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Original article

Substituted benzylaminoalkylindoles with preference for the σ_2 binding site☆

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Abstract

In the attempt to develop new σ ligands we synthesized a series of *N*-benzyl-3-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-*N*-methylpropan-1-amines and *N*-benzyl-4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-*N*-methylbutan-1-amines variously substituted on the phenyl ring. The displacement percentages of [^{3}H]-DTG and [^{3}H]-(+)-pentazocine determined in rat liver homogenates by these compounds at the fixed 100 nM concentration have been determined as a preliminary evaluation of their σ_1 and σ_2 affinity, respectively.

The results suggested that the phenyl substituents may positively modulate, in comparison with the unsubstituted compound, the ability to displace [^{3}H]-DTG from σ_2 sites, whereas the same phenyl substituents reduced the displacement percentages of [^{3}H]-(+)-pentazocine from σ_1 sites. Some of these compounds were selected for radioligand binding assays. Compounds with a butylene intermediate chain displayed the greatest binding affinity for σ_2 over σ_1 receptors. The butylene derivative with 2,4-dimethyl substitution on the phenyl ring showed the greatest σ_2 affinity ($\sigma_2K_i = 5.9$ nM) and an appreciable σ_2 over σ_1 selectivity ($\sigma_1K_i/\sigma_2K_i = 22$). The obtained results suggest that a butylene chain separating the indole moiety from variously substituted benzylamino groups may be required to their interaction with a hypothetical secondary σ_2 binding site.

Keywords: σ Receptors; Benzylaminoalkyl indole derivatives; Radioligand binding assays

1. Introduction

The σ receptor was first described as a subtype of opioid receptors [1]. Now the existence of σ sites has been established and the σ_1 and σ_2 subtypes are universally recognized [2]. The σ_1 protein has been purified and cloned from several animal species and humans [3,4]. This receptor has been identified to be a mammalian homologue of the yeast sterol C_8–C_7 isomerase. The molecular identity of the σ_2 receptor has not been fully determined [3,4]. The σ_1 subtype exhibits high affinity for (+)-benzomorphans such as (+)-pentazocine and (+)-*N*-allylnormetazocine (NANM, SKF-10,047) and reduced affinity for the corresponding (−)-enantiomers. (+)-Pentazocine shows a very low affinity for σ_2 receptors and represents a typical selective agonist used as tritiated ligand to label σ_1 receptors. Several compounds selectively binding the σ_1 receptors and σ_1 pharmacophoric models have been proposed by Glennon et al. [5–7] and Gund et al. [8]. However, known σ_2 receptor ligands generally display a poor selectivity profile. Selective σ_2 over σ_1 ligands such as ibogaine and the phenylmorphans CB-64D and CB-184 also show affinity for NMDA (ibogaine) and μ-opioid (CB-64D and CB-184) receptors [9,10]. The antipsychotic haloperidol and 1,3-di(2-tolyl)guanidine (DTG) possess high affinity for both σ subtypes [11]. DTG is the most used σ_2 radioligand but it needs a σ_1 masking

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agent. However, a number of benzamide derivatives, that have higher affinity and selectivity for σ_2 *versus* σ_1 receptors, have been recently reported [12].

The σ_1 receptors have several modulatory roles in neurotransmitter systems such as dopaminergic, serotoninergic, muscarinic systems [2,13,14] and in NMDA-stimulated neurotransmitter release [15]. Moreover, σ_1 receptors are involved in neuroprotective and antiamnesic activities [16], modulation of opioid analgesia [17] and attenuation of cocaine-induced locomotor activity and toxicity [18]. Besides, σ_1 antagonists have shown to be effective against negative symptoms of schizophrenia without producing extrapyramidal side effects [19,20].

On the contrary, σ_2 receptors may contribute to the acute side effects of typical neuroleptic drugs and σ_2 antagonists attenuate the extrapyramidal effects, dystonic reactions and tardive dyskinesia [2,13,21–23] suggesting their potential use in the treatment of psychoses [19,20]. Furthermore, σ_2 receptors are involved in regulation of cell proliferation and maintenance of cell viability. They are highly expressed in several tumoral cell lines [24,25], where σ_2 agonists produce morphological changes and apoptosis. The σ_2 receptor agonists promote Ca^{2+} release from endoplasmic reticulum and mitochondrial stores [26] with subsequent cell death by caspase-independent apoptosis [25]. Apoptosis may also be induced in tumoral cells by regulation of the sphingolipid pathway [27]. Therefore, σ_2 agonists may be useful as novel anticancer agents. Moreover, σ_2 selective ligands may be useful as imaging agents in cancer diagnosis by Positron Emission Tomography (PET) [28] and Single Photon Emission Computed Tomography (SPECT) [29,30].

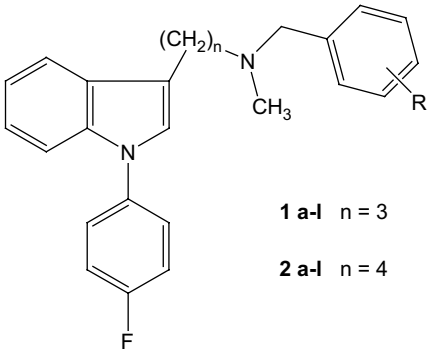
Thus, selective σ_1 and σ_2 agonists and antagonists may be potentially useful drugs for treatment of several pathologic conditions such as psychiatric disorders, cocaine abuse, memory and learning disorders, dyskinesia and dystonic reactions induced by classical antipsychotic drugs, cancer and tumor diagnosis. Now several compounds binding σ_1 receptors with high affinity and selectivity have been discovered, whereas σ_2 receptor ligands generally have poor selectivity over σ_1 receptors and new σ_2 ligands are needed in order to define the structural features that may improve their affinity and selectivity.

With the aim to develop new ligands with high affinity and selectivity for σ receptors, we synthesized the series of compounds **1a–l** and **2a–l** (Table 1).

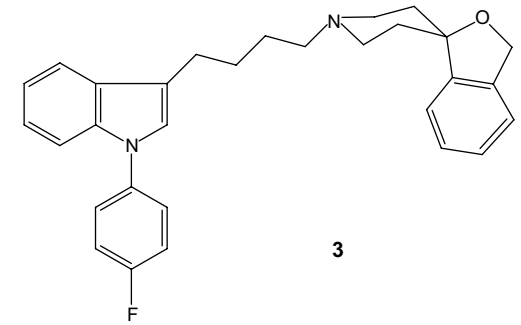
Compounds **2a–l** are structurally related to the indole derivative **3** (Lu 28-179) (Fig. 1) and analogs, characterized by high affinity and selectivity for σ_2 subtype over σ_1 subtype receptors [31].

Lu 28-179 is a member of a series of 3-(ω-aminobutyl)-1*H*-indoles variously substituted on the 1-position of the indole group and linked by the butylene chain to a spiro[isobenzofuran-1(3*H*),4′-piperidine] moiety [31]. All these spiropiperidines showed selectivity for σ_2 *versus* σ_1 binding sites and their IC_{50} values were below 1 nM for a majority of compounds. However, introduction of the 4-fluorophenyl substituent at the indole nitrogen atom produced compound **3** with the highest σ_2 binding affinity ($\sigma_1 IC_{50} = 17$ nM; $\sigma_2 IC_{50} = 0.12$ nM) and σ_2 over σ_1 selectivity ($\sigma_1 IC_{50}/\sigma_2 IC_{50} = 140$) in the series. Furthermore, shorter interspacing alkylene chains seem to reduce potency and selectivity. The introduction of substituents on the benzene moiety of the spiropiperidine ring system of Lu 28-179 produced effects on σ_1 and

Table 1
Yields and physical data of the synthesized compounds



R	Comp., $n=3$	Yield (%)	Anal. C, H, N	Comp., $n=4$	Yield (%)	Anal. C, H, N
H	**1a**	20	$C_{25}H_{25}N_2F$	**2a**	37	$C_{26}H_{27}N_2F$
2-Cl	**1b**	44	$C_{25}H_{24}N_2FCl$	**2b**	59	$C_{26}H_{26}N_2FCl$
3-Cl	**1c**	48	$C_{25}H_{24}N_2FCl$	**2c**	49	$C_{26}H_{26}N_2FCl$
4-Cl	**1d**	52	$C_{25}H_{24}N_2FCl$	**2d**	48	$C_{26}H_{26}N_2FCl$
3,4-$(Cl)_2$	**1e**	38	$C_{25}H_{23}N_2FCl_2$	**2e**	49	$C_{26}H_{25}N_2FCl_2$
2-Br	**1f**	46	$C_{25}H_{24}N_2FBr$	**2f**	59	$C_{26}H_{26}N_2FBr$
3-Br	**1g**	52	$C_{25}H_{24}N_2FBr$	**2g**	35	$C_{26}H_{26}N_2FBr$
4-Br	**1h**	46	$C_{25}H_{24}N_2FBr$	**2h**	38	$C_{26}H_{26}N_2FBr$
2-F	**1i**	46	$C_{25}H_{24}N_2F_2$	**2i**	50	$C_{26}H_{26}N_2F_2$
3-CH_3	**1j**	50	$C_{26}H_{27}N_2F$	**2j**	57	$C_{27}H_{29}N_2F$
4-CH_3	**1k**	52	$C_{26}H_{27}N_2F$	**2k**	57	$C_{27}H_{29}N_2F$
2,4-$(CH_3)_2$	**1l**	58	$C_{27}H_{29}N_2F$	**2l**	46	$C_{28}H_{31}N_2F$



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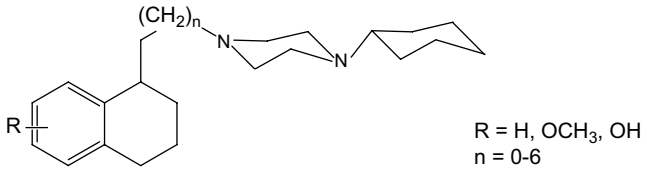

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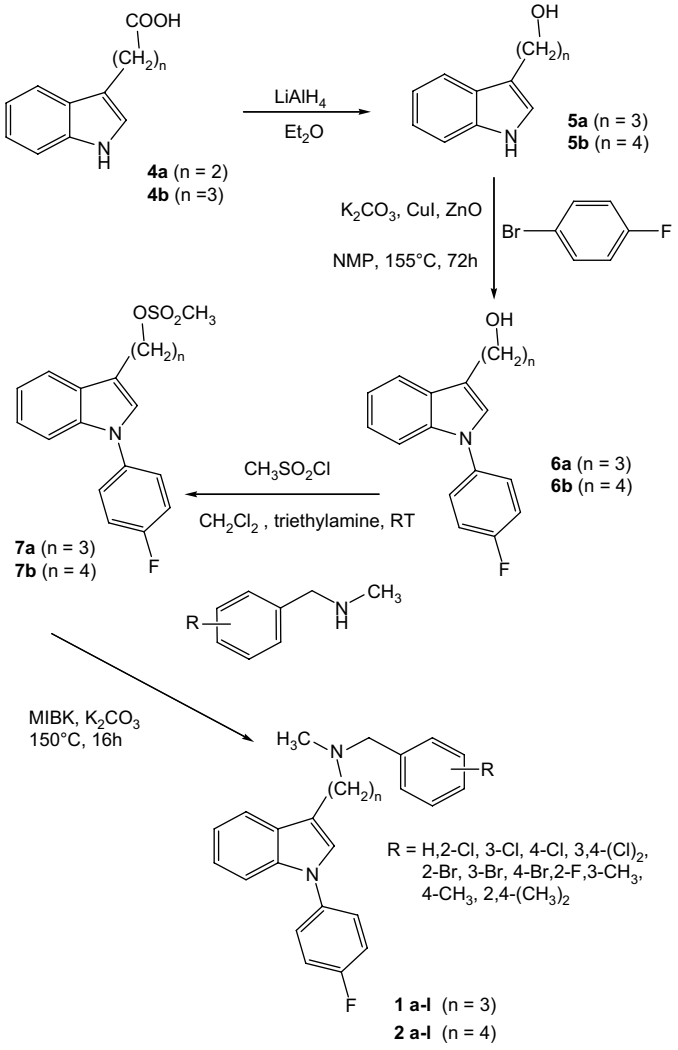
Fig. 1. Structures of the σ_2 selective ligands **3** and **8**.

σ_2 affinity and selectivity, indicating that this benzene ring may be involved in binding to σ_1 and σ_2 sites [32]. Furthermore, modifications of the structure of the spiropiperidine ring system producing a different spatial localization of the benzene ring relative to the basic nitrogen atom determined to a large extent the affinity for both σ_1 and σ_2 receptors [32]. The results of this study [32] indicated that both substituents on the benzene ring and their position relative to the basic nitrogen atom might influence the binding characteristics of the spiropiperidine derivatives under examination. The series of new indole derivatives **1a–l** and **2a–l** have been synthesized by replacing the spiro[isobenzofuran-1(3*H*),4′-piperidine] moiety of Lu 28-179 and analogous compounds with a variously substituted benzylamino group linked to the indole moiety by an alkylene chain, in order to verify if this simple modification may produce compounds with affinity for σ receptorial sites.

2. Chemistry

The substituted *N*-benzyl-3-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-*N*-methylpropan-1-amines **1a–l** and *N*-benzyl-4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-*N*-methylbutan-1-amines **2a–l** (Table 1) have been synthesized (Scheme 1) starting from 3-(1*H*-indol-3-yl)propanoic acid **4a** and 4-(1*H*-indol-3-yl)butanoic acid **4b**, which were reduced with $LiAlH_4$ to 3-(1*H*-indol-3-yl)propan-1-ol **5a** and 4-(1*H*-indol-3-yl)butan-1-ol **5b** following, with minimal modifications, a literature procedure [33]. By heating compounds **5a** and **5b** with 4-bromofluorobenzene in the presence of K_2CO_3, CuI and ZnO in 1-methyl-2-pyrrolidinone, the corresponding compounds 3-[1-(4-fluorophenyl)-1*H*-indol-3-yl]propan-1-ol **6a** and 4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]butan-1-ol **6b** [31] were obtained. By treatment of **6a** and **6b** with methanesulfonyl chloride the methanesulfonate esters **7a** and **7b** were prepared, from which compounds **1a–l** and **2a–l** were obtained by reaction with substituted benzylamines.



Scheme 1. Synthesis of compounds **1a–l** and **2a–l**.

3. Results and discussion

Since a four atom spacer appeared to be important for the σ_2 affinity of the spiropiperidine derivative **3** (Fig. 1) and analogous compounds [31], we retained in compounds **2a–l** ($n = 4$) (Table 1) the 1-(4-fluorophenyl)-indole moiety and the four carbon atoms alkylene chain, replacing the spiropiperidine moiety with the *N*-benzylamino group variously substituted on the aromatic ring.

The new indole derivatives **2a–l** have been designed, according to the σ_1-receptorial model proposed by Glennon et al. [5–7], with the assumption that the indole moiety may interact with a primary hydrophobic site corresponding to the phenyl "B" region [5–7], the basic N-atom linked by the alkylene chain ($n = 4$) to the indole moiety may interact with a receptorial proton-donor site and the substituted *N*-benzyl moiety may bind a secondary hydrophobic region similar to the phenyl "A" region of the σ_1-receptorial model [5–7] and modulate the binding affinity of the compounds for σ_1 or σ_2 receptors.

Actually, in a series of 4-(tetralin-1-yl)alkyl derivatives of 1-cyclohexylpiperazine **8** (Fig. 1) the little structural differences preferentially between σ_1 and σ_2 ligands allowed to hypothesize the existence of different secondary sites in the corresponding receptorial subtypes [34] with the intermediate chain length exerting a significant influence on σ_2 binding affinity.

The tetralin derivative **8** (R = 5-OCH_3, $n = 3$) was characterized by the greatest σ_2 affinity ($\sigma_2K_i = 0.34$ nM). If only the aromatic portion of this tetralin derivative is considered, the spacer corresponding to a three-methylene chain ($n = 3$) produced a butyl bridge connecting the aromatic portion with the piperazine ring [34].

On the basis of these considerations we maintained in the new compounds **2a–l** ($n = 4$) the butylene spacer present in the high σ_2 affinity compounds **3** and **8** (R = 5-OCH_3, $n = 3$) in order to verify if this spacer, together with the terminal substituted benzyl group, may produce receptorial interactions with the proposed σ_2 binding site [34].

Another series of compounds **1a–l** ($n = 3$) (Table 1) with a propylene chain and the same aromatic substitution pattern

was synthesized to evaluate the effect of this simple modification on σ receptor affinity and selectivity.

In a preliminary assay the displacement percentages of [^{3}H]-DTG from σ_2 receptors produced by compounds **1a–l** ($n = 3$) and **2a–l** ($n = 4$) were evaluated on rat liver homogenates at the fixed 100 nM concentration in the presence of (+)-pentazocine to mask σ_1 receptors (Table 2). The displacement percentages produced by compounds **1a–l** were in the range 27–85%, whereas all **2a–l** compounds were found to produce >50% inhibition of binding at σ_2 receptors (range 68–93%).

From these preliminary data it appeared that both the series of compounds produced displacement percentages of [^{3}H]-DTG from σ_2 receptors modulated by the substituents on the phenyl ring, but the butylene derivatives **2a–l** produced displacement percentages higher than those of the corresponding propylene derivatives **1a–l**.

Moreover, all the [^{3}H]-DTG displacement values from σ_2 sites produced by substituted compounds **1b–l** and **2b–l** were higher than those of the corresponding unsubstituted compounds **1a** and **2a**.

With the same approach the displacement percentages of [^{3}H]-(+)-pentazocine from σ_1 sites by the compounds **1a–l** and **2a–l** at the fixed 100 nM concentration were determined (Table 3). The displacement percentages were in the range 28–78% for compounds **1a–l** and 10–76% for compounds **2a–l** ($n = 4$).

Percentage reductions of [^{3}H]-(+)-pentazocine binding to σ_1 site, even if varied along with the substitution on the aromatic ring, were less than the percentage inhibition of the unsubstituted compounds, suggesting that aromatic substitution may be detrimental for the σ_1 binding of these compounds.

The unsubstituted compounds **1a** ($n = 3$) and **2a** ($n = 4$) and compounds **2c** and **2l**, which produced the greatest displacement percentages of [^{3}H]-DTG from σ_2 sites were selected, together with the corresponding compounds **1c** and **1l**, for determination of their K_i values at both receptor types (Table 4).

From the obtained results it appears that the substituents on the phenyl ring can modulate, according to the previously determined displacement percentage data, the σ_1 and σ_2 binding affinity of these compounds. As regards σ_1 receptors, the unsubstituted compounds **1a** ($n = 3$) and **2a** ($n = 4$) displayed σ_1 binding affinity higher than that of the corresponding substituted derivatives **1c**, **1l** and **2c**, **2l**, respectively. The most potent σ_1 ligand was the propylene derivative **1a**, whose σ_1K_i value was 20.8 nM with a selectivity ratio $\sigma_1K_i/\sigma_2K_i = 0.05$. Conversely, the σ_2 affinity of the substituted compounds **1c**, **1l** ($n = 3$) and **2c**, **2l** ($n = 4$) was higher than that of the unsubstituted compounds **1a** and **2a**, respectively, and dependent on the alkylene chain, with the butylene derivatives having higher affinity than the corresponding propylene compounds. The highest σ_2 binding affinity was attained by the butylene derivative **2l**, whose σ_2K_i value was 5.9 nM, suggesting an appreciable σ_2 affinity and selectivity of this compound over σ_1 sites ($\sigma_1K_i/\sigma_2K_i = 22$). On the other hand, the corresponding propylene derivative **1l** ($n = 3$), even if it is showing some preference for σ_2 sites, displayed reduced σ_2

Table 2
Displacement percentages of [^{3}H]-DTG from σ_2 sites

R	Comp., $n = 3$	% Mean[a,b] ± SD	Comp., $n = 4$	% Mean[a,b] ± SD
H	**1a**	27 ± 8	**2a**	68 ± 8
2-Cl	**1b**	40 ± 10	**2b**	87 ± 2
3-Cl	**1c**	59 ± 8	**2c**	89 ± 3
4-Cl	**1d**	59 ± 8	**2d**	85 ± 10
3,4-(Cl)$_2$	**1e**	39 ± 5	**2e**	69 ± 3
2-Br	**1f**	43 ± 1	**2f**	86 ± 7
3-Br	**1g**	62 ± 4	**2g**	78 ± 22
4-Br	**1h**	54 ± 9	**2h**	84 ± 10
2-F	**1i**	46 ± 9	**2i**	88 ± 8
3-CH$_3$	**1j**	64 ± 9	**2j**	85 ± 12
4-CH$_3$	**1k**	78 ± 5	**2k**	87 ± 8
2,4-(CH$_3$)$_2$	**1l**	85 ± 5	**2l**	93 ± 9
DTG, 3 nM		9 ± 5		
DTG, 30 nM		47 ± 10		
DTG, 300 nM		82 ± 2		

[a] Mean displacement percentages produced on rat liver homogenates by compounds **1a–l** ($n = 3$) and **2a–l** ($n = 4$) at the fixed 100 nM concentration in the presence of 100 nM (+)-pentazocine to mask σ_1-receptors.
[b] Data are expressed as mean values ± SD of 3 experiments performed in duplicate.

Table 3
Displacement percentages of [^{3}H]-(+)-pentazocine from σ_1 sites

R	Comp., $n = 3$	% Mean[a,b] ± SD	Comp., $n = 4$	% Mean[a,b] ± SD
H	**1a**	78 ± 5	**2a**	76 ± 1
2-Cl	**1b**	56 ± 7	**2b**	58 ± 5
3-Cl	**1c**	42 ± 17	**2c**	22 ± 5
4-Cl	**1d**	68 ± 9	**2d**	72 ± 11
3,4-(Cl)$_2$	**1e**	28 ± 12	**2e**	10 ± 8
2-Br	**1f**	41 ± 18	**2f**	46 ± 14
3-Br	**1g**	40 ± 5	**2g**	28 ± 10
4-Br	**1h**	71 ± 10	**2h**	70 ± 9
2-F	**1i**	59 ± 3	**2i**	49 ± 7
3-CH$_3$	**1j**	63 ± 27	**2j**	51 ± 11
4-CH$_3$	**1k**	69 ± 14	**2k**	71 ± 19
2,4-(CH$_3$)$_2$	**1l**	38 ± 11	**2l**	37 ± 8
Pentazocine, 1 nM		24 ± 12		
Pentazocine, 10 nM		60 ± 2		
Pentazocine, 100 nM		95 ± 2		

[a] Mean displacement percentages produced on rat liver homogenates by compounds **1a–l** ($n = 3$) and **2a–l** ($n = 4$) at the fixed 100 nM concentration.
[b] Data are expressed as mean values ± SD of 3 experiments performed in duplicate.

Table 4
Binding affinity (K_i ± SEM nM) and selectivity

Comp.	n	R	σ_1K_i, nM	σ_2K_i, nM	σ_1K_i/σ_2K_i ratio
1a	3	H	20.8 ± 1	444.3 ± 21	0.05
1c	3	3-Cl	98.9 ± 10	123.5 ± 23	0.80
1l	3	2,4-(CH$_3$)$_2$	118 ± 16	46.9 ± 12	2.5
2a	4	H	43 ± 7	57.7 ± 16	0.76
2c	4	3-Cl	201 ± 21	25.6 ± 9	7.9
2l	4	2,4-(CH$_3$)$_2$	129 ± 22	5.9 ± 2	22

affinity ($\sigma_2K_i = 46.9$ nM) and selectivity ($\sigma_1K_i/\sigma_2K_i = 2.5$) in comparison with compound **2l**. The obtained results suggest that the new compound **2l** ($n = 4$) and other butylene spaced compounds **2**, variously substituted on the phenyl ring, may interact with a secondary σ_2 site similar to the hydrophobic binding site "A" of the Glennon's σ_1 [5–7] model.

The indole moiety may establish a favorable interaction with a hydrophobic binding site resembling the σ_1 primary binding site proposed by Glennon and the butylene chain separating the N-basic atom seems to produce the most favorable distance between the primary and secondary hydrophobic centers. The positive and variable contribution to the σ_2 affinity of the substituents on the phenyl ring in compounds **1c**, **1l** and **2c**, **2l** and their negative effect on σ_1 affinity may encourage the design of structural modifications useful for the development of new ligands with higher σ_2 affinity and selectivity.

4. Experimental section

4.1. Chemistry

Melting points were determined with a Büchi 510 capillary apparatus, and are uncorrected. Infrared spectra in nujol mulls were recorded on a Jasko FT 200 spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were determined on a Varian Gemini 200 spectrometer, chemical shifts are reported as δ (ppm) in $CDCl_3$ solution. Reaction courses and product mixtures were routinely monitored by thin-layer chromatography (TLC) on silica gel precoated F_{254} Merck plates. Column chromatographies were performed using Backer 70–230 mesh silica gel60. ESI-MS spectra were obtained on a PE-API I spectrometer by infusion of a solution of the sample in MeOH. Elemental analyses (C, H, N) were performed on a Carlo Erba analyzer and were within ±0.3 of the theoretical value.

4.1.1. 3-(1H-Indol-3-yl)propan-1-ol **5a**

3-(1*H*-Indol-3-yl)propanoic acid **4a** (3 g, 15.8 mmol) in 50 ml of ethyl ether was stirred under reflux and 1.5 g (39.6 mmol) of $LiAlH_4$ in 50 ml of ethyl ether was added dropwise to the solution. After heating for 3 h, the solution was stirred at room temperature for additional 20 h. The solution was filtered and the excess of $LiAlH_4$ was eliminated by treating with water and then with a 1:3 mixture of concentrated H_2SO_4 and water. The aqueous phase was extracted with ethyl ether and the collected organic phases were dried on anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The obtained yellow oil was chromatographically pure and was used without further purification. Yield: 2.71 g (98%).

IR (nujol, cm^{-1}): 3345, 2935. ^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 1.9 (m, 2H, $-CH_2-\mathit{CH_2}-CH_2-OH$), 2.5 (br s, 1H, OH, disappearing on deuteration), 2.85 (t, 2H, $-\mathit{CH_2}-CH_2-CH_2-OH$), 3.75 (t, 2H, $-CH_2-CH_2-\mathit{CH_2}-OH$), 7.0 (s, 1H, CH ind.), 7.1–7.7 (m, 4H arom.), 8.1 (s, 1H, NH, disappearing on deuteration). Anal. Calcd for $C_{11}H_{13}NO$ (MW 175.23): C, 75.40; H, 7.48; N, 7.99%. Found: C, 75.26; H, 7.52; N, 8.08%.

4.1.2. 4-(1H-Indol-3-yl)butan-1-ol **5b**

In an analogous way 4-(1*H*-indol-3-yl)butan-1-ol **5b** [33] was prepared. Yield: 8.88 g (93%).

IR (nujol, cm^{-1}): 3350, 2927. ^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 1.24 (t, 2H, $-CH_2-\mathit{CH_2}-CH_2-CH_2-OH$), 1.73 (br s, 1H, OH, disappearing on deuteration), 2.82 (m, 2H, $-\mathit{CH_2}-CH_2-CH_2-CH_2-OH$), 3.52 (m, 2H, $-CH_2-CH_2-\mathit{CH_2}-CH_2-OH$), 3.71 (t, 2H, $-CH_2-CH_2-CH_2-\mathit{CH_2}-OH$), 6.99 (s, 1H, CH ind.), 7.08–8.02 (m, 4H arom.), 8.02 (s, 1H, NH, disappearing on deuteration). Anal. Calcd for $C_{12}H_{15}NO$ (MW 189.25): C, 76.16; H, 7.99; N, 7.40%. Found: C, 75.96; H, 7.69; N, 8.18%.

4.1.3. 3-[1-(4-Fluorophenyl)-1H-indol-3-yl]propan-1-ol **6a**

A mixture of 2.5 g (14.3 mmol) of 3-(1*H*-indol-3-yl)propan-1-ol **5a**, 4.24 g (24.25 mmol) of 4-bromofluorobenzene, 2.56 g (18.5 mmol) of potassium carbonate, 0.68 g (3.56 mmol) of CuI and 0.18 g (2.28 mmol) of ZnO in 100 ml of 1-methyl-2-pyrrolidinone (NMP) was heated at 155 °C for 72 h. After cooling the precipitated inorganic salts were filtered off and 20 ml of ethyl ether and 80 ml of 10% NaOH were added to the solution. The organic phase was separated, washed with NaCl solution and dried over anhydrous $CaCl_2$. The filtered solution was concentrated under reduced pressure and the remaining crude product was purified as an oil by column chromatography on silica gel (eluted with a 3:2 mixture of CH_3Cl and toluene). Yield: 1.54 g (40%).

IR (nujol, cm^{-1}): 3348. ^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 1.52 (s, 1H, OH, disappearing on deuteration), 2.06 (m, 2H, $-CH_2-\mathit{CH_2}-CH_2-OH$), 2.95 (t, 2H, $-\mathit{CH_2}-CH_2-CH_2-OH$), 3.8 (t, 2H, $-CH_2-CH_2-\mathit{CH_2}-OH$), 7.14–7.7 (m, 8H arom., 1H ind.). Anal. Calcd for $C_{17}H_{16}FNO$ (MW 269.31): C, 75.82; H, 5.99; N, 5.20%. Found: C, 75.66; H, 5.72; N, 5.08%.

4.1.4. 4-[1-(4-Fluorophenyl)-1H-indol-3-yl]butan-1-ol **6b**

In an analogous way 4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-butan-1-ol **6b** [31] was obtained. Yield: 1.6 g (40%).

IR (nujol, cm^{-1}): 3352. ^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 1.27 (t, 2H, $-\mathit{CH_2}-CH_2-CH_2-CH_2-OH$), 1.32 (br s, 1H, OH, disappearing on deuteration), 1.78 (m, 2H, $-CH_2-\mathit{CH_2}-CH_2-CH_2-OH$), 2.87 (m, 2H, $-CH_2-CH_2-\mathit{CH_2}-CH_2-OH$), 3.73 (t, 2H, $-CH_2-CH_2-CH_2-\mathit{CH_2}-OH$), 7.05–7.82 (m, 8H arom., 1H ind.). Anal. Calcd for $C_{18}H_{18}FNO$ (MW 283.34): C, 76.30; H, 6.40; N, 4.94%. Found: C, 76.55; H, 6.68; N, 5.12%.

4.1.5. 3-[1-(4-Fluorophenyl)-1H-indol-3-yl]propyl-1-methanesulfonate **7a**

To a solution of 1.54 g (5.72 mmol) of 3-[1-(4-fluorophenyl)-1*H*-indol-3-yl]propan-1-ol **6a** in 50 ml of CH_2Cl_2, 0.64 g (6.29 mmol) of triethylamine was added. The solution was stirred and cooled in an ice bath and 0.72 g (6.29 mmol) of methanesulfonyl chloride in 20 ml of dichloromethane was added dropwise by keeping the temperature below 5 °C. The temperature was allowed to reach room temperature and the mixture was stirred for additional 1.5 h. Water was added and the organic phase was separated and evaporated under reduced pressure. The solid residue

was crystallized from ethanol. Yield: 1.59 g (80%); melting point 65 °C.

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 2.19 (m, 2H, $-CH_2-CH_2-CH_2-OH$), 2.99 (t, 2H, $-CH_2-CH_2-CH_2-OH$), 3.03 (s, 3H, CH_3), 4.34 (t, 2H, $-CH_2-CH_2-CH_2-OH$), 7.1–7.7 (m, 8H arom., 1H ind.). Anal. Calcd for $C_{18}H_{18}FNO_3S$ (MW 347.1): C, 62.23; H, 5.22; N, 4.03%. Found: C, 62.46; H, 5.31; N, 4.18%.

4.1.6. 4-[1-(4-Fluorophenyl)-1H-indol-3-yl] butyl-1-methanesulfonate ***7b***

With the same procedure, 4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]butyl-1-methanesulfonate (**7b**) was obtained as an oil and purified by column chromatography on silica gel (eluted with a 9:1 mixture of dichloromethane and toluene). Yield: 1.3 g (80%).

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 2.19 (t, 2H, $-CH_2-CH_2-CH_2-CH_2-OH$), 2.99 (m, 2H, $-CH_2-CH_2-CH_2-CH_2-OH$), 3.03 (s, 3H, CH_3), 3.73 (m, 2H, $-CH_2-CH_2-CH_2-CH_2-OH$), 4.34 (t, 2H, $-CH_2-CH_2-CH_2-CH_2-OH$), 7.1–7.7 (m, 8H arom., 1H ind.). Anal. Calcd for $C_{19}H_{20}FNO_3S$ (MW 361.43): C, 63.14; H, 5.58; N, 3.88%. Found: C, 62.96; H, 5.34; N, 3.62%.

4.1.7. N-Benzyl-3-[1-(4-fluorophenyl)-1H-indol-3-yl] -N-methyl-propan-1-amine ***1a***

To 3-[1-(4-fluorophenyl)-1*H*-indol-3-yl]propy1 methanesulfonate **7a** (0.5 g, 1.4 mmol) in 50 ml of 4-methyl-2-pentanone (MIBK), 0.17 g (1.4 mmol) of *N*-methylbenzylamine and 0.4 g (2.7 mmol) of potassium carbonate were added. The mixture was heated under reflux at 150 °C for 16 h. After cooling, inorganic salts were filtered off and 4-methyl-2-pentanone was evaporated under reduced pressure. The remaining mixture was treated with ethyl acetate and water and the organic phase was separated, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The remaining crude oil was purified by column chromatography on silica gel, eluting with a 9:1 mixture of $CHCl_3$ and toluene. Yield: 0.20 g (40%).

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 2.05 (m, 2H, $-CH_2-CH_2-CH_2-N$), 2.36 (s, 3H, CH_3), 2.5 (t, 2H, $-CH_2-CH_2-CH_2-N$), 2.91 (t, 2H, $-CH_2-CH_2-CH_2-N$), 3.65 (s, 2H, CH_2), 7.0 (s, 1H ind.), 7.1–7.3 (m, 13H arom.). MS: *m/z* 373 [MH^+]. Anal. Calcd for $C_{25}H_{25}FN_2$ (MW 372.48): C, 80.61; H, 6.77; N, 7.52%. Found: C, 80.48; H, 6.92; N, 7.68%.

The following compounds **1b–l** and **2a–l** were similarly obtained. Yields are reported in Table 1.

4.1.8. N-(2-Chlorobenzyl)-3-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylpropan-1-amine ***1b***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 2.03 (m, 2H, $-CH_2-CH_2-CH_2-NH$), 2.32 (s, 3H, CH_3), 2.61 (t, 2H, $-CH_2-CH_2-CH_2-NH$), 2.89 (t, 2H, $-CH_2-CH_2-CH_2-NH$), 3.66 (s, 2H, CH_2), 7.02 (s, 1H ind.), 7.2–7.65 (m, 12H arom.). MS: *m/z* 407 [MH^+], 409 [$MH^+ + 2$]. Anal. Calcd for $C_{25}H_{24}ClFN_2$ (MW 406.92): C, 73.79; H, 5.94; N, 6.88%. Found: C, 73.58; H, 6.12; N, 7.03%.

4.1.9. N-(3-Chlorobenzyl)-3-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylpropan-1-amine ***1c***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 2.1 (m, 2H, $-CH_2-CH_2-CH_2-NH$), 2.36 (s, 3H, CH_3), 2.65 (t, 2H, $-CH_2-CH_2-CH_2-NH$), 2.86 (t, 2H, $-CH_2-CH_2-CH_2-NH$), 3.55 (s, 2H, CH_2), 7.05 (s, 1H ind.), 7.1–7.65 (m, 12H arom.). MS: *m/z* 407 [MH^+], 409 [$MH^+ + 2$]. Anal. Calcd for $C_{25}H_{24}ClFN_2$ (MW 406.92): C, 73.79; H, 5.94; N, 6.88%. Found: C, 73.92; H, 5.81; N, 6.63%.

4.1.10. N-(4-Chlorobenzyl)-3-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylpropan-1-amine ***1d***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 1.99 (m, 2H, $-CH_2-CH_2-CH_2-NH$), 2.25 (s, 3H, CH_3), 2.51 (t, 2H, $-CH_2-CH_2-CH_2-NH$), 2.9 (t, 2H, $-CH_2-CH_2-CH_2-NH$), 3.2 (s, 2H, CH_2), 7.04 (s, 1H ind.), 7.16–7.7 (m, 12H arom.). MS: *m/z* 407 [MH^+], 409 [$MH^+ + 2$]. Anal. Calcd for $C_{25}H_{24}ClFN_2$ (MW 406.92): C, 73.79; H, 5.94; N, 6.88%. Found: C, 73.56; H, 5.72; N, 6.99%.

4.1.11. N-(3,4-Dichlorobenzyl)-3-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylpropan-1-amine ***1e***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 2.02 (m, 2H, $-CH_2-CH_2-CH_2-NH$), 2.25 (s, 3H, CH_3), 2.51 (t, 2H, $-CH_2-CH_2-CH_2-NH$), 2.85 (t, 2H, $-CH_2-CH_2-CH_2-NH$), 3.47 (s, 2H, CH_2), 7.05 (s, 1H ind.), 7.15–7.69 (m, 11H arom.). MS: *m/z* 441 [MH^+], 443 [$MH^+ + 2$]. Anal. Calcd for $C_{25}H_{23}Cl_2FN_2$ (MW 441.37): C, 68.03; H, 5.25; N, 6.35%. Found: C, 68.25; H, 5.52; N, 6.19%.

4.1.12. N-(2-Bromobenzyl)-3-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylpropan-1-amine ***1f***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 2.03 (m, 2H, $-CH_2-CH_2-CH_2-NH$), 2.33 (s, 3H, CH_3), 2.62 (t, 2H, $-CH_2-CH_2-CH_2-NH$), 2.89 (t, 2H, $-CH_2-CH_2-CH_2-NH$), 3.61 (s, 2H, CH_2), 7.02 (s, 1H ind.), 7.2–7.7 (m, 12H arom.). MS: *m/z* 451 [MH^+], 453 [$MH^+ + 2$]. Anal. Calcd for $C_{25}H_{24}BrFN_2$ (MW 451.37): C, 66.52; H, 5.36; N, 6.21%. Found: C, 66.25; H, 5.53; N, 6.09%.

4.1.13. N-(3-Bromobenzyl)-3-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylpropan-1-amine ***1g***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 1.99 (m, 2H, $-CH_2-CH_2-CH_2-NH$), 2.26 (s, 3H, CH_3), 2.52 (t, 2H, $-CH_2-CH_2-CH_2-NH$), 2.87 (t, 2H, $-CH_2-CH_2-CH_2-NH$), 3.5 (s, 2H, CH_2), 7.03 (s, 1H ind.), 7.1–7.66 (m, 12H arom.). MS: *m/z* 451 [MH^+], 453 [$MH^+ + 2$]. Anal. Calcd for $C_{25}H_{24}BrFN_2$ (MW 451.37): C, 66.52; H, 5.36; N, 6.21%. Found: C, 66.73; H, 5.22; N, 6.40%.

4.1.14. N-(4-Bromobenzyl)-3-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylpropan-1-amine ***1h***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 1.98 (m, 2H, $-CH_2-CH_2-CH_2-NH$), 2.22 (s, 3H, CH_3), 2.5 (t, 2H, $-CH_2-CH_2-CH_2-NH$), 2.86 (t, 2H, $-CH_2-CH_2-CH_2-NH$), 3.48 (s, 2H, CH_2), 7.03 (s, 1H ind.), 7.19–7.69 (m, 12H arom.). MS: *m/z* 451 [MH^+], 453 [$MH^+ + 2$]. Anal. Calcd for

$C_{25}H_{24}BrFN_2$ (MW 451.37): C, 66.52; H, 5.36; N, 6.21%. Found: C, 66.64; H, 5.49; N, 6.37%.

4.1.15. N-(2-Fluorobenzyl)-3-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylpropan-1-amine ***1i***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 2.02 (m, 2H, $-CH_2-CH_2-CH_2-NH$), 2.3 (s, 3H, CH_3), 2.57 (t, 2H, $-CH_2-CH_2-CH_2-NH$), 2.88 (t, 2H, $-CH_2-CH_2-CH_2-NH$), 3.62 (s, 2H, CH_2), 7.06 (s, 1H ind.), 7.1–7.7 (m, 12H arom.). MS: *m/z* 391 [MH^+]. Anal. Calcd for $C_{25}H_{24}F_2N_2$ (MW 390.37): C, 76.90; H, 5.25; N, 6.35%. Found: C, 76.62; H, 5.40; N, 6.47%.

4.1.16. N-(3-Methylbenzyl)-3-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylpropan-1-amine ***1j***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 2.05 (m, 2H, $-CH_2-CH_2-CH_2-NH$), 2.27 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.54 (t, 2H, $-CH_2-CH_2-CH_2-NH$), 2.87 (t, 2H, $-CH_2-CH_2-CH_2-NH$), 3.51 (s, 2H, CH_2), 7.03 (s, 1H ind.), 7.05–7.71 (m, 12H arom.). MS: *m/z* 387 [MH^+]. Anal. Calcd for $C_{26}H_{27}FN_2$ (MW 386.50): C, 80.80; H, 7.04; N, 7.25%. Found: C, 80.92; H, 7.22; N, 7.03%.

4.1.17. N-(4-Methylbenzyl)-3-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylpropan-1-amine ***1k***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 2.12 (m, 2H, $-CH_2-CH_2-CH_2-NH$), 2.3 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 2.65 (t, 2H, $-CH_2-CH_2-CH_2-NH$), 2.85 (t, 2H, $-CH_2-CH_2-CH_2-NH$), 3.65 (s, 2H, CH_2), 7.06 (s, 1H ind.), 7.1–7.7 (m, 12H arom.). MS: *m/z* 387 [MH^+]. Anal. Calcd for $C_{26}H_{27}FN_2$ (MW 386.50): C, 80.80; H, 7.04; N, 7.25%. Found: C, 80.66; H, 6.90; N, 7.38%.

4.1.18. N-(2,4-Dimethylbenzyl)-3-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylpropan-1-amine ***1l***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 2.07 (m, 2H, $-CH_2-CH_2-CH_2-NH$), 2.29 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.58 (t, 2H, $-CH_2-CH_2-CH_2-NH$), 2.89 (t, 2H, $CH_2-CH_2-CH_2-NH$), 3.54 (s, 2H, CH_2), 6.98 (s, 1H ind.), 7.04–7.7 (m, 11H arom.). MS: *m/z* 401 [MH^+]. Anal. Calcd for $C_{27}H_{29}FN_2$ (MW 400.53): C, 80.96; H, 7.30; N, 6.99%. Found: C, 80.71; H, 7.04; N, 7.14%.

4.1.19. N-Benzyl-4-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methyl-butan-1-amine ***2a***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 1.55–1.89 (m, 4H, $-CH_2-CH_2-CH_2-CH_2-N$), 2.17 (s, 3H, CH_3), 2.46 (t, 2H, $-CH_2-CH_2-CH_2-CH_2-N$), 2.77 (t, 2H, $-CH_2-CH_2-CH_2-CH_2-N$), 3.51 (s, 2H, CH_2), 7.09 (s, 1H ind.), 7.11–7.77 (m, 13H arom.). MS: *m/z* 387 [MH^+]. Anal. Calcd for $C_{26}H_{27}FN_2$ (MW 386.50): C, 80.80; H, 7.04; N, 7.25%. Found: C, 80.61; H, 7.26; N, 7.10%.

4.1.20. N-(2-Chlorobenzyl)-4-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylbutan-1-amine ***2b***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 1.56–1.90 (m, 4H, $-CH_2-CH_2-CH_2-CH_2-N$), 2.20 (s, 3H, CH_3), 2.53 (t, 2H, $-CH_2-CH_2-CH_2-CH_2-N$), 2.84 (t, 2H, $-CH_2-CH_2-CH_2-CH_2-N$), 3.56 (s, 2H, CH_2), 7.09 (s, 1H ind.), 7.14–7.93 (m, 12H arom.). MS: *m/z* 421 [MH^+], 423 [$MH^+ + 2$]. Anal. Calcd for $C_{26}H_{26}ClFN_2$ (MW 420.95): C, 74.18; H, 6.23; N, 6.65%. Found: C, 74.32; H, 6.36; N, 6.43%.

4.1.21. N-(3-Chlorobenzyl)-4-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylbutan-1-amine ***2c***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 1.58–1.91 (m, 4H, $-CH_2-CH_2-CH_2-CH_2-NH$), 2.21 (s, 3H, CH_3), 2.45 (t, 2H, $-CH_2-CH_2-CH_2-CH_2-NH$), 2.84 (t, 2H, $-CH_2-CH_2-CH_2-CH_2-NH$), 3.48 (s, 2H, CH_2), 7.12 (s, 1H ind.), 7.14–7.76 (m, 12H arom.). MS: *m/z* 421 [MH^+], 423 [$MH^+ + 2$]. Anal. Calcd for $C_{26}H_{26}ClFN_2$ (MW 420.95): C, 74.18; H, 6.23; N, 6.65%. Found: C, 74.01; H, 6.12; N, 6.74%.

4.1.22. N-(4-Chlorobenzyl)-4-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylbutan-1-amine ***2d***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 1.60–1.89 (m, 4H, $-CH_2-CH_2-CH_2-CH_2-NH$), 2.26 (s, 3H, CH_3), 2.53 (t, 2H, $-CH_2-CH_2-CH_2-CH_2-NH$; $J = 6.71$), 2.84 (t, 2H, $-CH_2-CH_2-CH_2-CH_2-NH$; $J = 7.32$), 3.57 (s, 2H, CH_2), 7.09 (s, 1H ind.), 7.13–7.73 (m, 12H arom.). MS: *m/z* 421 [MH^+], 423 [$MH^+ + 2$]. Anal. Calcd for $C_{26}H_{26}ClFN_2$ (MW 420.95): C, 74.18; H, 6.23; N, 6.65%. Found: C, 74.33; H, 6.41; N, 6.60%.

4.1.23. N-(3,4-Dichlorobenzyl)-4-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylbutan-1-amine ***2e***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 1.56–1.93 (m, 4H, $-CH_2-CH_2-CH_2-CH_2-NH$), 2.20 (s, 3H, CH_3), 2.42 (t, 2H, $-CH_2-CH_2-CH_2-CH_2-NH$), 2.83 (t, 2H, $-CH_2-CH_2-CH_2-CH_2-NH$), 3.42 (s, 2H, CH_2), 7.04–7.76 (m, 11H arom., 1H ind.). MS: *m/z* 455 [MH^+], 457 [$MH^+ + 2$]. Anal. Calcd for $C_{26}H_{25}Cl_2FN_2$ (MW 455.39): C, 68.57; H, 5.53; N, 6.15%. Found: C, 68.72; H, 5.40; N, 6.02%.

4.1.24. N-(2-Bromobenzyl)-4-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylbutan-1-amine ***2f***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 1.60–1.93 (m, 4H, $-CH_2-CH_2-CH_2-CH_2-NH$), 2.24 (s, 3H, CH_3), 2.54 (t, 2H, $-CH_2-CH_2-CH_2-CH_2-NH$), 2.85 (t, 2H, $-CH_2-CH_2-CH_2-CH_2-NH$), 3.61 (s, 2H, CH_2), 7.04–7.78 (m, 12H arom., 1H ind.). MS: *m/z* 465 [MH^+], 467 [$MH^+ + 2$]. Anal. Calcd for $C_{26}H_{26}BrFN_2$ (MW 465.40): C, 67.10; H, 5.63; N, 6.02%. Found: C, 67.38; H, 5.42; N, 5.89%.

4.1.25. N-(3-Bromobenzyl)-4-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylbutan-1-amine ***2g***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 1.56–1.91 (m, 4H, $-CH_2-CH_2-CH_2-CH_2-NH$), 2.22 (s, 3H, CH_3), 2.47 (t, 2H, $-CH_2-CH_2-CH_2-CH_2-NH$; $J = 6.71$), 2.84 (t, 2H, $-CH_2-CH_2-CH_2-CH_2-NH$; $J = 7.32$), 3.49 (s, 2H, CH_2), 7.10 (s, 1H ind.), 7.16–7.83 (m, 12H arom.). MS: *m/z* 465 [MH^+], 467 [$MH^+ + 2$]. Anal. Calcd for $C_{26}H_{26}BrFN_2$ (MW 465.40): C, 67.10; H, 5.63; N, 6.02%. Found: C, 67.01; H, 5.73; N, 6.13%.

4.1.26. N-(4-Bromobenzyl)-4-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylbutan-1-amine ***2h***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 1.53–1.87 (m, 4H, –CH_2–CH_2–CH_2–CH_2–NH), 2.19 (s, 3H, CH_3), 2.43 (t, 2H, –CH_2–CH_2–CH_2–CH_2–NH), 2.81 (t, 2H, –CH_2–CH_2–CH_2–CH_2–NH), 3.43 (s, 2H, CH_2), 7.07 (s, 1H ind.), 7.12–7.89 (m, 12H arom.). MS: *m/z* 465 [MH^+], 467 [$MH^+ + 2$]. Anal. Calcd for $C_{26}H_{26}BrFN_2$ (MW 465.40): C, 67.10; H, 5.63; N, 6.02%. Found: C, 67.22; H, 5.54; N, 6.26%.

4.1.27. N-(2-Fluorobenzyl)-4-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylbutan-1-amine ***2i***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 1.60–1.95 (m, 4H, –CH_2–CH_2–CH_2–CH_2–NH), 2.24 (s, 3H, CH_3), 2.49 (t, 2H, –CH_2–CH_2–CH_2–CH_2–NH), 2.85 (t, 2H, –CH_2–CH_2–CH_2–CH_2–NH), 3.60 (s, 2H, CH_2), 6.95–7.79 (m, 12H arom., 1H ind.). MS: *m/z* 405 [MH^+]. Anal. Calcd for $C_{26}H_{26}BrFN_2$ (MW 404.49): C, 77.20; H, 6.48; N, 6.93%. Found: C, 77.41; H, 6.33; N, 7.08%.

4.1.28. N-(3-Methylbenzyl)-4-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylbutan-1-amine ***2j***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 1.61–1.91 (m, 4H, –CH_2–CH_2–CH_2–CH_2–NH), 2.17 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.47 (t, 2H, –CH_2–CH_2–CH_2–CH_2–NH), 2.85 (t, 2H, –CH_2–CH_2–CH_2–CH_2–NH), 3.49 (s, 2H, CH_2), 7.09 (s, 1H ind.), 7.13–7.75 (m, 12H arom.). MS: *m/z* 401 [MH^+]. Anal. Calcd for $C_{27}H_{29}FN_2$ (MW 400.53): C, 80.96; H, 7.30; N, 6.99%. Found: C, 81.12; H, 7.06; N, 7.15%.

4.1.29. N-(4-Methylbenzyl)-4-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylbutan-1-amine ***2k***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 1.69–1.99 (m, 4H, –CH_2–CH_2–CH_2–CH_2–NH), 2.35 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.70 (t, 2H, –CH_2–CH_2–CH_2–CH_2–NH; $J = 6.71$), 2.85 (t, 2H, –CH_2–CH_2–CH_2–CH_2–NH; $J = 7.32$), 3.82 (s, 2H, CH_2), 7.05–7.72 (m, 12H arom., 1H ind.). MS: *m/z* 401 [MH^+]. Anal. Calcd for $C_{27}H_{29}FN_2$ (MW 401.53): C, 80.96; H, 7.30; N, 6.99%. Found: C, 80.81; H, 7.41; N, 6.80%.

4.1.30. N-(2,4-Dimethylbenzyl)-4-[1-(4-fluorophenyl)-1H-indol-3-yl]-N-methylbutan-1-amine ***2l***

^{1}H NMR ($CDCl_3$–TMS) ppm (δ): 1.56–1.99 (m, 4H, –CH_2–CH_2–CH_2–CH_2–NH), 2.20 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.47 (t, 2H, –CH_2–CH_2–CH_2–CH_2–NH), 2.82 (t, 2H, –CH_2–CH_2–CH_2–CH_2–NH), 3.44 (s, 2H, CH_2), 6.93–7.84 (m, 11H arom., 1H ind.). MS: *m/z* 401 [MH^+]. Anal. Calcd for $C_{28}H_{31}FN_2$ (MW 414.56): C, 81.12; H, 7.54; N, 6.76%. Found: C, 80.93; H, 7.32; N, 6.91%.

4.2. Pharmacology

4.2.1. Radioligand binding assays

Membranes from rat liver were prepared according to Matsumoto et al. [35] and binding assays were performed according to Hellewell et al. [36] and Torrence-Campbell and Bowen [37], with slight modifications. For binding assays, 10 mM stock solutions of the compounds were prepared in 100% DMSO and diluted with 50 mM Tris–HCl buffer on the day of the experiment. The final DMSO concentration in the incubation tubes was 0.1%.

For σ_2 receptor assays, 150 μg of rat liver homogenate was incubated in 50 mM Tris–HCl, pH 8.0, in the presence of 100 nM (+)-pentazocine, 0.5 ml final volume. After 120 min at room temperature, incubation was stopped by rapid filtration under vacuum on GF/B filters pre-soaked in 0.5% polyethylenimine. For saturation analysis, increasing concentrations (0.3–300 nM) of [^{3}H]-DTG (Perkin–Elmer, specific activity 58.1 Ci/mmol) were used in the absence (total binding) and in the presence (nonspecific binding) of 10 μM haloperidol. K_d and B_{max} values were calculated by nonlinear regression using the SigmaPlot software and corresponded to 19.7 ± 3 nM and 8263 ± 420 fmol/mg protein, respectively (mean ± SEM of 3 experiments performed in duplicate). For competition experiments, a final concentration of 3 nM [^{3}H]-DTG was used and unlabelled DTG (3, 30 and 300 nM) was assayed as internal standard. When estimated, IC_{50} values were obtained using 11 increasing concentrations of the tested compound (0.1–10.000 nM). The corresponding K_i values were calculated by means of the Cheng–Prusoff equation, and utilizing the experimental one as the K_d value. The K_i values for the test compounds represent the mean ± SE of three separate determinations performed in duplicate.

For σ_1 receptor assays, 250 μg of rat liver homogenate was incubated in 50 mM Tris–HCl, pH 8.0, in 0.5 ml final volume. After 120 min at 37 °C the reactions were terminated as described above. For saturation analysis, increasing concentrations (0.3–50 nM) of [^{3}H]-(+)-pentazocine (Perkin–Elmer, specific activity 34.9 Ci/mmol) were used in the absence (total binding) and in the presence (nonspecific binding) of 10 μM haloperidol. The calculated K_d and B_{max} values were 16.7 ± 4 nM and 4842 ± 409 fmol/mg protein, respectively (mean ± SEM of 3 experiments performed in duplicate). For competition experiments, a final concentration of 1 nM [^{3}H]-(+)-pentazocine was used and unlabelled (+)-pentazocine (1, 10 and 100 nM) was assayed as internal standard. The K_i values of selected compounds were obtained as described above.

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