−)-15au): 98% ee; $[\alpha]^{22}_{546}$ -180° (c = 0.080, $CHCl_3$); mp 65 °C (dec); yield 57%. Anal. ($C_{22}H_{23}NO\cdot HCl$) C, H, N.

(+)-4-[(Naphthalen-1-yloxy)phenylmethyl]piperidine hydrochloride ((+)-15au): 94% ee; $[\alpha]^{22}_{546}$ 156° (c = 0.128, $CHCl_3$); mp 115 °C (dec); yield 77%. Anal. ($C_{22}H_{23}NO\cdot HCl$) C, H, N.

Pharmacological Methods. Drugs. All drugs used in binding experiments were obtained from commercial sources, except paroxetine, reboxetine, and venlafaxine, which were extracted from marketed pharmaceutical specialities Motivan (Faes Farma, S. A.), Norebox (Pharmacia & Upjohn), and Vandral (Wyeth), respectively.

(1) 5-HT$_{1A}$ and 5-HT$_{2A}$ Receptor Binding Assays. Binding of derivatives and standards at serotonin 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors was determined by radioligand assays following methods widely described for our group in other publications.[35−37] Briefly, the affinity for 5-HT$_{1A}$ receptors was determined by displacement of [^{3}H]-8-OH-DPAT binding in membranes from rat hippocampus, using 400−500 μg of protein and 1.5 nM [^{3}H]-8-OH-DPAT. Nonspecific binding was determined in the presence of 10 μM cold 5-HT. The incubation time was 30 min at 37 °C. Affinity for 5-HT$_{2A}$ receptors was determined by displacement of [^{3}H]ketanserin binding in membranes from rat prefrontal cerebral cortex, using 400−500 μg of protein and 0.8 nM [^{3}H]ketanserin. Nonspecific

binding was determined in the presence of 1 μM cold methysergide. The incubation time was 15 min at 37 °C.

(2) Serotonin Transporter (SERT) Binding Assay.[38] Adult male Wistar rats weighing 220−280 g were used. Animals were killed by decapitation and the whole brain with the exception of the brainstem and cerebellum was quickly removed, and the various areas were dissected, weighed, and immediately frozen at −70 °C. Cerebral cortex used for the binding experiments was homogenized with an Ultra-Turrax (setting 5 for 20 s) in 20 volumes of ice-cold 50 mM Tris-HCl (pH 7.4) buffer and centrifuged at 48 000*g* for 10 min (4 °C). The resulting pellet was resuspended in 20 volumes of ice-cold 50 mM Tris-HCl buffer (pH 7.4), incubated at 37 °C for 10 min, and then centrifuged once more at 48 000*g* for 10 min (4 °C). The final pellet was resuspended in 10 volumes of ice-cold 50 mM Tris-HCl buffer containing 120 mM NaCl and 5 mM KCl and was stored at −70 °C until use. At the time of the experiment, the membranes were diluted in the same ice-cold Tris−saline buffer (final dilution 1:100, wt/vol). Competition assays were performed in a final volume of 1 mL. To each assay tube were added the following: 0.1 mL of the displacer drug concentration (0.1 mL of vehicle if no competing drug was added) and 0.1 mL of [^{3}H]paroxetine (NEN, 15 Ci/mmol) in buffer (final concentration 0.2 nM). Nonspecific binding was determined using 10 μM cold fluoxetine. The binding experiment was initiated by addition of 0.8 mL of membrane suspension (550−600 μg of protein). The incubation time was 60 min at 25 °C.

(3) Norepinephrine Transporter (NET) Binding Assay.[4] Adult male Wistar rats weighing 220−280 g were used. Animals were killed by decapitation and the whole brain with the exception of the brainstem and cerebellum was quickly removed, and the various areas were dissected, weighed, and immediately frozen at −70 °C. Cerebral cortex used for the binding experiments was homogenized with an Ultra-Turrax (setting 5 for 20 s) in 30 volumes of ice-cold 50 mM Tris-HCl (pH 7.4) buffer containing 120 mM NaCl and 5 mM KCl and centrifuged at 40 000*g* for 10 min (4 °C). The resulting pellet was resuspended in 30 volumes of ice-cold 50 mM Tris-HCl saline buffer (pH 7.4), incubated at 37 °C for 10 min, and then centrifuged once more at 40 000*g* for 10 min (4 °C). The resuspension and centrifugation of the resulting pellet was repeated twice more under the same conditions. The final pellet was resuspended in 5 volumes of ice-cold 10 mM phosphate buffer containing 120 mM NaCl and 5 mM KCl and was stored at −70 °C until use. At the time of the experiment, the membranes were diluted in the same ice-cold phosphate−saline buffer (final dilution 1:70, wt/vol). Competition assays were performed in a final volume of 1 mL. To each assay tube were added the following: 0.1 mL of the displacer drug concentration (0.1 mL of vehicle if no competing drug was added) and 0.1 mL of [^{3}H]nisoxetine (NEN, 85 Ci/mmol) in buffer (final concentration 0.5−1 nM). Nonspecific binding was determined using 10 μM cold mazindol. The binding experiment was initiated by addition of 0.8 mL of membrane suspension (550−600 μg of protein). The incubation time was 30 min at 25 °C.

(4) Dopamine Transporter (DAT) Binding Assay.[39] Adult male Wistar rats weighing 220−280 g were used. Animals were killed by decapitation and the whole brain with the exception of the brainstem and cerebellum was quickly removed, and the various areas were dissected, weighed, and immediately frozen at −70 °C. Striatum used for the binding experiments was homogenized with an Ultra-Turrax (setting 5 for 20 s) in 10 volumes of ice-cold 10 mM phosphate buffer (pH 7.4) containing 0.32 M sucrose and centrifuged at 48 000*g* for 10 min (4 °C). The resulting pellet was resuspended in 10 volumes of ice-cold 10 mM phosphate buffer (pH 7.4), incubated at 37 °C for 10 min, and then centrifuged twice more at 48 000*g* for 10 min (4 °C). The final pellet was resuspended in 10 volumes of ice-cold 10 mM phosphate buffer and was stored at −70 °C until use. At the time of the experiment, the membranes were diluted in the same ice-cold phosphate−saline buffer (final dilution 1:140, wt/vol). Competition assays were performed in a final volume of 1 mL. To each assay tube were added the following: 0.1 mL of the displacer drug concentration (0.1 mL of vehicle if no competing drug was added) and 0.1 mL of [^{3}H]WIN-35428 (NEN, 83.5 Ci/mmol) in buffer (final concentration 0.5 nM). Nonspecific binding was determined using 10 μM cold mazindol. The binding experiment was initiated by addition of 0.8 mL of membrane suspension (300 μg of protein). The incubation time was 120 min at 4 °C.

For all described binding assays, after the incubation period the reaction was stopped by rapid vacuum filtration through Whatman GF/B presoaked filters (1% polyethylenimine in assay buffer), using a 24 Brandel cell harvester, followed by two washes with 5 mL of ice-cold assay buffer. The filters obtained were placed in scintillating poly(ethylene) vials with 5 mL of scintillation cocktail (Ecoscint-H, National Diagnostic) and equilibrated by shaking. The filter-retained radioactivity was counted the next day in a liquid scintillation counter (Kontron Betamatic V) with 48−52% of efficiency. For all binding assays, an initial screen was conducted at a concentration of 1 μM of each unknown derivative. If there was greater than 50% displacement of each specific radioligand used, subsequent experiments were performed and the data obtained were plotted as log concentration vs percent of specific binding and analyzed with GraphPad Prism (GraphPad Software, Inc.) version 3.0. IC_{50} values were calculated from each competition experiments with samples in triplicate, using 8−12 different concentrations of drugs dissolved and diluted in the different assay buffers. The inhibition constant K_i was calculated from IC_{50} value using the Cheng−Prusoff equation.[40] For each compound, the final K_i value was obtained as mean from two to four independent experiments. In all cases, the standard error mean (SEM) was less than 15%.

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