Latest Advances Towards the Discovery of 5-HT$_7$ Receptor Ligands

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Abstract: The 5-HT$_7$ receptor (5-HT$_7$R), characterized in 1993, is the most recently described member of the serotonin family. Since its discovery, 5-HT$_7$R has been the subject of extensive research due to its widespread distribution in the brain, suggestive of multiple central roles. The focus of this review is to illustrate the literature concerning developments of the last few years (2007-2010) towards the discovery of novel and selective 5-HT$_7$R ligands, agonists, antagonist and inverse agonists.

Keywords: 5-HT$_7$R, 5-HT$_7$ ligands, agonists, antagonists, G protein-coupled receptors, serotonin, serotonin receptor subtypes.

1. INTRODUCTION

Serotonin, isolated and named in 1948 by Rapport, was later chemically identified as 5-hydroxytryptamine (5-HT) [1, 2]. Since its isolation and characterization, 5-HT has been the subject of intense research due to its abundance in the central and peripheral nervous system (CNS/PNS), as well as in a number of non-neuronal tissues such as in the gastrointestinal (GI) tract, cardiovascular system and blood. It acts through the activation of at least fourteen 5-HT receptor subtypes, excluding splice variants. These receptors, according to the International Union of Pharmacology, have been classified on the basis of structural, functional, and pharmacological criteria, into seven distinct receptor classes: 5-HT$_1$ (including 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1e}$, and 5-HT$_{1F}$ subtypes), 5-HT$_2$ (5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$), 5-HT$_3$, 5-HT$_4$, 5-HT$_{5a}$, 5-HT$_6$, and 5-HT$_7$. All these receptors possess seven transmembrane domains and belong to the G protein-coupled receptors (GPCRs) family with the exception of 5-HT$_3$ receptor subtype which is a ligand-gated ion channel. 5-HT receptors control a variety of physiological functions and are involved in a number of pathological states.

Discovered in 1993, the 5-HT$_7$ receptor (5-HT$_7$R) is the last addition to the serotonin subfamily [3-5]. The protein possesses high sequence homology (90%) among different species (e.g. human, mouse, rat, guinea pig, and pig); whereas it possesses low (<40%) overall homology with other 5-HT receptors [6]. The 5-HT$_7$R exists, in human, in three different splice variants, namely 5-HT$_{7(a)}$, (b), (d), differing only in the length and amino acid composition of their carboxy terminal tail and are positively coupled with adenylyl cyclase (AC) through the activation of G_s proteins [4-5, 7-8]. 5-HT$_7$R is defined pharmacologically by its high affinity for 5-HT, 5-carboxytryptamine (5-CT), 5-methoxy-tryptamine, and methiothepin, moderate affinity for 8-OH-DPAT and ritanserin and low affinity for pindolol, sumatriptan, and buspirone [3-5]. Studies regarding the distribution of the 5-HT$_7$ binding sites, conducted in the presence of suitable pharmacological agents for non-5-HT$_7$R binding sites blockade, showed the highest density in the brain, mainly in the hypothalamus (including supra-chiasmatic nucleus), thalamus, hippocampus, brainstem, and cortex; whereas, in peripheral tissues, 5-HT$_7$R is mainly present on smooth muscle cells of blood vessels, heart, coronary artery, gastrointestinal tract, spleen, urinary tract, and kidney [9-15].

Since its discovery, this receptor has been the subject of intense research due to its widespread distribution in the brain suggestive of multiple central roles. Although investigation of functional significance of 5-HT$_7$R has been hampered for many years by the relative lack of specific tool drugs, a large amount of information has been collected to date due to the availability of selective antagonists (e.g. SB-269970 and DR-4004) and of constitutive knockout mice lacking 5-HT$_7$R [16-21]. The involvement of 5-HT$_7$R in a number of physio-pathological mechanisms has been highlighted by various studies. In particular, from a physiological point of view, a role of 5-HT$_7$R in circadian rhythm regulation and in thermoregulation has been clearly established [22-23]; a considerable body of evidence suggested 5-HT$_7$R involvement in processes of learning and memory, mood regulation, hippocampal signalling, nociception, and neuroendocrine regulation [24-31]. In the peripheral tissue a role of the 5-HT$_7$R has been suggested in ileum peristalsis, micturition reflex, control of blood pressure, and in the reproductive system [14-15, 32-35]. As a general consideration, it can be said that these physiological functions are in good agreement with 5-HT$_7$R distribution. With respect to physio-pathological processes involving 5-HT$_7$R in the CNS and/or in the periphery and the potential therapeutics application of selective 5-HT$_7$R ligands (agonist, antagonists, and/or partial agonists), some comprehensive overviews were recently published [14-15, 36-41]. Briefly, strong evidences suggested 5-HT$_7$R involvement in depression and sleep disorders. Moreover 5-HT$_7$R has been proposed to be involved in anxiety, obsessive compulsive disorders, schizophrenia, epilepsy, memory impairment, migraine, and substance abuse. In view of these

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outcomes, the 5-HT$_7$R can be considered an interesting and valuable target for drug development.

2. 5-HT$_7$ RECEPTOR LIGANDS

After the cloning and characterization of 5-HT$_7$R, a number of non-selective ligands showing high affinity toward this receptor were identified. Moreover, the high affinity for 5-HT$_7$R of a wide range of psychoactive drugs, such as typical and atypical antipsychotics, some antidepressants, together with almost exclusive expression of this receptor in the CNS has stimulated significant research interest. Different classes of non selective 5-HT$_7$R ligands are featured by: ergolines, aporphine derivatives, tricyclic neuroleptics, piperidine analogues, etc. However, due to the lack of selectivity, these compounds were not suitable pharmacological tools useful to clarify the functional significance of this receptor. Thus, the development of potent and selective 5-HT$_7$R ligands became an issue of key importance.

The first selective 5-HT$_7$R antagonists, belonging to different chemical classes, have been reported mainly by pharmaceutical companies. GlaxoSmithKline, as a result of a high-throughput screening (HTS) identified, in 1998, the first selective 5-HT$_7$R antagonist: SB-258719 (Fig. (**1**), **1** K_i = 32 nM), followed by SB-269970 (Fig. (**1**), **2** K_i = 1 nM) that is considered, to date, the standard selective 5-HT$_7$R antagonist, being >100-fold selective over a range of CNS targets including serotonergic (apart from the 5-HT$_{5A}$ receptor (50-fold) whose expression overlaps that of 5-HT$_7$R), adrenergic, and dopaminergic receptors [42-43]. However, it was recently found that SB-269970 is an effective antagonist at α_2 receptors in guinea pig in submucosal non cholinergic secretomotor neurons [44]. These results raise significant concerns about studies in which SB-269970 is used to identify receptor-mediating specific behaviours in the brain. SB-691673 (Fig. (**1**), **3** pK_i = 8.9) came from the optimization of a back-up series and features a diverse chemical structure from the above-mentioned sulfonamides [45]. Researchers at Meiji Seika Kaisha Ltd. patented another important class of selective 5-HT$_7$R antagonists belonging to the tetrahydrobenzindole family [17, 46-48]. The well known DR-4004 is the parent compound (Fig. (**1**), **4** 5-HT$_7$ pK_i = 8.48; 5-HT$_2$ pK_i = 7.37), and subsequent optimization of the selectivity profile is represented by DR-4365 and DR-4446 (Fig. (**1**), compounds **5**-**6** 5-HT$_7$R pK_i = 8.45 and 8.01, respectively; 5-HT$_{2A}$ pK_i = <6 and 6.02, respectively).

Compound **7**, one of the first described 5-HT$_7$R agonist (Fig. (**2**), pK_i = 7.79), was reported by Pfizer and possesses a (4,5-dihydroimidazol-2-yl)biphenylamine structure [49]. However, this derivative resulted to be endowed with affinity also for α_1 and α_2 adrenoceptors (pK_i = 6.68 and 7.71, respectively). Subsequently, Perrone and co-workers reported a novel class of 5-HT$_7$R agonists based on a 1-[ω-(4-aryl-1-piperazinyl)alkyl]-1-arylketone structure exemplified by compounds **8** and **9** (Fig. (**2**), K_i = 2.93 and 0.90 nM, respectively); however, selectivity over 5-HT$_{2A}$, α_1, and D$_4$ receptors remained somewhat unsatisfactory [50]. Subsequent optimization studies led to the synthesis of the agonist LP-44 (Fig. (**2**), **10**), endowed with high 5-HT$_7$R affinity (K_i = 0.22 nM), moderate 5-HT$_{1A}$R affinity (K_i = 52.7 nM), and very low affinity for 5-HT$_{2A}$R [51-52]. Finally, worthy of mention is the agonist AS-19 (Fig. (**2**), **11**) endowed with high affinity at the 5-HT$_7$R (pK_i = 9.2) and >80-fold selective over other serotonergic receptors (e.g. 5-HT$_{1A}$ pK_i = 7.1) [53]. However, it can be said that, to date, a standard selective agonist has not yet been adopted, and, in general, non selective 5-CT is commonly used as reference agonists.

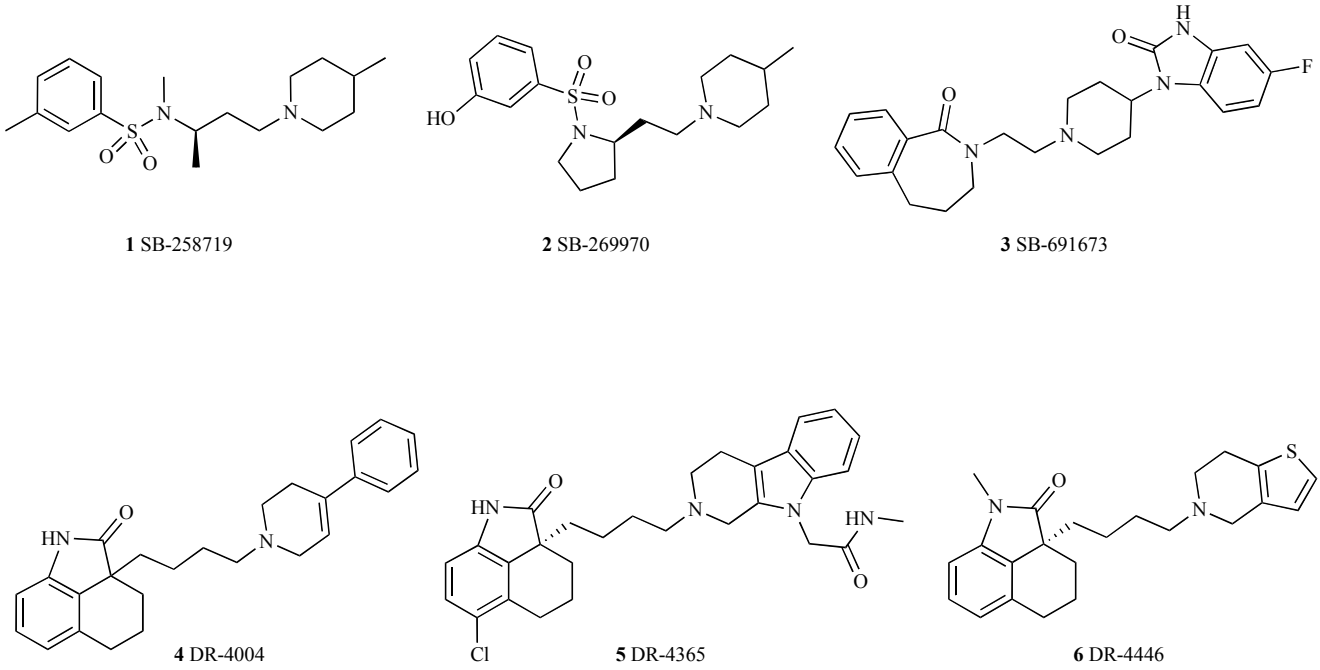
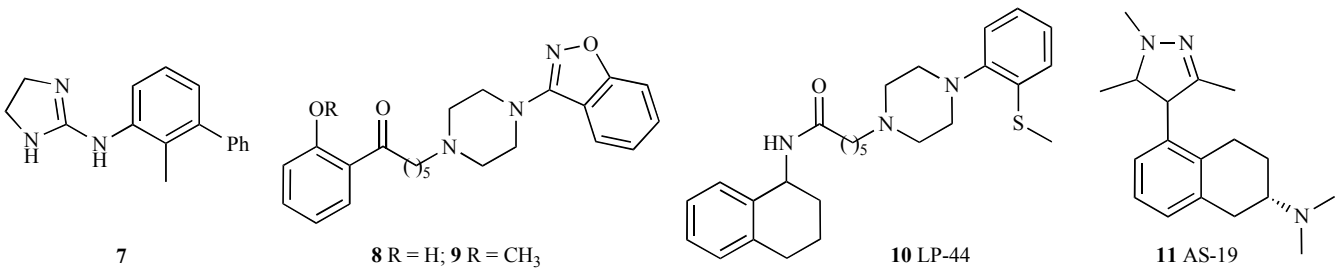


Fig. (1). Chemical structure of 5-HT$_7$R antagonists.



7 **8** R = H; **9** R = CH_3 **10** LP-44 **11** AS-19

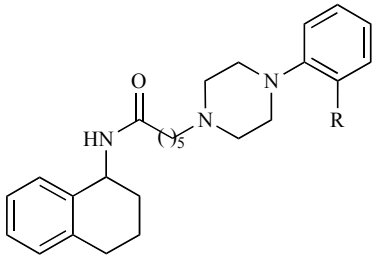
Fig. (2). Chemical structure of 5-HT_7R agonists.

During the last decade a number of pharmaceutical companies and academic research groups reported the identification of selective 5-HT_7R ligands and excellent reviews in the field were provided [40, 54-55]. A complete survey of the patent literature concerning 5-HT_7R ligands and pharmacophore models for 5-HT_7R agonists, antagonists and inverse agonists were recently reported [56-57]. Thus, they will not be discussed in this paper. The aim of the present overviews is to illustrate the literature concerning developments of the last few years (2007-2010) towards the discovery of novel and selective 5-HT_7R ligands.

2.1. Carboxamide Derivatives as 5-HT_7R Ligands

Perrone and co-workers, involved for several years in a research program aimed at the discovery of potent and selective serotonin 5-HT_7R based on arylpiperazine pharmacophore, discovered in 2004 ligands characterized by the *N*-(1,2,3,4-tetrahydronaphthalen-1-yl)-4-aryl-1-piperazinealkylamide structure exemplified by LP-44, (Fig. (**2**), **10** 5-HT_7 K_i = 0.22 nM) [40, 50-52]. Initial studies around this class served to optimize the 1,2,3,4-tetrahydronaphthalen-1-yl group and the connecting alkyl chain (five methylene units were preferred). However, due to the limited number of synthesized compounds, it was not possible to clearly elucidate the critical role of the substituent at the 2-position of the phenylpiperazine with respect to 5-HT_7R affinity, intrinsic activity, and selectivity. Therefore, novel 2-substitutedphenylpiperazine derivatives (Table **1**), covering a wide range of electronic, steric and polar properties, were designed to clarify structure-affinity and structure-activity relationships for the 5-HT_7R [58]. Binding data reported in Table **1** and functional assays suggested that some lipophilic substituents (SCH_3, $CH(CH_3)_2$, C_6H_5, $N(CH_3)_2$) (e.g. compounds **10** and **12a-c**) led to high affinity agonists, whereas OH and $NHCH_3$ residues (**12d** and **12e**) switched intrinsic activity toward antagonism (pA_2 = 7.20 and 7.7, respectively). However, a linear correlation (data not shown in the paper) was not observed between log k' values and pK_i values. Therefore, the lipophilicity of the 2-substituent did not seem to be the only requisite for high 5-HT_7R affinity.

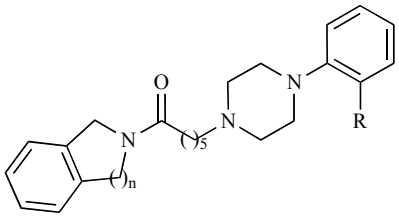
Table 1. Binding Affinities at 5-HT_7R for Compounds 12a-e[a]



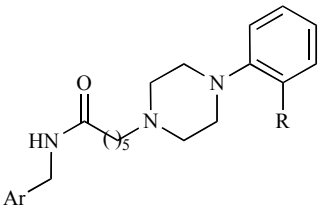
12 general formula

Compd	R	log k'	K_i (nM) ± SEM[a]			
			5-HT_7	5-HT_{1A}	5-HT_{2A}	D_{2L}
10	SCH_3	1.01	0.22 ± 0.08	52.7 ± 3.2	326 ± 35	7.3 ± 0.50
12a	$CH(CH_3)_2$	1.39	1.10 ± 0.40	167 ± 60	4824 ± 215	15.0 ± 4.1
12b	C_6H_5	1.71	0.13 ± 0.05	60.9 ± 2.5	1464 ± 180	224 ± 15
12c	$N(CH_3)_2$	1.26	0.90 ± 0.03	112 ± 8	559 ± 240	32.0 ± 5.6
12d	OH	0.45	11.4 ± 2.3	24.0 ± 6.3	3394 ± 225	987 ± 50
12e	$NHCH_3$	0.89	25.4 ± 1.6	133 ± 25	1587 ± 620	107 ± 7.8

[a]The values are the means ± SEM from three different independent experiments in triplicate. Receptors and radioligand used in binding assay: rat cloned 5-HT_7R and [^{3}H]LSD; human cloned 5-HT_{1A} and [^{3}H]8-OH-DPAT; rat cortex membranes 5-HT_{2A} and [^{3}H]ketanserin; human cloned D_{2L} and [^{3}H]spiroperidol.



13 general formula
13a R = C_6H_5, n = 2



14 general formula
14a Ar = 4-pyridinyl, R = C_6H_5
14b LP-211 Ar = 4-cyanophenyl, R = C_6H_5

Fig. (3). Chemical structure of 5-HT$_7$R ligands possessing general formula **13** and **14**.

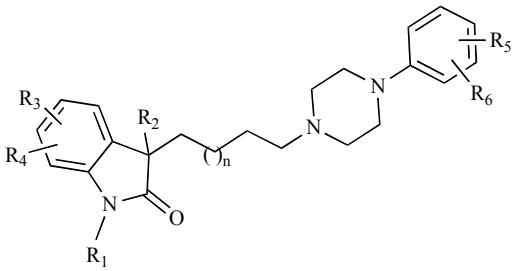
The most interesting compounds presented in the paper were **12a**, **12b**, behaving as 5-HT$_7$R partial agonists (EC_{50} = 0.90 and 1.77 μM, respectively) and **12c** (EC_{50} = 1.17 μM) behaving as 5-HT$_7$R potent full agonist. Moreover, these last compounds, being selective over 5-HT$_{1A}$, 5-HT$_{2A}$, and D_2 receptors, may be considered of relevant interest because of the lack, to the best of our knowledge, of potent and selective 5-HT$_7$R agonists.

More recently, the same research group presented a further optimization of the above mentioned class (Fig. (**3**), general formula **13** and **14**) with the aim of optimizing physicochemical properties required for blood-brain barrier penetration through the modulation of lipophilicity (ClogP) [59]. As a general trend, structural simplifications of the 1,2,3,4-tetrahydronaphthalen-1-yl group were detrimental for 5-HT$_7$R affinity, while 5-HT$_{1A}$ and D_2 receptors affinity were maintained. Nevertheless, compounds **13a**, **14a**, and **14b** (LP-211), showing lipophilicity values within the target range, exhibited an interesting profile, behaving as full competitive agonists at 5-HT$_7$R (K_i = 3.81, 0.98, and 0.58 nM, respectively; EC_{50} = 0.49, 0.31, and 0.60 μM, respectively), with appreciable selectivity (25- to 324-fold over 5-HT$_{1A}$ and 95- to 245-fold over D_2 receptors). Furthermore, LP-211 rapidly and freely distributed across the blood-brain barrier; although an unfavorable pharmacokinetic profile was detected (RA-7, *N*-dealkylation of the aliphatic chain linked to the piperazine nitrogen). However, *in vitro* binding assays revealed that RA-7 possessed higher 5-HT$_7$R affinity (K_i = 1.4 nM) than LP-211 and a better selectivity profile over a panel of 5-HT receptor subtypes, while LP-211 showed a certain affinity for 5-HT$_{2B}$ and 5-HT$_{2C}$ receptors (K_i = 67 and 91 nM, respectively). Further pharmacological studies suggested that LP-211 can be used as a 5-HT$_7$R agonist *in vivo* [60].

A series of potent 5-HT$_7$R ligands possessing an oxindole skeleton and structurally related to **13** were reported by EGIS Pharmaceuticals (Table **2**, general formula **15**) [61]. These compounds were designed as analogue of the tetrahydrobenzindole family patented by Kikuchi and corworkers (e.g. **4**-**6**) [17, 46-48, 54]. A number of structural modification were sequentially performed around the different pharmacophoric portion of the designed scaffold and the most interesting compounds (**15b**-**15j**) are depicted in Table **2**. SARs studies can be summarized as follows: (a) a tetramethylene spacer (n = 1) was optimal in terms of 5-HT$_7$R affinity and selectivity over 5-HT$_{1A}$R (**15b** vs **15a**); (b) substitution (R_1) at the oxindole nitrogen was detrimental for affinity at 5-HT$_7$R while enhanced 5-HT$_{1A}$R affinity (data not shown); (c) with respect to the 3-position of the oxindole an ethyl residue proved to be more favourable in term of binding profile and in term of metabolic stability with respect to unsubstituted analogues (e.g. **15c** vs **15d**); (d) modification of the substitution pattern of the phenylpiperazine moiety identified halogen residues (R_5 and R_6) as the best substituents at the 3- and/or the 4-position of the phenyl ring (**15b**-**15c** and **15e**-**15f**), conversely 2-substitutedphenylpiperazinyl analogues exhibited moderate reduction of affinity and/or selectivity with respect to 5-HT$_{1A}$R, (**15g**-**15h**) (these last results were not in agreement with what was observed in the structurally related series **13** discussed above); (e) derivatives possessing a piperidine residue instead of a piperazine ring resulted in a slight reduction of 5-HT$_7$R affinity (data not shown); (f) finally, the influence of substituents at the oxindole benzene ring (R_3 and R_4) was evaluated with the aim of improving metabolic stability in rats. As a general trend, the presence of one or more halogen at the 5- and/or 6- and/or 7-position maintained 5-HT$_7$R affinity in the low nanomolar range (e.g. **15i** and **15j**) and improved metabolic stability of **15j** vs **15c**. With respect to selectivity, the vast majority of tested compounds exhibited low 5-HT$_{1A}$R affinity. Compounds **15i** and **15d**, tested over a panel of GPCRs showed moderate to high affinity for 5-HT$_{2A}$R and α_1AR (5-HT$_{2A}$R K_i = 19.4 and 17.5 nM, respectively; α_1AR K_i = 71.3 and 42, respectively). In functional assays all the tested compounds behaved as antagonists. The results of *in vivo* studies showed good efficacy for compounds **15c** and **15d** in anxiolytic test (conflict drinking test (Vogel): 10 and >2.5 mg/Kg, respectively).

More recently, a new class of benzimidazolone-based 5-HT$_7$/5-HT$_{1A}$ receptor ligands (Fig. (**4**), general formula **16**) structurally related to the above mentioned family of oxindoles (**15**) was reported [62]. The first series of derivatives, possessing a two carbon linker and a substituted phenyl ring at the R_1 position was designed and synthesized based on the good superimposition of this structure with compound **17** (5-HT$_7$ K_i = 4.7 nM; 5-HT$_{1A}$ K_i = 9.9 nM) reported in 2005 by the research group of Rault [63]. Binding data showed a preference for the 5-HT$_{1A}$R with respect to 5-HT$_7$R (e.g. **16a** 5-HT$_{1A}$ K_i = 22 nM; 5-HT$_7$ K_i = 296 nM). With the aim of improving 5-HT$_7$R affinity and based on results obtained with the above mentioned derivatives (**12** and **15h**), in a subsequent series the linker

Table 2. Binding Affinities at 5-HT$_7$R for Compounds 15a-i[a]



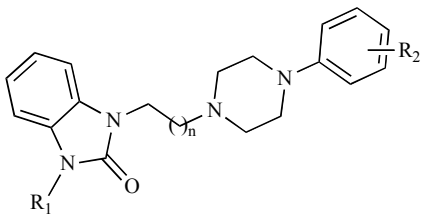
15 general formula

Compd	R_1	R_2	R_3	R_4	R_5	R_6	n	5-HT$_7$ K_i (nM)	5-HT$_{1A}$ % inhibition 10^{-7} nM
15a	H	CH_2CH_3	H	H	3-Cl	H	0	21	91
15b	H	CH_2CH_3	H	H	3-Cl	H	1	0.41	42
15c	H	CH_2CH_3	H	H	4-Cl	H	1	0.38	11
15d	H	H	H	H	4-Cl	H	1	7.0	10
15e	H	CH_2CH_3	H	H	4-F	H	1	0.43	10
15f	H	CH_2CH_3	H	H	3-Cl	4-F	1	0.60	14
15g	H	CH_2CH_3	H	H	2-Cl	H	1	5.11	51
15h	H	CH_2CH_3	H	H	2-OCH_3	H	1	5.38	79
15i	H	CH_2CH_3	6-F	H	4-Cl	H	1	0.79	9
15j	H	CH_2CH_3	5-Cl	7-Cl	4-Cl	H	1	10.13	5

[a]Receptors and radioligand used in binding assay: human recombinant 5-HT$_7$R and [^{3}H]LSD; rat 5-HT$_{1A}$ and [^{3}H]8-OH-DPAT.

length was increased and the aryl ring R_1 was removed. These two modifications, carried out together, were beneficial both to 5-HT$_{1A}$ and 5-HT$_7$ receptor affinity. Interesting selectivity over 5-HT$_{1A}$R was achieved with compounds **16b** and **16c** possessing a spacer of five methylene units and a phenylpiperazine or 4-chlorophenylpiperazine (5-HT$_7$ K_i = 6 and 7 nM, respectively; 5-HT$_{1A}$ K_i = 269 and 454 nM, respectively).

Another new class of 5-HT$_7$R ligands (Table **3**, general formula **18**), structurally related to the above mentioned family of oxindoles (**15**) and coming from structural modifications of their previously identified lead compound UCM-5600, was reported by Lopez-Rodriguez and co-workers [64]. This research group has been involved for several years in the discovery of new potent and selective serotonin 5-HT$_7$R ligands, being the first group which contributed to the elucidation of essential features for 7-HT$_7$R antagonism [40, 65-66]. The postulated ligand-based pharmacophore model for 5-HT$_7$R antagonism reported in 2003 consisted of five features: a positive ionizable atom (PI), a H-bonding acceptor group (HBA), and three hydrophobic regions (HYD$_1$-HYD$_3$); this model was validated and UCM-5600 (Table **3**) was selected as lead compound (5-HT$_7$ K_i = 89 nM; 5-HT$_{1A}$ 92% displacement of



16 general formula
16a R_1 = 4-$OCH_3C_6H_4$, R_2 = 2-OCH_3, n = 1
16b R_1 = H, R_2 = H, n = 4
16c R_1 = H, R_2 = 4-Cl, n = 4

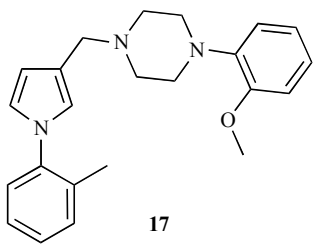


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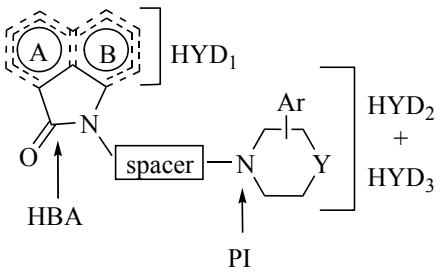
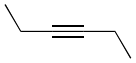
Fig. (4). Chemical structure of 5-HT$_7$R ligands **16** and **17**.

Table 3. Binding Affinities at 5-HT$_7$R for Compounds 18a-e[a]



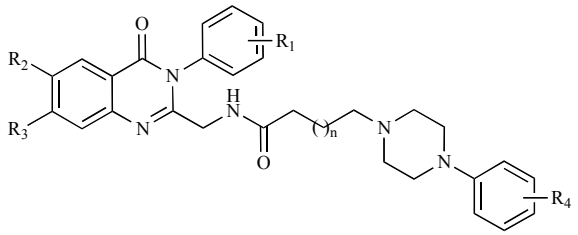
18 general formula

Compd	ring	spacer	Y	Ar	K_i (nM) ± SEM[a]	
					5-HT$_7$	5-HT$_{1A}$
UCM-5600	AB	$(CH_2)_5$	N	4-phenyl	89 ± 5	92%[b]
18a	A	$(CH_2)_4$	N	4-phenyl	>1000	360 ± 9
18b	B	$(CH_2)_4$	N	4-phenyl	74 ± 9	124 ± 15
18c	B		N	4-(naphth-1-yl)	>1000	26 ± 2
18d	B	$(CH_2)_4$	3,4-dihydroisoquinolin-2(1H)-yl		7 ± 2	219 ± 11
18e	B	$(CH_2)_3$	3,4-dihydroisoquinolin-2(1H)-yl		105 ± 12	>1000

[a]The values are the mean ± SEM of two to four different independent experiments in triplicate. Receptors and radioligand used in binding assay: human cloned 5-HT$_7$R and [^{3}H]LSD; human cloned 5-HT$_{1A}$ and [^{3}H]8-OH-DPAT. [b]Displacement of radioligand at 1 μM concentration.

radioligand at 1 μM concentration). Recently, structural modifications around different pharmacophoric features of UCM-5600 were reported with the aim of improving affinity at 5-HT$_7$R and clarifying determinants of 5-HT$_7$/5-HT$_{1A}$ receptor selectivity (Table **3**). SARs emerged from binding data suggested that: (a) the isoindolin-1-one moiety (ring A) was a less favourable HYD1 region than the 1,3-dihydro-2*H*-indol-2-one system (ring B) (e.g. **18a** vs **18b**) for 5-HT$_7$R affinity; (b) a spacer containing four or five methylene units (e.g. **18d** vs **18e**) was necessary for high 5-HT$_7$R affinity (in agreement with the optimal distance between HYD$_1$ and the basic center PI proposed in the pharmacophore model) and was preferred with respect to unsaturated alkyl chain (**18c**); (c) HYD$_2$ and HYD$_3$ pharmacophoric regions seemed to play an important role in receptor selectivity, being monocyclic system preferred for affinity at 5-HT$_7$R and detrimental towards 5-HT$_{1A}$R (e.g. **18d** vs **18b**). Among synthesized compounds, **18d** represented an interesting improvement over UCM-5600 in term of 5-HT$_7$R affinity (K_i = 7 nM) and in term of selectivity towards 5-HT$_{1A}$R (K_i = 219 nM). In functional assays, compound **18d** behaved as partial agonist.

A small focused library, based on a quinazolinone scaffold, was designed basing on interesting 5-HT$_7$R binding results coming from the screening of a small molecule library (Fig. (**5**), general formula **19**) [67]. Among the 85 synthesized compounds, mainly most interesting derivatives, e.g. **19a-19d**, possessed 2-OCH$_3$ or 2-OCH$_2$CH$_3$ as R$_1$ substituent, n = 1, and a fluorine residue at the 6- or 7-position of the quinazolinone ring (R$_2$ or R$_3$) (5-HT$_7$ K_i = 12-19 nM). Compound **19b** behaved as selective 5-HT$_7$R ligands over 5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_{2C}$, and D$_2$ receptors (IC$_{50}$ > 500 nM) while **19d** showed some affinity towards 5-HT$_{1A}$ (IC$_{50}$ = 120 nM) and D$_2$ reecptors (IC$_{50}$ = 140 nM).



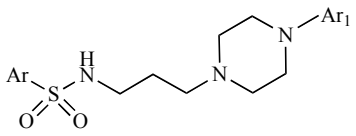
19 general formula
19a R$_1$ = H, R$_2$ = H, R$_3$ = F, R$_4$ = 2-OCH$_2$CH$_3$, n = 1; 5-HT$_7$ IC$_{50}$ = 19 nM
19b R$_1$ = H, R$_2$ = F, R$_3$ = H, R$_4$ = 2-OCH$_2$CH$_3$, n = 1; 5-HT$_7$ IC$_{50}$ = 12 nM
19c R$_1$ = 3-OCH$_3$, R$_2$ = F, R$_3$ = H, R$_4$ = 2-OCH$_2$CH$_3$, n = 1; 5-HT$_7$ IC$_{50}$ = 16 nM
19d R$_1$ = 4-OCH$_3$, R$_2$ = F, R$_3$ = H, R$_4$ = 2-OCH$_2$CH$_3$, n = 1; 5-HT$_7$ IC$_{50}$ = 16 nM

Fig. (5). Chemical structure of 5-HT$_7$R ligands possessing general formula **19**.

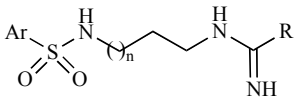
With the aim of rationalize these findings and design high-affinity 5-HT$_7$R ligands, binding profile of quinazolinones **19** (Fig. (**5**)) were subsequently used for a quantitative structure-activity relationship study using modified ant colony algorithm and adaptive neuro-fuzzy interference system [68].

2.2. Sulfonamide Based 5-HT$_7$R Ligands

Belonging to the sulphonamide class, SB-269970 (Fig. (**1**), **2**) was discovered in 2000 and, still to date, is regarded to be one of the most interesting 5-HT$_7$R ligand endowed

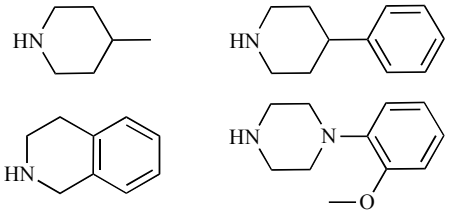


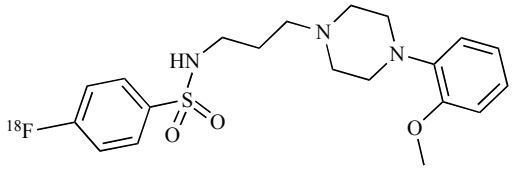
20 general formula
20a Ar = 4-$OCH_3C_6H_4$, Ar_1 = 2-$OCH_3C_6H_4$
20b Ar = 2-naphthyl, Ar_1 = 3-$CF_3C_6H_4$
20c Ar = 2-naphthyl, Ar_1 = 2-$OCH_3C_6H_4$



21 general formula:
Ar = 3-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, 2-naphthyl; n = 0,1,2;

R =





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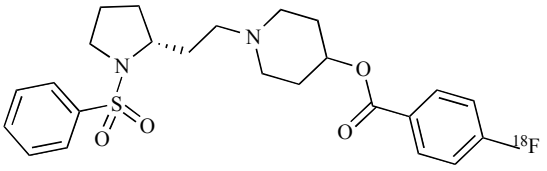


23

Fig. (6). Chemical structure of 5-HT_7R ligands **20**–**23**.

with favourable profile in term of affinity and selectivity. Recently, a number of SB-269970 analogues possessing a piperazine residue were designed and synthesized (Fig. (**6**), general formula **20**) [69]. SARs suggested that derivatives possessing a naphthalene residue (Ar) exhibited a slightly more favourable binding profile than the 4-methoxyphenyl substituted (e.g. **20c** vs **20a**, K_i = 20 and 37 nM, respectively) and the optimal aryl residues (Ar_1) linked at the piperazine ring are 2-$OCH_3C_6H_4$ and 3-CF_3 C_6H_4 (**20b** K_i = 12 nM). However, selectivity data, good over 5-HT_{2c} and 5-HT_6 receptors, were somewhat unsatisfactory over 5-HT_{1a} and 5-HT_{2a} (**20a-c** 5-HT_{1a} K_i = 4.6-272 nM; 5-HT_{2a} K_i = 85-5168 nM).

Soon after, another class of sulfonamide-based 5-HT_7R ligands was reported, characterized by a guanidine motif incorporated in the secondary amine (e.g. piperidine, piperazine, Fig. (**6**), general formula **21**) [67].

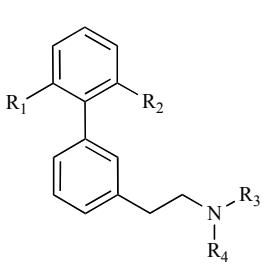
The compounds were synthesized by the use of solid phase methodology (SynPhase Lanterns) and binding data were in the high nanomolar range (K_i = 140-339 nM), with some selectivity over 5-HT_{1A}, and low selectivity over 5-HT_{2A} receptors. However, it should be mentioned that the purity of the synthesized compounds was not always satisfactory (purity determined by integration of the peak area at λ = 214 nm: 17-100%).

Very recently, two sulfonamide based ligands have been synthesized with the aim of developing a 5-HT_7R radiotracer for positron emission tomography (PET) (Fig. (**6**), compounds **22** and **23**) [71]. Radiolabeling of N-[3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl]-4-nitrobenzenesulfonamide did not afford compound **22** with satisfactory radiochemical yield while preliminary biological experiments by using compound **23** with autoradiographies failed to evidence any specific 5-HT_7R delineation. Furthermore, low brain penetration was observed for **23** probably due to rapid metabolic hydrolysis of the ester function.

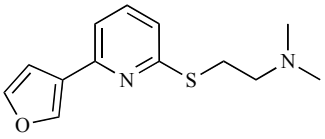
2.3. Bis-Arylamino Derivatives ad 5-HT_7R Ligands

Rault and co-workers in 2005, starting from the virtual screening of a chemolibrary, reported a novel class of 3-substituted arylpyrroles exemplified by compound **17** (Fig. (**4**), 5-HT_7 K_i = 4.7 nM; 5-HT_{1A} K_i = 9.9 nM) [63]. Further optimization of these ligands were recently reported by the same research group [72]. Besides low-affinity 5-HT_7R derivatives possessing a 1-aryl-1*H*-pyrrole-3-ethanamine structure (data not shown), some interesting aminoethyl-biphenyls were reported (Fig. (**7**), general formula **24**). Affinity and selectivity profiles in this series depends on the substitution pattern on the phenyl ring (R_1 and R_2). In general, the presence of a 2-substituent was essential for 5-HT_7R affinity (**24a-e** 5-HT_7 K_i = 6.2-8.6 nM), while the introduction of a second substituent at the 5-position improves selectivity over 5-HT_{1A}R (5-HT_{1A} **24b**, **24c**, and **24e** K_i = 443-1470 nM; **24a** and **24d** K_i = 4826 and 2250 nM, respectively).

Subsequently, novel bis-aryl derivatives related to **24** were reported [73]. The main structural modifications regarded: (a) the amine-containing aliphatic chain by the introduction of an oxygen or a sulphur residue and (b) the replacement of the central aryl ring with a phenyl, pyridine, diazine, or triazine moiety. In general, with the exception of derivative **25** (Fig. (**7**); K_i = 26 nM), these substitutions were not favourable for affinity at 5-HT_7R (K_i = 0.11-10 μM).



24 general formula
24a $R_1 = R_2 = OCH_3$, $R_3 = R_4 = CH_3$
24b $R_1 = R_3 = R_4 = CH_3$, $R_2 = H$
24c $R_1 = OCH_3$, $R_2 = H$, $R_3 = R_4 = CH_3$
24d $R_1 = R_2 = R_3 = R_4 = CH_3$
24e $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$



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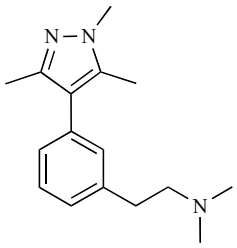


26 E-55888

Fig. (7). Chemical structure of 5-HT$_7$R ligands **24**-**26**.

Laboratorios del Dr Esteve SA Chemical-Pharmaceutical Group, in 2007, filed a patent application describing heterocyclicsubstituted 2-phenylethylamino derivatives as 5-HT$_7$R ligands [74]. This framework can be regarded as a structural simplification of 2-aminotetralin and indaneamine derivatives, discovered previously in the same laboratory [75-77], and analogues of the 3-substituted arylpyrroles developed by Rault and co-workers [63]. The compounds showed high affinity for 5-HT$_7$R receptor as well as high selectivity for this receptor in comparison to the 5-HT$_6$, the σ_1, the α_2 and the 5-HT$_1$ receptors. One of the most representative compound of this chemical class is E-55888 (Fig. (**7**), **26** K_i = 2.5 nM) possessing agonist properties at 5-HT$_7$R, and endowed with an excellent selectivity profile (with the exception of 5-HT$_{1A}$ receptors K_i = 700 nM) in fact no significant affinity was observed for other 5-HT receptor subtypes and 170 additional targets including receptors, transporters and ion channels [30].

2.4. Mixed Structures as 5-HT$_7$R Ligands

Leopoldo and co-workers reported the synthesis of analogues of compound **27a** designed according to the 'bivalent ligand' approach (Fig. (**8**), general formula **27**) [51, 78]. According to this approach and with the aim to increase the affinity for 5-HT$_7$R and the selectivity over related 5-HT$_{1A}$R, two pharmacophores were linked through a spacer and more in detail two moieties of the 5-HT$_7$/5-HT$_{1A}$ ligand **27a** (5-HT$_7$ K_i = 24.5 nM; 5-HT$_{1A}$ K_i = 2.37 nM) were linked through their 3-methoxy substituent by polymethylene chains of variable length. However the bivalent approach failed, in the best cases the dimers showed affinities for 5-HT$_7$R as high as the monomer such as compound **27b** and **27c** (5-HT$_7$ K_i = 25 and 28.5 nM, respectively; 5-HT$_{1A}$ K_i = 5.6 and 0.9 nM, respectively) with no improvement in selectivity. Moreover, some dimers displayed 5-HT$_{1A}$ receptor affinities slightly higher than monomer **27a** (e.g. **27c**).

Researchers from the Polish Academy of Science reported the synthesis of a series of MM-77 analogues (5-HT$_{1A}$ K_i = 6.4 nM; 5-HT$_7$ K_i = 90 nM) [40] with the aim of investigating the influence of different imide fragment on 5-HT$_{1A}$/5-HT$_7$ receptor selectivity (Fig. (**8**), general formula **28**) [79]. Binding data suggested that the presence of a tetramethylene alkyl spacer maintained high 5-HT$_{1A}$ and 5-HT$_7$ receptor affinities (5-HT$_{1A}$ K_i = 2.2-34 nM; 5-HT$_7$ K_i = 21-134 nM); while a cyclohexyl residue, detrimental for 5-HT$_7$R, strongly oriented affinity towards 5-HT$_{1A}$R (5-HT$_{1A}$ K_i = 0.3-9 nM; 5-HT$_7$ K_i = 221->5000 nM).

Derivatives of 7-alkylamino-8-alkoxy-purine-2,6-dione endowed with affinity at different serotonergic receptors were reported [80]. In general, synthesized compounds showed binding preference for the 5-HT$_{1A}$ and/or 5-HT$_{2A}$ receptors with the exception of compounds **29a** and **29b** (Fig. (**8**)) behaving as moderate selective 5-HT$_7$R ligands (5-HT$_7$ K_i = 57 and 83 nM, respectively; 5-HT$_{1A}$ K_i = 332 and 430 nM, respectively; 5-HT$_{2A}$ K_i = 920 and 1930 nM, respectively).

Recently Bojarsky and co-workers reported the development and the validation of a novel virtual screening cascade protocol for the identification of novel potential 5-HT$_7$R ligands [81]. By combining a miscellaneous of well known methodologies and software within an integrated framework and by using the Enamine screening database, the research group identified two benzodioxane derivatives (Fig. (**9**), **30a** and **30b**) not known before as 5-HT$_7$R ligands and endowed with moderate 5-HT$_7$R affinity (K_i = 197 and 295 nM, respectively). Even these derivatives were known to possess high affinity towards α_1 and 5-HT$_{1A}$ receptors, they could serve as novel hit compounds for the optimization of 5-HT$_7$R affinity and selectivity.

A series of aminopyrrolo[1,2-*a*]thieno[3,2-*e*]pyrazine derivatives as 5-HT$_7$R ligands were described (Fig. (**9**), e.g. **31**) [82]. Various substitutions on the piperazine ring were explored as well as replacement of the piperazine by other amines. Authors stated that 5-HT$_7$R affinity for this novel class was still lower than that observed for the 5-HT$_{1A}$R. However, binding data were not reported in the paper with

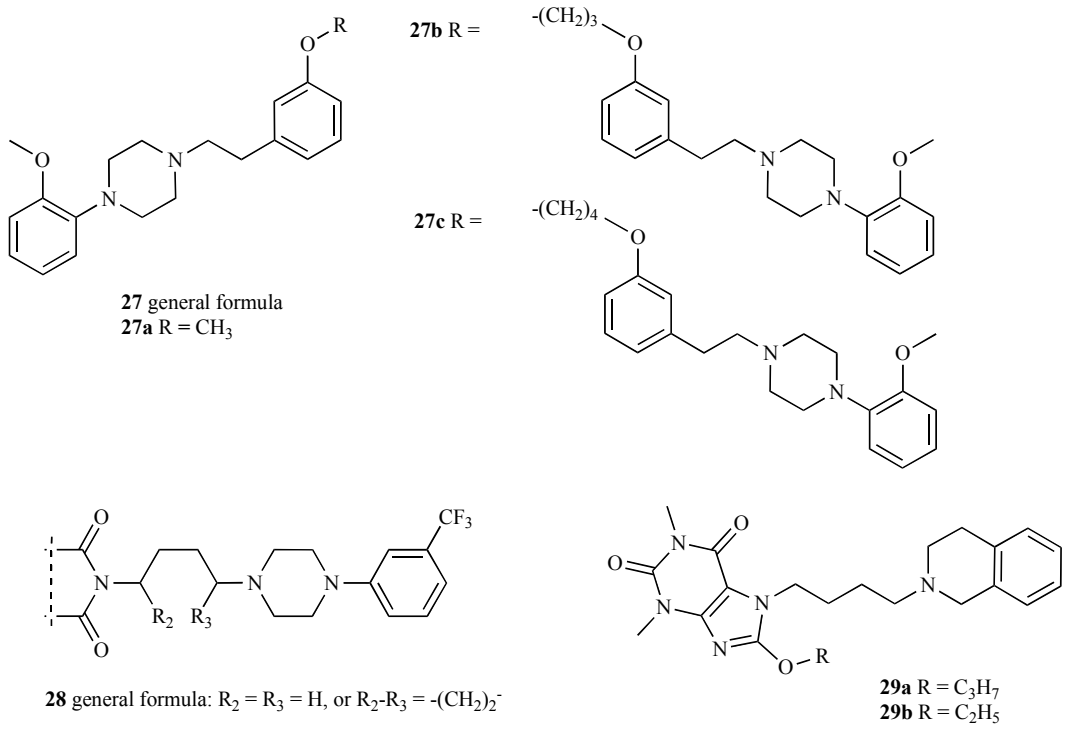


Fig. (8). Chemical structure of 5-HT$_7$R ligands **27**-**29**.

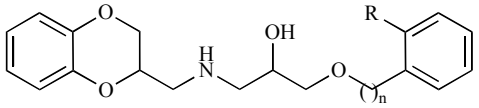
the exception of compound **31**, showing a preference for 5-HT$_{1A}$ (K_i = 15 nM) with respect to 5-HT$_7$ (K_i = 165 nM).

Exceptionally high affinity for the 5-HT$_7$R showed some dimebolin analogues (Fig. (**9**), **32a-c**), an old antihistamine drug (also known as dimebon or latrepirdine) with a broad spectrum of pharmacological activities targeting various GPCRs [83]. Dimebolin analogues, firstly designed as 5-HT$_6$R ligands, when tested in binding assays showed, as the parent compound, a rather broad spectrum of affinity at adrenergic, dopaminergic, and serotonergic receptors with very high-affinity for the 5-HT$_7$R (**32b** and **32c**, pK_i = 9.68 and 9.60 respectively). Dimebolin is currently under development by Pfizer and Medivation for the treatment of patients with Alzheimer's disease. Encouraging results were obtained in a phase II/III clinical trial (conducted with 183 patients with mild-to-moderate Alzheimer's disease); however, results from another subsequent phase III trial (600 patients) were unsatisfactory [84].

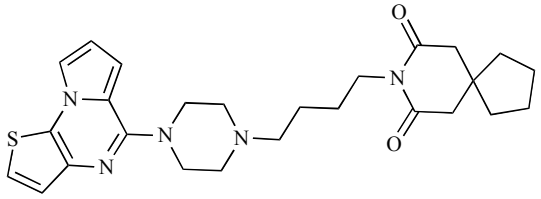
Very recently, novel tetrahydropyrido[3,2-*c*]pyrroles (Fig. (**9**), general formula **33**) were reported as 5-HT$_7$R antagonists by Johnson & Johnson Pharmaceutical R&D [85]. These compounds, possessing a central pyrrole moiety, were designed starting from the hit compound **33a** (5-HT$_7$ K_i = 14 nM) emerged from HTS. Three diversity point (R_1-R_3) were investigated by introducing them simultaneously in the novel molecules by an efficient one step synthesis. Most interesting compounds are reported in Fig. (**9**) and the following SARs can be drawn from binding data results: (a) replacement of the pyrazole core of **33a** with a pyrrole **33b** was detrimental for binding affinity at 5-HT$_7$R (K_i = 14 and 107 nM, respectively), (b) optimization of the diversity point R_1 afforded the best derivative of the series **33c** (K_i = 35 nM), (c) exploring substitution on the N-benzyl group (R_2) resulted in all cases in reduction of 5-HT$_7$R affinity (data not shown), and (d) substitution at the basic nitrogen (R_3) showed that only a methyl residue was able to maintain affinity in the low nanomolar range at 5-HT$_7$R (**33d** K_i = 36 nM). In functional assays compounds **33a-d** behaved as high affinity antagonists (pK_b = 7.2, 7.6, and 7.8, respectively); no selectivity data were reported for these novel tetrahydro-pyrido[3,2-*c*]pyrroles, with the exception of compound **33c** which behaved as α_1 adrenergic receptor ligands (K_i = 5 nM). Nevertheless, **33c** was selected for further *in vivo* studies and showed valuable drug-like properties resulting in an excellent brain penetration.

2.5. Dual Receptor Ligands: 5-HT$_{5A}$/5-HT$_7$ and M$_4$/5-HT$_7$

Suckling and co-workers have pursued the objective to discover novel dual ligands acting at 5-HT$_7$R and M$_4$ receptors [86-87]. According to the authors, novel molecules should be able to take advantage of a combination of specific activity at both receptor. More in detail, they suggested that drugs targeting serotoninergic and muscarinic receptors, and specifically 5-HT$_7$R antagonists and M$_4$ receptor agonists, can exert beneficial effects in schizophrenia and/or bipolar disorders [86-87]. In view of this assumption, the natural product library of SIDR (Strathclyde Innovations in Drug Research) was screened and the emerged hit compounds were optimized to give a first series of 5-HT$_7$R ligands endowed with low affinity towards M$_4$ receptor (Fig. (**10**), general formula **34**; compounds **34a** and **34b**; 5-HT$_7$ K_i = 26 and 9 nM, respectively; M$_4$ K_i = 35000 and 24000 nM, respectively). Subsequent optimization studies afforded derivatives possessing a 1,2,3,4-tetrahydroisoquinoline residue endowed with 5-HT$_7$/M$_4$ affinity in the high



30a T6068081 R = F, n = 0
30b T6053274 R = Cl, n = 1



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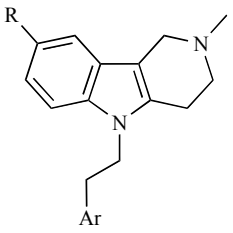
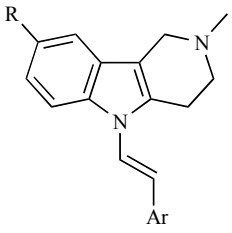
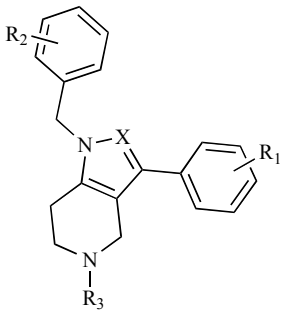


32a dimebolin R = CH_3, Ar = 2-methylpirid-5-yl
32b R = CH_3, Ar = C_6H_5

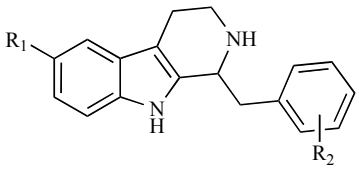


32c R = CH_3, Ar = C_6H_5

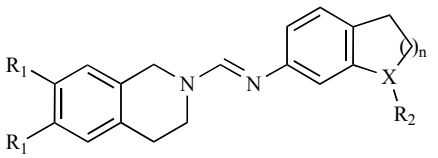


33 = general formula
33a R_1 = 4-Cl, R_2 = R_3 = H, X = N
33b R_1 = 4-Cl, R_2 = R_3 = H, X = CH
33c R_1 = 4-CH_3, R_2 = R_3 = H, X = CH
33d R_1 = 4-Cl, R_2 = H, R_3 = CH_3

Fig. (9). Chemical structure of 5-HT$_7$R ligands **30-33**.



34 general formula
34a R_1 = H, R_2 = 3-OCH_3
34b R_1 = H, R_2 = 3,4-OCH_2O



35 general formula
35a R_1 = OCH_3, R_2 = $OCOCH_3$, X = CH, n = 3
35b R_1 = OCH_3, R_2 = OH, X = CH, n = 1

Fig. (10). Chemical structure of dual receptor ligands possessing general formula **34-35**.

nanomolar range (Fig. (**10**), general formula **35**; compounds **35a** and **35b**; 5-HT$_7$ K_i = 0.5 and 0.4 μM, respectively; M_4 K_i = 0.2 and 0.3 μM, respectively).

Researchers at Hoffmann-La Roche, while looking for 5HT$_{5A}$ selective ligands, developed molecules able to bind both 5-HT$_{5A}$ and 5-HT$_7$ receptors [88]. The authors suggested that these novel dual ligands could be useful in the treatment of psychiatric diseases and/or sleep disorders and this approach was supported by the co-expression of these two serotonergic receptors in brain areas (e.g hippocampus, thalamus, hypothalamus, amygdale and cerebral cortex) involved in mood regulation and circadian clock [88]. New synthesized derivatives, characterized by the presence of a cyclic guanidine residue (Table **4**), came from optimization of 2-aminodihydroquinazolines **36a** and **36b** emerged from HTS of the Hoffmann-La Roche compound library by using recombinant human 5-HT$_{5A}$ receptors [88]. Different diversity points (R_1-R_7) were explored affording compound **36c** as the best of this first series. Further optimization regarded the synthesis of novel ligands by combining the best R_1-R_7 substituents previously identified. As a general trend, the effects were additive and high-affinity compounds, such as **36d** and **36e**, were obtained. In general, all the synthesized compounds showed high selectivity over 5-HT$_{2A}$, 5-HT$_3$, and 5-HT$_6$ receptors (>30-fold) and few compounds (e.g. **36d** had greater than 30-fold selectivity over 5-HT$_{1A}$ and 5-HT$_{2C}$). Moreover **36d**, screened over a number of aminergic GPCRs, emerged as the most selective. In functional assays, compounds **36d** and **36e** behaved as competitive antagonists at 5-HT$_{5A}$R (pA_2 = 8.52 and 8.13, respectively; 5-HT$_7$R activity not reported). Compound **36d** distributed to the brain after oral administration; however, brain penetration remained somewhat unsatisfactory for *in vivo* pharmacological studies. In a subsequent paper, the research group reported an optimization of the

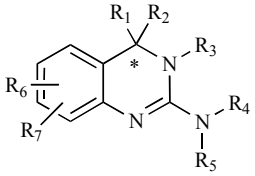
physiochemical properties of the above mentioned cyclic guanidines with the aim of developing a pharmacological tool, selective for 5-HT_{5A} receptors, for behavioural studies (Table **4**), general formula **36**, compounds **36f-g**) [89]. However, only high affinity 5-HT_{5A}/5-HT_7 dual ligands were obtained instead of selective 5-HT_{5A} receptor ligands. Compound **36f** was initially identified as one of the most representative compound (5-HT_{5A} pA_2 = 8.5; pK_a = 9.9, log $D_{7.4}$ = 0); however brain penetration after oral administration resulted modest for a compound targeting the CNS. In a more systematic investigation, the introduction of a difluoroethyl side chain resulted in (S)-**36g** high-affinity dual ligand (5-HT_{5A} pA_2 = 7.41) endowed with more than 30-fold selectivity over related serotonergic receptors (e.g. 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, and 5-HT_6) with the exception of 5-HT_{1A} (K_i = 56 nM). Moreover, compound (S)-**36g** showed high brain-to-plasma ratio and improved physiochemical properties ((R/S)-**36g** log $D_{7.4}$ = 1.5; pK_a = 8.9).

3. CONCLUDING REMARKS

Since the cloning of the 5-HT_7R, research towards the development of selective agonists and antagonists has generated a number of novel ligands endowed with different chemical structures. In the present review, we extensively discussed developments, over the last few years (2007-2010), in the medicinal chemistry field concerning the discovery of newer and more selective 5-HT_7R ligands and interesting achievements are herein reported. In particular, with respect to 5-HT_7R agonists, worthy of mention are LP-211 (**14b**) and E-55888 (**26**). A detailed pharmacological characterization of LP-211 revealed that it can be used as a 5-HT_7R agonist *in vivo* although some selectivity issues regarding LP-211 and its main metabolite RA-7 still remain open. E-55888 being, to the best of our knowledge, the most selective 5-HT_7R agonist helped to clarify the role of 5-HT_7R in the control of pain and should be considered for further studies on 5-HT_7R function. Besides agonists, compound **33c**, belonging to the novel tetrahydropyrido[3,2-*c*]pyrrole class, emerged as high affinity antagonist and, although some selectivity issues should be resolved, pharmacological studies *in vivo* showed valuable drug-like properties and an excellent brain penetration. Moreover, a number of the new 5-HT_7R ligands recently reported were designed to achieve improved pharmacokinetic profile with excellent results and this was confirmed by the *in vivo* data described so far. Thus, while no 5-HT_7R agonist or antagonist has entered clinical trials, the diversity of structures reported over these last three years for this receptor indicates continued interest in the development of more and more selective ligands coupled with suitable drug-like properties for preclinical evaluation.

Besides medicinal chemistry efforts, the combined use of classical pharmacology along with molecular biology and knockout animal models helped to achieve a better knowledge of the 5-HT_7R. Nowadays, it is clear the involvement of 5-HT_7R in a variety of CNS functions such as thermoregulation, circadian rhythm and REM sleep, migraine, depression, anxiety, obsessive–compulsive disorders, schizophrenia, epilepsy, pain, memory. However, results coming up from pharmacological studies with 5-HT_7R knockout mice and selective antagonists or agonists were sometimes quite contradictory or even opposite. Even if no satisfactory explanation for such observed discrepancies has been given so far, it was recently suggested that GPCR dimerization could be the possible key mechanism that can introduce diversity in 5-HT_7R signaling [41]. In other

Table 4. Binding Affinities at 5-HT_7R for Compounds 36a-g[a]



36 general formula

Compd	R_1	R_2	R_3	R_4	R_5	R_6	R_7	*	K_i (nM)[a]	
									5-HT_{5A}	5-HT_7
36a	H	H	H	H	H	5-Cl	H	-	99	793
36b	H	H	H	H	H	5-Cl	6-Cl	-	43	294
36c	CH_2CH_3	H	H	H	H	H	H	R/S	24	N.D.[b]
36d	CH_3	H	H	H	H	5-Cl	H	R/S	5.1	15.9
36e	CH_3	H	H	CH_3	H	5-Cl	H	R/S	10.8	15.3
36f	CH_3	H	H	H	H	5-Cl	H	S	1.6	6.0
36g	CH_3	H	H	CH_2CHF_2	H	5-Cl	H	S	6.8	24.8

[a]The values are the mean ± SEM of two to four different independent experiments in triplicate. Receptors and radioligand used in binding assay: human recombinant 5-HT_7R and [^{3}H]LSD; human recombinant 5-HT_{5A} and [^{3}H]LSD. [b]N.D. not tested.

words, in the proposed model, 5-HT$_7$R receptor resides in different dimeric contexts and initiates different signaling pathways, depending on the neuronal circuitry and/or brain region. While the use of 5-HT$_7$R knockout mice along with selective agonists or antagonists considerably improved our knowledge about 5-HT$_7$R, it also opened new promising directions for future pharmacological research which might give further insight in how distinct CNS functions are differentially regulated by the 5-HT$_7$R.

In conclusion, almost twenty years after its discovery, a sufficient amount of information has been collected which still makes 5-HT$_7$R a fascinating target for the development of future therapeutic agents.

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