Novel Potent σ_1 Ligands: *N*-[ω-(Tetralin-1-yl)alkyl]piperidine Derivatives

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A series of substituted *N*-[(tetralin-1-yl)alkyl]piperidines and a number of related *N*-di-*n*-propyl-[(tetralin-1-yl)alkyl]amines were prepared. Structural modifications such as piperidine substitutions, intermediate chain lengthening, and the nature of the aromatic ring were explored in order to identify structural requirements for selective σ_1 affinity. They were tested in radioligand binding assays on σ_1, 5-HT$_{1A}$ and 5-HT$_2$ serotonergic, PCP (phencyclidine), and D-2 dopaminergic receptors. Almost all the compounds reported here showed a high to superpotent σ_1 affinity, and some compounds also demonstrated a widespread selectivity over the other receptors. In [^{3}H]-(+)-pentazocine binding, 3,3-dimethyl-1-[3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperidine (**24**) and 3,3-dimethyl-1-[4-(1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-butyl]piperidine (**26**) reached the lowest K_i values (0.4 and 0.8 nM, respectively); compound **24** also demonstrated a considerable PCP affinity ($K_i = 34.2$ nM), whereas compound **26** was suitably selective. Furthermore the presence of a 4-benzyl substituent on the piperidine ring (compound **16**, $K_i = 3.9$ nM on σ_1 sites) caused an increase in 5-HT$_{1A}$ affinity ($K_i < 0.14$ nM).

Over the last few years, much research has been carried out with the aim of finding the psychotherapeutic value[1] of σ receptor ligands. However, the "σ receptor" concept itself has been criticized because of the lack of a specific endogenous σ ligand and because of its undefined biological role.[2] In this respect, functional roles of the σ receptor have recently been suggested[3] for neuromodulation in the central nervous system (CNS) and neurotoxicity in glial cells[4] and have been proven in rat melatonin synthesis.[5] Moreover, the σ receptor seems to be coupled to G-proteins[6] and has been correlated to effects associated with depression and schizophrenia[7] produced by the endogenous ligand neuropeptide Y.[8] Therefore potential therapeutic use has been foreseen for σ ligands in psychiatric diseases,[9−11] in the treatment of cocaine abuse,[12,13] and in neuroprotection.[14,15]

On the other hand, skepticism about whether the σ receptor exists is justified by the hypothesis[16] that σ sites might be enzymatic sites on cytochrome P-450. Definitive functional studies to clearly support the existence of a true σ receptor are therefore needed. Finding selective high-affinity σ ligands will contribute to verifying hypotheses regarding the physiological functions of σ receptors and to subsequent clinical use of σ agents.

The structures of prototypic, rather nonselective σ ligands[17] such as haloperidol, butaclamol, and (*R*)-(+)-3-(3-hydroxyphenyl)-*N*-propylpiperidine (3-PPP) or of moderate σ affinity benzomorphans, such as (+)-*N*-allylnormetazocine (NANM, SKF 10,047, **1**), present a piperidine ring linked to a phenyl group by a variably sized alkyl chain. In recent years, several compounds with this common structural feature have been derived

and are reported[2] to bind σ sites highly even though they had been tested with σ_1/σ_2 nonselective radioligands such as [^{3}H]-(+)-3-PPP or [^{3}H]DTG. Structural determinants for σ_1 affinity have been proposed after the introduction of selective σ_1 radioligands,[18] e.g., [^{3}H]SKF 10,047 and the more potent [^{3}H]-(+)-pentazocine (**2**). Lately, several different structures have proved to be high-affinity σ_1 ligands; examples include phenylalkylamines,[19] such as **3** and the piperidine derivative **4**, *N*-[(haloaryl)alkyl]-*N*-methyl-2-(1-pyrrolidinyl)ethylamines[20] **5** and related polyamines,[21] and (4-phenylpiperidinyl)alkyl esters of 1-arylcyclopentanecarboxylic acids[22] **6**, as well as several others. Of these DUP 734 (**7**) and some related piperidines[23] do not induce extrapyramidal side effects and tardive dyskinesia when tested in animals.

In this study we introduce a class of substituted *N*-[(tetralin-1-yl)alkyl]piperidines **15−26** (Table 1) and some related *N*-di-*n*-propyl[(tetralin-1-yl)alkyl]amines **27−29** (Table 2). They were developed from **8** and similar *N*-[(tetralin-1-yl)alkyl]piperazines, which have previously been studied,[24] mainly being tested on [^{3}H]DTG. In these novel structures the piperazine was replaced by a piperidine ring, since it has been reported[22,25] that 4-phenylpiperidines were more potent σ ligands than 1-phenylpiperazines. The 4-phenyl group was removed because it has been shown[26] to be unnecessary for σ affinity. Moreover, it seems to be responsible for a significant 5-HT$_{1A}$ affinity that has also been found[24] in open ring derivatives **9** and **10**.

The investigation was focused on σ_1 binding, and the tetralin moiety was retained as an important framework. It is present in (+)-pentazocine (**2**) and in semirigid or rigid structures of high-affinity σ ligands reported in the recent literature: benz[*f*]isoquinoline derivatives,[27] spiropiperidines,[28] and piperidinyltetralins.[29] Some *N*-di-*n*-propyl derivatives (compounds **27−29**) which can be considered piperidine open derivatives

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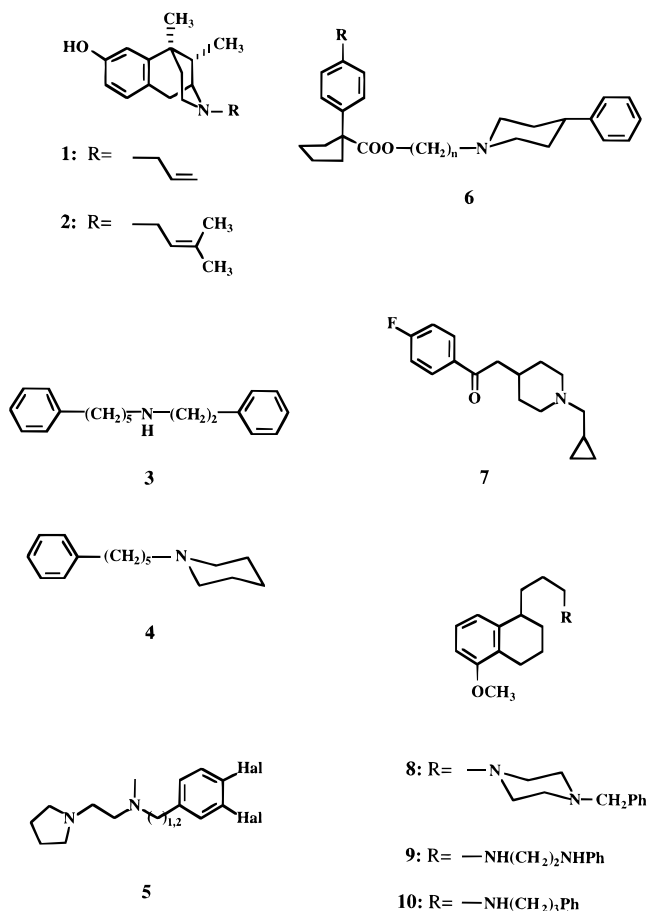* To whom correspondence should be addressed.
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Chart 1

1: R= (allyl)

2: R= (prenyl with two CH₃)

3

6

7

4

5

8: R= —N(piperidine)N—CH₂Ph

9: R= —NH(CH₂)₂NHPh

10: R= —NH(CH₂)₃Ph

were also synthesized. Indeed, it has been demonstrated that small *N*-alkyl groups were able to fit the secondary lipophilic σ receptorial site,[30] whereas *N*-desmethylation produced a decrease in affinity.[19] Some substituents such as 3,3-dimethyl (**24**−**26**), 4-benzyl (**15**, **16**), and [*c*]-fused phenyl (**17**) were inserted on the piperidine ring, in order to verify the extent to which the σ₁ receptor tolerated bulk substituents. A chain length of three or four methylene units was chosen in order to reproduce the optimally sized chain of phenylalkylamines related to the phenylpentylamine **3**. Finally, most of the products had an unsubstituted tetralin moiety, since substituents on the aromatic nucleus seemed to have little effect on σ binding.[26]

Chemistry

The synthetic pathway for the present compounds involved the preparation of standard key intermediate 1-(ω-haloalkyl) derivatives (Scheme 1) as described in our previous papers.[31,32] Final compounds **16**, **18**−**21**, **24**, **25**, and **27** with an intermediate three-membered alkyl chain (Table 1) were prepared from 1-(3-bromo-*n*-propyl)tetralins **13a**−**c** and 4-(3-bromo-*n*-propyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene (**13d**). These compounds were obtained from 1-tetralone, 5- or 7-methoxy-1-tetralone, and 4,5,6,7-tetrahydro-4-ketothianaphthene (i.e., 4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-one) by a Grignard reaction with cyclopropylmagnesium bromide[32] followed by dehydration with HBr and catalytic hydrogenation[31] of unsaturated intermediates **11a**−**d**.

Compounds with an intermediate four-membered alkyl chain (**15, 17, 22, 23, 26, 28, 29**) were similarly

prepared starting from 1-tetralone and 4-chloro-*n*-butylmagnesium bromide followed by dehydration with HCl, as described elsewhere.[31] Intermediate 4-(4-chloro-*n*-butyl)-1,2-dihydronaphthalene (**12a**) was employed to prepare unsaturated compounds **23** and **28**, while the remaining compounds were derived from 1-(4-chloro-*n*-butyl)-1,2,3,4-tetrahydronaphthalene (**14a**), yielded by catalytic hydrogenation of **12a**. These latter two intermediates have not previously been reported and are described in the Experimental Section. Key intermediates **12a**, **13a**−**d**, and **14a** were reacted in *N,N*-dimethylformamide or acetonitrile with the appropriate amines to give the final compounds.
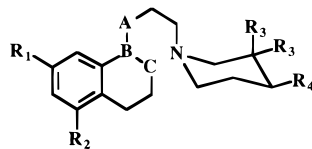
Pharmacology

Compounds **15**−**29** were evaluated for in vitro activity on σ₁, serotonin 5-HT₁A and 5-HT₂, PCP (phencyclidine), and dopamine D-2 receptors by radioreceptor binding assays. All of the compounds were used in the form of hydrogen oxalate salts except compounds **19** and **20** (hydrochloride salts). Controls were undertaken to ensure that oxalate did not interfere with the respective binding at the highest concentration used. The following specific ligands, tissue sources, and procedures were used (a) σ₁ receptors, [³H]-(+)-pentazocine, whole rat brain membranes;[33] (b) serotonin 5-HT₁A receptors, [³H]-serotonin, in the presence of 10^{-6} M ketanserin to mask 5-HT₂ receptors, rat hippocampus membranes (in this area at least one-half of the sites labeled by [³H]-5-HT are 5-HT₁A receptors displaying high affinity for 8-OH-DPAT);[34] (c) serotonin 5-HT₂ receptors, [³H]ketanserin, rat brain cortex membranes;[35] (d) PCP receptors, [³H]phencyclidine, rat hippocampus membranes;[36] and (e) dopamine D-2 receptors, [³H]spiroperidol, rat striatal membranes.[37,38] The following cold compounds were used as reference to define specific binding: (a) haloperidol, (b) 8-OH-DPAT in the presence of a saturating ketanserin concentration, (c) ketanserin, (d) (+)-*N*-allylnormetazocine (SKF 10,047), and (e) (+)-butaclamol.

Concentrations required to inhibit 50% of radioligand specific binding (IC₅₀) were determined by two to three independent experiments with samples in triplicate and six to nine different concentrations of the drug studied. Specific binding represented more than 70% of the total binding. The B_{max} and K_d values used to feed the Cheng−Prusoff equation to calculate K_i were calculated from saturation experiments using the latest version of the LIGAND computerized program as originally described by Munson and Rodbard.[39] The details of the pharmacological methods have been reported previously.[24]
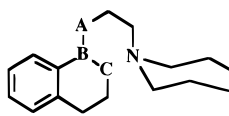
Results and Discussion

The novel class of piperidine derivatives reported here showed a high to superpotent σ₁ affinity; some compounds also demonstrated a widespread selectivity over D-2 dopaminergic and 5-HT₁A and 5-HT₂ serotonergic, as well as PCP, receptors (Table 3). When compared with their isosteric piperazine derivatives,[24] *N*-monosubstituted piperidines **19** and **20** showed an improved σ affinity along with a highly selective profile. Similar behavior was noted for compound **16** (K_i = 3.9 nM) with respect to its piperazine isoster (K_i = 25.7 nM) in the binding assays with [³H]-(+)-pentazocine, but compound

Table 1. Physical Properties

compd	R_1	R_2	A–B–C	R_3	R_4	formula[a]	mp (°C)	recryst solv[b]
15	H	H	$(CH_2)_2$–CH–CH$_2$	H	CH$_2$Ph	$C_{26}H_{35}N\cdot C_2H_2O_4$[c]	135–137	A
16	H	OCH$_3$	CH$_2$–CH–CH$_2$	H	CH$_2$Ph	$C_{26}H_{35}NO\cdot C_2H_2O_4\cdot^1/_2CH_3OH$	125–126	A
17[d]	H	H	$(CH_2)_2$–CH–CH$_2$	(phenyl-fused)		$C_{23}H_{29}N\cdot C_2H_2O_4$	173–175	B
18	H	H	CH$_2$–CH–CH$_2$	H	H	$C_{18}H_{27}N\cdot C_2H_2O_4$	181–184	A
19	OCH$_3$	H	CH$_2$–CH–CH$_2$	H	H	$C_{19}H_{29}NO\cdot HCl\cdot^3/_2H_2O$	126–128	C
20	H	OCH$_3$	CH$_2$–CH–CH$_2$	H	H	$C_{19}H_{29}NO\cdot HCl$	174–176	C
21[e]			CH$_2$–CH–CH$_2$	H	H	$C_{16}H_{25}NS\cdot C_2H_2O_4$	188–190	A
22	H	H	$(CH_2)_2$–CH–CH$_2$	H	H	$C_{19}H_{29}N\cdot C_2H_2O_4\cdot^1/_4CH_3OH$	150–152	A
23	H	H	$(CH_2)_2$–C≡CH	H	H	$C_{19}H_{27}N\cdot C_2H_2O_4$	156–157	A
24		OCH$_3$	CH$_2$–CH–CH$_2$	CH$_3$	H	$C_{21}H_{33}NO\cdot C_2H_2O_4$	166–167	A
25[e]			CH$_2$–CH–CH$_2$	CH$_3$	H	$C_{18}H_{29}NS\cdot C_2H_2O_4$	180–182	A
26	H	H	$(CH_2)_2$–CH–CH$_2$	CH$_3$	H	$C_{21}H_{33}N\cdot C_2H_2O_4$	156–158	A

[a] White to ivory-white crystalline powders, analyzed for C, H, N; results were within ±0.4% of the theoretical values for the formulas given. [b] A = methanol/ethyl ether; B = methanol; C = dichloromethane/ethyl ether. [c] C: calcd, 74.47; found, 75.00. H: calcd, 8.26; found, 8.75. [d] A benzene ring is [c]-fused with the piperidine to form a 1,2,3,4-tetrahydroisoquinolinyl bicycle. [e] In these compounds an unsubstituted [b]-fused thiophene ring replaces the benzene ring.
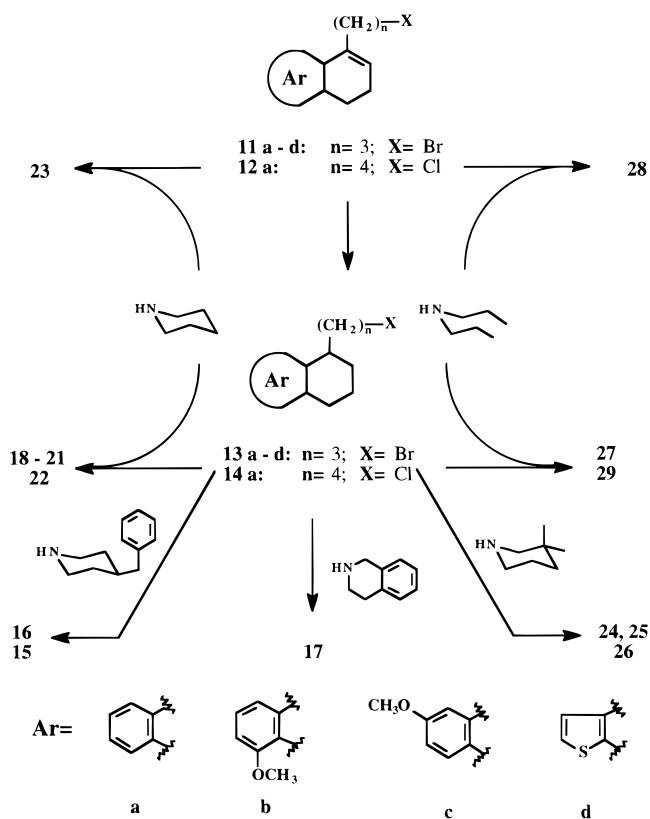
Table 2. Physical Properties

compd	A–B–C	formula[a]	mp (°C)[b]
27	CH$_2$–CH–CH$_2$	$C_{19}H_{31}N\cdot C_2H_2O_4$[c]	126–128
28	$(CH_2)_2$–C≡CH	$C_{20}H_{31}N\cdot C_2H_2O_4$[d]	114–116
29	$(CH_2)_2$–CH–CH$_2$	$C_{20}H_{33}N\cdot C_2H_2O_4$	112–114

[a] Analyses for C, H, N. [b] White crystalline powders from methanol/ethyl ether. [c] C: calcd, 69.39; found, 69.91. [d] H: calcd, 8.86; found, 9.34.

16 was still a mixed 5-HT$_{1A}$/σ_1 ligand with a potent serotonergic component ($K_i < 0.14$ nM) and negligible D-2 affinity ($K_i = 1300$ nM).

The removal of the methoxy group on the tetralin moiety and the lengthening of the intermediate chain from three to four methylene units (compound **15**) caused a dramatic drop in 5-HT$_{1A}$ affinity, whereas σ_1 affinity only underwent a small decrease ($K_i = 30$ nM). The same changes for compound **24** led to compound **26** without a significant lowering in σ_1 affinity. Where the phenyl group was fused onto the piperidine ring to form a tetrahydroisoquinoline derivative (compound **17**), 5-HT$_{1A}$ affinity increased but to a lesser extent than it did for compound **16**. Moreover, when the tetralin moiety was linked to a four-membered alkyl chain (compound **15**), the removal of the 4-benzyl substituent on the piperidine ring (compound **22**) produced a moderate increase in σ_1 affinity ($K_i = 4.7$ nM).

Regarding N-monosubstituted piperidines, a four-membered alkyl chain, as in compounds **22** and **23** ($K_i = 3.9$ nM), gave better results than a three-membered one, as in compound **18**. Furthermore, for the remaining N-[(tetralin-1-yl)propyl]piperidines, neither a methoxyl group (compounds **19**, **20**) nor the thiophene ring (compound **21**) were able to increase the σ_1 affinity showed by monosubstituted tetralins. It should be noted, in this respect, that compound **22** can be regarded as a partially stiffened analog of compound **4** ($K_i = 0.48$

Scheme 1

nM on σ_1 receptor[19]). Constraining a terminal methylene into the tetralin ring or the 1,2-dihydronaphthalene ring therefore failed to improve σ_1 binding, at least in the case of N-monosubstituted piperidines **22** and **23**.

It was very interesting that piperidine derivative **22** and di-n-propylamino derivative **29** exhibited exactly the same K_i value (4.7 nM) for σ_1 binding as did compounds **23** and **28** ($K_i = 3.9$ nM). Therefore it can be stated that the piperidine ring is inessential for achieving nanomolar σ_1 affinity, since an N-di-n-propyl group was able to simulate it. This was in agreement with the minimal difference between piperidine and the

Table 3. Binding Affinities[a]

compd	σ_1, [³H]-(+)-pentazocine, K_i (nM)	5-HT$_{1A}$, [³H]-5-HT,[b] K_i (nM)	PCP, [³H]phencyclidine		D-2, [³H]spiroperidol		5-HT$_2$, [³H]ketanserin	
			K_i (nM)	% displacement[c] 10 000 nM	K_i (nM)	% displacement[c] 5000 nM	K_i (nM)	% displacement[c] 5000 nM
15	30	285	>92 600		NT		NT	
16	3.9	<0.14	>92 600		1300		NT	
17	3.7	65.7	>92 600		NT		NT	
18	40	>1430		95		0		21
19	63.2[d]	>1430		88	>1850		>5520	
20	18.2	>1430	3240		>1850		>5520	
21	>3960	>1430	>92 600		NT		NT	
22	4.7	>1430	5560			27		64
23	3.9	>1430		92		0		12
24	0.4	898	34.2		>10 000		NT	
25	3.9	>1430	9.4		NT		NT	
26	0.8	>1430	>92 600		>10 000		NT	
27	6.7	400	48 100			0		51
28	3.9	357	2600			40		60
29	4.7	200	9910			31		66
haloperidol	10							
8-OH-DPAT		4.3						
SKF 10,047			370					
(+)-butaclamol					0.3			
ketanserin								34

[a] Data had ±SEM < 5% of mean values. NT = not tested. [b] In the presence of 10^{-6} M ketanserin to mask 5-HT$_2$ receptors. [c] Percent specific displacement of respective radioligands run in triplicate at the concentration indicated. [d] [³H]DTG as radioligand and guinea pig brain cortex membranes as tissue source were used (see refs 24 and 40).

N-methyl-*N*-*n*-propyl group found for other σ ligands.[26] Finally, 3,3-dimethyl substitution on the piperidine ring, as in compounds **24−26**, caused a substantial increase in σ_1 affinity compared with their unsubstituted analogs **20−22**, respectively. Indeed, in the overall binding experiment on [³H]-(+)-pentazocine, 3,3-dimethyl-piperidine derivative **24** demonstrated the lowest K_i value (0.4 nM) followed by **26** (K_i = 0.8 nM). Although compound **25** (K_i = 3.9 nM) was not a superpotent σ_1 ligand, it proved to be noticeably better than the corresponding nonmethylated compound **21**.

These results confirm Glennon's suggestion that relatively small substituents on the nitrogen atom "interact in a productive manner" with the σ_1 receptor, according to his schematic representation[19] of important features for σ_1 binding. The piperidine or the diisopropylamine moieties in the present compounds might act as the proximal lipophilic *N*-substituent that binds the secondary binding site. The primary hydrophobic site might be fitted by the tetralin moiety, which represents the distal hydrophobic group, as described by Gilligan[23] for the previous model. However, the hydrogen-bonding center hypothesized in such a model did not seem to be essential for σ_1 binding in the compounds we studied. Both σ_1 pharmacophore models have arisen from ligands with a substantially conformational flexibility and were based on an optimized five-membered spacer; however, some tolerance was permitted in the distance between the nitrogen atom and the distal phenyl group (6 ± 2 Å in Gilligan's model, 6−10 Å in Glennon's). Glennon's model was confirmed by our findings on tetralin derivatives, since in such compounds only a terminal methylene was constrained in a rigid conformation, whereas the remaining alkyl chain was free to bind at the σ_1 receptor, whether it was three- or four-membered. Changes in the point of attachment on the tetralin ring or on similar hydrophobic nuclei might produce more interesting results.

As far as selectivities were concerned, all tested compounds showed an acceptable selectivity profile versus D-2 dopaminergic and 5-HT$_2$ serotonergic recep-

tors. Furthermore, compound **26** demonstrated the best selectivities over PCP, 5-HT$_{1A}$ and 5-HT$_2$ serotonergic, and D-2 dopaminergic receptors. This was not so for compounds **24** and **25**, which exhibited the lowest K_i value for PCP binding (K_i = 34.2 and 9.4 nM, respectively). Therefore, it can be suggested that the two methyl groups on the piperidine bind an additional lipophilic site on the PCP receptor;[41] an intermediate chain of four methylene units (compound **26**) would seem to prevent this effect. Finally, the reported compounds proved to have negligible affinities toward PCP and 5-HT$_{1A}$ receptors, except for the few cases discussed above. In conclusion, 3,3-dimethylpiperidine derivatives are worthy of further investigation in order to contribute to the discovery of superpotent and highly selective σ_1 ligands and to explore the framework of the σ_1 sites.

Experimental Section

Chemistry. Column chromatographies were performed with 1:30 ICN silica gel (0.063−0.200 mm) as the stationary phase. Melting points were determined in open capillaries on a Gallenkamp electrothermal apparatus. Elemental analyses were performed by the Microanalytical Section of our department on solid samples only; the analytical results (C, H, N) were within ±0.4% of the theoretical values, unless otherwise stated. ¹H NMR spectra were recorded either on a Varian XL-200 or on a Bruker AM 300 WB instrument. Chemical shifts are reported in parts per million (ppm, δ). Recording of mass spectra was done on an HP 5995C gas chromatograph/mass spectrometer, electron impact 70 eV, equipped with an HP 59970A workstation. All compounds had NMR and mass spectra that were fully consistent with their structure. All of the spectral data of amines refer to their free bases.

4-(4-Chloro-*n*-butyl)-1,2-dihydronaphthalene (12a). The title compound was prepared starting from 1-bromo-4-chloro-butane (5.14 g, 30 mmol) and Mg turnings (0.73 g, 30 mmol) in anhydrous THF (30 mL). Then α-tetralone (2.92 g, 20 mmol) in the same solvent (30 mL) was added dropwise to the 4-chloro-*n*-butylmagnesium bromide formed. The mixture was reacted and worked up as previously described.[31] The compound **12a** (2.65 g) was obtained as a colorless oil with 60% overall yield: ¹H NMR (200 MHz, CDCl₃) 1.50−2.07 [mm, 4H, (C*H*₂)₂CH₂Cl], 2.12−2.65 (mm, 4H, 2 allyl CH₂), 2.80 (br t, 2H,

benzyl CH$_2$), 3.54 (t, 2H, $J = 7$ Hz, CH$_2$Cl), 5.90 (br t, 1H, vinyl CH), 7.10$-$7.55 (mm, 4H, aromatic); GC/MS m/z 222 (M$^+$ + 2, 5), 221 (M$^+$ + 1, 2), 220 (M$^+$, 15), 144 (47), 129 (100), 128 (46), 115 (21).

1-(4-Chloro-*n*-butyl)-1,2,3,4-tetrahydronaphthalene (14a). 4-(4-Chloro-*n*-butyl)-1,2-dihydronaphthalene (**12a**) (2.2 g, 10 mmol) in EtOH (100 mL) was hydrogenated in the presence of 5% palladium on activated carbon (200 mg) at normal pressure and room temperature until theoretical uptake was accomplished. The reaction mixture was filtered through Celite and evaporated to dryness to obtain **14a** as a nearly colorless oil in a quantitative yield. For analytical purposes a sample was purified on a silica gel column (petroleum ether/CH$_2$Cl$_2$, 9:1, as eluent): ^{1}H NMR (200 MHz, CDCl$_3$) 1.23$-$2.03 [mm, 10H, (CH$_2$)$_2$CH(CH$_2$)$_3$], 2.52$-$2.92 (mm, 3H, benzylic), 3.62 (t, 2H, $J = 7$ Hz, CH$_2$Cl), 6.90$-$7.32 (mm, 4H, aromatic); GC/MS m/z 224 (M$^+$ + 2, 2), 223 (M$^+$ + 1, 1), 222 (M$^+$, 6), 131 (100), 91 (20).

Synthesis of Final Tertiary Amine Derivatives 15$-$29. General Procedure. In a typical reaction 3.5 mmol of a 1-(ω-haloalkyl) derivative (**12a**, **13a$-$d**, **14a**) was refluxed in DMF or CH$_3$CN (20 mL) with an equimolar amount of the appropriate secondary amine and K$_2$CO$_3$. Working up was carried out as previously described.[32] The crude residue was chromatographed on a silica gel column (CHCl$_3$/MeOH, 95:5, as eluent, unless otherwise indicated), and the final compounds were obtained as almost colorless to pale yellow oils with a 70$-$80% yield, unless otherwise stated.

4-Benzyl-1-[4-(1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-butyl]piperidine (15): 65% yield; ^{1}H NMR (200 MHz, CDCl$_3$) 1.20$-$1.94 [mm, 17H, (CH$_2$)$_2$CH(CH$_2$)$_3$, piperidine CH$_2$CHCH$_2$ and CHNCH], 2.30 [t, 2H, $J = 7.6$ Hz, CH$_2$N(CH$_2$)$_2$], 2.53 (d, 2H, $J = 6.5$ Hz, CH$_2$Ph), 2.74 (br t, 3H, *endo* benzyl CH and CH$_2$), 2.91 (br d, 2H, $J = 11$ Hz, CHNCH), 7.02$-$7.33 (mm, 9H, aromatic); GC/MS m/z 363 (M$^+$ + 2, 1), 362 (M$^+$ + 1, 8), 361 (M$^+$, 28), 188 (100).

4-Benzyl-1-[3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperidine (16): eluted with CHCl$_3$; ^{1}H NMR (200 MHz, CDCl$_3$) 1.21$-$1.96 (mm, 15H), 2.31 (br t, 2H), 2.54 (d, 2H, $J = 6.5$ Hz), 2.56$-$2.83 (mm, 3H), 2.92 (br d, 2H, $J = 11$ Hz), 3.80 (s, 3H, OCH$_3$), 6.62$-$7.34 (mm, 8H); GC/MS m/z 379 (M$^+$ + 2, 1), 378 (M$^+$ + 1, 10), 377 (M$^+$, 35), 188 (100), 175 (21).

2-[4-(1,2,3,4-Tetrahydronaphthalen-1-yl)-*n*-butyl]-1,2,3,4-tetrahydroisoquinoline (17): eluted with CHCl$_3$; 97% yield; ^{1}H NMR (200 MHz, CDCl$_3$) 1.37$-$1.95 (mm, 10H), 2.55 [t, 2H, $J = 7.4$ Hz, chain-CH$_2$N], 2.71$-$2.87 (mm, 5H, benzylic), 2.89$-$2.99 (br t, 2H, *endo* NCH$_2$), 3.65 (s, 2H, benzyl NCH$_2$), 7.00$-$7.27 (mm, 8H, aromatic); GC/MS m/z 320 (M$^+$ + 1, 6), 319 (M$^+$, 25), 146 (100).

1-[3-(1,2,3,4-Tetrahydronaphthalen-1-yl)-*n*-propyl]-piperidine (18): ^{1}H NMR (300 MHz, CDCl$_3$) 1.36$-$1.86 (mm, 14H), 2.25$-$2.46 (mm, 6H), 2.68$-$2.80 (mm, 3H), 7.00$-$7.18 (mm, 4H); GC/MS m/z 258 (M$^+$ + 1, 3), 257 (M$^+$, 12), 98 (100).

1-[3-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperidine (19): ^{1}H NMR (200 MHz, CDCl$_3$) 1.38$-$1.90 (mm, 14H), 2.24$-$2.50 (mm, 6H), 2.62$-$2.82 (mm, 3H), 3.77 (s, 3H, OCH$_3$), 6.62$-$7.00 (mm, 3H); GC/MS m/z 288 (M$^+$ + 1, 3), 287 (M$^+$, 13), 98 (100), 85 (24).

1-[3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperidine (20): ^{1}H NMR (300 MHz, CDCl$_3$) 1.38$-$1.83 (mm, 14H), 2.25$-$2.46 (mm, 6H), 2.48$-$2.80 (mm, 3H), 3.78 (s, 3H), 6.60$-$7.10 (mm, 3H); GC/MS m/z 288 (M$^+$ + 1, 4), 287 (M$^+$, 18), 98 (100), 85 (22).

1-[3-(4,5,6,7-Tetrahydrobenzo[*b*]thien-4-yl)-*n*-propyl]-piperidine (21): eluted with CH$_2$Cl$_2$/MeOH, 9:1; ^{1}H NMR (200 MHz, CDCl$_3$) 1.35$-$2.00 (mm, 14H), 2.24$-$2.47 (mm, 6H), 2.62$-$2.78 (mm, 3H), 6.84 and 7.01 (2d, 2H, $J = 5.2$ Hz, aromatic); GC/MS m/z 265 (M$^+$ + 2, 2), 264 (M$^+$ + 1, 5), 263 (M$^+$, 26), 98 (100), 85 (25).

1-[4-(1,2,3,4-Tetrahydronaphthalen-1-yl)-*n*-butyl]-piperidine (22): 58% yield; ^{1}H NMR (300 MHz, CDCl$_3$) 1.23$-$1.89 (mm, 16H), 2.25$-$2.47 (mm, 6H), 2.68$-$2.81 (br t, 3H), 7.00$-$7.18 (mm, 4H); GC/MS m/z 272 (M$^+$ + 1, 3), 271 (M$^+$, 15), 98 (100).

1-[4-(1,2-Dihydronaphthalen-4-yl)-*n*-butyl]piperidine (23): ^{1}H NMR (300 MHz, CDCl$_3$) 1.35$-$1.68 (mm, 10H), 2.16$-$2.50 [mm, 10H, 2 allyl CH$_2$ and CH$_2$N(CH$_2$)$_2$], 2.70 (t, 2H, $J = 8.0$ Hz), 5.82 (br t, 1H, vinyl CH), 7.08$-$7.25 (mm, 4H); GC/MS m/z 270 (M$^+$ + 1, 7), 269 (M$^+$, 31), 124 (31), 98 (100).

3,3-Dimethyl-1-[3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperidine (24): ^{1}H NMR (200 MHz, CDCl$_3$) 0.94 (s, 6H, 2 CH$_3$), 1.21 [t, 2H, $J = 6$ Hz, CH$_2$C(CH$_3$)$_2$], 1.46$-$1.88 [mm, 10H, (CH$_2$)$_2$CH(CH$_2$)$_2$ and piperidine CH$_2$], 1.94$-$2.12 [br 2d, 2H, AB system, NCH$_2$C(CH$_3$)$_2$], 2.21$-$2.39 (mm, 4H, CH$_2$NCH$_2$), 2.54$-$2.83 (mm, 3H, benzylic), 3.80 (s, 3H, OCH$_3$), 6.60$-$7.15 (mm, 3H, aromatic); GC/MS m/z 316 (M$^+$ + 1, 6), 315 (M$^+$, 25), 126 (100).

3,3-Dimethyl-1-[3-(4,5,6,7-tetrahydrobenzo[*b*]thien-4-yl)-*n*-propyl]piperidine (25): ^{1}H NMR (200 MHz, CDCl$_3$) 0.94 (s, 6H), 1.20 (t, 2H, $J = 6$ Hz), 1.38$-$2.08 (mm, 12H), 2.20$-$2.36 (mm, 4H), 2.62$-$2.80 (mm, 3H), 6.85 and 7.03 (2 d, 2H, $J = 5.1$ Hz); GC/MS m/z 293 (M$^+$ + 2, 1), 292 (M$^+$ + 1, 5), 291 (M$^+$, 22), 126 (100), 113 (20).

3,3-Dimethyl-1-[4-(1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-butyl]piperidine (26): eluted with CHCl$_3$; 47% yield; ^{1}H NMR (200 MHz, CDCl$_3$) 0.93 (s, 6H), 1.16$-$1.29 (mm, 2H), 1.32$-$1.92 (mm, 12H), 2.00 (s, 2H), 2.20$-$2.36 (mm, 4H), 2.75 (br t, 3H), 7.03$-$7.21 (mm, 4H); GC/MS m/z 300 (M$^+$ + 1, 2), 299 (M$^+$, 7), 126 (100).

N,N-Di-*n*-propyl-3-(1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propylamine (27): 61% yield; ^{1}H NMR (300 MHz, CDCl$_3$) 0.89 (t, 6H, $J = 7.3$ Hz, 2 CH$_3$), 1.50$-$1.87 [mm, 12H, 2 CH$_2$CH$_3$, (CH$_2$)$_2$CH(CH$_2$)$_2$], 2.66$-$2.85 [mm, 9H, CH$_2$N(CH$_2$)$_2$ and benzylic], 7.00$-$7.17 (mm, 4H, aromatic); GC/MS m/z 274 (M$^+$ + 1, 2), 273 (M$^+$, 12), 244 (50), 131 (25), 129 (22), 114 (100), 115 (20), 86 (26).

N,N-Di-*n*-propyl-4-(1,2-dihydronaphthalen-4-yl)-*n*-butylamine (28): 53% yield; ^{1}H NMR (300 MHz, CDCl$_3$) 0.85 (t, 6H, $J = 7.3$ Hz), 1.37$-$1.57 (mm, 8H), 2.15$-$2.27 (mm, 2H), 2.33$-$2.52 [mm, 8H, CH$_2$(CH$_2$)$_2$CH$_2$N(CH$_2$)$_2$], 2.71 (t, 2H, $J = 8.0$ Hz), 5.83 (t, 1H, $J = 4.5$ Hz, vinyl CH), 7.08$-$7.26 (mm, 4H); GC/MS m/z 286 (M$^+$ + 1, 7), 285 (M$^+$, 28), 256 (76), 141 (34), 129 (23), 128 (30), 117 (25), 115 (22), 114 (100), 86 (33).

N,N-Di-*n*-propyl-4-(1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-butylamine (29): 52% yield; ^{1}H NMR (300 MHz, CDCl$_3$) 0.87 (t, 6H, $J = 7.3$ Hz), 1.24$-$1.87 (mm, 14H), 2.52$-$2.80 (mm, 9H), 7.00$-$7.17 (mm, 4H); GC/MS m/z 288 (M$^+$ + 1, 3), 287 (M$^+$, 16), 258 (79), 131 (20), 114 (100), 86 (28).

Hydrogen Oxalate Salts. Anhydrous oxalic acid in Et$_2$O (3 g/100 mL) was added dropwise to a solution of the amine in a minimum amount of CH$_2$Cl$_2$ until the precipitation was completed. After filtration, the solid was washed with cold Et$_2$O and recrystallized three times from the solvent reported in Tables 1 and 2.

References

(1) Walker, J. M.; Bowen, W. D.; Walker, F. O.; Matsumoto, R. R.; de Costa, B.; Rice, K. C. Sigma receptors: biology and function. *Pharmacol. Rev.* **1990**, *42*, 355$-$402.

(2) Abou-Gharbia, M.; Ablordeppey, S. Y.; Glennon, R. A. Sigma Receptors and their Ligands: The Sigma Enigma. *Annu. Rep. Med. Chem.* **1993**, *28*, 1$-$10.

(3) Wyrick, S. D.; Booth, R. G. Progress in sigma receptor research. *Drugs Future* **1995**, *20*, 1033$-$1044.

(4) Vilner, B. J.; De Costa, B. R.; Bowen, W. D. Cytotoxicity of sigma ligands: Sigma receptor-mediated effects on cellular morphology and viability. *J. Neurosci.* **1995**, *15*, 117$-$134.

(5) Steardo, L.; Monteleone, P.; d'Istria, M.; Serino, I.; Maj, M.; Cuomo, V. (+)-N-Allylnormetazocine Enhances N-Acethyltransferase Activity and Melatonin Synthesis: Preliminary Evidence for a Functional Role of Sigma Receptors in the Rat Pineal Gland. *J. Pharmacol. Exp. Ther.* **1995**, *275*, 845$-$849.

(6) Monnet, F. P.; Blier, P.; Debonnel, G.; De Montigny, C. Modulation by sigma ligands of N-methylaspartate-induced [^{3}H]-noradrenalin release in rat hippocampus: G-protein dependency. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1992**, *346*, 32$-$39.

(7) Nakagawara, M.; Sato, Y. Neuropeptide Y: Psychopharmacological and clinical aspects. *Yakubutsu-Seishin-Kodo* **1994**, *14*, 117−127.

(8) Bouchard, P.; Dumont, Y.; Fournier, A.; St. Pierre, S.; Quirion, R. Evidence for in vivo interactions between neuropeptide Y-related peptides and sigma receptors in mouse hippocampal formation. *J. Neurosci.* **1993**, *13*, 3926−3931.

(9) Gilligan, P. J.; Tam, S. W. Sigma receptor ligands: potential drugs for the treatment of CNS disorders? *Drugs News Perspect.* **1994**, *7*, 13−18.

(10) Debonnel, G. Current Hypotheses on Sigma Receptors and Their Physiological Role: Possible Implications in Psychiatry. *J. Psychiatr. Neurosci.* **1993**, *18*, 157−172.

(11) Gewirtz, G. R.; Gorman, J. M.; Volavka, J.; Macaluso, J.; Gribkoff, G.; Taylor, D. P. BMY-14802, a sigma receptor ligand for the treatment of schizophrenia. *Neuropsychopharmacology* **1994**, *10*, 37−40.

(12) Menkel, M.; Pontecorvo, M.; Katz, J.; Witkin, J. M. Selective σ ligands block stimulant effects of cocaine. *Eur. J. Pharmacol.* **1991**, *201*, 251−252.

(13) Izenwasser, S.; Hauck Newman, A.; Katz, J. L. Cocaine and several σ receptor ligands inhibit dopamine uptake in rat caudate-putamen. *Eur. J. Pharmacol.* **1993**, *243*, 201−205.

(14) Taylor, D. P.; Yevich, J. P.; Dextraze, P.; Moon, S. L.; Behling, S. H.; Defnet, J.; Geissler, M. In *Multiple Sigma and PCP Receptor Ligands: Mechanism for Neuromodulation and Neuroprotection?* Kamenka, J.-M., Domino, E. F., Ed.; NPP Books: Ann Arbor, MI, 1992; pp 767−778.

(15) De Loore, K. L.; Lesage, A. S.; Peeters, L.; Leysen, J. E. Various sigma ligands exert long-term protection against glutamate toxicity in primary hippocampal neurones; apparent non involvement of identified sigma-2 sites. *Neurosci. Res. Commun.* **1994**, *14*, 43−52.

(16) Lehmann, J. Sigma Receptor, Schizophrenia and Cytochrome P-450. *Drugs News Perspect.* **1991**, *4*, 208−210.

(17) Largent, B. L.; Wikström, H.; Gundlach, A. L.; Snyder, S. H. Structural Determinants of σ Receptor Affinity. *Mol. Pharmacol.* **1987**, *32*, 772−784.

(18) Quirion, R.; Bowen, W. D.; Itzhak, Y.; Junien, J. L.; Musacchio, J. M.; Rothman, R. B.; Su, T.-P.; Tam, S. W.; Taylor, D. P. A proposal for the classification of sigma binding sites. *Trends Pharmacol. Sci.* **1992**, *13*, 85−86.

(19) Glennon, R. A.; Ablordeppey, S. Y.; Ismaiel, A. M.; El-Ashmawy, M. B.; Fischer, J. B.; Burke Howie, K. J. Structural Features important for σ_1 Receptor Binding. *J. Med. Chem.* **1994**, *37*, 1214−1219.

(20) He, X.; Bowen, W. D.; Lee, K. S.; Williams, W.; Weinberger, D. R.; de Costa, B. R. Synthesis and Binding Characteristics of Potential SPETC Imaging Agents for σ-1 and σ-2 Binding Sites. *J. Med. Chem.* **1993**, *36*, 566−571.

(21) de Costa, B. R.; He, X.; Dominguez, C.; Cutts, J.; Williams, W.; Bowen, W. D. A New Approach to the Design of σ-2 Selective Ligands: Synthesis and Evaluation of N-[2-(3,4-Dichlorophenyl)-ethyl]-N-methyl-2-(1-pyrrolidinyl)ethylamine-Related Polyamines at σ-1 and σ-2 Receptor Subtypes. *J. Med. Chem.* **1994**, *37*, 314−321.

(22) Hudkins, R. L.; Mailman, R. B.; DeHaven-Hudkins, D. L. Novel (4-Phenylpiperidinyl)- and (4-Phenylpiperazinyl)alkyl- Spaced Esters of 1-Phenylcyclopentanecarboxylic Acids as Potent σ-Selective Compounds. *J. Med. Chem.* **1994**, *37*, 1964−1970.

(23) Gilligan, P. J.; Cain, G. A.; Christos, T. E.; Cook, L.; Drummond, S.; Johnson, A. L.; Kergaye, A. A.; McElroy, J. F.; Rohrbach, K. W.; Schmidt, W. K.; Tam, S. W. Novel Piperidine σ Receptor Ligands as Potential Antipsychotic Drugs. *J. Med. Chem.* **1992**, *35*, 4344−4361.

(24) Berardi, F.; Colabufo, N. A.; Giudice, G.; Perrone, R.; Tortorella, V.; Govoni, S.; Lucchi, L. New σ and 5-HT$_{1A}$ Receptor Ligands: ω-(Tetralin-1-yl)-n-alkylamine Derivatives. *J. Med. Chem.* **1996**, *39*, 176−182.

(25) Glennon, R. A.; Yousif, M. Y.; Ismaiel, A. M.; El-Ashmawy, M. B.; Herndon, J. L.; Fischer, J. B.; Server, A. C.; Burke Howie, K. J. Novel 1-Phenylpiperazine and 4-Phenylpiperidine Derivatives as High-Affinity σ Ligands. *J. Med. Chem.* **1991**, *34*, 3360−3365.

(26) Ablordeppey, S. Y.; Fischer, J. B.; Burke Howie, K. J.; Glennon, R. A. Design, Synthesis and Binding of Sigma Receptor Ligands derived from Butaclamol. *Med. Chem. Res.* **1992**, *2*, 368−375.

(27) Russell, M. G. N.; Baker, R.; Billington, D. C.; Knight, A. K.; Middlemiss, D. N.; Noble, A. J. Benz[f]isoquinoline Analogues as High-Affinity σ Ligands. *J. Med. Chem.* **1992**, *35*, 2025−2032.

(28) Chambers, M. S.; Baker, R.; Billington, D. C.; Knight, A. K.; Middlemiss, D. N.; Wong, E. H. F. Spiropiperidines as High-Affinity, Selective σ Ligands. *J. Med. Chem.* **1992**, *35*, 2033−2039.

(29) Gilligan, P. J.; Kergaye, A. A.; Lewis, B. M.; McElroy, J. F. Piperidinyltetralin σ Ligands. *J. Med. Chem.* **1994**, *37*, 364−370.

(30) El-Ashmawy, M.; Ablordeppey, S. Y.; Issa, H.; Gad, L.; Fischer, J. B.; Burke Howie, K. J.; Glennon, R. A. Further investigation of 5-phenylpentylamine derivatives as novel sigma receptor ligands. *Med. Chem. Res.* **1992**, *2*, 119−126.

(31) Perrone, R.; Berardi, F.; Colabufo, N. A.; Leopoldo, M.; Tortorella, V.; Fiorentini, F.; Olgiati, V.; Ghiglieri, A.; Govoni, S. High Affinity and Selectivity on 5-HT$_{1A}$ Receptor of 1-Aryl-4-[(1-tetralin)alkyl]piperazines. 2. *J. Med. Chem.* **1995**, *38*, 942−949.

(32) Perrone, R.; Berardi, F.; Colabufo, N. A.; Tortorella, V.; Fiorentini, F.; Olgiati, V.; Vanotti, E.; Govoni, S. Mixed 5-HT$_{1A}$/D-2 Activity of a New Model of Arilpiperazines: 1-Aryl-4-[3-(1,2-dihydronaphthalen-4-yl)-n-propyl]piperazines. 1. Synthesis and Structure-Activity Relationships. *J. Med. Chem.* **1994**, *37*, 99−104.

(33) Cagnotto, A.; Bastone, A.; Mennini, T. [^{3}H](+)-Pentazocine binding to rat brain σ_1 receptors. *Eur. J. Pharmacol.* **1994**, *266*, 131−138.

(34) Peroutka, S. J. Pharmacological Differentiation and Characterization of 5-HT$_{1A}$, 5-HT$_{1B}$, and 5-HT$_{1C}$ Binding Sites in Rat Frontal Cortex. *J. Neurochem.* **1986**, *47*, 529−540.

(35) Mir, A. K.; Hilbert, M.; Tricklebank, M. D.; Middlemiss, D. M.; Kidd, E. J.; Fozard, J. R. MDL72832 a potent and stereoselective ligand at central and peripheral 5-HT$_{1A}$ receptors. *Eur J. Pharmacol.* **1988**, *149*, 107−120.

(36) Zukin, S. R.; Zukin, S. Specific [^{3}H]phencyclidine binding in rat central nervous system. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 5372−5376.

(37) Briley, M.; Langer, S. Z. Two binding sites for [^{3}H]-spiroperidol on rat striatal membranes. *Eur. J. Pharmacol.* **1978**, *50*, 283−294.

(38) Lucchi, L.; Moresco, M. R.; Govoni, S.; Trabucchi, M. Effect of chronic ethanol treatment on dopamine receptor subtypes in rat striatum. *Brain Res.* **1988**, *449*, 347−351.

(39) Munson, P. J.; Rodbard, D. Ligand: a versatile computerized approach for characterization of ligand binding systems. *Anal. Biochem.* **1980**, *107*, 220−239.

(40) Weber, E.; Sonders, M.; Quarum, M.; Mc Lean, S.; Pou, S.; Keana, J. F. W. 1,3-Di(2-[5-^{3}H]tolyl)guanidine a selective ligand that labels σ-type receptors for psychotomimetic opiates and antipsychotic drugs. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 8784−8788.

(41) Carroll, F. I.; Abraham, P.; Parham, K.; Bai, X.; Zhang, X.; Brine, G. A.; Mascarella, S. W.; Martin, B. R.; May, E. L.; Sauss, C.; Di Paolo, L.; Wallace, P.; Walker, J. M.; Bowen, W. D. Enantiomeric N-Substituted N-Normetazocines: A Comparative Study of Affinities at σ, PCP and μ Opioid Receptors. *J. Med. Chem.* **1992**, *35*, 2812−2818.

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