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Preliminary communication

Synthesis and preliminary pharmacological results on new naphthalene derivatives as 5-HT_4 receptor ligands

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Abstract – The indole derivative GR 113808 is currently used as the reference ligand for labelling the 5-HT_4 serotoninergic receptors. Previous works in our laboratories established the bioisosteric equivalency of the indole heterocycle and naphthalene in a series of melatonin receptor ligands. Based on this knowledge we designed new analogues of GR 113808 by introducing two bioisosteric modifications: firstly, the indole ring was replaced by a naphthalene one and secondly, the ester linkage was replaced by an amide group. Compound **8** emerged within this novel series as it displayed high and selective affinity at 5-HT_4 receptors (Ki 5-HT_4 = 6 nM, Ki 5-HT_3 = 100 nM, Ki values at other 5-HT receptors were higher than 1 000 nM). Compound **8** is currently undergoing further pharmacological evaluation. © 2000 Éditions scientifiques et médicales Elsevier SAS

serotonin / 5-HT receptor

1. Introduction

During the last decade the multiplicity of serotoninergic receptors and the variety of diseases in which they are implicated have given an enormous impetus in the search for selective serotoninergic ligands with useful therapeutic values. The 5-HT_4 receptors are of high clinical interest because of their role in the regulation of gastrointestinal motility in certain cardiac effects and their potential implication in the management of various affective disorders [1–7]. The 5-HT_4 receptor that is a member of the seven transmembrane spanning G-protein-coupled family of receptors is positively coupled to adenylate cyclase and exists in two isoforms (5-HT_4S and 5-HT_4L) that differ in the length and sequence of their carboxy termini [8, 9]. The 5-HT_4 receptor is widely distributed in the central nervous system and peripheral tissues [10–12]. In the periphery, the receptor plays an important role in the function of several organ responses, including the alimentary tract, bladder, heart and adrenal gland. These wide localizations are predictive of a potentially large therapeutic usefulness. Since its discovery, significant advances have been made in the understanding of the physiology and pharmacology of the 5-HT_4 receptor. These advances have led to the development of several 5-HT_4 receptor agonists and antagonists that may have therapeutic usefulness in the treatment of peripheral disorders such as irritable bowel syndrome, gastroparesis, urinary incontinence and cardiac arrhythmias [13]. The 5-HT_4 receptors are activated by indoles [14–16], benzamides [17, 18], benzimidazolones [19] and 1,8-naphthalimides (i.e. 5-hydroxytryptamine, mixed 5HT_3 antagonist-5HT_4 agonist such as cisapride, BIMU 1 and (S)-RS 56532, respectively, *figure 1*).

5-HT_4 antagonists include benzoates [20, 21], indolecarboxylates [22] and benzodioxanes [23] (i.e. SDZ 205557, GR 113808, ICS 205930 and SB 204070, respectively, *figure 2*). GR 113808 and SB 204070 are two highly potent and selective 5-HT_4 antagonists [21, 24–26]. However, there is no clear evidence as to their in vivo activity as they are predicted to be rapidly inactivated by esterases. On the other hand, most 5-HT_4 antagonists generally display relatively poor 5-HT_4 versus 5-HT_3 selectivity [27]. For example, the indole-tropane derivative tropisetron (ICS 205930, *figure 2*), an anti-emetic

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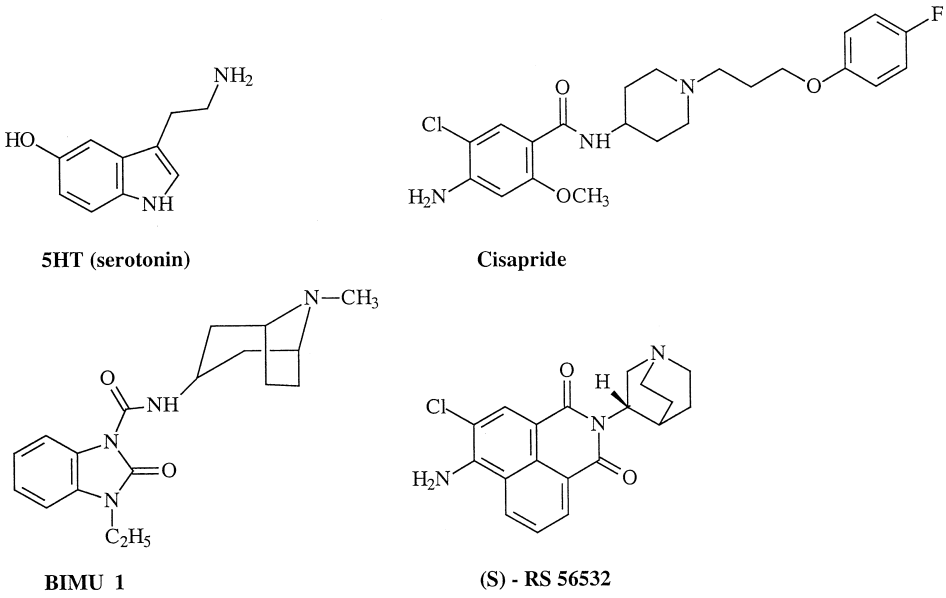


Figure 1. Structures of some $5HT_4$ agonists.

$5HT_3$ antagonist used in the prophylaxis and treatment of nausea and vomiting induced by chemotherapy or radiotherapy, and in the postoperative period [28] behaves like a 5-HT_4 antagonist at high concentrations [29–31].

However, in contrast the indole derivative GR 113808 has greatly facilitated the studies on 5-HT_4 receptors since it exhibited a selectivity for the 5-HT_4 receptor over rat cerebrocortical 5-HT_3 receptors; its tritiated form is currently used to label 5-HT_4 sites [25, 32, 33].

The various 5-HT_4 ligands may find a wide variety of therapeutic applications, both at peripheral and central levels. The most interesting 5-HT_4-related pathogenesis is in the gastrointestinal tract [34]. Indeed, the benzamide derivatives such as cisapride have been shown to possess therapeutic value in this area; this compound has been shown to have beneficial effects on dyspepsia, gastro-oesophagial reflux disease and to a lesser extent gastroparesis [15]. It has also been suggested that 5-HT_4

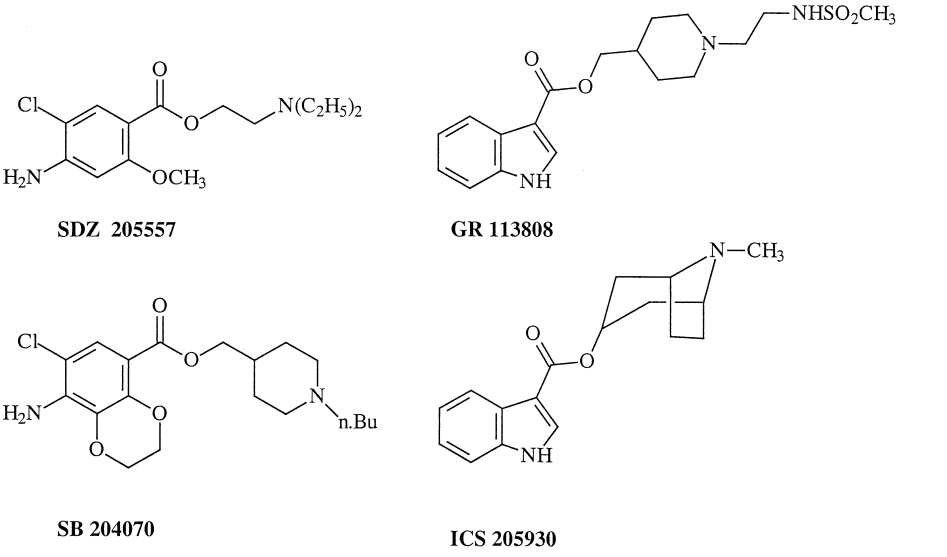


Figure 2. Structures of some $5HT_4$ antagonists.

agonists could be helpful in treating tachycardia and some other more serious heart diseases [1, 4]. At a central level, many speculations have been advanced concerning the treatment of neuropsychiatric disorders [35, 36] and consequently selective 5-HT_4 agonists or antagonists may find applications as psychotherapeutic drugs.

Considering GR 113808 as a very promising pharmacological tool we attempted the synthesis of GR 113808 analogues with hopefully improved metabolic stability [37]. We therefore introduced two structural modifications on this lead:

1) we first replaced the indole ring present in GR 113808 with a naphthalene one. Indeed, previous works established the bioisosteric equivalency of indole and naphthalene among a series of melatonin and sumatriptan analogues [38–40]. Among the melatonin analogues, several compounds were found to be more active than the endogenous ligand itself. In the same way, some sumatriptan analogues were found to display 5-HT_1-like affinity as important as that exhibited by sumatriptan.

2) The ester linkage of GR 113808 was replaced by a benzamide group, which is expected to confer higher metabolic stability.

This paper describes the synthesis of six naphthalenic analogues of GR 113808 (**6–8** and **13–15**) and their affinity for two serotoninergic receptors, $5HT_3$ and $5HT_4$ receptor.

2. Chemistry

Access to compounds **6–8** is reported on *figure 3*: isonipecotic acid **(1)** was transformed into its ethyl ester **(2)** by action of thionyl chloride in absolute ethanol. Introduction of an N-benzyl protecting group on **2** was performed in absolute ethanol using benzyl chloride and anhydrous potassium carbonate to give compound **3**, which was then reduced using $LiAlH_4$ in dry THF to yield (1-benzyl-piperidin-4-yl)methanol **(4)**. Reaction of 1-naphthoyl chloride with **4** in anhydrous chloroform led to the ester **6**, which was N-debenzylated to **7** by hydrogenolysis in methanol in the presence of ammonium formate and 10% palladium on charcoal. Compound **7** was finally reacted with N-(2-chloroethyl)-methylsulfonamide in dry acetone in the presence of potassium carbonate to give compound **8**.

The amide analogues **13–15** were synthesized according to the approach shown on *figure 4*.

Reaction of 4-aminomethylpiperidine **(9)** with benzaldehyde in absolute ethanol gave the imino derivative **10** which was then protected with a benzyl group using the same procedure as that previously described for the synthesis of compound **3** to give **11**. Hydrolysis of the imino group of **11** was performed in acid aqueous medium to give **12** which was then reacted with 1-naphthoyl chloride **(5)** using the same procedure as that previously employed for the synthesis of **6**. This led to compound **13** which was then debenzylated in methanol under hydrogen pressure in the presence of palladium on activated charcoal to yield **14**. Substitution by the methylsulfonamidoethyl side-chain to give final target compound **15** was performed in the same way as above for compound **8**.

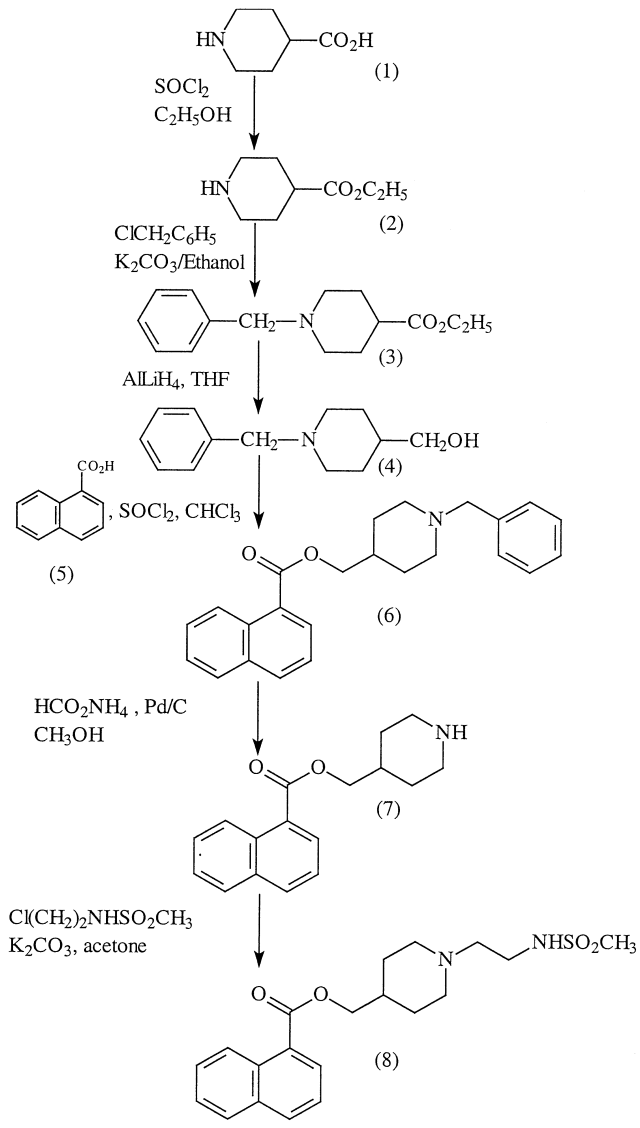


Figure 3. Synthesis of compounds **6–8**.

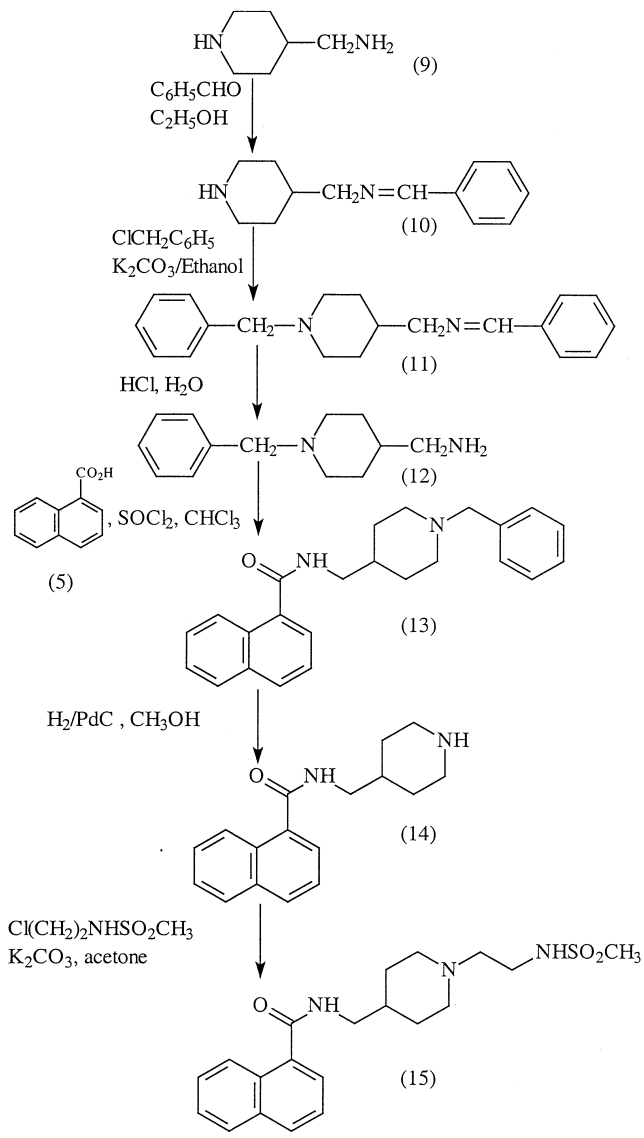


Figure 4. Synthesis of compounds **13–15**.

3. Results and discussion

Affinity for 5-HT receptors including 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3 as well as 5-HT_4 subtypes were determined. Except at 5-HT_3 and 5-HT_4 receptors, all tested compounds were found with weak or no affinity at the other 5-HT receptors (Ki > 1 000 nM). *Table I* displays the affinity values which were obtained on 5-HT_3 and 5-HT_4 receptors.

The most interesting compound **8** is the strict naphthalene analogue of GR 113808. Its 5-HT_4 receptor affinity

Table I. 5-HT_3 and 5-HT_4 affinities (Ki in nM) for compounds **6–8** and **13–15***.

Compound	5-HT_3[a]	5-HT_4[b]
6	1	3
7	3	100
8	100	6
13	> 1000	>1 000
14	500	>1 000
15	>1 000	>1 000

* Tissue preparations and radioligands used for affinity determinations: [a] NG-108-15 cells and [^{3}H]-BRL 43694; [b] guinea-pig hippocampus and [^{3}H]-GR 113808.

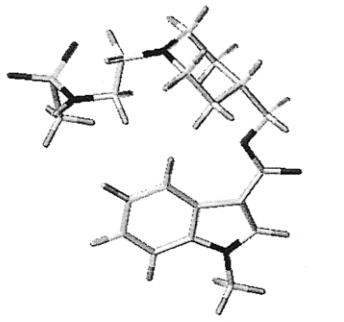
(6 nM) is 40 times less active than GR 113808 (0.15 nM) that exhibits a 5-HT_4 versus 5-HT_3 selectivity (Ki (5-HT_4)/Ki (5-HT_3) = 17) [41]. Deletion of the substituent on the nitrogen atom of the piperidine ring (compound **7**) leads to a loss of 5-HT_4 affinity (about 20-fold) combined with a higher 5-HT_3 affinity (30-fold). This is not surprising since it was known that an aromatic group, a connecting acyl group (or an equivalent pharmacophore), and a basic amine are the general components of the structure–activity relationships required for high 5-HT_3 affinity [42]. Substitution of the piperidine nitrogen with a lipophilic group such as a benzyl (compound **6**) leads to high affinities both at 5-HT_3 and 5-HT_4 receptors (in the nanomolar range). Replacement of the ester group of GR 113808 with its bioisosteric amide equivalent led to compounds **(13–15)**, devoid of affinity for all the 5-HT receptors tested.

In an effort to understand the reason for this apparent discrepancy in our design, we undertook molecular modelling studies to explore the conformational behaviour of GR 113808 and the naphthalene analogues **8** and **15**. We used the classical 'random search' procedure as implemented in SYBYL [43].

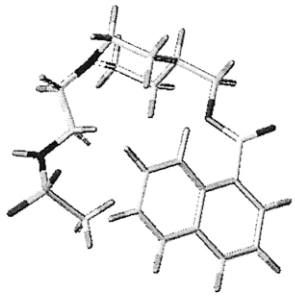
The outcome produced by the random search procedure for compound GR 113808 consists of 450 conformers. 230 duplicates are removed on the basis of their similarity with the lower energy conformation. The 220 remaining conformers spread over an energy range of 10.5 kcal.mol^{-1} above the most stable one. The lowest energy conformer is reported in *figure 5*.

The random search procedure applied to compound **8** retains 931 conformers. Similar structures are eliminated to produce a conformational space containing 609 conformers, spread over an energy range of 10.2 kcal.mol^{-1} above the lowest energy minimum. The lowest energy conformer is presented in *figure 5*.

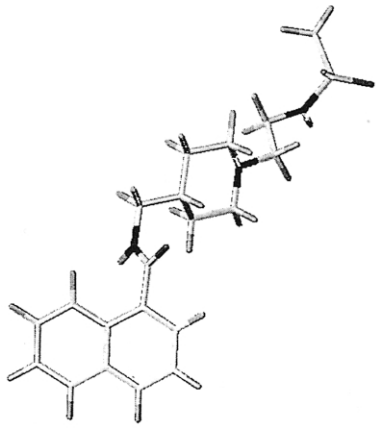
Using the random search procedure for generating the compound **15** conformational space, we retained 525



(GR113808)



(8)



(15)

Figure 5. Lowest energy conformers of compounds GR 113808, **8** and **15**.

conformers. 223 similar structures were eliminated to provide a conformational space containing 302 conformers spread over an energy range of 4.8 kcal.mol^{-1} above the most stable. The lowest energy conformer is reported in *figure 5*.

From these studies it appears that the side-chains of both molecules are highly flexible and the difference in the pharmacological activities between the ester derivatives and the amidic derivative are to be related to the difference of configuration between the ester and the amide moieties. The ester function favours a Z configuration, while the amide function always adopts an E configuration in low-energy conformers, as shown in *figure 5*. For GR 113808 we registered an energy difference of 8.2 kcal.mol^{-1} between Z and E configurations of the most stable conformers. This difference also appears for compound **8** for which it reaches a value of 5.6 kcal.mol^{-1}.

4. Conclusion

In conclusion, we have designed, synthesized and tested a limited series of naphthalene analogues of GR 113808, among which one compound **(8)** emerged since it displayed 5-HT$_4$ affinity and selectivity closely comparable to those displayed by GR 113808. Compound **8** has been selected for further pharmacological evaluations in animal models.

5. Experimental section

5.1. Chemistry

Compounds **6–8** and **13–15** were characterized by elemental analyses, IR and ^{1}H-NMR spectra. IR spectra were recorded on a Perkin-Elmer 297 spectrometer using KBr tablets; wave numbers are expressed in cm^{-1}. The ^{1}H-NMR spectra were obtained on a Brücker WP 80 SY (80 MHz) apparatus with Me_4Si as internal standard and with $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts (ppm) are reported in the δ scale. Melting points were determined using a Büchi SMP-20 apparatus and are uncorrected. Elemental analyses were determined at the CNRS analytical centre of Vernaison (France) and are within ± 0.4% of the theoretical values. Compounds **1**, **5** and **9** were purchased from Aldrich Chemicals.

5.1.1. (Piperidin-4-yl)ethylcarboxylate hydrochloride **2**

Isonipecotic acid (0.01 mol, 1.29 g) was dissolved in absolute ethanol (50 mL). The solution was cooled to 0 °C and $SOCl_2$ (0.04 mol) was added dropwise. The mixture was then heated under reflux for 3 h, the solvent was evaporated in vacuo and the residue was dissolved in a 10% aqueous solution of NaOH (50 mL) and extracted with chloroform. The organic layer was dried over $CaCl_2$, and evaporated in vacuo. The residue was dissolved in dry ethanol and HCl was bubbled to give the hydrochloride derivative **2** which was recrystallized from absolute ethanol. Yield = 95%, m.p. 140–142 °C. IR ν (cm^{-1}):

3 000–2 400 (NH^+), 1 710 (CO). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.3 (m, 3H, CH_3), 2.0–2.7 (m, 5H, COCH + $N(CH_2)_2$), 3.0–3.5 (m, 4H, $C(CH_2)_2$), 4.2 (m, 2H, CH_2CO), 9.5 (s, 2H, NH_2^+). Anal. $C_8H_{15}NO_2$. HCl (C, H, N).

5.1.2. (1-Benzylpiperidin-4-yl)ethylcarboxylate hydrochloride **3**

A suspension of compound **2** (0.01 mol, 1.57 g) in ethanol (50 mL) was stirred at room temperature. Benzyl chloride (0.012 mol, 1.50 g) and K_2CO_3 (0.02 mol, 2.80 g) were added and the reaction was pursued for 72 h. The solvent was then evaporated in vacuo and water added (50 mL). The desired compound was extracted by ether; and the organic layer was dried over $CaCl_2$ and evaporated in vacuo. The resulting residue was dissolved in dry acetone and HCl was bubbled into the solution to produce a precipitate of the hydrochloride. This precipitate was then filtered, dried and recrystallized from acetone to give compound **3**. Yield = 88%, m.p. 116–118 °C. IR ν (cm^{-1}): 3 000–2 900 (CH alkyles), 2 700–2 500 (NH^+), 1 720 (CO). ^{1}H-NMR (DMSO, d_6) δ (ppm): 1.10 (m, 3H, CH_3), 1.80–2.10 (m, 6H, $CH_2N(CH_2)_2$), 2.80 (m, 5H, $CH(CH_2)_2$), 4.20 (m, 2H, CO_2CH_2), 7.30–7.80 (m, 5H, H aromatic), 11.50 (s, 1H, NH^+). Anal. $C_{15}H_{21}NO_2$. HCl (C, H, N).

5.1.3. (1-Benzylpiperidin-4-yl)methanol **4**

A suspension of $AlLiH_4$ (0.04 mol, 1.5 g) in dry THF was stirred at 0 °C; A solution of compound **3** (0.01 mol, 2.5 g) in dry THF (50 mL) was added dropwise. The obtained mixture was refluxed for 3 h and then cooled. Ethylacetate (200 mL), water (40 mL), and a 2 N aqueous solution of NaOH (10 mL) were added. The obtained mineral precipitate was filtered; the filtrate was evaporated and water (50 mL) was added. Extraction with chloroform, drying over $CaCl_2$ and evaporation of the organic layer gave an oily residue which was immediately used for the following step. Yield = 80%. IR ν (cm^{-1}) 3 500–3 200 (OH), 3 000–2 700 (CH alkyles). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.20–2.00 (m, 8H, $N(CH_2CH_2)_2$), 2.80–3.00 (m, 2H, CH + OH), 3.50 (m, 4H, CH_2 OH + CH_2Ph), 7.30–7.50 (m, 5H, H aromatic). Anal. $C_{13}H_{19}NO$ (C, H, N).

5.1.4. 1-[(1-Benzylpiperidin-4-yl)carboxymethyl]naphthalene **6**

1-Naphthoic acid (**5**) (0.01 mol, 1.72 g) was dissolved in dry chloroform; $SOCl_2$ (0.04 mol, 4.8 g) was added and the mixture was refluxed for 4 h. The solvent and the residual $SOCl_2$ were removed in vacuo. Dry chloroform was then added to the residual solid material corresponding to naphthoylchloride. The suspension was cooled to ~ 0 °C and (1-benzylpiperidin-4-yl)methanol **(4)** (0.01 mol, 2.05 g) previously dissolved in chloroform (50 mL) was added dropwise. The mixture was refluxed for 6 h; the solvent was evaporated in vacuo, ether (100 mL) was added and the resulting precipitate was filtered, dried and recrystallized from toluene. Yield = 70%, m.p. 123–125 °C. IR ν (cm^{-1}) 3 100–2 800 (CH alkyles), 2 700–2 300 (NH^+), 1 700 (CO). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.90–2.60 (m, 8H, $N(CH_2CH_2)_2$), 3.50 (m, 1H, CH), 4.10–4.50 (m, 4H, CH_2CO_2 + CH_2aryl), 12.50 (s, 1H, NH^+). Anal. $C_{24}H_{25}NO_2$ (C, H, N).

5.1.5. 1-[(Piperidin-4-yl)methyloxycarbonyl]naphthalene hydrochloride **7**

Compound **6** (0.01 mol, 0.36 g) was dissolved in methanol (50 mL), palladium on charcoal (2 g) and ammonium formate (0.1 mol, 6.3 g) were added. The mixture was heated under reflux for 3 h. After cooling, the mixture was filtered and the filtrate was evaporated in vacuo; 1 N aqueous solution of NaOH was added to basify the solution which was then extracted with ethyl acetate. The organic layer was dried over $CaCl_2$, evaporated and the residue was dissolved in dry acetone. HCl was bubbled into the solution and the resulting precipitate was filtered, dried and recrystallized from ethanol/ether (1:1). Yield = 53%, m.p. 182–184 °C. IR ν (cm^{-1}): 3 000–2 700 (NH^+), 1 700 (CO). ^{1}H-NMR (DMSO, d_6) δ (ppm): 1.5–2.3 (m, 5H, $CH(CH_2)_2$), 2.9–3.3 (m, 4H, $N(CH_2)_2$), 4.3 (m, 2H, CH_2CO_2), 7.5–8.7 (m, 7H, H aromatic). Anal. $C_{17}H_{19}NO_2$.HCl (C, H, N).

5.1.6. 1-[(1-(2-(Methylsulfonamido)ethyl)piperidin-4-yl)methyloxycarbonyl]naphthalene hydrochloride **8**

A suspension of compound **7** (0.01 mol, 2.7 g) in dry acetone, K_2CO_3 (0.04 mol, 5.5 g) and (1-chloro-2-methylsulfonamido)ethane (0.015 mol, 2.4 g) was heated to reflux for 24 h. The mixture was cooled, the filtrate was evaporated and petroleum ether was added under stirring. The obtained precipitate was filtered, dried and dissolved in absolute ethanol into which HCl was bubbled. The formed precipitate was filtered, dried and recrystallized from absolute ethanol. Yield = 45%, m.p. 170–172 °C. IR ν (cm^{-1}): 3 300 ($NHSO_2$), 3 000–2 700 (CH alkyles), 1 700 (CO), 1 310, 1 160 (SO_2). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.5–2.3 (m, 5H, $CH(CH_2)_2$), 2.7 (s, 3H, SO_2CH_3), 3.0–3.2 (m, 4H, $N(CH_2)_2$), 3.4–3.6 (m, 4H, -CH_2–CH_2-), 4.5 (d, 2H, CH_2CO_2 J = 12.63 Hz), 7.2 s, 1H, NH), 7.7–9.2 (m, 7H, H aromatic). Anal. $C_{20}H_{26}N_2O_4S$.HCl (C, H, N).

5.1 7. 4-Benzylideneaminomethylpiperidine **10**

4-Aminomethylpiperidine (0.01 mol, 1.15 g) was dissolved in absolute ethanol (20 mL), benzaldehyde

(0.01 mol, 0.11 g) was added, and the mixture was heated under reflux for 24 h. After cooling, the solvent was stripped in vacuo. The resulting oil was used as such for the next synthetic step. IR ν (cm^{-1}): 3 500–3 200 (NH), 2 900 (CH alkyles), 1 650 (C=N). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.5–3.0 (m, 9H, $CH(CH_2–CH_2)_2$), 2.1 (s, 1H, NH), 3.5 (d, 2H, NCH_2, J = 9.2 Hz), 7.3–7.8 (m, 5H, H aromatic), 8.25 (s, 1H, CH=N). Anal. $C_{13}H_{18}N_2$ (C, H, N).

5.1.8. 1-Benzyl-4-benzylideneaminomethylpiperidine **11**

4-Benzylideneaminomethylpiperidine **(10)** (0.01 mol, 2 g), benzyl chloride (0.012 mol, 1.5 g), anhydrous K_2CO_3 (0.02 mol, 2.8 g) and acetone (50 mL) were stirred for 12 h at room temperature. The mixture was filtered, the filtrate was evaporated and the obtained oil was used as such in the next step. IR ν (cm^{-1}): 2 900 (CH alkyles), 1 650 (C=N). Anal. $C_{20}H_{24}N_2$ (C, H, N).

5.1.9. 1-Benzyl-4-amino-methylpiperidine hydrochloride **12**

A suspension of compound **11** (0.01 mol, 2.9 g) in a 10% aqueous solution of HCl (10 mL) was heated at 40 °C for 4 h. After cooling, chloroform (50 mL) was added. The aqueous layer was isolated and a 40% aqueous solution of NaOH was added (pH 7–8) and extracted with chloroform (50 mL). The organic layer was dried over $CaCl_2$, evaporated and the residue was dissolved in anhydrous diethyl ether in which HCl was bubbled. The obtained precipitate was filtered, dried and recrystallized from acetone. Yield = 55%, m.p. > 230 °C. IR ν (cm^{-1}): 3 600–3 200 (NH_3^+), 2 500–2 400 (NH^+), 3 100–2 800 (CH alkyles). ^{1}H-NMR (DMSO, d_6), δ (ppm): 1.5–2.1 (m, 5H, $CH(CH_2)_2$), 2.5–3.0 (m, 4H, $N(CH_2)_2$), 3.3 (d, 2H, NCH_2, J = 8.6 Hz), 4.2 (s, 2H, NCH_2 aryl), 7.4–7.7 (m, 5H, H aromatic), 8.35 (s, 3H, NH_3^+), 11.25 (s, 1H, NH). Anal. $C_{13}H_{20}N_2$.HCl (C, H, N).

5.1.10. N-[(1-Benzylpiperidin-4-yl)methyl)]naphth-1-yl carboxamide **13**

Naphthoyl chloride was synthesized as described above. A mixture of 1-benzyl-4-aminomethylpiperidine (**12**) (0.01 mol, 2 g) and K_2CO_3 (0.02 mol, 2.8 g) in chloroform/water (15 mL and 5 mL, respectively) was stirred for 0.5 h at room temperature. Naphthoyl chloride (0.01 mol, 1.9 g) previously dissolved in chloroform (10 mL) was added dropwise and the mixture was stirred at room temperature for 12 h. The organic layer was then dried over $CaCl_2$, evaporated and the residue was recrystallized from ethanol/water (40:60). Yield = 60%, m.p. 146–148 °C. IR ν (cm^{-1}): 3 280 (NH), 1 630–1 610 (CO). ^{1}H-NMR ($CDCl_3$) δ (ppm): 13–2.0 (m, 8H, $N(CH_2CH_2)_2$), 2.9 (m, 1H, CH), 3.0 (t, 2H, CH_2-piperidinyl, J = 6.2 Hz), 3.6 (s, 2H, CH_2Ph), 6.10 (s, 1H, CONH), 7.20–7.90 (m, 12H, aromatic). Anal. $C_{24}H_{26}N_2O$ (C, H, N).

5.1.11. N-(Piperidin-4-yl-methyl)naphth-1-yl carboxamide hydrochloride **14**

Compound **13** (0.01 mol, 3.6 g) was dissolved in methanol (100 mL). Palladium on charcoal was added and the mixture was heated under hydrogen atmosphere at 50 °C for 4 days. After cooling, the solvent was evaporated in vacuo. The residue was dissolved in acetone and HCl was bubbled. The obtained precipitate was filtered, dried and recrystallized from acetonitrile. Yield 62%, m.p. 118–119 °C. IR ν (cm^{-1}): 3 250 (NH), 2 900–2 800 (CH alkyles), 2 500 (NH^+), 16 315 (CO). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.3–2.1 (m, 5H, $CH(CH_2)_2$), 2.6–3.3 (m, 6H, CH_2-piperidinyl + $N(CH_2)_2$), 7.0–8.3 (m, 7H, H aromatic), 8.70 (s, 1H, CONH), 9.0 (s, 2H, NH_2^+). Anal. $C_{17}H_{20}N_2O$.HCl (C, H, N).

5.1.12. N-(1-Methylsulfonamidoethylpiperidin-4-ylmethyl)naphth-1-yl carboxamide hydrochloride **15**

Starting from **14** (0.01 mol, 2.7 g), compound **15** was synthesized in the same way as **8**. Recrystallization was performed from absolute ethanol. Yield = 55%, m.p. 168–170 °C. IR ν (cm^{-1}): 3 240 (CONH + SO_2NH), 2 900–2 800 (CH alkyles), 2 500 (NH^+), 1 615 (CO), 1 300, 1 135 (SO_2). ^{1}H-NMR (DMSO, d_6) δ (ppm): 1.6–2.0 (m, 5H, $CH(CH_2)_2$), 2.9 (s, 3H, SO_2CH_3), 3.4 (m, 6H, $(CH_2)_2NCH_2$), 3.5 (d, 2H, CH_2-piperidinyl, J = 10.52 Hz), 7.10 (s, 1H, $NHSO_2$), 7.40–8.10 (m, 7H, H aromatic), 8.6 (s, 1H, NHCO), 10.4 (s, 1H, NH^+). Anal. $C_{20}H_{27}N_3O_3$ S.HCl (C, H, N).

5.2. Molecular modelling studies

Molecular modelling studies were performed using SYBYL software version 6.5 running on Silicon Graphics Indigo 2 R4000 workstation.

Three-dimensional models of all compounds were built from standard fragments library and their geometry was subsequently optimized using the Tripos force field including the electrostatic term calculated from Gasteiger and Hückel atomic charges. The method of Powell available in Maximin2 procedure was used for energy minimization until the gradient value was smaller than 10^{-3} kcal.mol^{-1}.Å. Throughout all calculations, an 8 Å cut-off radius was used to properly take into account all the non-bonded interactions and the dielectric constant was set to 1.0.

For each compound, a conformational search using the process ‘random search’ as implemented in SYBYL was performed to identify its lowest energy conformations by

perturbing randomly all the rotatable bonds of the molecule. The completeness of the search was reached when 3 000 conformations were generated or when each conformation was found at least six times. An RMS value of 0.2 Å was set to differentiate two conformers. The conformations produced by the random conformational search are fully optimized and can be used immediately for further analysis.

Then they were ordered by increasing energy and the similarity between the minimized structures was evaluated by comparing the RMS measured between all heavy atoms. Equivalent conformations (with an RMS less than 0.4 Å) are discriminated and the remaining low-energy conformations are used for further investigations.

5.3. Pharmacological studies

The $5HT_4$ affinities (Ki) were determined in guinea-pig hippocampus tissue using ^{3}H-GR 113808 as radioligand following a procedure adapted from Grossman et al. [44]. The $5HT_3$ affinities (Ki) were measured using NG-108-15 cells and ^{3}H-BRL 43694 as radioligand. For all binding assays, competing drug, non-specific, total and radioligand bindings were defined in triplicate

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