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Substituted 1-Phenyl-2-cyclopropylmethylamines with High Affinity and Selectivity for Sigma Sites

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Abstract—A series of 1-phenyl-2-cyclopropylmethylamines structurally related to (+)- and (−)-**MPCB** were synthesized and their binding affinities for σ_1, σ_2, opioid and dopamine (D_2) receptors were evaluated. Substitution of the *cis-N*-normetazocine with different aminic moieties provided compounds with high affinity and selectivity for σ binding sites with respect to opioid and dopamine (D_2) receptors. The observed increase in σ_2 affinity as compared to the parent (+)-**MPCB**, supports the idea that the particular stereochemistry of (+)-*cis-N*-normetazocine affects σ_1 selectivity but does not affect σ_1 affinity. The (±)-*cis* isomers of methyl 2-[(1-adamantylamino)methyl]-1-phenylcyclopropane-1-carboxylate (**18**) displayed a higher affinity and selectivity for the σ_1 and σ_2 receptor subtypes compared to the (±)-*trans* **19**. Interestingly, the enantiomer (−)-*cis* **18** displayed a preference for σ_1 receptor subtype whereas the (+)-*cis* **18** did for σ_2. These results prompt us to synthesize compounds with modification of nitrogen and carboxyl groups. The compounds obtained showed high affinities and selectivity for σ sites. Moreover, modifications of carboxyl groups provided compounds with the highest affinities in the series. In particular, compound **25** with reverse-type ester showed a K_i of 0.6 and 4.05 nM for σ_1 and σ_2 binding sites, respectively.

Introduction

Sigma (σ) receptors are characterized as nonopiate sites which bind certain benzomorphan opioids with high affinity.[1] The investigation of ligands for σ site receptors has been the object of several studies designed to elucidate their physiological role. Sigma receptors are widely distributed within the central nervous system[2] and peripheral tissue[3] of many species. Moreover, σ sites are expressed in a wide variety of human and rodent tumor cell lines. It has been proposed that σ receptors may represent potential targets for diagnostic tumor imaging agents.[4] In addition, the binding affinity of typical and atypical antipsychotic drugs for σ sites and the possible modulation on release and biosynthesis of several neurotransmitters[5,6] suggests their potential involvement as neuromodulators in affective disorders, schizophrenia and motor control.[7–11]

At present, there are pharmacological data which support the existence of at least two σ subtypes, namely σ_1 and σ_2.[12] This conclusion is based on studies which demonstrate that (+) enantiomers of opiate ligands, such as (+)-pentazocine and (+)-SKF 10,047, have a higher affinity for σ_1 over σ_2 subtypes. Other σ ligands, such as haloperidol and DTG [1,3-di-2-(tolyl)guanidine], do not discriminate between σ_1 and σ_2 sites.

The isolation and cloning of guinea pig liver and human placental σ_1 sites have been reported.[13,14] The cloned protein is not related to any known mammalian protein, but it is similar to a fungal protein involved in cholesterol biosynthesis.[15,16] The proteins corresponding to the σ_2 site have not been cloned, but a recent report suggests that they are distinct macromolecules with a particular mode of association with the cell membrane.[17]

Several studies on structure–affinity relationships for several classes of σ ligands, such as benzomorphans, phenylalkylamines, guanidines and derivatives of U50,488 have been reported.[18] Recently, we reported the synthesis and binding affinities of 2′-methoxycarbonyl-2′-phenyl-1′-cyclopropylmethyl normetazocine derivatives (**MPCB**, Fig. 1)[19–21] in order to investigate κ-opioid selective ligands that discriminate between opioid and σ_1 binding sites. In these studies, we observed that the two diastereoisomers, (−)-**MPCB** and

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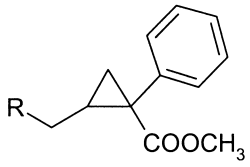


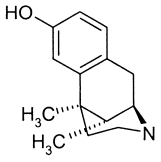
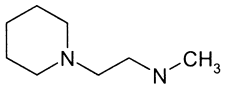
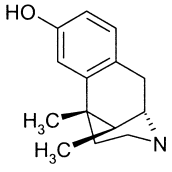
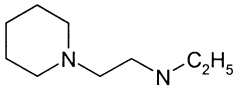
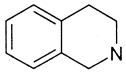
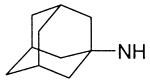
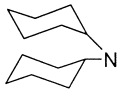
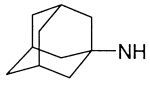
Compound	R	Compound	R
(–)[a]-*cis*[b]-(1*S*;2*R*)-**MPCB**		(±)-*cis*[b]-**16**	
(+)[a]-*cis*[b]-(1*S*;2*R*)-**MPCB**		(±)-*cis*[b]-**17**	
(±)-*cis*[b]-**14**		(±)-*cis*[b]-**18**	
(±)-*cis*[b]-**15**		(±)-*trans*[b]-**19**	

Figure 1. Chemical structures of (−)-**MPCB**, (+)-**MPCB** and compounds **14**–**19**. [a] The (−) and (+) are related to *cis*-*N*-normetazocine nucleus; [b] *cis* and *trans* are related to cyclopropane ring.

(+)-**MPCB**, possess high selectivity for κ-opioid and σ_1 binding sites, respectively. Specifically, (−)-**MPCB** exhibited a binding affinity of 240 nM for the κ-opioid receptors, >1000 nM for σ_1 sites and >25,000 nM for μ- and δ-opioid receptors, while (+)-**MPCB** showed binding affinity of 66.7 nM for σ_1 sites and >1000 nM for κ-, μ- and δ-opioid receptors.

To further evaluate the structure–activity relationships of **MPCB** analogues with respect to affinity and selectivity for the σ receptor subtypes, we synthesized a new series of 1-methoxycarbonyl-1-phenyl-2-cyclopropylmethylamines in which the *cis*-*N*-normetazocine nucleus has been substituted with the 1,2,3,4-tetrahydroisoquinoline **14**, *N*,*N*-dicyclohexylamine **15**, *N*-methyl-*N*(2-piperidin-1-ylethyl)amine **16**, *N*-ethyl-*N*-(2-piperidin-1-ylethyl)amine **17** and 1-adamantanamine **18**–**19** moieties (Fig. 1). To obtain further insight into the requirements of σ_1 and σ_2 recognition sites, we also synthesized the enantiomers of methyl *cis*-2-[(1-adamantylamino)methyl]-1-phenylcyclopropane-1-carboxylate (**20** and **21**) and some *cis*-1-phenyl-2-cyclopropylmethyl derivatives (**22**–**26**) with modification on the nitrogen substituent and/or on the carboxylic group. The syntheses and biological evaluation of these analogues are reported herein.

Chemistry

Our retrosynthetic analysis of the synthesis of compounds **14**–**26** is shown in Figure 2. In order to obtain the halogen or tosyl intermediate we started from lactone **1**. Subsequently, the nucleophilic displacement with the appropriate amines provided the final compounds.

Specifically, the lactone (±)-**1** and acid (±)-**5** were prepared as reported in the literature.[22] Enantiomers **3** were obtained by treatment of lactone (±)-**1** with *R*-(+)-α-methylbenzylamine, followed by flash chromatographic separation of the two diastereoisomeric amides **2** (Scheme 1). The subsequent hydrolysis of **2** with 1N 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

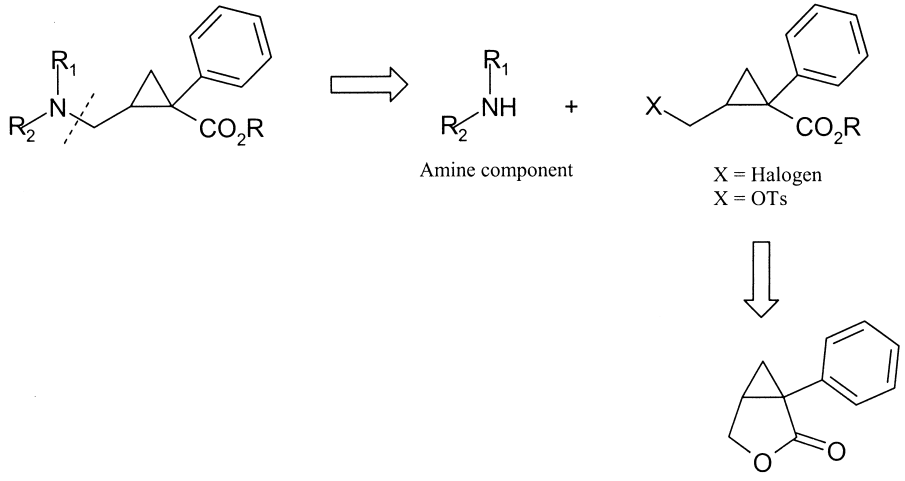
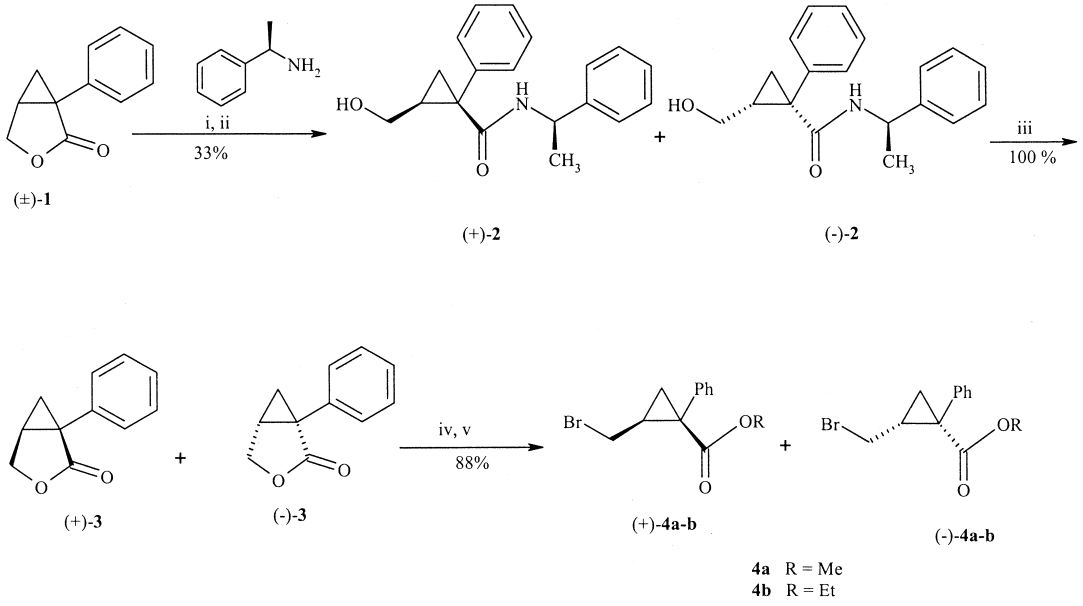
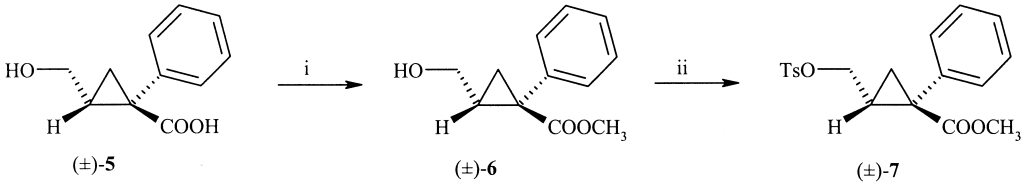


Figure 2. Retrosynthetic analysis and strategy for the synthesis of compounds **14**–**26**.



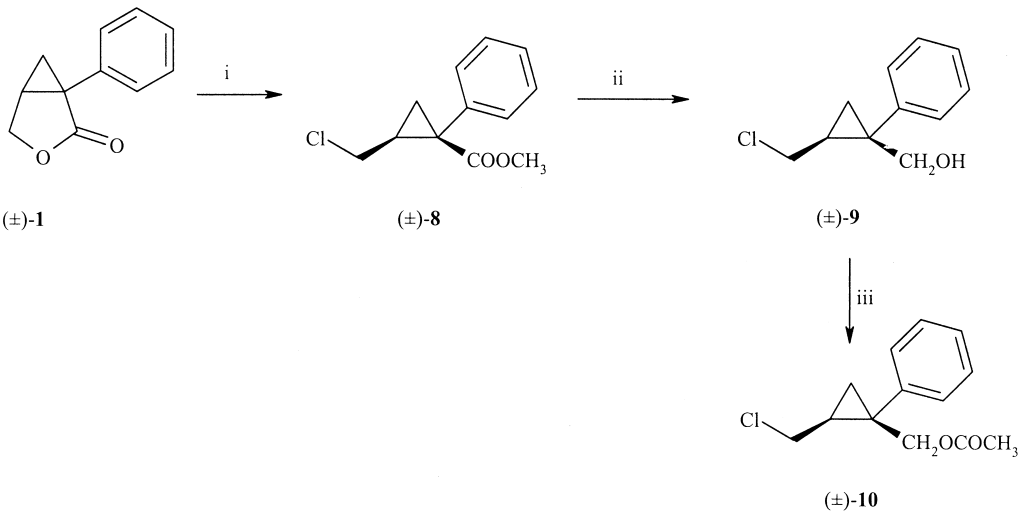
Scheme 1. Synthesis of methyl or ethyl *cis*-2-(bromomethyl)-1-phenylcyclopropanecarboxylate **4a**–**b**. Reagents and conditions: (i) (*R*)-(+)-α-methylbenzylamine; dry toluene; 2-hydroxypiridine; reflux; 24 h; (ii) flash chromatography; (iii) 1N H_2SO_4 in dioxane/H_2O; 85 °C; 16 h; (iv) HBr/CH_3COOH (33%); 80 °C; 2 h; (v) benzene; $SOCl_2$; ROH/3N HCl; 5 h.



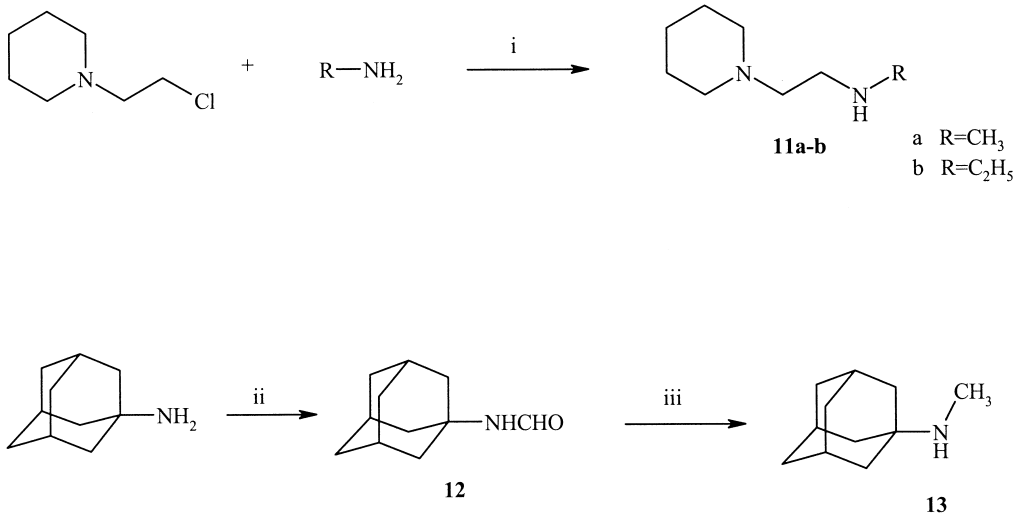
Scheme 2. Synthesis of methyl (±)-*trans*-2-([(4-methylphenyl)sulfonyl]oxymethyl)-1-phenylcyclopropanecarboxylate (±)-**7**. Reagents and conditions: (i) CH_3OH/HCl; reflux; 4 h; (ii) CH_2Cl_2; *p*-toluensulfonyl chloride; pyridine; 12 h.

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

The syntheses of tosyl and chloro esters (±)-**7** and (±)-**10** are shown in Schemes 2 and 3. Esterification with anhydrous HCl/CH_3OH and subsequent treatment with tosyl chloride and pyridine in CH_2Cl_2 afforded ester (±)-**7** in an 80% overall yield (Scheme 2). Compound **9** was obtained in a good yield by treatment of chloromethyl ester **8**, synthesized as reported in the literature,[22] with alane–*N*,*N*-dimethylethylamine complex (Scheme 3). The same reaction with the bromomethyl and ethyl ester derivatives of **8** (compound **4**) provided low yields



Scheme 3. Synthesis of (±)-*cis*-[2-(chloromethyl)-1-phenylcyclopropyl]methanol (±)-**9** and (±)-*cis*-[2-(chloromethyl)-1-phenylcyclopropyl]methyl acetate (±)-**10**. Reagents and conditions: (i) benzene; $ZnCl_2$; $SOCl_2$; CH_3OH/3N HCl; 5 h; (ii) THF; $C_2H_5N(CH_3)_2{\cdot}AlH_3$; 0 °C; 2.5 h; THF; acetyl chloride; 4-dimethylaminopyridine; r.t; 20 h.



Scheme 4. Synthesis of amines **11a**–**b** and **13**. Reagents and conditions: (i) H_2O; r.t; 2 h; (ii) EtOCHO; reflux; 12 h; (iii) THF; $LiAlH_4$; 40 °C; 5 h.

of expected compounds. The simple acylation of **9** with commercially available acetyl chloride in anhydrous THF provided compound **10**.

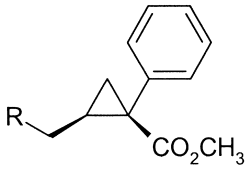
Synthesis of the amine component of the target structures is shown in Scheme 4. The amines **11a** and **11b** were obtained by the reaction of 1-(2-chloroethyl)-piperidine with methyl- or ethylamine in water.[23,24] The formylation of 1-adamantanamine with ethyl formate and subsequent reduction of amide **12** with $LiAlH_4$ produced the *N*-methyladamantan-1-amine **13**.[25–27] Nucleophilic substitution of the cyclopropylphenyl derivatives with the appropriate amine provided the final compounds **14**–**26** (Tables 1 and 2) as shown in Scheme 5.

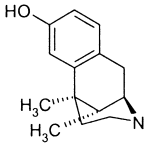
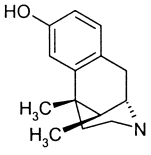
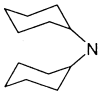
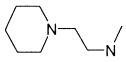
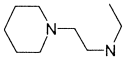
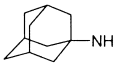
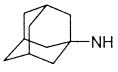
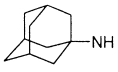
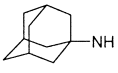
Results and Discussion

The binding data for compounds **14**–**19** and **20**–**26** are reported in Tables 1 and 2. All compounds showed moderate to high affinity for σ_1 and σ_2 sites and negligible affinity for the opioid and dopaminergic D_2 receptors. The data reported in Table 1 confirm the high steric and structural tolerability of the σ_1 binding sites. In general, substitution of the (+)-*cis*-*N*-normetazocine nucleus of **MPCB** with 1,2,3,4-tetrahydroisoquinoline (**14**), *N*,*N*-dicyclohexyl (**15**), *N*-methyl-*N*-(2-piperidin-1-ylethyl)amine (**16**) and *N*-ethyl-*N*-(2-piperidin-1-yl-ethyl)amine (**17**) provided compounds with similar binding affinities. A notable increase in binding affinity was obtained by substitution of the (+)-*cis*-*N*-normetazocine moiety of (+)-**MPCB** with 1-adamantanamine (**18**). This compound displayed a 20-fold increase in affinity for the σ_1 subtypes as compared to (+)-**MPCB**.

With regard to stereochemical considerations, the *cis* racemic mixture (**18**) displayed a higher affinity for the σ_1 and σ_2 receptor subtypes than did the *trans* racemic mixture (**19**). Moreover, the *cis* enantiomers (−)-**18** and

Table 1. Binding affinities [K_i±SEM (nM)] of (−)-**MPCB**, (+)-**MPCB** and compounds **14–19**



Compound	R	[^{3}H](+)Pentaz (σ_1)	[^{3}H]DTG (σ_2)	[^{3}H]Nalox (opioid)	[^{3}H]Spirop (D_2)
(−)-**MPCB**		> 10,000	> 10,000	378±12	> 10,000
(+)-**MPCB**		66.7±2.2	3980±42	> 10,000	> 10,000
(±)-**14**		61±4.2	141.7±12.7	5000 < IC_{50} < 10,000	> 10,000
(±)-**15**		93.2±3.5	204.3±31.5	> 10,000	> 10,000
(±)-**16**		61.4±1.7	32.9±0.8	5000 < IC_{50} < 10,000	> 10,000
(±)-**17**		34±0.8	80.8±1.5	> 10,000	> 10,000
(±)-**18**		3±0.4	23±6.4	5000 < IC_{50} < 10,000	> 10,000
(−)-**18**		4±0.7	35±0.4	> 10,000	> 10,000
(+)-**18**		234±21.4	39.4±3.9	> 10,000	> 10,000
(±)-**19**[a]		226±13.7	135±11.4	5000 < IC_{50} < 10,000	> 10,000
DTG[b]		59±1.3	31.7±1.7	ND[c]	ND[c]

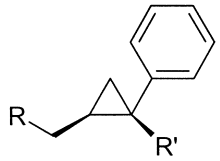
[a]*trans* configuration.
[b]1,3-Di(2-tolyl)guanidine.
[c]Not detected.

(+)-**18** showed different binding profiles for the σ_1 and σ_2 sites (Table 1). In particular, the levo-isomer (−)-**18** was more selective for σ_1 whereas the dextro-isomer (+)-**18** was selective for σ_2 sites.

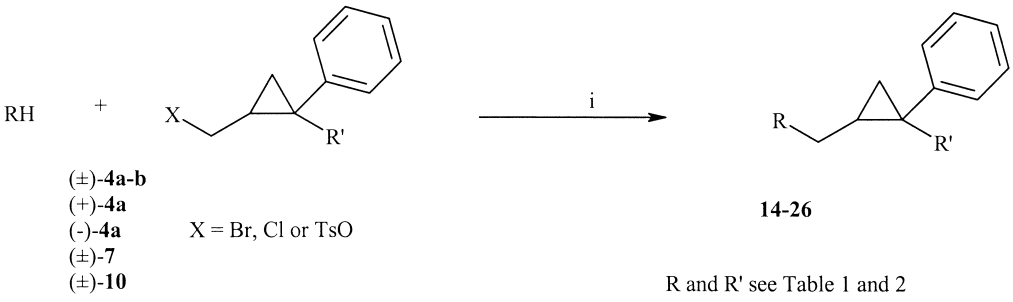
As reported in Table 2, modification on the amino moiety of compound **18**, by substitution of 1-adamantanamine with 1-adamantylmethanamine (**20**), (1-adamantyl)-ethylamino (**21**) or *N*-methyladamantanamine (**22**) resulted in decreased σ_1 affinity and an increased σ_2 affinity.

These results seem to provide evidence that a small increase of distance between adamantane nucleus and

Table 2. Binding affinities [K_i±SEM (nM)] of compounds **20**–**26**



Compound	R	R	[^{3}H](+)Pentaz (σ_1)	[^{3}H]DTG (σ_2)	[^{3}H]Nalox (opioid)	[^{3}H]Spirop (D_2)
(±)-**20**		$COOCH_3$	11.5±3.7	12.7±4.8	> 10,000	5000 < IC_{50} < 10,000
(±)-**21**		$COOCH_3$	99.3±10	45.2±1.5	> 10,000	> 10,000
(±)-**22**		$COOCH_3$	12±1.2	11.2±0.8	> 10,000	> 10,000
(±)-**23**		$COOC_2H_5$	1.29±0.4	35.8±3.7	> 10,000	> 10,000
(±)-**24**		CH_2OH	5.3±1.2	2.22±1.0	> 10,000	> 10,000
(±)-**25**		CH_2OCOCH_3	0.6±0.04	4.05±0.5	> 10,000	> 10,000
(±)-**26**		CH_2OCOCH_3	2.5±1.3	7.4±0.9	> 10,000	> 10,000



Scheme 5. Synthesis of final compounds **14**–**26**. Reagents and conditions: (i) DMF; $NaHCO_3$; 70 °C; 8 h.

nitrogen atom or the increase of lipophilic bulk for σ_1 was critical, but it improves σ_2 affinity.

Modification of the carboxyester group (**23**–**26**) provided compounds with a very high affinity for σ_1 and σ_2 sites. In particular, compound **23** with carboxyethylester displayed a reduced σ_2 affinity with an improved selectivity compared to (±)-**18**. Moreover, compounds **25** and **26** with reverse-type ester showed the highest affinity of the series and a preference for σ_1 with respect to σ_2 sites.

The substitution of the carboxyester with hydroxymethylenic group provided compound **24** with a reverse σ_1 and σ_2 preference and the highest affinity of the series for σ_2 binding sites.These data seem to suggest that an increase of lipophilic bulk and the presence of the carboxyester group on this position are opportune for σ_1 binding sites but not for σ_2. However, in order to evaluate the stereoelectronic effects on σ_1 and σ_2 receptor sites other studies are in progress.

Conclusion

In this study we have reported the synthesis and binding affinities with respect to σ_1, σ_2, opioid and dopamine D_2 receptors of a new series of 1-phenyl-2-cyclopropylmethylamine derivatives structurally related to **MPCB**.

Substitution of the *cis*-*N*-normetazocine nucleus with 1-adamantanamine provided compounds with higher affinity and selectivity for σ sites than opioid and dopamine (D_2) receptors.

Stereochemical analysis of the cyclopropane ring revealed that the *cis*-isomers display enhanced binding profile as compared to the *trans*-isomers and the (−)-*cis* and (+)-*cis* enantiomers exhibit opposite selectivity for σ_1 and σ_2 sites respectively. This observation supports current evidence which suggests σ_1 and σ_2 are pharmacologically different. Moreover, the equal or higher affinity of the racemic mixture **18** for σ sites with respect to

enantiomers (−)-**18** and (+)-**18** might suggest a favorable allosteric modulation, as reported in several studies.[28–30]

In addition, with compounds **20**–**26**, we have evaluated structural modifications to nitrogen substituent and to the carboxylic group with respect to compound (±)-**18**.

The binding data showed that these structural modifications gave compounds **23**–**26** with the highest affinity for σ receptors and afforded new insight into the design of specific and high affinity ligands for either σ_1 or σ_2 receptor subtypes.

Materials and Methods

Chemistry

Reagents were purchased from Aldrich Chemicals Co. unless otherwise specified. Melting points were determined on a Buchi 530 capillary apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on pre-coated silica gel 60 F_{254} aluminum sheets (Merck); visualization was accomplished under UV or in an iodine chamber. Merck silica gel 60, 230–400 mesh, was used for flash column chromatography. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity INOVA (200 MHz) spectrometer with TMS as an internal standard. Optical rotations were determined in MeOH (c = 1) with a Perkin–Elmer 241 polarimeter. Infrared spectra were recorded on a 1600 FT-IR Perkin–Elmer instrument and are consistent with the assigned structures. Elemental analyses were measured on an elemental analyzer (Model 1106, Carlo Erba). Analyses are indicated by symbols of the elements. Analytical results obtained for those elements were within ±0.4% of the theoretical values. Molecular weights of the obtained products were determined by EI MS (70 eV) on a Kratos 2S RFA spectrometer using a Tektronix 4205 computer system. Analytical HPLC was carried out on a Waters Model 600-E, using a spherisorb column 10 SIL 10 μm, 25 cm × 0.46 cm silica gel, flow 3 mL/min, λ = 254 nm.

(1*R*,2*S*)-2-(Hydroxymethyl)-1-phenyl-*N*-[(1*R*)-1-phenylethyl]cyclopropanecarboxamide and (1*S*,2*R*)-2-(hydroxymethyl)-1-phenyl-*N*-[(1*R*)-1-phenylethyl]cyclopropanecarboxamide (2). *R*(+)-α-Methylbenzylamine (8.8 mL, 78 mmol) and 2-hydroxypyridine (3.24 g, 34 mmol) were added to a solution of (±)-*cis*-2-oxo-1-phenyl-3-oxabicyclo[3.1.0]hexane (**1**) (6 g, 34 mmmol) in dry toluene (20 mL). The mixture was heated to reflux for 24 h. After evaporation in vacuo the residue was dissolved in CH_2Cl_2 and washed with 0.5N HCl (4×20 mL) and then with H_2O. After drying with anhydrous Na_2SO_4, the solvent was evaporated and the diastereoisomers (+)- and (−)-**2** were separated by flash chromatography using cyclohexane:ethyl acetate (60:40).

The first eluted fraction was (+)-**2**: 33% yield; mp 74–75 °C; R_f 0.33; $[\alpha]_{20}^{D}$ +96°; (HPLC) rt = 5.22 (cyclohexane:ethyl acetate 57:43), anal. ($C_{19}H_{21}NO_2$) C, H, N. The second fraction was (−)-**2**: 32% yield; mp 101–102 °C; R_f 0.23; $[\alpha]_{D}^{20}$ −44°; (HPLC) rt = 6.71 (cyclohexane:ethyl acetate 57:43); anal. ($C_{19}H_{21}NO_2$) C, H, N.

(1*R*,2*S*)- and (1*S*,2*R*)-2-Oxo-1-phenyl-3-oxabicyclo[3.1.0]-hexane (3). Compound (+)- or (−)-**2** (20 g, 67.7 mmol) was added to a solution of 1N H_2SO_4 (140 mL) in dioxane/H_2O. The mixture was stirred at 85 °C for 16 h. After cooling the mixture was diluted with H_2O (50 mL) and subsequently extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were washed with H_2O and brine, dried with anhydrous Na_2SO_4 and the solvents were evaporated in vacuo to give the desired lactones **3**. (+)-**3**: 1.16 g, 100%; mp 55–56 °C; R_f 0.65 (ethyl acetate:cyclohexane 6:4); IR (KBr): ν(C=O) 1754 cm^{-1}; $[\alpha]_{D}^{20}$ +78°; MS: *m*/*z* 174 [M]$^+$; anal. ($C_{11}H_{10}O_2$) C, H. (−)-**3**: 1.16 g, 100%; mp 54–55 °C; R_f 0.65 (ethyl acetate:cyclohexane 6:4); IR (KBr): ν(C=O) 1754 cm^{-1}; $[\alpha]_{20}^{D}$ −76°; MS: *m*/*z* 174 [M]$^+$; anal. ($C_{11}H_{10}O_2$) C, H.

Methyl (+)-(1*R*,2*S*)-2-(bromomethyl)-1-phenylcyclopropanecarboxylate (4a). Compound **3** (1.24 g, 7.11 mmol) was added to a solution of hydrogen bromide in 33% acetic acid (12 mL) and the resulting mixture was stirred at 80 °C for 2 h. After cooling to 40 °C, the reaction mixture was poured into an ice-H_2O bath to obtain the (1*R*,2*S*)-2-(bromomethyl)-1-phenylcyclopropanecarboxylic acid as a white precipitate which was filtered and dried in vacuo [1.66 g, 91%; mp 148 °C; IR (KBr): ν (C=O) 1665; ^{1}H NMR ($CDCl_3$) δ 1.61 (dd, 1H *J* = 4.8, 9.0 Hz), 1.88 (dd, 1H, *J* = 4.8, 7.0 Hz), 2.12–2.22 (m, 1H), 3.72 (dd, 1H, *J* = 10.2, 11.4 Hz), 3.94 (dd, 1H, *J* = 5.6, 11.4 Hz), 5.28 (br s, 1H), 7.29–7.50 (m, 5H)]. Subsequently, $SOCl_2$ (1.24 mL, 16.9 mmol) was added to a solution of (1*R*,2*S*)-2-(bromomethyl)-1-phenylcyclopropanecarboxylic acid (1.66 g, 6.5 mmol) in anhydrous benzene (8 mL) at 0 °C. After heating to reflux for 5 h, the reaction was cooled to 0° C and a solution of 3N CH_3OH/HCl (2.76 mL) was added dropwise and allowed to stir overnight at room temperature. The mixture was evaporated in vacuo and the residue dissolved in Et_2O, washed with a solution of 4% $NaHCO_3$ and dried over anhydrous Na_2SO_4. The solvent was then evaporated in vacuo to give the desired ester (+)-**4a** (1.67 g, 88%): mp 53–55 °C; R_f 0.57 (toluene:chloroform 8:2); IR (KBr): ν(C=O) 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.52 (dd, 1H *J* = 4.6, 8.5 Hz), 1.78 (dd, 1H, *J* = 4.6, 7.5 Hz), 2.05–2.12 (m, 1H), 3.72 (dd, 1H, *J* = 10.0, 11.2 Hz), 3.80 (s, 3H), 3.89 (dd, 1H, *J* = 5.6, 11.2 Hz), 7.29–7.50 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 22.32, 27.54, 38.36, 38.91, 50.51, 118.30, 125.32, 128.65, 138.41, 173.61; MS: *m*/*z* 269 [M]$^+$; anal. ($C_{12}H_{13}BrO_2$) C, H.

The following compounds were prepared using the above procedure.

Methyl (-)-(1*R*,2*S*)-2-(bromomethyl)-1-phenylcyclopropanecarboxylate (4a). (1.61 g, 85%); mp 53–55 °C; R_f 0.57 (toluene:chloroform 8:2); IR (KBr): ν(C=O) 1716 cm^{-1}; MS: *m*/*z* 269 [M]$^+$; anal. ($C_{12}H_{13}BrO_2$) C, H.

Methyl (±)-*cis*-2-(bromomethyl)-1-phenylcyclopropanecarboxylate (4a). (1.65 g, 87%); mp 53–55 °C; R_f 0.57

(toluene:chloroform 8:2); IR (KBr): ν(C=O) 1716 cm^{-1}; MS: *m/z* 269 $[M]^+$; anal. ($C_{12}H_{13}BrO_2$) C, H.

Ethyl (±)-*cis*-2-(bromomethyl)-1-phenylcyclopropanecarboxylate (4b). (1.61, 80%); mp 60–61 °C; R_f 0.57 (toluene:chloroform 8:2); IR (KBr): ν(C=O) 1714 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J* = 7.0), 2.09–2.31 (m, 2H), 2.35–2.40 (m, 1H), 3.42–3.50 (m, 2H) 3.98 (q, 2H, *J* = 7.0), 7.28–7.55 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 13.20, 22.18, 27.79, 39.59, 39.71, 60.32, 121.32, 125.32, 128.34, 135.22, 174.32. MS: *m/z* 283 $[M]^+$; anal. ($C_{13}H_{15}BrO_2$) C, H.

Methyl (±)-*trans*-2-(hydroxymethyl)-1-phenylcyclopropanecarboxylate (6). A solution of *cis*-2-(hydroxymethyl)-1-phenylcyclopropanecarboxylic acid **5** (353 mg, 1.83 mmol) in 3N HCl in CH_3OH (10 mL) was heated to reflux for 4 h. HCl gas was bubbled through the reaction mixture until the reaction was complete. The solvent was evaporated and the residue dissolved in $CHCl_3$ and washed with a solution of 4% $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the solid product **6**. (0.34 g, 98%); mp 69–70 °C; R_f 0.6 (ethyl acetate: cyclohexane 7:3); IR (KBr): ν(C=O) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (dd, 1H, *J* = 7.6, 8.5 Hz), 1.80 (dd, 1H, *J* = 7.6, 7.9 Hz), 1.95–2.05 (m, 1H), 3.52 (s, 3H), 3.62 (dd, 1H, *J* = 4.5, 9.5 Hz), 3.89 (dd, 1H, *J* = 4.5, 11.2 Hz), 4.78 (br s, 1H) 7.29–7.50 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 20.12, 26.44, 34.63, 51.11, 60.22, 124.23, 127.05, 128.41, 138.90 173.41; MS: *m/z* 206 $[M]^+$; anal. ($C_{12}H_{14}O_3$) C, H.

Methyl (±)-*trans*-2-([(4-methylphenyl)sulfonyl]oxymethyl)-1-phenylcyclopropanecarboxylate (7). With vigorous stirring pyridine (3.5 mL) and *p*-toluensulfonyl chloride (700 mg, 3.67 mmol) were added to a solution of methyl (±)-*trans*-2-(hydroxymethyl)-1-phenylcyclopropanecarboxylate (**6**) (376.5 mg, 1.82 mmol) in CH_2Cl_2 (10 mL) cooled to 0 °C. After 12 h, the reaction was quenched with ice, dissolved in Et_2O (40 mL) and washed with a solution of 2N HCl and then with a solution of 4% $NaHCO_3$. The ether solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product that was used without further purification.

Methyl (±)-*cis*-2-(chloromethyl)-1-phenylcyclopropanecarboxylate (8).[22] A catalytic amount of $ZnCl_2$ and $SOCl_2$ (2.7 mL, 36.7 mmol) was added dropwise to a solution of compound (±)-**1** (2.06 g, 11.9 mmol) in 4 mL of dry benzene at 0 °C. After heating to reflux for 5 h, the reaction mixture was cooled to 0 °C and a solution of 3N HCl in CH_3OH (3 mL) was added dropwise and allowed to stir overnight at room temperature. The mixture was evaporated in vacuo and the residue dissolved in Et_2O, washed with a solution of 4% $NaHCO_3$ and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to provide an oil which was purified by flash chromatography using cyclohexane:toluene (6:4) to give the desired ester **8** (2.19 g, 82%); mp 43–45 °C; R_f 0.52 (toluene:chloroform 8:2); IR (KBr): ν(C=O) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.53 (dd, 1H *J* = 4.8, 8.8 Hz), 1.85 (dd, 1H, *J* = 4.8, 7.0 Hz), 2.00–2.12 (m, 1H), 3.66 (s, 3H),3.79 (dd, 1H, *J* = 10.0, 11.2 Hz), 3.99 (dd, 1H, *J* = 5.6, 11.2 Hz), 7.26–7-50 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 23.02, 28.44, 38.36, 37.98, 49.31, 50.25 120.42, 127.11, 129.45, 138.11, 173.7; ^1H NMR ($CDCl_3$) δ 1.52 (dd, 1H *J* = 4.6, 8.5 Hz), 1.78 (dd, 1H, *J* = 4.6, 7.5 Hz), 2.05–2.12 (m, 1H), 3.72 (dd, 1H, *J* = 10.0, 11.2 Hz), 3.80 (s, 3H), 3.89 (dd, 1H, *J* = 5.6, 11.2 Hz), 7.29–7.50 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 22.32, 27.54, 38.36, 38.91, 50.51, 118.30, 125.32, 128.65, 138.41, 173.61; MS: *m/z* 224 $[M]^+$; anal. ($C_{12}H_{13}ClO_2$) C, H.

(±)-*cis*-[2-(Chloromethyl)-1-phenylcyclopropyl]methanol (9). A solution of compound **8** (1 g, 4.45 mmol) in anhydrous THF (5 mL) was added dropwise to a 0.5 M solution of alane–*N*,*N*-dimethylethylamine complex (9 mL, 4.48 mmol) in anhydrous THF (10 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 2.5 h and quenched with a H_2O:THF (1:1) solution to give a white precipitate. The mixture was dissolved in 1N HCl and extracted with Et_2O (3×30 mL). The organic extracts were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography using cyclohexane:ethyl acetate (9:1) to obtain 668 mg of compound **9** (0.66 g, 76%); mp 30–31 °C; R_f 0.6 (cyclohexane:ethyl acetate 5:5); ^1H NMR ($CDCl_3$) δ 0.92 (dd, 1H, *J* = 7.2, 8.3 Hz), 1.15 (dd, 1H, *J* = 7.7, 8.3 Hz), 1.34–1.63 (m, 1H), 3.40–3.46 (m, 2H), 3.98–4.15 (m, 2H), 4.51 (br s, 1H), 7.29–7.52 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 18.22, 25.54, 37.46, 48.05, 68.45, 121.72, 125.35, 128.32, 142.91; MS: *m/z* 196 $[M]^+$; anal. ($C_{11}H_{13}ClO$) C, H.

(±)-*cis*-[2-(Chloromethyl)-1-phenylcyclopropyl]methyl acetate (10). A solution of (±)-*cis*-[2-(chloromethyl)-1-phenylcyclopropyl]methanol (**9**) (668 mg, 3.4 mmol) and 4-dimethylaminopyridine (250 mg, 2.03 mmol) was added under vigorous stirring to a solution of acetyl chloride (2 mL, 28.1 mmol) in anhydrous THF at room temperature. After 20 h, the reaction was quenched with brine (10 mL) and extracted with Et_2O (3×20 mL). The organic extracts were washed with a 4% solution of $NaHCO_3$, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Subsequently, the crude product was purified by flash chromatography eluting with cyclohexane:ethyl acetate (9.5:0.5) to provide 780 mg of compound **10**. Yield 96%; mp 68–70 °C; R_f 0.58 (cyclohexane:ethyl acetate, 9:1); IR (KBr): ν(C=O) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (dd, 1H, *J* = 7.4, 8.3 Hz), 1.02 (dd, 1H, *J* = 7.8, 8.3 Hz), 1.31–1.40 (m, 1H), 2.2 (s, 3H), 3.38–3.45 (m, 2H), 4.48–4.70 (m, 2H), 7.15–7.55 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 18.33, 22.35, 27.03, 35.21, 47.32, 70.22, 122.12, 124.88,128.66, 141.12, 169.89; MS: *m/z* 238 $[M]^+$; anal. ($C_{13}H_{15}ClO_2$) C, H.

***N*-Methyl-*N*-(2-piperidin-1-ylethyl)amine (11a).** A solution of 1-(2-chloroethyl)-piperidine hydrochloride (11.9 g, 64 mmol) in H_2O (50 mL) was added dropwise to a solution of 40% methylamine in water (50 mL) at room temperature under vigorous stirring. After 2 h, NaOH (20.2 g, 5.06 mol) was added to the reaction mixture.

The aqueous solution was then extracted with Et_2O and dried over anhydrous Na_2SO_4. After solvent evaporation under reduced pressure, the crude product was purified by flash chromatography eluting with $CHCl_3$: CH_3OH:30% ammonia solution (8:1.8:0.2) to give 7.05 g of the amine **11a**. A portion of the product was dissolved in Et_2O and treated with a solution of $H_2C_2O_4$ to obtain the oxalate salt as a white solid. The analytically pure sample was obtained by recrystallization from methanol (7.1 g, 78%); mp 192–194 °C; R_f 0.23 ($CHCl_3$: CH_3OH:30% ammonia solution 8:1.8:0.2); MS m/z 142 $[M]^+$; anal. ($C_8H_{18}N_2 \cdot H_2C_2O_4 \cdot H_2O$) C, H, N.

Using the above mentioned procedure, the ***N*-ethyl-*N*-(2-piperidin-1-ylethyl)amine** (**11b**) was prepared in 87% yield; mp 230–232 °C (oxalate salt); R_f 0.25 ($CHCl_3$: CH_3OH:30% ammonia solution 8:1.8:0.2); MS m/z 156 $[M]^+$; anal. ($C_9H_{20}N_2 \cdot H_2C_2O_4 \cdot 0.5H_2O$) C, H, N.

1-Adamantylformamide (12). A solution of 1-adamantanamine (500 mg, 3.3 mmol) in ethyl formate (EtOCHO) (50 mL) was stirred and refluxed for 12 h. The EtOCHO was evaporated under reduced pressure and the product was recrystallized from *n*-hexane/ethyl acetate (592 mg, 100%); mp 138–139 °C; MS: m/z 179 $[M]^+$; anal. ($C_{11}H_{17}NO$) C, H, N.

***N*-Methyladamantan-1-amine (13).** A solution of 1-adamantylformamide (**12**) (588 mg, 3.27 mmol) in anhydrous THF was added dropwise to a suspension of $LiAlH_4$ (624 mg, 16,4 mmol) in anhydrous THF. The reaction was stirred at 40 °C for 5 h and then quenched with H_2O (3 mL) at −7 °C. After filtration, the white precipitate was triturated and washed with Et_2O (40 mL). The organic mixture was dried over Na_2SO_4 and evaporated in vacuo. The residue was dissolved in C_2H_5OH and a solution of C_2H_5OH/HCl was added. Evaporation under reduced pressure gave *N*-methyladamantan-1-amine hydrochloride which was crystallized from ethanol (0.51 g, 95%); mp 242–244 °C; MS: m/z 165 $[M]^+$; anal. ($C_{11}H_{19}N.HCl.0.2H_2O$) C, H, N.

Methyl 2-[3,4-dihydroisoquinolin-2(1*H*)-ylmethyl]-1-phenylcyclopropanecarboxylate (14). $NaHCO_3$ (168 mg, 2 mmol) and compound **4a** (150 mg, 0.66 mmol) were added to a solution of 1,2,3,4-tetrahydroisoquinoline hydrochloride (170 mg, 1 mmol) in DMF (7 mL). The reaction mixture was stirred at 70 °C for 8 h. The solvent was evaporated under reduced pressure and the residue was dissolved in $CHCl_3$ and washed with a solution of 4% $NaHCO_3$. The mixture was dried over anhydrous Na_2SO_4, evaporated in vacuo and the crude product was purified by flash chromatography with $CHCl_3$: cyclohexane:EtOH (6:4.5:0.5). Compound **14** was then dissolved in THF and treated with a solution of $H_2C_2O_4$ in THF to give the oxalate salt as a white solid. The analytically pure sample was obtained by recrystallization from methanol/diethyl ether (127 mg, 60%); mp 160–165 °C; ^{1}H NMR (DMSO-d_6) δ 1.54 (dd, 1H, J = 4.4, 7.0 Hz), 1.68 (t, 1H, J = 4.4 Hz), 2.02 (m, 1H), 3.09–3.55 (m, 6H), 3.56 (s, 3H, OCH_3), 4.28 (s, 2H), 5.8 (br s, 2H), 7.18–7.38 (m, 9H); ^{13}C NMR (DMSO-d_6) δ 20.76, 23.21, 25.67, 38.84, 49.23, 52.67, 52.78, 54.41, 126.85, 127.63, 127.79, 128.52, 128.82, 129.49, 130.14, 131.86, 139.53, 164.30, 172.11; MS: m/z 321 $[M]^+$; anal. ($C_{21}H_{23}NO_2 \cdot 0.9H_2C_2O_4 \cdot 0.5H_2O$) C, H, N.

The following compounds were prepared using the above procedure.

Methyl (±)-*cis*-2-[(dicyclohexylamino)methyl]-1-phenylcyclopropanecarboxylate (15). (0.2 g, 30%); mp 147–149 °C; ^{1}H NMR (DMSO-d_6) δ 0.85–1.85 (m, 23H), 2.96–3.03 (m, 2H), 3.18 (dd, 1H, J = 5.0, 12.6 Hz), 3.29 (dd, 1H, J = 8.9, 12.6 Hz), 3.52 (s, 3H), 6.20 (br s, 2H), 7.42–7.79 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 20.54, 22.47, 24.82, 26.33, 28.81, 35.54, 45.73, 50.82, 62.41, 126.52, 127.32, 132.61, 139.44, 168.31, 172.12; MS: m/z 369 $[M]^+$; anal. ($C_{24}H_{35}NO_2 \cdot 0.5H_2C_2O_4 \cdot 2H_2O$) C, H, N.

Methyl (±)-*cis*-2-{[methyl(2-piperidin-1-ylethyl)amino]-methyl}-1-phenylcyclopropanecarboxylate (16). (0.15 g, 40%); mp 210–212 °C; ^{1}H NMR (DMSO-d_6) δ 1.41 (dd, 1H, J = 4.2, 7.5 Hz), 1.45–1.95 (m, 8H), 2.49 (s, 3H), 2.83–3.22 (m, 10H), 3.56 (s, 3H), 6.50 (br s, 4H), 7.28–7.34 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 20.44, 21.61, 22.79, 24.41, 33.76, 40.66, 50.43, 51.79, 52.65, 52.79, 55.00, 127.51, 128.53, 130.09, 139.94, 163.87, 172.26; MS: m/z 330 $[M]^+$; anal. ($C_{20}H_{30}N_2O_2 \cdot 1.8H_2C_2O_4 \cdot H_2O$) C, H, N.

Methyl (±)-*cis*-2-{[ethyl(2-piperidin-1-ylethyl)amino]-methyl}-1-phenylcyclopropanecarboxylate (17). (0.2 g, 90%); mp 166–168 °C; ^{1}H NMR (DMSO-d_6) δ 1.11 (t, 3H, J = 6.8 Hz), 1.41 (dd, 1H, J = 5.4, 8.8 Hz), 1.42–1.97 (m, 8H), 2.87–3.35 (m, 12H), 3.55 (s, 3H), 6.05 (br s, 3H), 7.21–7.45 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 9.98, 20.68, 21.62, 22.88, 24.34, 33.82, 46.78, 47.12, 50.81, 51.79, 5275, 52.94, 127.58, 128.58, 130.19, 139.97, 164.05, 172.39; MS: m/z 344 $[M]^+$; anal. ($C_{21}H_{32}N_2O_2 \cdot 1.5H_2C_2O_4 \cdot 1.5H_2O$) C, H, N.

Methyl (±)-*cis*-2-[(1-adamantylamino)methyl]-1-phenylcyclopropanecarboxylate (18). (70 mg, 15%); mp 248–250 °C; ^{1}H NMR (DMSO-d_6) δ 1.48 (dd, 1H, J = 4.0, 9.2 Hz), 1.51–198 (m, 14H), 2.05–2.20 (m, 4H), 3.12 (dd, 1H, J = 7.5, 12.6 Hz), 3.50 (dd, 1H, J = 5.5, 12.6 Hz), 3.60 (s, 3H), 4.80 (br s, 2H), 7.20–7.45 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 19.85, 23.31, 28.35, 34.22, 35.88, 38.08, 46.25, 52.98, 61.01, 127.41, 128.61, 130.80, 139.35, 165.50, 172.19; MS: m/z 339 $[M]^+$; anal. ($C_{22}H_{29}NO_2 \cdot 0.5H_2C_2O_4 \cdot 1.5H_2O$) C, H, N.

Methyl (±)-*trans*-2-[(1-adamantylamino)methyl]-1-phenylcyclopropanecarboxylate (19). (95 mg, 18%); mp 252–254 °C; ^{1}H NMR (DMSO-d_6) δ 1.40–1.85 (m, 14H), 1.85–2.22 (m, 4H), 2.84–3.00 (m, 2H), 3.55 (s, 3H), 4.65 (br s, 3H), 7.25–7.47 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 19.87, 23.21, 28.89, 33.60, 35.06, 37.49, 39.24, 52.43, 55.95, 127.66, 128.31, 131.25, 134.38, 164.51, 173.20; MS: m/z 339 $[M]^+$; anal. ($C_{22}H_{29}NO_2 \cdot H_2C_2O_4$) C, H, N.

Methyl (−)-(1*S*,2*R*)-2-[(1-adamantylamino)methyl]-1-phenylcyclopropanecarboxylate [(−)-18]. (89 mg, 22%); mp 248–250 °C; $[\alpha]_{20}^{D}$ −50°; ^{1}H NMR (DMSO-d_6) δ 1.45

(dd, 1H, $J=4.0$, 9.1 Hz), 1.50–2.00 (m, 14H), 2.08–2.25 (m, 4H), 3.14 (dd, 1H, $J=7.2$, 12.1 Hz), 3.53 (dd, 1H, $J=5.4$, 12.1 Hz), 3.61 (s, 3H), 5.5 (br s, 2H), 7.27–7.45 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 20.58, 23.31, 27.98, 34.50, 35.66, 38.40, 45.91, 51.02, 60.92, 126.33, 128.03, 131.00, 139.02, 166.48, 172.20; MS: m/z 339 $[M]^+$; anal. ($C_{22}H_{29}NO_2 \cdot 0.6H_2C_2O_4$) C, H, N.

Methyl (+)-(1*R*,2*S*)-2-[(1-adamantylamino)methyl]-1-phenylcyclopropanecarboxylate [(+)-18]. (80 mg, 18%); mp 105–112 °C; $[\alpha]_{20}^{D}$ +49°; ^{1}H NMR (DMSO-d_6) δ 1.47 (dd, 1H, $J=4.1$, 9.1 Hz), 1.50–2.00 (m, 14H), 2.08–2.25 (m, 4H), 3.14 (dd, 1H, $J=7.2$, 12.1 Hz), 3.50 (dd, 1H, $J=5.4$, 12.1 Hz), 3.59 (s, 3H), 6.2 (br s, 2H), 7.28–7.50 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 19.98, 23.10, 28.01, 33.98, 35.00, 39.65, 46.00, 51.32, 61.22, 126.15, 128.32, 131.50, 139.10, 165.98, 172.50; MS: m/z 339 $[M]^+$; anal. ($C_{22}H_{29}NO_2 \cdot 0.7H_2C_2O_4 \cdot 2H_2O$) C, H, N.

Methyl (±)-*cis*-2-{[(1-adamantylmethyl)amino]methyl}-1-phenylcyclopropanecarboxylate (20). (120 mg, 57%); mp 210–212 °C; ^{1}H NMR (DMSO-d_6) δ 1.41 (dd, 1H, $J=4.6$, 8.7 Hz), 1.46–1.80 (m, 13H), 1.82–2.10 (m, 4H), 2,6 (s, 2H) 3.22 (dd, 1H, $J=5.0$, 12.6 Hz), 3.45 (dd, 1H, $J=9.0$, 12.6 Hz), 3.60 (s, 3H), 5.8 (br s, 3H), 7.27–7.45 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 19.80, 23.71, 27.08, 35.95, 37.80, 39.45, 44.71, 45.80, 52.75, 60.97, 127.44, 128.29, 130.41, 139.61, 164.27, 172.09; MS: m/z 353 $[M]^+$; anal. ($C_{23}H_{31}NO_2 \cdot H_2C_2O_4 \cdot 0.2H_2O$) C, H, N.

Methyl (±)-*cis*-2-({[1-(1-adamantyl)ethyl]amino}methyl)-1-phenylcyclopropanecarboxylate (21). (125 mg, 66%); mp 190–191 °C; ^{1}H NMR (DMSO-d_6) (1:1 diastereoisomeric mixture) δ 1.14 (d, 3H, $J=6.6$ Hz), 1.16 (d, 3H, $J=6.6$ Hz), 1.40 (dd, 1H, $J=4.0$, 8.8 Hz) 1.45–1.80 (m, 13H), 1.84–2.10 (m, 4H), 2.83 (q, 1H, $J=6.6$ Hz), 3.10–3.30 (m, 1H), 3.35–3.45 (m, 1H), 3.57 (s, 3H), 3.58 (s, 3H), 5.4 (br s, 3H), 7.20–7.45 (m, 5H); ^{13}C NMR (DMSO-d_6) (1:1 diastereoisomeric mixture) δ 10.28, 10.57, 20.06, 21.23, 23.68, 24.07, 2752, 33.20, 34.21, 34.81, 34.87, 36.11, 36.92, 43.96, 44.91, 52.57, 52.58, 61.59, 62.47, 127.31, 128.05, 128.18, 129.95, 130.26, 139.43, 139.54, 164.53, 172.01; MS: m/z 367 $[M]^+$; anal. ($C_{22}H_{29}NO_2 \cdot H_2C_2O_4$) C, H, N.

Methyl (±)-*cis*-2-{[1-adamantyl(methyl)amino]methyl}-1-phenylcyclopropanecarboxylate (22). (135 mg, 42%); mp 181–184 °C; ^{1}H NMR (DMSO-d_6) δ 1.51 (dd, 1H, $J=4.1$, 8.8 Hz), 1.60–1.78 (m, 7H), 1.82–2.23 (m, 10H), 2.75 (s, 3H), 3.25–3.50 (m, 2H), 3.58 (s, 3H), 5.40 (br s, 2H), 7.22–7.45 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 20.65, 23.75, 28.92, 32.38, 34.10, 35.07, 35.52, 46.81, 52.62, 62.97, 127.31, 128.19, 130.07, 139.31, 164.63, 172.04; MS: m/z 353 $[M]^+$; anal. ($C_{23}H_{31}NO_2 \cdot 0.5H_2C_2O_4 \cdot 1.5H_2O$) C, H, N.

Ethyl (±)-*cis*-2-[(1-adamantylamino)methyl]-1-phenylcyclopropanecarboxylate (23). (98 mg, 35%); mp 210–212 °C; ^{1}H NMR (DMSO-d_6) δ 1.07 (t, 3H, $J=7$ Hz), 1.49 (dd, 1H, $J=4.0$, 8.8 Hz), 1.54–2.00 (m, 13H), 2.10–2.22 (m, 4H), 3.12 (dd, 1H, $J=7.4$, 12.7 Hz), 3.46 (dd, 1H, $J=5.8$, 12.7 Hz), 4.00 (q, 2H, $J=7$ Hz), 5.00 (br s, 3H), 7.20–7.42 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 14.26, 20.47, 24.57, 28.72, 34.18, 35.38, 36.93, 37.88, 56.68, 60.50, 127.39, 130.41, 139.80, 164.48, 171.95; MS: m/z 353 $[M]^+$; anal. ($C_{23}H_{31}NO_2 \cdot H_2C_2O_4$) C, H, N.

(±)-*cis*-{2-[(1-Adamantylamino)methyl]-1-phenylcyclopropyl}methanol (24). (0.18 g 76%); mp 282–283 °C; ^{1}H NMR (DMSO-d_6) δ 1.05 (dd, 1H, $J=5.0$, 8.6 Hz), 1.11 (dd, 1H, $J=5.5$, 8.6 Hz), 1.46 (m, 1H) 1.58 (m, 6H), 1.87 (m, 6H), 2.14 (m, 3H), 3.11 (dd, 1H, $J=6.4$, 12.2 Hz), 3.29 (dd, 1H, $J=5.1$, 12.2 Hz), 3.53 (d, 1H, $J=11.6$ Hz), 4.10 (d, 1H, $J=11.6$ Hz), 5.60 (br s, 3H), 7.15–7.45 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 17.51, 20.28, 28.42, 31.72, 35.21, 37.79, 40.12, 55.94, 64.74, 126.29, 128.01, 128.72, 143.93; MS: m/z 311 $[M]^+$; anal. ($C_{21}H_{29}NO_2 \cdot HCl \cdot 0.2H_2O$) C, H, N.

(±)-*cis*-{2-[(1-Adamantylamino)methyl]-1-phenylcyclopropyl}methyl acetate (25). (97 mg, 28%); mp 210–211 °C; ^{1}H NMR (DMSO-d_6) δ 1.09 (dd, 1H, $J=7.6$, 8.2 Hz), 1.25 (dd, 1H, $J=7.4$, 8.2 Hz), 1.41 (m, 1H), 1.50–1.78 (m, 6H), 1.80–1.95 (m, 6H), 1.97 (s, 3H) 2.05–2.22 (m, 3H), 2.90 (dd, 1H, $J=5.6$, 12.5 Hz), 3.42 (dd, 1H, $J=8.7$, 12.5 Hz), 4.30 (d, 1H, $J=12.4$ Hz), 4.38 (d, 1H, $J=12.4$ Hz), 5.00 (br s, 3H), 7.18–7.41 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 17.66, 21.10, 21.50, 28.78, 29.51, 35.43, 37.88, 40.91, 56.71, 67.52, 127.16, 128.69, 128.75, 142.94, 165.19, 170.92; MS: m/z 353 $[M]^+$; anal. ($C_{23}H_{31}NO_2 \cdot H_2C_2O_4 \cdot 0.4H_2O$) C, H, N.

(±)-*cis*-(2-{[1-Adamantyl(methyl)amino]methyl}-1-phenylcyclopropyl)methyl acetate (26). (110 mg, 15%); mp 132–133 °C; ^{1}H NMR (DMSO-d_6) δ 1.10 (dd, 1H, $J=7.3$, 8.3 Hz), 1.28 (dd, 1H, $J=7.0$, 8.3 Hz), 1.40 (m, 1H), 1.50–1.90 (m, 12H), 1.99 (s, 3H), 2.10–2.32 (m, 3H), 2.73 (s, 3H), 2.92 (dd, 1H, $J=5.8$, 12.8 Hz), 3.44 (dd, 1H, $J=8.5$, 12.8 Hz), 4.33 (d, 1H, $J=12.7$ Hz), 4.41 (d, 1H, $J=12.7$ Hz), 5.50 (br s, 3H), 7.20–7.44 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 17.36, 20.98, 21.32, 28.80, 29.32, 32.00, 35.27, 36.90, 40.05, 55.80, 68.52, 127.51, 128.44, 128.81, 141.09, 164.12, 171.32; MS: m/z 367 $[M]^+$; anal. ($C_{24}H_{33}NO_2 \cdot H_2C_2O_4 \cdot 1.5H_2O$) C, H, N.

Biological Evaluation

Radioligand binding assays

$Sigma_1$ binding assays were carried out on guinea pig brain membranes prepared by the method described by Matsumoto et al.[31] and the protein content was evaluated.[32] The binding assay was performed as described by DeHaven et al.[33] Each tube contained 500 μg of membrane protein, 3 nM [^{3}H]-pentazocine (31.6 Ci/mmol; the value of the apparent dissociation constant (K_d) was 4.3±0.8 nM, $n=3$). Non-specific binding was determined by addition of 10 μM haloperidol. The reaction was performed for 150 min at 37 °C and terminated by filtering the solution through Whatman GF/B glass filters that were presoaked in a 0.5% polyethylenimine solution.

$Sigma_2$ binding assays were carried out on guinea pig brain membranes prepared as described by Mach et al.[34]

These were incubated with 3 nM [^{3}H]-DTG [1,3-di-2-(tolyl)-guanidine] (35 Ci/mmol; $K_d = 9.9 \pm 0.8$ nM; $n = 3$) in the presence of 100 nM (+)-NANM (*N*-allyl-normetazocine) to mask sigma1 receptor sites. Incubations were carried out in 50 mM Tris–HCl (pH 8.0) for 120 min at room temperature and assays were terminated by the addition of ice-cold 10 mM Tris–HCl (pH 8.0) followed by filtration through Whatman GF/B glass fibers. Non-specific binding was evaluated in the presence of 5 μM DTG.

Total opioid receptor binding was assessed on rat brain membranes prepared as previously reported[19] and incubated in the presence of [^{3}H]-naloxone (55.5 Ci/mmol; $K_d = 6.6 \pm 0.7$ nM; $n = 3$). Non-specific binding was evaluated in the presence of 10 μM naloxone. Binding assays for the κ-opioid receptor were carried out on membranes obtained from guinea pig cerebella using [^{3}H]-U69,593 (62 Ci/mmol; $K_d = 1.98 \pm 0.4$; $n = 3$) in the presence of 300 nM D-Ala,[2] N-MePhe,[4] Gly-ol[5]-enkephalin and 300 nM D-Ala[2]-D-Leu[5]-enkephalin to block the μ and δ receptors.

Dopaminergic (D_2) receptor binding assays were performed using 0.5 nM [^{3}H]-spiroperidol (18.5 Ci/mmol; $K_d = 0.5 \pm 0.08$ nM; $n = 3$) and rat striatal membranes as reported by Briley and Langer.[35] Non-specific binding assays were measured in the presence of 10 μM haloperidol.

Inhibition constants (K_i values) for test compounds were calculated using the EBDA/LIGAND program,[36] purchased from Elsevier/Biosoft.

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