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Synthesis and pharmacological evaluation of potent and enantioselective σ_1 and σ_2 ligands☆

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Abstract

In a previous study we found that substitutions of the (+)-*cis*-*N*-normetazocine nucleus of (+)-**MPCB** with 1-adamantanamine provide the compound (±)-**10** with high affinity and selectivity for σ receptors. Starting with this result we have synthesized a new series of eight 1-phenyl-2-cyclopropylmethylamines structurally related to (±)-**10**, and binding affinities, with respect to σ_1, σ_2, opioid and dopaminergic D_2 receptors, have been reported. All compounds showed a negligible opioid and dopaminergic affinity and high selectivity for σ receptors. Modifications on the amino moiety and methylcarboxyester group of **10** provide compounds with different σ_1 and σ_2 binding affinity and selectivity. Moreover, we have also synthesized the respective enantiomers of componds (±)-**10** and (±)-**18** in order to evaluate the enantioselectivity for σ_1 and σ_2 receptors. The binding data showed that carboxymethylester on the cyclopropane ring was more critical for enantioselectivity than the hydroxymethylenic group. In fact, the (−)-**10** enantiomer showed a preference for σ_1 whereas (+)-**10** showed a preference for σ_2. © 2001 Elsevier Science S.A. All rights reserved.

Keywords: Sigma receptors; Ligands; Stereoselectivity

1. Introduction

The existence of sigma (σ) receptors was first reported in 1976 by Martin et al. to explain the behavioural psychotomimetic effects induced by some opioid ligands such as (±)-*N*-allyl-normetazocine (SKF 10,047) and related derivatives. This hypothesis prompted intense studies in order to clarify the pharmacological role of these receptors [1]. Binding studies soon showed that (±)-SKF 10,047 binds different types of receptors. In particular, (−)-SKF 10,047 binds to μ and κ opioid receptors, whereas (+)-SKF 10,047 binds to the phencyclidine site (PCP) on the NMDA receptor channel and also to a site designed as a σ receptor. The ineffective antagonism of naloxone for the effects induced by σ ligands confirmed that the σ site is not an opioid receptor.

The binding affinity of (+)-SKF 10,047 for PCP sites and the similarity of in vivo pharmacological effects produced by phencyclidine and (+)-SKF 10,047 led to the consideration that sigma receptors and PCP sites were identical. However, subsequent studies provided evidence that these binding sites represent typical protein entities different from other known neurotransmitter or hormone receptor families.

At present, pharmacological data support the identification of at least two subtypes of binding sites, namely σ_1 and σ_2 [2]. Typical neuroleptics such as haloperidol, DTG [1,3-di-2-(tolyl)guanidine], laevo-isomers of normetazocine derivatives showed high to moderate affinity for both subtypes with no selectivity between the two sites. Dextro-isomers of normetazocine derivatives such as (+)-pentazocine and (+)-SKF 10,047 exhibit high affinity and selectivity for σ_1 receptors.

Sigma receptors are widely distributed in many areas of the central nervous system [3] and in peripheral tissues [4] such as liver, gastrointestinal tract, kidney, placenta and in endocrine related structures.

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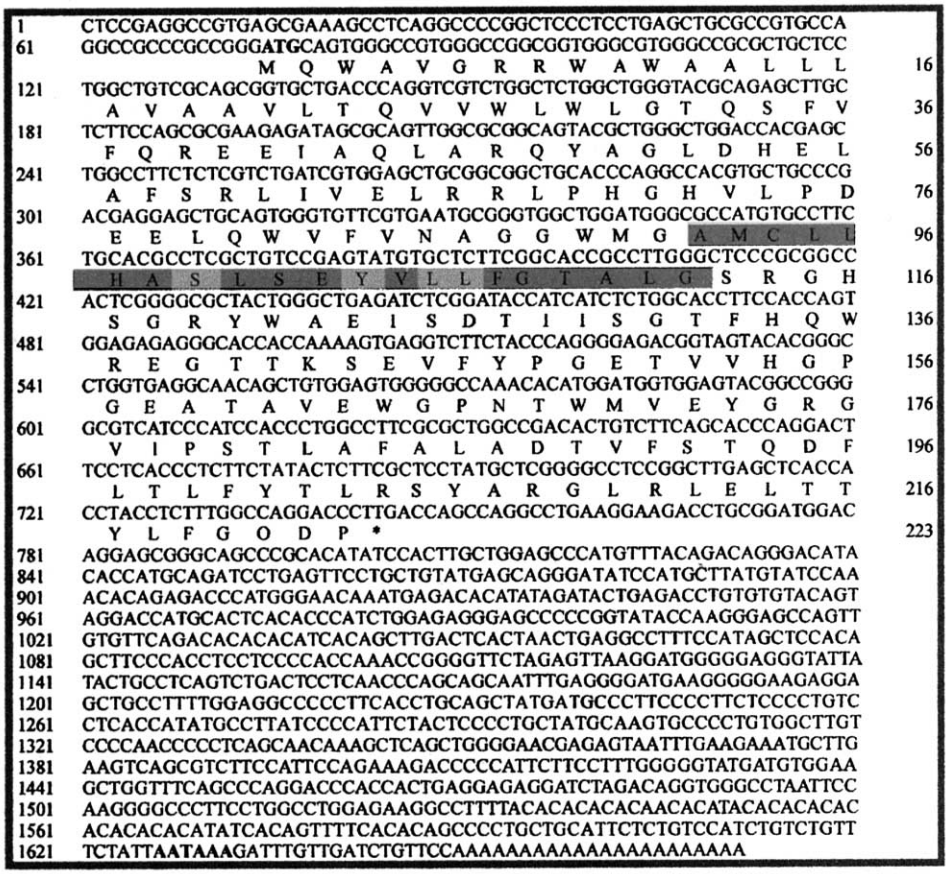


Fig. 1. Human σ_1 receptor cDNA and amino acid sequence. The numbers on the left refer to nucleotide sequence; numbers on the right refer to amino acid sequence. The shaded sequence shows the putative transmembrane domain with amino acid residues critical for ligand binding.

The physiological and biochemical role of the σ_1 and σ_2 receptors has not been clearly determined. However, significant advances have been reported in order to explain many pharmacological actions of these binding sites. In particular, σ_1 receptors seem to modulate the biosynthesis and release of the neurotransmitters dopamine, acetylcholine and glutamate [5]. Moreover, it seems they are involved in antiamnesic and neuroprotective activity [6] and also in modulation of opioid analgesia [7].

Recently, the cloning of guinea pig liver [8] and human placental [9] σ_1 receptors (Fig. 1), has provided evidence that this protein is not related to any mammalian protein but it has homology to the fungal $\Delta^{8,7}$ sterol-isomerase. These data with the significant affinity of progesterone for σ_1 receptors suggest a functional role in neurosteroid metabolism [10].

The protein corresponding to the σ_2 receptors has not been cloned, but recent reports suggest that they are distinct proteins with typical cellular localization [11]. The ability of many σ_2 ligands to induce anomalies in motor control and high density of σ_2 receptors in central nervous areas such as cerebellum, substantia nigra and red nucleus suggest that σ_2 receptors could be responsible for irreversible disorder such as tardive dyskinesia induced by neuroleptic drugs [12]. Moreover, the extremely high expression in rodent and human tumor cell lines of σ_2 receptors and apoptotic cytotoxicity of many σ_2 ligands provide evidence that it could be involved in cell viability and proliferation [13].

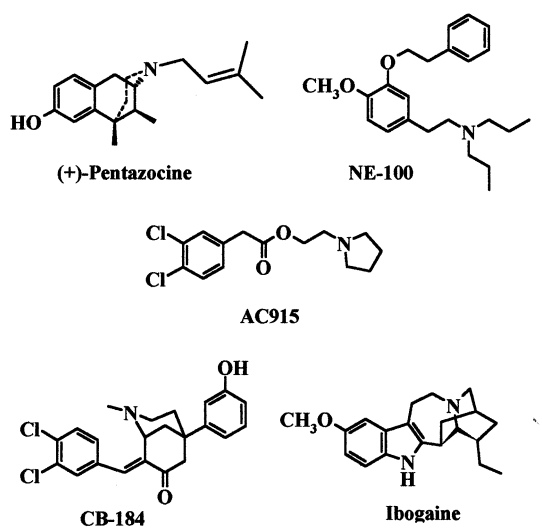
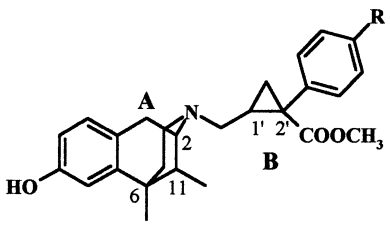


Fig. 2. σ_1 and σ_2 selective compounds.

Table 1
Binding affinity to σ_1, κ, μ and δ receptors (K_i, nM)



Compound	A	B	R	σ_1	κ	μ	δ
(+)-MPCB	2*S*,6*S*,11*S*	(±)-*cis*	H	75	>1000	>1000	>1000
(+)-MPCB-a	2*S*,6*S*,11*S*	1′*R*,2′*S*	H	66.7	>1000	>1000	>1000
(+)-MPCB-b	2*S*,6*S*,11*S*	1′*S*,2′*R*	H	1381	>1000	>1000	>1000
(−)-MPCB	2*R*,6*R*,11*R*	1′*R*,2′*S*	H	>1000	240	>25000	>25000
(−)-MPCB	2*R*,6*R*,11*R*	1′*S*,2′*S*	H	>1000	2640	>25000	>25000
(+)-CCB	2*S*,6*S*,11*S*	(±)-*cis*	Cl	430	>1000	>1000	>1000
(−)-CCB	2*R*,6*R*,11*R*	(±)-*cis*	Cl	1050	0.41	>25000	>25000

Several classes of compounds such as normetazocines, phenylalkylamines, guanidines, U50,488 derivatives and others bind σ receptors [14]. However, few ligands are selective for σ_1 or σ_2 subtypes with respect to other receptor systems.

At the moment, a few selective σ_1 receptor ligands are available, i.e. (+)-pentazocine, NE-100 [15] and AC915 (Fig. 2) [16]. However, for σ_2 receptors no selective ligand is available. In particular, compounds such as CB-184 [17], and Ibogaine [18], showed high selectivity for σ_2 with respect to σ_1 but they also possess high activity for opioid and NMDA receptors, respectively.

Therefore, the discovery of selective agonists or antagonists of σ_1 and σ_2 receptors may provide potential drugs for psychosis, neuroprotection, motor control, cancer treatment and diagnosis with non-invasive tumor imaging agents.

Recently, in our laboratory we have synthesized a series of 2′-methoxycarbonyl-2′-phenyl-1′-cyclopropylmethyl normetazocine derivatives [19–21] (Table 1) in order to obtain compounds with selectivity for κ-opioid and σ receptors respectively.

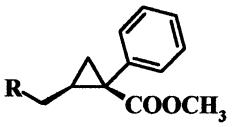
The first data obtained confirm that the stereochemistry of the *cis*-*N*-normetazocine nucleus was pivotal to obtaining selective compounds for opiod or σ receptors. Moreover, the stereochemistry of substituents on the cyclopropane ring modulates the affinity and selectivity with respect to κ opioid and σ receptors.

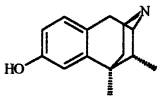
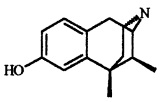
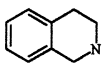
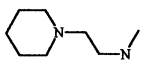
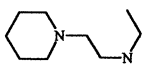
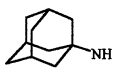
Therefore, considering the good σ_1 binding affinity of (+)-**MPCB** and the 2′-methoxycarbonyl-2′-phenyl-1′-cyclopropylmethyl moiety as a useful framework in order to obtain further selective insights into the requirements of σ_1 and σ_2 receptor subtypes, we synthesized a series of 1-methoxycarbonyl-1-phenyl-2-cyclopropylmethylamines [22] in which the *cis*-*N*-normetazocine nucleus has been substituted with 1,2,3,4-tetrahydroisoquinoline (Table 2), *N*,*N*-dicyclohexylamine, *N*-methyl-*N*(2-piperidin-1-ylethyl)amine, *N*-ethyl-*N*-(2-piperidin-1-ylethyl)amine and 1-adamantanamine.

The binding affinity reported confirms the high structural tolerability of σ_1 receptors and shows that the substitution of the *cis*-*N*-normetazocine nucleus of **MPCB** with 1,2,3,4-tetrahydroisoquinoline, *N*,*N*-dicyclohexyl, *N*-methyl-*N*-(2-piperidin-1-ylethyl)amine and *N*-ethyl-*N*-(2-piperidin-1-ylethyl)amine provided compounds with similar binding affinities. A notable increase in binding affinity was obtained by substituting the (+)-*cis*-*N*-normetazocine moiety of (+)-**MPCB** with 1-adamantanamine. This compound displayed a 20 fold increase in affinity for the σ_1 subtypes as compared to (+)-**MPCB**. The modification of (+)-**MPCB** with these amines provides an increase of σ_2 affinity and a negligible affinity for opioid receptors.

These results prompted us to synthesize new 1-phenyl-2-cyclopropylmethylamine derivatives structurally related to the compound methyl (±)-*cis*-2-[(1-adamantilammino)methyl]-1-phenyl-cyclopropanecarboxylate (Fig. 3). We have also synthesized the enantiomers of racemic compounds with higher affinity and selectivity for σ receptors in order to evaluate the importance of stereochemistry with respect to σ_1 and σ_2 subtype receptors.

Table 2
Binding affinities $K_i \pm$ SEM (nM)



Compd.	R	σ_1[a]	σ_2[b]	opioid[c]
(–)-MPCB		>10 000	>10 000	378 ± 12
(+)-MPCB		66.7 ± 2.2	3980 ± 42	>10 000
(±)		61 ± 4.2	141.7 ± 12.7	5000<IC_{50}<10 000
(±)	$(C_6H_{11})_2N$	93.2 ± 3.5	204.3 ± 31.5	>10 000
(±)		61.4 ± 1.7	32.9 ± 0.8	5000<IC_{50}<10 000
(±)		34 ± 0.8	80.8 ± 1.5	>10 000
(±)-10		3 ± 0.4	23 ± 6.4	5000<IC_{50}<10 000
DTG		59 ± 1.3	31.7 ± 1.7	ND[d]

[a] [^{3}H](+)Pentazocine; [b] [^{3}H]DTG or 1,3-Di(2-tolyl)guanidine/(+)-NANM; [c] [^{3}H]Naloxone; [d] Not detected.

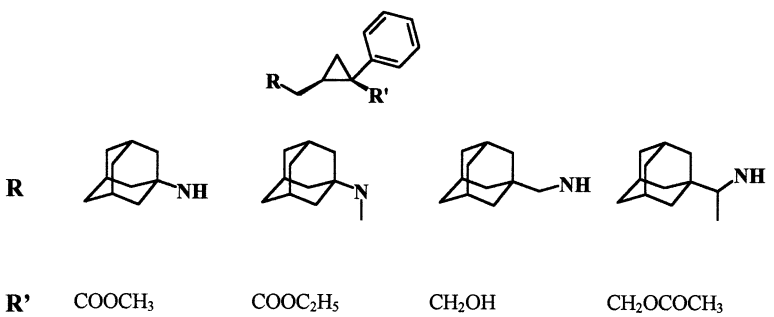


Fig. 3. Compounds **10**–**18**.

2. Chemistry

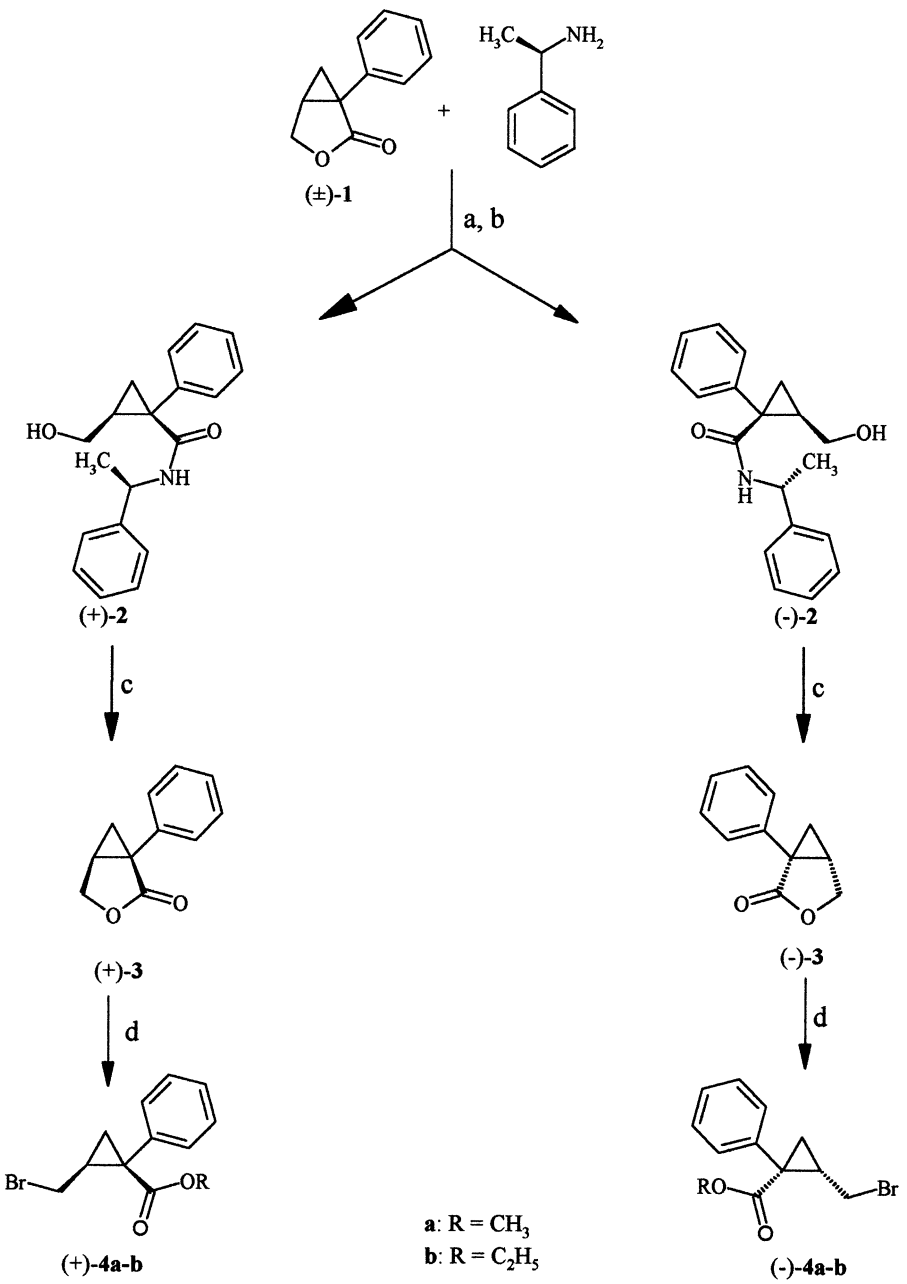
Enantiomers **3** were obtained by treatment of lactone (±)-**1** [22] with *R*-(+)-α-methylbenzylamine, followed by flash chromatographic separation of the two diastereoisomeric amides **2** (Scheme 1). The subsequent hydrolysis of **2** with 1 N H_2SO_4 in dioxane/H_2O gave the expected enantiomers (+)- and (−)-**3**. Configurational assignment of **3** was based on previously reported ^{1}H NOE NMR data and molecular mechanic calculations on the individual diastereoisomeric acid derivatives of **MPCB** [19–21]. In addition, compound **4**

was synthesized in racemic form by treatment of lactone **1** with HBr/CH_3COOH (33%) and subsequent esterification of the bromoacid derivatives with $SOCl_2$ and methanol or ethanol/3 N HCl.

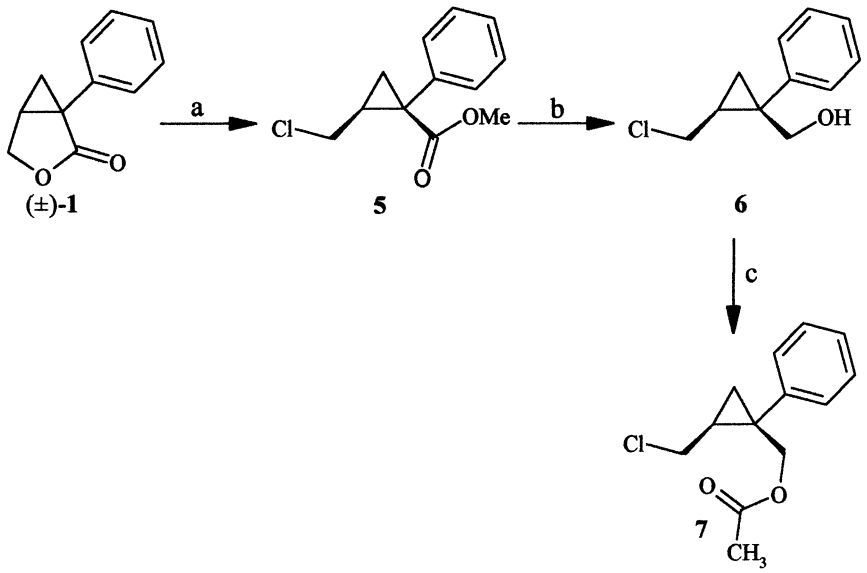
Compound **7** was obtained in a good yield by treatment of chloromethyl ester **5** [22] with alane-*N*,*N*-dimethylethylamine complex (Scheme 2). The same reaction with the bromomethyl and ethyl ester derivatives **4** provided low yields of the expected compound.

The simple acylation of **6** with commercially available acetyl chloride in anhydrous THF provided compound **10**.

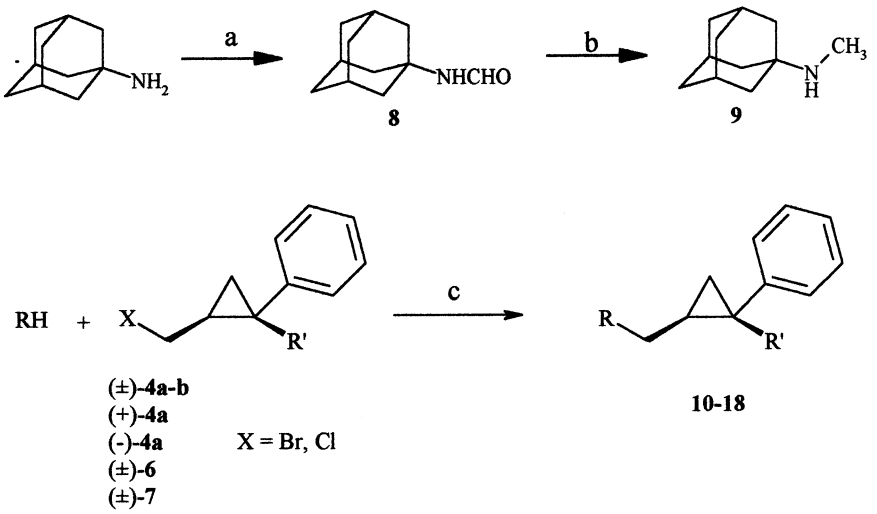
The formylation of 1-adamantanamine (Scheme 3) with ethyl formate and subsequent reduction of amide **8** with $LiAlH_4$ produced the *N*-methyladamantan-1-amine **9**. Nucleophilic substitution of the cyclopropylphenyl derivatives with the appropriate amine provided the final compounds (Fig. 3).



Scheme 1. (a) (*R*)-(+)-α-methylbenzylamine, dry toluene, 2-hydroxypiridine, reflux 24 h; (b) flash chromatography; (c) 1 N H_2SO_4 in dioxane/H_2O, 85°C, 16 h; (d) HBr/CH_3COOH (33%), 80°C, 2 h; benzene, $SOCl_2$, ROH/3 N HCl, 5 h.



Scheme 2. (a) benzene, $ZnCl_2$, $SOCl_2$, CH_3OH/3 N HCl, 5 h; (b) THF, $C_2H_5N(CH_3)_2{\cdot}AlH_3$, 0°C; 2.5 h; (c) THF, acetyl chloride, 4-dimethylaminopyridine, r.t., 20 h.



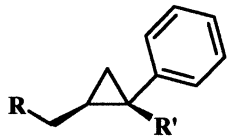
Scheme 3. (a) EtOCHO, reflux 12 h; (b) THF, $LiAlH_4$, 40°C, 5 h; (c) DMF, $NaHCO_3$, 70°C, 8 h.

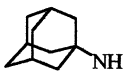
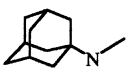
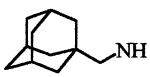
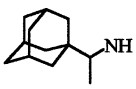
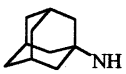
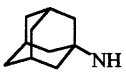
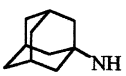
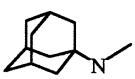
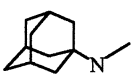
3. Results and discussion

As reported previously, several classes of ligands for different pharmacological systems interact with σ receptors. The purpose of this work is to obtain selective σ_1 and σ_2 ligands with respect to the other receptor systems. For this reason, all compounds (**10**–**18**) were tested for binding affinity at σ_1, σ_2, and also at opioid and dopaminergic D_2 receptors (Tables 3 and 4). Binding data for σ_1 receptors were obtained using [^{3}H]-(+)-pentazocine [22] as a specific ligand and brain membranes of guinea pig. Moreover, for specific σ_2 binding data we used [^{3}H]-DTG in the presence of (+)-NANM (*N*-allyl-normetazocine 100 nM) as a masking agent for σ_1 receptor sites. The membranes used for σ_2 receptors were the same as used for σ_1 receptors in order to delineate a different pattern of affinity in the same tissues and animal species. The total opioid and dopaminergic D_2 receptor binding assays were performed respectively, as reported in Ref. [22].

The binding affinities for compounds **11**–**13** (Table 3) showed that the substitution of the 1-adamantanamine nucleus (**10**) with *N*-methyladamantanamine (**11**), 1-adamantylmethanamine (**12**) and (1-adamantyl)ethylamino (**13**) was detrimental for σ_1 but not for σ_2 receptors.

Table 3
Binding affinity to σ_1, σ_2, opioid and dopaminergic (D_2) receptors (K_i, nM)



Compd.	R	R′	σ_1[a]	σ_2[b]	Opioid[c]	D_2[d]
(±)-**10**		$COOCH_3$	3	23	>5000	>10 000
(±)-**11**		$COOCH_3$	12	11.2	>10 000	>10 000
(±)-**12**		$COOCH_3$	11.5	12.7	>10 000	>5000
(±)-**13**		$COOCH_3$	99.3	45.2	>10 000	>10 000
(±)-**14**		$COOC_2H_5$	1.29	35.8	>10 000	>10 000
(±)-**15**		CH_2OH	5.3	2.22	>10 000	>10 000
(±)-**16**		CH_2OCOCH_3	0.6	4.05	>10 000	>10 000
(±)-**17**		CH_2OCOCH_3	2.5	7.4	>10 000	>10 000
(±)-**18**		CH_2OH	1.2	6.6	>10 000	>10 000

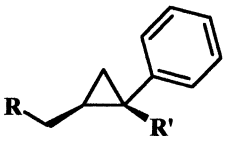
[a] [^{3}H](+)Pentazocine; [b] [^{3}H]DTG or 1,3-Di(2-tolyl)guanidine/(+)-NANM; [c] [^{3}H]Naloxone; [d] [^{3}H]Spiroperidol.

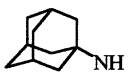
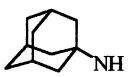
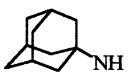
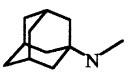
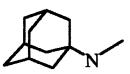
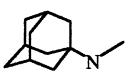
The compound **14** with carboxyethylester substituent on the cyclopropane ring has the best selectivity of the series with an improved affinity for σ_1 and reduced affinity for σ_2 receptors. In contrast, reduction of the carboxyester group to the hydroxymethylenic substituent (**15**) provides a reverse preference with respect to the starting **10**. In addition, modification of the carboxymethylester group to the reverse-type ester **16** gave a notable improvement with a σ_1 subnamolar affinity (0.6 nM).

Considering these first data, it seems that the carboxymethylester group and an increase of lipophilic bulk on this position of the cyclopropane ring were opportune for σ_1 binding sites but not for σ_2.

The derivatives **17** with both modifications on amino moiety and carboxymethyl group substantially confirmed the trend of parent compounds **11** and **16**. However, **18** seems to show a small exception to this result because no preference for the σ_2 receptor has been obtained with respect to **11** and **15**.

Table 4
Binding affinity to σ_1, σ_2, opioid and dopaminergic (D_2) receptors (K_i, nM)



Compd.	R	R′	σ_1[a]	σ_2[b]	Opioid[c]	D_2[d]
(±)-**10**		$COOCH_3$	3	23	>5000	>10 000
(+)-**10**		$COOCH_3$	234	39.4	>10 000	>10 000
(−)-**10**		$COOCH_3$	4	35	>10 000	>10 000
(±)-**18**		CH_2OH	1.2	6.6	>10 000	>10 000
(+)-**18**		CH_2OH	1.26	2.75	>10 000	>10 000
(−)-**18**		CH_2OH	1.39	2.69	>10 000	>10 000

[a] [^{3}H](+)Pentazocine; [b] [^{3}H]DTG or 1,3-Di(2-tolyl)guanidine/(+)-NANM; [c] [^{3}H]Naloxone; [d] [^{3}H]Spiroperidol.

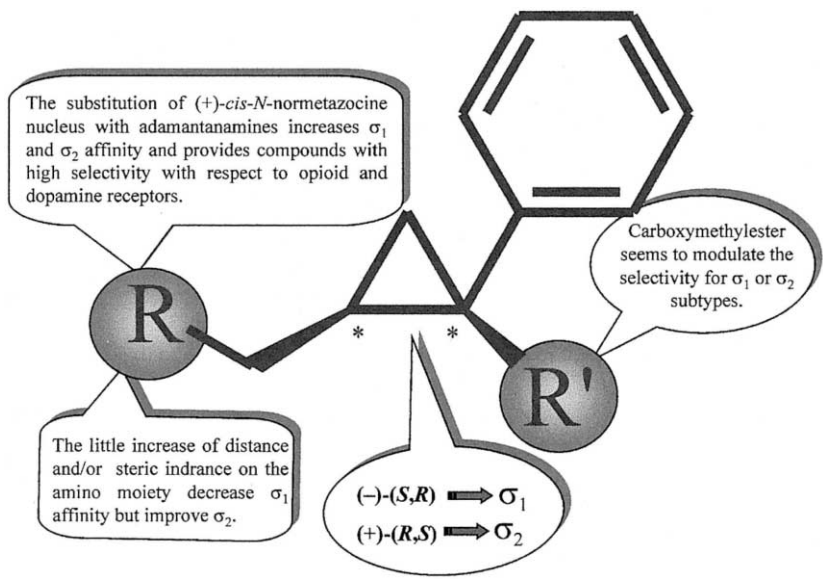


Fig. 4. Graphical representation of SAR data.

Considering the stereoselectivity of 1-phenyl-2-cyclopropylmethylamine derivatives, at present only enantiomers of compounds **10** and **18** (Table 4) have been synthesized and evaluated. It seems that the carboxymethyl group is more critical for enantioselectivity compared to the hydroxymehtyl substituent on the cyclopropane ring. In fact, only the enantiomers of **10** showed a reverse preference for σ_1 and σ_2 receptors, with (−)-(*S*,*R*)-**10** enantiomer for σ_1 and (+)-(*R*,*S*)-**10** for σ_2 respectively.

As reported in Tables 3 and 4 all compounds showed a negligible or no affinity for opioid and dopaminergic D_2.

In conclusion, we have reported our research on the 1-phenyl-2-cyclopropyl-methylamine derivatives as probes for σ_1 and σ_2 receptors. These data, schematically reported in Fig. 4, provide new insight for the design of new selective ligands for σ_1 and σ_2 receptors. Moreover, the very high affinity for σ_2 receptors of compounds with the methyl substituent on the nitrogen of the adamantanamine moiety (**17**, **18**) and suitable labeling by ^{11}C-methylation of these amines could give useful tumor imaging agents for PET (positron emission tomograph) analysis.

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