The Emergence of Selective 5-HT_{2B} Antagonists Structures, Activities and Potential Therapeutic Applications

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Abstract: 5-HT_2 receptors mediate a large array of physiological and behavioral functions in humans *via* three distinct subtypes: 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}. While selective 5-HT_{2A} antagonists have been known for some time, knowledge of the precise role played by the 5-HT_{2B} receptor was hampered by the existence of solely 5-HT_{2B}/5-HT_{2C} mixed antagonists.

However, selective 5-HT_{2B} antagonists began recently to emerge in the literature. Indeed, four structural classes belonging to the piperazine, indole, naphthylpyrimidine and tetrahydro-β-carboline scaffolds were reported. In this paper, we will briefly review the structural and pharmacological features of selective 5-HT_{2B} antagonists, including patent literature of the last five years.

Keywords : 5-HT_{2B}, receptor, antagonist, serotonin, review.

Dedicated to the memory of Professor Jean-Luc Fauchère

INTRODUCTION

Serotonin (5-hydroxytryptamine, 5-HT), a major neurotransmitter first discovered in the CNS in 1948, has been the focus of intensive research [1]. Seven different 5-HT receptors have been identified (5-HT_1 to 5-HT_7), each family possessing multiple receptor subtypes both within and between species, thus leading to 14 serotonin receptor subtypes known to date [2]. At the molecular level, they belong to the G-protein coupled receptor family which modulate cell activities via second messenger systems. 5-HT_3 receptors are an exception in this respect since they directly activate a gated ion channel thus inducing cell depolarization.

Very recently research in the area focused particularly on the 5-HT_2 receptor, for which three different subtypes namely 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} are known. This group of receptor subtypes is highly homologous with respect to their entire molecular sequence (approximately 80% of amino acid identity in the transmembrane domain) and therefore the synthesis and characterization of high affinity and selective antagonists is a prerequisite for defining the pharmacological implication of each member of the group.

This mini-review will focus on recently discovered 5-HT_{2B} receptor ligands as regards their structural and pharmacological features. The literature of the last five years including patents will be covered.

THE 5-HT_{2B} RECEPTOR SUBTYPE

Initially reported as a 5-HT_1 like receptor and then as a 5-HT_{2F} receptor [3], the 5-HT_{2B} receptor shares structural and pharmacological features with the two other members of the 5-HT_2 family, namely the 5-HT_{2A} and 5-HT_{2C} subtypes. This close molecular resemblance together with the lack of discriminative agonists and antagonists have made difficult the precise functional characterizations of the 5-HT_{2B} and 5-HT_{2C} receptor subtypes.

Indeed, until recently, the understanding of the 5-HT_{2B} receptor role was hampered by the lack of selective antagonists, only mixed 5-HT_{2B}/5-HT_{2C} ligands with almost identical affinities for the two receptors being reported. Nevertheless, it has been shown that the 5-HT_{2B} receptor is coupled via a heterotrimeric GTP binding protein, Gq, to phospholipase C leading to an increase of inositol phosphates and intracellular Ca^{2+} [1,4].

Additionally, in several cell lines the 5-HT_{2B} receptor has been implicated in the activation of the cNOS and iNOS transduction pathways [5] as well as in the release of arachidonic acid via phospholipase A_2 activation [6].

The tissue distribution of the 5-HT_{2B} receptor is still a matter of controversy depending on the animal species investigated. Thus Northern blot analysis and PCR amplification indicated that human 5-HT_{2B} mRNA transcripts are expressed mainly in peripheral tissues (such as pancreas, liver, kidney, uterus, trachea and small intestine), although significant levels have been also detected in cerebral cortex and the whole brain [7,8,9]. A number of reports indicated that no 5-HT_{2B} mRNA transcript was detected in the rat brain [10,11], while immunochemical studies have demonstrated the presence of 5-HT_{2B} receptor in the cerebellum, lateral septum, dorsal hypothalamus and media amygdala [12].

Functionally, the 5-HT_{2B} receptor was first characterized in the rat stomach fundus [13,11], while other studies demonstrated that activation of the 5-HT_{2B} receptor is associated with vascular contractility in DOCA-salt hypertensive rats [14], endothelial dependent relaxation in rat jugular vein [15], contraction of human intestinal muscle [16] and relaxation of pig pulmonary artery [17].

From the standpoint of therapeutic applications, there is increasing evidence that the 5-HT_{2B} receptor located on endothelial cells of meningeal blood vessels could be

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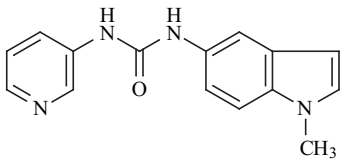
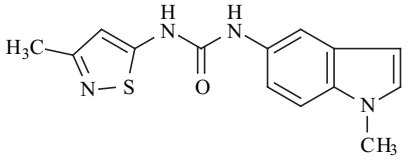
Arylureas



1 (SB-200646A)



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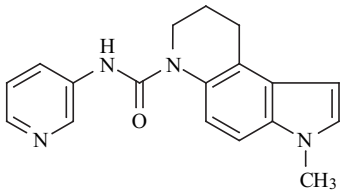

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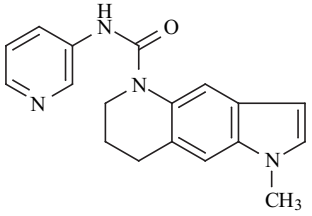

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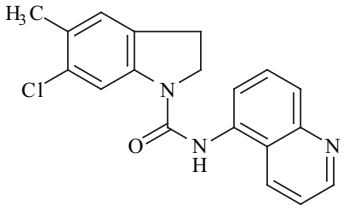
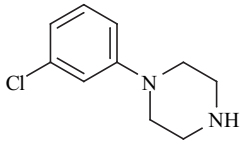
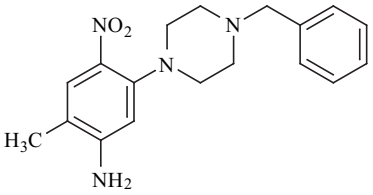


5 (SB-215505)

Arylpiperazines

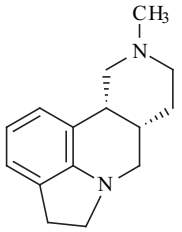


6 (m-CPP) (partial agonist)



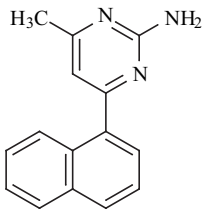
7 (EGIS-7625)

Indolonaphthyridine

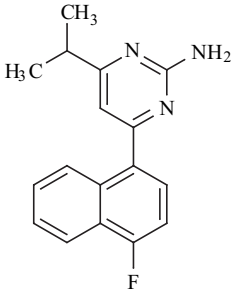


8 (SDZSER-082)

Pyrimidines



9 (RS-27354)



10 (RS-127445 or MT-500)

Fig. (1). Chemical structures of 5-HT_{2B} ligands.

implicated in the pathophysiology of migraine via the NO pathway [3,18,19].

Additionally, recent studies showed that the 5-HT_{2B} receptor mediates the excitatory effects of serotonin in human colon [20] indicating that antagonists of this receptor might be valuable for the treatment of irritable bowel syndrome (IBS) [21,22].

Recent literature reports on high affinity and selective 5-HT_{2B} receptor ligands shed more light on the functional role of this receptor subtype.

A limited number of different molecular scaffolds that have been reported to bind to the 5-HT_{2B} receptor are depicted in Fig. (**1**) and (**2**). The structural and the known pharmacological features of these compounds are described below.

ARYLUREAS

This class of compounds initially developed by SmithKline Beecham is represented by the pyridylurea **1** (SB-200646A) [23]. The affinity for the 5-HT_{2A} receptor is rather low but the compound seems to act only slightly better on the 5-HT_{2B} than on the 5-HT_{2C} receptor (Table 1). Conformational restriction within a six membered ring lowers the 5-HT_{2C} affinity to the level observed for 5-HT_{2A} (**3** and **4** - Table 1) without lowering the action on the 5-HT_{2B} (pA_2 = 7.22 and pA_2 = 7.27 respectively - Table 1) [24]. These results indicate that an increase in 5-HT_{2B} receptor selectivity is induced by this modification. Replacement of the pyridine ring in **1** by a methylisothiazolyl ring as in **2** (SB-204741), increases even more the action on the 5-HT_{2B} receptor (pA_2 = 7.95 - Table 1), the affinity for the other two receptors remaining low.

Moreover, **2** did not show any appreciable affinity for a panel of 12 aminergic receptors tested [24].

Table 1. 5-HT$_{2A}$ and 5-HT$_{2C}$ Receptors Affinities and 5-HT$_{2B}$ Inhibitory Potency of Miscellaneous Scaffolds

	pKi		pA$_2$; pKi*; pK$_B$**
	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_{2B}$
1	< 5.2	6.96	7.41
2	< 5.2	5.82	7.95
3	< 5.2	< 5.2	7.22
4	< 5.2	5.39	7.27
5	6.77	7.66	8.30* [28]
6	6.7 [30]	7.07 [4]	7.92* [4]
7	6.5	7.0	9.4 9.5
8	6.2	7.3	7.34**
10	6.3	6.4	9.5*

*,** Note : This column contains affinity values (pKi or pK$_B$) as reported in the corresponding references (see text).

Compound **5** (SB-215505), a different kind of diarylurea, was also described as a selective 5-HT$_{2B}$ receptor antagonist (pA$_2$ = 9.80). Initially this compound was disclosed in a patent [25] as a 5-HT$_{2C}$ antagonist, but was shown to inhibit two central 5-HT$_{2B}$ receptor-mediated responses, namely the anxiolytic-like effect (0.3 and 1 mg/kg, oral administration) induced by BW-723C86, a 5-HT$_{2B}$ agonist, and the hyperphagia (20 mg/kg, sub-cutaneous administration) induced by the same compound in freely feeding animals [26]. Nevertheless since only a fourfold selectivity towards 5-HT$_{2B}$ is observed (pKi = 8.30 and 7.66 for 5-HT$_{2B}$ and 5-HT$_{2C}$ respectively - Table 1), its physiological action should be interpreted with caution [27].

ARYLPIPERAZINES

These types of structures have been known for a long time to be ligands for the serotonin receptor [28].Thus, the *meta*-chlorophenyl piperazine **6** (m-CPP) [29], an active metabolite of the antidepressant trazodone, is a partial agonist with almost equal affinity for both 5-HT$_{2B}$ and 5-HT$_{2C}$ (pKi = 7.92, pKi = 7.07 respectively) [4], and has been used as a pharmacological tool to study the functional role of these receptor subtypes.

Also based on the arylpiperazine scaffold, compound **7** (EGIS-7625 – Table 1) is a powerful antagonist at the 5-HT$_{2B}$ receptor. Thus, in the rat stomach fundus and the rabbit jugular vein, pA$_2$ values of 9.4 and 9.5 respectively were observed (5-HT$_{2B}$) while a pA$_2$ of 6.7 was measured in the rat pulmonary artery (5-HT$_{2A}$). The affinity for the 5-HT$_{2C}$ receptor was measured in the pig brain (pKi = 7) [30,31]. However, it should be stressed that caution is necessary in linking a pharmacological effect with the 5-HT$_{2B}$ receptor in this case since the same compound exhibits a Ki of 6 nM for the sigma receptor.

INDOLONAPHTHYRIDINES

Discovered in a random screening program, compound **8** (SDZSER-082) is an antagonist at the 5-HT$_{2B}$ receptor (pK$_B$ = 7.34 in the rat stomach fundus – Table 1) with a low affinity for the 5-HT$_{2A}$ receptor, but does not discriminate between the 5-HT$_{2C}$ and 5-HT$_{2B}$ subtypes (Table 1) [32]. Indeed, **8** inhibits in vivo, in a dose-dependent manner, MK-212 (a 5-HT$_{2C}$ agonist) induced hypophagia thus revealing a centrally acting 5-HT$_{2C}$ pathway.

PYRIMIDINES

In 1997, a Roche patent disclosed pyrimidine derivatives that are selective 5-HT$_{2B}$ antagonists [33]. The original lead, **9** (RS-27354) was discovered by screening a library of 200 compounds. A larger than 100-fold selectivity (5-HT$_{2B}$ versus 5-HT$_{2A}$ and 5-HT$_{2C}$ receptor subtypes) was observed. However, the poor half-life ($t_{1/2}$ = 15 min) due to premature metabolization was a major drawback [34,35]. Introduction of a fluorine atom on the naphthyl moiety as well as replacement of the methyl with an isopropyl residue led to **10** (RS-127445, MT-500) with a far better pharmacokinetic profile. Indeed, the half-life of **10** found in rats was 1.8 hours (intra-peritoneal administration, 62% bioavailability) and 0.8 hours (oral administration, 14% bioavailability) while in monkeys the half-life found after oral administration was 2.5 hours with a bioavailability of less than 1% [34]. No effect on blood pressure or heart rate and no toxicity were seen in rats and dogs at single doses of up to 2 g/kg [35].

In man, **10** displayed a half-life of 12 hours (oral doses of 200 to 500 mg) and no adverse side effects were observed in phase I clinical trials [34].

In vivo studies showed that **10** is a high affinity 5-HT$_{2B}$ receptor antagonist [36] with a pKi of 9.5 (Table 1). Blockade of 5-HT-evoked inositol phosphate formation (pK$_B$ = 9.5) and of 5-HT-evoked increase in intracellular calcium (pIC$_{50}$ = 10.4) were observed. This compound also inhibited the 5-HT-evoked contraction of the rat isolated stomach fundus (pA$_2$ = 9.5) and the (±) α-methyl-5-HT-mediated relaxation of the rat jugular vein (pA$_2$ = 9.9). All these findings clearly demonstrated that **10** (RS-127445) is a 5-HT$_{2B}$ receptor subtype antagonist.

The implication of the 5-HT$_{2B}$ receptor in migraine is well documented [3,18,19] but is still a matter of debate [37]. Indeed, in a double blind study on nineteen migraineurs, **6** (m-CPP), a 5-HT$_{2B}$ /5HT$_{2C}$ agonist, was shown to induce more migraines than the placebo [38]. Moreover, selective 5-HT$_{2B}$ receptor antagonists were able to counteract the m-CPP-induced dural extravasation in a dose-dependent manner [39], thus supporting the 5-HT$_{2B}$ receptor mediation of migraine headache.

In this respect it was shown that **10** given intraperitoneally (1 and 2.5 mg/kg) effectively abolished the m-CPP induced (1 mg/kg, intravenous administration) plasma extravasation in the dura mater of anesthetized rats.

Also, **10**, administered intravenously (2 and 5.0 mg/kg) to anesthetized rats attenuated (30 and 41%, respectively) the capsaicin-evoked expression of c-fos in the cervical trigeminal nucleus cauda [34].

Due to its profile, **10** (RS-127445, MT-500) is currently undergoing phase I clinical trials for the prophylactic treatment of migraine.

Moreover, **10** has been shown to dose-dependently inhibit the serotonin-induced contraction of human colon longitudinal smooth muscle (1 and 100 μM) [20].

Accordingly, claims in the patent literature invoke the general use of 5-HT_{2B} antagonists, and more specifically compound **10**, in the treatment of irritable bowel syndrome (IBS) [21,22]. This approach is an interesting alternative to the current therapy of IBS involving 5-HT_3 and/or 5-HT_4 receptor ligands.

TETRAHYDRO-β-CARBOLINES

Other compounds binding to the 5-HT_{2B} receptor are based on the tetrahydro-β-carboline scaffold. Thus the well-known yohimbine **11** (Fig. **2**) is essentially equally active on 5-HT_{2B} and 5-HT_{2A} receptors (Table 2). However simplification of this structure afforded derivatives **12**, **13**, **14**, (Fig. **2**) with a marked selectivity (> 100 fold) for the 5-HT_{2B} versus 5-HT_{2A} and 5-HT_{2C} receptors (Table 2) [40]. Moreover, oral activity was observed for **13** (LY-272015) at 30 mg/kg using an ex vivo inhibition of serotonin-induced contraction in the rat stomach fundus [41].

Our own research in this area concentrated around β-carbolines possessing a cyclobutane carboxylic ester moiety at the 1 position [42]. Representative compounds of this series are indicated in Fig. (**3**).

Of the compounds synthesized in this carboline series, derivative **15** bearing a chlorine substituent was the first to show a good affinity for the 5-HT_{2B} receptor. However, the selectivity for the different subtypes was poor. Little improvement in selectivity was obtained by the introduction of an additional chlorine atom on the indole part of the molecule. Indeed both regioisomers **16** and **17** possess excellent affinities for the 5-HT_{2B} subtype but the affinity for the 5-HT_{2A} and 5-HT_{2C} subtypes is only slightly lower (Table 3). However, a dramatic increase in selectivity was

Table 2. Rat 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} Affinities of the Yohimbine Derived Scaffold

	p K_i	p K_B	p K_i
	5-HT_{2A}	5-HT_{2B} (rat stomach fundus)	5-HT_{2C}
11	5.79	6.92	<5.00
12	7.18	9.17	6.90
13	7.65	9.86	7.92
14	7.71	9.80	7.61

Table 3. 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} Receptor Affinities and Selectivities for the Tetrahydro-β-Carbolines

	IC_{50} (M)*			Selectivity	
	5-HT_{2A}	5-HT_{2B}	5-HT_{2C}	5-HT_{2A}/ 5-HT_{2B}	5-HT_{2C}/ 5-HT_{2B}
15	$2.4.10^{-7}$	$4.7.10^{-9}$	$8.3.10^{-8}$	51	17
16	$6.3.10^{-8}$	$1.88.10^{-9}$	$6.9.10^{-8}$	33	36
17	$2.96.10^{-8}$	$9.55.10^{-10}$	$3.43.10^{-8}$	31	36
18	$1.7.10^{-6}$	$1.7.10^{-9}$	8.10^{-8}	1000	47

* IC_{50} values measured by Cerep, 128 rue Danton – 92500 RUEIL MALMAISON - FRANCE

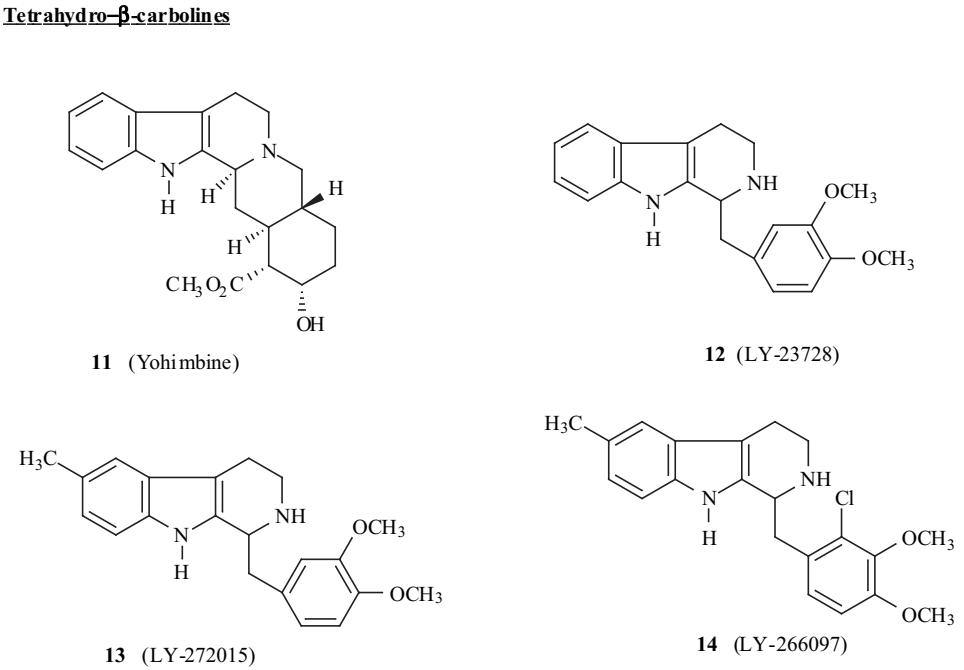
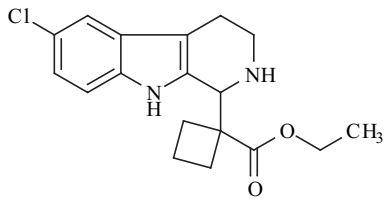


Fig. (2). Yohimbine derived scaffold.



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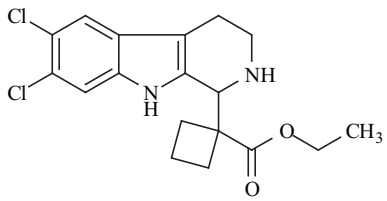

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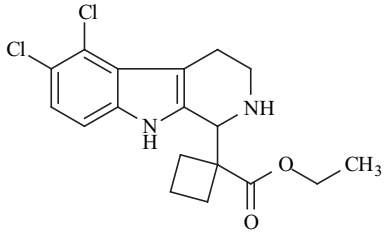

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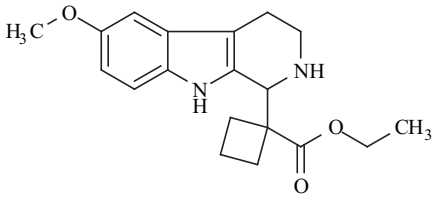

18

Fig. (3). Representative tetrahydro-β-carboline scaffold antagonists.

achieved with compound **18** bearing a methoxy substituent on the indole moiety. Thus, this pharmacomodulation lowered the 5-HT$_{2A}$ affinity by more than 10 fold and slightly increased the 5-HT$_{2B}$ affinity (ratio: 5-HT$_{2A}$/5-HT$_{2B}$ = 1000; 5-HT$_{2C}$/5-HT$_{2B}$ = 47 – Table 3).

Morever, functional experiments using CHO-cells expressing the human 5-HT$_{2B}$ receptor confirmed the antagonist behavior of this compound. Inhibition of 5-HT$_{2C}$ responses in vivo have also been observed [43].

CONCLUSIONS

The last decade has witnessed a growing interest in the study of serotonin receptors. In particular, the functional role identification of the various subtypes has been the center of investigations in both industry and academia. In this respect the discovery of selective antagonists for every subtype is mandatory.

Specific 5-HT$_{2B}$ receptor antagonists, the subject of this review, are still in their infancy and a unified picture has yet to emerge. However, recent data reported in the literature has revealed 5-HT$_{2B}$ antagonists based on a diversity of scaffolds that are sufficiently selective to point out the possible function and therefore therapeutic applications of this serotonin receptor notably in migraine and/or in the pathophysiology of IBS. Further research in this area is warranted.

ACKNOWLEDGEMENT

We thank D. Passerieux for extensive literature search.

ABBREVIATIONS

5-HT = 5-Hydroxytryptamine

CNS = Central Nervous System

cNOS = Constitutive NO Synthase

iNOS = Inducible NO Synthase

PCR = Polymerase Chain Reaction

DOCA = Deoxycorticosterone acetate

IBS = Irritable Bowel Syndrome

NO = Nitric Oxide

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