4-(Tetralin-1-yl)- and 4-(Naphthalen-1-yl)alkyl Derivatives of 1-Cyclohexylpiperazine as σ Receptor Ligands with Agonist σ_2 Activity

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Several 1-cyclohexylpiperazine derivatives related to σ_2 receptor ligand 1-cyclohexyl-4-[3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)propyl]piperazine (**33**, $K_i = 0.34$ nM) were synthesized and tested in radioligand binding assays, to attempt a structure−affinity relationship study. Intermediate alkyl chain length and methoxyl group position on the tetralin nucleus were varied. A few naphthalene analogues were also prepared. High affinities were found in σ_2 receptor binding for almost all compounds, some of which displayed K_i values in subnanomolar range, but low σ_2/σ_1 selectivities were found. The highest σ_2 affinities were displayed by compounds with an intermediate alkyl chain of three (**32** and **43**) or five methylenes (**39** and **46**). Quite high σ_1 receptor affinity was found for compounds with a four-methylene chain; **36** ($K_i = 0.036$ nM) and **45** ($K_i = 0.22$ nM) displaying good σ_1/σ_2 selectivity (406- and 139-fold, respectively). Moreover, homologues of compound **33** displayed also satisfactory selectivities over dopamine D_2-like, serotonin 5-HT_3, and adrenergic α_1 receptors. These compounds and a few others were tested in the inhibition of the electrically evoked contractions in guinea pig bladder and were demonstrated to be full σ_2 agonists. The activity values correlated well to the affinity scale (EC_{50} in μM range). **33** and related compounds are proposed as a class of potential antineoplastic and PET diagnosis agents.

Interest in σ (sigma) receptors has been growing during the past few years, supported by the hope of finding novel drugs for the treatment of several central nervous system diseases.[1−4] The σ receptor was originally classified as an opioid receptor subtype; then it was erroneously identified with the phencyclidine site on the NMDA receptor channel.[5] More recently, at least two σ receptor subtypes, namely σ_1 and σ_2 receptors, have been currently recognized[6] and a third one, the σ_3 receptor, has been proposed.[7] At present, σ receptors are considered to be a unique receptor family that is localized in the cell cytoplasm of brain; internal organs; and endocrine, immune, and reproductive tissues,[8−10] and they are overexpressed by several tumor cell lines.[11] Also EBP, the human sterol $\Delta^8-\Delta^7$ isomerase, is thought to belong to the σ receptor family, on the basis of its pharmacological, but not structural, homology with the mammalian σ_1 receptorial protein.[12] Moreover, EBP has been proved to bind the antitumoral drug tamoxifen.[13] Furthermore, a correlation has been pointed out between the binding site of tamoxifen-like ligands named AEBS (antiestrogen-binding site) and σ_2 receptor but not σ_1 receptor.[14] The cytotoxicity displayed by some dual AEBS/σ ligands suggested that AEBS belongs to the σ family. The most studied subtype of this family is the σ_1 receptor, which has been cloned also in human.[15] On the basis of their neuroregulative[10] and neuroprotective functions,[16] σ_1 agents could be potentially used for the treatment of depression and psychiatric disorders[17] as well as amnesia and mental improvement.[18]

In contrast, the σ_2 receptor suffers from a lower degree of knowledge, because of the lack of high-affinity, selective ligands. Nevertheless, there is evidence that σ_2 receptors are involved in Ca^{2+} release from endoplasmic reticulum and mithocondrial membrane.[19] In particular, σ_2 receptor agonists promote depletion of cytoplasm Ca^{2+} stores with subsequent cell death by caspase-independent apoptosis.[20] Recent findings suggest that apoptosis may be induced in tumor cells by regulation of the sphingolipid biosynthetic pathway.[21] Thus, σ_2 agonists could be used as novel antineoplastic agents. Moreover, they decrease the expression of a *p*-glicoprotein, which acts as an efflux pump for classical antitumor agents. In this way, σ_2 agonists may potentiate the cytotoxicity, by reversing drug resistance in tumor cell.[10] On the other hand, σ_2 receptor antagonists have been demonstrated to limit the motor extrapyramidal side effects[10] caused by typical antipsychotic agents[22] and to attenuate convulsions caused by cocaine.[23,24] Furthermore, σ_2 selective ligands can play an important role as tracers for in vivo visualization of σ_2 receptors, as biomarkers of tumor proliferation,[25] and for imaging tumor diagnosis by SPECT scintigraphy[26,27] and PET analysis.[28] Therefore, the finding of high-affinity and selective σ_2 agents is a stimulating target in the area of the current σ receptor research.

Several structures are known to bind selectively the σ_1 receptor, and a pharmacophoric model has been proposed for σ_1 ligands.[29] Unfortunately, known σ_2 receptor ligands generally display a poor selectivity profile, particularly over the σ_1 receptor. DTG (1,3-di-2-tolylguanidine, **1**; Chart 1) is the most used σ_2 radioligand, but it needs a σ_1 masking agent. Haloperidol also binds σ_1, adrenergic α_1, and dopamine D_2, D_3, and D_4

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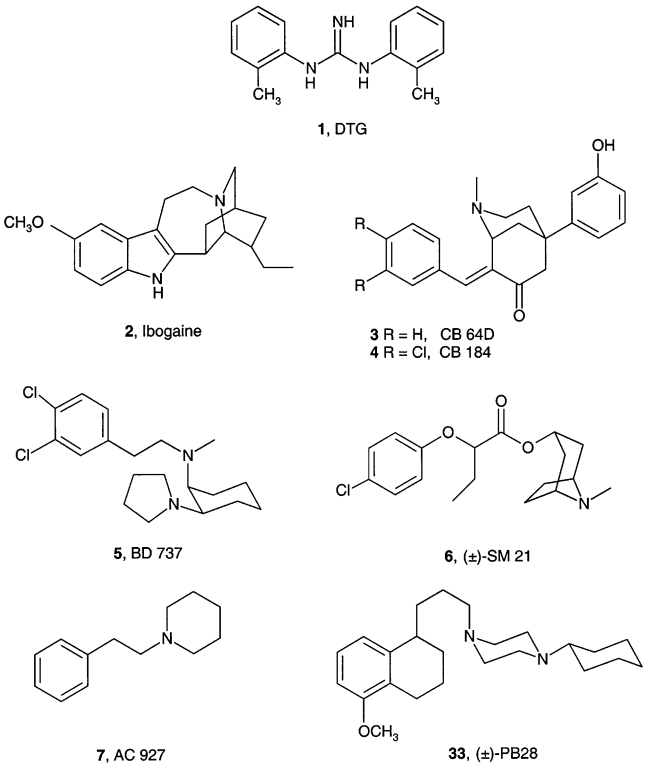
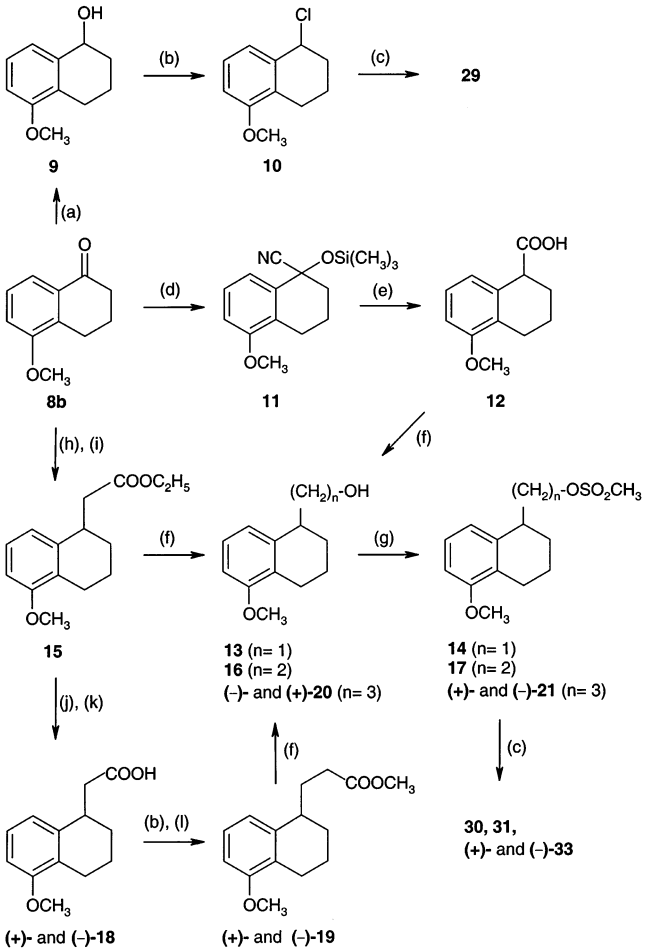
Chart 1



receptors; 2-(4-benzylpiperidino)-1-(4-hydroxyphenyl)-1-propanol (ifenprodil) binds the σ_1 receptor, the polyamine site of NMDA, and the adrenergic α_2 receptor. The short list of relatively selective σ_2 agonists[19,21] (Chart 1) includes a low-affinity natural alkaloid ibogaine (**2**);[30] the morphans (+)-(1*R*,5*R*)-(*E*)-8-benzylidene-5-(3-hydroxyphenyl)-2-methyl-2-azabiciclo[3.3.1]nonan-7-one (CB 64D, **3**) and its 3,4-dichlorobenzylidene analogue (CB 184, **4**),[31] which bind also the μ opioid receptor; and the high-affinity and σ_2/σ_1 poorly selective (−)-(1*S*,2*R*)-(*Z*)-*N*-[2-(3,4-dichlorophenyl)ethyl]-*N*-methyl-2-(1-pyrrolidinyl)cyclohexylamine (BD 737, **5**).[32] Moderate affinity is displayed by the selective σ_2 ligands (±)-3α-tropanyl 2-(4-chlorophenoxy)butyrate [(±)-SM 21, **6**],[33] and *N*-(2-phenylethyl)piperidine (AC 927, **7**),[34] which are claimed as σ_2 antagonist agents (Chart 1).[35,21] In the attempt to define a structure−affinity relationship (SAfiR) for a short series of simple phenylethyl- and phenylpropylpiperidines, it has recently been proposed that the phenylpropylamine moiety is a potential pharmacophore for selective σ_2 ligands.[36]

In our first work on σ ligands, the compound 1-cyclohexyl-4-[3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)propyl]piperazine [(±)-PB28, **33**] emerged as a purportedly new σ_2 ligand (Chart 1).[37] **33** was then chosen as a lead compound, because the presence of the cyclohexyl substituent resulted in a high σ_2 receptor affinity and a moderate selectivity.[38,39] In an effort to define a SAfiR, a series of racemic analogues of **33** retaining the 4-cyclohexylpiperazine structural feature was prepared and assayed at σ receptors in this work (Tables 1 and 2). The effects of the following changes were investigated: the intermediate alkyl chain length in the homologues of **33** (**29**−**31** and **37**, **39**, and **40**); the C-1 chirality [(+)-**33** and (−)-**33**]; and the methoxyl group position (compounds **34** and **35**), its removal (compounds **32, 36** and **38**), and its replacement by a

Scheme 1[a]



[a] (a) $NaBH_4$; (b) $SOCl_2$; (c) cyclohexylpiperazine; (d) $(CH_3)_3SiCN$, ZnI_2; (e) $SnCl_2{\cdot}2H_2O$, CH_3COOH, HCl; (f) $LiAlH_4$; (g) CH_3SO_2Cl; (h) NaH, $(C_2H_5O)_2P(O)CH_2COOC_2H_5$; (i) H_2, 10% Pd/C; (j) NaOH; (k) (+)-(*R*)- or (−)-(*S*)-1-phenylethylamine; (l) CH_2N_2, Ag^+, CH_3OH.

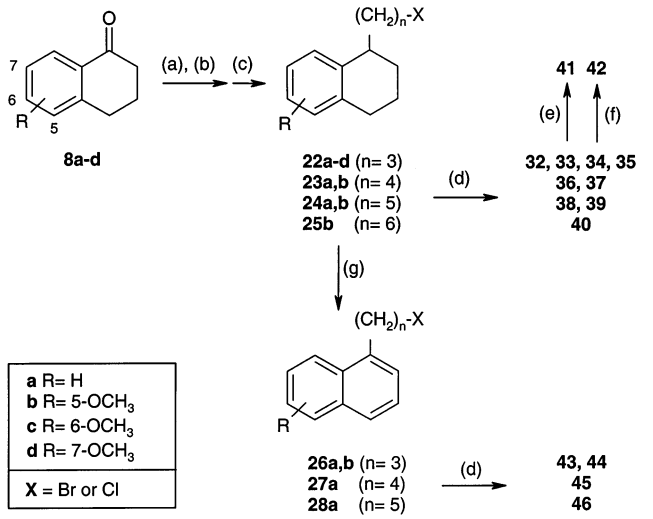
hydroxyl function (compounds **41** and **42**). Finally, the naphthalene derivatives **43**−**46** were prepared, to overcome complications due to the C-1 chirality of tetralins. The phenylethylamine **7** was also synthesized and tested as a reference compound. Moreover, we recently measured a good σ_2 agonist activity for **33** in a functional assay on guinea pig bladder.[39] This result prompted us to explore the structure−activity relationship (SAR) in addition to the SAfiR for some compounds of this series of **33** analogues.

Chemistry

The synthesis of the final compounds **29**−**31**, (+)-**33**, and (−)-**33** is depicted in Scheme 1. Related intermediate compounds were obtained starting from 5-methoxy-1-tetralone **8b**. Intermediate **10** was prepared by reducing **8b** to the corresponding alcohol **9** with $NaBH_4$ and subsequent treatment with $SOCl_2$.[40] The alkylation of cyclohexylpiperazine with compound **10** gave the final compound **29**, bearing no intermediate alkyl chain.

Compound **11** was obtained by reaction of **8b** with trimethylsilyl cyanide and ZnI_2. Intermediate **11** was then hydrolyzed, dehydrated, and reduced in a single step,[41] to afford the carboxylic acid **12**, which was subsequently reduced with $LiAlH_4$. The resulting alcohol **13** was treated with mesyl chloride[42] to give mesylate

Scheme 2[a]



[a] (a) Cyclopropylmagnesium bromide or $BrMg(CH_2)_nCl$; (b) HCl or HBr; (c) H_2, 5% Pd/C; (d) cyclohexylpiperazine; (e) 48% HBr; (f) BBr_3; (g) DDQ.

14. Its upper homologues **17**, (+)-**21**, and (−)-**21** were prepared via the ester **15**, which was obtained from **8b** and triethyl phosphonoacetate and then reduced to the corresponding alcohol **16** as previously reported.[43] **16** was converted to its methansulfonate **17** as for compound **14**. The parallel synthesis[42] of each of the enantiomers (+)- and (−)-**21** and the determination of their absolute configuration[44] have already been reported. The ester **15** was hydrolyzed and the resulting carboxylic acid was resolved in the two enantiomers in high optical purity with (+)-(*R*)- and (−)-(*S*)-1-phenylethylamine. Elongation of the alkyl chain was carried out separately on the acids (+)-**18** and (−)-**18** to obtain the esters (+)-**19** and (−)-**19**, which were reduced to the alcohols (−)-**20** and (+)-**20**, respectively. (−)-**20** and (+)-**20** were treated with mesyl chloride to afford the corresponding derivatives (+)-(*S*)-**21** and (−)-(*R*)-**21**. Mesylates **14**, **17**, (+)-(*S*)-**21** and (−)-(*R*)-**21** were reacted with cyclohexylpiperazine to give the final compounds **30**, **31**, (+)-(*S*)-**33**, and (−)-(*R*)-**33**, respectively.

The synthesis of the final compounds **32**−**46** is depicted in Scheme 2. A usual route was followed to prepare haloalkyl intermediates **22**−**25** from the corresponding methoxy-1-tetralones **8a**−**d** and the appropriate Grignard reagent, as already reported for intermediates **22a**,**b**,**d**[45] **22c**,[43] **23a**,[46] **23b**,[43] and **24a**.[42] Haloalkyl derivatives **22a**,**b**, **23a**, and **24a** underwent aromatization with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) to afford the corresponding haloalkylnaphthalenes **26a**,**b**, **27a** and **28a**.[47] Finally, all the haloalkyl compounds **22**−**28** were derivatized with cyclohexylpiperazine to give the final amine compounds **32**−**40** and **43**−**46**. The synthesis and properties of compounds **33**[37] and **35**[48] have been already described.

The phenolic derivatives **41** and **42** were obtained by demethylation of the corresponding methoxy compounds **33** and **34** with HBr and BBr_3, respectively. All of the final amine compounds were converted to the dihydrochloride salts with gaseous HCl in the usual way. Their physical properties are listed in Table 1, along with the calculated values of the logarithm of partition coefficient (ClogP).[49]

Table 1. Physical Properties

compound	formula[a]	% yield	mp,[b] °C	ClogP
29	$C_{21}H_{32}N_2O{\cdot}2HCl{\cdot}^1/_2H_2O$	80	234	5.07
30	$C_{22}H_{34}N_2O{\cdot}2HCl{\cdot}^1/_2H_2O$	75	235	4.28
31	$C_{23}H_{36}N_2O{\cdot}2HCl$	70	235	4.66
32	$C_{23}H_{36}N_2{\cdot}2HCl$	80	240	5.27
33[c]				5.19
(+)-(*S*)-**33**	$C_{24}H_{38}N_2O{\cdot}2HCl$	74	242	5.19
(−)-(*R*)-**33**	$C_{24}H_{38}N_2O{\cdot}2HCl$	74	230	5.19
34	$C_{24}H_{38}N_2O{\cdot}2HCl$	80	207	5.19
35[d]				5.19
36	$C_{24}H_{38}N_2{\cdot}2HCl$	60	241	5.80
37	$C_{25}H_{40}N_2O{\cdot}2HCl$	57	234	5.72
38	$C_{25}H_{40}N_2{\cdot}2HCl{\cdot}^1/_4H_2O$	60	243	6.32
39	$C_{26}H_{42}N_2O{\cdot}2HCl$	60	226	6.24
40	$C_{27}H_{44}N_2O{\cdot}2HCl$	62	288	6.77
41	$C_{23}H_{36}N_2O{\cdot}2HCl{\cdot}H_2O$	40	260	4.60
42	$C_{23}H_{36}N_2O{\cdot}2HCl{\cdot}H_2O$	60	222	4.60
43	$C_{23}H_{32}N_2{\cdot}2HCl$	80	245	4.85
44	$C_{24}H_{34}N_2O{\cdot}2HCl{\cdot}^1/_2H_2O$	75	248	4.77
45	$C_{24}H_{34}N_2{\cdot}2HCl{\cdot}^1/_3H_2O$	55	241	5.38
46	$C_{25}H_{36}N_2{\cdot}2HCl$	55	241	5.91

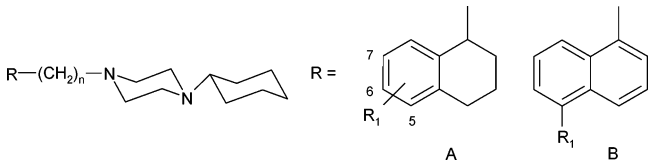
[a] Elemental analyses for C, H, N were within ±0.4% of the theoretical values for the formulas given. [b] Recrystallized from MeOH/Et_2O; all samples decomposed. [c] See ref 37. [d] See ref 48.

Biology

Receptor Binding Studies. The target compounds **29**−**46** and (+)-(*S*)- and (−)-(*R*)-**33**, as dihydrochloride salts, were evaluated for in vitro affinity at σ_1 and σ_2 receptors by radioreceptor binding assays. The following specific radioligands and tissue sources were used: (a) σ_1 receptor, (+)-[^{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-benzazocine-8-ol), guinea pig brain membranes without cerebellum; (b) σ_2 receptor, [^{3}H]DTG in the presence of 1 μM (+)-pentazocine to mask σ_1 receptors, rat liver membranes. The following compounds were used to define the specific binding, reported in parentheses: (a) (+)-pentazocine (84−89%) and (b) DTG (87−95%). Compounds **33**, **29**−**31**, **37**, **39** and **40** were also tested for in vitro affinity at dopamine D_2, adrenergic α_1, and serotonin 5-HT_3 receptors in order to evaluate the contribution of these interfering receptors in the functional biological assay in guinea pig bladder. The following radioligands and tissues were used: (c) dopamine D_2-like, [^{3}H]spiroperidol (8-[4-(4-fluorophenyl)-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro[4,5]-decan-4-one), rat striatum; (d) adrenergic α_1 receptor, [^{3}H]prazosin [1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)piperazine], rat cortex; (e) serotonin 5-HT_3 receptor, [^{3}H]granisetron (BRL 43694, 1-methyl-*N*-[(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1*H*-indazole-3-carboxamide), rat cortex. The corresponding specific bindings were defined in the presence of (c) 10 μM haloperidol, (d) 10 μM phentolamine, and (e) 1 μM ondansetron, respectively (80−90% of total binding). 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 Prism v. 3.0, GraphPad software.[50]

Isolated Organ Bath Assays. The functional biological assays were carried out in guinea pig bladder, where σ_2 agonists are known to dose dependently inhibit

Table 2. Binding Affinities and Selectivities



				$K_i \pm$ SEM (nM)			K_i ratio	
compound	R	R^1	n	σ_1	σ_2	D_2[a]	σ_1/σ_2	σ_2/σ_1
29	A	5-OCH_3	0	0.40 ± 0.02	7.90 ± 1.60	1160 ± 140		20
30	A	5-OCH_3	1	0.31 ± 0.10	16.4 ± 4.2	4260 ± 90		53
31	A	5-OCH_3	2	1.57 ± 0.41	21.1 ± 3.4	1620 ± 270		13
32	A	H	3	0.61 ± 0.08	0.68 ± 0.03			1.1
33[b]	A	5-OCH_3	3	13.6 ± 1.9	0.34 ± 0.02	604 ± 24	40	
(+)-(*S*)-**33**	A	5-OCH_3	3	2.45 ± 0.21	8.65 ± 1.96			3.5
(−)-(*R*)-**33**	A	5-OCH_3	3	5.54 ± 1.95	2.09 ± 0.39		2.7	
34	A	6-OCH_3	3	0.36 ± 0.12	5.42 ± 0.64			15
35	A	7-OCH_3	3	9.04 ± 1.02	1.22 ± 0.17	479 ± 13[c]	7.4	
36	A	H	4	0.036 ± 0.015	14.6 ± 3.7			406
37	A	5-OCH_3	4	1.54 ± 0.36	3.58 ± 0.55	3670 ± 450		2.3
38	A	H	5	1.45 ± 0.35	7.85 ± 0.49			5.4
39	A	5-OCH_3	5	1.52 ± 0.63	0.35 ± 0.09	2450 ± 380	4.3	
40	A	5-OCH_3	6	3.07 ± 0.70	103 ± 23	3480 ± 140		34
41	A	5-OH	3	5.40 ± 0.40	2.66 ± 0.66		2	
42	A	6-OH	3	0.69 ± 0.05	1.12 ± 0.17			1.6
43	B	H	3	2.16 ± 0.63	0.69 ± 0.08		3.1	
44	B	OCH_3	3	1.57 ± 0.15	9.24 ± 1.37			5.9
45	B	H	4	0.22 ± 0.03	30.5 ± 8.7			139
46	B	H	5	2.40 ± 0.47	0.57 ± 0.08		4.2	
7, AC 927[d]				309 ± 15	194 ± 23		1.6	
(+)-pentazocine				3.05 ± 0.33				
1, DTG					28.2 ± 1.4			

[a] The same compounds tested here at the dopamine D_2-like receptor were also assayed at the adrenergic α_1 and serotonergic 5-HT_3 receptor, obtaining $K_i > 7500$ and $K_i > 700$ nM, respectively, for all compounds. [b] Data already reported along with 5-HT_{1A} receptor affinity value ($K_i = 258 \pm 17$, ref 38). For an extended binding profile to the L-type Ca^{2+} channel and μ, κ, δ opioid and ORL-1 receptors, see ref 39. Therein the σ_1 affinity value ($K_i = 15.2 \pm 1.1$ nM) was determined using haloperidol to define the specific binding, and the σ_2 affinity value ($K_i = 0.80 \pm 0.04$ nM) was determined with 100 nM (+)-pentazocine as masking agent. [c] Datum already reported along with 5-HT_{1A} and α_1 receptor affinity values ($K_i = 718 \pm 64$ and $K_i > 800$ respectively, ref 48). [d] Literature data: σ_1, $K_i = 88.5 \pm 13.6$; σ_2, $K_i = 112 \pm 3.3$ (ref 36).

electrically evoked contractions.[39] The σ_2 activity found was devoid of σ_1 receptor contribution, as the σ_1 receptor was desensitized by a dressing bath solution with 5 μM (+)-pentazocine. Concentrations required to inhibit 50% of twitch in electrically bladder stimulation (EC_{50}) were determined by using six to nine different concentrations of the drug studied in two or three experiments using the Prism v. 3.0, GraphPad software.

Results and Discussion

Radioligand Binding. Almost all these 1-cyclohexylpiperazines displayed high affinities toward σ_1 (K_i = 0.036−13.6 nM) and σ_2 receptors (K_i = 0.34−30.5 nM) when tested in radioligand binding assays (Table 2). The sole piperazine **40** showed moderate σ_2 receptor affinity (K_i = 103 nM), whereas **7** moderately bound both σ subtype receptors. Low affinities were recorded for the compounds tested at dopamine D_2-like, adrenergic α_1, and serotonin 5-HT_3 receptors, so that their selectivities were suitable for avoiding interferences in the guinea pig bladder functional assay. The highest σ_1 receptor affinity (K_i = 0.036 nM) and selectivity (406-fold) were reached by compound **36**, but considerable K_i values were also obtained for compounds **45**, **30**, **34**, **29**, **32**, and **42** (K_i = 0.22−0.69 nM). Interestingly, except for compound **32**, the highest affinity σ_1 receptor ligands and the highest affinity σ_2 receptor ligands were not the same compounds. Unfortunately, no new compound exceeded **33** in σ_2 affinity (K_i = 0.34 nM) and selectivity ($K_i(\sigma_1/\sigma_2)$ = 40-fold) neither did its enantiomers. High σ_2 receptor affinity was also reached by compounds **39**, **46**, **32**, and **43** (K_i = 0.35−0.69 nM), but σ_2/σ_1 selectivity was <8-fold (7.4-fold for **35**).

In general, high values of calculated logarithm of partition coefficient (ClogP), ranging from 4.28 to 6.77 were observed for these compounds (Table 1). The highest σ subtype affinities did not appear to be linked to a maximum peak in the ClogP scale. ClogP values around 5.0 seemed to be required for σ_1 and not much higher (around 5.5) for σ_2 receptor affinity, if similar K_i values in the subnanomolar range were compared. However, no clear correlation appeared to exist between selective σ subtype binding and ClogP values.

***σ*$_1$ SAfiR.** The σ_1 receptor affinity did not seem to be much influenced by the chain length in the 5-methoxytetralin derivatives, since very high σ_1 affinities were retained by all the homologues in this series, except for compound **33** (K_i = 13.6 nM). The chainless compound **29** and compound **30** with a one-methylene chain displayed subnanomolar K_i values, whereas their homologues with a four- to six-methylene chain displayed nanomolar K_i values. Similarly, among the series of desmethoxytetralins **32**, **36**, and **38** and naphthalenes **43**, **45**, and **46**, the derivatives **36** and **45** with a four-

methylene chain displayed the lowest K_i values (0.036 and 0.22 nM). **33** showed the lowest σ_1 affinity in this series, probably because the 5-methoxyl group did not allow **33** to fit properly the σ_1 receptor, whereas the desmethoxytetralin **32** and the 6-methoxytetralin **34** fitted. The detrimental presence of 5- and 7-methoxyl substituents could be due to a steric hindrance in the tetralinpropyl series, as also supported by the tetralinbutyl compound **37** when compared to **36**. These differences became negligible for the upper homologues **38**−**40**. Chirality at C-1 of the tetralin nucleus did not significantly influence σ_1 affinity, even if lower K_i values were found for each enantiomer, the lowest being for (+)-**33**, compared to the racemic **33**. No significant difference was observed for hydroxylated derivatives **41** and **42** compared to the respective methoxylated counterparts **33** and **34**. The introduction of the naphthalene moiety (compounds **43**-**46**) did not lead to meaningful changes, with the exception of butyl derivative **45** (K_i = 0.22 nM). This latter compound displayed a lower affinity than the corresponding tetralin **36**, but presented good σ_1 selectivity (139-fold). Interestingly, these new naphthalenic σ_1 ligands were devoid of problems resulting from the presence of a stereogenic center as in 1-tetralin derivatives. Then, the long-chain tetralinalkylamine moiety was tolerated, a four-membered intermediate alkyl chain being the most suitable. Therefore, these results were consistent with the proposed phenylpentylamine pharmacophore.[51]

However, the very high σ_1 affinity found for the short-chain compounds **29**−**31** proved the importance of the *N*-cyclohexyl moiety and it cannot be likely excluded that **29**−**31** bound σ_1 receptor through the cyclohexyl-linked N atom (N-1). Moreover, when compared to the corresponding 3,3-dimethylpiperidines previously studied,[52] the 6-methoxy derivative **34** and the desmethoxytetralins **32**, **36**, and **38** demonstrated marked enhancements in σ_1 affinity. In particular, the four-methylene chain in compound **36** dramatically increased σ_1 receptor affinity and selectivity, and a significant increase also occurred for desmethoxytetralin **32**, despite its three-methylene chain. Instead, restrained σ_1 affinity improvement was noted for 5-methoxytetralins **33**, (+)-**33**, and (−)-**33**, but not for **37** and 7-methoxytetralin **35**. The fact that the *N*-cyclohexyl moiety proved to be indifferent for σ_1 receptor binding in the 5-methoxytetralin series[38] and that the previously[52] and presently examined 5-methoxytetralins suffered from the same hindrance suggested a common mode of binding by N-4 with minor *N*-cyclohexyl involvement. The σ_1-affinity enhancement, much more strengthened for desmethoxyl **36** than 5-methoxyl **37** with respect to the corresponding 3,3-dimethylpiperidines, supported the above stated hypothesis.

All these results strongly suggested the cooperative participation of the *N*-cyclohexyl moiety in addition to the phenylpentylamine scaffold,[29] to the exclusion of 5-methoxy and 7-methoxytetralinpropyl derivatives. Indeed, the *N*-cyclohexylpiperazine moiety demonstrated its ability to productively replace *N*-phenylalkyl substituents,[53] resulting in more potent σ_1 binding. According to the σ_1 receptor model proposed by Glennon,[29] these 1-cyclohexylpiperazines, and in particular compound **36**, turned out to properly bind the secondary site by a cyclohexyl ring as well as the primary hydrophobic site by a tetralin or naphthalene moiety. On the other hand, high σ_2 binding affinities were recorded at the same time, making it difficult to reach high σ_1 selectivity. Therefore, the tetralin and naphthalene moieties played an important role in driving selectivity more than σ_1 binding affinity. Even if a terminal N atom (here N-1) has been demonstrated to be unessential for σ_1 binding,[51] further investigations need to be driven in order to explore which is essential between the N-1 and cyclohexyl group in these new compounds.

***σ*$_2$ SAfiR.** In the 5-methoxytetralin series the intermediate chain length appeared to exert a significant influence on σ_2 binding affinity. The lowest K_i values were displayed by compound **33** (0.34 nM) and **39** (0.35 nM) bearing an intermediate chain of three and five methylenes, respectively, whereas **37**, with a four-methylene chain, was 1 order of magnitude less potent. The chainless compound **29** and compounds **30** and **31**, bearing a one-methylene and two-methylene chain, respectively, were moderate-affinity σ_2 ligands. Compound **40**, bearing a six-methylene chain, showed a dramatic fall (300-fold) to the lowest σ_2 affinity (K_i = 103 nM) in this series. A similar alternate-affinity trend was found for the desmethoxytetralins **32**, **36**, **38** and the naphthalenes **43**, **45**, **46**. Therefore, *n*-propyl-chain compounds **32** and **43** as well as *n*-pentyl-chain compound **46** possessed optimal intermediate chain length. As an exception, compound **38** did not display as high a σ_2 affinity as expected. Among the tetralinpropyl derivatives, the 5-methoxylated isomer **33** reached the lowest K_i value. The 5-methoxyl group seemed to contribute to an accessory binding, and probably the 6- and 7-methoxyl groups (compounds **34** and **35**) exerted a slight hydrophobic hindrance, since their absence resulted in a higher affinity (compound **32**). In fact, desmethylation of **33** to the 5-hydroxy derivative **41** was detrimental, whereas desmethylation of **34** to the 6-hydroxy **42** was beneficial. Desmethoxytetralins **32**, **36**, and **38** presented K_i values slightly higher than the corresponding 5-methoxy derivatives, supporting the advantageous influence of the 5-methoxyl group in σ_2 binding. Moreover, the 5-methoxyl group was able to increase σ_2 selectivity in **33** with respect to **32**. The lack of a methoxyl group for **33** resulted in retained high σ_2 affinity (compound **32**), whereas for **39** it resulted in more than a 20-fold falling of affinity (compound **38**). (−)-**33** displayed a K_i value 4-fold lower than (+)-**33**, but both enantiomers surprisingly displayed σ_2 binding affinity lower than **33**. Oxidation of **33** to the naphthalene **44** led to a σ_2 affinity worsening, whereas oxidation of **38** to **46** improved σ_2 affinity.

These 1-cyclohexylpiperazines substantially increased σ_2 affinity, when compared to some corresponding 3,3-dimethylpiperidines.[52] K_i values of such piperidines were in 172−318 nM range, likely because of 3,3-dimethyl group hindrance. Nevertheless, for those analogues with highest σ_2 affinity (indanes and 5-methoxyindanes), the same σ_2-affinity trend was observed in consequence of chain elongation. Compounds with a three- or a five-membered chain demonstrated comparable σ_2 affinity, higher than that of their four- and six-membered homologues. This behavior of 3,3-dimeth-

Table 3. Inhibition of Electrically Evoked Twitch in Guinea Pig Bladder

compound	$EC_{50} \pm SEM$[a], μM	compound	$EC_{50} \pm SEM$[a], μM
29	6.97 ± 0.09	**39**	4.90 ± 0.20
30	11.5 ± 0.6	**40**	25.3 ± 0.8
31	16.1 ± 0.2	**43**	1.82 ± 0.13
33	2.62 ± 0.20[b]	**46**	2.95 ± 0.17
(+)-(*S*)-**33**	1.75 ± 0.25	(+)-pentazocine	(14%)[b,c]
(−)-(*R*)-**33**	1.50 ± 0.20	**1**, DTG	6.90 ± 2.50[b]
37	9.94 ± 0.76	**7**, AC 927	(41%)[c]

[a] Mean of three independent experiments. [b] From ref 39. [c] EC_{50} not obtained, percentage inhibition at 30 μM given in parentheses.

ylpiperidines confirmed that 1-cyclohexylpiperazines bound σ_2 receptor through the N-4 atom. A quite remarkable enhancement occurred for the 5-methoxytetralin **33** (606-fold) and its desmethoxy derivative **32** (298-fold) having a three-methylene chain. **32** also displayed an enhancement in σ_1 affinity, proving to be a quite subtype-unselective σ ligand.

Therefore, the *N*-cyclohexylpiperazine moiety was demonstrated to increase σ_2 receptor affinity compared to the *N*-alkylpiperazine moiety[38] and related phenylpropylamine, phenyl-, and benzylpiperidine moieties,[53] supporting the presence of a binding site corresponding to the secondary site of σ_1 receptor model.[29] This similarity resulted in a low selectivity, as high σ_1 and σ_2 affinities proved for compound **32**. σ_1 Affinity was high anyway, so just a poor selectivity was obtained only in compounds **33**, **35**, **39**, **46**, and **43** with a three- or five-methylene chain. In addition to the *N*-cyclohexylpiperazine moiety, a 5-methoxytetralin or a naphthalene nucleus linked to a suitable-length chain was required to bind σ_2 receptor with high affinity, as compound **40** proved. Although binding through N-1 atom cannot be quite excluded, the most valid explication can be that all the members of this 1-cyclohexylpiperazine series bind the σ_2 receptor through N-4 linked to a phenylbutyl moiety. Such a spacer can be found in haloperidol, ibogaine (**2**), and as a folded chain in compounds **3** and **4**. The high σ_2 affinity shown by *n*-pentyl-chain compounds could be due to a chain conformational adaptation that was favored by the 5-methoxyl group as in **39**. This could take place considering that five-methylene chains are highly flexible and that the bicyclic nucleus orientates as in a compound with a three-methylene chain.

Functional Assay and σ_2 SAR. The six homologues and the two enantiomers of the lead compound **33** were chosen for functional activity evaluation in the in vitro isolated organ. The naphthalene derivatives **43** and **46** were also tested as high-affinity σ_2 ligands. Results given by **33**, (+)-pentazocine, and DTG were obtained in a previous work, where **33** (EC_{50} = 2.62 μM) proved to be a σ_2 agonist in such an assay.[39] All newly tested compounds dose dependently inhibited electrically evoked contractions in guinea pig bladder (EC_{50} = 1.50−25.3 μM), demonstrating a rank order similar to that of the corresponding σ_2 affinity values (Table 3). In particular, all tested subnanomolar-affinity σ_2 ligands displayed micromolar activity. Then the same SAfiR considerations and ClogP correlation previously discussed are valid for this SAR, particularly for homologues of **33**. Independently of C-1 chirality, the highest activities were obtained for (+)- and (−)-**33** (EC_{50} = 1.75 and 1.50 μM, respectively), as well as for the naphthalene derivatives **43** and **46** (EC_{50} = 1.82 and 2.95 μM, respectively). Interestingly, *n*-pentyl-chain σ_2 agonists **39** and **46** showed a little lower activity than *n*-propyl-chain agonists **33** and **43**, respectively, although their affinities were comparable. However, not great differences in activity were observed depending on chain length. This corroborates the above stated hypothesis on the basic role played by the *N*-cyclohexylpiperazine moiety in binding the σ_2 receptor. Only the low-affinity σ_2 ligand **40** showed a moderate activity (EC_{50} = 25.3 μM), whereas **7** was not able to inhibit the twitch. Thus, this latter compound can be likely claimed as a σ_2 antagonist in this assay. The experiments were carried out by previous σ_1 receptor desensitization. However, since twitch inhibition mediated by the σ_2 receptor was demonstrated to be rather unaffected by the σ_1 receptor,[39] this class of high-affinity σ_2 receptor ligands proved to be full agonists independent of their selectivity over σ_1 receptor.

Conclusions

Several high-affinity σ_2 receptor ligands with low selectivity over the σ_1 receptor were found in this class of 1-cyclohexylpiperazines. The best results were obtained when the intermediate chain length was of three or five methylenes. Nevertheless, high-affinity σ_1 receptor ligands were present in this class. Among the other compounds, the tetralin **36** and the naphthalene **45**, both bearing a four-methylene intermediate chain, emerged as highly σ_1-selective ligands. The presence of the piperazine ring implemented the N-binding opportunities, resulting in more complicated SAfiR studies, but the presence of an aromatic bicycle, sometimes methoxy-substituted, led to a better selectivity. The structural features for binding the σ_2 receptor seem to be very similar to those for the σ_1 receptor, differing only in chain length and orientation of the terminal moiety. The existence of a secondary σ_2 binding site was supported by the high affinity of these 1-cyclohexylpiperazines and was corroborated by the low affinity and antagonist activity of **7**. In a next work in progress, we are exploring whether the piperazine N atom or the cyclohexyl ring is essential for σ_2 receptor binding in this class of ligands. **33** was confirmed as the most selective σ_2 receptor ligand, but high activity was displayed by naphthalene derivatives too. On the basis of the functional assay, **33** and related 1-cyclohexylpiperazines are claimed as novel σ_2 agonist agents. Moreover, the σ_2 agonist activity of **33** was confirmed by our preliminary results, displaying its high cytotoxic and antiproliferative effects both in human SK-N-SH neuroblastoma cells and rat C6 glioma cells (from the Interlab Cell Line Collection).[54] Therefore, **33** and related σ_2 agonists are proposed as a class of potential antineoplastic and PET diagnosis agents.

Experimental Section

Chemistry. Column chromatography was performed with 1:30 ICN silica gel 60 Å (63−200 μm) as the stationary phase. Melting points were determined in open capillaries on a Gallenkamp electrothermal apparatus. Elemental analyses (C, H, N) were performed on a Eurovector Euro EA 3000 analyzer for the dihydrochloride salts of the target compounds; the analytical results were within ±0.4% of the theoretical values.

^{1}H NMR spectra were recorded either on a Varian EM-390 at 90 MHz where indicated (TMS as internal standard) or on a Mercury Varian 300 MHz instrument, with $CDCl_3$ as solvent. All values are reported in ppm (δ). Recording of mass spectra was done on an Agilent 6890-5973 MSD gas chromatograph/mass spectrometer; only significant *m/z* peaks, with their percentage of relative intensity in parentheses, are reported. 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 Acros and were used without any further purification.

1-Chloro-5-methoxy-1,2,3,4-tetrahydronaphthalene (10). Thionyl chloride (1.3 mL, 18.5 mmol) was added to a stirred solution of 1-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene (**9**) (2.16 g, 12.3 mmol) in toluene (30 mL) at 15 °C. After 30 min, the mixture was heated at 55−60 °C for 2 h and then cooled. H_2O and ice were added, and the organic phase was extracted, dried, and evaporated under reduced pressure. The title compound was achieved as a pale yellow oil in 85% yield after purification by refrigerated column chromatography with petroleum ether/AcOEt 8:2 as eluent: ^{1}H NMR δ 1.82−2.36 [m, 4H, $(CH_2)_2$], 2.41−2.70 (m, 2H, benzyl CH_2), 3.78 (s, 3H, OCH_3), 5.30 (t, 1H, J = 7 Hz, CHCl), 6.66−7.25 (m, 3H, aromatic); GC−MS *m/z* 198 (M^+ + 2, 10), 197 (M^+ + 1, 4), 196 (M^+, 29), 161 (100), 115 (26).

5-Methoxy-1,2,3,4-tetrahydronaphthalene-1-methyl methanesulfonate (14): pale yellow oil; ^{1}H NMR δ 1.60−2.10 [m, 4H, $CH(CH_2)_2$], 2.60−2.80 (m, 2H, benzyl CH_2), 2.90−3.10 (s+m, 4H, OSO_2CH_3 and benzyl CH), 3.81 (s, 3H, OCH_3), 4.20−4.40 (m, 2H, $CH_2OSO_2CH_3$), 6.70−7.30 (m, 3H, aromatic); GC−MS *m/z* 272 (M^+ + 2, 3), 271 (M^+ + 1, 8), 270 (M^+, 48), 175 (31), 174 (100), 161 (87), 159 (64), 146 (39), 115 (25).

5-Methoxy-1,2,3,4-tetrahydronaphthalene-1-ethyl methanesulfonate (17): pale yellow oil; ^{1}H NMR (90 MHz) δ 1.50−2.31 [m, 6H, $(CH_2)_2CHCH_2$], 2.60−2.90 (m, 2H, benzyl CH_2), 2.90−3.10 (s+m, 4H, OSO_2CH_3 and benzyl CH), 3.81 (s, 3H, OCH_3), 4.20−4.40 (m, 2H, CH_2OSO_2), 6.60−7.30 (m, 3H, aromatic); GC−MS *m/z* 286 (M^+ + 2, 6), 285 (M^+ + 1, 14), 284 (M^+, 80), 188 (34), 161 (100), 160 (98), 157 (43), 129 (23), 115 (28).

1-(5-Chloropentyl)-5-methoxy-1,2,3,4-tetrahydronaphthalene (24b) was a yellow oil which was eluted with petroleum ether/CH_2Cl_2 9:1 in 50% yield: ^{1}H NMR (90 MHz) δ 1.34−2.08 [m, 12H, $(CH_2)_2CH(CH_2)_4$], 2.58−2.98 (m, 3H, benzylic), 3.60 (t, 2H, J = 6 Hz, CH_2Cl), 3.90 (s, 3H, OCH_3), 6.68−7.28 (m, 3H, aromatic); GC−MS *m/z* 268 (M^+ + 2, 7), 267 (M^+ + 1, 4), 266 (M^+, 20), 162 (36), 161 (100).

1-(6-Chlorohexyl)-5-methoxy-1,2,3,4-tetrahydronaphthalene (25b) was obtained as a yellow oil in 48% yield eluting with petroleum ether/CH_2Cl_2 9:1: ^{1}H NMR (90 MHz) δ 1.18−2.10 [m, 14H, $(CH_2)_2CH(CH_2)_5$], 2.50−3.00 (m, 3H, benzylic), 3.60 (t, 2H, J = 6 Hz, CH_2Cl), 3.78 (s, 3H, OCH_3), 6.68−7.28 (m, 3H, aromatic); GC−MS *m/z* 282 (M^+ + 2, 16), 280 (M^+, 42), 162 (63), 161 (100).

Aromatization to 1-(ω-Haloalkyl)naphthalenes (26−28). General Procedure. In a standard reaction, one of the haloalkyltetralins **22a**,**b** **23a**, or **24a** (1.0 mmol) was refluxed with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (2.5 mmol) in toluene (50 mL) with stirring. After 4 h the mixture was cooled, the excess of DDQ was filtered off, and toluene was evaporated under reduced pressure. The residue was purified by column chromatography (petroleum ether/CH_2Cl_2 8:2 as eluent) to afford the desired compound. All title compounds were colorless or pale yellow oils.

1-(3-Bromopropyl)naphthalene (26a): 70% yield; ^{1}H NMR (90 MHz) δ 1.70−2.00 (m, 2H, CH_2CH_2Br), 3.23 (t, 2H, J = 7.5 Hz, benzylic), 3.43 (t, 2H, J = 7.5 Hz, CH_2Br), 7.31−8.10 (m, 7H, aromatic); GC−MS *m/z* 250 (M^+ + 2, 33), 249 (M^+ + 1, 5), 248 (M^+, 33), 141 (100), 115 (21).

1-(3-Bromopropyl)-5-methoxynaphthalene (26b): 65% yield; ^{1}H NMR (90 MHz) δ 2.05−2.45 (m, 2H, CH_2CH_2Br), 3.20 (t, 2H, J = 7.5 Hz, benzylic), 3.45 (t, 2H, J = 7.5 Hz, CH_2Br), 3.88 (s, 3H, OCH_3), 7.10−8.00 (m, 6H, aromatic); GC−MS *m/z* 280 (M^+ + 2, 43), 279 (M^+ + 1, 7), 278 (M^+, 43), 199 (57), 171 (100), 158 (22), 128 (28).

1-(4-Chlorobutyl)naphthalene (27a): 40% yield; ^{1}H NMR (90 MHz) δ 1.70−2.01 [m, 4H, $(CH_2)_2CH_2Cl$], 2.80−3.21 (m, 2H, benzylic), 3.30−3.70 (m, 2H, CH_2Cl), 6.70−8.20 (m, 7H, aromatic); GC−MS *m/z* 220 (M^+ + 2, 11), 219 (M^+ + 1, 5), 218 (M^+, 33), 141 (100).

1-(5-Chloropentyl)naphthalene (28a): 48% yield; ^{1}H NMR (90 MHz) δ 1.65−2.05 [m, 6H, $(CH_2)_3CH_2Cl$], 2.80−3.20 (m, 2H, benzylic), 3.30−3.70 (m, 2H, CH_2Cl), 6.70−8.20 (m, 7H, aromatic); GC−MS *m/z* 234 (M^+ + 2, 19), 233 (M^+ + 1, 9), 232 (M^+, 49), 142 (33), 141 (100), 115 (24).

4-Cyclohexyl-1-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)piperazine (29). 1-Chloro-5-methoxy-1,2,3,4-tetrahydronaphthalene (**10**) (0.19 g, 1.0 mmol) was refluxed with an equimolar amount of cyclohexylpiperazine, Na_2CO_3 (0.21 g, 2.0 mmol), and NaI (0.015 g, 0.1 mmol) in acetonitrile (150 mL) for 24 h. After cooling, the mixture was evaporated to dryness and H_2O was added to the residue. The aqueous phase was then extracted twice with ethyl acetate, and the collected organic phases were dried over Na_2SO_4 and evaporated under reduced pressure. The crude residue was chromatographed eluting with CH_2Cl_2/MeOH 9:1 to afford compound **29** as a colorless oil: ^{1}H NMR δ 1.14−1.30 and 1.60−1.75 [m, 10H, cyclohexyl $(CH_2)_5$], 1.78−2.10 [m, 4H, $CH(CH_2)_2$], 2.18−2.35 (m, 1H, NCH), 2.40−2.82 (m, 10H, piperazine and benzyl CH_2), 3.70−3.88 (s+m, 4H, OCH_3 and benzyl CH), 6.69−7.36 (m, 3H, aromatic); GC−MS *m/z* 329 (M^+ + 1, 13), 328 (M^+, 50), 202 (32), 201 (23), 189 (50), 188 (34), 176 (33), 168 (21), 167 (100), 161 (67), 160 (73), 125 (22). Anal. ($C_{21}H_{32}N_2O\cdot 2HCl\cdot {}^1/_2H_2O$) C, H, N.

General Procedure To Obtain Final 4-(1-Cyclohexyl)-piperazine Derivatives (30−40, 43−46). In a typical reaction, a representative intermediate (1.0 mmol) among 1-(ω-haloalkyl)tetrahydronaphthalenes **22**−**25**, 1-(ω-haloalkyl)-naphthalenes **26**−**28**, or mesylalkyl derivatives **14**, **17**, and **21** was stirred and refluxed overnight with cyclohexylpiperazine (0.20 g, 1.2 mmol) and Na_2CO_3 (0.127 g, 1.2 mmol) in acetonitrile. The mixture was worked up as reported for compound **29**. Purification by column chromatography (CH_2Cl_2/MeOH 95:5 as eluent, unless otherwise indicated) afforded final compounds as colorless or pale yellow oils.

1-Cyclohexyl-4-[(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]piperazine (30): eluted with CH_2Cl_2/MeOH 9:1; ^{1}H NMR δ 1.02−1.32 and 1.60−1.88 [m, 10H, cyclohexyl $(CH_2)_5$], 1.89−1.99 [m, 4H, $CH(CH_2)_2$], 2.20−2.38 (m, 1H, CHN), 2.41−2.78 (m, 12H, piperazine, $CHCH_2N$ and benzyl CH_2), 2.86−3.01 (m, 1H, benzyl CH), 3.78 (s, 3H, OCH_3), 6.61−7.10 (m, 3H, aromatic); GC−MS *m/z* 342 (M^+, 0.7), 182 (22), 181 (100). Anal. ($C_{22}H_{34}N_2O\cdot 2HCl\cdot {}^1/_2H_2O$) C, H, N.

1-Cyclohexyl-4-[(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)ethyl]piperazine (31) eluted with CH_2Cl_2/MeOH 9:1:^{1}H NMR δ 1.02−1.32 (m, 5H, cyclohexylic), 1.61−1.96 [m, 11H, 5 cyclohexylic and $(CH_2)_2CHCH_2CH_2N$], 2.15−2.30 (m, 1H, NCH), 2.35−2.72 (m, 12H, piperazine, $CHCH_2CH_2N$ and benzyl CH_2), 2.75−2.86 (m, 1H, benzyl CH), 3.78 (s, 3H, OCH_3), 6.60−7.10 (m, 3H, aromatic); GC−MS *m/z* 357 (M^+ + 1, 17), 356 (M^+, 61), 195 (100), 182 (23), 181 (80). Anal. ($C_{23}H_{36}N_2O\cdot$ 2HCl) C, H, N.

1-Cyclohexyl-4-[3-(1,2,3,4-tetrahydronaphthalen-1-yl)-propyl]piperazine (32): ^{1}H NMR δ 1.05−1.40 [m, 6H, cyclohexyl $(CH_2)_3$], 1.50−1.70 (m, 6H, $CHCH_2CH_2CH_2$ and cyclohexyl 2 CH_2), 1.74−2.00 [m, 6H, $CH_2CH(CH_2)_2$], 2.21−2.45 (m, 3H, CHN and CH_2N), 2.52−2.80 (m, 11H, piperazine, benzylic), 7.00−7.15 (m, 4H, aromatic); GC−MS *m/z* 342 (M^+ + 2, 1), 341 (M^+ + 1, 11), 340 (M^+, 42), 297 (26), 230 (23), 181 (100). Anal. ($C_{23}H_{36}N_2\cdot 2HCl$) C, H, N.

(+)-(*S*)- and (−)-(*R*)-1-Cyclohexyl-4-[3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)propyl]piperazine [(+)-(*S*)-33, (−)-(*R*)-33]: ^{1}H NMR and GC−MS data are the same reported for racemic compound **33**;[37] $[\alpha]_D$ = + 4.7 ° (*c* = 1.0, MeOH); $[\alpha]_D$ = − 4.7 ° (*c* = 1.0, MeOH). Anal. ($C_{24}H_{38}N_2O\cdot 2HCl$) C, H, N.

1-Cyclohexyl-4-[3-(6-methoxy-1,2,3,4-tetrahydronaph-

thalen-1-yl)propyl]piperazine (34): ^{1}H NMR δ 1.18−1.40 [m, 6H, cyclohexyl $(CH_2)_3$], 1.51−1.72 (m, 6H, $CHCH_2CH_2CH_2$ and cyclohexyl 2 CH_2), 1.78−1.88 [m, 4H, endo $(CH_2)_2$], 1.90−2.00 (m, 2H, eso $CHCH_2$), 2.33−2.48 (m, 3H, CHN and CH_2N), 2.52−2.88 (m, 11H, piperazine and benzylic), 3.78 (s, 3H, OCH_3), 6.58−7.10 (m, 3H, aromatic); GC−MS *m/z* 372 (M^+ + 2, 3), 371 (M^+ + 1, 23), 370 (M^+, 79), 327 (23), 260 (31), 181 (100), 161 (21), 112 (23). Anal. ($C_{24}H_{38}N_2O$·2HCl) C, H, N.

1-Cyclohexyl-4-[4-(1,2,3,4-tetrahydronaphthalen-1-yl)-butyl]piperazine (36): ^{1}H NMR δ 1.00−1.31 [m, 6H, cyclohexyl $(CH_2)_3$], 1.38−2.10 [m, 14H, $(CH_2)_2CH(CH_2)_3$ and cyclohexyl 2 CH_2], 2.11−2.80 (m, 14H, piperazine, benzylic, CHN and CH_2N), 6.80−7.21 (m, 4H, aromatic); GC−MS *m/z* 356 (M^+ + 2, 2), 355 (M^+ + 1, 18), 354 (M^+, 61), 311 (41), 244 (24), 181 (100), 111 (21). Anal. ($C_{24}H_{38}N_2$·2HCl) C, H, N.

1-Cyclohexyl-4-[4-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)butyl]piperazine (37): ^{1}H NMR δ 1.01−1.21 [m, 6H, cyclohexyl $(CH_2)_3$], 1.23−1.95 [m, 14H, $(CH_2)_2CH(CH_2)_3$ and cyclohexyl 2 CH_2], 2.21−2.30 (m, 1H, CHN), 2.33 (t, 2H, J = 8 Hz, CH_2N), 2.38−2.75 (m, 11H, piperazine and benzylic), 3.78 (s, 3H, OCH_3), 6.65−7.05 (m, 3H, aromatic); GC−MS *m/z* 386 (M^+ + 2, 2), 385 (M^+ + 1, 18), 384 (M^+, 61), 341 (31), 274 (31), 181 (100). Anal. ($C_{25}H_{40}N_2O$·2HCl) C, H, N.

1-Cyclohexyl-4-[5-(1,2,3,4-tetrahydronaphthalen-1-yl)-pentyl]piperazine (38): ^{1}H NMR δ 1.00−1.89 [m, 20H, cyclohexyl $(CH_2)_5$ and $(CH_2)_2CHCH_2(CH_2)_3$], 1.90−2.10 (m, 2H, $CHCH_2$), 2.41 (t, 2H, J = 8 Hz, CH_2N), 2.50−3.01 (m, 12H, piperazine, benzylic and CHN), 6.90−7.15 (m, 4H, aromatic); GC−MS *m/z* 370 (M^+ + 2, 1), 369 (M^+ + 1, 18), 368 (M^+, 61), 325 (35), 237 (44), 181 (100), 131 (25), 111 (24). Anal. ($C_{25}H_{40}N_2$·2HCl·$^1/_4$$H_2O$) C, H, N.

1-Cyclohexyl-4-[5-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)pentyl]piperazine (39): ^{1}H NMR δ 1.12−1.85 [m, 22H, cyclohexyl $(CH_2)_5$ and $(CH_2)_2CH(CH_2)_4$], 2.21−2.39 (m, 3H, CHN and CH_2N), 2.41−2.75 (m, 11H, piperazine and benzylic), 3.78 (s, 3H, OCH_3), 6.65−7.05 (m, 3H, aromatic); GC−MS *m/z* 400 (M^+ + 2, 3), 399 (M^+ + 1, 23), 398 (M^+, 75), 355 (32), 237 (54), 181 (100). Anal. ($C_{26}H_{42}N_2O$·2HCl) C, H, N.

1-Cyclohexyl-4-[6-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)hexyl]piperazine (40): ^{1}H NMR δ 1.11−2.15 [m, 24H, cyclohexyl $(CH_2)_5$ and $(CH_2)_2CH(CH_2)_5$], 2.23−2.38 (m, 3H, CH_2N and CHN), 2.41−2.82 (m, 11H, piperazine and benzylic), 3.80 (s, 3H, OCH_3), 6.65−7.11 (m, 3H, aromatic); GC−MS *m/z* 414 (M^+ + 2, 3), 413 (M^++ 1, 17), 412 (M^+, 58), 369 (27), 251 (30), 181 (100). Anal. ($C_{27}H_{44}N_2O$·2HCl) C, H, N.

1-Cyclohexyl-4-[3-(5-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)propyl]piperazine (41). Compound **33** (0.37 g, 1.0 mmol) was refluxed in 48% HBr (25 mL) for 12 h under stirring. After cooling, the mixture was washed with 6N KOH and extracted three times with CH_2Cl_2. The collected organic layers were dried and evaporated under reduced pressure to afford an oily residue which was purified by chromatography to afford the target compound: ^{1}H NMR δ 1.05−1.28 [m, 6H, cyclohexyl $(CH_2)_3$], 1.45−1.95 [m, 12H, $(CH_2)_2CH(CH_2)_2$ and cyclohexyl 2 CH_2], 2.21−2.48 (m, 3H, benzylic), 2.50−2.80 (m, 11H, piperazine, CH_2N and CHN), 4.80−5.40 (broad s, 1H, OH, D_2O exchanged), 6.60−7.05 (m, 3H, aromatic); GC−MS *m/z* 357 (M^+ + 1, 13), 356 (M^+, 51), 313 (26), 181 (100). Anal. ($C_{23}H_{36}N_2O$·2HCl·H_2O) C, H, N.

1-Cyclohexyl-4-[3-(6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)propyl]piperazine (42). A solution of BBr_3 (0.12 mL, 1.3 mmol) in anhydrous CH_2Cl_2 was added dropwise to a solution of compound **34** (0.50 g, 1.35 mmol) in the same solvent cooled at −78 °C under N_2. The mixture was stirred overnight and allowed to reach room temperature. After cooling, the reaction was quenched with H_2O and then with a solution of K_2CO_3. The resulting mixture was extracted with CH_2Cl_2. The organic layers were collected, dried over Na_2SO_4, and then concentrated to dryness to afford a brown yellow solid. Purification by crystallization from diethyl ether gave the title compound: ^{1}H NMR δ 1.18−1.38 [m, 6H, cyclohexyl $(CH_2)_3$], 1.54−2.00 [m, 12H, cyclohexyl 2 CH_2, $(CH_2)_2CH(CH_2)_2$], 2.20−2.80 (m, 14H, benzylic, piperazine, CHN and CH_2N), 4.90−5.40 (broad s, 1H, OH, D_2O exchanged), 6.50−7.05 (m, 3H, aromatic); GC−MS *m/z* 357 (M^+ + 1, 18), 356 (M^+, 68), 313 (27), 246 (25), 181 (100), 112 (22). Anal. ($C_{23}H_{36}N_2O$·2HCl·H_2O) C, H, N.

1-Cyclohexyl-4-[3-(naphthalen-1-yl)propyl]piperazine (43): ^{1}H NMR δ 1.08−1.98 [m, 12H, cyclohexyl $(CH_2)_5$ and $CH_2CH_2CH_2$], 2.20−2.32 (m, 1H, CHN), 2.46 (t, 2H, J = 7.5 Hz, CH_2N), 2.50−2.71 (m, 8H, piperazine), 3.07 (t, 2H, J = 7.5 Hz, benzylic), 7.30−8.11 (m, 7H, aromatic); GC−MS *m/z* 338 (M^+ + 2, 3), 337 (M^+ + 1, 24), 336 (M^+, 88), 293 (37), 195 (100), 181 (77), 141 (40), 111 (22). Anal. ($C_{23}H_{32}N_2$·2HCl) C, H, N.

1-Cyclohexyl-4-[3-(5-methoxynaphthalen-1-yl)propyl]-piperazine (44): ^{1}H NMR δ 1.00−1.40 [m, 8H, cyclohexyl $(CH_2)_4$], 1.80−2.10 (m, 4H, cyclohexyl CH_2 and $CH_2CH_2CH_2$), 2.20−2.41 (m, 1H, CHN), 2.45 (t, 2H, J = 7.5 Hz, CH_2N), 2.51−2.80 (m, 8H, piperazine), 3.03 (t, 2H, J = 7.6 Hz, benzylic), 3.97 (s, 3H, OCH_3), 6.81−8.15 (m, 6H, aromatic); GC−MS *m/z* 368 (M^+ + 2, 4), 367 (M^+ + 1, 27), 366 (M^+, 100), 195 (87), 181 (60), 171 (28). Anal. ($C_{24}H_{34}N_2O$·2HCl·$^1/_2$$H_2O$) C, H, N.

1-Cyclohexyl-4-[4-(naphthalen-1-yl)butyl]piperazine (45): ^{1}H NMR δ 1.01−2.00 [m, 14H, cyclohexyl $(CH_2)_5$ and $CH_2(CH_2)_2CH_2N$], 2.08−2.15 (m, 1H, CHN), 2.38 (t, 2H, J = 7.5 Hz, CH_2N), 2.40−2.71 (m, 8H, piperazine), 3.08 (t, 2H, J = 7 Hz, benzylic), 7.20−8.10 (m, 7H, aromatic); GC−MS *m/z* 352 (M^+ + 2, 3), 351 (M^+ + 1, 23), 350 (M^+, 79), 307 (45), 240 (24), 181 (100), 141 (37). Anal. ($C_{24}H_{34}N_2$·2HCl·$^1/_3$$H_2O$) C, H, N.

1-Cyclohexyl-4-[5-(naphthalen-1-yl)pentyl]piperazine (46): ^{1}H NMR δ 1.00−2.10 [m, 16H, cyclohexyl $(CH_2)_5$ and $CH_2(CH_2)_3CH_2N$], 2.38 (t, 2H, J = 7.5 Hz, CH_2N) 2.50−2.85 (m, 9H, piperazine and CHN), 3.08 (t, 2H, J = 7 Hz, benzyl CH_2), 7.20−8.10 (m, 7H, aromatic); GC−MS *m/z* 366 (M^+ + 2, 3), 365 (M^+ + 1, 21), 364 (M^+, 74), 321 (41), 254 (21), 181 (100), 141 (35), 111 (22). Anal. ($C_{25}H_{36}N_2$·2HCl) C, H, N.

Radioligand Binding Assays. All the procedures followed to perform the binding assays were previously described. The σ_1 and σ_2 receptor binding determinations were carried out according to the method of Matsumoto et al.[55] Dopamine D_2-like receptor binding was carried out according to the work of Briley and Langer.[56] Adrenergic α_1 receptor binding was carried out according to the method of Glossmann and Hornung,[57] and serotonin 5-HT_3 receptors binding was determined according to Hall et al.[58] The radioligands (+)-[^{3}H]pentazocine, [^{3}H]DTG, [^{3}H]spiroperidol, [^{3}H]prazosin, and [^{3}H]granisetron were purchased from Perkin-Elmer Life Sciences (Zaventem, Belgium). Male Dunkin guinea pigs and Wistar Hannover rats (250−300 g) were from Harlan, Italy.

Guinea Pig Bladder Functional Assay. The activity evaluation of σ_2 receptor ligands in electrically stimulated guinea pig bladder was performed according to the work of Colabufo et al.[39] Guinea pigs (200−300 g) were killed by decapitation and their bladders were removed and quickly washed in Krebs solution (118 mM NaCl, 4.75 mM KCl, 2.45 mM $CaCl_2$, 1.71 mM $MgCl_2$, 25.0 mM $NaHCO_3$, 0.93 mM KH_2PO_4, 11.0 mM glucose). The detrusor strip section was placed in 20 mL organ baths containing Krebs solution bubbled with 5% CO_2 and 95% O_2 gas at 37.0 °C. The strips were placed under a 1 g load, and contractility was measured using Fort 10 transducers original WPI, connected to a PowerLab 4/20 ADInstrument recorder. To the Krebs solution were added 1 μM atropine to mask muscarinic receptors; 1 μM indomethacin, as a cyclooxygenase inhibitor; and 1 μM ketanserin to mask 5-HT_2 serotonin receptors. The desensitization of σ_1 receptors was obtained by equilibrating the tissue for 75 min with 5 μM (+)-pentazocine and replacing every 15 min the dressed solution. Using Krebs solution without (+)-pentazocine, the tissue was washed and then stimulated at 2.0 Hz using a Panlab Digital Stimulator Letica 12106 at 150 mA, 1 ms in duration with longitudinally platinum electrodes positioned in the organ bath. Following a 90−120 min equilibrium period, during which the Krebs solution was changed several times, test compounds were administrated in a cumulative dose,

allowing a minimum of 3 min before additional compound was added to the bath. All compounds were tested in a dose ranging from 1.0 to 50 μM. The effectiveness of a given compound to inhibit electrically induced contraction was measured as the percent change from baseline conditions. The concentration of a given test compound to produce a half-maximal inhibition of the electrically induced contraction (EC_{50}) was determined with a nonlinear curve fit program (Prism v. 3.0, GraphPad) using the mean response of at least three separate trials as the given response for a single concentration.

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