Synthesis of Chiral 1-[ω-(4-Chlorophenoxy)alkyl]-4-methylpiperidines and Their Biological Evaluation at σ_1, σ_2, and Sterol $\Delta_8-\Delta_7$ Isomerase Sites

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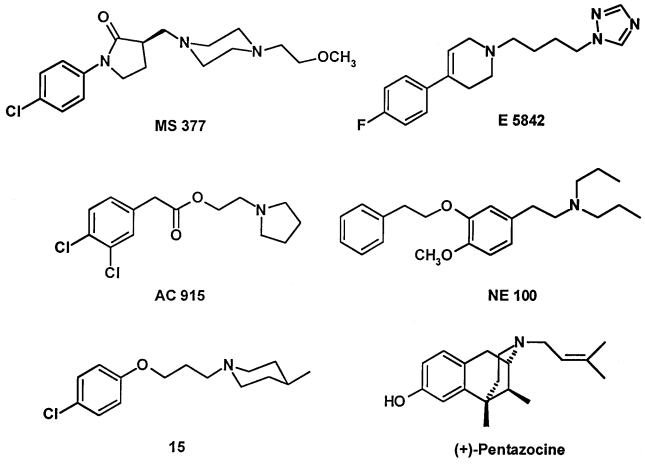
Sumitomo's patented σ ligand 1-[3-(4-chlorophenoxy)propyl]-4-methylpiperidine (**15**), which has been claimed as agent for CNS disorders and neuropathies, and its lower homologue **12** were prepared along with related chiral (4-chlorophenoxy)alkylpiperidines. They were tested at σ_1, σ_2, and sterol $\Delta_8-\Delta_7$ isomerase (SI) sites by in vitro radioligand binding assays, to evaluate the influence of a chiral center in the alkyl chain on the selective σ_1 binding relative to other σ family sites. Generally high σ_1-site affinities were found, so that the chirality introduced by a methyl substitution resulted in slight differences. Nevertheless, the shorter oxyethylenic chain was beneficial to increase σ_1 selectivity. However, the (−)-(*S*)-4-methyl-1-[2-(4-chlorophenoxy)-1-methylethyl]piperidine ((−)-(*S*)-**17**) reached the highest σ_1 affinity (K_i = 0.34 nM) and the best selectivity relative to the σ_2 site (547-fold). Compound (−)-(*S*)-**17** displayed also a moderate selectivity (11-fold) relative to the SI site.

Introduction

Since the findings that several neuroleptic drugs bind σ receptors,[1,2] a growing interest in σ ligands has been driven by the need of atypical antipsychotics devoid of motor side effects that are displayed by the classical neuroleptics. The hope of employing σ agents in psychosis[3,4] has been reinforced by the observation that σ receptors decreased in postmortem schizophrenic brains.[5] At the moment, σ receptors are recognized to be intracellular cytoplasmatic sites, distinguished in at least σ_1 and σ_2 subtypes.[6] Both subtypes are widely distributed in CNS (central nervous system),[7] liver, kidney,[8] lung, and in endocrine, immune, and reproductive tissues,[9] and are overexpressed in several tumor cell lines.[10,11] Direct functional assays are unknown. Nevertheless, deduced σ_1 receptor functions in CNS include modulatory roles on K^+ and Ca^{2+} channels[12,13] and on dopaminergic,[14] NMDA (*N*-methyl-D-aspartate),[7] serotonergic,[15] muscarinic[16] neurotransmission, and opioid analgesia.[17] The σ_1 receptor coupling to G-protein[18,19] is a controversial matter, and σ_1 receptorial protein has recently been indicated as a voltage-gated K^+ channel subunit.[20] Moreover, the structural homology of mammalian cloned σ_1 receptor with a yeast sterol-isomerase (ERG2 protein) has suggested the σ_1 receptor intervention in steroid biosynthesis.[21] This seems to be confirmed by the colocalization on THP1 cells[22] of σ_1 receptor and sterol $\Delta_8-\Delta_7$ isomerase (SI) or EBP (emopamil binding protein), the functional mammalian counterpart of ERG2-p. The σ_2 subtype plays a role in the regulation of cell proliferation and apoptosis,[23] through the control of intracellular Ca^{2+} storage and depletion.[24] The activity at the σ_2 site has also been thought accountable for EPS (extrapyramidal symptoms)[25−27] that recent findings attribute to the σ_1 site too.[28] Although a real intrinsic activity cannot be ascribed to the σ ligands, putative σ_1 agonists have been proposed as antidepressants[13,15] and antiamnesics[13,29] in learning and memory impairment. Putative antagonists are thought to be useful agents for preventing neurodamage[30,31] and treating cocaine abuse,[32,33] schizophrenia,[34] and other neurological disorders.[35] The σ_2 site ligands have been proposed as antineoplastic agents.[23] Furthermore, both σ_1 and σ_2 ligands are required as cancer diagnostic tools for PET analysis.[36]

Chart 1



Novel promising agents with selective affinity for σ_1 site are shown in Chart 1. (+)-(*R*)-1-(4-Chlorophenyl)-3-[4-(2-methoxyethyl)piperazin-1-yl]methyl-2-pyrrolidinone (MS 377)[37] was claimed to be clinically active on schizophrenia, without EPS liability,[38] and 4-(4-fluorophenyl)-1-[4-(1,2,4-triazol-1-yl)butyl]-1,2,3,6-tetrahydropyridine (E 5842) exhibited an atypical antipsychotic profile and did not induce catalepsy, a symptom of EPS.[39] A wide variety of structures are known to bind σ receptors, among which several arylalkylamines are included. Structural similarities such as 4-chloro- and (4-methoxy)phenylalkylamine moieties are shared by

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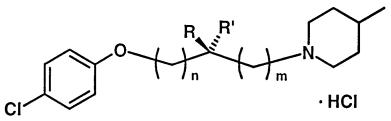
Table 1. Physical Properties



compd	n	m	R	R′	formula[a]	mp, °C	recryst solvent[b]	$[\alpha]_D$[c]
12	0	1	H	H	$C_{14}H_{20}ClNO\cdot HCl$	190−2	A	
(−)-(*R*)-**13**	0	1	H	CH_3	$C_{15}H_{22}ClNO\cdot HCl$	162−4	B	−34
(+)-(*S*)-**13**	0	1	CH_3	H	$C_{15}H_{22}ClNO\cdot HCl$	162−4	B	+36
(−)-(*R*)-**14**	0	2	H	CH_3	$C_{16}H_{24}ClNO\cdot HCl$	163−4	B	−8
(+)-(*S*)-**14**	0	2	CH_3	H	$C_{16}H_{24}ClNO\cdot HCl$	163−4	B	+10
15	1	1	H	H	$C_{15}H_{22}ClNO\cdot HCl$	205−6[d]	A	
(+)-(*R*)-**16**	1	1	H	CH_3	$C_{16}H_{24}ClNO\cdot HCl$	145−7	B	+5
(−)-(*S*)-**16**	1	1	CH_3	H	$C_{16}H_{24}ClNO\cdot HCl$	144−6	B	−4
(+)-(*R*)-**17**	1	0	CH_3	H	$C_{15}H_{22}ClNO\cdot HCl$	180−1	A	+2.7
(−)-(*S*)-**17**	1	0	H	CH_3	$C_{15}H_{22}ClNO\cdot HCl$	180−1	A	−2.7
(−)-(*R*)-**18**	2	0	CH_3	H	$C_{16}H_{24}ClNO\cdot HCl$	165−7	A	−2.5
(+)-(*S*)-**18**	2	0	H	CH_3	$C_{16}H_{24}ClNO\cdot HCl$	166−7	A	+2.5
AC 915·HCl					$C_{14}H_{17}Cl_2NO_2\cdot HCl$	165−7	MeOH/Et_2O	

[a] Elemental analyses for C, H, and N were within ±0.4% of the theoretical values for the formulas given. [b] A: EtOH/AcOEt, B: AcOEt. [c] (c = 1.5, MeOH). [d] Sumitomo's patented compound (see ref 42: 130−2 °C).

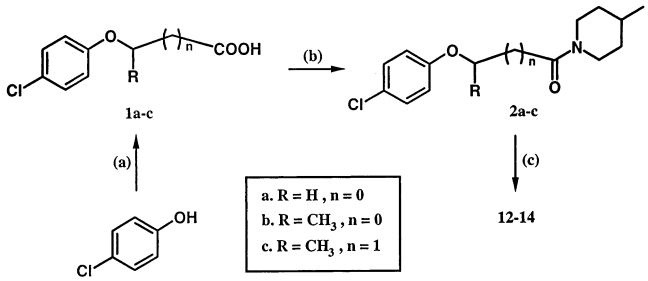
highly selective σ_1 ligands 2-(1-pyrrolidinyl)ethyl ester of 3,4-dichlorophenylacetic acid (AC 915)[40] and *N*,*N*-dipropyl-2-[4-methoxy-3-(2-phenylethoxyl)phenyl]ethylamine (NE 100)[41] (Chart 1). So the potent σ ligand 1-[3-(4-chlorophenoxy)propyl]-4-methylpiperidine (**15**, Chart 1) with high selectivity relative to dopamine D_2 receptors was patented as an agent for the treatment of CNS disorders and neuropathies.[42] SAFIRs of *N*-(phenylalkyl)piperidines have been extensively studied,[43,44] and the importance of a tertiary nitrogen atom as a pharmacophoric element and of the changes in surrounding structure for the σ_1 receptor binding has been recently pointed out.[45] The stereochemistry appears to regulate mainly σ ligands selectivity. For example, (+)-*N*-substituted *N*-normetazocines preferentially bind σ receptors whereas their (−)-enantiomers bind opioid receptors.[46,47] (+)-Pentazocine (Chart 1), a classical σ_1 receptor ligand of such a class, and related (+)-(1*S*,5*S*,9*S*)-compounds display higher σ_1 receptor affinity and selectivity relative to σ_2 receptor subtype than their corresponding (−)-(1*R*,5*R*,9*R*)-isomers.[48,49]

Therefore, in pursuing our search for selective σ-subtype ligands we prepared the compound **15** and its homologue **12** along with some chiral related isomers (compounds **13, 14, 16-18**, Table 1), to evaluate the influence exerted by the presence of a stereogenic center near the pharmacophoric nitrogen atom on the selective binding at σ_1 site. The chiral center was originated by inserting a methyl group in any position of the intermediate chain. Affinities and selectivities were evaluated at σ_1, σ_2, and SI sites by in vitro radioligand binding assays. In fact, we recently found that some high-affinity σ_1 ligands such as tetralinalkyl-3,3-dimethylpiperidines, SA 4503, and BD 1008 displayed high affinity also toward EBP site.[50]

Chemistry

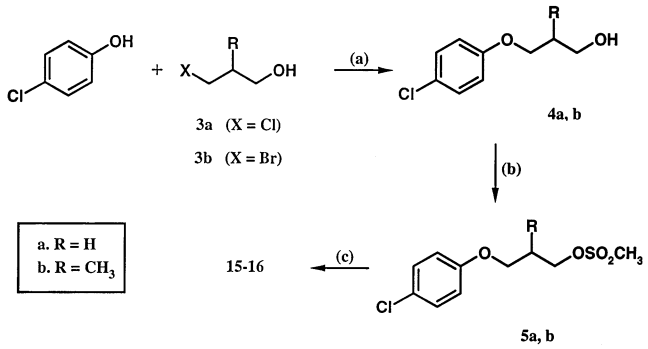
Three different routes were employed to prepare aryloxyalkylpiperidines **12**−**18** (Schemes 1−3). Compounds **12**−**14** were prepared starting from carboxylic acids **1a**−**c** (Scheme 1). The acid **1a** was commercially available, whereas (*R*)-**1b** and (*S*)-**1b** were easily prepared by the Mitsunobu reaction[51] from 4-chlorophenol

Scheme 1[a]



[a] (a) (*R*)-$CH_3CH(OH)COOMe$ or (*S*)-$CH_3CH(OH)COOEt$, Ph_3P, DEAD, dry THF; NaOH, THF; (b) 4-methylpiperidine, DCC, dry CH_2Cl_2; (c) BMS, dry THF; HCl/Et_2O.

Scheme 2[a]

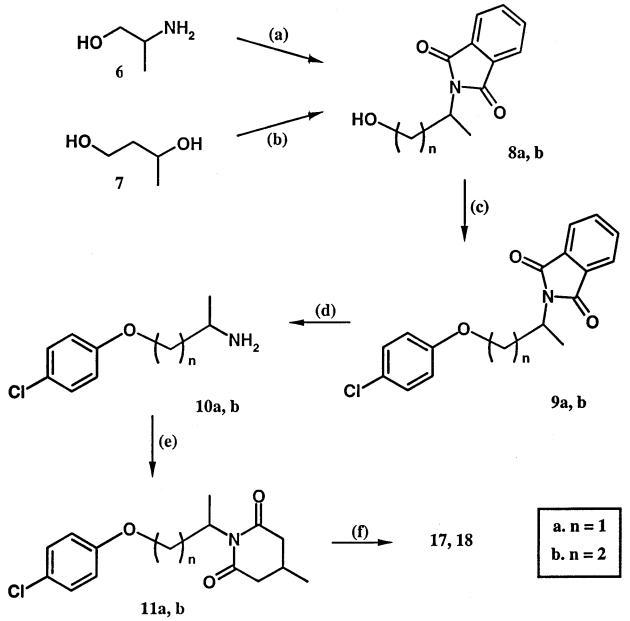


[a] (a) 10% NaOH; (b) MsCl, Et_3N, dry CH_2Cl_2, 0 °C; (c) 4-methylpiperidine, NaOH, H_2O/*i*-PrOH; HCl/Et_2O.

with (*S*)-ethyl and (*R*)-methyl lactate, respectively, followed by alkaline hydrolysis. Homologues (*R*)-**1c** and (*S*)-**1c** were obtained by resolution of the racemic acid as previously reported.[52] They all were condensed with 4-methylpiperidine in the presence of dicyclohexylcarbodiimide (DCC) to the corresponding amides **2a**−**c**. These latter were readily reduced to amines **12**−**14** with borane−methyl sulfide complex (BMS).

Compounds **15** and **16** were prepared (Scheme 2) starting from the condensation reaction between 4-chlorophenol and the appropriate commercially available 3-halopropanols **3a** and (*R*)- and (*S*)-**3b** yielding the corresponding alcohols **4a**,**b** which were derivatized to

Scheme 3[a]



[a] (a) Phthalic anhydride, Et_3N, toluene; (b) see ref 54; (c) 4-chlorophenol, Ph_3P, DEAD (or DIAD), dry THF; (d) 55% N_2H_4, $AcOH/CH_3OH$; (e) 3-methylglutaric anhydride, dry THF; AcCl; (f) BMS, dry THF; HCl/Et_2O.

the methylsulfonates **5a**,**b** and finally reacted with 4-methylpiperidine to give the desired amines.

For the preparation of aryloxyalkylpiperidines **17** and **18**, a different synthetic approach was followed (Scheme 3). The key step of this pathway was the preparation of the phthalimido alcohol intermediates **8a**,**b** from the commercially available enantiomers of alaninol (**6**) and 1,3-butanediol (**7**), respectively. However, phthalimides (*R*)- and (*S*)-**8a** were obtained by simply reacting (*R*)- or (*S*)-**6** with phthalic anhydride,[53] whereas (*R*)- and (*S*)-**8b** were prepared starting from (*S*)- and (*R*)-**7**, respectively, by a previously reported three-step procedure[54] in which, also, a complete inversion of configuration occurred. Intermediates **8a**,**b** were reacted with 4-chlorophenol, under Mitsunobu conditions, to give compounds **9a**,**b**. Hydrazinolysis of these latter easily yielded the aryloxyalkylamines **10a**,**b**. A treatment with 3-methylglutaric anhydride, prepared in situ, and acetyl chloride[55] provided the piperidindione derivatives **11a**,**b** which were readily reduced with borane−methyl sulfide to give the desired amines **17** and **18**.

All of the final optically active aryloxyalkylpiperidines had enantiomeric excesses >95% as determined by ^1H NMR spectroscopy of the diastereomeric salts obtained using *S*-2-(4-chlorophenoxy)phenylacetic acid[56] as chiral solvating agent. The compound AC 915 was synthesized according to the literature[40] and identified by GC/MS and 300 MHz ^1H NMR analyses. Since the preparation of its oxalic acid salt failed, it was converted in the hydrochloride salt, whose purity was proved by elemental microanalysis.

Receptor Binding Studies. The target compounds **12**−**18** and the reference compound AC 915, as hydrochloride salts, were evaluated for in vitro affinity at σ_1 and σ_2 receptors and at sterol $\Delta_8-\Delta_7$ isomerase site by radioreceptor binding assays. The specific radioligands and tissue sources were respectively: (a) σ_1 site, (+)-[^{3}H]-pentazocine ((+)-[2*S*-2α,6α,11*R*)]-1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol), guinea-pig brain membranes without cerebellum; (b) σ_2 site, [^{3}H]-DTG (1,3-di(2-tolyl)guanidine) in the presence of 1 μM (+)-pentazocine to mask σ_1 receptors, rat liver membranes; (c) sterol $\Delta_8-\Delta_7$ isomerase site, (±)-[^{3}H]-emopamil, guinea-pig liver membranes. The following compounds were used to define the specific binding, reported in parentheses: (a) (+)-pentazocine (82−89%), (b) DTG (85−94%), (c) (±)-ifenprodil (72−82%).

Concentrations required to inhibit 50% of radioligand specific binding (IC_{50}) were determined by using six to nine different concentrations of the drug studied in two or three experiments with samples in duplicate. Scatchard parameters (K_d and B_{max}) and apparent inhibition constants (K_i) values were calculated using the GraphPad Prism software.[57]

Results and Discussion

All tested compounds are good σ_1 ligands (Table 2). Sumitomo's patented compound **15** showed high affinity toward σ_1 site, but the affinity values for σ_2 site and sterol $\Delta_8-\Delta_7$ isomerase site result in low selectivities. However, all chiral phenoxypropyl analogues with a methyl group on the intermediate chain (compounds **14**, **16**, and **18**) displayed the same behavior. Therefore neither the methyl position nor the configuration of the chiral carbon atom influenced considerably the affinity and selectivity, in the oxypropyl chain series. The intermediate chain shortening from compound **15** to compound **12** resulted in a slight improvement of the σ_1 site affinity (K_i = 0.86 nM) and in a appreciable rise in selectivity relative to σ_2 site (278-fold).

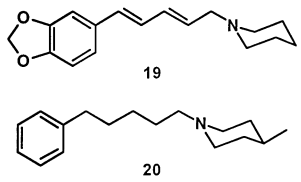
Considering the phenoxyethyl derivatives with the methyl group in α-position to the nitrogen atom, the compound (−)-(*S*)-**17** demonstrated an improvement in σ_1 site affinity (K_i = 0.34 nM) and selectivity (547-fold) compared to its upper homologous compound (+)-(*S*)-**18** (K_i = 2.69 nM) and to its enantiomer (+)-(*R*)-**17** (K_i = 1.18 nM). On the contrary, the selectivity relative to SI worsened for compound (−)-(*S*)-**17** compared to the same above compounds. When the methyl group was placed in β-position to the nitrogen atom, the affinity decreased from compound (+)-(*R*)-**16** to compound with the same configuration (−)-(*R*)-**13** whereas it remained comparable proceeding from compound (−)-(*S*)-**16** to compound (+)-(*S*)-**13**. As regards the isomers with the methyl group in α-position to the oxygen atom, higher affinities were observed for compound (−)-(*R*)-**14** compared to its homologue with the same configuration (−)-(*R*)-**13**, whereas the main difference between their respective enantiomers (+)-(*S*)-**14** and (+)-(*S*)-**13** was a decrease in the σ_2 site affinity (K_i = 318 nM) for this latter.

For each pair of enantiomers examined, little differences in the affinities were observed, except for compound (−)-(*S*)-**17** compared to its enantiomer (+)-(*R*)-**17**, as already seen. Therefore, the stereochemistry of the chiral center inserted in the intermediate chain did not influence the selectivity, unless the chiral center is adjacent to the nitrogen atom and the intermediate chain is shortened. The best selectivity values were substantially reached on account of moderate affinities toward the σ_2 site. These results confirm that more

Table 2. Binding Affinities and Selectivities

	$K_i \pm$ SEM (nM)			K_i ratio	
compound	σ_1	σ_2	sterol $\Delta_8-\Delta_7$ isomerase (SI)	σ_2/σ_1	SI/σ_1
12	0.86 ± 0.11	239 ± 15	3.70 ± 0.20	278	4.3
(−)-(*R*)-**13**	12.6 ± 1.90	332 ± 16	35.1 ± 10.6	26	2.8
(+)-(*S*)-**13**	1.81 ± 0.28	318 ± 76	3.38 ± 1.67	176	1.9
(−)-(*R*)-**14**	1.83 ± 0.36	65.9 ± 14.3	12.0 ± 0.2	36	6.6
(+)-(*S*)-**14**	1.40 ± 0.28	13.9 ± 2.1	30.1 ± 6.3	10	22
15	1.78 ± 0.34	38.6 ± 7.6	9.65 ± 0.35	22	5.4
(+)-(*R*)-**16**	1.09 ± 0.09	40.8 ± 3.8	14.5 ± 3.4	37	13
(−)-(*S*)-**16**	1.70 ± 0.43	62.0 ± 2.2	18.7 ± 5.6	36	11
(+)-(*R*)-**17**	1.18 ± 0.05	52.3 ± 10.5	27.5 ± 7.1	44	23
(−)-(*S*)-**17**	0.34 ± 0.11	186 ± 12	3.73 ± 0.98	547	11
(−)-(*R*)-**18**	2.21 ± 0.79	15.1 ± 3.6	7.79 ± 2.38	7	3.5
(+)-(*S*)-**18**	2.69 ± 0.43	31.6 ± 1.1	37.0 ± 1.3	12	14
AC 915·HCl	2.51 ± 0.68	$>10^4$	$>10^4$		
(+)-pentazocine	2.70 ± 0.25				
DTG		31.2 ± 2.10			
(±)-ifenprodil			2.71 ± 0.04		

Chart 2



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20

stringent structural requirements are needed for σ_2 in comparison to σ_1 receptor binding, suggesting that a shorter chain with less conformational freedom coupled with the eutomeric (*S*)-configuration leads to a reduced flexibility of the ligand. Therefore, an oxyethylenic chain between the phenyl ring and the piperidine nitrogen atom strengthens the configurational requirement so as to improve the σ_1 site binding and reduce σ_2 site binding at once. In confirmation of that, one can suppose that (−)-(*S*)-**17** could likely assume a conformation similar to the stereochemistry of the already reported compound **19** (Chart 2, σ_1, K_i= 0.86 nM and σ_2 , K_i = 554 nM).[45] Moreover, although the 4-methylpiperidine derivative **20** emerged therein as the most active σ_1 ligand, the best selectivity relative to the σ_2 site was reached by compound **19**, probably due to its partially constrained alkyl chain.

Finally, no compound displayed a SI affinity greater than the σ_1 site affinity, even if the respective K_i values ran rather parallel. Indeed, the most selective σ_1 ligands **12**, (+)-(*S*)-**13** and (−)-(*S*)-**17** are also the best SI ligands. Similarly, in this series the compound (−)-(*R*)-**13** demonstrated the lowest affinities toward the sites tested. Only the compound (+)-(*R*)-**17** resulted moderately selective relative to both the σ_2 and SI sites.

Conclusions

The slight differences found in the high affinities toward the σ_1 site demonstrate that the chirality in the intermediate chain of the phenoxypropylpiperidines **14**, **16**, and **18** generally does not exert an important influence on the σ_1 site binding. Nevertheless, a shorter oxyethylenic chain was beneficial to increase σ_1 relative to σ_2 site selectivity. Moreover, when in such a chain the methyl substituent is adjacent to the piperidine nitrogen atom, the chiral center appears to be more determinant, possibly due to the more constrained compounds generated. Therefore, the (−)-(*S*)-4-methyl-1-[2-(4-chlorophenoxy)-1-methyl]ethylpiperidine ((−)-(*S*)-**17**) reached the highest σ_1 affinity (Ki = 0.34 nM) and the best selectivity relative to σ_2 site (547-fold). Compound (−)-(*S*)-**17** displayed also a moderate selectivity (11-fold) relative to the SI site.

Experimental Section

Chemical Methods. Column chromatography was performed on ICN silica gel 60 Å (63−200 μm) as the stationary phase. Melting points were determined in open capillaries on a Gallenkamp electrothermal apparatus and are uncorrected. Mass spectra were recorded with a HP GC/MS 6890−5973 MSD spectrometer, electron impact 70 eV, equipped with HP chemstation. ^{1}H NMR spectra were recorded in $CDCl_3$ either on a Varian EM-390 (when 90 MHz is indicated), using tetramethylsilane as internal standard, or on a Bruker AM 300 WB (300 MHz) spectrometer. For optical isomers, NMR spectra are identical and reported only for one of the two enantiomers. Chemical shifts are expressed as parts per million (δ). Infrared spectra were registered on a Perkin-Elmer FT-IR spectrophotometer (Spectrum one). Microanalyses of solid compounds were carried out with a Carlo Erba mod. 1106 analyzer; the analytical results are within ±0.4% of the theoretical values. Optical rotations were measured with a Perkin-Elmer 341 polarimeter at room temperature (20 °C): concentrations are expressed as g/100 mL. Chemicals were from Aldrich and were used without any further purification.

(+)-(*R*)- and (−)-(*S*)-2-(4-Chlorophenoxy)propanoic Acids [(+)-(*R*)-1b, (−)-(*S*)-1b]. A solution of diethyl azodicarboxylate (DEAD, 11 mmol) in dry THF (45 mL) was added dropwise to a mixture of (*S*)-ethyl or (*R*)-methyl lactate (10 mmol), 4-chlorophenol (10 mmol), and triphenylphosphine (10 mmol) in dry THF (85 mL). The reaction mixture was stirred at room-temperature overnight, under N_2 atmosphere. The solvent was evaporated, and a mixture of Et_2O and hexane (1:1) was added in order to precipitate the formed triphenylphosphine oxide, which was filtered off. This procedure was repeated several times. The filtrate was evaporated to dryness, and the crude product was dissolved in THF (125 mL) and added of 1 N NaOH (125 mL). The mixture was stirred at room-temperature overnight after which the organic solvent was evaporated, and the remaining aqueous phase was washed twice with $CHCl_3$, acidified with 2 N HCl and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure affording a solid which was crystallized from hexane. Yield: 80−85%. Spectroscopic properties and optical rotation values were identical to the data reported in the literature.[58]

Preparation of Aryloxyalkanoylpiperidines (2a−c). General Procedure. To a stirred solution of the appropriate 4-chlorophenoxyalkanoic acid **1** (5 mmol) in anhydrous CH_2Cl_2 (25 mL) were added *N*,*N*′-dicyclohexylcarbodiimide (DCC, 5.2 mmol) and 4-methylpiperidine (5.2 mmol). The resulting

mixture was stirred overnight at room temperature. Then it was diluted with CH_2Cl_2 (80 mL), and the precipitate was filtered off. The organic layer was washed with 2 N HCl (2 × 75 mL), followed by brine (1 × 75 mL), $NaHCO_3$ saturated solution (2 × 75 mL), and brine (1 × 75 mL); then it was dried over Na_2SO_4 and filtered. The solvent was evaporated in vacuo to afford a white solid which was chromatographed on silica gel column (petroleum ether/ethyl acetate 7:3 as eluent). Compounds **2a**−**c** were obtained as pale yellow oils in 52−70% yields.

4-Methyl-1-[2-(4-chlorophenoxy)-1-oxoethyl]piperidine (2a): 56% yield; ^{1}H NMR: δ 0.92 (d, 3H, CH_3), 1.02−1.19 (m, 2H, NCH_2CH_2), 1.50−1.90 (m, 3H, CH and NCH_2CH_2), 2.59, 3.01, 3.87 and 4.48 (4m, 4H, 2 NCH_2), 4.63 (s, 2H, OCH_2), 6.83−7.24 (m, 4H, aromatic); GC/MS *m*/*z* 269 (M^+ + 2, 31), 267 (M^+, 85), 140 (100); FT-IR 1651 cm^{-1} (C═O).

(−)-(*R*)-4-Methyl-1-[2-(4-chlorophenoxy)-1-oxopropyl]-piperidine [(−)-(*R*)-2b]: 58% yield; $[\alpha]_D = -10$ (*c* = 1.5, MeOH); ^{1}H NMR: δ 0.75−1.00 (dd, 3H, piperidine CH_3), 1.01−1.18 (m, 2H, NCH_2CH_2), 1.50−1.93 (m, 6H, CH_3, piperidine CH and NCH_2CH_2), 2.54 (q, 1H, 1 of $N(CH_2)_2$), 2.93 (m, 1H, 1 of $N(CH_2)_2$), 4.05−4.25 (m, 1H, 1 of $N(CH_2)_2$), 4.47 (d, 1H, 1 of $N(CH_2)_2$), 4.88 (q, 1H, OCH), 6.77−7.24 (m, 4H, aromatic); GC/MS *m*/*z* 283 (M^+ + 2, 9), 281 (M^+, 27), 126 (100); FT-IR 1658 cm^{-1} (C═O).

(+)-(*S*)-4-Methyl-1-[2-(4-chlorophenoxy)-1-oxopropyl]-piperidine [(+)-(*S*)-2b]: 70% yield; $[\alpha]_D = +9$ (*c* = 1.5, MeOH).

(+)-(*R*)-4-Methyl-1-[3-(4-chlorophenoxy)-1-oxobutyl]piperidine [(+)-(*R*)-2c]: 52% yield; $[\alpha]_D = +19$ (*c* = 1.5, MeOH); ^{1}H NMR: δ 0.91 (d, 3H, piperidine CH_3), 0.95−1.15 (m, 2H, NCH_2CH_2), 1.34 (d, 3H, CH_3), 1.45−1.77 (m, 3H, piperidine CH and NCH_2CH_2), 2.40−2.70 (m, 2H, CHCO and 1 of $N(CH_2)_2$), 2.75−3.15 (m, 2H, CHCO and 1 of $N(CH_2)_2$), 3.87 (bb, 1H, 1 of $N(CH_2)_2$), 4.54 (bb, 1H, 1 of $N(CH_2)_2$), 4.82−4.96 (m, 1H, OCH), 6.75−7.24 (m, 4H, aromatic); GC/MS *m*/*z* 297 (M^+ + 2, 2), 295 (M^+, 6), 168 (100); FT-IR 1639 cm^{-1} (C═O).

(−)-(*S*)-4-Methyl-1-[3-(4-chlorophenoxy)-1-oxobutyl]piperidine [(−)-(*S*)-2c]: 52% yield; $[\alpha]_D = -18$ (*c* = 1.5, MeOH).

Preparation of Aryloxyalkylpiperidine Hydrochlorides (12−14). General Procedure. A solution of borane−methyl sulfide complex (BMS, 12 mmol) in anhydrous THF (3 mL) was carefully added dropwise to a stirred and cooled solution of the appropriate amide **2** (3 mmol) in anhydrous THF (15 mL). The reaction mixture was refluxed with stirring for 4h, cooled to 0 °C, and carefully added with methanol (15 mL) dropwise to destroy the boran complex excess. Then 6 N HCl (15 mL) was added, and the resulting mixture was refluxed with stirring for 1h. After distilling off the organic solvents, the mixture was allowed to cool at room temperature and alkalized with 6 N NaOH. The aqueous solution was extracted with $CHCl_3$ (3 × 40 mL), and the combined organic extracts were washed with brine (1 × 40 mL), dried over Na_2SO_4, and filtered. Evaporation of the solvent in vacuo afforded the desired piperidines as pale yellow oils in quantitative yields. The corresponding hydrochloride salts were prepared by adding a HCl saturated ethereal solution to an ethereal solution of the amine. Recrystallization solvent, $[\alpha]_D$, crystallization formula and melting point are listed in Table 1. All of the title compounds were obtained as white crystalline powders.

4-Methyl-1-[2-(4-chlorophenoxy)ethyl]piperidine hydrochloride (12): ^{1}H NMR: δ 1.02 (d, 3H, CH_3), 1.50−1.70 (m, 1H, CH), 1.75−2.21 (m, 4H, 2 piperidine NCH_2CH_2), 2.65−2.85 and 3.10−3.25 (m, 2H, 2 piperidine NCH), 3.36 (q, 2H, CH_2N), 3.38−3.45 and 3.56−3.70 (m, 2H, 2 piperidine NCH), 4.52 (t, 2H, OCH_2), 6.78−7.30 (m, 4H, aromatic), 12.45 (br s, 1H, NH^+, D_2O exchanged); GC/MS *m*/*z* (free amine) 253 (M^+, 2), 112 (100).

(−)-(*R*)- and (+)-(*S*)-4-Methyl-1-[2-(4-chlorophenoxy)-propyl]piperidine hydrochlorides [(−)-(*R*)-13, (+)-(*S*)-13]: ^{1}H NMR: δ 0.98 (d, 3H, piperidine CH_3), 1.26 (d, 3H, CH_3), 1.44−1.63 (m, 1H, piperidine CH), 1.65−2.10 (m, 4H, 2 NCH_2CH_2), 2.57−2.83 and 2.97−3.16 (m, 3H, 2 piperidine NCH and 1 of CH_2N), 3.17−3.54 and 3.65−3.80 (m, 3H, 2 piperidine NCH and 1 of CH_2N), 5.34−5.39 (m, 1H, OCH), 6.90−7.24 (m, 4H, aromatic), 12.41 (br s, 1H, NH^+, D_2O exchanged); GC/MS *m*/*z* (free amine) 267 (M^+, 2), 112 (100).

(−)-(*R*)- and (+)-(*S*)-4-Methyl-1-[3-(4-chlorophenoxy)-butyl]piperidine hydrochlorides [(−)-(*R*)-14, (+)-(*S*)-14]: ^{1}H NMR: δ 1.01 (d, 3H, piperidine CH_3), 1.28 (d, 3H, CH_3), 1.45−1.70 (m, 1H, piperidine CH), 1.72−1.88 (m, 2H, 2 piperidine NCH_2CH), 1.90−2.10 (m, 2H, 2 piperidine NCH_2CH), 2.13−2.25 (m, 1H, 1 of $OCHCH_2$), 2.26−2.47 (m, 1H, 1 of $OCHCH_2$), 2.52−2.70 and 2.90−3.15 (m, 4H, 2 piperidine NCH and CH_2N), 3.15−3.65 (m, 2H, 2 piperidine NCH), 4.35−4.53 (m, 1H, OCH), 6.73−7.24 (m, 4H, aromatic), 12.14 (br s, 1H, NH^+, D_2O exchanged); GC/MS *m*/*z* (free amine) 281 (M^+, 3), 112 (100).

Preparation of Aryloxyalkyl Alcohols (4a,b). General Procedure. Compound **3a** (or **3b**) (12 mmol) was added to a stirred solution of 4-chlorophenol (15 mmol) in 10% NaOH (10 mL). The resulting mixture was refluxed with stirring for 45 min and then was allowed to cool to room temperature and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with 10% NaOH (2 × 10 mL) followed by brine (2 × 10 mL); then they were dried over Na_2SO_4 and filtered. The solvent was evaporated in vacuo to afford **4a** (or **4b**); colorless oils in 30−45% yields.

3-(4-Chlorophenoxy)-1-propanol (4a): 45% yield; ^{1}H NMR (90 MHz): δ 1.85−2.20 (m, 3H, $CH_2CH_2CH_2$ and OH, D_2O exchanged), 3.85 (t, 2H, CH_2OH), 4.10 (t, 2H, $ArOCH_2$), 6.70−7.40 (m, 4H, aromatic); GC/MS *m*/*z* 188 (M^+ + 2, 11), 186 (M^+, 32), 128 (100).

(−)-(*R*)-3-(4-Chlorophenoxy)-2-methyl-1-propanol [(−)-(*R*)-4b]: 31% yield; $[\alpha]_D = -8$ (*c* = 1.8, MeOH); ^{1}H NMR (90 MHz): δ 1.05 (d, 3H, CH_3), 1.80 (bb, 1H, OH, D_2O exchanged), 1.90−2.30 (m, 1H, CH), 3.70 (d, 2H, CH_2OH), 3.93 (d, 2H, $ArOCH_2$), 6.70−7.30 (m, 4H, aromatic); GC/MS *m*/*z* 202 (M^+ + 2, 7), 200 (M^+, 22), 128 (100).

(+)-(*S*)-3-(4-Chlorophenoxy)-2-methyl-1-propanol [(+)-(*S*)-4b]: 30% yield; $[\alpha]_D = +10$ (*c* = 1.8, MeOH).

Preparation of Aryloxyalkylsulfonates (5a,b). General Procedure. A solution of methanesulfonyl chloride (4.6 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise to a stirred and ice-bath cooled solution of **4a** (or **4b**) (4.2 mmol) and triethylamine (6.8 mmol) in anhydrous CH_2Cl_2 (15 mL). The reaction mixture was stirred at 0 °C for 3 h and then was carefully poured into ice−water. The organic layer was separated and washed with cold 10% HCl (2 × 10 mL) followed by brine (2 × 10 mL), $NaHCO_3$ saturated solution (2 × 10 mL), and finally with brine (2 × 10 mL). Then it was dried over Na_2SO_4 and filtered. The solvent was evaporated in vacuo to afford **5a** (or **5b**) as a pale yellow oil which was used for the next step without any further purification.

O-Methanesulfonyl-3-(4-chlorophenoxy)-1-propanol (5a): 81% yield; GC/MS *m*/*z* 266 (M^+ + 2, 20), 264 (M^+, 51), 137 (100).

(*S*)-O-Methanesulfonyl-3-(4-chlorophenoxy)-2-methyl-1-propanol [(*S*)-5b]: 83% yield; GC/MS *m*/*z* 280 (M^+ + 2, 12), 278 (M^+, 30), 128 (100).

(*R*)-O-Methanesulfonyl-3-(4-chlorophenoxy)-2-methyl-1-propanol [(*R*)-5b]: 96% yield.

Preparation of Aryloxyalkylpiperidine Hydrochlorides (15, 16). General Procedure. To a solution of NaOH (4 mmol) in water (10 mL) and 2-propanol (5 mL) was added 4-methylpiperidine (3 mmol). The resulting mixture was cooled to 0 °C and stirred for 10 min, and then a solution of **5a** (or **5b**) (3 mmol) in 2-propanol (10 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h and then warmed at 50 °C for 4 h; the solvent was removed under reduced pressure, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The collected organic extracts were washed with 1 N NaOH (2 × 10 mL) followed by brine (2 × 10 mL) and extracted with 6 N HCl (3 × 20 mL). The aqueous phase was alkalized with 6 N NaOH and extracted with $CHCl_3$ (3 × 30 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated in vacuo to afford **15** (or **16**); pale yellow oils

in 40−62% yields. The corresponding hydrochloride salts were prepared according to the procedure reported above for compounds **12**−**14** obtaining white crystalline powders. Recrystallization solvent, $[\alpha]_D$, crystallization formula, and melting point are listed in Table 1.

4-Methyl-1-[3-(4-chlorophenoxy)propyl]piperidine hydrochloride (15): ^{1}H NMR: δ 1.01 (d, 3H, CH_3), 1.45−1.70 (m, 1H, CH), 1.70−1.88 (m, 2H, 2 piperidine NCH_2CH), 1.90−2.25 (m, 2H, 2 piperidine NCH_2CH), 2.44 (m, 2H, OCH_2CH_2), 2.54−2.75 and 2.95−3.25 (m, 4H, 2 piperidine NCH and CH_2N), 3.25−3.38 and 3.50−3.65 (m, 2H, 2 piperidine NCH), 4.02 (t, 2H, $ArOCH_2$), 6.73−7.24 (m, 4H, aromatic), 12.14 (br s, 1H, NH^+, D_2O exchanged); GC/MS *m*/*z* (free amine) 269 (M^+ + 2, 4), 267 (M^+, 11), 112 (100).

(+)-(*R*)- and (−)-(*S*)-4-Methyl-1-[3-(4-chlorophenoxy)-2-methyl-propyl]piperidine hydrochlorides [(+)-(*R*)-16, (−)-(*S*)-16]: ^{1}H NMR: δ 1.01 (d, 3H, piperidine CH_3), 1.27 (d, 3H, CH_3), 1.40−1.70 (m, 1H, piperidine CH), 1.70−1.89 (m, 2H, 2 piperidine NCH_2CH), 2.02−2.26 (m, 2H, 2 piperidine NCH_2CH), 2.50−2.74 and 3.00−3.24 (m, 4H, OCH_2CH, 2 piperidine NCH and 1 of CH_2N), 2.74−2.90 (m, 1H, 1 of CH_2N), 3.25−3.68 (m, 2H, 2 piperidine NCH), 3.84−3.94 (m, 1H, 1 of OCH_2), 4.00−4.14 (m, 1H, 1 of OCH_2), 6.78−7.24 (m, 4H, aromatic), 11.97 (br s, 1H, NH^+, D_2O exchanged); GC/MS *m*/*z* (free amine) 283 (M^+ + 2, 2), 281 (M^+, 5), 112 (100).

(−)-(*R*)-2-Phthalimido-1-propanol [(−)-(*R*)-8a]. A suspension of phthalic anhydride (3.93 g; 26.6 mmol), triethylamine (0.37 mL; 2.65 mmol), and (*R*)-2-amino-1-propanol **6** (2.00 g, 26.6 mmol) in toluene (40 mL) was placed into a round-bottomed flask equipped with a Dean−Stark apparatus. The mixture was refluxed for 5.5 h and then was allowed to cool to room temperature. The solvent was removed under vacuum to give a white solid which was dissolved in AcOEt (50 mL) and washed with 2 N HCl (2 × 20 mL) and $NaHCO_3$ saturated solution (2 × 20 mL) followed by brine. The organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure to give a white solid (3.68 g) which was purified by crystallization (petroleum ether/AcOEt) to afford 2.84 g of the title compound as white crystals (52% yield); $[\alpha]_D = -36$ (c = 1.3, MeOH); mp 87−88 °C; ^{1}H NMR (90 MHz): δ 1.45 (d, 3H, CH_3), 2.50−3.00 (bb, 1H, OH, D_2O exchanged), 3.70−4.20 (m, 2H, CH_2OH), 4.30−4.70 (m, 1H, CH), 7.50−7.90 (m, 4H, aromatic); GC/MS *m*/*z* 205 (M^+, 0.1), 174 (100); FT-IR 1689 cm^{-1} (C=O).

Compound (+)-(*S*)-**8a** was obtained according to the procedure reported above for the compound (−)-(*R*)-**8a** using (*S*)-2-amino-1-propanol as starting material.

(+)-(*S*)-2-Phthalimido-1-propanol [(+)-(*S*)-8a]: 49% yield; $[\alpha]_D = +34$ (c = 1.3, MeOH); mp 87−88 °C.

Preparation of Aryloxyalkylphthalimido Derivatives (9a,b). General Procedure. To a stirred solution of 4-chlorophenol (10 mmol) and triphenylphosphine (10 mmol) in anhydrous THF (40 mL) was added the appropriate phthalimido alcohol **8** (5 mmol) in anhydrous THF (10 mL). After the mixture was cooled to 0 °C, a solution of diethyl azodicarboxylate (DEAD, or diisopropyl azodicarboxylate, DIAD) (10 mmol) in anhydrous THF (10 mL), was added dropwise, and the reaction mixture was stirred overnight at room temperature, under N_2 atmosphere. The solvent was removed under vacuum, and the residue was purified on a silica gel column (petroleum ether/AcOEt 8:2 as eluent) to afford the compound **9a** (or **9b**); pale yellow oils in 75−98% yields.

(+)-(*R*)-2-Phthalimido-1-(4-chlorophenoxy)propane [(+)-(*R*)-9a]: 98% yield; $[\alpha]_D = +15$ (c = 1.0, MeOH); ^{1}H NMR: δ 1.55 (d, 3H, CH_3), 4.13 (q, 1H, 1 of OCH_2), 4.50 (t, 1H, 1 of OCH_2), 4.77 (m, 1H, CHN), 6.70−7.20 (m, 4H, aromatic), 7.65−7.90 (m, 4H, aromatic); GC/MS *m*/*z* 317 (M^+ + 2, 3), 315 (M^+, 10), 188 (100).

(−)-(*S*)-2-Phthalimido-1-(4-chlorophenoxy)propane [(−)-(*S*)-9a]: 96% yield; $[\alpha]_D = -15$ (c = 1.0, MeOH).

(−)-(*R*)-3-Phthalimido-1-(4-chlorophenoxy)butane [(−)-(*R*)-9b]: 75% yield; $[\alpha]_D = -84$ (c = 1.3, $CHCl_3$); ^{1}H NMR: δ 1.54 (d, 3H, CH_3), 2.10−2.25 (m, 1H, 1 of OCH_2CH_2), 2.50−2.71 (m, 1H, 1 of OCH_2CH_2), 3.85−4.00 (m, 2H, OCH_2), 4.61−4.70 (m, 1H, CHN), 6.75−7.12 (m, 4H, aromatic), 7.61−7.92 (m, 4H, aromatic); GC/MS *m*/*z* 331 (M^+ + 2, 1), 329 (M^+, 4), 202 (100).

(+)-(*S*)-3-Phthalimido-1-(4-chlorophenoxy)butane [(+)-(*S*)-9b]: 96% yield; $[\alpha]_D = +84$ (c = 1.3, $CHCl_3$).

Preparation of Aryloxyalkylamines (10a,b). General Procedure. Glacial CH_3COOH (2.5 mL, 44 mmol) and 55% $NH_2NH_2 \cdot xH_2O$ (2.5 mL, 44 mmol) were added to a stirred solution of the appropriate aryloxyalkylphthalimido derivative **9** (6.6 mmol) in MeOH (50 mL). The reaction mixture was refluxed with stirring for 7 h, and then it was allowed to cool and stir overnight at room temperature. The solvent was removed under vacuum, and the residue was alkalized with 6 N NaOH and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated to dryness affording the expected amine. The pale yellow oils **10a**,**b** (32−77% yields) were used for the next step without any further purification.

(*R*)-2-Amino-1-(4-chlorophenoxy)propane [(*R*)-10a]: 43% yield; GC/MS *m*/*z* 187 (M^+ + 2, 3), 185 (M^+, 9), 44 (100).

(*S*)-2-Amino-1-(4-chlorophenoxy)propane [(*S*)-10a]: 32% yield.

(*R*)-3-Amino-1-(4-chlorophenoxy)butane [(*R*)-10b]: 77% yield; GC/MS *m*/*z* 201 (M^+ + 2, 3), 199 (M^+, 9), 44 (100).

(*S*)-3-Amino-1-(4-chlorophenoxy)butane [(*S*)-10b]: 49% yield.

Preparation of Aryloxyalkylpiperidindiones (11a, b). General Procedure. A solution of 3-methylglutaric acid (5 mmol) in acetyl chloride (5 mL) was stirred under reflux for 3 h. After cooling, the acetyl chloride excess was removed under reduced pressure. The oily residue was dissolved in dry THF (5 × 20 mL), and the solvent was distilled off under vacuum for five times. To the afforded light brown solid was added a solution of the appropriate amine **10** (5 mmol) in dry THF (10 mL). The reaction mixture was stirred overnight at room temperature, the solvent was evaporated under vacuum, and acetyl chloride (5.5 mL) was added to the oily residue. After refluxing for 5 h, the mixture was evaporated to dryness under reduced pressure affording a red-brown oil which was dissolved in CH_2Cl_2 and washed with Na_2CO_3 saturated solution, brine, and 2 N HCl followed by brine. The organic layer was dried over Na_2SO_4 and filtered. The solvent was evaporated in vacuo to afford the desired compound. The brown oils **11a**,**b** (42−96% yields) were used for the next step without any further purification.

(*R*)-1-(4-Chlorophenoxy)-2-(4-methyl-2,6-piperidindion-1-yl)propane [(*R*)-11a]: 89% yield; GC/MS *m*/*z* 295 (M^+, 0.2), 168 (100).

(*S*)-1-(4-Chlorophenoxy)-2-(4-methyl-2,6-piperidindion-1-yl)propane [(*S*)-11a]: 79% yield.

(*R*)-1-(4-Chlorophenoxy)-3-(4-methyl-2,6-piperidindion-1-yl)butane [(*R*)-11b]: 96% yield; GC/MS *m*/*z* 309 (M^+, 1), 182 (100).

(*S*)-1-(4-Chlorophenoxy)-3-(4-methyl-2,6-piperidindion-1-yl)butane [(*S*)-11b]: 42% yield.

Preparation of Aryloxyalkylpiperidine Hydrochlorides (17, 18). General Procedure. A solution of borane−methyl sulfide complex (BMS, 25 mmol) in anhydrous THF (15 mL) was added dropwise to a stirred and cooled solution of the appropriate aryloxyalkylpiperidindione **11** (5 mmol) in anhydrous THF (30 mL). The reaction mixture was refluxed with stirring for 4 h, cooled to 0 °C, and carefully added with MeOH (40 mL) dropwise to destroy the excess of borane complex. Then, 2 N HCl (70 mL) was added, and the resulting mixture was refluxed with stirring for 2 h. After the organic solvents were distilled off, the mixture was allowed to cool at room temperature and alkalized with 6 N NaOH. The aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the combined organic extracts were washed with brine (1 × 40 mL), dried over Na_2SO_4, and filtered. Evaporation of the solvent in vacuo afforded the desired piperidine. Compounds **17** and **18** were obtained as pale yellow oils in 46−96% yields. The corresponding hydrochloride salts were prepared by adding a HCl saturated ethereal solution to an ethereal solution of the amine. Recrystallization solvent, $[\alpha]_D$, crystal-

lization formula, and melting point are listed in Table 1. All of them were obtained as white crystalline powders.

(+)-(*R*)- and (−)-(*S*)-4-Methyl-1-[2-(4-chlorophenoxy)-1-methyl-ethyl]piperidine hydrochlorides [(+)-(*R*)-17, (−)-(*S*)-17]: ^{1}H NMR: δ 1.04 (d, 3H, piperidine CH_3), 1.58 (d, 3H, CH_3), 1.50−1.90 and 2.10−2.24 (m, 5H, 2 piperidine NCH_2CH_2 and piperidine CH), 2.78−3.10 and 3.18−3.38 (m, 2H, 2 piperidine NCH), 3.42−3.74 (m, 3H, 2 piperidine NCH and CH_3CHN), 4.22−4.36 (dd, 1H, 1 of OCH_2), 4.48−4.62 (dd, 1H, 1 of OCH_2), 6.80−7.40 (m, 4H, aromatic), 12.20 (bb, 1H, NH^+, D_2O exchanged); GC/MS *m*/*z* (free amine) 267 (M^+, 0.2), 126 (100).

(−)-(*R*)- and (+)-(*S*)-4-Methyl-1-[3-(4-chlorophenoxy)-1-methyl-propyl]piperidine hydrochlorides [(−)-(*R*)-18, (+)-(*S*)-18]: ^{1}H NMR: δ 1.02 (d, 3H, piperidine CH_3), 1.46 (d, 3H, CH_3), 1.40−2.25 (m, 6H, 2 piperidine NCH_2CH_2, 1 of OCH_2CH_2 and piperidine CH), 2.60−2.95 and 2.96−3.30 (m, 3H, 2 piperidine NCH and 1 of OCH_2CH_2), 3.30−3.60 (m, 3H, 2 piperidine NCH and CH_3CHN) 3.90−4.20 (m, 2H, OCH_2), 6.80−7.40 (m, 4H, aromatic), 11.80 (bb, 1H, NH^+, D_2O exchanged); GC/MS *m*/*z* (free amine) 281 (M^+, 5), 126 (100).

Biological Methods. (+)-[^{3}H]-Pentazocine and [^{3}H]-DTG were obtained from PerkinElmer Life Sciences (Zaventem, Belgium). [^{3}H]-(±)-Emopamil was purchased from American Radiolabeled Chemicals Inc. (St. Louis, MO). (+)-Pentazocine was obtained from Sigma-RBI (Milan, Italy), and DTG and ifenprodil were purchased from Tocris Cookson Ltd., UK. Male Dunkin guinea-pigs and Wistar Hannover rats (250−300 g) were from Harlan, Italy.

Radioligand Binding Assays. All procedures followed to perform the binding assays at σ_1 site,[26] σ_2 site,[26] and sterol $\Delta_8-\Delta_7$ isomerase site (EBP)[59] were previously described.[50]

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