Serotonin 5-HT$_7$ Receptor Antagonists

M.L. López-Rodríguez[a,*], B. Benhamú[a], M.J. Morcillo[b], E. Porras[a], J.L. Lavandera[a] and L. Pardo[c]

[a]*Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense, E-28040 Madrid, Spain,* [b]*Facultad de Ciencias, Universidad Nacional de Educación a Distancia, E-28040 Madrid, Spain,* [c]*Laboratori de Medicina Computacional, Unitat de Bioestadística and Institut de Neurociències, Universitat Autònoma de Barcelona, E-08193 Cerdanyola del Vallès, Barcelona, Spain*

Abstract: The 5-HT$_7$R is the most recent addition to the burgeoning family of serotonin receptors. Preliminary evidences suggest that it may be involved in depression, control of circadian rhythms, and relaxation in a variety of vascular smooth muscles, indicating the high potential of 5-HT$_7$R ligands as new therapeutic drugs. During the last four years several selective 5-HT$_7$R antagonists have been discovered, and we have recently contributed to this field with the definition of a pharmacophoric hypothesis for 5-HT$_7$R antagonism and a computational model of ligand-receptor interaction of new naphtholactam and naphthosultam derivatives acting at this receptor. This article will review the development of 5-HT$_7$R antagonists with an emphasis on selective antagonists, their structural requirements and ligand-receptor interactions, as well as the potential therapeutic opportunities surrounding 5-HT$_7$R ligands.

Keywords: Serotonin, 5-HT$_7$ receptor antagonists, pharmacophore model, computational model, ligand-receptor interaction

INTRODUCTION

Serotonin (5-hydroxytryptamine, 5-HT) is an important neurotransmitter discovered over 50 years ago and, at present, it continues to generate interest as one of the most attractive targets for medicinal chemist, due to its implication in a large variety of behavioural and physiological processes both in peripheral and central nervous systems [1-5]. Molecular cloning and gene expression techniques have led to the characterisation of fourteen serotonin receptor subtypes, which can be classified in seven subfamilies (5-HT$_{1-7}$) [6-9] based on pharmacological properties, second messenger coupling and sequence data. These receptors belong to the superfamily of G protein-coupled receptors (GPCRs) [10, 11], except the 5-HT$_3$ subtype, which is a ligand gated cation channel receptor.

The 5-HT$_7$ is the most recent addition to the burgeoning family of 5-HT receptors and was identified from cloning studies before the corresponding endogenous receptor was found [12, 13]. This receptor is positively coupled to adenylyl cyclase through G_s when expressed in cell lines [14]. The 5-HT$_7$R has been cloned from mouse [15], rat [16, 17], guinea pig [18] and human [19] and exhibits a low sequence homology with other 5-HT receptors. Splice variants have been identified [20-22] in rat and human, which display similar tissue distribution and pharmacological and functional characteristics. The binding profile appears consistent across species and between cloned and native 5-HT$_7$Rs. The distribution of the 5-HT$_7$R in rat and guinea pig has been studied by autoradiography using [^{3}H]-5-CT and by mRNA localisation analysis, and high levels of the receptor have been observed in the brain where it is localised in the thalamus, hypothalamus, brainstem and hippocampus. In the periphery the highest levels of 5-HT$_7$R mRNA have been found in blood vessels of different species, as well as in the human coronary artery and certain vascular smooth muscle cells.

Although the biological functions of the 5-HT$_7$R have not been fully clarified, early pharmacological data suggest that it may be involved in disturbance of circadian rhythms [23, 24], such as jet lag and delayed sleep-phase syndrome. Therefore, a 5-HT$_7$R ligand might be a useful therapeutic agent for the treatment of sleep disorders. It is also believed that a deregulated circadian rhythm could lead to mental fatigue and depression. Thus, one of the consequent mechanisms of antidepressant treatment could be the modulation of a possible dysrhythmic circadian function in depression, in which the 5-HT$_7$R might be one of the key players [25]. The fact that antipsychotic agents exhibit a high affinity for the 5-HT$_7$R leads to the speculation that this receptor might provide a target for the treatment of psychotic disorders [26-29]. In the periphery, the 5-HT$_7$R plays a role in smooth muscle relaxation in a variety of tissues [30-35] and so it might be involved in diseases such as irritable bowel syndrome [36] or migraine [37].

Clearly, the 5-HT$_7$R may be of value as a novel therapeutic target. Nevertheless, the clinical utility of 5-HT$_7$R agents awaits the development of selective ligands. Despite intense research efforts in this area, very few compounds with significant 5-HT$_7$R antagonist activity and selectivity have been reported to date. Information on the structural properties of the 5-HT$_7$R agents also remains unknown and its determination represents a critical step for developing specific compounds.

Within this field, the search for new ligands with high affinity and selectivity for the 5-HT$_7$R is highly desirable because of the potential to find new therapeutic drugs. This

*Address correspondence to this author at the Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense, E-28040 Madrid, Spain; Tel: 34-91-394-4239; Fax: 34-91-394-4103; Email: mluzir@quim.ucm.es

1568-0150/04 $45.00+.00

review covers the development of 5-HT_7R antagonists with an emphasis on the selective antagonists, their structural requirements and ligand-receptor interactions, as well as the potential therapeutic opportunities surrounding 5-HT_7R ligands.

5-HT_7R ANTAGONISTS

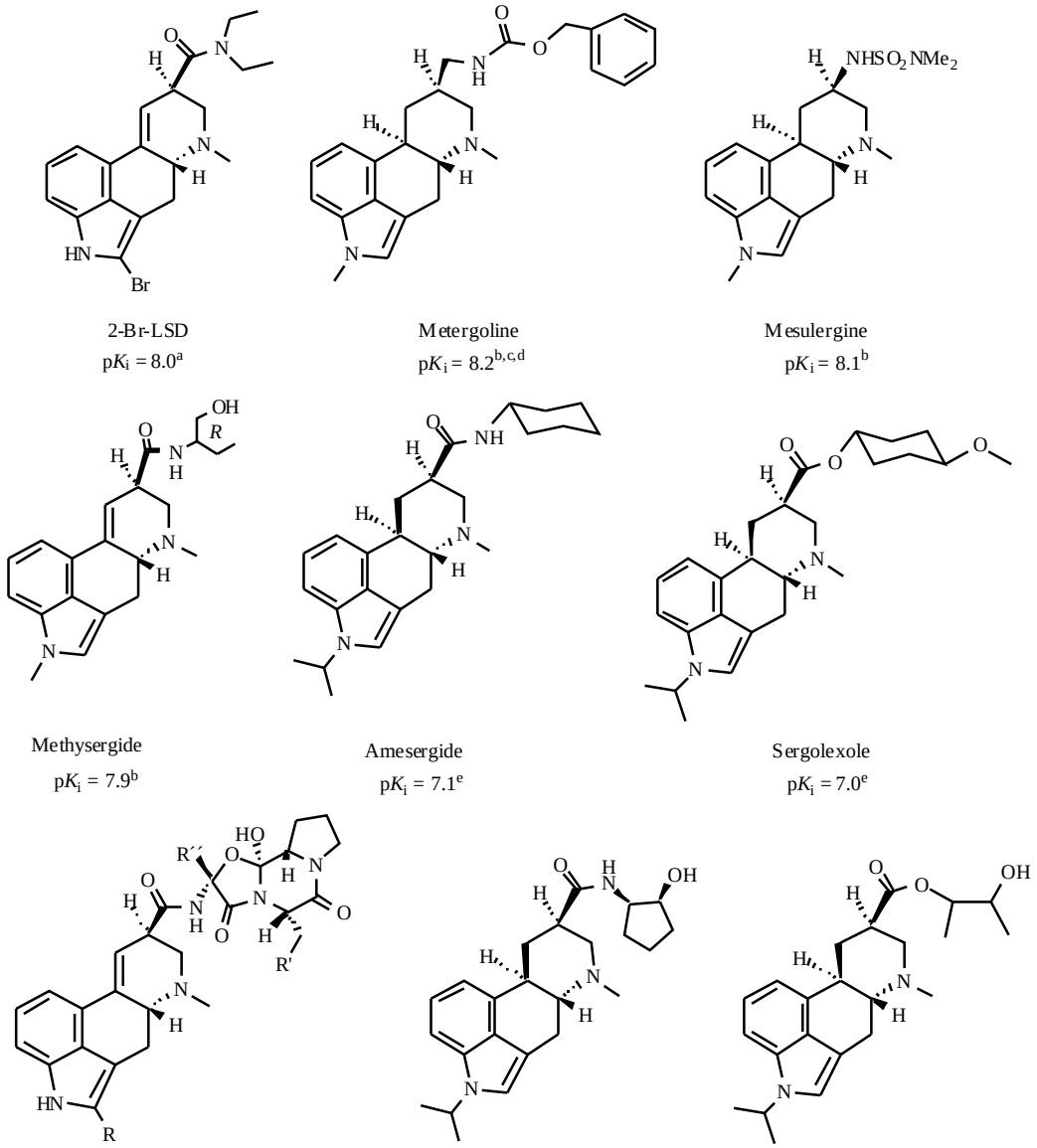
Non-selective Antagonists

During the last years the lack of selective 5-HT_7R ligands has hampered the investigation of the (patho)physiological role of this receptor, which has been derived from localization analyses and studies using non-selective ligands.

From a chemical structure standpoint, non-selective 5-HT_7R antagonists can be classified in five classes: ergolines, antipsychotic tricyclic analogues, piperidines, phenylpiperazines, and aporphine derivatives.

Ergolines

Compounds containing the tetracyclic ergoline skeleton (Fig. **1**), such as 2-Br-LSD [15], metergoline [17, 19, 38-40], mesulergine [12, 17, 39-41], methysergide [12, 17, 39],



[a] Ref. [15]. [b] Ref. [17]. [c] Ref. [19]. [d] Ref. [38]. [e] Ref. [42]. [f] Ref. [39].

Fig. (1). Structures of ergolines acting as non-selective 5-HT_7R antagonists.

amesergide [42], sergolexole [42], ergotamine [15, 43], bromocriptine [39], LY215840 [42] and LY53857 [42], exhibit moderate affinity for the 5-HT$_7$R and a wide spectrum of pharmacological activities, and find application in the treatment of a variety of clinical conditions. Probably the most important of their many indications [44] are post-partum hemorrhage, migraine and other vascular headaches, orthostatic hypotension, senile cerebral insufficiency, and Parkinson's disease.

Antipsychotic Tricyclic Analogues

Clozapine [17, 45] (Fig. **2**) is an atypical antipsychotic agent, which is effective in treating symptoms of schizophrenia while maintaining lower risk of inducing extrapyramidal side effects than classic neuroleptics [46, 47]. While it has been generally assumed that D_2 and 5-HT$_{2A}$ receptors mediate clozapine's antipsychotic activity, some authors suggest the possibility that its high affinity for 5-HT$_6$ and/or 5-HT$_7$ receptors may participate in the mechanism of action of this atypical antipsychotic agent [48].

Other antipsychotic tricyclic analogues (Fig. **2**), such as methiothepin [12, 17], (+)-butaclamol [15, 16], mianserin [12, 16], cyproheptadine [12, 17], amitriptyline [17, 49-51] and maprotiline [51], have also shown affinity for the 5-HT$_7$R.

Piperidine Derivatives

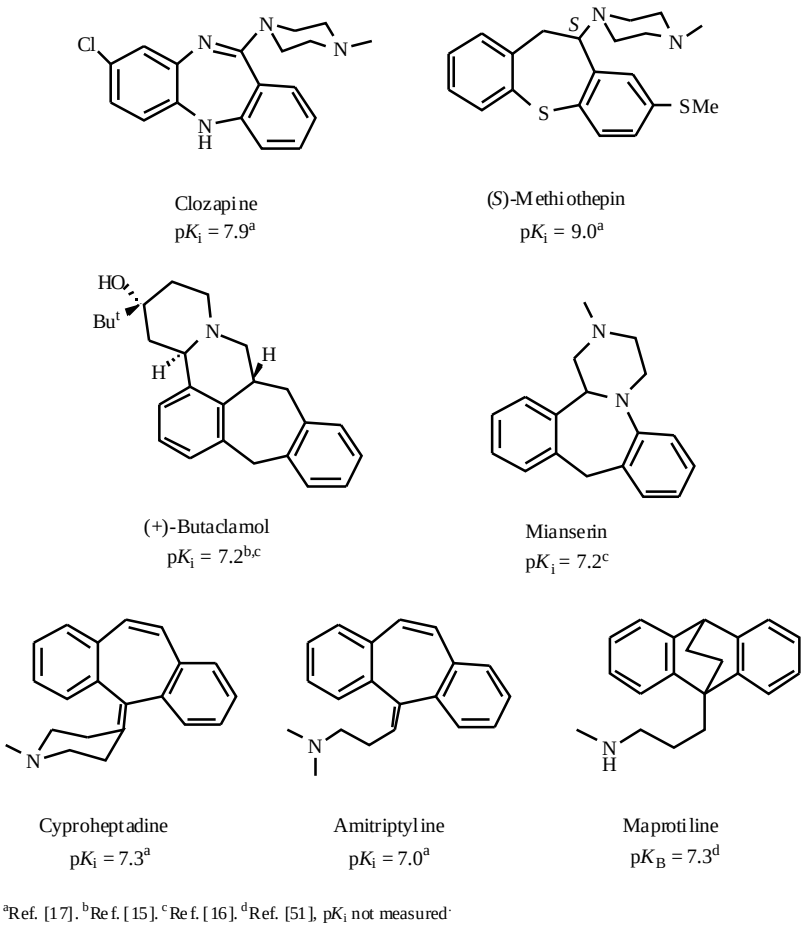
Some piperidine derivatives (Fig. **3**) can be considered as non-selective 5-HT$_7$R antagonists. For example, spiperone [15, 16], a 5-HT$_{1A}$/5-HT$_2$ antagonist, and ritanserin [12, 17], a 5-HT$_2$ antagonist, both exhibit 5-HT$_7$R affinity.

Phenylpiperazines

Phenylpiperazines such as 1-(*m*-chlorophenyl)piperazine (mCPP) and 1-(*m*-trifluoromethylphenyl)piperazine (TFMPP) (Fig. **4**) are classic serotonin ligands that display antagonist activity at the human 5-HT$_7$R, and low affinity and poor selectivity for this binding site [17, 52, 53]. In this way mCPP, which is the active metabolite of several psychotropic agents, exhibits affinity for the 5-HT$_7$R and for at least five other 5-HT receptors (5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{2A}$, 5-HT$_{2C}$ and 5-HT$_3$).

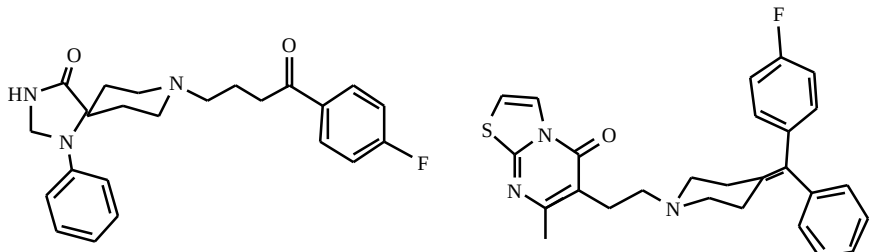
Aporphine derivatives

A.M. Johansson *et al*. [54-56] have recently designed aporphine derivatives as a new class of 5-HT$_7$R ligands. Some of them have appeared to be 5-HT$_7$R antagonists with moderate selectivity vs. serotonin 5-HT$_{1A}$ and dopamine D_{2A} receptors (Table **1**), and may be considered as valuable structural leads in future efforts to obtain selective 5-HT$_7$R agents. Also, due to their rigid structure these aporphine



[a]Ref. [17]. [b]Ref. [15]. [c]Ref. [16]. [d]Ref. [51], pK_i not measured.

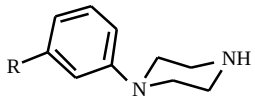
Fig. (2). Structures of antipsychotic tricyclic analogues acting as non-selective 5-HT$_7$R antagonists.



[a]Ref. [16]. [b]Ref. [17].

Fig. (3). Structures of piperidine derivatives acting as non-selective 5-HT_7R antagonists.

derivatives can be useful template moieties as a complement to other scaffolds available to medicinal chemists involved in studies of GPCRs.



aRef. [17].

Fig. (4). Structures of phenylpiperazines acting as non-selective 5-HT_7R antagonists.

Selective Antagonists

The first selective 5-HT_7R antagonist described is the sulphonamide derivative SB-258719 [57-59], which was identified in 1998 by high-throughput screening of the SmithKline Beecham Compound Bank. SB-258719 showed a modest affinity (pK_i = 7.5) but was selective over a range of other receptors (serotoninergic, adrenergic and dopaminergic) (Table **2**). One year later C. Kikuchi *et al.* reported the identification, also by high-throughput screening, of the tetrahydrobenzindole DR4004 [60, 61] as a 5-HT_7R antagonist with high affinity (pK_i = 8.7) but only moderate selectivity over other serotonin receptors (Table **3**). More recently, it has been demonstrated that DR4004 also has functional activity at the dopamine D_2 receptor that may contribute to some of its in vivo effects [62].

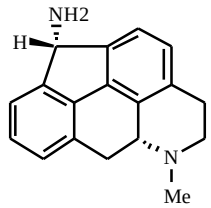
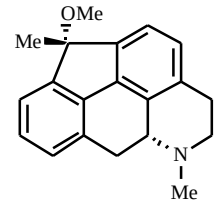
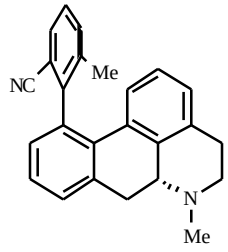
SB-258719 and DR4004 were the starting tools to elucidate the biological role of 5-HT_7Rs in the CNS and the periphery, and in the subsequent years both ligands have been used by their inventors as leading compounds to obtain more potent and selective 5-HT_7R antagonists.

In this way optimisation of SB-258719 by conformational restraint of the side chain has led to an increase of affinity and selectivity for the 5-HT_7R in analogues SB-258741 [63] and SB-269970 [63] (Table **2**). The potential clinical interest of SB-258741 in the therapy of various CNS disorders has been studied [64], in particular in models of schizophrenia where it has demonstrated no antipsychotic effect on its own [65]. SB-269970 is the 5-HT_7R antagonist with the highest affinity (pK_i = 8.9) and the best selectivity known to date (Table **2**), and for this reason this ligand has been tritiated [66, 67] to be used as radioligand in the study of 5-HT_7R localisation and in the assessment of affinity of new ligands for this receptor. SB-269970 is CNS penetrant and its potential utility for the treatment of depression and/or circadian rhythm disorders has been investigated [68], but its pharmakokinetic profile is not optimum to be used in clinic, almost certainly due to the presence of the phenolic hydroxyl group. Thus, a rational SAR study around SB-269970 was carried out by the same authors resulting in the identification of the structurally related analogue SB-656104 [69], which retains high affinity (pK_i = 8.7) and selectivity for the 5-HT_7R (Table **2**) but has a greatly improved pharmacokinetic profile.

On the other hand, related analogues of DR4004 have been recently described, which present a structural restriction in the molecule. Among them DR4365 [70] exhibited high affinity (pK_i =8.45) for the 5-HT_7R with high selectivity over other 5-HT receptors but 5-HT_{1A} (pK_i = 6.89) (Table **3**), and was confirmed to display antagonist activity in a functional model of 5-HT_7R activation. In this tetrahydrobenzindole derivative the phenyl ring is fixed to the tetrahydropyridine ring by C-N bonds to form a tetrahydropyridoindole system, and the authors suggest that this planar structure might be important for the high selectivity of these compounds for the 5-HT_7R. Other fused-ring tetrahydropyridine derivatives were synthesised by the same authors. In particular, the tetrahydrothienopyridine derivative DR4446 [71] (Table **3**) has been characterised as a potent and selective 5-HT_7R antagonist, and the $^{11}CH_3$-labelled analogue is being used as a *in vivo* radioligand for PET imaging of the 5-HT_7 site distribution [72]. Also, chemical modifications of DR4004 were performed with the aim of improving its metabolic stability. In this study, compound DR4485 was identified to retain high affinity and selectivity for the 5-HT_7R [73] (Table **3**), additionally showing oral bioavailability so it should be useful for evaluating the therapeutic potential of 5-HT_7R antagonists.

During the preparation of this review, GlaxoSmithKline has reported the identification of a novel series of selective 5-HT_7R antagonists [74] structurally different from their earlier aryl sulfonamides (Table **2**) mentioned above. This was accomplished by modification of an initial candidate

Table 1. Affinities of Aporphine Derivatives Acting as 5-HT$_7$R Antagonists

Compound	*Ki* (nM)		
	5-HT$_7$	5-HT$_{1A}$	D$_{2A}$
	18.0[a]	355[a]	2250[a]
	1.1[a]	16.9[a]	71.0[a]
	3.79[b]	142[b]	498[b]

[a]Ref. [54]. [b]Ref. [56]

identified in high throughput screening. Among them compound SB-691673, characterised as a potent 5-HT$_7$R antagonist (pK_i = 8.65) with >100-fold selectivity over a range of serotonin and dopamine receptors (Table **2**), is the most promising analogue of this series.

STRUCTURE-AFFINITY RELATIONSHIP STUDIES OF 5-HT$_7$R ANTAGONISTS

The ability to bind 5-HT$_7$Rs selectively represents a goal with both theoretical and clinical significance. Development of compounds to achieve this goal and an understanding of the regulation of the 5-HT$_7$R can proceed more effectively if the molecular bases for ligand interactions with the 5-HT$_7$R are understood. However, few quantitative structure-activity relationship (QSAR) studies or computational models have been carried out using 5-HT$_7$R ligands.

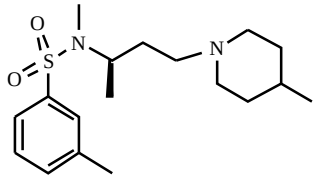
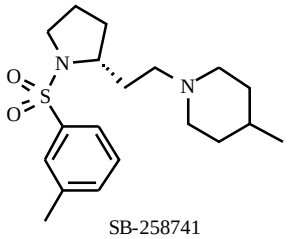
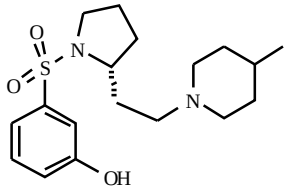
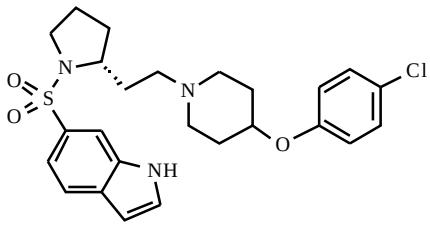
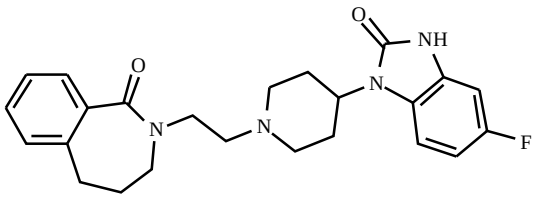
3D-QSAR: Comparative Molecular Field Analysis (CoMFA)

Recently, a CoMFA of a training set of 17 compounds with affinity for the 5-HT$_7$R was performed [75], using *R*-lisuride (Fig. **5a**) as the template. However, this model does not discriminate between agonist and antagonist ligands. The final cross-validated model accounted for >85% of the variance in the compound affinity data (mean values: q^2 = 0.779 ± 0.015 and SEP = 1.249 ± 0.043). The contour map derived from the CoMFA model illustrated several potentially important aspects of drug interactions at the 5-HT$_7$R (Fig. **5b**). Steric bulk was highly favoured over most regions of the receptor for high-affinity drug-receptor interactions; particularly a sterically favoured region that lies near the cationic nitrogen is of some importance in differentiating ligand-binding affinity. A second important characteristic is that hydrogen-bonding regions are highly significant predictors for high affinity 5-HT$_7$R ligands. The regions in which positive charge is favoured include the vicinity of the hydrogen-bonding nitrogen and the regions near the five- and six-membered rings. Furthermore, 3D-chemical database search queries derived from this model yielded all four of the highest affinity compounds of the training set. These results offer possibilities for identifying new ligands for the 5-HT$_7$R.

Pharmacophore Model

In a contribution of our group, an initial pharmacophore model for 5-HT$_7$R antagonism has been reported using compounds belonging to different chemical classes (selective and non-selective) [76]. This model represents the first approach to the rational design of agents acting at this serotonin receptor. Recently, we have carried out an optimisation and validation of this preliminary hypothesis [77] with the incorporation of new 5-HT$_7$R antagonists using CATALYST 4.5 programme. The essential structural requirements for selective 5-HT$_7$R antagonism consist of a basic nitrogen atom (PI), a H-bonding acceptor group (HBA)

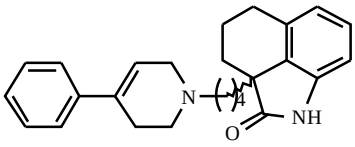
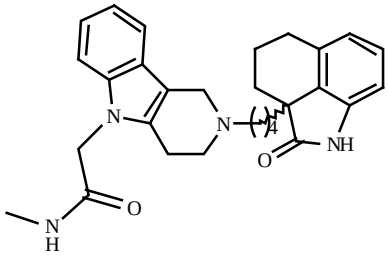
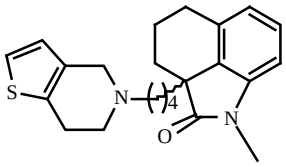
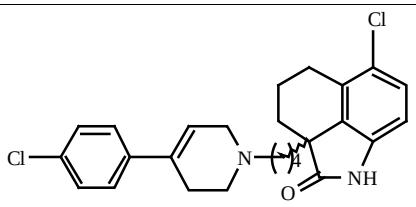
Table 2. Affinities of Selective 5-HT$_7$R Antagonists Developed by GlaxoSmithKline

Compound	*pK*i							
	5-HT$_7$	5-HT$_{1A}$	5-HT$_{2A}$	5-HT$_4$	5-HT$_{5A}$	5-HT$_6$	α_{1B}	D$_2$
 SB-258719	7.5[a]	<5.1[a]	<4.8[a]	<5.0[a]	---	<4.8[a]	<4.8[a]	5.4[a]
 SB-258741	8.5[b]	6.0[b]	<5.3[b]	<5.0[b]	---	---	<5.5[b]	5.8[b]
 SB-269970	8.9[b]	<5.0[b]	<5.0[b]	5.9[b]	7.2[b]	5.2[b]	<5.0[b]	6.5[b]
 SB-656104	8.7[c]	6.25[c]	7.2[c]	5.72[c]	6.74[c]	6.07[c]	6.66[c]	---
 SB-691673	8.65[d]	6.32[d]	6.52[d]	---	5.83[d]	<5.3[d]	---	6.63[d]

[a]Ref. [57]. [b]Ref. [63]. [c]Ref. [69]. [d]Ref. [74]

and three hydrophobic regions (HYD), at the distances represented in Fig. **6a**. To validate this model, a series of new naphtholactam and naphthosultam derivatives of general structure **I** [76, 77] were designed to interact with any or all pharmacophoric features simultaneously (Fig. **6b**). In this series, compounds with an optimum length of 4-5 methylene units in the spacer mapped in an efficient way the pharmacophore model (Fig. **6c**), as revealed by the conformational analysis performed with CATALYST 4.5 programme. A systematic structure-affinity relationship study on this class of compounds has allowed us to confirm that the model incorporates the essential structural features for 5-HT$_7$R antagonism, thereby illustrating how it can be used in the discovery of new classes of 5-HT$_7$R ligands. The iterative refinement of this pharmacophore by addition of new antagonists to the former training set may be used in the future to generate better affinity models for the design of novel 5-HT$_7$R ligands.

Table 3. Affinities of Selective 5-HT$_7$R Antagonists Developed by Kikuchi *et al.* (Meiji Seika Kaisha Ltd)

Compound	*pK*i					
	5-HT$_7$	5-HT$_{1A}$	5-HT$_2$	5-HT$_4$	5-HT$_6$	D$_2$
 DR4004	8.67[a]	6.77[a]	7.01[a]	<6.0[a]	6.28[a]	6.98[a]
 DR4365	8.45[b]	6.89[b]	<6.0[b]	6.31[b]	<6.0[b]	---
 DR4446	8.01[c]	6.11[c]	6.02[c]	<6.0[c]	<6.0[c]	---
 8.14d DR4485	8.14[d]	6.5[d]	<6.0[d]	<6.0[d]	<6.0[d]	---

[a]Ref. [60]. [b]Ref. [70]. [c]Ref. [71]. [d]Ref. [73].

Molecular Model of Ligand-Receptor Interactions

In order to help rationalise the structure-affinity relationship observations made for 5-HT$_7$R ligands, a computational model (Fig. **7**) of the transmembrane domain of the receptor complexed with the naphtholactam derivative **I** (pK_i = 7.1; X = CO, n = 5, Y = N, R = phenyl; see Fig. **6b**) has recently been constructed [77] from the crystal structure of rhodopsin. This 3D model has permitted to approach the molecular details of the ligand-receptor interaction. The NH group of the protonated piperazine ring of the ligand forms the frequently proposed ionic interaction with the O_δ atom of Asp$^{3.32}$. The carbonylic oxygen of the ligand is interacting with the hydroxyl groups of Ser$^{5.42}$ and Thr$^{5.43}$. The extensive naphtholactam ring favours the π−σ aromatic-aromatic interaction with the side chain of Phe$^{6.52}$ in the face-to-edge orientation (T-shaped). Finally, the phenyl ring attached to the piperazine ring expands between transmembrane helices 3 and 7, and interacts with the aromatic side chains of Phe$^{3.28}$ and Tyr$^{7.43}$ (Fig. **7**).

Remarkably, the independent generation of a 3D model of ligand-5-HT$_7$R interaction has provided similar conclusions than that from the proposed pharmacophore model for 5-HT$_7$R antagonism [77]: *i)* the HBA feature of the pharmacophore model binds Ser$^{5.42}$ and Thr$^{5.43}$; *ii)* the HYD1 feature interacts with Phe$^{6.52}$; *iii)* the PI feature forms an ionic interaction with Asp$^{3.32}$; and *iv)* the HYD3 feature interacts with a set of aromatic residues (Phe$^{3.28}$, Tyr$^{7.43}$).

Taken together, these results may provide the tools for predicting the affinity of related compounds and for guiding the design and synthesis of new ligands with predetermined affinities.

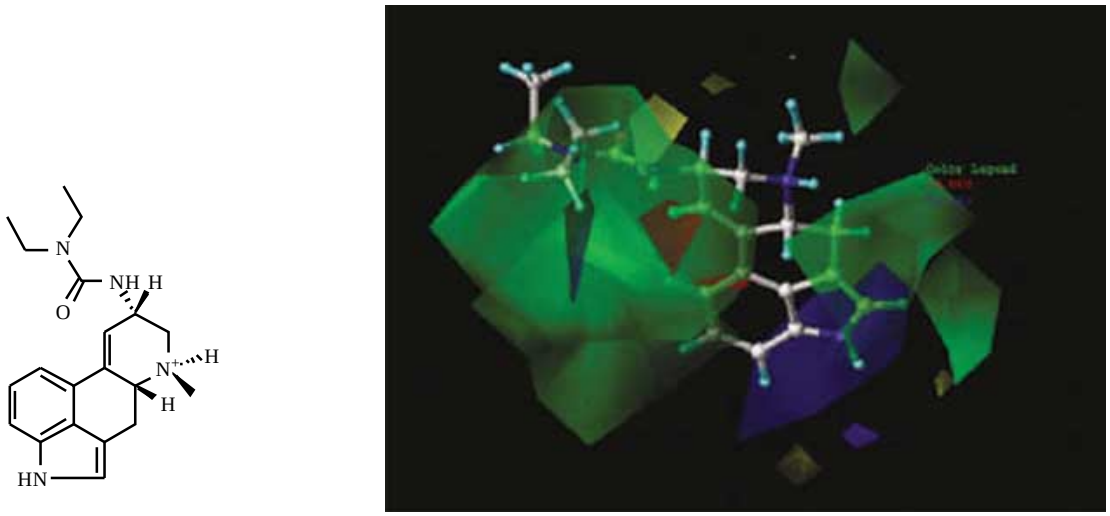


Fig. (5). (a) 2D structure of *R*-lisuride, compound used as template for the alignment of the molecules included in the CoMFA study. **(b)** Contour map relating compound affinity at 5-HT$_7$Rs to electrostatic and steric intermolecular interaction fields using lisuride. Positive electrostatic charge is favored (blue) or not favored (red) for high-affinity (80:20). Steric bulk is favored (green) or not favored (yellow) for for high-affinity (80:20). See reference [75].

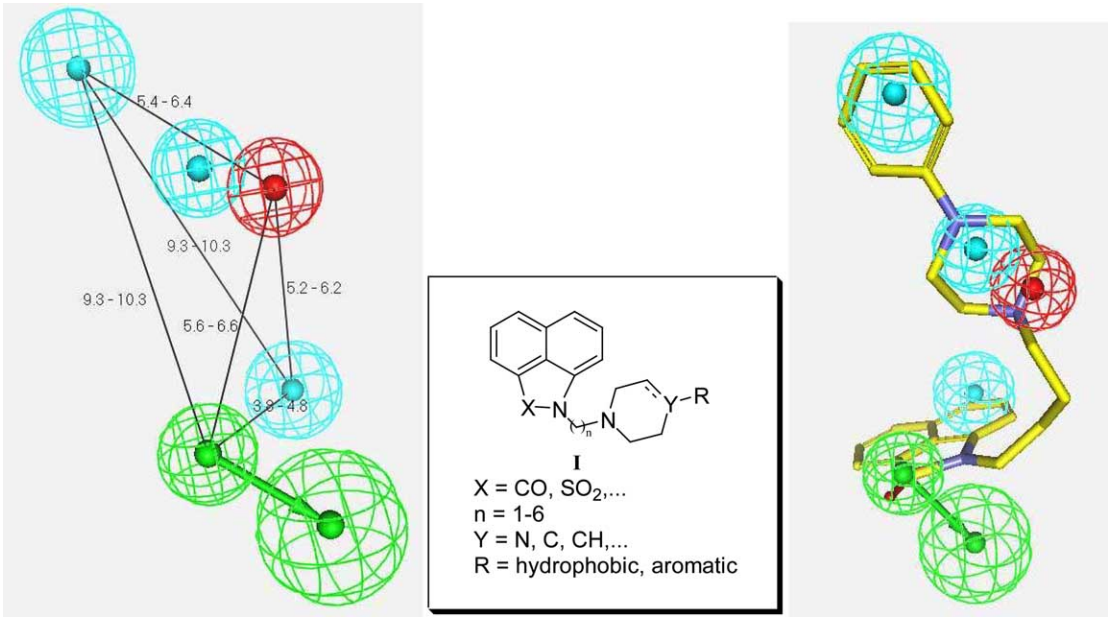


Fig. (6). (a) Pharmacophore model for selective 5-HT$_7$R antagonists. **(b)** Designed naphtholactam and naphthosultam derivatives of general structure **I**. **(c)** Designed compound **I** (X = CO, n = 4, Y = N, R = phenyl) mapped on the hypothesis generated for 5-HT$_7$R antagonists.

POTENTIAL THERAPEUTIC OPPORTUNITIES SURROUNDING 5-HT$_7$R LIGANDS

Little is known about the regulation and function of the 5-HT$_7$R since the pharmacological evaluation of this novel GPCR has been hampered by the lack of selective ligands. However, studies combining non-selective agents with molecular biological techniques have substantiated the evidence that the 5-HT$_7$R has a significant physiological and pathophysiological relevance. In addition, the recent discovery of the selective antagonist SB-269970 (Table **2**) represents a major advancement in the determination of the biological functions of this receptor. Therefore, although the development activity surrounding 5-HT$_7$R ligands is still in its infancy, this situation is expected to change soon.

Sleep Disorders

The central circadian pacemaker in mammals is located in the suprachiasmatic nuclei (SCN) of the hypothalamus [78]. These nuclei generate an endogenous circadian signal that controls the daily timing of multiple secondary oscillators that are dispersed throughout the mammalian system. The timing of the circadian pacemaker is adjusted

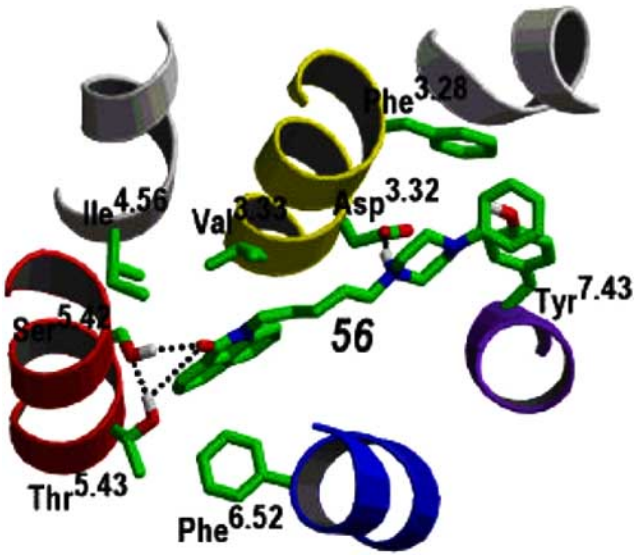


Fig. (7). Detailed view of the molecular model of the complex between compound **I** (X = CO, n = 5, Y = N, R = phenyl) and the transmembrane helix bundle of the 5-HT$_7$R constructed from the crystal structure of rhodopsin.

each day by exposure to external light-dark cycles and by non-photic signals. In humans, the biological clock governing circadian rhythms plays a critical role in jet lag, work shift performance, sleep-wake cycles, and manifestation of certain psychiatric disorders. The neurotransmitter 5-HT has been shown *in vivo* and *in vitro* to reset or phase shift circadian rhythms of neural activity in the SCN [79, 80]. In this way, the 5-HT$_7$R is a strong candidate for mediating these *in vivo* effects of the 5-HT on the activity of light-sensitive SCN cells, and the possible function may be the regulation of the interaction between photic and non-photic stimuli received in the circadian pacemaker [14, 23, 24, 81, 82]. Additionally, the decrease of 5-HT$_7$Rs in the dorsal raphe nuclei with the aging suggests that these receptors play an important role in the aging of the circadian timing system [83, 84]. Therefore, selective 5-HT$_7$R ligands could be useful in the treatment of circadian rhythm disorders such as jet lag and sleep disorders, and this hypothesis is supported by the preliminary pharmacological studies carried out with the 5-HT$_7$R antagonist SB-269970 [68].

Depression

It is believed that a disregulated circadian rhythm can lead to mental fatigue and depression. Recent studies suggest that antidepressants produce functional effects in a hypothalamic region associated with phase-shift responses, during the appropriate circadian time, and consistent with activation of the 5-HT$_7$R [85]. Moreover, the downregulation of the 5-HT$_7$R in response to chronic treatment with antidepressants supports the role of this receptor in depression [86, 87]. Likewise, chronic exposure to antidepressants elicits the enhancement of 5-HT$_7$R mediated adenylyl cyclase activation in rat frontocortical astrocytes [88]. Thus, the modulation of 5-HT$_7$R activity may contribute to the therapeutic effects of antidepressants. Nevertheless, further studies with selective 5-HT$_7$R ligands are awaited to elucidate the possible involvement of this receptor in depression and in the antidepressant therapeutic response.

Schizophrenia

Expression of mRNA for 5-HT$_7$Rs in midline, thalamic and limbic structures suggests a possible involvement of this receptor in psychiatric disorders, such as schizophrenia, for which a role of limbic structure dysfunction has been described [29, 89]. The fact that the 5-HT$_7$R is targeted by several antipsychotics of second generation, such as risperidone and clozapine, led to the speculation that this receptor could be implicated in their mechanism of action and may mediate the therapeutic actions of these compounds [90, 91]. Recently, the 5-HT$_7$R antagonist SB-258741 has been tested in several animal models of schizophrenia, and preliminary results indicate that this specific antagonist is not expected to have an antipsychotic effect on its own in clinic [65]. However, the possibility that a combination of 5-HT$_7$R antagonism with a dopaminergic D_2 and/or 5-HT$_{2A}$ receptor antagonist, such as risperidone, may have beneficial effect in the treatment of schizophrenia can not be discarded.

On the other hand, the above mentioned role of the 5-HT$_7$R in the regulation of circadian rhythm phase shifts may be interesting, considering that some people afflicted with schizophrenia experience a reversal of the sleep-wake cycle accompanied by severe insomnia [92].

Cardiovascular Diseases

The complexity of cardiovascular effects produced by 5-HT has been explained by its capacity to interact with specific receptors. Abundant evidences sustain the hypothesis that the 5-HT-induced late depressor response is mainly mediated by vascular 5-HT$_7$Rs [93]. The hypotension induced via activation of this receptor is almost exclusively caused by vasodilatation of the systemic vasculature, confined to skeletal muscle, carcass, mesentery/pancreas and adrenal vascular beds [94]. These findings reveal an interesting role for the 5-HT$_7$R in the regulation of arterial blood pressure, and this novel receptor may therefore represent a target for antihypertensive therapy.

Migraine

Migraine is a disturbance of high incidence nowadays and its effect on quality of life is significant. Currently available drugs for migraine attacks consist in acute therapies of aborting an attack once it has started rather than preventing it. In this respect, 15% of migraine sufferers would benefit from prophylactic treatment; however, the availability of molecules that effectively prevent migraine attacks with an acceptable tolerability profile is extremely limited. The development of migraine prophylactics therefore represents an unmet clinical need with considerable commercial potential.

The complex neurological alterations implicated in the pathogenesis of migraine are still poorly understood. Nevertheless, abnormalities of serotoninergic function

during a migraine attack have been documented [95], and evidence implicating 5-HT receptors (5-HT_{1B}, 5-HT_{1D}, 5-HT_{1F}) in the etiology of migraine is convincing. The 5-HT_7R mediated vasodilator mechanism operates in vascular structures that have been implicated in migraine, such as the middle cerebral and the external carotid arteries [37, 96, 97]. In addition, increasing data support the concept that 5-HT_7R activation is responsible for the initial dilatation of cerebral vessels, and the subsequent activation of sensory pathways, consequent neurogenic inflammation around the meningeal vessels, neural sensitization and the activation of pain pathways. 5-HT_7R antagonists therefore stand to offer an effective approach to the unmet field of migraine prophylaxis, a finding supported by clinical observations.

Since most of the compounds that show prophylactic effect against migraine, such as methergoline, methysergide, dihydroergotamine, LY215840, sergolexole, lisuride, mianserin, amitriptyline, chlorpromazine and cyproheptadine, display relatively high affinity for the 5-HT_7R [98, 99], vascular and neural 5-HT_7Rs might be important targets of these drugs. Clinical trials with selective 5-HT_7R antagonists will be awaited with interest so the potential involvement of this receptor in migraine pathogenesis and preventive treatment is elucidated.

Other Therapeutic Possibilities

Cognitive Disorders

The 5-HT_7R shows a regional distribution in brain areas implicated in cognitive disorders, such as hippocampus, amygdala and cortex, and some studies have suggested that this receptor might play a role in learning and memory processes [100, 101]. In this way, a recent report demonstrates that the 5-HT_7R antagonist DR 4004 might be useful to restore poor learning consolidation conditions and deficient memory [102].

Nociception

The drugs currently used to treat pain and inflammation have well-known side effects. It is therefore important to pursue alternative drug therapies to inhibit nociceptive and inflammatory processes. The 5-HT_7R is positively linked to cAMP and it is thought to be involved in mediating 5-HT induced hyperalgesia [103]. Although the mechanisms undertaking the facilitation of nociception by this receptor are unclear, one of the possibilities is that the increased expression of these receptors on pre-terminals neurons might increase substance P or glutamate releasing from primary afferent fibers in the spinal cord to facilitate nociception [104]. On the other hand, the 5-HT_7R expressed in lumbar dorsal root ganglia might also be involved in antinociception [105]. Therefore, evidence is accumulating to suggest that the 5-HT_7R may be involved in pain, hyperalgesia and neurogenic inflammation by mediating excitatory responses in the neural system.

Irritable Bowel Syndrome (IBS)

The irritable bowel syndrome (IBS) constitutes a major health problem with gastrointestinal (GI) symptoms. Thus, IBS is a functional bowel disorder in which abdominal discomfort or pain is associated with altered bowel habits and with features of disordered defecation. The rationale for investigations on 5-HT_7R ligands in IBS rests mainly on the fact that serotonin has a number of well documented motor effects on the GI tract and can produce hyperalgesia in several experimental models [36]. Preliminary evidence suggests that 5-HT_7Rs mediate smooth muscle relaxation at least in the human colon. Hypomotility remains an attractive therapeutic target in IBS and the new generation of prokinetics includes several non-selective 5-HT_7R ligands [33]. For this reason the 5-HT_7R is now emerging as possible target of drug action in the treatment of functional IBS disorder.

Immune system

The immune system, like the nervous system, has long been considered to be a self-regulated system. There are, however, interactions between these two systems, with several pathways linking them, and one of these mediators is 5-HT. The 5-HT_7R is present in a variety of peripheral tissues including constituents of the immune system [106]. Thus, this receptor might be involved in the bidirectional communication of the nervous and immune systems. Moreover, lesions of the brain, especially of the hypothalamus and limbic system, where 5-HT_7R mRNA is highly expressed, have influence in immune system parameters.

Neuroendocrine Role

A putative regulatory neuroendocrine role for 5-HT_7Rs has been suggested in hypothalamic neurones, where they were directly involved in the 5-HT-induced release of luteinizing hormone-releasing hormone (LHRH) [107]. It was also shown that the effect of 5-HT on adrenocorticotropin hormone (ACTH) secretion is mediated by 5-HT_7Rs [108]. Otherwise, a recent report suggests that 5-HT stimulates aldosterone secretion through 5-HT_7Rs due to the presence of mRNA in the adrenal cortex [109].

There is now evidence that the 5-HT_7R has a significant physiological and pathophysiological relevance and it represents a novel therapeutic target. Nevertheless, the clinical utility of 5-HT_7R agents awaits the development of new selective ligands. Although the development activity surrounding 5-HT_7R ligands is still in its infancy, this situation is expected to change soon, and continuing research of this serotonin receptor subtype provides a promising future for a variety of diseases.

ACKNOWLEDGEMENT

The work carried out at the Universidad Complutense and Universitàt Autònoma which is included in the review was supported by Ministerio de Ciencia y Tecnología (BQU2001-1457).

ABBREVIATIONS

ACTH	=	Adrenocorticotropin hormone
5-CT	=	5-Carboxamidotryptamine
CNS	=	Central nervous system
mCPP	=	1-(*m*-Chlorophenyl)piperazine

CoMFA = Comparative Molecular Field Analysis
GPCR = G protein-coupled receptor
GI = Gastrointestinal
HBA = H-bonding acceptor
HYD = Hydrophobic region
5-HT = 5-Hydroxytryptamine (serotonin)
IBS = Irritable bowel syndrome
LHRH = Luteinizing hormone-releasing hormone
PI = Positive ionizable
QSAR = Quantitative structure-activity relationship
SCN = Suprachiasmatic nuclei
TFMPP = 1-(*m*-Trifluoromethylphenyl)piperazine

REFERENCES

[1] Baumgarten, H.G.; Göthert, M. *Serotoninergic Neurons and 5-HT Receptors in the CNS*; Handb. Exp. Pharm.; Springer-Verlag: Berlin, **1997**, Vol. 129.
[2] Gerhardt, C.C.; van Heerikhuizen, H. *Eur. J. Pharmacol.*, **1997**, *334*, 1-23.
[3] Martin, G.R.; Eglen, R.M.; Hoyer, D.; Hamblin, M.W.; Yocca, F. Eds. *Advances in Serotonin Receptor Research: Molecular Biology, Signal Transmission, and Therapeutics*; *Ann. N. Y. Acad. Sci.: New York, USA*, **1998**.
[4] Barnes, N.M.; Sharp, T. *Neuropharmacology*, **1999**, *38*, 1083-1152.
[5] Hoyer, D.; Hannon, J.P.; Martin, G.R. *Biochem. Behav.*, **2002**, *71*, 533-554.
[6] Hoyer, D.; Martin, G. *Neuropharmacology*, **1997**, *36*, 419-428.
[7] Uphouse, L. *Neurosci. Biobehav. Rev.*, **1997**, *21*, 679-698.
[8] Humphrey, P.P.A. *Ann. N. Y. Acad. Sci.*, **1997**, *812*, 1-13.
[9] Saxena, P.R.; De Vries, P.; Villalón, C.M. *Trends Pharmacol. Sci.*, **1998**, *19*, 311-316.
[10] Bikker, J.A.; Trumpp-Kallmeyer, S.; Humblet, C. *J. Med. Chem*., **1998**, *41*, 2911-2927.
[11] Klabunde, T.; Hessler, G. *ChemBioChem.*, **2002**, *3*, 928-944.
[12] Eglen, R.M.; Jasper, J.R.; Chang, D.J.; Martin, G.R. *Trends Pharmacol. Sci.*, **1997**, *18*, 104-107.
[13] Vanhoenacker, P.; Haegeman, G.; Leysen, J.E. *Trends Pharmacol. Sci*., **2000**, *21*, 70-77.
[14] Lovenberg, T.W.; Baron, B.M.; de Lecea, L.; Miller, J.D.; Prosser, R.A.; Rea, M.A.; Foye, P.E.; Racke, M.; Slone, A.L.; Siegel, B.W.; Danielson, P.E.; Sutcliffe, J.G.; Erlander, M.G. *Neuron*, **1993**, *11*, 449-458.
[15] Plassat, J.-L.; Amlaiky, N.; Hen, R. *Mol. Pharmacol.*, **1993**, *44*, 229-236.
[16] Ruat, M.; Traiffort, E.; Leurs, R.; Tardivel-Lacombe, J.; Diaz, J.; Arrang, J.-M.; Schwartz, J.-C. *Proc. Natl. Acad. Sci. USA*, **1993**, *90*, 8547-8551.
[17] Shen, Y.; Monsma, F.J. Jr.; Metcalf, M.A.; Jose, P.A.; Hamblin, M.W.; Sibley, D.R. *J. Biol. Chem.*, **1993**, *268*, 18200-18204.
[18] Tsou, A.-P.; Kosaka, A.; Bach, C.; Zuppan, P.; Yee, C.; Tom, L.; Alvarez, R.; Ramsey, S.; Bonhaus, D.W.; Stefanich, E.; Jakeman, L.; Eglen, R.M.; Chan, H.W. *J. Neurochem.*, **1994**, *63*, 456-464.
[19] Bardt, J.A.; Zgombick, J.; Adham, N.; Vaysse, P.; Branchek, T.A.; Weinshank, R.L. *J. Biol. Chem.*, **1993**, *268*, 23422-23426.
[20] Heidmann, D.E.A.; Metcalf, M.A.; Kohen, R.; Hamblin, M W. *J. Neurochem.*, **1997**, *68*, 1372-1381.
[21] Liu, H.; Irving, R.H.; Coupar, I.M. *Life Sci.*, **2001**, *69*, 2467-2475.
[22] Krobert, K.A.; Levy, F.O. *Br. J. Pharmacol.*, **2002**, *135*, 1563-1571.
[23] Ehlen, J.C.; Grossman, G.H.; Glass, J.D. *J. Neurosci.*, **2001**, *21*, 5351-5357.
[24] Smith, B.N.; Sollars, P.J.; Dudek, E.E.; Pickard, G.E. *J. Biol. Rhythms*, **2001**, *16*, 25-38.
[25] Neumaier, J.F.; Sexton, T.J.; Yracheta, J.; Diaz, A.M.; Brownfield, M. *J. Chem. Neuroanat.*, **2001**, *21*, 63-73.
[26] Roth, B.L.; Meltzer, H.Y.; Khan, N. *Adv. Pharmacol.*, **1998**, *42*, 482-485.
[27] Mullins, U.L.; Gianutsos, G.; Eison, A.S. *Neuropsychopharmacology*, **1999**, *21*, 352-367.
[28] Errico, M.; Crozier, R.A.; Plummer, M.R.; Cowen, D.S. *Neuroscience*, **2001**, *102*, 361-367.
[29] Gill, C.H.; Soffin, E.M.; Hagan, J.J.; Davies, C.H. *Neuropharmacology*, **2002**, *42*, 82-92.
[30] Leung, E.; Walsh, L.K.M.; Pulido-Rios, M.T.; Eglen, R.M. *Br. J. Pharmacol.*, **1996**, *117*, 926-930.
[31] Morecroft, I.; MacLean, M.R. *Br. J. Pharmacol.*, **1998**, *125*, 69-78.
[32] Terrón, J.A.; Falcón-Neri, A. *Br. J. Pharmacol.*, **1999**, *127*, 609-616.
[33] Prins, N.H.; Briejer, M.R.; van Bergen, P J.E.; Akkermans, L.M.A.; Schuurkes, J.A.J. *Br. J. Pharmacol*., **1999**, *128*, 849-852.
[34] Centurión, D.; Sánchez-López, A.; Ortiz, M.I.; De Vries, P.; Saxena, P.R.; Villalón, C.M. *Naunyn-Schmiedeberg´s Arch. Pharmacol*., **2000**, *362*, 169-176.
[35] Howarth, C.J.; Prince, R.I.; Dyker, H.; Lösel, P.M.; Seinsche, A.; Osborne, R.H. *J. Insect Physiol.*, **2002**, *48*, 43-52.
[36] De Ponti, F.; Tonini, M. *Drugs*, **2001**, *61*, 317-332.
[37] Terrón, J.A. *Eur. J. Pharmacol.*, **2002**, *439*, 1-11.
[38] To, Z.P.; Bonhaus, D.W.; Eglen, R.M.; Jakeman, L.B. *Br. J. Pharmacol*., **1995**, *115*, 107-116.
[39] Bourson, A.; Kapps, V.; Zwingelstein, C.; Rudler, A.; Boess, F.G.; Sleight, A.J. *Naunyn-Schmiedeberg´s Arch. Pharmacol.*, **1997**, *356*, 820-826.
[40] Hemedah, M.; Coupar, I.M.; Mitchelson, F.J. *Br. J. Pharmacol.*, **1999**, *126*, 179-188.
[41] Clemett, D.A.; Kendall, D.A.; Cockett, M.I.; Marsden, C.A.; Fone, K.C.F. *Br. J. Pharmacol*., **1999**, *127*, 236-242.
[42] Cushing, D.J.; Zgombick, J.M.; Nelson, D.L.; Cohen, M.L. *J. Pharmacol. Exp. Ther*., **1996**, *277*, 1560-1566.
[43] Villalón, C.M.; Heiligers, J.P.C.; Centurión, D.; De Vries, P.; Saxena, P.R. *Br. J. Pharmacol*., **1997**, *121*, 1187-1195.
[44] Mantegani, S.; Brambilla, E.; Varasi, M. *Fármaco*, **1999**, *54*, 288-296.
[45] Roth, B.L.; Craigo, S.C.; Choudhary, M.S.; Uluer, A.; Fredrick, A.U.; Monsma, J.Jr.; Shen, Y.; Meltzer, H.Y.; Sibley, D.R. *J. Pharmacol. Exp. Ther*., **1994**, *268*, 1403-1410.
[46] Meltzer, H.Y.; Fatemi, S.H. The Role of Serotonin in Schizophrenia and the Mechanism of Action on Anti-psychotic Drugs. In *Serotonergic Mechanisms in Antipsychotic Treatment.* Kane, J.M.; Moller, H.J.; Awouters, F. Eds.; Marcel Decker: New York, 1996, pp 77-107.
[47] Zhukovskaya, N.L.; Neumaier, J.F. *Neurosci. Lett.*, **2000**, *288*, 236.
[48] Brunello, N.; Masotto, C.; Steardo, L.; Markstein, R.; Racagni, G. *Neuropsychopharmacology*, **1995**, *13*, 177-213.
[49] Monsma, F.J.; Shen, Y.; Ward, R.P.; Hamblin, M.W.; Sibley, D.R. *Mol. Pharmacol.*, **1993**, *43*, 320-327.
[50] Yau, J.L.W.; Olsson, T.; Noble, J.; Seckl, J.R. *Mol. Brain Res.*, **1999**, *70*, 282-287.
[51] Lucchelli, A.; Santagostino-Barbone, M.G.; D´Agostino, G.; Masoero, E.; Tonini, M. *Naunyn-Schmiedeberg´s Arch. Pharmacol.*, **2000**, *362*, 284-289.
[52] Gommans, J.; Hijzen, T.H.; Maes, R.A.A.; Olivier, B. *Psychopharmacology*, **1998**, *137*, 292-302.
[53] Wood, M.; Chaubey, M.; Atkinson, P.; Thomas, D.R. *Eur. J. Pharmacol.*, **2000**, *396*, 1-8.
[54] Linnanen, T.; Brisander, M.; Unelius, L.; Sundholm, G.; Hacksell, U.; Johansson, A.M. *J. Med. Chem.*, **2000**, *43*, 1339-1349.
[55] Linnanen, T.; Brisander, M.; Mohell, N.; Johansson, A.M. *Bioorg. Med. Chem. Lett.*, **2001**, *11*, 367-370.
[56] Linnanen, T.; Brisander, M.; Unelius, L.; Rosqvist, S.; Nordvall, G.; Hacksell, U.; Johansson, A.M. *J. Med. Chem.*, **2001**, *44*, 1337-1340.
[57] Forbes, I.T.; Dabbs, S.; Duckworth, D.M.; Jennings, A.J.; King, F.D.; Lovell, P.J.; Brown, A.M.; Collin, L.; Hagan, J.J.; Middlemiss, D.N.; Riley, G.J.; Thomas, D.R.; Upton, N. *J. Med. Chem.*, **1998**, *41*, 655.
[58] Thomas, D.R.; Gittins, S.A.; Collin, L.L.; Middlemiss, D.N.; Riley, G.; Hagan, J.; Gloger, I.; Ellis, C.E.; Forbes, I.T.; Brown, A.M. *Br. J. Pharmacol*., **1998**, *124*, 1300.
[59] Lloyd, A.W. *Drugs Discov. Today*, **1998**, *3*, 295-298.
[60] Kikuchi, C.; Nagaso, H.; Hiranuma, T.; Koyama, M. *J. Med. Chem.*, **1999**, *42*, 533-535.

[61] Lloyd, A.W. *Drugs Discov. Today*, **1999**, *4*, 289-291.
[62] Kogan, H.A.; Marsden, C.A.; Fone, K.C.F. *Eur. J. Pharmacol.*, **2002**, *449*, 105-111.
[63] Lovell, P.J.; Bromidge, S.M.; Dabbs, S.; Duckworth, D.M.; Forbes, I.T.; Jennings, A.J.; King, F.D.; Middlemiss, D.N.; Rahman, S.K.; Saunders, D.V.; Collin, L.L.; Hagan, J.J.; Riley, G.J.; Thomas, D.R. *J. Med. Chem.*, **2000**, *43*, 342-345.
[64] Pouzet, B. *CNS Drug Rev.*, **2002**, *8*, 90-100.
[65] Pouzet, B.; Didriksen, M.; Arnt, J. *Pharmacol. Biochem. Behav.*, **2002**, *71*, 655-665.
[66] Atkinson, P.J.; Thomas, D.R.; Hagan, J.J.; Middlemiss, D.N.; Price, G.W. *Br. J. Pharmacol.*, **2000**, *129*, 132P.
[67] Thomas, D.R.; Atkinson, P.J.; Ho, M.; Bromidge, S.M.; Lovell, P.J.; Villani, A.J.; Hagan, J.J.; Middlemiss, D.N.; Price, G.W. *Br. J. Pharmacol.*, **2000**, *130*, 409.
[68] Hagan, J.J.; Price, G.W.; Jeffrey, P.; Deeks, N.J.; Stean, T.; Piper, D.; Smith, M.I., Upton, N.; Medhurst, A.D.; Middlemiss, D.N.; Riley, G.J.; Lovell, P.J.; Bromidge, S.M.; Thomas, D.R. *Br. J. Pharmacol.*, **2000**, *130*, 539-548.
[69] Forbes, I.T.; Douglas, S.; Gribble, A.D.; Ife, R.J.; Lightfoot, A.P.; Garner, A.E.; Riley, G.J.; Jeffrey, P.; Stevens, A.J.; Stean, T.O.; Thomas, D.R. *Bioorg. Med. Chem. Lett.*, **2002**, *12*, 3341-3344.
[70] Kikuchi, C.; Ando, T.; Watanabe, T.; Nagaso, H.; Okuno, M.; Hiranuma, T.; Koyama, M. *J. Med. Chem.*, **2002**, *45*, 2197-2206.
[71] Kikuchi, C.; Hiranuma, T.; Koyama, M. *Bioorg. Med. Chem. Lett.*, **2002**, *12*, 2549-2552.
[72] Zhang, M.-R.; Haradahira, T.; Maeda, J.; Okauchi, T.; Kida, T.; Obayashi, S.; Suzuki, K.; Suhara, T. *J. Labelled Compd. Rad.*, **2002**, *45*, 857.
[73] Kikuchi, C.; Suzuki, H.; Hiranuma, T.; Koyama, M. *Bioorg. Med. Chem. Lett.*, **2003**, *13*, 61-64.
[74] Forbes, I.T.; Cooper, D.G.; Dodds, E.K.; Douglas, S.E.; Gribble, A.D.; Ife, R.J.; Lightfoot, A.P.; Meeson, M.; Campbell, L.P.; Coleman, T.; Riley, G.J.; Thomas, D.R. *Bioorg. Med. Chem. Lett.*, **2003**, *13*, 1055-1058.
[75] Wilcox, R.E.; Ragan, J.E.; Pearlman, R.S.; Brusniak, M.Y.-K.; Eglen, R.M.; Bonhaus, D.W.; Tenner, T.E.; Miller, J.D. Jr. *J. Comput. Aided Mol. Des.*, **2001**, *15*, 883-909.
[76] López-Rodríguez, M.L.; Porras, E.; Benhamú, B.; Ramos, J.A.; Morcillo, M.J.; Lavandera, J.L. *Bioorg. Med. Chem. Lett.*, **2000**, *10*, 1097-1100.
[77] López-Rodríguez, M.L.; Porras, E.; Morcillo, M.J.; Benhamú, B.; Soto, L.J.; Lavandera, J.L.; Ramos, J.A.; Olivella, M.; Campillo, M.; Pardo, L. *J. Med. Chem.*, **2003**, in press.
[78] Schwartz, W.J.A. *Adv. Inter. Med.*, **1993**, *38*, 81-106.
[79] Prosser, R.A.; Heller, H.C.; Miller, J.D. *Brain Res.*, **1994**, *644*, 67-73.
[80] Rea, M.A.; Glass, J.D.; Colwell, C.S. *J. Neurosci.*, **1994**, *14*, 3635-3642.
[81] Ying, S.-W.; Rusak, B. *Brain Res.*, **1997**, *755*, 246-254.
[82] Belenky, M.A.; Pickard, G.E. *J. Comp. Neurol.*, **2001**, *432*, 371-388.
[83] Duncan, M.J.; Short, J.; Wheeler, D.L. *Brain Res.*, **1999**, *829*, 39-45.
[84] Quintero, J.E.; McMahon, D.G. *J. Neurophysiol.*, **1999**, *82*, 533-539.
[85] Duncan, W. *Pharmacol. Ther.*, **1996**, *71*, 253-312
[86] Sleight, A.J.; Carolo, C.; Petit, N.; Zwingelstein, C.; Bourson, A. *Mol. Pharmacol.*, **1995**, *47*, 99-103.
[87] Yau, J.L. W.; Noble, J.; Widdowson, J.; Seckl, J.R. *Mol. Brain Res.*, **1997**, *45*, 182-186.
[88] Shimizu, M.; Nishida, A.; Zensho, H.; Yamawaki, S. *J. Pharmacol. Exp. Ther.*, **1996**, *279*, 1551-1558.
[89] East, S.Z.; Burnet, P.W.J.; Kerwin, R.W.; Harrison, P.J. *Schizophr. Res.*, **2002**, *57*, 15-26.
[90] Arnt, J.; Skarsfeldt, T. *Neuropsychopharmacology*, **1998**, *18*, 63-66.
[91] Masellis, M.; Basile, V.S.; Meltzer, H.Y.; Lieberman, J.A.; Sevy, S.; Goldman, D.A.; Hamblin, M.W.; Macciardi, F.M.; Kennedy, J.L. *Schizophr. Res.*, **2001**, *47*, 49-58.
[92] Benca, R.M. *Neurol. Clin.*, **1996**, *14*, 739-764.
[93] Terrón, J.A. *Br. J. Pharmacol.*, **1997**, *121*, 563-571.
[94] De Vries, P.; De Visser, P.A.; Heiligers, J.P.C.; Villalón, C.M.; Saxena, P.R. *Naunyn-Schmiedeberg´s Arch. Pharmacol.*, **1999**, *359*, 331-338.
[95] Humphrey, P.P.A. *J. Neurol.*, **1991**, *238*, S38-S44.
[96] Terrón, J.A. *Proc. West. Pharmacol. Soc*., **1998**, *41*, 247-251.
[97] Terrón, J.A.; Bouchelet, I.; Hamel, E. *Neurosci. Lett.*, **2001**, *302*, 9-12.
[98] Terrón, J.A. *Drugs*, **1998**, *1*, 302-310.
[99] Tfelt-Hansen, P.; Saxena, P.R. Antiserotonin Drugs in Migraine Prophylaxis. In *The Headaches*, 2nd ed. Olesen, J.; Tfelt-Hansen, P.; Welch, K.M.A., Eds.; Lippincott, Williams and Wilkins: Philadelphia, pp 467-476.
[100] Meneses, A. *Rev. Neurosci.*, **1998**, *9*, 1-13.
[101] Meneses, A. *Neurosci. Biobehav. Rev.*, **1999**, *23*, 1111-1125.
[102] Meneses, A.; Terrón, J.A. *Behav. Brain Res.*, **2001**, *21*, 21-28.
[103] Pierce, P.A.; Xie, G.-X.; Levine, J.D.; Peroutka, S.J. *Neuroscience*, **1996**, *70*, 553-559.
[104] Garraway, S.M.; Hochman, S. *Br. J. Pharmacol.*, **2001**, *132*, 1789-1798.
[105] Wu, S.-X.; Zhu, M.; Wang, W.; Wang, Y.-Y.; Li, Y.-Q.; Yew, D.T. *Neurosci. Lett.*, **2001**, *307*, 183-186.
[106] Mössner, R.; Lesch, K.-P. *Brain Behav. Immun.*, **1998**, *12*, 249-271.
[107] Héry, M.; Francois-Bellan, A.M.; Héry, F.; Deprez, P.; Becquet, D. *Endocrine*, **1997**, *7*, 261-265.
[108] Jorgensen, H.; Knigge, U.; Kjaer, A.; Warberg, J. *J. Neuroendocrinol.*, **1999**, *11*, 283-290.
[109] Lenglet, S.; Louiset, E.; Delarue, C.; Vaudry, H.; Contesse, V. *Endocrinology*, **2002**, *143*, 1748-1760.

Received: April 16, 2003 Accepted: August 30, 2003