Introduction
Alzheimer’s disease (AD), the most common cause of dementia among older people, is characterized by behavioral disorders and a progressive decline in memory function. Senile plaques, neurofibrillary tangles, and cholinergic dysfunction are major hallmarks of the disease. Clinical and preclinical studies point to neuronal and synaptic loss and synaptic impairment and associated neurochemical alterations of several transmitter systems as the main factors underlying both cognitive and neuro-psychiatric symptoms. The use of acetylcholinesterase inhibitors for treating cognitive decline in AD, based on early findings of a cholinergic deficit, has been clinically applied for more than a decade but provides only modest benefits in most patients. Therefore, there is still an ongoing search for new treatments that will demonstrate greater efficacy against cognitive dysfunction.

Increasing evidence supports the role of the serotonergic system in learning and memory processes. Extensive serotonergic denervation has been described in AD, although it is not yet fully understood whether these changes are a cause or a consequence of the neurodegeneration in the illness [1]. The identification of seven serotonin (5-HT) receptor families (5-HT<sub>1</sub> to 5-HT<sub>7</sub>), the 5-HT transporter (SERT) in mammalian species, and the drugs that are selective for these sites has helped clarify their specific roles in learning and memory.

The 5-HT<sub>6</sub> receptor is the most recently identified member of the 5-HT receptor superfamily. The 5-HT<sub>6</sub> receptor is involved in affective disorders, anxiety and depression, epilepsy, and obesity. Initially, interest in the 5-HT<sub>6</sub> receptors was triggered by evidence showing that certain anti-psychotics are able to bind to these receptors. Now, however, interest in these receptors lies in the role that they play as well as the therapeutic potential of 5-HT<sub>6</sub> receptor compounds in learning and memory processes. Currently, some 5-HT<sub>6</sub> receptor ligands are being subjected to clinical development processes for future use as potential anti-dementia, anti-psychotic, and anti-obese drugs, although the mechanisms associated with the 5-HT<sub>6</sub> receptor activation/blockade are not completely understood. In any case, information regarding the pharmacology of 5-HT<sub>6</sub> receptors is still quite limited.

This article will focus on preclinical and clinical studies that describe the effects of 5-HT<sub>6</sub> receptor compounds on cognition and the purported mechanism of action by which 5-HT<sub>6</sub> receptor compounds may affect learning and memory in AD. Several up-to-date reviews on this receptor can be found in the literature [2-4]. This paper gives a comprehensive review on the state of art of the 5-HT<sub>6</sub> receptors, focusing on articles published in recent years (Figure 1).

Structure and localization of 5-HT<sub>6</sub> receptors
Initially cloned from striatal tissue [5], the rat 5-HT<sub>6</sub> receptor gene encodes a protein of 438 amino acids and
shares 89% homology with the human form [6,7]. The 5-HT$_6$ receptor belongs to the G-protein-coupled receptor (GPCR) family, displaying seven transmembrane domains. They are quite different from all other 5-HT receptors: they are characterized by a short, third cytoplasmatic loop and a long C-terminal tail and contain one intron located in the middle of the third cytoplasmatic loop. The 5-HT$_6$ receptor has no known functional isoforms. A non-functional truncated splice variant of the 5-HT$_6$ receptor has been identified but appears not to have any physiological significance. Kohen and colleagues [6] identified a silent polymorphism at base pair 267 (C267T). Although there is evidence linking this polymorphism to several syndromes that affect cognition, including dementia, AD, and schizophrenia, these findings have not always been replicated and their significance has not yet been determined.

5-HT$_6$ receptor expression is restricted mainly within the central nervous system (CNS). In situ hybridization and northern blot studies revealed an exclusive distribution of 5-HT$_6$ mRNA in the rat CNS, and the highest density was found in the olfactory tubercle, followed by the frontal and entorhinal cortices, dorsal hippocampus (that is, dentate gyrus and CA1, CA2, and CA3 regions), nucleus accumbens, and striatum. Lower levels were observed in the hypothalamus, amygdala, substantia nigra, and several diencephalic nuclei. These findings have been corroborated by immunolocalization and radioligand-binding studies, which showed a similar distribution of 5-HT$_6$ receptor protein in the rat CNS [8,9]. Therefore, 5-HT$_6$ receptors appear to be localized in brain areas involved in learning and memory processes.

5-HT$_6$ receptor signaling
Interestingly, it has been suggested that both 5-HT$_6$ receptor agonists and antagonists may have pro-cognitive activities, implying that activation and inhibition of this receptor could evoke similar responses. The selective 5-HT$_6$ receptor agonist LY-586713 caused a bell-shaped dose-response curve on hippocampal brain-derived neurotrophic factor (BDNF) mRNA expression. It also increased the Arc mRNA levels, and this effect was blocked by the 5-HT$_6$ receptor antagonist SB-271046. However, in some brain regions, the antagonist was not able to block the agonist effect and, in fact, induced an increase in Arc expression [10], consistent with a potential differential mechanism. An excellent review [11] regarding the effects of 5-HT$_6$ receptor agonists and antagonists on cognition in normal adult rats and in rodent models of psychiatric disorders, as well as data obtained from some clinical studies, suggested that agonists and antagonists are able to act on receptors located on distinct neuronal populations.

The mechanism for paradoxically similar effects of agonist/antagonists on cognition could be related to the existence of alternative biochemical pathways activated by 5-HT$_6$ receptors. The 5-HT$_6$ receptor is a GPCR that positively stimulates adenylate cyclase activity, meaning
that, upon agonist activation, cAMP formation is increased. In fact, activity on adenylate cyclase confers the classic definition as agonist/antagonist on 5-HT<sub>6</sub> receptors. 5-HT<sub>6</sub> receptor coupling to G<sub>α</sub>s has been widely described, but coupling of 5-HT<sub>6</sub> receptors to other G<sub>α</sub> protein subunits (G<sub>α</sub>q or G<sub>α</sub>i), using a scintillation proximity assay/antibody-immunocapture technique, has also been recently reported [12]. In addition, the coupling of 5-HT<sub>6</sub> receptors to Ca<sup>2+</sup> signaling by using a chimeric G-protein has been reported [13]. It has been reported that, with a yeast two-hybrid assay, the carboxyl-terminal region of the 5-HT<sub>6</sub> receptor interacts with the Fyn-tyrosine kinase, a member of the Src family of non-receptor protein-tyrosine kinases [14]. This same study showed that the activation of 5-HT<sub>6</sub> receptor activated the extracellular signal-regulated kinase1/2 via a Fyn-dependent pathway. These findings suggest that Fyn plays an important role in 5-HT<sub>6</sub> receptor-mediated signaling pathways in the CNS. In addition, improvement in learning, associated with the administration of the 5-HT<sub>6</sub> receptor antagonist SB-271046 in the Morris water maze learning task, is associated with increased phosphoextracellular signal-regulated kinase1/2 (pERK1/2) levels [15]. All of these data suggest that 5-HT<sub>6</sub> receptors activate the ERK1/2 via a Fyn-dependent pathway (Figure 2). At this point, it is worth mentioning a purported relationship between Fyn and Tau. Tau is a microtubule-associated protein and, in a hyperphosphorylated state, a main component of neurofibrillary tangles, one of the pathologic hallmarks of AD. Most of the Tau phosphorylation sites that have been routinely characterized are serine and threonine residues, but recent reports state that Tau can be phosphorylated at tyrosine residues by kinases, including Fyn. In addition, pERK1 is one of the kinases involved in Tau phosphorylation. Therefore, it is possible to suggest that modulation of 5HT<sub>6</sub> receptors might lead to increased tau phosphorylation. In other words, it is even possible to speculate that 5HT<sub>6</sub> receptor modulation might, in the short term, improve cognitive function (as described in the following sections) but, over a longer term, enhance the neurodegenerative processes in AD. A physical interaction between 5-HT<sub>6</sub> receptor and the Jun activation domain-binding protein-1 (Jab-1), using different experimental approaches, has also been described, suggesting another signal transduction pathway for these receptors [16].

However, it should be noticed that drugs that are considered to be a reference agonist/antagonist upon 6-HT<sub>6</sub> receptors might be regulating 5-HT<sub>6</sub> receptor-independent events. In an investigation of the effects of EMD386088, a 5-HT<sub>6</sub> receptor agonist, on cell viability, it was found that EMD386088 potentiated cell death in different cultured neuronal cell lines and that these cytotoxic effects, regardless of the presence of 5-HT<sub>6</sub> receptors, were mediated by the downregulation of ERK1/2 activities. Furthermore, the specific 5-HT<sub>6</sub> receptor antagonist SB258585 potentiated cell death and induced an increase in the concentration of intracellular Ca<sup>2+</sup>, whereas EMD386088, or 5-HT<sub>6</sub>, did not affect calcium concentration [17]. Therefore, these compounds that have been intensively used as 5-HT<sub>6</sub> receptor ligands could display 5-HT<sub>6</sub> receptor-independent effects.

**Neurochemical mechanisms mediating 5-HT<sub>6</sub> receptor functions**

A postsynaptic location of 5-HT<sub>6</sub> receptors is expected because quantitative reverse transcription-polymerase chain reaction distribution of serotonin 5-HT<sub>6</sub> receptor mRNA in the CNS of rats subjected to a selective serotonergic lesion using 5,7-dihydroxytryptamine has shown that 5-HT<sub>6</sub> receptors are present within 5-HT projection fields and not in serotonergic raphe neurons [18]. Therefore, 5-HT<sub>6</sub> receptors appear to be located in neurons that are not serotonergic.

It has been consistently described that the influence of 5-HT<sub>6</sub> receptors on memory is mediated, at least partially, by increased cholinergic neurotransmission. Behavioral studies have shown that 5-HT<sub>6</sub> receptor blockade leads to an increase in behaviors such as the number of yawns or stretches in rats. These behaviors are largely dependent on the cholinergic system because they are reversed by muscarinic antagonists. Further supporting this cholinergic mediation, 5-HT<sub>6</sub> receptor antagonists increase acetylcholine release both in vitro [19] and in vivo [20].

However, the purported localization of 5-HT<sub>6</sub> receptors on cholinergic neurons was discarded because a selective cholinergic lesion, induced by injection of the selective immunotoxin 192-IgG-Saporin, failed to alter the density of 5-HT<sub>6</sub> receptor mRNA or protein expression in the deafferentated frontal cortex [19]. Therefore, the effects of 5-HT<sub>6</sub> receptor ligands on cholinergic neurons could be mediated by other neurotransmitter systems, such as the glutamatergic system [21]. Treatment with a 5-HT<sub>6</sub> receptor antagonist or atypical anti-psychotics with high affinities for 5-HT<sub>6</sub> receptors, such as clozapine, enhanced glutamate levels in the frontal cortex and hippocampus. On the other hand, 5-HT<sub>6</sub> receptor agonism attenuated stimulated glutamate levels elicited by high KCl treatment [22]. A recent work aimed to study the effect of 5-HT<sub>6</sub> receptor activation on glutamatergic transmission by means of whole-cell patch-clamp electrophysiological recordings from medium spiny neurons of the striatum and layer V pyramidal neurons of the prefrontal cortex. 5-HT<sub>6</sub> receptor activation by the novel agonist ST1936 reduced the frequency of spontaneous excitatory postsynaptic currents. 5-HT<sub>6</sub> receptor activation also reduced the amplitude of spontaneous excitatory
postsynaptic currents recorded from medium spiny neurons, suggesting a mechanism of action involving postsynaptic 5-HT$_6$ receptors. The inhibitory effect of ST1936 on glutamatergic transmission was prevented by the selective 5-HT$_6$ receptor antagonist SB258585 [23].

It has also been shown that 5-HT$_6$ receptors may be expressed on GABAergic spiny neurons of the striatum. The co-localization of glutamic acid decarboxylase and 5-HT$_6$ receptors in rat cerebral cortex and hippocampus has also been demonstrated, and almost 20% of 5-HT$_6$-like immunoreactive neurons have been shown to be GABAergic [24]. It can be suggested, on the basis of all these data regarding localization of 5-HT$_6$ receptors and on the basis of data from releasing experiments [22,25], that 5-HT$_6$ receptor agonists/antagonists modulate cholinergic or glutamatergic systems (or both) via disinhibition of GABAergic neurons.

5-HT$_6$ receptor ligands

Since the initial discovery of the first ligands in the late 1990s by using high-throughput screening technologies on compound libraries, a growing number of scientific publications and patent applications have developed [26]. The synthesis of 5-HT$_6$ receptor ligands has been very successful, and a number of highly potent ligands have been reported [27].

At the preclinical level, 5-HT$_6$ receptor medicinal chemistry is benefiting from knowledge that has been acquired since the discovery of the receptor using tools such as pharmacophore modeling, three-dimensional molecular docking or structure similarity algorithms. As a result, an increasing number and diversity of novel, highly selective 5-HT$_6$ receptor ligands of all functional types have been reported, although the principal efforts have been focused on antagonism. Some of these compounds have been used extensively as pharmacological tools (that is, Ro-04-6790 or SB-271046). The search for new 5-HT$_6$ receptor ligands continues. A new 5-HT$_6$ receptor agonist, ST1936, was recently reported. ST1936 bound to human 5-HT$_6$ receptors with good affinity (K$_i$ = 28.8 nM) and behaved as a full 5-HT$_6$ agonist on cloned cells; it was able to increase Ca$^{2+}$ concentration and phosphorylation of Fyn kinase and regulate the activation of ERK1/2 (downstream target of Fyn kinase). These effects were completely antagonized by 5-HT$_6$ receptor blockade with selective antagonists [28]. Epinimocyclohepta[b]indole analogs [29], tetracyclic tryptamines with the rigidized N-arylsulphonyl, N-arylcobarbonyl, and N-benzyl substituents [30], or conformationally restricted N(1)-arylsulfonyl-3-aminoalkoxy indoles [31] have been shown to have acceptable ADME (absorption, distribution, metabolism, and excretion) properties, adequate brain penetration, and favorable pharmacokinetic profile. Using a newly devised chemocentric informatics methodology for drug discovery integration showed that selective estrogen receptor modulators are putative ligands of 5-HT$_6$ receptors [32]. Positive results in animal models of cognition have been reported for both lead compounds.
(that is, L-483518, Ro-4368144, BGC20-761, or E-6801) and newly synthesized ligands, further confirming the involvement of this receptor in cognitive processes and its therapeutic potential. However, despite encouraging results at a preclinical level, very few 5-HT₆ receptor selective ligands (and all of them acting as antagonists) have reached the clinical phases of development for the treatment of cognitive disorders.

The development of a positron emission tomography (PET) radioligand for imaging 5-HT₆ receptors in the brain would, for the first time, enable in vivo imaging of this target along with assessment of its involvement in disease pathophysiology. Based on the aforementioned, the development of N-[3,5-dichloro-2-(methoxy)phenyl]-4-(methoxy)-3-(1-piperazinyl)benzenesulphonamide (SB399885), a selective and high-affinity (pKi = 9.11) 5-HT₆ antagonist radiolabeled with carbon-11 by O-methylation of the corresponding desmethyl analog with [¹¹C]MeOT, has been described. PET studies with [¹¹C]SB399885 in baboons showed fast uptake followed by rapid clearance in the brain. Poor brain entry and inconsistent brain uptake of [¹¹C]SB399885 compared with known 5-HT₆ receptor distribution limit its usefulness [33]. Recently, the development of GSK215083 (GlaxoSmithKline, Uxbridge, Middlesex, UK) has been reported. This compound was radiolabeled with ¹¹C via methylation. The in vivo properties of [¹¹C]-GSK215083 have been evaluated in pigs, non-human primates, and human subjects. [¹¹C]-GSK215083 readily entered the brain in all three species, leading to a heterogeneous distribution (striatum > cortex > cerebellum) that is consistent with reported 5-HT₆ receptor densities and distribution determined by tissue-section autoradiography in preclinical species and humans [34].

**Experimental approaches to the role of 5-HT₆ receptors in cognition**

Following the discovery of 5-HT₆ receptor ligands with good brain penetration, a growing body of preclinical evidence has supported the use of 5-HT6 receptor antagonism for treating cognitive dysfunction. In two excellent reviews, Meneses and colleagues [4] (2011) and Fone [11] (2008) described the effects of 5-HT₆ receptor agonists and antagonists on cognition. The first indirect evidence of 5-HT₆ receptor involvement in memory was obtained by using antisense oligonucleotides. A few years later, pharmacological blockade of 5-HT₆ receptor was shown to produce promnesic or antiamnesic effects (or both) in a number of memory tasks, including water maze, passive avoidance, autoshaping, fear conditioning, novel object recognition, or social memory [35]. Further support came from studies based on how learning paradigms decrease 5-HT₆ receptor expression [15,36], whereas 5-HT₆ receptor overexpression of 5-HT₆ receptors in the striatum, achieved by targeted gene delivery, led to cognition impairments in a reward-based instrumental learning task, a striatum-dependent learning model [37]. Different 5-HT₆ receptor antagonists have been reported to be active in the novel object discrimination test in rats and to improve water maze retention, even in aged rats [38], although failing to alter acquisition of spatial learning. In senescent mice, the effects of 5-HT₆ receptor blockade with SB-271046 were assessed in the novel object recognition test for evaluating recognition memory (a component of episodic-like memory) and in spontaneous alternation task in the T-maze for evaluating working memory. It was found that deficits in consolidation of both non-spatial recognition memory and working memory performances were reversed by 5-HT₆ receptor blockade [39].

One of the more consistent findings regarding the involvement of 5-HT₆ receptors in memory is the ability of the 5-HT₆ receptor antagonist to reverse a scopolamine-induced cognitive deficit in the Morris water maze or novel object recognition test [40]. This finding would be in line with the hypothesis that 5-HT₆ receptor functions are mediated, at least partially, by a modulation of the cholinergic neurotransmission. In an extensive study regarding the effects of the 5-HT6 receptor antagonist SB-271046 in mice presenting a scopolamine-induced cholinergic disruption of memory, it was found that SB-271046 was able to reverse the scopolamine-induced deficits in working memory and to reverse the deficits of acquisition and retrieval of aversive learning, whereas scopolamine-induced deficits in episodic-like memory (acquisition and retrieval) were partially counteracted by 5-HT₆ receptor blockade. However, SB-271046 alone failed to affect working memory, recognition memory, and aversive learning performances [39], but it appears that 5-HT₆ receptor blockade is more consistently effective in alleviating memory deficits than increasing memory in normally functioning animals [41]. Interestingly, a combined treatment of SB-271046 with an acetylcholinesterase inhibitor produced an additive increase in passive avoidance and significantly reversed scopolamine-induced amnesic effects [41]. Similarly, this combined administration of subthreshold doses of two novel selective 5-HT₆ antagonists, compounds CMP X and CMP Y, with the acetylcholinesterase inhibitor donepezil (Aricept®, Eisai, Tokyo, Japan) (approved for symptomatic treatment of AD) enhanced memory performance in young Wistar rats with cognitive deficits induced by scopolamine [40]. This suggests that the administration of 5-HT₆ receptor antagonists with acetylcholinesterase inhibitors has potentially additive-enhancing effects on cognition.

Lu AE58054, a 5-HT₆ receptor antagonist, reversed cognitive impairment induced by subchronic phencyclidine in
a novel object recognition test in rats [42]. Ro 04-6790 also reversed impairment in learning consolidation produced by the NMDA receptor antagonist MK-801, and the antagonist PRX-07034 restored the impairment of novel object recognition in the social isolation rearing model, both of which showed behavioral changes that resemble the core defects observed in schizophrenia [11]. SB271046 has also been shown to reverse memory disturbances in experimental models of stress-related psychiatric disorders that have been associated with an impairment of the hypothalamic-pituitary-adrenal axis reactivity [43].

In contrast to the works cited above, those by Russell and Dias [44] and Lindner and colleagues [45] failed to detect any effects of Ro 04-6790 or SB-271046 upon acquisition of an autoshaping task, scopolamine-induced deficits in contextual fear conditioning, or retention of a water maze task. In the same way, two selective 5-HT6 receptor antagonists, Ro-4368554 and SB-258585, showed differential effects on cognition, depending on the paradigm that was used [46]. Both compounds showed cognition-enhancing effects in object recognition, whereas only SB-258585 was able to prevent the scopolamine-induced deficit in the Morris water maze test. Neither Ro-4368554 nor SB-258585 prevented scopolamine-induced impairment in contextual fear conditioning. Similarly, both compounds were ineffective on MK-801-induced deficits in contextual fear conditioning and spatial working memory. In addition, Fone [11], Kendall and colleagues [47], and Meneses and colleagues [4] reported that selective 5-HT6 receptor agonists appear to restore memory impairments in the novel object discrimination paradigm. More intriguing were the results obtained when combining non-active doses of the 5-HT6 receptor agonist E-6801 and the 5-HT6 receptor antagonist SB-271046, which produced an improvement in novel object discrimination. In addition, E-6801, alone and at a non-active dose, was able to synergistically improve the activity of non-active doses of donepezil (an acetylcholinesterase inhibitor) and memantine (an NMDA receptor antagonist) [47]. Thus, both 5-HT6 receptor agonist and antagonist compounds show pro-cognitive activity in preclinical studies, although the explanation for their paradoxically analogous effect is still not clear.

**5-HT6 receptors and Alzheimer’s disease**

Significant reductions in 5-HT6 receptor density in cortical areas of patients with AD have been found, although the reductions in 5-HT6 receptor density were unrelated to cognitive status before death [48]. Since 5-HT6 receptor blockade induces acetylcholine release, reductions in 5-HT6 receptors may represent an effort to restore acetylcholine levels in a deteriorated cholinergic system. In addition, it has been reported that a dysregulation of 5-HT6 receptor activation by 5-HT in the temporal cortex may be related to behavioral symptoms in AD [49]. In this sense, preclinical data suggest a possible role for 5-HT6 receptors in depression and anxiety. Two selective 5-HT6 antagonists (SB-399885 and SB-271046) and donepezil (an acetylcholinesterase inhibitor) were evaluated in the rat forced swimming test because this test is known to identify drugs with antidepressant activity. Systemic administration of the 5-HT6 receptor antagonist produced a significant reduction in the immobility time in the rat forced swimming test, with a similar profile in terms of 5-HT6 receptor occupancy, measured by binding assay. These data suggest that 5-HT6 antagonists, at doses corresponding to those that occupy central 5-HT6 receptors, could have an antidepressant effect in humans. This may differentiate 5-HT6 antagonists from acetylcholinesterase inhibitors with respect to mood control in the symptomatic treatment of AD [50]. However, once again, the results of pharmacological studies are equivocal since both blockade and stimulation of 5-HT6 receptors may evoke antidepressant and anxiolytic-like effects.

A number of 5-HT6 receptor antagonists have successfully undergone phase I clinical studies (healthy volunteers) and some have been evaluated in clinical phase II studies (patients) for the treatment of AD [51]. Two of these compounds appear to be showing positive results. Two phase II trials using SB-742457 (GlaxoSmithKline) have recently been completed in subjects with mild-to-moderate AD. The first was a dose-ranging trial comparing SB-742457 with placebo, and the second was an exploratory study with SB-742457 and donepezil arms. Overall, these studies demonstrated that SB-742457 is well tolerated in patients with AD. SB-742457 produced an improvement in both cognitive and global function in AD as assessed by ADAS-cog (Alzheimer’s Disease Assessment Scale-cognitive subscale) and CIBIC+ (Clinician’s Interview-Based Impression of Change-plus Caregiver Input), respectively [52]. Other clinical phase II studies are being performed, either alone or as add-on therapy with the acetylcholine esterase inhibitor, donepezil. This is the case for Lu-AE-58054 (SGS-518; Lundbeck, Copenhagen, Denmark) or PF-05212365 (SAM-531; Pfizer Inc, New York, NY, USA). Other compounds that are in different phases of clinical trials are SUVN-502 (Suven Life Sciences Ltd., Hyderabad, India) or AVN-322 (Avineuro Pharmaceuticals, San Diego, CA, USA) or PRX-07034 (Epiq Pharmaceuticals, Lexington, MA, USA). In any case, treatment with 5-HT6 receptor antagonists provides symptomatic treatment that might improve cognition, perhaps via modulating neurotransmitter-related mechanisms.

Besides these selective compounds, dimebon (latrepirdine, also known as dimebolin), originally developed as
an antihistamine drug, is worth mentioning. This compound shows good affinity for 5-HT₆ receptors (kᵢ = 34 nM). Dimebon received widespread publicity as a potential therapy for AD following a very positive phase 2 study [53]. However, a more recent multinational phase 3 study showed no improvements [54].

**Concluding remarks**

Since the discovery of 5-HT₆ receptor in 1993 and subsequent development of selective antagonists, a growing number of studies support the use of serotonin 5-HT₆ receptor antagonism as a promising mechanism for treating cognitive dysfunction. Over the past 20 years, several studies with structurally different compounds have shown that not only antagonists but also 5-HT₆ receptor agonists improve learning and memory in animal models. In addition, the potential therapeutic use of 5-HT₆ receptor ligands in mood disorders associated with AD, such as anxiety, depression, or schizophrenia, has been reported. Therefore, ligands acting on 5-HT₆ receptors are attracting attention as potential candidates for the treatment of AD. However, the full characterization of the functional profile of the 5-HT₆ receptor is still pending.

Currently, 5-HT₆ receptors have obvious pharmaceutical potential in terms of related patents. Several 5-HT₆-targeted compounds, mainly antagonists, are regarded as powerful drug candidates for the treatment of a range of neuropathological disorders, including AD [26]. However, the failure of compounds such as dimebon points to the hypothesis that the crucial point regarding compounds acting on 5-HT₆ receptors is the intracellular pathways activated after the interaction of the compound with the receptor. Therefore, perhaps it is a question not only of developing an agonist or antagonist with good affinity but also of developing compounds able to activate the necessary mechanisms for the pro-cognitive effects. It is expected that, in the near future, the drug discovery process will benefit from the complexity of functional responses associated with 5-HT₆ receptors and that new molecules will enter in the scenario of treating AD.

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