New σ and 5-HT_{1A} Receptor Ligands: ω-(Tetralin-1-yl)-*n*-alkylamine Derivatives

Francesco Berardi,* Nicola A. Colabufo, Giuseppe Giudice, Roberto Perrone,* and Vincenzo Tortorella
Dipartimento Farmaco-chimico, Università di Bari, via Orabona, 4, 70126 Bari, Italy

Stefano Govoni and Laura Lucchi
Istituto di Scienze Farmacologiche, Università di Milano, via Balzaretti, 9, 20133 Milano, Italy

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Two series of compounds that are structurally related to benzomorphans, derived by structural modification of arylpiperazines with high 5-HT_{1A} affinity and moderate σ affinity, were prepared in order to increase σ affinity and selectivity. All new compounds are *N*-substituted-ω-(1,2,3,4-tetrahydronaphthalen-1-yl)- or -ω-(1,2-dihydronaphthalen-4-yl)-*n*-alkylamines with, in some cases, a methoxy group on the tetralin moiety. They were tested in radioligand binding assays on σ ([^{3}H]DTG and [^{3}H]-(+)-pentazocine), D-2 dopaminergic, 5-HT_{1A} and 5-HT_2 serotonergic, and PCP (phencyclidine) receptors. A first set of compounds bearing a 4-(1-substituted)piperazine moiety as terminal fragment on the alkyl chain showed moderate to high σ affinity (K_i = 5.3−139 nM), the most active and selective being 1-cyclohexyl-4-[3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperazine **(14)**, with probable pronounced σ_2 affinity (K_i = 5.3 nM on [^{3}H]DTG and K_i = 71 nM on [^{3}H]-(+)-pentazocine). Moreover, compound **13**, a 1-benzylpiperazine analogue of **14**, preserved a dual high 5-HT_{1A} and σ affinity (K_i = 3.6 nM on [^{3}H]-5-HT and K_i = 7.0 nM on [^{3}H]DTG). The second set of compounds includes some *N*-phenylalkyl derivatives of 3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propylamine that can be considered to be open-chain derivatives of 4-substituted-1-arylpiperazines. Among these compounds that had a lower activity toward σ binding sites, a high 5-HT_{1A} affinity was found for the *N*-(3-phenylpropyl) derivative **21** (K_i = 4.4 nM) which demonstrated very good selectivity.

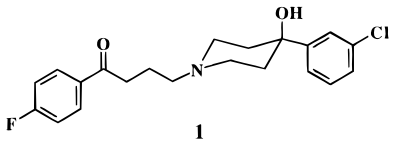
Introduction

The traditional antipsychotic therapy by D-2 antagonists causes extrapyramidal symptoms (EPS) or tardive diskinesia (TD). In order to avoid these side effects, some atypical antipsychotic drugs[1] such as clozapine, remoxipride, and risperidone have been proposed, as these have alternative modes of action. Among these, activity of the σ receptor seems to hold hopeful prospects.[2,3]

In recent years, the σ binding sites have been demonstrated to be distinct from opioid receptors[4] and from the PCP/NMDA (phencyclidine/*N*-methyl-D-aspartate) receptor complex,[5,6] but the biological function of putative σ receptors remains unknown,[7] and no endogenous σ neurotransmitter has been identified.[4] For this reason σ sites are more correctly identified as binding sites than receptors. At the moment three σ site subtypes are recognized, namely σ_1, σ_2,[8] and more recently σ_3,[9,10] and several SARs (structure−activity relationships) have been developed in order to find structural determinants for characterizing σ binding sites.[11−15]

Starting from haloperidol **(1)**, a nonselective σ ligand, several piperidine and piperazine derivatives have been developed[16,17] and reported as selective σ ligands.[18,19] Moreover, structures such as BMY 14802 **(2)** and cinuperone **(3)** entered clinical trials for treatment of central nervous system (CNS) disorders,[3] but they present a nonselective binding profile such that an understanding of their clinical behavior is difficult.

Recently we reported[20] multireceptorial binding data for a series of 1-aryl-4-(1-tetralinyl)-*n*-propylpiperazines **(4)** that demonstrated high 5-HT_{1A} serotonergic affinity. In that study, σ receptor binding assays were carried out, and as all tested compounds showed IC_{50} values ranging from 10^{-8} to 10^{-7} M, no σ SAR study was possible.



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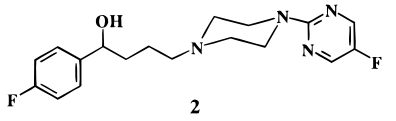

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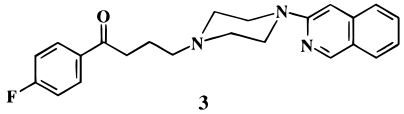

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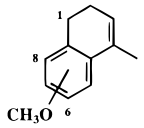
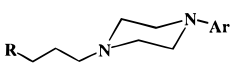
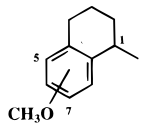
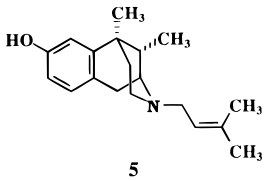
a) R= 



4a,b

b) R= 



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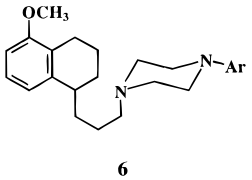

6

* To whom correspondence should be addressed.
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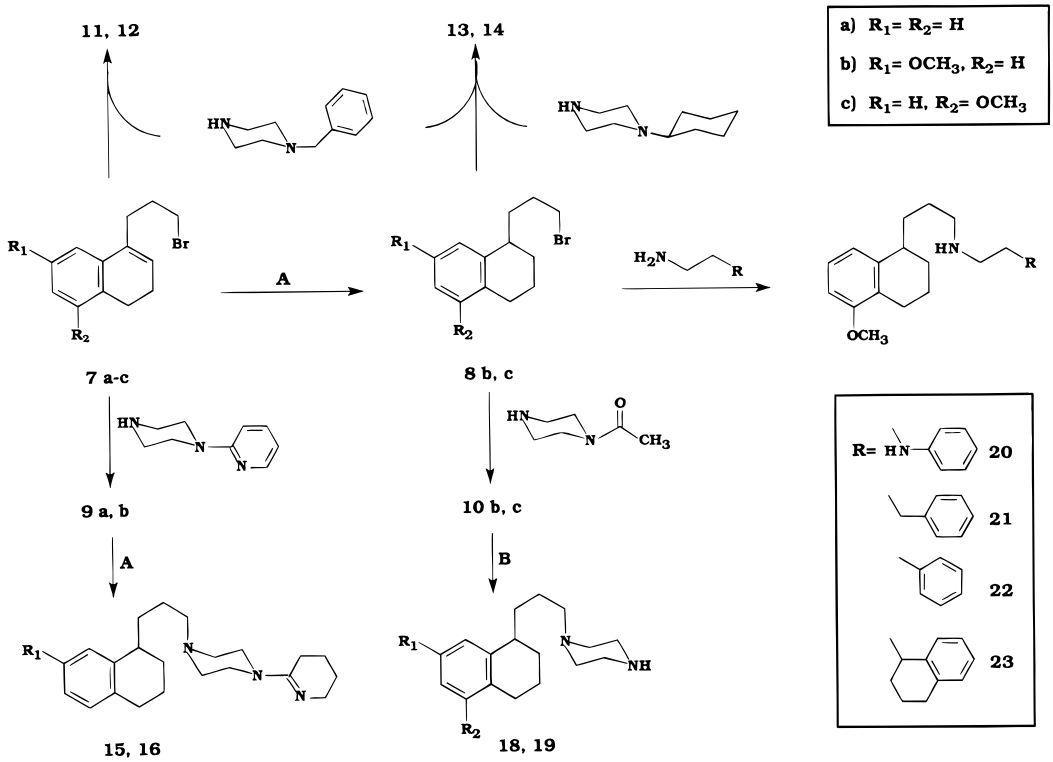
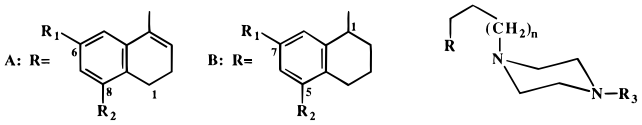
Scheme 1[a]



[a] Reagents: (A) H_2, 10% Pd/C; (B) HCl.

Table 1. Physical Properties for **11**−**19**



compd	R	R_1	R_2	R_3	n	formula[a]	mp, °C	recryst solv
11	A	H	H	CH_2Ph	1	$C_{24}H_{30}N_2 \cdot 2HCl$	243−245	MeOH
12	A	H	OCH_3	CH_2Ph	1	$C_{25}H_{32}N_2O \cdot 2HCl \cdot H_2O$	262−264	MeOH
13	B	H	OCH_3	CH_2Ph	1	$C_{25}H_{34}N_2O \cdot 2HCl$	267−269	MeOH
14	B	H	OCH_3	cyclohexyl	1	$C_{24}H_{38}N_2O \cdot 2HCl \cdot {}^1/_2H_2O$	256−258	MeOH/Et_2O
15	B	H	H	2-THP[b]	1	$C_{22}H_{33}N_3 \cdot 2HCl \cdot H_2O$	273−275	MeOH/Et_2O
16	B	OCH_3	H	2-THP[b]	1	$C_{23}H_{35}N_3O \cdot 2HCl \cdot {}^1/_3H_2O$	243−245	MeOH/Et_2O
17	B	H	OCH_3	2-THP[b]	2	$C_{24}H_{37}N_3O \cdot 3HCl$	264−266	MeOH/Et_2O
18	B	OCH_3	H	H	1	$C_{18}H_{28}N_2O \cdot 2HCl \cdot H_2O$	273−275	MeOH/Et_2O
19	B	H	OCH_3	H	1	$C_{18}H_{28}N_2O \cdot 2HCl \cdot {}^1/_3H_2O$	235−237	MeOH/Et_2O

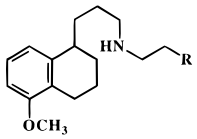
[a] C, H, and N analyses were within ±0.4% of the theoretical values for the formulas given. [b] 2-THP = 2-(3,4,5,6-tetrahydropyridyl).

Furthermore, all tested 1-arylpiperazines showed poor σ selectivity profile versus dopamine and serotonin receptors, whereas better selectivity was achieved by eliminating the *N*-aryl substituent.

In fact 1-[3-(1,2-dihydro-6-methoxynaphthalen-4-yl)-*n*-propyl]piperazine (**4a**: 6-OCH_3, Ar = H), which had been reported[21] to be inactive toward 5-HT$_{1A}$, 5-HT$_2$, and D-2 receptors, was subsequently tested in new binding assays[22] and, although a striking σ affinity value was not observed, an undoubted σ selectivity was nevertheless evident.

With these findings as a starting point, in an effort to contribute to defining the structural requirement for binding to the σ receptor and to discover highly selective σ ligands, two series of compounds deriving from arylpiperazines **4** were prepared (Scheme 1) and tested. In the first set, the aryl substituent was modified or eliminated (Table 1), and in the second one the piperazine ring was opened (Table 2).

Table 2. Physical Properties for **20**−**23**



compd	R	formula[a]	mp, °C	recryst solv
20	NHPh	$C_{22}H_{30}N_2O \cdot 2HCl$	195−197	MeOH/Et_2O
21	CH_2Ph	$C_{23}H_{31}NO \cdot HCl$	136−137	$CHCl_3$/Et_2O
22	Ph	$C_{22}H_{29}NO \cdot HCl$	122−126	MeOH/Et_2O
23	THN[b]	$C_{26}H_{35}NO \cdot HCl$[c]	111−113	$CHCl_3$/Et_2O

[a] Analyses for C, H, N. [b] THN = 1-(1,2,3,4-tetrahydronaphthalenyl). [c] H: calcd, 8.76; found, 9.21.

In particular the tetralin nucleus of arylpiperazines **4** underwent limited changes, since it is present in benzomorphan structures, like σ ligand (+)-pentazocine **(5)**, whereas the *N*-1-phenyl substituent was replaced by a *N*-benzyl **(11**−**13)** or reduced to a cyclohexyl **(14)**; similarly *N*-1-(2-pyridyl) derivatives were partially hy-

Table 3. Binding Affinities and Selectivities

	K_i, nM[a]					
	σ		5-HT_{1A}	PCP	K_i ratio	
compd	[^{3}H]DTG	[^{3}H]-(+)-pentazocine	[^{3}H]-5-HT[b]	[^{3}H]PCP	5-HT_{1A}/σ	PCP/σ
11	66		214	8430	3.2	128
12	139		>1430	98%[c]	>10	
13	7.0	25.7	3.6	3890	0.5	556
14	5.3	71	28.6	>92600	5.4	>17400
15	43.8	111	44.2	94%[c]	1	
16	29		414	91%[c]	14	
17	46.5	396	37.1	8330	0.8	
18	270		>1430	79%[c]	>5	
19	>877		>1430	80%[c]		
20	265		14.1	2130	0.05	8
21	152		4.4	25000	0.03	164
22	159		31.4	20400	0.2	128
23	469		22.8	100%[c]	0.05	
cimetidine	inactive					
scopolamine	inactive					
DTG	37.3					
haloperidol	4.2	10				
8-OH-DPAT			4.3			
SKF10047				370		

[a] Data had ±SEM < 5% of mean values. [b] In the presence of 10^{-6} M ketanserin as 5-HT_2 blocker. [c] Data expressed as percent inhibition at concentration of 10^{-5} M.

drogenated to 2-(3,4,5,6-tetrahydropyridyl) derivatives **(15−17)**; two compounds **(18** and **19)** were *N*-4-unsubstituted to explore the true importance of 1,4-disubstitution of piperazine, even in reduced tetralinylalkyl derivatives. Opening the piperazine ring in *N*-phenylpiperazines **4** led to the phenylaminoethyl derivative **20** and its isosteric analogue **21**, of which compound **22** was a lower homologue. Finally, compound **23** was chosen as a semirigid derivative of **21**.

Chemistry

All final compounds were synthesized by Grignard reactions starting from 1-tetralone or methoxy-1-tetralones. The respective key intermediates of compounds **11−16** and **18−23**, the 4-(3-bromo-*n*-propyl)-1,2-dihydronaphthalenes **7a−c** (Scheme 1) were obtained as previously described,[21] whereas compound **17** (Table 1) was prepared in the same way as compounds **15** and **16**, via 4-(4-chloro-*n*-butyl)-8-methoxy-1,2-dihydronaphthalene.[20] Dihydronaphthalene derivatives **11** and **12** were obtained from **7a** and **7c**, respectively, as previously reported[21] for arylpiperazines. Tetralin derivatives **13** and **14** were prepared by the same reaction from 3-(bromopropyl)tetralin **8c**[20] as were the 1-(2-pyridyl)piperazine derivatives **9a**,**b** from dihydronaphthalenes **7a**,**b**. Subsequent catalytic hydrogenation of 1-(2-pyridyl)piperazines **9a**,**b** as hydrochloride salts led to the doubly reduced tetralinyltetrahydropyridyl compounds **15** and **16**. The exact structures of these derivatives, in particular with reference to the position of the double bond, were confirmed by COSY experiments. Monosubstituted piperazines **18** and **19** were afforded by hydrolysis of *N*-acetyl derivatives **10b**,**c**, respectively, that were derived from **8b**,**c** as already reported[21] for a corresponding unsaturated compound. Finally, amines **20−23** were prepared in the usual way from **8c** with appropriate commercially available amines, except for 2-(1,2,3,4-tetrahydronaphthalen-1-yl)ethylamine[23] which was synthesized by reducing the corresponding nitrile[24] with $LiAlH_4$, as for the arylpiperazine analogue.[25]

Pharmacology

The compounds **11−23** were evaluated for in vitro activity on σ, serotonin 5-HT_{1A} and 5-HT_2, PCP (phencyclidine), and dopamine D-2 receptors by radioreceptor binding assays. All of the compounds were used in the form of hydrochloride salts. The following specific ligands and tissue sources were used. (a) σ receptors: [^{3}H]DTG (1,3-di-*o*-tolylguanidine), guinea pig brain cortex membranes. (b) σ_1 receptors: [^{3}H]-(+)-pentazocine, whole rat brain membranes. (c) Serotonin 5-HT_{1A} receptors: [^{3}H]serotonin, rat hippocampus membranes. (d) Serotonin 5-HT_2 receptors: [^{3}H]ketanserin, rat brain cortex membranes. (e) PCP receptors: [^{3}H]phencyclidine, rat hippocampus membranes. (f) Dopamine D-2 receptors: [^{3}H]spiroperidol, rat striatal membranes.

The following cold compounds were used as reference to define specific binding: (a) DTG, (b) haloperidol (see methods), (c) 8-OH-DPAT in the presence of a saturating ketanserin concentration, (d) ketanserin, (e) (+)-*N*-allylnormetazocine (SKF10,047), (f) (+)-butaclamol.

Concentrations required to inhibit 50% of radioligand specific binding (IC_{50}) were determined by two to three independent experiments with samples in triplicate and six to nine different concentrations of the drug studied. The specific binding, defined as described above in the Pharmacological Methods, represented more than 70% of the total binding. The B_{max} and K_d values used to feed the Cheng−Prusoff[26] 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.[27]

Results and Discussion

All 1,4-disubstituted piperazine derivatives **(11−17)** demonstrated moderate to high σ affinity (Table 3), their K_i reaching nanomolar range (K_i = 5.3−139 nM), superior than the DTG value for compounds **13** and **14** (K_i = 7.0 and 5.3 nM, respectively). Compared with the corresponding 1-phenylpiperazine derivatives,[20] the replacement of a phenyl with a cyclohexyl or a benzyl group in the above compounds attained enhanced σ

affinity whereas (1,2-dihydronaphthalen-4-yl)-*n*-propylpiperazines **11** and **12** failed in that respect.

No satisfactory improvements were obtained by reducing the 2-pyridyl group to a 2-(3,4,5,6-tetrahydropyridyl) ring **(15−17)**.

Additional changes in structure, such as lengthening of the intermediate chain **(17)** or methoxyl group displacement **(16)** or its disappearance **(15)** from the tetralin moiety, did not produce significant variations in affinity.

However, an additional lipophilic group was needed as substituent on the piperazine *N*-1 position, since the unsubstituted *N*-1 derivatives **18** and **19** showed low σ affinity, neither being better than the corresponding unsaturated derivative **4a** (6-OCH$_3$, Ar = H).

Opening the piperazine ring **(20−23)** represents a crucial alteration, probably because of the loss of tertiary nitrogen and of a cyclic spacer: compound **20** showed a lower affinity than the corresponding arylpiperazine derivative.

Because of a nondiscriminant behavior by [^{3}H]DTG among σ_1 and σ_2 subtypes of binding sites, an additional σ_1 assay was carried out versus [^{3}H]-(+)-pentazocine for more σ active compounds **(13** and **14)**. Results showed nearly preferential σ_2 affinity, in particular the (+)-pentazocine/DTG ratio was >10 for compound **14**.

Another aim of the study was to describe selectivity versus dopamine and serotonin receptors. All tested compounds weakly displaced [^{3}H]spiroperidol on the D-2 dopaminergic receptor, compounds **11** and **23** having a K_i of 732 and 849 nM, respectively, and the remainder **(12−22)** a K_i of more than 1850 nM while the reference compound butaclamol had K_i = 0.3 nM. When such results are considered, σ affinity may be explained on the basis of the spatial similarity between 1-phenyl-2-aminopropane, the primary pharmacophore proposed for benzomorphans by Glennon and co-workers,[28] and the side chain of compounds **13** and **14** if it is considered to be folded on itself **(6)**, like in the template of the octahydrobenzoquinolines.[13] Moreover, the absence of a 1-phenyl-2-aminoethane moiety as in haloperidol **(1)** may explain the lack of D-2 affinity.

Similar results were derived from [^{3}H]ketanserin binding on the 5-HT$_2$ serotonin receptor for all tested compounds (K_i > 2600 nM, ketanserin, K_i = 34 nM).

With regard to the [^{3}H]-5-HT binding, the tissue chosen and the definition of specific binding with 8-OH-DPAT suggest an interaction with 5-HT$_{1A}$ sites. In this assay some compounds **(11**, **13−15**, and **17**) presented a dual σ/5-HT$_{1A}$ affinity, whereas non-piperazine compounds **20**, **21**, and **23** demonstrated quite a selective 5-HT$_{1A}$ profile.

Moreover, the compounds with highest σ affinity **(13** and **14)** showed a high K_i value for [^{3}H]PCP (phencyclidine) binding, so that quite a good selectivity versus the PCP receptor was evident. That is in agreement with the receptorial model that discriminates σ binding sites from the PCP site on the basis of an additional lipophilic site.[14]

It may be concluded that for phenylpiperazines, compounds with high 5-HT$_{1A}$ affinity, a replacement of an aryl with a benzyl group, or rather, with a cyclohexyl group, leads to a probable slightly selective σ_2 ligand **(14)** or to a mixed σ/5-HT$_{1A}$ affinity compound with a D-2 and PCP selective profile **(13)**. Because of the presence of a chiral center in the tetralin ring of such compounds, further stereochemical investigations are needed on the enantiomers, in order to clarify the exact classification of these compounds as σ ligands. Finally, compound **21** is noteworthy for its good 5-HT$_{1A}$ affinity and its excellent selectivity, although its template is quite different from an arylpiperazine.

Experimental Section

Chemistry. Column chromatographies were performed with 1:30 Merck silica gel 40 (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. ^{1}H NMR spectra were recorded either on a Varian XL-200 (when indicated) or on a Bruker AM 300 WB instrument. The latter was also used for decoupling spectra and carrying out COSY experiments. 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.

Amination of (3-Bromopropyl)hydronaphthalenes. General Procedure To Obtain Compounds 9a,b, 10b,c, 11−14, and 20−23. The 1-(3-bromopropyl)-1,2,3,4-tetrahydronaphthalene derivative **(7a−c)** or the 4-(3-bromopropyl)-1,2-dihydronaphthalene derivative **(8b**,**c)** (3.5 mmol) was refluxed in DMF (20 mL) with an equimolar amount of the appropriately substituted piperazine or amine and sodium carbonate. Working up was carried out as previously described.[21] The crude residue was chromatographed on a silica gel column ($CHCl_3$/CH_3OH, 95:5, as eluent, unless otherwise indicated) and the final compounds were obtained as an almost colorless to pale yellow oil.

1-(2-Pyridyl)-4-[3-(1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperazine (9a). 9a was prepared from **7a** and 1-(2-pyridyl)piperazine and eluted with $CHCl_3$ (75% yield): ^{1}H NMR ($CDCl_3$) 1.71−1.81 (mm, 2H, $CH_2CH_2CH_2N$), 2.21−2.26 (mm, 2H, *endo* CH_2), 2.42−2.56 [mm, 8H, $CH_2CH_2CH_2N$ and $CH_2N(CH_2)_2$], 2.72 (t, 2H, J = 8.0 Hz, benzyl CH_2), 3.53 [t, 4H, J = 5.1 Hz, $(CH_2)_2N$], 5.86 (t, 1H, J = 4.5 Hz, vinyl), 6.57−8.18 (mm, 8H, aromatic); GC/MS *m*/*z* 335 (M^+ + 2, 2), 334 (M^+ + 1, 13), 333 (M^+, 52), 226 (35), 214 (40), 121 (29), 107 (100).

1-Acetyl-4-[3-(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperazine (10b). The title compound was obtained from **8b** and 1-acetylpiperazine with a 93% yield: ^{1}H NMR (200 MHz, $CDCl_3$) 1.45−1.90 [mm, 8H, $CH(CH_2CH_2)_2$], 2.10 (s, 3H, CH_3), 2.26−2.54 [mm, 6H, $CH_2N(CH_2)_2$], 2.60−2.88 (mm, 3H, benzylic), 3.38−3.72 [mm, 4H, $(CH_2)_2NCO$], 3.81 (s, 3H, OCH_3), 6.60−7.10 (mm, 3H, aromatic); GC/MS *m*/*z* 332 (M^+ + 2, 1), 331 (M^+ + 1, 6), 330 (M^+, 26), 141 (100), 128 (22), 99 (24).

1-Acetyl-4-[3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperazine (10c). 10c was prepared from **8c** and 1-acetylpiperazine with 86% yield: ^{1}H NMR (200 MHz, $CDCl_3$) 1.48−1.88 [mm, 8H, $CH(CH_2CH_2)_2$], 2.10 (s, 3H, CH_3), 2.22−2.98 [mm, 9H, $CH_2N(CH_2)_2$ and benzylic], 3.38−3.72 [mm, 4H, $(CH_2)_2NCO$], 3.82 (s, 3H, OCH_3), 6.60−7.28 (mm, 3H, aromatic); GC/MS *m*/*z* 332 (M^+ + 2, 1), 331 (M^+ + 1, 8), 330 (M^+, 33), 141 (100), 128 (22), 99 (31).

1-Benzyl-4-[3-(1,2-dihydronaphthalen-4-yl)-*n*-propyl]-piperazine (11). Starting from **7a** and 1-benzylpiperazine, **11** was obtained with 95% yield, after elution with $CHCl_3$: ^{1}H NMR ($CDCl_3$) 1.66−1.76 (mm, 2H, $CCH_2CH_2CH_2N$), 2.20−2.25 (mm, 2H, $C{=}CHCH_2$), 2.37−2.68 (mm, 12H, piperazine and $CCH_2CH_2CH_2N$), 2.71 (t, 2H, J = 8.0 Hz, benzylic), 3.49 (s, 2H, NCH_2Ph), 5.84 (t, 1H, J = 4.5 Hz, vinyl CH), 7.10−7.31 (mm, 9H, aromatic); GC/MS *m*/*z* 348 (M^+ + 2, 2), 347 (M^+ + 1, 17), 346 (M^+, 68), 255 (36), 128 (25), 91 (100).

1-Benzyl-4-[3-(1,2-dihydro-8-methoxynaphthalen-4-yl)-*n*-propyl]piperazine (12). The title compound was prepared from **7c** and 1-benzylpiperazine and eluted with $CHCl_3$ (72% yield). ^{1}H NMR ($CDCl_3$) 1.60−1.74 (mm, 2H, $CCH_2CH_2CH_2N$), 2.14−2.25 (mm, 2H, $C{=}CHCH_2$), 2.36−2.47 (mm, 12H, piperazine and $CCH_2CH_2CH_2N$), 2.71 (t, 2H, J = 8.2 Hz, benzylic), 3.51 (s, 2H, NCH_2Ph), 3.81 (s, 3H, OCH_3), 5.84 (t, 1H, J = 4.5 Hz, vinyl CH), 6.74−7.38 (mm, 8H, aromatic); GC/MS *m*/*z* 378 (M^+ + 2, 4), 377 (M^+ + 1, 27), 376 (M^+, 100), 285 (35), 189 (34), 91 (46).

1-Benzyl-4-[3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperazine (13). Compound **8c** was reacted with 1-benzylpiperazine in toluene to give **13** with 86% yield: ^{1}H NMR ($CDCl_3$) 1.46−1.81 [mm, 6H, $CH(CH_2CH_2)_2$], 2.34−2.73 (mm, 13H, piperazine, $CH_2CH_2CH_2N$ and benzylic), 3.50 (s, 2H, NCH_2Ph), 3.81 (s, 3H, OCH_3), 6.61−7.35 (mm, 8H, aromatic); GC/MS *m*/*z* 380 (M^+ + 2, 4), 379 (M^+ + 1, 28), 378 (M^+, 98), 189 (100), 161 (19), 134 (21), 91 (98).

1-Cyclohexyl-4-[3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperazine (14). 14 was prepared from **8c** and 1-cyclohexylpiperazine and eluted with $CHCl_3$ (70% yield): ^{1}H NMR ($CDCl_3$) 1.04−1.34 (mm, 6H, cyclohexyl), 1.51−2.15 [mm, 12H, cyclohexyl $NCH(CH_2)_2$ and $CH(CH_2CH_2)_2$], 2.19−2.73 (mm, 14H, piperazine, NCH, $CH_2CH_2CH_2N$ and benzylic), 3.78 (s, 3H, OCH_3), 6.61−7.24 (mm, 3H, aromatic); GC/MS *m*/*z* 372 (M^+ + 2, 2), 371 (M^+ + 1, 12), 370 (M^+, 46), 181 (100), 125 (22), 112 (27).

***N*-[3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]-*N′*-phenylethylenediamine (20). 20** was prepared from **8c** and *N*-phenylethylenediamine (70% yield): ^{1}H NMR ($CDCl_3$) 1.45−1.87 [mm, 10H, $CH(CH_2CH_2)_2$ and 2 NH, D_2O exchanged], 2.50−2.80 (mm, 5H, benzylic and $CHCH_2CH_2CH_2$-NH), 2.84−2.88 (mm, 2H, $NHCH_2CH_2NHPh$), 3.20 (mm, 2H, CH_2CH_2NHPh), 3.79 (s, 3H, OCH_3), 6.60−7.19 (mm, 8H, aromatic); GC/MS *m*/*z* 340 (M^+ + 2, 1), 339 (M^+ + 1, 5), 338 (M^+, 18), 232 (61), 201 (58), 159 (21), 107 (100).

3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-(3-phenyl-*n*-propyl)-*n*-propylamine (21). Title compound was prepared from **8c** and 3-phenyl-*n*-propylamine in the molar ratio 1:3, respectively, eluting with CH_2Cl_2/CH_3OH, 9:1 (88% yield): ^{1}H NMR ($CDCl_3$) 1.41−1.86 [mm, 11H, $CH(CH_2CH_2)_2$, $CH_2CH_2CH_2Ph$, and NH, D_2O exchanged], 2.58−2.74 (mm, 9H, benzylic and CH_2NHCH_2), 3.79 (s, 3H, OCH_3), 6.62−7.30 (mm, 8H, aromatic); GC/MS *m*/*z* 339 (M^+ + 2, 1), 338 (M^+ + 1, 9), 337 (M^+, 37), 232 (18), 201 (22), 161 (21), 148 (33), 118 (49), 44 (100).

3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-(2-phenylethyl)-*n*-propylamine (22). 22 was prepared from **8c** and 2-phenylethylamine was eluted with CH_2Cl_2/CH_3OH, 9:1 (65% yield): ^{1}H NMR ($CDCl_3$) 1.45−1.82 [mm, 9H, $CH(CH_2CH_2)_2$ and NH, D_2O exchanged], 2.49−2.89 (mm, 9H, benzylic and CH_2NHCH_2), 3.78 (s, 3H, OCH_3), 6.61−7.31 (mm, 8H, aromatic); GC/MS *m*/*z* 324 (M^+ + 1, 2), 323 (M^+, 7), 233 (17), 232 (100), 159 (21), 147 (18).

3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-[2-(1,2,3,4-tetrahydronaphthalen-1-yl)ethyl]-*n*-propylamine (23). Compound **8c** was refluxed in benzene with 2-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)ethylamine to give **23** which was chromatographed with $CHCl_3/Et_2O$, 1:1, as eluent (40% yield): ^{1}H NMR ($CDCl_3$) 1.48−1.90 [mm, 15H, $CH(CH_2CH_2)_2$, $CH_2CHCH_2CH_2$, and NH, D_2O exchanged], 2.52−2.86 (mm, 10H, benzylic and CH_2NHCH_2), 3.78 (s, 3H, OCH_3), 6.62−7.17 (mm, 7H, aromatic); GC/MS *m*/*z* 379 (M^+ + 2, 4), 378 (M^+ + 1, 29), 377 (M^+, 100), 232 (29), 201 (27), 158 (33), 130 (25).

4-[3-(1,2,3,4-Tetrahydronaphthalen-1-yl)-*n*-propyl]-1-[2-(3,4,5,6-tetrahydropyridyl)]piperazine (15). The hydrochloride salt of 1-(2-pyridyl)piperazine derivative **9a** (2.0 mmol) was dissolved in C_2H_5OH/CH_3OH, 1:1 (20 mL), and hydrogenated in the presence of a catalytic amount of 10% palladium on activated carbon. At the end of the absorption of hydrogen (24−36 h at normal pressure and room temperature), the mixture was filtered on Celite and concentrated under reduced pressure. The residue was taken up with a 1% sodium carbonate solution (20 mL) and extracted twice with $CHCl_3$. The solvent was evaporated to obtain the product **15** in quantitative yield as a colorless oil: ^{1}H NMR ($CDCl_3$) 1.50−1.88 [mm, 12H, $C{=}NCH_2CH_2CH_2$ and $CH(CH_2CH_2)_2$], 2.14 (t, 2H, $N{=}CCH_2$), 2.27−2.67 [mm, 6H, $CH_2N(CH_2)_2$], 2.71−2.74 (mm, 3H, benzylic), 3.29 [t, 4H, J = 5.1 Hz, $(CH_2)_2NC$], 3.48 (t, 2H, J = 5.7 Hz, $C{=}NCH_2$), 7.00−7.24 (mm, 4H, aromatic); GC/MS *m*/*z* 341 (M^+ + 2, 1), 340 (M^+ + 1, 2), 339 (M^+, 9), 241 (21), 228 (19), 124 (33), 111 (100).

4-[3-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]-1-[2-(3,4,5,6-tetrahydropyridyl)]piperazine (16). 16 was prepared from **9b** hydrochloride[21] as described for compound **15**: ^{1}H NMR ($CDCl_3$) 1.48−1.88 [mm, 12H, $C{=}NCH_2CH_2CH_2$ and $CH(CH_2CH_2)_2$], 2.17 [t, 2H, J = 6.6 Hz, $N{=}CCH_2$], 2.27−2.46 [mm, 6H, $CH_2N(CH_2)_2$], 2.63−2.71 (mm, 3H, benzylic), 3.29 [t, 4H, J = 5.0 Hz, $(CH_2)_2NC$], 3.48 (t, 2H, J = 5.7 Hz, $C{=}NCH_2$), 3.75 (s, 3H, OCH_3), 6.62−6.97 (mm, 3H, aromatic); GC/MS *m*/*z* 371 (M^+ + 2, 1), 370 (M^+ + 1, 8), 369 (M^+, 28), 271 (25), 258 (21), 124 (35), 111 (100).

4-[4-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-butyl]-1-[2-(3,4,5,6-tetrahydropyridyl)]piperazine (17). 17 was prepared from 4-(4-chloro-*n*-butyl)-8-methoxy-1,2-dihydronaphthalene and 1-(2-pyridyl)piperazine to give 1,2-dihydronaphthalene intermediate, which was hydrogenated as hydrochloride salt to compound **17**, as reported for **15**: ^{1}H NMR ($CDCl_3$) 1.23−1.85 [mm, 14H, $CH(CH_2)_3CH_2N$, *endo* CH_2CH_2], 2.18 [t, 2H, J = 6.6 Hz, $N{=}CCH_2$], 2.32 [t, 2H, J = 7.4 Hz, $CH_2N(CH_2)_2$], 2.40 [br t, 4H, J = 5.0 Hz, $CH_2N(CH_2)_2$], 2.61−2.74 (mm, 3H, benzylic), 3.31 [t, 4H, J = 5.0 Hz, $(CH_2)_2NC$], 3.48 (t, 2H, J = 5.7 Hz, $C{=}NCH_2$), 3.78 (s, 3H, OCH_3), 6.61−7.10 (mm, 3H, aromatic); GC/MS *m*/*z* 385 (M^+ + 2, 1), 384 (M^+ + 1, 11), 383 (M^+, 40), 161 (10), 124 (40), 111 (100).

1-[3-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperazine (18). The *N*-acetyl derivative **10b** (1.0 g, 3.0 mmol) was refluxed in 2 N HCl (45 mL) for 2 h. After cooling, the mixture was made alkaline with sodim carbonate and extracted three times with CH_2Cl_2. The organic layers were dried (Na_2SO_4), and the solvent was evaporated to produce 0.80 g (2.8 mmol, 93% overall yield) of compound **18** as a colorless oil. Hydrochloride salt was prepared as described below in the general procedure: ^{1}H NMR (200 MHz, $CDCl_3$) 1.50−1.84 [mm, 8H, $CH(CH_2CH_2)_2$], 1.95 (br s, 1H, D_2O exchanged, NH), 2.29 [mm, 6H, $CH_2N(CH_2)_2$], 2.63−2.73 (mm, 3H, benzylic), 2.89 [t, 4H, J = 4.9 Hz, $(CH_2)_2NH$], 3.76 (s, 3H, OCH_3), 6.62−6.98 (mm, 3H, aromatic); GC/MS *m*/*z* 290 (M^+ + 2, 1), 289 (M^+ + 1, 6), 288 (M^+, 29), 246 (17), 99 (100).

1-[3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperazine (19). Compound **19** was prepared from **10c** (1.0 g, 3.0 mmol) as described for **18**: pale yellow oil (0.70 g, 2.4 mmol, 81% overall yield): ^{1}H NMR (200 MHz, $CDCl_3$) 1.51−1.81 [mm, 8H, $CH(CH_2CH_2)_2$], 1.93 (br s, 1H, D_2O exchanged, NH), 2.29 [mm, 6H, $CH_2N(CH_2)_2$], 2.59−2.74 (mm, 3H, benzylic), 2.89 [t, 4H, J = 5.5 Hz, $(CH_2)_2NH$], 3.79 (s, 3H, OCH_3), 6.61−7.12 (mm, 3H, aromatic); GC/MS *m*/*z* 290 (M^+ + 2, 1), 289 (M^+ + 1, 7), 288 (M^+, 33), 246 (16), 99 (100), 86 (22).

Hydrochloride Salts. General Procedure. The hydrochloride salts were prepared by adding an HCl ethereal solution to a CH_2Cl_2 solution of amine followed by recrystallization from CH_3OH/Et_2O, unless otherwise reported. They were obtained as white to sand yellow crystals or crystalline powders; their crystallization formulas and melting points are reported in Tables 1 and 2.

Pharmacological Methods. Procedures involving use of small laboratory rodents and their care were conducted in conformity with institutional guidelines that are in compliance with National laws and policies (EEC Council Directive 86/609 and Italian Government act 116/January 27, 1992).

***σ* Binding Site Assays: [^{3}H]DTG Binding.** The method adopted was originally described by Weber et al.[29] In brief, male Guinea pigs (Charles River, Italy) were sacrificed by cervical dislocation, the brains were rapidly removed, and fresh cerebral cortices were dissected and homogenized in 10 volumes (wet wt/vol) of 0.32 M sucrose with a Brinkmann Polytron (setting 5 for 15 s). The homogenate was centrifuged at 900*g* at 4 °C; the pellet was discarded, and the supernatant was centrifuged at 48000*g* for 20 min at 4 °C. The resulting pellet was resuspended in 10 volumes (based on the original

weight) of Tris·HCl buffer (50 mM, pH 7.4) and incubated at 37 °C for 30 min. The suspension was then centrifuged at 48000*g* for 20 min at 4 °C. The pellet was either used for the assay or cryopreserved at −80 °C until assayed. The final pellet was resuspended in Tris·HCl buffer (50 mM, pH 7.4). For displacement experiments, various concentrations (10^{-10}−10^{-5} M) of the tested compound and 0.9 nM of tritiated DTG were used. The tubes were incubated for 90 min at room temperature, and the incubations were terminated by vacuum filtration through Whatman GF/B filters. The filters were washed three times with 5 mL of ice-cold Tris·HCl buffer, and the radioactivity bound to the filters was measured by liquid scintillation spectrometry. Specific [^{3}H]DTG binding was defined as the difference between binding in the absence and binding in the presence of cold DTG (1 μM).

[^{3}H]-(+)-Pentazocine Binding. The experiments were performed following the method described by Cagnotto et al.[30] with minor modifications as briefly described. Male Sprague−Dawley rats (Charles River, Italy) were sacrificed by decapitation, the brains were rapidly removed, and the whole brain minus the cerebellum and ponsmedulla oblongata was homogenized in 50 volumes (wet wt/vol) of 50 mM Tris·HCl buffer, pH 7.8, with a Brinkmann Polytron (setting 5 for 3 × 15 s). The omogenate was centrifuged at 48000*g* for 10 min at 4 °C. The pellets were washed four times by resuspension and centrifugation. The final pellets were either resuspended in the incubation buffer or stored at −80 °C until assayed. The tubes were incubated for 120 min at 25 °C, and the incubations were terminated by vacuum filtration through Whatman GF/B filters presoaked in 0.5% polyethylenimine. The filters were washed three times with 5 mL of ice-cold Tris·HCl buffer, and the radioactivity bound to the filters was measured by liquid scintillation spectrometry. Specific [^{3}H]-(+)-pentazocine binding was defined as the difference between binding in the absence and binding in the presence of 10 μM haloperidol. Although this compound is not specific, it is a potent displacer, the choice was dictated by the difficulties in obtaining cold pentazocine, due to the restrictions in Italy on laboratory use of substances of potential abuse, under narcotics bureau regulations.

PCP Receptor Binding Assay. The binding was performed as described by Zukin and Zukin[31] with minor modifications. Male Sprague−Dawley rats (Charles River, Italy) were sacrificed by decapitation, the brains were rapidly removed, and the hippocampus was dissected and frozen on dry ice. The hippocampus was then homogenized in 25 volumes (wet wt/vol) of 50 mM Tris·HCl buffer, pH 7.7, with a Brinkmann Polytron (setting 5 for 3 × 15 s). The homogenate was centrifuged at 48000*g* for 10 min at 4 °C. The pellet was washed twice by resuspension and centrifugation. The final pellet was either resuspended in the incubation buffer or stored at −80 °C until assayed. For displacement experiments, various concentrations (10^{-10}−10^{-5} M) of the tested compound and 10.0 nM of [^{3}H]phencyclidine were used. The tubes were incubated for 20 min at 37 °C, and the incubations were terminated by addition of 6 mL of ice-cold Tris·HCl buffer and immediate vacuum filtration through Whatman GF/B filters presoaked in 0.5% polyethylenimine. The filters were washed twice with 6 mL of Tris·HCl buffer, and the radioactivity bound to the filters was measured by liquid scintillation spectrometry. Specific [^{3}H]phencyclidine binding was defined as the difference between binding in the absence and binding in the presence of 10 μM (+)-*N*-allylnormetazocine (SKF 10,047).

Serotonin Receptors Binding Assays. 5-HT$_{1A}$ Binding. Hippocampi from male Sprague−Dawley rats were homogenized in 25 volumes (based on the wet weight) of ice-cold Tris·HCl buffer (50 mM, pH 7.6). The homogenate was centrifuged at 48000*g* for 15 min and then washed with the same buffer. The pellet was resuspended in 25 volumes of the same buffer and incubated at 37 °C for 15 min. After the incubation the homogenate was centrifuged at 48000*g* for 15 min. The final pellet was frozen and stored at −80 °C until assayed. For the binding assay each tube received, to achieve a final volume of 1 mL, 50 mM Tris·HCl containing 4 mM $CaCl_2$, 5.7 mM ascorbic acid, and 10 mM pargyline (pH 7.6), 10 mg of tissue suspension (0.8 mL), 20 nM [^{3}H]5-HT (0.1 mL, 27 Ci mmol^{-1}, NEN), and various concentrations (10^{-10}−10^{-5} M) of the tested compound (0.1 mL). The tubes were incubated for 15 min at 37 °C, and the incubations were terminated by vacuum filtration through Whatman GF/B filters. The filters were washed three times with 4 mL of ice-cold 50 mM Tris·HCl buffer, pH 7.4, and the radioactivity bound to the filters was measured by liquid scintillation spectrometry. 5-HT$_{1A}$ specific binding was defined as the difference between binding in the absence and binding in the presence of 10^{-5} M 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) and using 10^{-5} M ketanserin to saturate 5-HT$_2$ binding sites.

5-HT$_2$ Binding. The radioligand assay was conducted essentially as reported elsewhere (Mir et al.[32]). Cerebral cortex from male Sprague−Dawley rats (180−220 g) was homogenized in 50 volumes of ice-cold Tris·HCl buffer (50 mM, pH 7.4 at 22 °C) with a Brinkmann Polytron (setting 5 for 15 s), and the homogenate was centrifuged at 48000*g* for 10 min. The supernatant was discarded, and the pellet was resuspended and preincubated for 10 min at 37 °C. The pellet was washed twice and resuspended in 100 volumes of Tris·HCl buffer as described above. To each tube were added the following: 0.1 mL of the drug dilution (0.1 mL of water if no competing drug was added), 0.1 mL of [^{3}H]ketanserin in Tris·HCl buffer to achieve a final assay concentration of 0.35 nM, and 0.8 mL of resuspended membranes. The tubes were incubated for 15 min at 37 °C, and the incubations were terminated by vacuum filtration through Whatman GF/B filters. The filters were washed three times with 5 mL of ice-cold Tris·HCl buffer, and the radioactivity bound to the filters was measured by liquid scintillation spectrometry. Specific [^{3}H]ketanserin binding was defined as the difference between binding in the absence and binding in the presence of 1 μM cold ketanserin.

D-2 Dopaminergic Binding Assay. The binding assay for D-2 dopaminergic receptors was essentially as described by Briley and Langer[33] and successively modified by Lucchi et al.[34] Corpora striata of male Sprague−Dawley rats were homogenized in 100 volumes of Tris·HCl buffer (50 mM, pH 7.4) with a Brinkmann Polytron (setting 5 for 15 s); the homogenate was then centrifuged at 48000*g* for 10 min. The supernatant was discarded, and the pellet was washed once. The final pellet was resuspended in 250 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, and 0.1% pargyline. Each assay tube contained 0.1 mL of drug dilution, 0.1 mL of [^{3}H]-spiroperidol to achieve a final concentration of 0.25 nM, and 0.7 mL of resuspended membranes. The tubes were incubated for 15 min at 37 °C, and the incubations were terminated by vacuum filtration through Whatman GF/B filters. The filters were washed three times with 4 mL of ice-cold Tris·HCl buffer, and the radioactivity bound to the filters was measured by liquid scintillation spectrometry. Specific [^{3}H]spiroperidol binding was defined as the difference between binding in the absence and binding in the presence of butaclamol (1 μM).

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References

(1) Howard, H. R.; Seeger, T. F. Novel Antipsychotics. *Annu. Rep. Med. Chem.* **1993**, *28*, 39−47.
(2) Deutsch, S. I.; Weizman, A.; Goldman, M. E. The sigma receptor: A novel site implicated in psychosis and antipsychotic drug efficacy. *Clin. Neuropharmacol.* **1988**, *11*, 105−119.
(3) Gilligan, P. J.; Tam, S. W. Sigma receptor ligands: potential drugs for the treatment of CNS disorders? *Drug News Perspect.* **1994**, *7*, 13−18.
(4) 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.
(5) Largent, B. L.; Gundlach, A. L.; Snyder, S. H. Pharmacological and autoradiographic discrimination of sigma and phencyclidine receptor binding sites in brain with (+)-[^{3}H]SKF 10,047, (+)-[^{3}H]-3-(3-hydroxyphenyl)-*N*-(1-propyl)piperidine and [^{3}H]-1-[1-(2-thienyl) cyclohexyl]piperidine. *J. Pharmacol. Exp. Ther.* **1986**, *238*, 739−745.

(6) Quirion, R.; Chicheportiche, R.; Contreras, P. C.; Johnson, K. M.; Lodge, D.; Tam, S. W.; Woods, J. H.; Zukin, S. R. Classification and nomenclature of phencyclidine and sigma receptor sites. *Trends Neurosci.* **1987**, *10*, 444−446.
(7) De Haven-Hudkins, D. L.; Fleissner, L. C.; Ford-Rice, F. Y. Characterization of the binding of [^{3}H]-(+)-pentazocine to σ recognition sites in guinea pig brain. *Eur. J. Pharmacol.* **1992**, *227*, 371−378.
(8) 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.
(9) Booth, R. G.; Wyrick, S. D., Baldessarini, R. J.; Kula, N. S., Myers, A. M.; Mailman, R. B. A new sigma-like receptor recognized by novel phenylaminotetralins: ligand binding and functional studies. *Mol. Pharmacol.* **1993**, *44*, 1232−1239.
(10) Booth, R. G.; Wyrick, S. D. A novel brain receptor recognized by phenylaminotetralins may represent a sigma (σ_3) receptor subtype. *Med. Chem. Res.* **1994**, *4*, 225−237.
(11) Largent, B. L.; Wilkström, H.; Gundlach, A. L.; Snyder, S. H. Structural Determinants of σ Receptor Affinity. *Mol. Pharmacol.* **1987**, *32*, 772−784.
(12) Manallack, D. T.; Wong, M. G.; Costa, M.; Andrews, P. R.; Beart, P. M. Receptor Site Topographies for Phencyclidine-like and σ Drugs: Predictions from Quantitative Conformational, Electrostatic Potential, and Radioreceptor Analyses. *Mol. Pharmacol.* **1988**, *34*, 863−879.
(13) Ablordeppey, S. Y.; El-Ashmawy, M. B.; Glennon R. A. Analysis of the structure-activity relationships of sigma receptor ligands. *Med. Chem. Res.* **1991**, *1*, 425−438.
(14) 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.
(15) Glennon, R. A.; Ablordeppey, S. Y.; Ismaiel A. M.; El-Ashmawy M. B.; Fischer, J. B.; Burke Howie, K. Structural Features important for σ_1 Receptor Binding. *J. Med. Chem.* **1994**, *37*, 1214−1219.
(16) Ablordeppey, S. Y.; Issa, H.; Fischer, J. B.; Burke Howie, K. J.; Glennon R. A. Synthesis and Structure-affinity relationship studies of sigma ligands related to haloperidol. *Med. Chem. Res.* **1993**, *3*, 131−138.
(17) Jaen, J. C.; Caprathe, B. W.; Pugsley T. A.; Wise, L. D.; Akunne H. Evaluation of the Effects of the Enantiomers of Reduced Haloperidol, Azaperol and Related 4-Amino-1-arylbutanols on Dopamine and σ Receptors. *J. Med. Chem.* **1993**, *36*, 3929−3936.
(18) 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.
(19) Hudkins, R. L.; Mailman, R. B.; De Haven-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.
(20) 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.
(21) 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.
(22) Formerly unpublished results: IC$_{50}$ = 652 nM on [^{3}H]DTG for σ receptor, IC$_{50}$ > 10^4 nM on [^{3}H]prazosin for α_1 receptor.
(23) New, J. S.; Yevich, J. P. Synthesis of Substituted Ethyl- and Propylamines. *Synthesis* **1983**, *5*, 388−389.
(24) Reimann, E.; Dammertz, W. Synthese von 3-(1-Tetralyl)- und 3-[5-(5,6,7,8-Tetrahydro)-chinolyl]-alanin. (Bicyclic α-amino acids. IV: Synthesis of 3-(1-tetralinyl)- and 3-(5,6,7,8-tetrahydro-5-quinolinyl)alanine.) *Arch. Pharm.* **1983**, *316*, 297−302.
(25) Perrone, R.; Berardi, F.; Leopoldo, M.; Tortorella, V.; Lograno, M. D.; Daniele, E.; Govoni, S. 5-HT and DA receptor affinity of arylpiperazine derivatives with terminal benzamide fragment. *Farmaco* **1994**, *49*, 567−572.
(26) Cheng, Y. C.; Prusoff, W. H. Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50 per cent inhibition (I$_{50}$) of an enzymatic reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108.
(27) Munson, P. J.; Rodbard, D. Ligand: a versatile computerized approach for characterization of ligand binding systems. *Anal. Biochem.* **1980**, *107*, 220−239.
(28) Glennon, R. A.; Smith, J. D.; Ismaiel, A. M.; El-Ashmawy, M.; Battaglia, G.; Fischer, J. B. Identification and Exploitation of the σ-Opiate Pharmacophore. *J. Med. Chem.* **1991**, *34*, 1094−1098.
(29) 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.
(30) Cagnotto, A.; Bastone, A.; Mennini, T. [^{3}H](+)-Pentazocine binding to rat brain σ_1 receptors. *Eur. J. Pharmacol.* **1994**, *266*, 131−138.
(31) 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.
(32) 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.
(33) Briley, M.; Langer, S. Z. Two binding sites for [^{3}H]-spiroperidol on rat striatal membranes. *Eur. J. Pharmacol.* **1978**, *50*, 283−294.
(34) 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.

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