Bioorganic & Medicinal Chemistry 19 (2011) 7612–7622

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and binding assays of novel 3,3-dimethylpiperidine derivatives with various lipophilicities as σ_1 receptor ligands

Savina Ferorelli, Carmen Abate, Maria P. Pedone, Nicola A. Colabufo, Marialessandra Contino, Roberto Perrone, Francesco Berardi *

Dipartimento Farmacochimico, Università degli Studi di Bari, Via Orabona 4, I-70125 Bari, Italy

ARTICLE INFO

Article history:
Received 28 July 2011
Revised 4 October 2011
Accepted 7 October 2011
Available online 17 October 2011

Keywords:
σ_1 Ligands
3,3-Dimethylpiperidines
Structure–activity relationship
Δ_8–Δ_7 Sterol isomerase binding
σ Binding

ABSTRACT

Starting from two carbocyclic analogs, a series of 3,3-dimethylpiperidine derivatives was prepared and tested in radioligand binding assays at σ_1 and σ_2 receptors, and at Δ_8–Δ_7 sterol isomerase (SI) site. The novel compounds mostly bear heterocyclic rings or bicyclic nucleus of differing lipophilicities. Compounds **18a** and **19a,b** demonstrated the highest σ_1 affinity (K_i = 0.14–0.38 nM) with a good selectivity versus σ_2 binding. Among them, **18a** had the lowest *C*log*D* value (3.01) and only **19b** was selective versus SI too. Generally, it was observed that more planar and hydrophilic heteronuclei conferred a decrease in affinity for both σ receptor subtypes.

1. Introduction

The recent high interest in sigma receptors descends from the discovery that both σ_1 and σ_2 subtypes[1] are overexpressed in many human and nonhuman tumors.[2–4] For this reason, the pharmacological study on σ-receptor ligands plays an important role in the cancer research for potential clinical treatment and imaging diagnosis applications by means of positron emission tomography (PET), and single photon emission computed tomography (SPECT) techniques.[5,6]

The σ_1 receptor shows no homology with other mammalian proteins and shares 30% identity with the yeast Δ_8–Δ_7 sterol isomerase (SI), so that the belonging of σ receptors to the family of sterol isomerases was proposed.[7] The σ_1 receptor is a 29-kDa single protein and its gene was cloned from guinea pig liver,[8] mouse kidney, JAR human choriocarcinoma cell line, and from rat and mouse brain.[9] The σ_2 receptor subtype was not reproduced by clonation, and its structure has not been fully identified yet.[10,11] The σ_1 receptors are distributed in many peripheral tissues of the endocrine and immune systems (e.g., adrenal gland, testis, ovary, spleen, and blood leukocytes)[12] but they are also concentrated in the central nervous system (CNS), particularly in brainstem motor regions.[13,14] They are located on the cell and endoplasmic reticulum (ER) membranes[15,16] and are formed by two transmembrane domains with one extracellular loop.[17] The σ_1 receptor has been proven to regulate voltage-gated potassium channels, intracellular Ca^{2+} release,[18] and intracellular displacement of galactosylceramide-enriched membrane microdomains.[19] The modulation of ion channels in the plasma membrane can regulate the membrane excitability,[18] and modulate the effects of cocaine.[18] A recent study identified the σ_1 receptor as a novel ER chaperone.[20] In the CNS the σ_1 receptors are involved in various neurotransmitter systems, such as glutamatergic, dopaminergic, serotonergic, adrenergic, and cholinergic systems,[21] so that this receptor plays an important role in neuropsychiatric and neurodegenerative diseases. σ_1 Receptor ligands have been proposed and tried clinically for anxiety, depression, schizophrenia, learning and memory improvement, cocaine addiction, and drug abuse.[18]

Several unrelated structures are known to bind selectively the σ_1 receptor, and the (+)-pentazocine represents a typical selective agonist used also as a tritiated radioligand (Fig. 1). Other selective σ_1 ligands have been developed and are routinely used for studying σ receptors. Examples are 1-[2-(3,4-dimethoxyphenyl)ethyl]-4-(3-phenylpropyl)piperazine (**SA 4503**), *N*,*N*-dipropyl-2-[4-methoxy-3-(2-phenylethoxy)phenylethylamine (**NE 100**), and *N*-[(2*Z*)-3-(3-chloro-4-cyclohexylphenyl)-2-propen-1-yl]-*N*-ethylcyclohexanamine hydrochloride (**SR 31747A**) (Fig. 1). Currently, the number of σ_1 ligands is increasing with the development of new compounds such as 1′-benzyl-3-methoxy-3,4-dihydrospiro[[2]-benzopyran-1, 4′-piperidine][22] (**A**) and (±)-2-(1-benzylpiperidin-4-yl)-2,3-dihydrotiocromen-4-one,[23] (**B**) which display high σ_1 receptor affinity and selectivity.

In our previous works, about σ ligands, we investigated σ subtype selectivity in the class of 3,3-dimethyl-*N*-[ω-(tetralin-1-yl and indan-1-yl)alkyl]piperidine.[24,25] High σ_1-receptor affinity and

* Corresponding author. Tel.: +39 080 5442751; fax: +39 080 5442231.
E-mail address: berardi@farmchim.uniba.it (F. Berardi).

0968-0896/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2011.10.023

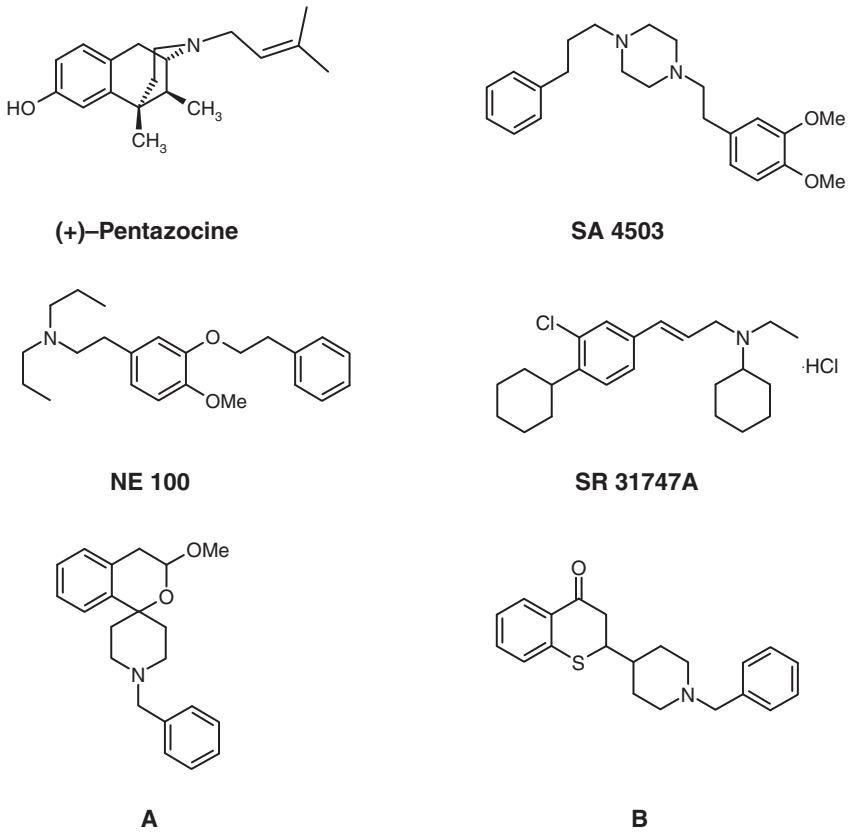


Figure 1. Structures of representative σ_1 ligands.

a certain σ_1/σ_2 selectivity were obtained with an intermediate alkyl chain of four methylenes with a 6-methoxytetralin (**1**) or indane (**2**) nucleus (Table 1). The tetralin and the indane derivatives have been designed to interact with the primary hydrophobic site of the σ_1 receptor model proposed by Glennon,[26–28] and the basic nitrogen atom of 3,3-dimethylpiperidine may interact with a receptor proton–donor site. Moreover, among various methylpiperidine derivatives, the ligands bearing the 3,3-dimethylpiperidine moiety selectively bind to σ_1 relative to σ_2 receptor, although they possessed high lipophilicity values.[29] In an extension of these works, we synthesized other analogs in order to obtain compounds with better selectivity for σ_1 receptor subtype, with suitable lipophilicity values for optimal pharmacokinetics. Therefore we prepared and tested a series of 3,3-dimethylpiperidine derivatives presenting different levels of lipophilicity, where the carbocyclic moieties were mostly replaced by various heteronuclei. Starting from **1** and **2** as lead compounds, more lipophilic upper homologs benzosuberanes were prepared. Less lipophilic compounds were obtained by replacement of indane and tetralin rings with heterocyclic rings. Tetrahydroindole, tetrahydrobenzothiophene, and benzosuberane derivatives were synthesized and investigated as racemates. Other heterocyclic nuclei were chosen to avoid inconvenient stereogenic centers, also because the stereoselectivity in these series of compounds plays a marginal role. Furthermore, the length of the intermediate chain, and consequently its flexibility, were varied in some cases. Given the pharmacological similarity between σ_1 receptor and SI, we conducted SI binding assays for a number of compounds.[7,25]

2. Chemistry

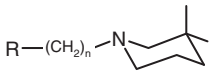
The synthesis of final compounds **13, 16, 17, 18a,c**, and **19a,b**, is depicted in Scheme 1. The key intermediates **8a, 9a, 10a,c**, and **11a,b** were prepared from ketones **4–7** via Grignard reaction as already reported.[30] The compound **8a** was prepared after derivatization of the 6,7-dihydro-1*H*-indol-4(5*H*)-one (**3**) to its *N*-tosyl derivative **4**,[31] whereas 6,7-dihydro-1-benzofuran-4(5*H*)-one (**5**), 6,7-dihydro-1-benzothiophen-4(5*H*)-one (**6**), and 6,7,8,9-tetrahydrobenzo[7]annulen-5-one (**7**) were from a commercial source. The intermediate **10a** has been previously obtained and reported.[32] The intermediate compound **12** was prepared by alkylation of 3,3-dimethylpiperidine with bromopropyl derivative **8a**. The final compound **13** was prepared by deprotection of the corresponding tosyl derivative **12** in the presence of K_2CO_3.[33] Bromopropylderivatives **9a** and **10a** were aromatizated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to afford the corresponding bromopropylnaphthalenes **14** and **15**.[34] The final compounds **16, 17, 18c**, and **19a,b** were obtained from the intermediates **14, 15, 10c**, and **11a,b**, respectively, and 3,3-dimethylpiperidine,[25] as for compound **12**. Compound **18a** has already been reported as its oxalate salt.[32]

The preparation of the (benzofuranyl)methyl compound **22** is depicted in Scheme 2. 2-Hydroxymethyl-1-benzofuran[35] (**20**) treated with thionyl chloride provided chloromethyl compound **21**, which was derivatized with 3,3-dimethylpiperidine to give the final amine compound **22**.

The preparation of final compounds **28–31** is depicted in Scheme 3. The esters **24a,b**[36] were obtained by reaction of indole **23a** and benzotriazole **23b**, respectively, with ethyl acrylate, and were reduced by $LiAlH_4$ to the alcohols **26a,b**. Similarly, the alcohol **26c** was obtained from commercially available ester **25**. By treating each of these alcohols and the commercial product 4-cyclohexylbutan-1-ol (**26d**) with mesyl chloride, the corresponding mesyl derivatives **27a–d** were prepared.[24] These derivatives were reacted with 3,3-dimethylpiperidine to give the final amine compounds **28–31**.[25]

The preparation of final thiazole-containing derivatives **34** and **36–38** is depicted in Scheme 4. 2-Amino-5,6-dihydro-1,3-ben-

Table 1
*C*log*D* values, binding affinities and selectivities for target compounds



Compound	R	*n*	*C*log*D*[a]	K_i ± SEM (nM)			K_i ratio σ_2/σ_1
				σ_1	σ_2	SI	
1[b]	5-Methoxytetralin-1-yl	4	4.51	2.12 ± 0.30	247 ± 52	0.67 ± 0.19	117
2[b]	Indan-1-yl	4	4.03	1.75 ± 0.12	242 ± 59	1.54 ± 0.01	138
13	4,5,6,7-Tetrahydroindol-4-yl	3	1.82	27.1 ± 2.7	119 ± 41	NT[c]	4.4
16	Benzofuran-4-yl	3	2.97	63.5 ± 7.0	42.3 ± 9.8	1.1	0.7
17	Benzothiophen-4-yl	3	4.67	52.0 ± 12.0	63.6 ± 12.6	0.9	1.2
18a	4,5,6,7-Tetrahydrobenzothiophen-4-yl	3	3.01	0.21 ± 0.01[d]	38	3.07 ± 1.43	~180
18c	4,5,6,7-Tetrahydrobenzothiophen-4-yl	5	4.79	78%[e]	28.1 ± 2.1	2.11 ± 1.00	
19a	Benzosuberan-1-yl[f]	3	3.88	0.38 ± 0.18	37.5 ± 0.1	0.2	101
19b	Benzosuberan-1-yl[f]	4	5.15	0.14 ± 0.04	65.9 ± 12.0	7.3	471
22	Benzofuran-2-yl	1	2.98	3690 ± 890	1810 ± 100	NT	0.4
28	Indol-1-yl	3	2.74	50.9 ± 11.1	194 ± 26	NT	3.8
29	Benzotriazol-1-yl	3	1.71	339 ± 16	1990 ± 490	NT	5.6
30	Indol-3-yl	3	2.31	41.6 ± 7.2	110 ± 17	NT	2.6
31	Cyclohexyl	4	4.06	1.02 ± 0.22	19.6 ± 1.9	3.8	19
34	4,5,6,7-Tetrahydrobenzothiazol-7-one-2-aminocarbonyl	1	3.19	$>10^4$	$>10^4$	$>10^4$	
36	4,5,6,7-Tetrahydrobenzothiazol-7-one-2-amino	2	2.74	$>10^4$	$>10^4$	$>10^4$	
37	Benzothiazol-2-amino	2	2.96	566 ± 160	742 ± 80	115	1.3
38	Thiazol-2-amino	2	1.28	459 ± 27	3330 ± 1030	1400 ± 470	7.2
41	3,3-Dimethylpiperidin-1-yl	4	1.32	14.1 ± 2.6	414 ± 148	213	29
(+)-Pentazocine				3.16 ± 0.34			
DTG					34.3 ± 1.6		
(±)-Ifenprodil						15.0 ± 2.5	

[a] Referred to the corresponding free bases at pH 7.4.
[b] From Ref. 25.
[c] Not tested.
[d] Previous result for oxalate salt in rat brain membranes, K_i > 3960 (Ref. 32).
[e] Pecentage of binding inhibition at 10^{-10} M compound.
[f] I. e. 6,7,8,9-tetrahydrobenzo[7]annulen-5-yl.

zothiazol-7(4*H*)-one[37] (**32a**) and the commercially available 2-amino-1,3-benzothiazole (**32b**) and 2-amino-thiazole (**32c**) were subjected to acetylation with chloroacethyl chloride to achieve chloroacetamides **33a–c**. Compounds **33a** was derivatized with 3,3-dimethylpiperidine to give the final compounds **34**. Compounds **33a–c** were then reduced with $LiAlH_4$ to the corresponding chloroderivatives **35a–c**. Finally, all the haloalkyl compounds **35a–c** were derivatized with 3,3-dimethylpiperidine to give the final amine compounds **36–38**.[25]

The preparation of final bis-3,3-dimethylpiperidine derivative **41** is depicted in Scheme 5. Bisimide intermediate **40** was obtained by derivatization of 2,2-dimethylglutaric acid (**39**) to the 2,2-dimethylglutaryl chloride and subsequent cyclization with butane-1,4-diamine. Reduction of this latter compound with $LiAlH_4$ led to the final diamine compound **41**.

The final amine compounds **16**, **17**, **18a,c**, **19a,b**, **22**, **29**, **31**, **34–38**, and **41** were converted to the corresponding hydrochloride salts with gaseous HCl in anhydrous Et_2O, and then the salts were recrystallized from MeOH/Et_2O. These salts were used for receptor binding experiments, whereas the compounds **13**, **28**, and **30** were used as free bases. The binding results are listed in Table 1, along with the calculated values of the logarithm of the distribution coefficient (*C*log*D*) at pH 7.4 for the corresponding free bases.[38]

3. Biology

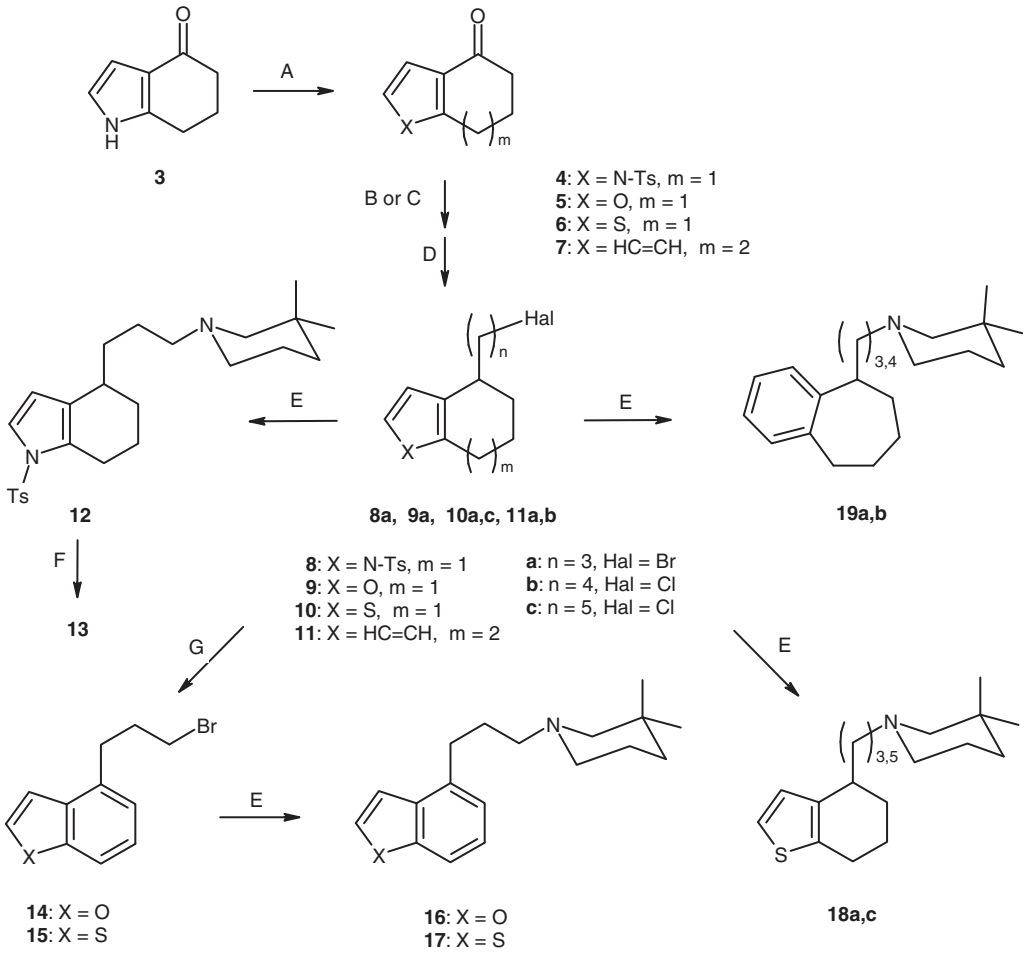
3.1. Receptor binding studies

All the compounds listed in Table 1 were evaluated by radioreceptor binding assays for in vitro affinity at σ_1 and σ_2 receptors and almost all of them were evaluated, at least once, at mammalian Δ_8–Δ_7 sterol isomerase (SI) site. The specific radioligands and tissue sources were respectively: (a) σ_1 receptor, (+)-[^{3}*H*]-pentazocine ((+)-[2*S*-(2α,6α,11*R*)]-1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocine-8-ol), guinea-pig brain membranes without cerebellum; (b) σ_2 receptor, [^{3}H]-DTG in the presence of 1 μM (+)-pentazocine to mask σ_1 receptors, rat liver membranes; and (c) SI site, (±)-[^{3}H]-emopamil, guinea-pig liver membranes. The following compounds were used to define the specific binding reported in parentheses: (a) (+)-pentazocine (72–88%), (b) compound DTG (87–96%), and (c) (±)-ifenprodil (70–85%). Concentrations required to inhibit 50% of radioligand specific binding (IC_{50}) were determined by using 6–9 different concentrations of the drug studied in two or three experiments with samples in duplicate. Scatchard parameters (K_d and B_{max}) and apparent inhibition constants (K_i) values were determined by nonlinear curve fitting, using the Prism, version 3.0, GraphPad software.[39]

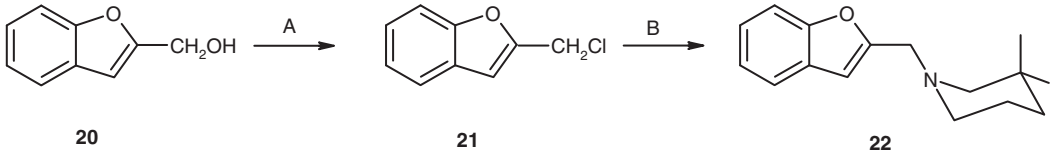
4. Results and discussion

4.1. Radioligand binding

The binding data for the new compounds synthesized and the lead compounds **1** and **2** are reported in Table 1 and are expressed as K_i values. For all the compounds the *C*log*D* values are reported and they are included in the 1.28–5.15 range. Among all the 3,3-dimethylpiperidine derivatives only compounds **18a**, **19a,b**, and **31** displayed high affinity towards σ_1 receptor (K_i = 0.14–1.02 nM). Compounds **19a,b** showed subnanomolar σ_1 receptor affinity (K_i = 0.38 and 0.14 nM, respectively) and high selectivities for σ_1 relative to σ_2 receptor (101- and 471-fold, respectively). Moreover, the apparent Hill slope values for **19a,b** were ~1. Compounds **13**, **16**, **17**, **28**, **30**, and **41** showed moderate affinities toward σ_1 receptor (K_i = 14.1–63.5 nM), but their σ_1 relative to σ_2 selectivity was less than five-fold, except for **41** (29-fold). All the other compounds demonstrated either poor or no affinity for both σ receptor

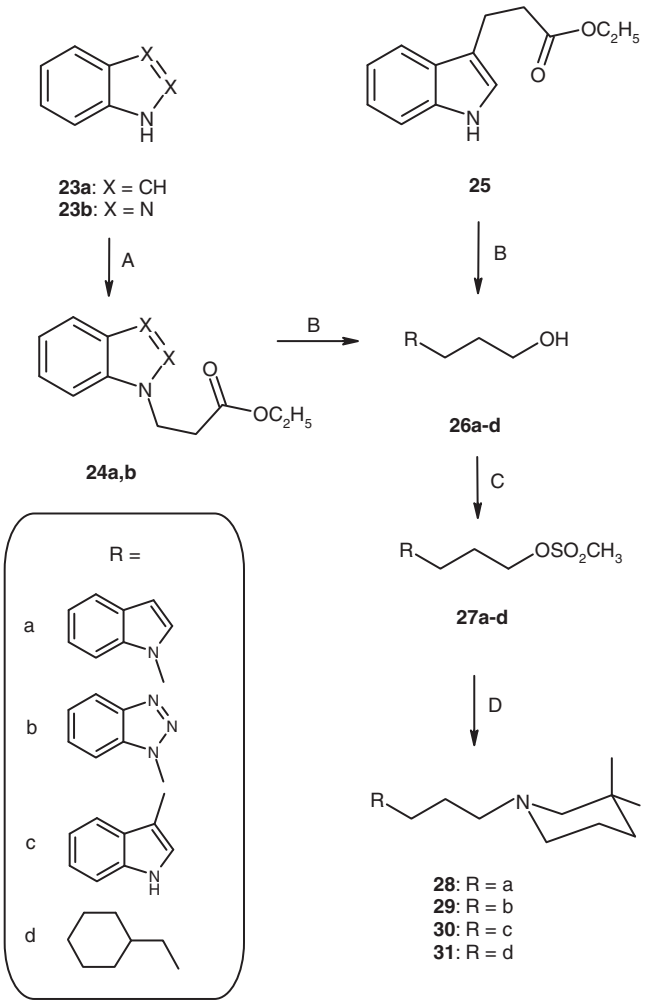


Scheme 1. Synthesis of 3,3-dimethylpiperidine derivatives **13**, **16**, **17**, **18a**,**c**, and **19a**,**b**. Reagents: (A) tosyl chloride; (B) cyclopropyl bromide, Mg and then HBr; (C) Cl–$(CH_2)_{4,5}$–Br, Mg; (D) H_2, 5% Pd/C; (E) 3,3-dimetylpiperidine; (F) MeOH/H_2O, K_2CO_3; (G) DDQ.



Scheme 2. Synthesis of 3,3-dimethylpiperidine (benzofuranyl)methyl derivative **22**. Reagents: (A) $SOCl_2$; (B) 3,3-dimethylpiperidine.

subtypes (compounds **22**, **29**, **34**, and **36**–**38**). However, compound **18c** did not show concentration-dependent behavior, probably because of its highly lipophilic structure. Affinity toward σ_2 receptor was only moderate (K_i = 19.6–65.9 nM) for compounds **16**, **17**, **18a,c**, **19a,b**, and **31**, so that no σ_1/σ_2 selectivity was recorded for compounds **16** and **17**. For some compounds the SI affinity was also tested and compound **19a** showed one of the highest affinities known towards SI (K_i = 0.2 nM). Among these 3,3-dimethylpiperidine derivatives only the highest-affinity σ_1 ligand **19b** can be considered selective relative to SI site too (~50-fold). Furthermore, it possesses also the highest *C*log *D* values (5.15). Compared to the lead compounds **1** and **2**, the σ_1 affinity seems to be strongly influenced by the replacement of the tetralin and the indane moieties with other nuclei. Indeed, only compounds **19a,b** with a more lipophilic benzosuberane nucleus and three- or four-methylene intermediate chain, displayed very high affinities toward σ_1 receptor. Therefore, the compound **19b** demonstrated better affinity and selectivity (471-fold) for σ_1 receptor than compounds **1** and **2**, whose structural requirements are in accordance with those for **19b**. Taking into consideration the highest-affinity σ_1 ligand **18a** (K_i = 0.21 nM), a convenient reduced *C*log *D* value and a good selectivity relative to σ_2 binding were recorded. Elongation of the intermediate chain to five methylenes (compound **18c**) led to a more flexible and highly lipophilic compound, which bound in a nonspecific manner at σ_1 receptors. Also interesting are the data of compound **31**, since it demonstrated good σ_1 receptor affinity (K_i = 1.02 nM) in the same magnitude order as lead compounds. Nevertheless, it revealed an about 10-fold higher σ_2 receptor affinity, and so a worse selectivity. In this compound again a lipophilic nucleus as the cyclohexyl ring and a four-membered intermediate chain are present. The reduced affinity of compounds **13** compared to compound **18a**, might be due to the presence of the =NH function in the latter compound. The benzofuran **16** and benzothiophene **17** displayed comparable lower σ_1 affinity and selectivity versus σ_2 receptor. From comparison of tetrahydrobenzothiophene **18a** to benzothiophene **17** it emerges that a rather planar bicyclic structure appeared to be



Scheme 3. Synthesis of 3,3-dimethylpiperidine derivatives **28**–**31**. Reagents: (A) CH=CH–COOEt; (B) $LiAlH_4$; (C) CH_3SO_2Cl; (D) 3,3-dimethylpiperidine.

detrimental for σ_1 binding. This is confirmed by all bicyclic compounds with an extensive electronic conjugation, compared to partially cycloaliphatic ones. When an =NH function was present in the moiety vicariant tetralin or indane, lipophilicity mostly decreases, but also a hydrogen-bonding donor function was provided. For compound **29**, a considerable decrease in the σ_1 and σ_2 affinity (K_i = 339 and 1990 nM, respectively) was observed probably because of higher hydrophilicity of benzotriazole nucleus compared to indole **13**, **28**, and **30**. The compounds **22**, **34**, and **36–38** displayed a dramatic decrease in σ_1 receptor affinity: eventually, more hydrophilic heteronuclei decreased σ_1 receptor and sometimes also σ_2 receptor binding. In addition their shorter chain (one- or two-methylene) might prevent the interaction with the σ_1 receptor primary hydrophobic site.

Although an accurate correlation between σ subtype binding and *C*log*D* was not pointed out, in general the compounds with the lowest *C*log*D* values displayed poor affinities toward σ receptors.

As for binding at SI site, the compound **19a** provided an affinity comparable to that at σ_1 receptor and its K_i value was the highest (0.2 nM) in this class. Also compounds **16** and **17** displayed good SI affinities (K_i = 1.1 and 0.93 nM, respectively) which, together with a moderate σ binding, led these compounds to be selective relative to σ receptors. However these SI binding data have only an indicative value because they were mostly obtained from a unique experiment.

5. Conclusions

With the aim of targeting σ_1 receptors whose density is high in the CNS and in tumors, we synthesized a series of 3,3-dimethylpiperidine derivatives with a wide range of lipophilicity in order to reach a compromise between pharmacodynamic and pharmacokinetics requirements. Lipophilicity of drugs is a determining factor with a log*D* <3.0 (pH 7.4) considered suitable for their entrance in both the CNS[40] and peripheral tumors.[41] The only compound of the series potentially reaching this compromise was **18a** which presented a nanomalor σ_1 affinity, appreciable σ_1/σ_2 selectivity and an optimal lipophilicity (*C*log*D* = 3.01). Compounds with lower *C*log*D* values were in general characterized by decreased σ_1 affinity or σ_1/σ_2 selectivity. On the other hand, compounds with higher *C*log*D* values were in general accompanied by noteworthy σ_1 affinities. In fact, compound **19b** presented the highest σ_1 affinity and σ_1/σ_2 selectivity of the series, but its *C*log*D* (5.15) value was too high to be considered optimal. Apparently, a correlation between σ subtype binding and *C*log*D* values exists although not strictly consistent. Furthermore rather planar bicyclic structure appeared detrimental for σ_1 binding, in accordance with a recent work, in which nonplanar tricyclic compounds derived from *Stemona* alkaloids displayed nanomolar σ_1 receptor affinity.[42] Overall, new insights for the σ_1 receptors binding were given and the promising σ_1 receptor ligand **18a** was developed.

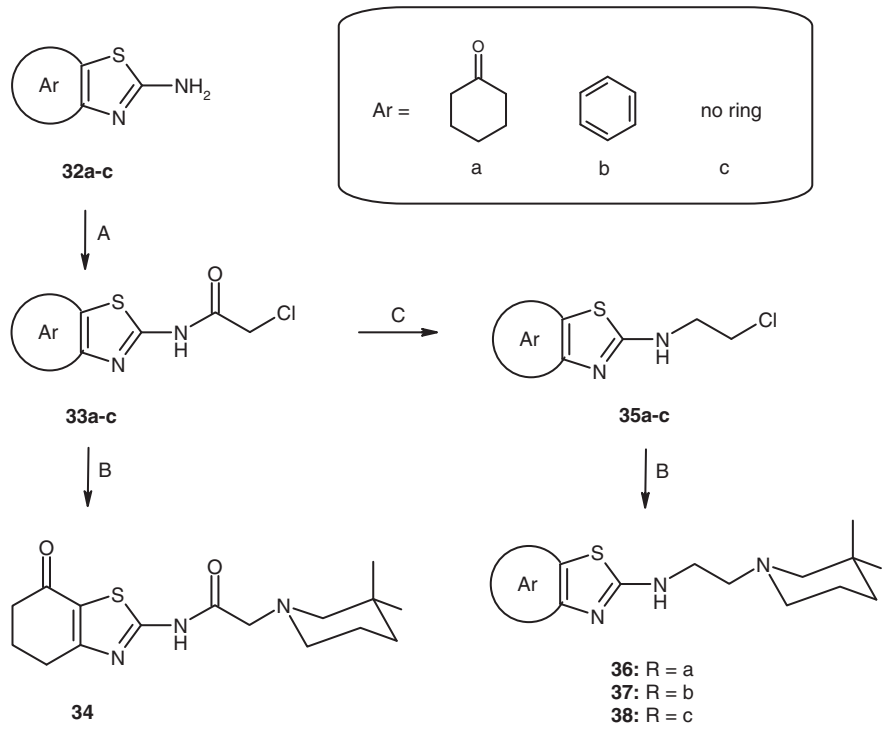
6. Experimental section

6.1. Chemistry

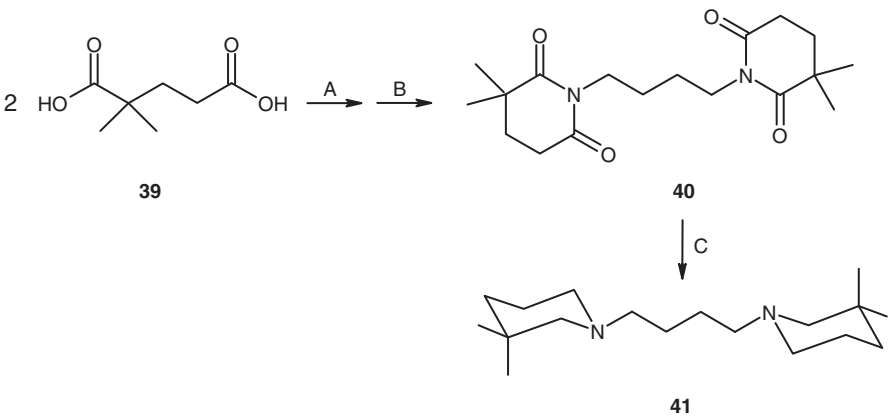
Both column chromatography and flash column chromatography were performed with 60 Å pore size silica gel as the stationary phase (1:30 w/w, 63–200 μm particle size, from ICN and 1:15 w/w, 15–40 μm particle size, from Merck, respectively). Melting points were determined in open capillaries on a Gallenkamp electrothermal apparatus. Purity of tested compounds was established by combustion analysis, confirming a purity >95%. Elemental analyses (C, H, N) were performed on an Eurovector Euro EA 3000 analyzer; the analytical results were within ±0.4% of the theoretical values, unless otherwise indicated. ^{1}H NMR spectra were recorded on a Mercury Varian 300 MHz using $CDCl_3$ as solvent, unless otherwise reported. The following data were reported: chemical shift (δ) in ppm, multiplicity (s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet), integration and coupling constants in hertz. Recording of mass spectra was done on an Agilent 6890-5973 MSD gas chromatograph/mass spectrometer and on an Agilent 1100 series LC–MSD trap system VL mass spectrometer; only significant *m*/*z* peaks, with their percentage of Infrared spectra were recorded on a Perkin–Elmer FTIR Spectrum one. Relative absorbance intensity is reported in parentheses. Chemicals were from Aldrich and Across and were used without any further purification.

6.1.1. *N*-Tosyl-6,7-dihydro-1*H*-indol-4-(5*H*)-one (4)

To a solution of 6,7-dihydro-1*H*-indol-4-(5*H*)-one (**3**) (2.50 g, 18.5 mmol) in toluene (37 mL) was added tetrabutylammonium hydrogensulfate (0.46 g, 1.35 mmol) and a 50% aqueous solution of KOH (23 mL). The mixture was stirred, at room temperature for 10 min, under a stream of N_2. Then, a solution of *p*-toluenesulfonyl chloride (3.70 g, 19.5 mmol) in toluene (37 mL) was added and the reaction mixture was stirred for 4 h, at room temperature. The separated organic mixture was washed with H_2O (3 × 10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to afford the crude white solid (4.0 g), which was recrystallized by ethanol. Title compound (4.01 g) was obtained in 75% yield. ^{1}H NMR δ 2.04–2.12 (m, 2H, $COCH_2CH_2CH_2$), 2.36–2.46 (m + s, 5H, $COCH_2CH_2CH_2$, CH_3), 2.96 (t, 2H, *J* = 6.0 Hz, $COCH_2CH_2CH_2$), 6.61 (d, 1H,



Scheme 4. Synthesis of 3,3-dimethylpiperidine thiazole-containing derivatives **34** and **36–38**. Reagents: (A) $ClCH_2COCl$, ethylenglycol dimethylether, Et_3N; (B) 3,3-dimethylpiperidine; (C) $BF_3O(C_2H_5)_2$, $(CH_3)_2S{\cdot}BH_3$.



Scheme 5. Synthesis of bis-3,3-dimethylpiperidine derivative **41**. Reagents: (A) $SOCl_2$; (B) $H_2N–(CH_2)_4–NH_2$; (C) $LiAlH_4$.

J = 3.5 Hz, *CH*CHN), 7.23 (d, 1H, *J* = 3.5 Hz, CH*CH*N), 7.34–7.74 (m, 4H, aromatic); GC–MS *m/z* 290 (M^++1, 19), 289 (M^+, 100), 155 (50), 134 (73), 106 (66), 91 (96), 107 (100).

6.1.1.1. 4-(3-Bromopropyl)-1-tosyl-1*H*-4,5,6,7-tetrahydroindole (8a). The crude residue was chromatographed on a silica gel column with petroleum ether/CH_2Cl_2 (8/2) as eluent. (0.70 g), 41% yield. ^{1}H NMR δ 1.78–3.00 (m + s, 14H, $(CH_2)_3CH(CH_2)_2CH_2Br$ and CH_3), 3.34–3.50 (m, 2H, CH_2Br), 6.35–6.39 (m, 1H, NCHC*H*), 7.18–7.20 (m, 1H, NC*H*CH), 7.29–7.68 (m, 4H, aromatic); GC–MS *m/z* 397 (M^++2, 8), 396 (M^++1, 2), 395 (M^+, 8), 274 (100).

6.1.1.2. 4-(3-Bromopropyl)-4,5,6,7-tetrahydrobenzofuran(9a). The crude residue was chromatographed on a silica gel column with petroleum ether/CH_2Cl_2 (95/0.5) as eluent. Title compound (0.30 g) was obtained in 15% yield. ^{1}H NMR δ 1.15–2.05 (m, 8H, $CH_2(CH_2)_2CH(CH_2)_2CH_2Br$), 2.48–2.65 (m, 3H, benzylic CH_2 and CH), 3.48 (t, 2H, *J* = 6 Hz, CH_2Br), 6.24–7.27 (m, 2H, aromatic); GC–MS *m/z* 244 (M^++2, 22), 243 (M^++1, 3), 242 (M^+, 22), 121 (100).

6.1.1.3. 4-(5-Chloropentyl)-4,5,6,7-tetrahydro-1-benzothiophene (10c). The crude residue was chromatographed on a silica gel column with petroleum ether/CH_2Cl_2 (9/1) as eluent. Title compound (0.43 g) was obtained in 25% yield. ^{1}H NMR δ 1.26–1.76 (m, 8H, $CH_2(CH_2)_2CH_2Cl$ and endo CH_2CH_2), 1.55–1.62 (m, 4H, $CHCH_2(CH_2)_2CH_2CH_2Cl$), 2.52–2.84 (m, 3H, benzylic CH_2 and CH), 3.45 (t, 2H, *J* = 7 Hz, CH_2Cl), 6.60–7.08 (m, 2H, aromatic); GC–MS *m/z* 244 (M^++1, 7), 243 (M^+, 3), 137 (100).

6.1.1.4. 5-(3-Bromopropyl)-6,7,8,9-tetrahydrobenzo[7]annulene (11a). ^{1}H NMR δ 1.40–1.91(m, 10H, $(CH_2)_3CH(CH_2)_2CH_2Br$), 2.70–2.90 (m, 3H, benzylic CH_2 and CH), 3.31–3.71(m, 2H, CH_2Br), 7.02–7.18 (m, 4H, aromatic); GC–MS *m/z* 268 (M^++2, 7), 267 (M^++1, 4), 266 (M^+, 5), 145 (100).

6.1.1.5. 5-(4-Chlorobutyl)-6,7,8,9-tetrahydrobenzo[7]annulene (11b). ^{1}H NMR δ 1.18–1.91(m, 12H, $(CH_2)_3CH(CH_2)_3CH_2Br$), 2.72–2.88 (m, 3H, benzylic CH_2 and CH), 3.60 (t, 2H, J = 7 Hz, CH_2Cl), 7.02–7.11 (m, 4H, aromatic); GC–MS *m/z* 238 (M^++2, 9), 237 (M^++1, 5), 236 (M^+, 24), 145 (100).

6.1.1.6. 4-[3-(3,3-Dimethylpiperidin-1-yl)-propyl]-1-tosyl-1*H*-4,5,6,7-tetrahydroindole (12). 4-(3-Bromopropyl)-1-tosyl-1*H*-4,5,6,7-tetrahydroindole (**8a**) (0.38 g, 0.95 mmol) was stirred and refluxed overnight in CH_3CN with 3,3-dimethylpiperidine (0.14 g, 1.3 mmol) and Na_2CO_3. The work up was carried out as previously described.[24] The crude residue was purified by column chromatography using CH_2Cl_2/MeOH (9:1) as eluent to give the target compound as a yellow oil in 92% yield; ^{1}H NMR δ 0.9 (s, 6H, $C(CH_3)_2$), 1.21–1.38 (m, 4H, CCH_2CH_2), 1.58–1.77 (m, 8H, $CH(CH_2CH_2)_2$), 1.98–2.38 (m, 6H, $CH_2N(CH_2)_2$), 2.41 (s, 3H, CH_3), 2.58–2,85 (m, 3H, benzylic), 6.13–7.79 (m, 6H, aromatic); GC–MS *m/z* 429 (M^++1, 4), 428 (M^+, 9), 126 (100).

6.1.1.7. 3,3-Dimethyl-1-[3-(1*H*-4,5,6,7-tetrahydroindol-4-yl)propyl]piperidine (13). Tosyl derivative **12** (0.080 g, 0.187 mmol) was stirred and refluxed in MeOH and H_2O with K_2CO_3 (0.100 g, 0.73 mmol) for 44 h under N_2. Then the mixture was cooled, and the solvent was removed in vacuo to give a brown oil. This oil was dissolved in H_2O and slowly acidified to pH 2–4 with 20% HCl while maintaining efficient cooling and stirring. The aqueous solution was saturated with solid NaCl and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with H_2O (3 × 10 mL) and brine (3 × 10 mL), dried (Na_2SO_4) and concentrated in vacuo to afford a brown oil. The crude residue was purified by column chromatography using CH_2Cl_2/MeOH (9:1) as eluent to give the target compound as a yellow oil in 65% yield; ^{1}H NMR δ 1.10 (s, 6H, $C(CH_3)_2$), 1.41–1.48 (m, 4H, CCH_2CH_2), 1.50–1.65 (m, 8H, $CH(CH_2CH_2)_2$), 2.16–2.38 (m, 6H, $CH_2N(CH_2)_2$), 2.58–2,78 (m, 3H, benzylic), 5.15 (s, 1H, NH), 5.69–6.20 (m, 2H, aromatic); GC–MS *m/z* 275 (M^++1, 2), 274 (M^+, 21), 273 (100), 160 (32), 126 (45).

6.1.1.8. 4-(3-Bromopropyl)-1-benzofuran (14). The haloalkyl compound **9a** (1.9 g, 8.0 mmol) was refluxed with 2,2-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (4.3 g, 20 mmol) in toluene (100 mL) under stirring. This reaction was carried out as previously described.[32] Crude product was purified by column chromatography using petroleum ether/CH_2Cl_2 (8:2) as eluent to give the target compound as a yellow oil (0.23 g, 12% yield); ^{1}H NMR δ 2.25 (m, 2H, J = 6.3 Hz, CH_2CH_2Br), 2.98–3.10 (m, 2H, benzylic), 3.42 (t, 2H, J = 6.3 Hz, CH_2Br), 6.84 (d, 1H, J = 2.3 Hz, OCHCH), 7.05–7.39 (m, 3H, aromatic), 7.62 (d, 1H, J = 2.2 Hz, OCH); GC–MS *m/z* 240 (M^++2, 49), 239 (M^++1, 7), 238 (M^+, 47), 131 (100).

6.1.1.9. 4-(3-Bromopropyl)-1-benzothiophene (15). This compound was prepared as for compound **14**. Crude product was purified by column chromatography using petroleum ether/ethyl acetate (8:2) as eluent to give the target compound as a yellow oil (0.51 g, 26% yield); ^{1}H NMR δ 2.27 (m, 2H, J = 6.3 Hz, CH_2CH_2Br), 3.13 (t, 2H, J = 7.1 Hz, benzylic), 3.44 (t, 2H, J = 6.6 Hz, CH_2Br), 7.18–7.77 (m, 5H, aromatic); GC–MS *m/z* 256 (M^++2, 53), 255 (M^++1, 8), 254 (M^+, 50), 147 (100).

6.1.1.10. 2-Chloromethyl-1-benzofuran (21). Thionyl chloride (11.2 mmol, 0.8 mL) was added in a dropwise manner to a solution of (1-benzofuran-2-yl)methanol (**20**) (1.19 g, 8.0 mmol) in THF (5.92 mL) and DMF (1.66 mL) at 60 °C. Subsequently, the solution was stirred at room temperature for 1 h. Then the solvent was evaporated under reduced pressure and the crude residue was dissolved in H_2O and extracted with ethyl acetate (3 × 20 mL). The collected organic extracts were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure to afford a residue as yellow oil (1.3 g) in 98% yield. The crude residue was not further purified. ^{1}H NMR δ 4.78 (s, 2H, CH_2Cl), 6.78 (s, 1H, OCCH), 7.18–7.60 (m, 4H aromatic); GC–MS *m/z* 169 (M^++3, 0.9), 168 (M^++2, 9), 167 (M^++1, 3), 166 (M^+, 28), 131 (100).

6.1.2. General procedure to obtain final amine compounds 16, 17, 18a,c, 19a,b, and 22

In a typical reaction, a representative intermediate (1.0 mmol) among 1-(ω-haloalkyl) derivatives **14**, **15**, **10a,c**, **11a,b**, and **21** respectively, was stirred and refluxed overnight with 3,3-dimethylpiperidine (1.2 mmol) and Na_2CO_3 (1.2 mmol) in CH_3CN. The mixture was worked up as reported for compound **12**. Purification by column chromatography (CH_2Cl_2/MeOH 9:1 as eluent, unless otherwise indicated) afforded final compounds as colorless or pale yellow oils.

6.1.2.1. 1-[3-(1-Benzofuran-4-yl)propyl]-3,3-dimethylpiperidine (16). ^{1}H NMR δ 0.94 (s, 6H, $C(CH_3)_2$), 1.17–1.30 (m, 2H, piperidine CCH_2), 1.55–1.69 (m, 2H, piperidine CCH_2CH_2), 1.85 (quintet, 2H, J = 7.7 Hz, $ArCH_2CH_2$), 2.01 (s, 2H, CCH_2N), 2.21–2.38 (m, 4H, $N(CH_2)_2$), 2.87 (t, 2H, J = 7.7 Hz, benzylic), 6.80–6.83 (m, 1H, OCHCH), 7.05–7.39 (m, 3H, aromatic), 7.59 (d, 1H, J = 2.5 Hz, OCH); GC–MS *m/z* 272 (M^++1, 8), 271 (M^+, 35), 126 (100). The corresponding hydrochloride salt was recrystallized from MeOH/Et_2O: mp 205–207 °C. Anal. ($C_{18}H_{25}NO{\cdot}HCl{\cdot}0.25\ H_2O$) C, H, N.

6.1.2.2. 1-[3-(1-Benzothiophen-4-yl)propyl]-3,3-dimethylpiperidine (17). ^{1}H NMR δ 0.96 (s, 6H, $C(CH_3)_2$), 1.15–1.28 (m, 2H, piperidine CCH_2), 1.55–1.68 (m, 2H, piperidine CCH_2CH_2), 1.88 (quintet, 2H, J = 7.6 Hz, $ArCH_2CH_2$), 2.01 (s, 2H, CCH_2N), 2.22–2.38 (m, 4H, $N(CH_2)_2$), 2.99 (t, 2H, J = 7.7, benzylic), 7.14–7.76 (m, 5H, aromatic); GC–MS *m/z* 289(M^++2, 3), 288 (M^++1, 10), 287 (M^+, 41), 126 (100). The corresponding hydrochloride salt was recrystallized from MeOH/Et_2O: mp 210–212 °C. Anal. ($C_{18}H_{25}NS{\cdot}HCl$) C, H, N.

6.1.2.3. 3,3-Dimethyl-1-[3-(4,5,6,7-tetrahydro-1-benzothiophen-4-yl)propyl]piperidine (18a). This compound, already reported as oxalate salt, was converted to the hydrochloride salt and then recrystallized from MeOH/Et_2O: mp 195–197 °C. Anal. ($C_{18}H_{29}NS{\cdot}HCl{\cdot}0.25H_2O$) C, H, N.

6.1.2.4. 3,3-Dimethyl-1-[5-(4,5,6,7-tetrahydro-1-benzothiophen-4-yl)pentyl]piperidine (18c). ^{1}H NMR δ 1.05 (s, 6H, $C(CH_3)_2$), 1.15–1.57 (m, 8H, piperidine CCH_2CH_2, $CHCH_2(CH_2)_3CH_2N$), 1.58–1.98 (m, 8H, CCH_2N, $CHCH_2(CH_2)_4N$, and endo $CH(CH_2)_2$), 2.18–2.58 (m, 4H, piperidine NCH_2CH_2), 2.61–2.92 (m, 5H, $(CH_2)_4CH_2N$ and benzylic), 6.80–7.08 (m, 2H, aromatic); GC–MS *m/z* 321 (M^++2, 1), 320 (M^++1, 5), 319 (M^+, 19), 126 (100). The corresponding hydrochloride salt was recrystallized from MeOH/Et_2O: mp 166–169 °C. Anal. ($C_{20}H_{33}NS{\cdot}HCl{\cdot}0.25H_2O$) C, H, N.

6.1.2.5. 3,3-Dimethyl-1-[3-(6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-yl)propyl]piperidine (19a). ^{1}H NMR δ 0.90 (s, 6H, $C(CH_3)_2$), 1.10–1.28 (m, 2H, piperidine CCH_2CH_2], 1.35–1.88 (m, 12H, endo $CH(CH_2)_3$, $CH(CH_2)_2CH_2N$, and piperidine CCH_2CH_2), 1.90–2.05 (m, 2H, $CH(CH_2)_2CH_2N$), 2.20–2.32 (m, 4H, piperidine CH_2NCH_2), 2.69–2.91 (m, 3H, benzilic), 6.96–7.59 (m, 4H, aromatic); GC–MS *m/z* 301 (M^++2, 1), 300 (M^++1, 10), 299 (M^+ 37), 126 (100). The corresponding hydrochloride salt was recrystallized from MeOH/Et_2O: mp 172–174 °C. Anal. ($C_{21}H_{33}N{\cdot}HCl{\cdot}0.25H_2O$) C, H, N.

6.1.2.6. 3,3-Dimethyl-1-[4-(6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-yl)butyl]piperidine (19b). ^{1}H NMR δ 0.90 (s, 6H, $C(CH_3)_2$), 1.10–1.38 (m, 6H, $CHCH_2(CH_2)_2CH_2N$, endo $CHCH_2CH_2$), 1.40–1.92

(m, 10H, NCH_2CCH_2, $CHCH_2(CH_2)_3N$ and endo $CHCH_2CH_2CH_2$), 1.93–2.05 (m, 2H, piperidine CCH_2CH_2), 2.15–2.38 (m, 4H, CH_2NCH_2), 2.72–2.92 (m, 3H, benzilic), 7.02–7.18 (m, 4H, aromatic); GC–MS *m/z* 315 (M^++2, 0.6), 313 (M^+ 21), 126 (100). The corresponding hydrochloride salt was recrystallized from MeOH/Et_2O: mp 189–191 °C. Anal. ($C_{22}H_{35}N{\cdot}HCl{\cdot}0.8H_2O$) C, H, N.

6.1.2.7. 3,3-Dimethyl-1-[(1-benzofuran-2-yl)methyl]piperidine (22). ^1H NMR δ 0.94 (s, 6H, $C(CH_3)_2$), 1.17–1.29 (m, 2H, CCH_2CH_2), 1.58–1.70 (m, 2H, CCH_2CH_2), 2.08–2.18 (m, 2H, piperidine NCH_2C), 2.38–2.48 (m, 2H, piperidine NCH_2CH_2), 3.62 (s, 2H, $OCCH_2N$), 6.58 (s, 1H, OCCH), 7.15–7.68 (m, 4H, aromatic); GC–MS *m/z* 245 (M^++2, 0.6), 244 (M^++1, 6), 243 (M^+, 35), 131 (100). The corresponding hydrochloride salt was recrystallized from MeOH/Et_2O: mp 188–190 °C. Anal. ($C_{16}H_{21}NO{\cdot}HCl$) C, H, N.

6.1.2.8. 3-(Indol-1-yl)propionic acid, ethyl ester (24a). Ethyl acrylate (4.5 mL, 42 mmol) and K_2CO_3 (5.9 g, 43 mmol) were added to a stirred mixture of indole (**23a**) (4.41 g, 42 mmol) in DMF (30 mL). The reaction mixture was stirred at room temperature for 7 h and then concentrated under reduced pressure. The residue was taken up with CH_2Cl_2 (30 mL) and washed with H_2O (2 × 10 mL) The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to give an orange-colored oil (8.57 g, 94% yield); ^1H NMR δ 1.21 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 2.82 (t, 2H, *J* = 6.8 Hz CH_2CH_2CO), 4.12 (q, 2H, *J* = 7.1 Hz, OCH_2CH_3), 4.46 (t, 2H, *J* = 6.8 Hz, NCH_2), 6.49 (dd, 1H, *J* = 3.85 Hz, *J′* = 0.69 Hz, aromatic NCHCH) 7.09–7.67 (m, 5H, aromatic); GC–MS *m/z* 219 (M^++2, 1), 218 (M^++1, 14), 217 (M^+, 72), 130 (100). FT-IR: 2982, 1731 cm^{-1}.

6.1.2.9. 3-(1*H*-1,2,3-Benzotriazol-1-yl)propionic acid, ethyl ester (24b). This compound was prepared as for **24a** starting from 1,2,3-benzotriazole (**23b**) (5.00 g, 42 mmol) in DMF (30 mL). The crude yellow oil was purified by flash column chromatography using petroleum ether/EtOAc (7:3) as eluent to give the target compound as a white solid (6.44 g, 70% yield); ^1H NMR δ 1.17 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 3.09 (t, 2H, *J* = 6.7 Hz CH_2CH_2CO), 4.10 (q, 2H, *J* = 7.1 Hz, OCH_2CH_3), 4.91 (t, 2H, *J* = 6.7 Hz, NCH_2), 7.33–8.06 (m, 4H aromatic); GC–MS *m/z* 221 (M^++2, 1), 220 (M^++1, 11), 219 (M^+, 55), 104 (100). FT-IR: 2983, 1735, 1451 cm^{-1}.

6.1.3. General procedure to obtain alcohols 26a–c

A solution of one of the esters **24a,b** and ethyl 3-(1*H*-indol-3-yl)propanoate (**25**) (0.75 mmol) was added in a dropwise manner to a suspension of $LiAlH_4$ (1 mmol) in dry THF (20 mL) kept at 0 °C under a stream of N_2. The mixture was stirred under reflux for 6 h (12 h for compound **26c**). After cooling to 0 °C, the reaction mixture was added with H_2O, until the hydride was destroyed, and it was filtered through Celite®. The filtrate was evaporated under reduced pressure and the crude residue was dissolved in H_2O and extracted with CH_2Cl_2 (3 × 20 mL). The collected organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to afford a residue.

6.1.3.1. 3-(1H-Indol-1-yl)propan-1-ol (26a). The crude residue as a yellow oil was purified by column chromatography, using petroleum ether/$CHCl_3$ (1:1) as eluent, to give the target compound as a white oil in 41% yield; ^1H NMR δ 1.50 (broad s, 1H, OH, D_2O exchanged), 2.04–2.11 (m, 2H, $CH_2CH_2CH_2OH$), 3.60 (t, 2H, *J* = 6.7 Hz, CH_2OH), 4.29 (t, 2H, *J* = 5.9 Hz, NCH_2), 6.49–7.65 (m, 6H, aromatic); GC–MS *m/z* 177 (M^++2, 0.5), 176 (M^++1, 8), 175 (M^+, 56), 130 (100). FT-IR: 3385, 2924, 1662 cm^{-1}.

6.1.3.2. 3-(1H-1,2,3-Benzotriazol-1-yl)propan-1-ol (26b). The crude residue as a brown solid was purified by column -chromatography, using ethyl acetate/CH_2Cl_2 (8:2) as eluent, to give the target compound as an orange-colored oil in 86% yield; ^1H NMR δ 1.87 (broad s, 1H, OH, D_2O exchanged), 2.20–2.38 (m, 2H, $CH_2CH_2CH_2OH$), 3.65 (t, 2H, *J* = 6.6 Hz, CH_2OH), 4.81 (t, 2H, *J* = 5.5 Hz, NCH_2), 7.35–8.07 (m, 4H, aromatic); GC–MS *m/z* 179 (M^++2, 0.5), 178 (M^++1, 6), 177 (M^+, 48), 91 (100). FT-IR: 3386, 2951, 2881, 1733 cm^{-1}.

6.1.3.3. 3-(1H-Indol-3-yl)propan-1-ol (26c). The crude residue as a yellow oil was purified by column chromatography, using CH_2Cl_2/ethyl acetate (7:3) as eluent to give the target compound as an orange oil in 31% yield; ^1H NMR δ 1.53 (broad s, 1H, OH, D_2O exchanged), 1.95–2.05 (m, 2H, $CH_2CH_2CH_2OH$), 2.89 (t, 2H, *J* = 6.0 Hz, CCH_2), 3.73 (t, 2H, *J* = 6.1 Hz, CH_2OH), 6.99–7.63 (m, 5H, aromatic), 7.98 (s, 1H, NH); GC–MS *m/z* 177 (M^++2, 0.3), 176 (M^++1, 5), 175 (M^+, 34), 130 (100). FT-IR: 3413, 2937 cm^{-1}.

6.1.4. General procedure to obtain methanesulfonates 27a–d

Mesyl chloride (0.54 mmol) in CH_2Cl_2 was added to a solution of an appropriate alcohol among compounds **26a–c** and 4-cyclohexylbutan-1-ol (**26d**) (1 mmol) and Et_3N (1 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The reaction was worked up as previously described.[23]

6.1.4.1. 3-(1*H*-Indol-1-yl)propylmethanesulfonate(27a) . The crude residue was obtained as an orange-colored oil in 52% yield and was not purified; ^1H NMR δ 1.92–2.04 (m, 2H, $CH_2CH_2CH_2O$), 3.00 (s, 3H, CH_3), 3.55 (t, 2H, *J* = 5.6 Hz, CH_2O), 4.05 (t, 2H, *J* = 6.5 Hz, NCH_2), 6.47–7.65 (m, 6H aromatic); GC–MS *m/z* 255 (M^++2, 3), 254 (M^++1, 7), 253 (M^+, 43), 130 (100).

6.1.4.2. 3-(1H-1,2,3-Benzotriazol-1-yl)propyl methanesulfonate (27b). The crude residue as a brown oil was purified by column chromatography, using ethyl acetate/CH_2Cl_2 (8:2) as eluent, to give the target compound as a white solid in 60% yield; ^1H NMR δ 2.49 (m, 2H, $CH_2CH_2CH_2O$), 3.0 (s, 3H, CH_3), 4.24 (t, 2H, *J* = 5.7 Hz, CH_2O), 4.81 (t, 2H, *J* = 6.6 Hz, NCH_2), 7.37–8.09 (m, 4H, aromatic); GC–MS *m/z* 257 (M^++2, 2), 256 (M^++1, 4), 255 (M^+, 35), 120 (100).

6.1.4.3. 3-(1H-Indol-3-yl)propyl methanesulfonate (27c). The crude residue obtained as an orange-colored oil in 83% yield was not purified; ^1H NMR δ 2.18 (m, 2H, $CH_2CH_2CH_2O$), 2.95 (s, 3H, CH_3), 4.11–4.30 (m, 2H, CCH_2); 4.26 (t, 2H, *J* = 6.0 Hz, CH_2O), 7.01–8.02 (m, 5H aromatic), 7.98 (s, 1H, NH); GC–MS *m/z* 255 (M^++2, 1), 254 (M^++1, 3), 253 (M^+, 24), 130 (100).

6.1.4.4. 4-Cyclohexylbutyl methanesulfonate (27d). The crude residue obtained as yellow oil in 81% yield was not purified. ^1H NMR (90 MHz) δ 0.90–1.90 (m, 17H, $C_6H_{11}(CH_2)_3$), 2.91–3.10 (m, 5H, CH_2O and CH_3); GC–MS *m/z* 152 (1), 109 (37), 96 (100).

6.1.5. General procedure to obtain final amine compounds 28–31

Starting from an intermediate (1.0 mmol) among mesylalkyl derivatives **27a–d** the title compounds were obtained as general procedure described for compounds **16–19** and **22**.

6.1.5.1. 3,3-Dimethyl-1-[3-(1*H*-indol-1-yl)propyl]piperidine (28). ^1H NMR δ 1.02 (s, 6H, $C(CH_3)_2$), 1.20–1.38 (m, 4H, CCH_2CH_2), 1.60–1.78 (m, 2H, $ArCH_2CH_2$), 1.95–2.48 (m, 6H, $CH_2N(CH_2)_2$), 4.24 (t, 2H, *J* = 6.6, $ArCH_2$), 6.45–7.65 (m, 6H, aromatic); GC–MS *m/z* 271 (M^++1, 8), 270 (M^+, 40), 126 (100).

6.1.5.2. 3,3-Dimethyl-1-[3-(1*H*-1,2,3-benzotriazol-1-yl)propyl] piperidine (29). ^1H NMR δ 1.02 (s, 6H, $C(CH_3)_2$), 1.18–1.26 (m, 2H, CCH_2CH_2), 1.50–1.78 (m, 2H, CCH_2CH_2), 1.98–2.50 (m, 8H,

$CH_2CH_2N(CH_2)_2$), 4.73 (t, 2H, J = 6.6, ArCH_2), 7.24–8.09 (m, 4H, aromatic); GC–MS m/z 273 (M^++1, 0.8), 272 (M^+, 4), 126 (100). The corresponding hydrochloride salt was recrystallized from MeOH/Et_2O: mp 198–200 °C. Anal. ($C_{16}H_{24}N_4$·HCl·0.5H_2O) C, H, N.

6.1.5.3. 3,3-Dimethyl-1-[3-(1*H*-indol-3-yl)propyl]piperidine (30) . ^{1}H NMR δ 1.02 (s, 6H, C(CH_3)$_2$), 1.20–1.38 (m, 4H, piperidine CCH_2CH_2), 1.65–1.85 (m, 2H, ArCH_2CH_2), 1.95–2.14 (m, 2H, NCH_2C), 2.60–2.78 (m, 4H, CH_2NCH_2), 2.79 (t, 2H, J = 7.3 Hz, ArCH_2), 6.96–7.59 (m, 5H, aromatic), 8.06–8.18 (broad s, 1H, NH, D_2O exchanged); GC–MS m/z 271 (M^++1, 2), 270 (M^+ 12), 126 (100).

6.1.5.4. 3,3-Dimethyl-1-[(4-cyclohexyl)butyl]piperidine (31). ^{1}H NMR δ 0.9 (m, 8H, CHCH_2 and C(CH_3)$_2$), 1.04–1.36 (m, 11H, cyclohexyl), 1.38–1.50 (m, 2H, $CHCH_2CH_2$), 1.52–1.78 (m, 6H, piperidine CCH_2CH_2 and CH_2CH_2N), 1.99 (s, 2H, NCH_2C), 2.16–2.36 (m, 4H, CH_2NCH_2); GC–MS m/z 252 (M^++1, 0.6), 251 (M^+, 3.5), 126 (100). The corresponding hydrochloride salt was recrystallized from MeOH/Et_2O: mp 225–226 °C. Anal. ($C_{17}H_{33}N$·HCl·0.1H_2O) C, H, N.

6.1.6. General procedure to obtain chloroacetamides 33a–c

To a solution of the appropriate amine among 2-amino-5,6-dihydro-1,3-benzothiazol-7-(4*H*)-one (**32a**), 2-amino-1,3-benzothiazole (**32b**), and 2-amino-thiazole (**32c**) (1 mmol) in ethylenglycol dimethylether (10 mL), kept at 0 °C, some drops of Et_3N were added and then, a solution of chloroacethyl chloride (1.2 mmol) in the same solvent (2 mL) was added dropwise. The mixture was stirred under reflux for 6 h and the solvent was evaporated under reduced pressure. The residue was partitioned between CH_2Cl_2 and 20% aqueous Na_2CO_3. The separated organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to yield one of compounds **33a–c** as a crude residue. The alkaline aqueous solution was acidified to pH 2–4 with 3 N HCl and extracted with ethyl acetate (3 × 20 mL). The collected organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to afford more target compound.

6.1.6.1. 2-Chloro-*N*-[7(4*H*)-oxo-5,6-dihydro-1,3-benzothiazol-2-yl]acetamide (33a). The crude residue as a brown oil was purified by column chromatography, using CH_2Cl_2/CH_3OH (8:2) as eluent to give the target compound as a white semisolid in 75% yield; ^{1}H NMR δ 2.18–2.30 (quintet, 2H, J = 6.0 Hz, $COCH_2CH_2$), 2.61 (t, 2H, J = 6.5 Hz, $COCH_2CH_2CH_2$), 2.88–2.98 (m, 2H, $COCH_2CH_2$), 3.89 (s, 2H, CH_2Cl), 6.20 (broad s, 1H, NH, D_2O exchanged); GC–MS m/z 246 (M^++2, 13), 245 (M^++1, 4), 244 (M^+, 34), 168 (100).

6.1.6.2. *N*-(1,3-Benzothiazol-2-yl)-2-chloroacetamide (33b) The crude residue was obtained as a brown oil in 80% yield and was not purified; ^{1}H NMR δ 4.15 (s, 2H, CH_2Cl), 8.05 (broad s, 1H, NH, D_2O exchanged), 7.25–8.10 (m, 4H, aromatic); GC–MS m/z 228 (M^++2, 12), 227 (M^++1, 4), 226 (M^+, 32), 150 (100).

6.1.6.3. 2-Chloro-*N*-(1,3-thiazol-2-yl)acetamide (33c). The crude residue was obtained as a brown semisolid in 20% yield and was not purified; ^{1}H NMR δ 4.30 (s, 2H, CH_2Cl), 6.20 (broad s, 1H, NH, D_2O exchanged), 7.06 (d, 1H, J = 3.6 Hz, NCH), 7.52 (d, 1H, J = 3.7 Hz, SCH); GC–MS m/z 178 (M^++2, 9), 177 (M^++1, 2), 176 (M^+, 25), 100 (100).

6.1.7. General procedure to obtain compounds 35a–c

To a solution of one of the acetamides **33a–c** (1 mmol) in dry THF (5 mL) was added BF_3·O(C_2H_5)$_2$ (0.13 mL, 1 mmol). While the mixture was stirred under reflux, a solution of $(CH_3)_2S$·BH_3 (0.08 mL, 0.09 mmol) in the same solvent (2 mL) was added dropwise. Still the reaction was stirred under reflux for 6 h. After the mixture of reaction was cooled at 0 °C, a solution of 6 N HCl (0.16 mL, 1 mmol) was added dropwise. The reaction was continued stirring under reflux for 1 h. Then the reaction mixture was cooled at 0 °C and alkalized dropwise with a solution of 6 N NaOH. The aqueous solution was extracted with CH_2Cl_2 (3 × 20 mL), the collected organic phases were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure.

6.1.7.1. 2-(2-Chloroethylamino)-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one (35a). The crude residue was an orange-colored oil and was purified by column chromatography using $CHCl_3$/CH_3OH (9:1) as eluent to give the target compound as a yellow oil in 30% yield; ^{1}H NMR (DMSO-d_6) δ 2.18–2.30 (quintet, 2H, J = 6.2 Hz, $COCH_2CH_2$), 2.61 (t, 2H, J = 6.4 Hz, $COCH_2CH_2CH_2$), 2.88–2.98 (m, 2H, $COCH_2CH_2$), 3.70–3.85 (m, 4H, $NHCH_2CH_2Cl$), 7.90 (broad s, 1H, NH, D_2O exchanged); GC–MS m/z 232 (M^++2, 19), 231 (M^++1, 6), 230 (M^+, 49), 154 (100).

6.1.7.2. *N*-(2-Chloroetyl)-1,3-benzothiazol-2-amine (35b) . The crude residue was purified by column chromatography using petroleum ether/ethyl acetate (8:2) as eluent to give the target compound as a yellow oil in 37% yield. ^{1}H NMR (DMSO-d_6) δ 3.61–3.78 (m, 2H, $NHCH_2$), 3.78–3.82 (m, 2H, CH_2Cl), 6.98–7.67 (m, 4H, aromatic), 8.29 (s, 1H, NH, D_2O exchanged); GC–MS m/z 214 (M^++2, 14), 213 (M^++1, 4), 212 (M^+, 37),150 (100).

6.1.7.3. *N*-(2-Chloroethyl)-1,3-thiazol-2-amine (35c). The crude residue was purified by column chromatography using ethyl acetate/CH_2Cl_2 (6:4) as eluent to give the target compound as a yellow oil in 63% yield; ^{1}H NMR (DMSO-d_6) δ 3.49–3.60 (m, 2H, $NHCH_2$), 3.78 (t, 2H, J = 6.0 Hz, CH_2Cl), 6.61 (d, 1H, J = 3.6 Hz, NCH), 6.99 (d, 1H, J = 3.6 Hz, SCH), 7.80 (broad s, 1H, NH, D_2O exchanged); GC–MS m/z 164 (M^++2, 13), 163 (M^++1, 3), 162 (M^+, 34), 113 (100), 100 (63).

6.1.8. General procedure to obtain final amine compounds 34, and 36–38

Starting from an intermediate (1.0 mmol) among 1-(ω-haloalkyl) derivatives **33a**, and **35a–c**, respectively, the title compounds were obtained as for compounds **16–19** and **22**.

6.1.8.1. 2-(3,3-Dimethylpiperidin-1yl)-*N*-[7(4*H*)-oxo-5,6-dihydro-1,3-benzothiazol-2-yl]acetamide (34). ^{1}H NMR δ 1.06 [s, 6H, C(CH_3)$_2$], 1.25–1.39 (m, 2H, piperidine CCH_2CH_2), 1.65–1.86 (m, 2H, piperidine CCH_2CH_2), 2.18 (quintet, 2H, J = 6.4 Hz, $COCH_2CH_2$), 2.20–2.45 (m, 2H, NCH_2C), 2.48–2.70 (m, 4H, $COCH_2CH_2$ and piperidine NCH_2), 2.91 (t, 2H, J = 6.2 Hz, $COCH_2CH_2CH_2$), 3.20–3.45 (s, 2H, $COCH_2N$), 8.10 (s, 1H, NH, D_2O slowly exchanged); GC–MS m/z 323 (M^++2, 1), 322 (M^++1, 4), 321 (M^+, 21), 126 (100). The corresponding hydrochloride salt was recrystallized from MeOH/Et_2O: mp 250 °C (dec). Anal. ($C_{16}H_{23}N_3O_2S$·HCl·0.5H_2O) C, H, N.

6.1.8.2. 2-(3,3-Dimethylpiperidin-1yl)-*N*-[7(4*H*)-oxo-5,6-dihydro-1,3-benzothiazol-2yl]aminoethane (36). ^{1}H NMR δ 1.11 (s, 6H, C(CH_3)$_2$), 1.38–1.48 (m, 2H, piperidine CCH_2CH_2), 1.69–1.98 (m, 6H, piperidine CCH_2CH_2, NCH_2C and $COCH_2CH_2$), 2.48–2.80 (m, 6H, piperidine NCH_2CH_2 and $COCH_2CH_2CH_2$), 2.82–3.10 (m, 2H, $HNCH_2CH_2N$), 3.50–3.91 (m, 3H, $HNCH_2CH_2N$ and NH, D_2O exchanged); GC–MS m/z 309 (M^++2, 2), 307 (M^+, 22), 126 (100). The corresponding hydrochloride salt was recrystallized from MeOH/Et_2O: mp 265 °C (dec). Anal. ($C_{16}H_{25}N_3OS$·HCl·0.5H_2O) C, H, N.

6.1.8.3. 2-(3,3-Dimethylpiperidin-1-yl)-*N*-(1,3-benzothiazol-2-yl)aminoethane (37). ^{1}H NMR δ 0.98 (s, 6H, C(CH_3)$_2$), 1.27 (m, 2H, CCH_2CH_2), 1.58–1.78 (m, 2H, CCH_2CH_2), 2.06–2.29 (m, 2H,

NCH_2C), 2.30–2.56 (m, 2H, piperidine NCH_2), 2.58–2.80 (m, 2H, $HNCH_2CH_2N$), 3.42–3.64 (m, 2H, $HNCH_2CH_2N$), 6.01–6.42 (broad s, 1H, NH, D_2O exchanged), 7.02–7.61 (m, 4H, aromatic); GC–MS *m/z* 290 (M^++1, 0.4), 289 (M^+, 1.3), 139 (60), 126 (100). The corresponding hydrochloride salt was recrystallized from MeOH/Et_2O: mp 197 °C (dec). Anal. ($C_{16}H_{23}N_3S{\cdot}HCl{\cdot}0.5H_2O$) C, H, N.

6.1.8.4. 2-(3,3-Dimethylpiperidin-1-yl)-*N*-(1,3-thiazol-2-yl)aminoethane (38). ^1H NMR δ 0.95 (s, 6H, $C(CH_3)_2$), 1.19–1.32 (m, 2H, CCH_2CH_2), 1.58–1.70 (m, 2H, CCH_2CH_2); 2.08–2.19 (m, 2H, NCH_2C); 2.36–2.57 (m, 2H, piperidine NCH_2), 2.62 (t, 2H, *J* = 5.5 Hz, $HNCH_2CH_2N$), 3.37 (t, 2H, *J* = 5.5 Hz, $HNCH_2CH_2N$); 5.80–6.10 (broad s, 1H, NH, D_2O exchanged), 6.47 (d, 1H, *J* = 3.6 Hz, SCH), 7.10 (d, 1H, *J* = 3.8 Hz, NCH); GC–MS *m/z* 240 (M^++1, 0.1), 239 (M^+, 0.9), 139 (33), 126 (100). The corresponding hydrochloride salt was recrystallized from MeOH/Et_2O: mp 206 °C (dec). Anal. ($C_{12}H_{21}N_3S{\cdot}2HCl{\cdot}0.5H_2O$) C, H, N. H: Calculated 7.53, Found 6.88.

6.1.8.5. 3,3-Dimethyl-1-[4-(3,3-dimethyl-2,6-dioxo-piperidin-1-yl)butyl]piperidine-2,6-dione (40). 2,2-Dimethylpentanedioyl dichloride (5.26 g, 26.7 mmol), prepared with the corresponding dicarboxylic acid **39** and $SOCl_2$, was added in a dropwise manner to a solution of butane-1,4-diamine (1.05 g, 12.0 mmol,) in ethylenglycol dimethylether (5.0 mL) and DMF (1.66 mL) at 60 °C. The solution was stirred under reflux for 12 h. Then the solvent was evaporated under reduced pressure, the crude residue was dissolved in H_2O and slowly alkalized to pH 12–14 with 3 N NaOH. The aqueous solution was extracted with ethyl acetate (3 × 20 mL). The collected organic extracts were washed with a solution of 2 N HCl, then with H_2O, and dried (Na_2SO_4) and evaporated under reduced pressure to afford a yellow oil as residue. The crude residue was purified by column chromatography using CH_2Cl_2/MeOH (9:1) as eluent to give the target compound as a yellow solid in 52% yield, (2.10 g). ^1H NMR δ 1.25 (s, 12H, $2C(CH_3)_2$), 1.35–1.50 (m, 4H, $NCH_2(CH_2)_2CH_2N$), 1.70–1.91 (m, 4H, $2CCH_2CH_2$), 2.61–2.78 (m, 4H, 2 CH_2CO), 3.68–3.70 (m, 4H, 2 NCH_2). GC–MS *m/z* 338 (M^++2, 0.6), 337 (M^++1, 3), 336 (M^+, 15), 195 (89), 182 (99), 154 (100).

6.1.8.6. 3,3-Dimethyl-1-[4-(3,3-dimethylpiperidin-1-yl)butyl] piperidine (41). A solution of diimide **40** (0.3 g, 0.89 mmol) in dry ethyl ether (15 mL) was added in a dropwise manner to a suspension of $LiAlH_4$ (0.066 g, 1.74 mmol) in dry ethyl ether (5 mL) kept at 0 °C under a stream of N_2. The mixture was stirred at room temperature for 21 h. After cooling to 0 °C, the reaction mixture was added with H_2O, until the hydride was destroyed. The mixture was filtered through Celite® and the filtrate was evaporated under reduced pressure. The aqueous mixture was extracted with CH_2Cl_2 (3 × 20 mL). The collected organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to afford a residue which was purified by conversion into hydrochloride salt in ethyl ether. Pure product was recrystallized from dry ethyl ether. Free base: ^1H NMR δ 0.92 (s, 12H, $2C(CH_3)_2$), 1.12–1.25 (m, 4H, $2CH_2CH_2N$), 1.40–1.71 (m, 8H, 2-piperidine CCH_2CH_2N), 1.91–2.52 (m, 12H, $2CH_2N(CH_2)_2$); GC–MS *m/z* 280 (M^+, 7), 126 (100). Hydrochloride: mp 254 °C dec. Anal. ($C_{18}H_{36}N_2{\cdot}HCl$) C, H, N. H: Calculated 10.84, Found 11.46.

7. Radioligand binding assays

All the procedures followed to perform the binding assays were previously described.[25] σ_1 and σ_2 receptor binding were carried out according to Matsumoto et al.[43] and Δ_8–Δ_7 SI according to Moebius et al.[44] The radioligands [^{3}H]-DTG (30 Ci/mmol) and (+)-[^{3}H]-pentazocine (34 Ci/mmol) were purchased from PerkinElmer Life Sciences (Zavantem, Belgium). [^{3}H]-(±)-Emopamil (83 Ci/mmol) was purchased from American Radiolabeled Chemicals Inc. (St. Louis, MO). (+)-Pentazocine was obtained from Sigma–Aldrich-RBI s.r.l. (Milan, Italy). DTG and (±)-ifenprodil were purchased from Tocris Cookson Ltd., UK. Male Dunkin guinea-pigs and Wistar Hannover rats (250–300 g) were from Harlan, Italy.

Supplementary data

Supplementary data (Elemental analyses of the end products.) associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.10.023.

References and notes

1. Quirion, R.; Bowen, W. D.; Itzhak, Y.; Junien, J. L.; Musacchio, J. M.; Rothman, R. B.; Su, T.-P.; Tam, S. W.; Taylor, D. P. *Trends Pharmacol. Sci.* **1992**, *13*, 85.
2. Bem, W. T.; Thomas, G. E.; Mamone, J. Y.; Homan, S. M.; Levy, B. K.; Johnson, F. E.; Coscia, C. J. *Cancer Res.* **1991**, *51*, 6558.
3. Vilner, B. J.; John, C. S.; Bowen, W. D. *Cancer Res.* **1995**, *55*, 408.
4. Wang, B.; Rouzier, R.; Albarraccin, C. T.; Sahin, A.; Wagner, P.; Yang, Y.; Smith, T. L.; Meric-Bernstam, F.; Aldaz, C. M.; Hortobagyi, G. N.; Pusztai, L. *Breast Cancer Res. Treat.* **2004**, *87*, 205.
5. van Waarde, A.; Rybcznska, A. A.; Ramakrishnan, N. K.; Ishiwata, K.; Elsinga, P. H.; Dierckz, R. A. J. O. *Curr. Pharm. Des.* **2010**, *16*, 3519.
6. Hashimoto, K.; Ishiwata, K. *Curr. Pharm. Des.* **2006**, *12*, 3857.
7. Moebius, F. F.; Striessnig, J.; Glossmann, H. *Trends Pharmacol. Sci.* **1997**, *18*, 67.
8. Hanner, M.; Moebius, F. F.; Flandorfer, A.; Knaus, H. G.; Striessnig, J.; Kempner, E.; Glossmann, H. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 8072.
9. Guitart, X.; Codonym, X.; Monroy, X. *Psychopharmacology* **2004**, *174*, 301.
10. Abate, C.; Mosier, P. D.; Berardi, F.; Glennon, R. A. *Cent. Nerv. Syst. Agents Med. Chem.* **2009**, *9*, 246.
11. Xu, J.; Zeng, C.; Chu, W.; Pan, F.; Rothfuss, J. M.; Zhang, F.; Tu, Z.; Zhou, D.; Zeng, D.; Vangveravong, S.; Johnston, F.; Spitzer, D.; Chang, K. C.; Hotchkiss, R. S.; Hawkins, W. G.; Wheeler, K. T.; Mach, R. H. *Nat. Commun.* **2011** (e-pub ahead of print July, doi:10.1038ncomms1386).
12. Chen, Y.; Hajipour, A. R.; Sievert, M. K.; Arbabian, M.; Ruoho, A. E. *Biochemistry* **2007**, *46*, 3532.
13. Bouchard, P.; Quirion, R. *Neuroscience* **1997**, *76*, 467.
14. Walker, J. M.; Bowen, W. D.; Walker, F. O.; Matsumoto, R. R.; De Costa, B.; Rice, K. C. *Pharmacol. Rev.* **1990**, *42*, 355.
15. Kekuda, R.; Prasad, P. D.; Fei, Y. J.; Leibach, F. H.; Ganapathy, V. *Biochem. Biophys. Res. Commun.* **1996**, *229*, 553.
16. Seth, P.; Leibach, F. H.; Ganapathy, V. *Biochem. Biophys. Res. Commun.* **1997**, *241*, 535.
17. Pal, A. et al *Mol. Pharmacol.* **2007**, *72*, 921.
18. Cobos, E. J.; Entrena, J. M.; Nieto, F. R.; Cendan, C. M.; Del Pozo, E. *Curr. Neuropharmacol. J.* **2008**, *6*, 344.
19. Hayashi, T.; Su, T. P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *265*, 14949.
20. Hayashi, T.; Su, T. P. *Cell* **2007**, *131*, 595.
21. Hindmarch, I.; Hashimoto, K. *Hum. Psychopharmacol. Clin. Exp.* **2010**, *25*, 193.
22. Maier, C. A.; Wünsch, B. *J. Med. Chem.* **2002**, *45*, 438.
23. Piergentili, A.; Amantini, C.; Del Bello, F.; Giannella, M.; Mattioli, L.; Palmery, M.; Perfumi, M.; Pigini, M.; Santoni, G.; Tucci, P.; Zotti, M.; Quaglia, W. *J. Med. Chem.* **2010**, *53*, 1261.
24. Berardi, F.; Santoro, S.; Perrone, R.; Tortorella, V.; Govoni, S.; Lucchi, L. *J. Med. Chem.* **1998**, *41*, 3940.
25. Berardi, F.; Ferorelli, S.; Colabufo, N. A.; Leopoldo, M.; Perrone, R.; Tortorella, V. *Bioorg. Med. Chem.* **2001**, *9*, 1325.
26. Glennon, R. A.; Ablordeppey, S. Y.; Ismaiel, A. M.; el-Ashmawy, M. B.; Fischer, J. B.; Howie, K. B. *J. Med. Chem.* **1994**, *37*, 1214.
27. Ablordeppey, S. Y.; Fischer, J. B.; Law, H.; Glennon, R. A. *Bioorg. Med. Chem.* **2002**, *10*, 2759.
28. Glennon, R. A. *Mini-Rev. Med. Chem.* **2005**, *5*, 927.
29. Berardi, F.; Ferorelli, S.; Abate, C.; Pedone, M. P.; Colabufo, N. A.; Contino, M.; Perrone, R. *J. Med. Chem.* **2005**, *48*, 8237.
30. Berardi, F.; Colabufo, N. A.; Giudice, G.; Perrone, R.; Tortorella, V.; Govoni, S.; Lucchi, L. *J. Med. Chem.* **1996**, *39*, 176.
31. Hodson, H. F.; Madge, D. J.; Slawin, A. N. Z.; Widdoson, D. A.; Williams, D. J. *Tetrahedron* **1994**, *50*, 1899.
32. Berardi, F.; Giudice, G.; Perrone, R.; Tortorella, V.; Govoni, S.; Lucchi, L. *J. Med. Chem.* **1996**, *39*, 4255.
33. Gribble, G. W.; Saulnier, M. G.; Obaza-Nutaitis, J. A.; Ketcha, D. M. *J. Org. Chem.* **1992**, *57*, 5891.
34. Teran, C.; Miranda, R.; Santana, L.; Teijeira, M.; Uriarte, E. *Synthesis* **1997**, 1384.
35. Wahab Khan, M.; Jahangir Alam, M.; Rashid, M. A.; Chowdhury, R. *Bioorg. Med. Chem.* **2005**, *13*, 4796.
36. Nakatsuka, S.; Asano, O.; Goto, T. *Heterocycles* **1986**, *24*(8), 2109.
37. McIntyre, N. A.; McInnes, C.; Griffiths, G.; Barnett, A. L.; Kontopidis, G.; Slawin, A. M. Z.; Jackson, W.; Thomas, M.; Zheleva, D. I.; Wang, S.; Blake, D. G.; Westwood, N. J.; Fischer, P. M. *J. Med. Chem.* **2010**, *53*, 2136.
38. *ACD Labs version 7.09*, Advanced Chemistry Development Inc.: Toronto, Canada.

39. *Prism Software*, version 3.0 for Windows; GraphPad Software, Inc.: San Diego, CA, **1998**.
40. Waterhouse, R. N. *Mol. Imaging Biol.* **2003**, *5*, 376.
41. Mach, R. H.; Wheeler, K. T. *Cent. Nerv. Syst. Agents Med. Chem.* **2009**, *9*, 230.
42. Frankowski, K. J.; Setola, V.; Evans, J. M.; Neuenswander, B.; Roth, B. L.; Aubé, J. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 6727.
43. Matsumoto, R. R.; Bowen, W. D.; Tom, M. A.; Nhi Vo, V.; Truong, D. D.; de Costa, B. R. *Eur. J. Pharmacol.* **1995**, *280*, 301.
44. Moebius, F. F.; Hanner, M.; Knaus, H. G.; Weber, F.; Striessnig, J.; Glossmann, H. *J. Biol. Chem.* **1994**, *269*, 29314.