Articles

(+)-*cis*-*N*-Ethyleneamino-*N*-normetazocine Derivatives. Novel and Selective σ Ligands with Antagonist Properties

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A series of (+)-cis-*N*-normetazocine derivatives has been described, and their affinities for σ_1, σ_2, and phencyclidine (PCP) sites and opioid, muscarinic (M_2), dopamine (D_2), and serotonin (5-HT_2) receptors were evaluated. The effect of the N-substitution with a substituted ethylamino spacer was investigated. Compounds **8c**−**11c** displayed high affinities for σ_1 sites and for opioid receptors. Substitution of the second basic nitrogen either with alkyl or cycloalkyl substituents give compounds (**1a**−**6a**) with high affinity and selectivity for σ_1 binding sites. Compounds **1a**−**5a** were further characterized in vivo, and their agonist/antagonist activity was evaluated. In mouse, compound **1a** and **2a** as well as haloperidol suppressed in a dose-related manner the stereotyped behavior induced by (+)-SKF 10,047. Compounds **3a**−**5a** and (+)-pentazocine do not affect the stereotyped behavior induced by ip injection of (+)-SKF 10,047. Therefore, from this series of compounds we identified potent and selective σ_1 ligands which might prove useful to unveil the functional role of σ_1 sites.

Introduction

σ binding sites display a unique drug selectivity pattern and anatomical distribution in the central nervous system and in peripheral tissues.[1] Proteins with the characteristics of σ recognition sites have been purified,[2−5] and recently a 24 kD protein was cloned using degenerate oligonucleotides and cDNA library screening.[6] Thus far, at least two subtypes of σ binding sites have been pharmacologically characterized.[7,8] According to this classification, σ_1 binding sites display high affinity for haloperidol, 1,3-di(2-tolyl)guanidine (DTG), and (+)-*cis*-benzomorphans, such as (+)-pentazocine and (+)-*N*-allyl-*N*-normetazocine (NANM or (+)-SKF10,047), whereas σ_2 binding sites are characterized by high affinity for haloperidol and DTG, but low affinity for (+)-*cis*-benzomorphans.

σ binding sites seem to be implicated in a wide variety of functions, ranging from the motor control to the synthesis and/or release of several neurotransmitters or cell proteins.[9−13] Recent observations suggest that σ binding sites may be also implicated in the cell growth and proliferation.[14,15] Although their physiological significance is not yet completely known, the potential involvement of σ sites in affective disorders and in schizophrenia has been suggested.[16,17] Many of these pharmacological studies have been carried out with ligands showing reduced selectivity; thus, the results are difficult to interpret. In addition, although selective ligands have been synthesized in recent years,[18−24] it is still difficult to define which σ ligands act as agonists or antagonists at these sites. Several researchers have proposed that σ ligands which are associated with psychotomimetic effects are agonists (for instance, (+)-pentazocine and (+)-SKF 10,047), while compounds such as haloperidol, rimcazole, and NE-100 (*N*,*N*-dipropyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine monohydrochloride), which block the binding and several pharmacological actions of these agonists are considered antagonists.[25−28] In agreement with this hypothesis, Pasternak and co-workers[29−31] have extensively investigated possible functional interactions between σ_1 and opioid receptors. They have suggested that in addition to other activities, σ_1 sites comprise a tonically active antiopioid system. In fact, they have found that (+)-pentazocine, acting as σ_1 agonist, antagonizes opioid-induced analgesia; on the contrary, haloperidol, acting as σ antagonist, greatly enhances this latter effect. Nevertheless, there is still controversy regarding this classification; for instance, Matsumoto et al.[24] have defined BD-1047 (*N*-[2-(3,4-dichlorophenyl)-ethyl]-*N*-methyl-2-(dimethylamino)ethylamine) and BD-1063 (1-[2-(3,4-dichlorophenyl)ethyl]-4-methylpiperazine) as σ antagonists capable of attenuating the dystonia produced by DTG and haloperidol. Therefore, the lack of specific antagonists has been a relevant impediment to the progress in research on σ sites.

As previously mentioned, (+)-*cis*-benzomorphan derivatives are generally considered σ agonists; although, only for (+)-SKF 10,047 and (+)-pentazocine is there pharmacological evidence supporting their agonistic properties.[1,32] Moreover, studies of σ sites using (+)-SKF 10,047 resulted in confusion with phencyclidine

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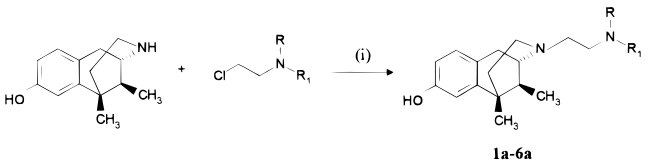
Table 1. Physical Properties of N-Alkylated *cis*-(+)-*N*-Normetazocine Derivatives

compd	R	R_1	method of synthesis	yield (%)	mp (°C)	formula[c]	$[\alpha]^{23}_D$,[d] deg
1a	$-(CH_2)_5-$		A	62	184−186[a]	$C_{21}H_{32}N_2O\cdot C_2H_2O_4\cdot 2.5H_2O$	+40
2a	$-(CH_2)_2-O-(CH_2)_2-$		A	70	205−206[a]	$C_{20}H_{30}N_2O_2\cdot C_2H_2O_4\cdot 0.5H_2O$	+40
3a	$-(CH_2)_6-$		A	35	187−189[a]	$C_{22}H_{34}N_2O\cdot C_2H_2O_4\cdot 1.5H_2O$	+60
4a	$-(CH_2)_4-$		A	67	181−182[a]	$C_{20}H_{30}N_2O\cdot C_2H_2O_4\cdot 1.5H_2O$	+44
5a	C_2H_5	C_2H_5	A	63	182−184[a]	$C_{20}H_{32}N_2O\cdot C_2H_2O_4\cdot 1.5H_2O$	+48
6a	CH_3	CH_3	A	70	180−182[a]	$C_{18}H_{28}N_2O\cdot C_2H_2O_4\cdot 2\ H_2O$	+52
7c	C_6H_{11}	H	B	34	174−175[a]	$C_{22}H_{34}N_2O\cdot 2C_2H_2O_4\cdot 0.5H_2O$	+78
8c	C_6H_5	H	B	85	64−65[b]	$C_{22}H_{28}N_2O\cdot H_2O$	+74
9c	C_6H_5	CH_3	B	61	67−68[b]	$C_{23}H_{30}N_2O\cdot 0.5H_2O$	+90
10c	C_6H_5	C_2H_5	B	77	220[a]	$C_{24}H_{32}N_2O\cdot C_2H_2O_4\cdot 0.5H_2O$	+88
11c	$CH_2C_6H_5$	H	B	35	178−179[a]	$C_{23}H_{30}N_2O\cdot 2C_2H_2O_4$	+84

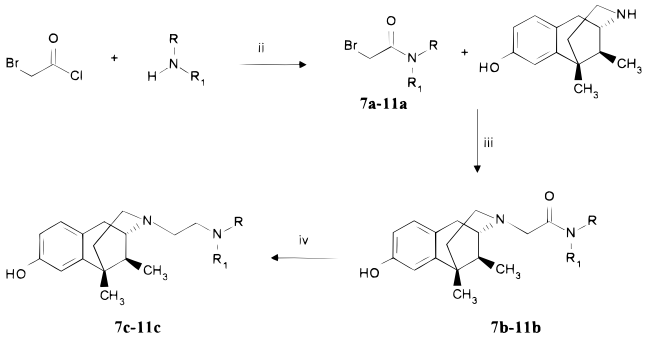
[a] Oxalate salt. [b] Free amine. [c] Elemental analyses were within ±0.4% of the theoretical values. [d] All optical rotations were determined in ethanol (c = 1.00).

Scheme 1. General Method for the Preparation of *N*-Alkyl-*cis*-(+)-*N*-normetazocine Derivatives (**1a**−**6a**)[a]



[a] (i) CH_3OH, $NaHCO_3$.

Scheme 2. General Method for the Preparation of *N*-Alkyl-*cis*-(+)-*N*-normetazocine Derivatives (**7c**−**11c**)[a]



[a] (ii) THF, 4-(dimethylamino)pyridine; (iii) CH_3OH, $NaHCO_3$; (iv) THF, diborane.

(PCP) site of the *N*-methyl-D-aspartate (NMDA), since this (+)-benzomorphan binds both σ and PCP binding sites.[33] Several studies on *cis*-(+)- and *cis*-(−)-*N*-normetazocine derivatives have been carried out in order to clarify the structure−affinity relationship and have confirmed that the nucleus of *cis*-(+)-*N*-normetazocine with suitable N-substituents is a good pharmacophore to probe σ_1 binding sites.[34−39] Carroll et al.[34] have examined a series of enantiomeric (+)-*cis*-benzomorphans at σ and PCP sites and opioid receptors. The results have indicated that, in general, lipophilic groups on the nitrogen may improve selectivity and potency at σ sites, and the greatest improvement was observed with a *N*-benzyl substituent. However, it has not been deeply investigated if any constituent of this class may act as a σ antagonist. Thus, to obtain new insights on structural requirements, we synthesized a novel series of substituted *N*-ethyleneamines of *cis*-(+)-*N*-normetazocine to discriminate among σ sites and other receptor systems, which may represent additive binding sites for several σ ligands, and to evaluate their agonist and antagonist properties.

Chemistry

cis-(+)-(1*S*,5*S*,9*S*)-*N*-Normetazocine was separated by racemic mixture as reported by Brine et al.[40] Compounds **1a**−**6a** were prepared by alkylation of *cis*-(+)-*N*-normetazocine with commercially available chloroethylamines (Scheme 1). Compounds **7a** and **11a** were prepared by acylation of respective amines with bromoacetyl chloride in anhydrous THF, at −5 °C (Scheme 2). The respective bromo amides **7a**−**11a** gave the amides **7b**−**11b** by alkylation of *cis*-(+)-*N*-normetazocine in MeOH at 50 °C using $NaHCO_3$. Reduction of the resulting amides with diborane in anhydrous THF provided the final compounds **7c**−**13c**. Physical and analytical data for compounds **1a**−**6a** and **7c**−**11c** are shown in Table 1.

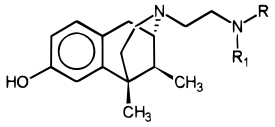
Results

As shown in Table 2, σ_1 binding affinities of compounds **1a**−**4a** with the second nitrogen atom part of a cyclic ring system, such as piperidine, morpholine, azepine, or pyrrolidine, respectively, range between 7.4 and 20.1 nM. Compounds **5a** and **6a**, supporting a diethyl or a dimethyl N-substituent, have an affinity of 15.2 and 19.8 nM, respectively, while **7c** with the cyclohexyl N-substituent shows reduced affinity (K_i = 41.6 nM). The affinities for σ_2 sites are lower than those for σ_1 sites, ranging between 114 and 378 nM, and **4a** shows the greatest selectivity for σ_1 with respect to σ_2 subtype sites (σ_1/σ_2 ratio = 35). All of these compounds have a very low affinity for opioid receptors (K_i ranging between 1466 and 12 290 nM). Moreover, **1a** and **2a** do not display any significant affinity for κ opioid receptors (K_i > 25 000 nM) (data not shown). Compounds **1a**, **2a, 4a**, and **7c** are also highly selective for the σ sites relative to PCP, whereas **3a** displays the highest affinity for PCP site (K_i = 50.2 nM) and *N*-ethyl and *N*-methyl derivatives (**5a** and **6a**, respectively) show low affinity for this binding site (Table 2).

Compounds **8c** and **9c** have the highest affinity for σ_1 sites (K_i = 5.9 and 5.6 nM, respectively). However, these compounds do not show notable selectivity for σ_1 binding sites despite the presence of a *cis*-(+)-*N*-normetazocine nucleus. In fact, they also have significant affinity for opioid receptors (K_i = 79.8 and 28.8 nM, respectively). Moreover, the substitution of methyl with ethyl group or phenyl with benzyl on the second basic nitrogen provides compounds **10c** and **11c** with a lower affinity for σ_1 sites and opioid receptors.

With regard to other receptors systems, compounds **1a**−**6a** and **7c**, displaying moderate to high affinity for σ_1 binding sites, have a very low or a negligible affinity for muscarinic (M_2), dopamine (D_2), and serotonin (5-

Table 2. Binding Affinities of N-Substituted *cis*-(+)-*N*-Normetazocine Derivatives to σ, Opioid, and PCP Binding Sites



			$K_i \pm$ SEM (nM)[a]			
compd	R	R_1	[^{3}H]-(+)-Pentaz.[b] (σ_1)	[^{3}H]DTG[b] (σ_2)	[^{3}H]Nalox. (opioid)	[^{3}H](+)-SKF 10,047[b,d] (PCP)
1a	$-(CH_2)_5-$		9.6 ± 0.8	114 ± 10	12000 ± 340	>10000
2a	$-(CH_2)_2O(CH_2)_2-$		13.4 ± 1.3	300 ± 12	8168 ± 170	>10000
3a	$-(CH_2)_6-$		20.1 ± 1.8	151 ± 10	9128 ± 197	50.2 ± 0.9
4a	$-(CH_2)_4-$		7.4 ± 0.7	260 ± 11	3800 ± 120	>10000
5a	C_2H_5	C_2H_5	15.2 ± 2.1	378 ± 13	12290 ± 210	7645 ± 228
6a	CH_3	CH_3	19.8 ± 2.8	347 ± 15	2888 ± 98	3380 ± 123
7c	C_6H_{11}	H	41.6 ± 3.3	328 ± 12	1466 ± 45	>10000
8c	C_6H_5	H	5.9 ± 0.2	111 ± 9	79.8 ± 8.4	nd[e]
9c	C_6H_5	CH_3	5.6 ± 0.2	124 ± 10	28.8 ± 2.3	nd[e]
10c	C_6H_5	C_2H_5	42.2 ± 3.8	151 ± 11	211 ± 20	nd[e]
11c	$CH_2C_6H_5$	H	29.6 ± 3.2	187 ± 14	366 ± 22	nd[e]
haloperidol			1.6 ± 0.3	12.7 ± 2.4	>10000	nd[e]
(+)-pentaz.			6.1 ± 0.9	1440 ± 293	2370 ± 95	4320 ± 140
(+)-SKF 10,047			169 ± 9.82	*c*	1900 ± 39	448 ± 33

[a] Values are the mean of three separate experiments each carried out in duplicate. [b] All curves were best fit to a one-site model. [c] σ_2 Binding assays were carried out in the presence of 200 nM of (+)-SKF 10,047 to mask σ_1 binding sites; thus, it was not feasible to evaluate the K_i of this compound. [d] PCP binding assays were carried out in the presence of 5 μM of haloperidol to mask σ binding sites. [e] nd = not determined.

Table 3. Binding Affinities of N-Substituted *cis*-(+)-*N*-Normetazocine Derivatives to Muscarinic (M_2), Dopamine (D_2), and Serotonin (5-HT_2) Receptors

	$K_i \pm$ SEM (nM)[a]		
compd	[^{3}H]-*N*-methyl-scopolamine (M_2)	[^{3}H]spiroperidol (D_2)	[^{3}H]ketanserine (5-HT_2)
1a	7800 ± 350	>10000	>10000
2a	419 ± 34	>10000	>10000
3a	1840 ± 130	>10000	>10000
4a	1950 ± 110	>10000	>10000
5a	1990 ± 80	>10000	>10000
6a	>10000	>10000	>10000
7c	>10000	>10000	>10000
haloperidol	238 ± 13	1.95 ± 0.2	34 ± 8
(+)-SKF 10047	>10000	>10000	>10000

[a] Values are the mean of three separate experiments each carried out in duplicate. All curves were best fit to a one-site model.

HT_2) receptors (Table 3). Only **2a** has appreciable affinity for the muscarinic M_2 receptor (K_i = 419 nM).

According to the above-reported binding assays, compounds **1a**−**5a**, displaying little affinity for opioid receptors, were selected to be assayed in an in vivo model developed to evaluate the potential antipsychotic activity of σ_1 antagonists.[41] Compounds **1a** and **2a**, when administered ip in the mouse, suppressed in a dose-related manner the stereotyped behavior observed following ip injection of the σ_1 agonist (+)-SKF 10,047. The ED_{50} values were 0.82 mg/kg for **1a** and 0.88 mg/kg for **2a**, respectively, while for haloperidol, chosen as reference compound, the ED_{50} was 0.12 mg/kg. On the contrary, compounds **3a**−**5a** and (+)-pentazocine, when administered ip in the mouse, up to the dose of 5 mg/kg, do not affect the stereotyped behavior induced by ip injection of (+)-SKF 10,047.

Compounds **1a** and **2a** do not impair rotarod perfomance in mice when administered ip up to the dose of 30 mg/kg. Moreover, these compounds, contrary to the (+)-SKF 10,047, do not cause any significant behavioral effects and ataxia in the mouse up to the dose of 30 mg/kg, as evaluated adopting the scoring scale described by Tanaka et al.[41] (data not shown).

Discussion

Previous reports showed that the *cis*-(+)-*N*-normetazocine nucleus represents an established pharmacophore for σ ligands with fair to good selectivity with respect to opioid and PCP binding sites. Moreover, it has been also observed in other series, such as *N*-[2-(3,3-dichlorophenyl)ethyl]-*N*-methyl-2-(1-pyrrolinyl)ethylamine[42] derivatives, that optimal σ binding affinity and selectivity was mainly due to the presence of an diaminoethylene spacer. Here, we reported the synthesis, binding affinities [for σ_1, σ_2, PCP, opioid, muscarinic (M_2), dopamine (D_2), and serotonin (5-HT_2) receptors], and in vivo experiments to fully evaluate the agonist/antagonist properties of a new series of *N*-ethylamino-substituted *cis*-(+)-*N*-normetazocine derivatives.

All (+)-cis-*N*-normetazocine derivatives synthesized maintain a notable affinity for σ_1 binding sites in comparison with the reference compounds [(+)-pentazocine and (+)-SKF 10,047]. Compounds **1a**−**6a** and **7c** suggest that an optimal σ_1 binding affinity can be achieved with the presence of the second basic nitrogen tied into a cycloalkyl ring. However, an increase in the cycloalkyl ring size (**1a**−**4a**) reduces σ_1 affinity.

In the series **8c**−**11c** with an aromatic N-substituent, **8c** and **9c** show high σ_1 affinity. The introduction of lipophilic bulky substituents provides compounds **10c** and **11c** with a lower affinity.

Nevertheless, all *cis*-(+)-*N*-normetazocine derivatives synthesized show a σ_2/σ_1 binding ratio (ranging from 35 to 3.6) lower than that of (+)-pentazocine (σ_1/σ_2 = 236). Thus, the presence of an ethyleneamino spacer on (+)-cis-*N*-normetazocine nucleus seems to increase σ_2 binding affinity in comparison with (+)-pentazocine and other reported compounds.[34] However, the substituents on the ethyleneamino spanner chain were capable to modulate the selectivity with the respect to opioid and PCP binding sites. In fact, alkyl and cycloalkyl deriva-

tives do not have affinity for opioid receptors, in contrast with the analogues with aromatic substituents. These compounds show significant opioid affinities, and this effect is clearly represented by the compound **8a** which shows an higher affinity for opioid receptors (79.8 nM) when compared with other already reported analogues devoid of the second basic nitrogen.[34]

According with a previous study,[34] compounds **1a**, **2a**, **4a**−**6a**, and **7c** show that more lipophilic N-substituents seem to reduce the affinity for PCP sites. Compound **3a** represents an exception to this trend.

With respect to agonist/antagonist assays, among the tested compounds (**1a**−**5a**), **1a** and **2a** supporting a piperidine and a morpholine ring, respectively, antagonize the (+)-SKF 10,047-induced stereotyped behavior, while compounds **4a** and **5a** do not affect this behavior at all.

It is noteworthy that compounds **1a** and **2a** suppress the (+)-SKF 10,047-induced stereotyped behavior as well as the purported σ antagonist haloperidol. The in vivo experiments seem to suggest that these compounds display antagonist properties with respect to (+)-SKF 10,047. It has been reported that (+)-SKF 10,047 and other benzomorphan derivatives may cause stereotyped behavior and ataxia in rodents acting as "agonists" at σ-like sites.[42] However, compounds **1a** and **2a** do not produce any ataxia or stereotyped behavior in the mouse, thus further supporting the hypothesis that it is unlikely that they may act as an "agonists" at σ sites to cause psychotomimetic effects.[43]

The high selectivity of **1a** and **2a** for σ binding sites, with their lack of significant affinity for other receptor systems, including PCP, opioid, and dopamine D_2, which may represent other additive binding sites for several σ ligands,[33] provide strong support that these antagonist effect could be mediated by σ_1 sites.

In conclusion, we presented evidence that the N-substitution of *cis*-(+)-*N*-normetazocine nucleus with an ethylamino spacer provide compounds with a reduced σ_2/σ_1 selectivity, but with the retention of a good affinity for σ_1 sites and selectivity with respect to other binding sites. Moreover, we presented evidence that suitable functionalization may afford compounds with antagonist σ_1 properties.

Experimental Section

Reagents were purchased from Aldrich Chemical 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 precoated 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. Optical rotations were determined in MeOH solution 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). Molecular weights of the obtained products were determined by MS on a Kratos 2S RFA spectrometer using a Tektronix 4205 computer system.

Method A. General Procedure for N-Alkylation of *cis*-(+)-*N*-Normetazocine Derivatives 1a−6a. *cis*-(+)-*N*-Normetazocine (200 mg, 0.92 mmol), chloroethylamine monohydrochloride **1**−**6** (1.38 mmol), $NaHCO_3$ (115.9 mg, 1.38 mmol), and a catalytic amount of potassium iodide were added in 5 mL of dry MeOH, and the mixture was stirred at 50 °C for 4 h. The mixture reaction was cooled and diluted with 85 mL of ethyl acetate and 15 mL of water. The organic layer was separated, washed with saturated aqueous brine solution, dried over anhydrous sodium sulfate, and filtered. The filtrate was evaporated in vacuo to yield the free bases, which were purified by silica gel flash column chromatography using $CHCl_3$:EtOH (95:5) as eluent. The compounds **1a**−**6a** were dissolved in THF and treated with a solution of $H_2C_2O_4 \cdot 2H_2O$ in THF to give the oxalate salts as white solids. The analytically pure samples were obtained by recrystallization.

(+)-6(*S*),11(*S*)-Dimethyl-3-[2-(piperidin-1-yl)ethyl]-1,2,3,4,5,6-hexahydro-2(*S*),6-methanobenzazocin-8-ol oxalate (1a): 62% yield; mp 184−186 °C; $[\alpha]^{23}_D = +40°$ (*c* 1.0, EtOH); MS (EI) *m*/*z* 328 (M^+). Anal. ($C_{21}H_{32}N_2O \cdot C_2H_2O_4 \cdot 2.5H_2O$) C, H, N.

(+)-6(*S*),11(*S*)-Dimethyl-3-[2-(morpholin-4-yl)ethyl]-1,2,3,4,5,6-hexahydro-2(*S*),6-methanobenzazocin-8-ol oxalate (2a):[44] 70% yield; mp 205−206 °C; $[\alpha]^{23}_D = +40°$ (*c* 1.0, EtOH); MS (EI) *m*/*z* 330 (M^+). Anal. ($C_{20}H_{30}N_2O_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

(+)-6(*S*),11(*S*)-Dimethyl-3-[2-(Azepan-1-yl)ethyl]-1,2,3,4,5,6-hexahydro-2(*S*),6-methanobenzazocin-8-ol oxalate (3a): 35% yield; mp 187−189 °C; $[\alpha]^{23}_D = +60$ (*c* 1.0, EtOH); MS (EI) *m*/*z* 342 (M^+). Anal. ($C_{22}H_{34}N_2O \cdot C_2H_2O_4 \cdot 1.5H_2O$) C, H, N.

(+)-6(*S*),11(*S*)-Dimethyl-3-[2-(pyrrolidin-1-yl)ethyl]-1,2,3,4,5,6-hexahydro-2(*S*),6-methanobenzazocin-8-ol oxalate (4a): 67% yield; mp 181−182 °C; $[\alpha]^{23}_D = +44°$ (*c* 1.0, EtOH); MS (EI) *m*/*z* 314 (M^+). Anal. ($C_{20}H_{30}N_2O \cdot C_2H_2O_4 \cdot 1.5H_2O$) C, H, N.

(+)-6(*S*),11(*S*)-Dimethyl-3-[2-(Diethylamino)ethyl]-1,2,3,4,5,6-hexahydro-2(*S*),6-methanobenzazocin-8-ol oxalate (5a): 63% yield; mp 182−184 °C; $[\alpha]^{23}_D = +48°$ (*c* 1.0, EtOH); MS (EI) *m*/*z* 316 (M^+). Anal. ($C_{20}H_{32}N_2O \cdot C_2H_2O_4 \cdot 1.5H_2O$) C, H, N.

(+)-6(*S*),11(*S*)-Dimethyl-3-[2-(Dimethylamino)ethyl]-1,2,3,4,5,6-hexahydro-2(*S*),6-methanobenzazocin-8-ol oxalate (6a): 70% yield; mp 180−182 °C; $[\alpha]^{23}_D = +52°$ (*c* 1.0, EtOH); MS (EI) *m*/*z* 288 (M^+). Anal. ($C_{18}H_{28}N_2O \cdot C_2H_2O_4 \cdot 2H_2O$) C, H, N.

Method B. General Procedure for the Synthesis of 2-Bromo-*N*,*N*-disubstituted-acetamide Derivatives 7a−11a. To a solution of bromoacetyl chloride (4.7 g, 30 mmol) in 10 mL of dry THF cooled at 0 °C was added dropwise, under vigorous stirring, a solution of amine (20 mmol) and 4-(dimethylamino)pyridine (1.1 g, 9.4 mmol) in dry THF (20 mL). After 1 h the reaction mixture was quenched with H_2O and extracted with $CHCl_3$. The organic extract was washed with a saturated $NaHCO_3$ solution, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude products **7a**−**11a** were used with no further purification.

General Procedure for N-Substitution of *cis*-(+)-*N*-Normetazocines 7b−11b. These compounds were prepared by the same procedure described for **1a**−**6a**, starting from **7a**−**11a**. The crude products **7b**−**11b** were purified by silica gel flash chromatography using cyclohexane:ethyl acetate (70:30) as eluent.

(+)-*N*-Cyclohexyl-2-(8-hydroxy-6(*S*),11(*S*)-dimethyl-2,4,5,6-tetrahydro-1*H*-2(*S*),6-methanobenzazocin-3-yl)-acetamide (7b): 91% yield; mp 233−237 °C; MS (EI) *m*/*z* 356-(M^+).

(+)-2-(8-Hydroxy-6(*S*),11(*S*)-dimethyl-2,4,5,6-tetrahydro-1*H*-2(*S*),6-methanobenzazocin-3-yl)-*N*-phenylacetamide (8b): 69% yield; mp 256−258 °C; MS (EI) *m*/*z* 350 (M^+).

(+)-2-(8-Hydroxy-6(*S*),11(*S*)-dimethyl-2,4,5,6-tetrahydro-1*H*-2(*S*),6-methanobenzazocin-3-yl)-*N*-methyl-*N*-phenylacetamide (9b): 88% yield; mp 224−226 °C; MS (EI) *m*/*z* 364 (M^+).

(+)-*N*-Ethyl-2-(8-hydroxy-6(*S*),11(*S*)-dimethyl-2,4,5,6-tetrahydro-1*H*-2(*S*),6-methanobenzazocin-3-yl)-*N*-phenylacetamide (10b): 71% yield; mp 96−98 °C; MS (EI) *m*/*z* 378 (M^+).

(+)-*N*-Benzyl-2-(8-hydroxy-6(*S*),11(*S*)-dimethyl-2,4,5,6-

tetrahydro-1*H*-2(*S*),6-methanobenzazocin-3-yl)acetamide (11b): 91% yield; mp 103−106 °C; MS (EI) *m*/*z* 364 (M^+).

General Procedure for the Reduction of *cis*-(+)-*N*-Substituted-*N*-normetazocine Derivatives 7c−11c. To a 1 M solution of diborane in THF,[45] cooled at 0 °C and under nitrogen atmosphere, a solution of the appropriate *cis*-(+)-*N*-substituted-*N*-normetazocine **7b**−**11b** in anhydrous THF (5 mL) was slowly added. The reaction, under nitrogen atmosphere, was heated to reflux for 8 h and cooled at room temperature, and 2 mL of a 6 M hydrochloric acid solution was added slowly. THF was removed by distillation at atmospheric pressure. $NaHCO_3$ saturated solution (15 mL) was added to aqueous phase, and the latter was extracted with $CHCl_3$ (30 mL). The organic mixture was dried with anhydrous Na_2SO_4 and evaporated in vacuo to give the free bases **7c**−**11c**, which were purified by silica gel flash chromatography using $CHCl_3$:cyclohexane:EtOH (50:45:5) as eluent. The purified compounds **7c**−**11c** dissolved in THF were treated with a solution of $H_2C_2O_4 \cdot 2H_2O$ in THF to give the oxalate salts as white solids. The analytically pure samples were obtained by recrystallization.

(+)-3-(2-Cyclohexylaminoethyl)-6(*S*),11(*S*)-dimethyl-1,2,3,4,5,6-hexahydro-2(*S*),6-methanobenzazocin-8-ol oxalate (7c): 34% yield; mp 174−175 °C; $[\alpha]^{23}_D = +78°$ (*c* 1.0, EtOH); MS (EI) *m*/*z* 342(M^+). Anal. ($C_{22}H_{34}N_2O \cdot 2C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

(+)-6(*S*),11(*S*)-Dimethyl-3-(2-phenylaminoethyl)-1,2,3,4,5,6-hexahydro-2(*S*),6-methanobenzazocin-8-ol oxalate (8c): 85% yield; mp (free base) 64−65 °C; $[\alpha]^{23}_D = +74°$ (*c* 1.0, EtOH); MS (EI) *m*/*z* 336 (M^+). Anal. ($C_{22}H_{28}N_2O \cdot H_2O$) C, H, N.

(+)-6(*S*),11(*S*)-Dimethyl-3-[2-(methylphenylamino)ethyl]-1,2,3,4,5,6-hexahydro-2(*S*),6-methanobenzazocin-8-ol oxalate (9c): 61% yield; mp (free base) 67−68 °C; $[\alpha]^{23}_D = +90°$ (*c* 1.0, EtOH); MS (EI) *m*/*z* 350 (M^+). Anal. ($C_{23}H_{30}N_2O \cdot 0.5H_2O$) C, H, N.

(+)-6(*S*),11(*S*)-Dimethyl-3-[2-(ethylphenylamino)ethyl]-1,2,3,4,5,6-hexahydro-2(*S*),6-methanobenzazocin-8-ol oxalate (10c): 77% yield; mp 220 °C; $[\alpha]^{23}_D = +88°$ (*c* 1.0, EtOH); MS (EI) *m*/*z* 364 (M^+). Anal. ($C_{24}H_{32}N_2O \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

(+)-6(*S*),11(*S*)-Dimethyl-3-(2-benzylaminoethyl)-1,2,3,4,5,6-hexahydro-2(*S*),6-methanobenzazocin-8-ol oxalate (11c): 35% yield; mp 178−179 °C; $[\alpha]^{23}_D = +84°$ (*c* 1.0, EtOH); MS (EI) *m*/*z* 350 (M^+). Anal. ($C_{23}H_{30}N_2O \cdot 2C_2H_2O_4$) C, H, N.

Radioligand Binding Assays. Binding to σ_1 Sites. σ_1 binding assay was carried out on guinea pig brain membranes prepared by the method of Matsumoto et al.,[24] and protein content was evaluated.[46] Binding assay was performed as described by DeHaven et al.[47] Briefly, each tube contains 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, $n = 3$). Nonspecific binding was determined by adding 10 μM haloperidol. The reaction was performed for 150 min at 37 °C and terminated by filtration over Whatman GF/B glass filters that were presoaked in a 0.5% polyethylenimine solution.

Binding to σ_2 Sites. σ_2 binding assay was carried out on guinea pig brain membranes prepared as described by Mach et al.[48] These were incubated with 3 nM [^{3}H]DTG (35 Ci/mmol; $K_d = 9.9 \pm 0.8$ nM; $n = 3$) in the presence of 200 nM (+)-SKF 10,047 to mask σ_1 sites. Incubation was 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. Nonspecific binding was evaluated in the presence of 5 μM DTG.

Binding to Opioid Receptors. Total opioid receptor binding was assessed on rat brain membranes prepared as previously reported[49] and incubated in the presence of [^{3}H]-naloxone (55.5 Ci/mmol; $K_d = 6.6 \pm 0.7$ nM; $n = 3$). Nonspecific binding was evaluated in the presence of 10 μM naloxone. In the case of κ opioid receptor assays, binding was carried out on membranes obtained from guinea pig cerebella and 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 μ and δ receptors, respectively, and to direct the binding of the radioligand to κ receptors.[49]

Binding to PCP Sites. PCP binding assay was carried out on rat brain membranes following the procedure described by Largent et al.[50] In a final assay volume of 0.25 mL, 10 nM [^{3}H](+)-SKF 10,047 (49.2 Ci/mmol) was incubated in the presence of various concentrations of each compound with tissue homogenate (450 μg of protein/assay tube) for 30 min at room temperature. Binding assays were carried out in the presence of 5 μM haloperidol to specifically block σ sites. Nonspecific binding was estimated with 100 μM (+)-SKF 10,047. According to Largent et al.,[50] this assay procedure allows to estimate binding affinity of compounds interacting with PCP sites.

Binding to Dopaminergic (D_2) Receptors. Dopaminergic (D_2) receptor binding assay was 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 according to Briley and Langer;[51] nonspecific binding assay was measured in the presence of 10 μM haloperidol.

Binding to 5-HT_2 Receptors. Serotoninergic (5-HT_2) receptor binding assay was performed using 1 nM [^{3}H]-ketanserin (77.1 Ci/mmol; $K_d = 1.49 \pm 0.4$; $n = 3$) and guinea pig frontal cortex membranes according to the procedure described by Tam et al.;[52] nonspecific binding was measured in the presence of 1 μM methisergide.

Binding to Muscarinic (M_2) Receptors. Muscarinic (M_2) receptor binding assay was carried out in rat heart membranes prepared by the method of Waelbroeck et al.[53] Binding assay was performed in the presence of 0.5 nM of [^{3}H]-*N*-methylscopolamine (79.5 Ci/mmol; $K_d = 0.24 \pm 0.06$ nM; $n = 3$). Nonspecific binding was determined in the presence of 10 μM atropine for 120 min; the reaction was carried at room temperature and terminated by filtration on Whatman GF/B filter.

The concentration of the test compounds causing 50% inhibition of radioligand (IC_{50}) was determined from concentration−response curves in which at least 10 concentrations of test compounds were examined. Inhibition constants (K_i values) for the binding of test compounds were calculated using the EBDA/LIGAND program,[54] purchased from Elsevier/Biosoft.

Behavioral Studies. Male Swiss mice (25−30 g, Charles River, Italy) were placed individually into clear acrylic cages and left for 1 h to acclimatize to the new environment. Thirty minutes after the ip administration of haloperidol, compounds **1a**−**5a**, or (+)-pentazocine (dissolved in the vehicle) or vehicle alone (0.5% carboxymethyl cellulose in water, w/v), (+)-SKF 10,047 (30 mg/kg, ip) was administrated. Behavioral scores for 5-min periods started 10 min after (+)-SKF 10,047 administration and lasted for 40 min. The scoring scale adopted is reported by Tanaka et al.[41] Ten mice were treated with vehicle, and groups of 10 or 6 mice were treated with haloperidol (0.01−1 mg/kg) and compounds **1a**−**5a** (0.01−5 mg/kg) or (+)-pentazocine. The total score of the vehicle-treated group was defined as 100% and ED_{50} values for treated mice were determined using log-probit conversion of data.

Rotarod Test. Groups of six Swiss male mice (25−30 g) were treated with the vehicle (0.5% carboxymethyl cellulose in water, w/v) or test compound administered intraperitoneally 30 min before being placed on an accelerated rotarod (Ugo Basile, Milan, Italy) and provided three opportunities to maintain balance on the bar. Rats that failed to maintain balance in the least one of three separate trials were considered impaired.

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