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Serotonin 5-HT$_6$ Receptor Antagonists for the Treatment of Cognitive Deficiency in Alzheimer's Disease

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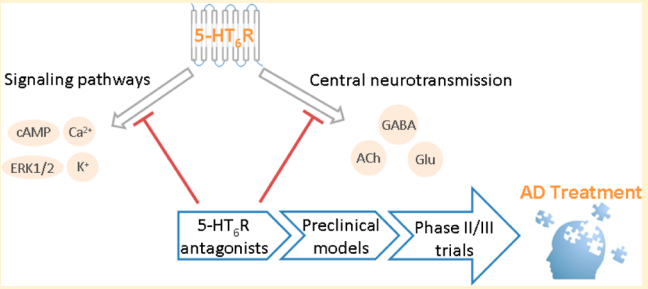
Supporting Information

ABSTRACT: Alzheimer's disease (AD) is one of the most frequent causes of death and disability worldwide and has a significant clinical and socioeconomic impact. In the search for novel therapeutic strategies, serotonin 5-HT$_6$ receptor (5-HT$_6$R) has been proposed as a promising drug target for cognition enhancement in AD. This manuscript reviews the compelling evidence for the implication of this receptor in learning and memory processes. We have summarized the current status of the medicinal chemistry of 5-HT$_6$R antagonists and the encouraging preclinical findings that demonstrate their significant procognitive behavioral effects in a number of learning paradigms, probably acting through modulation of multiple neurotransmitter systems and signaling pathways. The results of the ongoing clinical trials are eagerly awaited to shed some light on the validation of 5-HT$_6$R antagonists as a new drug class for the treatment of symptomatic cognitive impairment in AD, either as stand-alone therapy or in combination with established agents.



1. INTRODUCTION

According to the United Nations and the World Health Organization, a combination of declining fertility and increasing life expectancy is a phenomenon that is resulting in an unprecedented growth of elderly populations worldwide.[1] An unfortunate result of this trend is the concomitant rise in the number of people suffering from age-related neurodegenerative disorders. Today, neurodegenerative diseases are among the most frequent causes of death and disability worldwide and have a significant clinical and socioeconomic impact. One of the most common types of neurodegenerative diseases and the leading cause of dementia is Alzheimer's disease (AD), characterized by progressive and chronic deterioration of cognitive functions, including memory, thinking, and reasoning. Early manifestations of AD include forgetfulness, impaired ability to focus, and changes in mood and personality. As the disease progresses, there is a loss of computational ability, in addition to word-finding problems and difficulty with ordinary activities. Ultimately, the disease leads to severe memory loss, complete disorientation, social withdrawal, loss of independence, and to death within 3−9 years after diagnosis. More than 35 million people worldwide (5.5 million in the United States) are suffering from AD today.[2] The disease ravages the minds of patients, burdens families, and currently costs the American health care system $200 billion a year.[3] Unfortunately, these dramatic statistics are expected to get much worse in the near future; if no new medicines are found to prevent, delay, or stop the progression of AD, the number of people affected in America will jump to 15 million by 2050, according to the Alzheimer's Association. Hence, AD has many dimensions both at the individual level (decreasing quality of life among the elderly) and on societies as a whole, creating a potentially unsustainable economic burden and demand on social systems and health-care related institutions.

In the therapeutic approach to AD, a distinction needs to be drawn between neurodegeneration (the progressive neuronal cell death that causes the pathology) and cognitive impairment (a clinical manifestation of the disease). As in other neurodegenerative diseases, the neuronal cell death goes "hand in hand" with the loss of cognition, and cognitive deficits are the most noticeable symptoms of the disease progression. Medicines currently available for AD do not address the pathological causes of the progressive neurodegeneration but are designed to enhance memory function, alleviating the cognitive symptoms of the disease. These cognition enhancers or "nootropic" drugs would obviously be of greater benefit if administered with the additional therapeutic option represented by neuroprotective agents. Although the underlying mechanism of AD is yet unknown, two key hallmarks involved in the pathogenesis of neurodegeneration in AD are the appearance in the brain of amyloid plaques (abnormal clusters of β-amyloid protein fragments formed extraneuronally) and of neurofibrillary tangles

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(twisted fibers made primarily of tau protein that accumulates intraneuronally).[4,5] These are thought to be the main causes of the disease due to their association with oxidative stress and neuroinflammation, which ultimately contribute to neurodegeneration. Thus, ongoing research is focused on neuroprotective compounds acting as disease-modifying therapies that may stop or slow neuronal apoptosis and subsequent disease progression. These potentially exciting treatments are based on the so-called amyloid cascade hypothesis (vaccines, β- and γ-secretase inhibitors) or tau-neurotoxicity associated drug targets (such as glycogen synthase kinase 3 and presenilin 1).[6−8]

Nevertheless, the primary therapeutic treatment for the symptomatic cognitive loss associated with AD is a cholinergic replacement strategy, represented by four Food and Drug Administration (FDA) approved acetylcholinesterase inhibitors (AcChEIs) (tacrine, donepezil, rivastigmine, and galantamine).[6,9] These drugs are employed to reduce the rate at which acetylcholine is degraded, thereby increasing the concentration of acetylcholine in the brain and combating the cholinergic deficit caused by the death of cholinergic neurons. At present, only the so-called cholinergic hypothesis (more specifically, with AcChEIs) has provided clinical evidence of an adequate level of efficacy and reliability in AD treatment, with the exception of the relatively recent FDA approval of memantine.[9,10] This therapeutic agent is an *N*-methyl-D-aspartic acid (NMDA) receptor antagonist that combats the excessive activation of this receptor by its endogenous agonist glutamate in the brain, a process thought to contribute to the cognitive symptoms of the disease. Memantine may have additional nonsymptomatic benefits compared with AcChEI drugs, since in vitro and in vivo findings suggest its potential neuroprotective effect.[11] Inhibiting the NMDA receptor probably allows regulation of the excess of intracellular calcium levels that result after the excitotoxicity process triggered by an overstimulation of the receptor and contributes to block the cell death cascades. Memantine is recommended both as monotherapy and in combination with AcChEIs, and the latter approach is very commonly used, despite a lack of clear evidence that one approach is superior to the other.[10] For more than a decade, AcChEIs have been widely prescribed for the treatment of cognitive symptoms in AD. However, there are a number of limitations associated with this drug class such as peripheral side effects (nausea, vomiting, diarrhea, and tremors), efficacy only in a limited number of patients, mostly in mild to moderate stages of the disease, and modest benefits in most patients. Substantial opportunity therefore exists for the development of new symptomatic therapies against cognitive dysfunction, with improved efficacy and tolerability.

In this line, there is increasing evidence that shows that alterations in acetylcholine receptors may account for the progression of cognitive decline.[12] The modulation of metabotropic muscarinic acetylcholine receptors (mAcChRs) and ionotropic nicotinic acetylcholine receptors (nAcChRs) is known to facilitate learning and memory processes. Hence, in addition to new AcChEIs, novel cholinergic-based strategies are under preclinical or clinical development and additional studies are needed to assess their therapeutic benefit in cognition disorders.[13] These include mAcChRs ligands (M1 agonists, M2 antagonists, and positive allosteric modulators (PAMs)), and nAcChRs agonists and PAMs.[14,15] Remarkably, AcChEI galantamine, approved for AD treatment, also acts as a PAM of α7 nAcChR.[14]

Although current therapy to treat cognition impairment is focused on relieving acetylcholine deficit, there remains a continued loss of cognitive function that needs to be better addressed and against which acetylcholine-increasing therapies are lacking.[16] Thus, there is an ongoing search for agents that modulate other G-protein-coupled receptors (GPCRs) and that are expected to display advantages over drugs targeting the cholinergic system exclusively. In the search for new medicines to treat cognitive decline in AD patients, dopaminergic, serotonergic, and adrenergic receptors are three classes of GPCRs that may be related to noncholinergic cognitive dysfunction resulting from neuronal toxicity in neurodegenerative diseases, as reported in recent reviews.[17−21] Their modulations stimulate intracellular responses through distinct signal transduction pathways, resulting in the release of different neurotransmitters that can subsequently influence cognition and memory processes. In particular, the serotonergic system has resurfaced as an important player in the field and is suggested to have promise in generating novel therapies for neurodegenerative diseases.[22] Within the seven families of serotonin (5-hydroxytryptamine, 5-HT) receptors (5-HT_{1-7}) there are at least 13 distinct GPCRs.[23] Evidence from preclinical and clinical studies has indicated the role of 5-HT and several of its receptors (especially 5-HT_{1A}, 5-HT_4, and 5-HT_6 subtypes) in different aspects of cognitive dysfunction, such as cognitive deficits, learning, and memory decline.[22,24] Among them, the 5-HT_6 receptor (5-HT_6R) has shown enormous expectation as a drug target for the development of cognitive enhancers, based on localization, pharmacology, and behavioral data accumulated. This manuscript reviews the implication of the serotonin 5-HT_6R in learning and memory processes, focusing on the preclinical and limited clinical studies that describe the promising therapeutic potential of its antagonists for the treatment of cognitive disorders, specifically in AD patients.

2. 5-HT_6 RECEPTORS AND COGNITION

The 5-HT_6R is among the latest identified members of the 5-HT receptor family and is a particularly interesting receptor subtype because of its relatively low level of sequence homology (<50%) compared to other serotonin receptors, unique distribution, intriguing pharmacology, and multiple cellular signaling pathways activated by the receptor in the central nervous system (CNS).[25,26] Although the mechanisms associated with the 5-HT_6R activation/blockade are not completely understood, its ligands have demonstrated possible utility as antidepressant and anxiolytic agents in affective and psychotic disorders, as well as for the treatment of obesity and related metabolic syndrome.[27,28] However, a progressively increasing focus on the 5-HT_6R as a potential target for cognitive disorders has been clearly noted in the past 10 years, as quantified by the number of scientific articles relating to the involvement of this receptor in learning and memory processes. For instance, a search in the Web of Science (Thomsom Reuters) in 2004 for the terms "5-HT_6 and memory or learning or cognitive" produced 145 articles, whereas the same search in 2013 yielded 618 publications. Thus, in the past decade approximately 473 papers have appeared that implicate 5-HT_6 receptors in learning and memory processes. Hence, currently the most promising therapeutic indication for 5-HT_6R ligands is as cognition enhancers in diseases associated with cognitive impairment, such as AD and other neurodegenerative diseases. This topic has been reviewed by several authors.[11,29−38]

Initially cloned by Monsma and Ruat and respective coworkers in 1993,[39,40] the rat 5-HT_6R gene encodes a protein of

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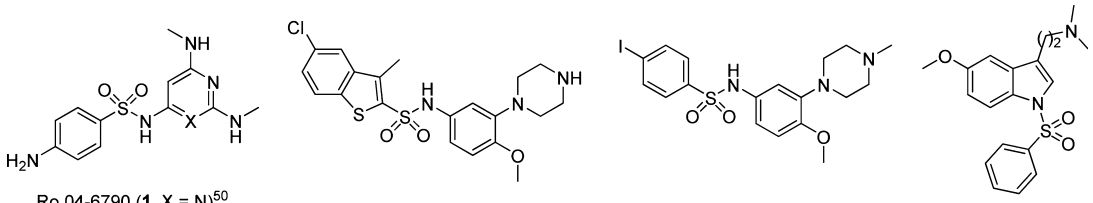

Figure 1. First identified 5-HT_6R antagonists **1**−**5**.

438 amino acids and shares 89% homology with the human form that was cloned by Kohen et al. 3 years later.[41] The 5-HT_6R belongs to the GPCRs superfamily for which an increasing number of crystal structures are available.[42] In particular, the crystal structures of two members of the serotonin family, 5-HT_{1B} and 5-HT_{2B} receptors, bound to ergotamine were released in 2013.[43] All these structures share the common architecture of seven-plasma-membrane-spanning (or transmembrane) domains (TMs, which also term these proteins as 7TM receptors) connected to each other through three extracellular (EL) and three intracellular (IL) loops, as well as a disulfide bridge between EL 2 and TM 3. In addition, GPCRs contain an extracellular N-terminal region and a cytoplasmic C-terminal tail with an α-helix (Hx8) parallel to the cell membrane.

Interestingly, the 5-HT_6R is widely expressed in both rats and humans and is restricted almost exclusively within the CNS, providing the potential that compounds acting through this receptor might have limited peripheral side effects. The distribution of 5-HT_6R protein obtained by immunolocalization and autoradiographic binding studies is in good agreement with the 5-HT_6R mRNA findings from in situ hybridization and Northern blot experiments, with a remarkably similar pattern of expression of the receptors between rat and human brains.[39−41,44−46] The higher density of the 5-HT_6R has been found in striatum, olfactory tubercle, nucleus accumbens, hippocampus, and cerebral cortex. Of particular importance in the study of 5-HT_6 receptors are the low levels and different distribution detected in the mouse brain, compared with rats and humans.[46,47] Such findings would appear to challenge the translational relevance of mouse models for the evaluation of 5-HT_6R ligands. As pointed out earlier, cognition dysfunction is one of the primary manifestations of several neurodegenerative diseases; in particular, cognitive decline is the defining symptom for AD. The localization of 5-HT_6 receptors in brain areas involved in learning and memory processes appears to be the initial hypothesis that identified this receptor as a putative target for AD.

Since the identification and cloning of the 5-HT_6R 2 decades ago, tremendous effort has been made in elucidating the regulation and function of the receptor. Before selective 5-HT_6R ligands were available, antisense oligonucleotides (AOs) targeting 5-HT_6R mRNA were initially used to study the functional role of the receptor. It was found that receptor down-regulation in rats after intracerebroventricular injection of 5-HT_6R AOs resulted in behavioral changes that could be blocked by the muscarinic antagonist atropine, suggesting a modulatory role for the receptor on cholinergic function.[48] Also, administration of 5-HT_6R AOs enhanced retention task performance in normal rats in the Morris water maze reference memory test.[49] These interesting results provided the first indirect evidence suggesting the involvement of 5-HT_6 receptors in cognitive processes.

The significance of the 5-HT_6R blockade was confirmed when the first 5-HT_6R antagonists Ro 04-6790 (**1**),[50] Ro 63-0563 (**2**),[50] and SB-271046 (**3**)[51,52] (Figure 1) were discovered in the late 1990s. Similar to the AOs studies, administration of these antagonists led to an increase in behaviors that could be reversed by muscarinic antagonists, then appearing to be mediated by increased cholinergic neurotransmission in the CNS.[53,54] This inhibitory role of the 5-HT_6R in acetylcholine neurotransmission supported the functional implication of 5-HT_6 receptors in memory and learning processes. Thus, the 5-HT_6R as an attractive drug target in cognitive disorders became apparent after similar results were obtained for administration of either an AO or a 5-HT_6R antagonist.

The availability during the following years of a number of potent and selective 5-HT_6R antagonists (see section 3) allowed studies of the receptor function in much greater detail. To date, a plethora of preclinical studies with these tool molecules have provided compelling evidence that 5-HT_6 receptors are involved in cognition. Indeed, pharmacological blockade of the 5-HT_6R has been shown to produce significant procognitive effects in a number of learning paradigms in animal models, including water maze, autoshaping task, passive avoidance, fear conditioning, spatial learning, novel object recognition, and social recognition tests (see section 4).

These behavioral studies, however, did not elucidate the neurochemical mechanisms by which the 5-HT_6R is able to influence cognitive function, which are still under investigation. Selective lesioning studies have described that 5-HT_6 receptors are not present in serotonergic neurons of the raphe, indicating a probable postsynaptic role for these receptors that do not act as autoreceptors (i.e., receptors that regulate their own neurotransmitter release).[55] Therefore, 5-HT_6 receptors appear to be located in neurons that are not serotonergic. Microdialysis studies have shown that cognitive-enhancing 5-HT_6R antagonists have the ability to cause a significant increase in acetylcholine levels, as well as to reverse cognition deficits elicited after the administration of anticholinergic agents.[56,57] These studies supported the serotonergic−cholinergic interaction observed in the behavioral studies and further confirmed the role of the 5-HT_6R in the cholinergic system, which has been consistently described as one of the most important mechanisms pertaining to AD.

However, a paucity of 5-HT_6 receptors localized on cholinergic neurons has been reported,[57] suggesting that the effects of 5-HT_6R antagonists could be mediated by other neurotransmitters. In fact, additional in vivo microdialysis studies have revealed that in addition to the functional role in the cholinergic system, the 5-HT_6R may also play a role in other neurotransmission systems, which can possibly contribute to the

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effects of receptor antagonists in memory and cognition processes. Thus, in vivo treatment with a 5-HT$_6$R antagonist resulted in increases of the extracellular levels of the excitatory amino acid glutamate in rat brain.[58] On the contrary, 5-HT$_6$R activation attenuated stimulated glutamate levels elicited by high KCl treatment.[59] This provided evidence of a direct or indirect modulatory role of the 5-HT$_6$R in the glutamatergic neurotransmission system, known to participate in learning and memory processes. The involvement of the 5-HT$_6$R in the glutamatergic system was further confirmed by a behavioral study in rats where pretreatment with the noncompetitive NMDA receptor antagonist dizocilpine (MK-801) prevented the procognitive effect of 5-HT$_6$R antagonist **1** in a novel object recognition test.[60] These findings suggest an important therapeutic potential for the use of 5-HT$_6$R antagonists in ameliorating the loss of glutamatergic neurons observed in AD patients.

Finally, another key component in the activity profile of 5-HT$_6$R antagonists may be their ability to modulate the γ-aminobutyric acid (GABA) receptor, considering that 5-HT$_6$ receptors have been found to be expressed on GABAergic neurons.[61] In a microdialysis study, administration of a 5-HT$_6$R agonist caused release of the neurotransmitter GABA in rat cortex. This response was blocked when the animals were pretreated with a 5-HT$_6$R antagonist, suggesting a relationship between the receptor and GABAergic activity.[62] Considering that GABA release causes inhibition of glutamatergic transmission, it is postulated that the blockade of 5-HT$_6$ receptors will result in enhancement of excitatory neurotransmission and subsequent improvement of cognition performance.

It is well-known that learning and memory potentiation is related to both increased excitatory activity in glutamatergic systems and decreased inhibitory activity in GABAergic systems.[63] Therefore, on the basis of all these data from releasing experiments, it can be suggested that the memory and cognitive enhancement by 5-HT$_6$R antagonists is possibly achieved through modulation of multiple neurotransmitter systems, including at least serotonergic, cholinergic, glutamatergic, and GABAergic systems (Figure 2).[37]

Further evidence in support of the role of 5-HT$_6$ receptors in memory and learning is presented by studies during which learning paradigms decreased 5-HT$_6$R expression in rat brain,[64,65] whereas overexpression of 5-HT$_6$ receptors in the striatum led to cognition impairment in a learning model.[66] Furthermore, the authors were able to reverse the effects of the memory dysfunction by the administration of the highly selective 5-HT$_6$R antagonist SB-258585 (**4**)[52] (Figure 1). In humans, the expression of 5-HT$_6$ receptors was also investigated, and a significant decline in the receptor density was found in the cortex of post-mortem AD patients with respect to control subjects.[67] However, conflicting results were obtained for the correlation of the decrease in 5-HT$_6$R density with the cognitive status of the patients before death.[37]

Finally, a silent polymorphism at base pair 267 (C267T) was identified at the human 5-HT$_6$R,[41] and subsequently a significant increase in this allele was found in AD patients in a comparative study with control subjects.[68] This association study suggested that the C267T allele might have clinical importance as a genetic risk factor for AD. These findings, however, have not always been replicated, and the significance of this 5-HT$_6$R polymorphism on cognition-related syndromes has not yet been determined.[69,70]

Despite the volume of positive data that have been generated in behavioral, neurochemical, and localization studies, relatively limited understanding is available on the precise mode of action of 5-HT$_6$R antagonists at the level of biochemical pathways. Of importance is that surprisingly, 5-HT$_6$R agonists such as R-13c (2-chloro-*N*-(3-{[(2*R*)-1-methylpyrrolidin-2-yl]methyl}-1*H*-indol-5-yl)benzenesulfonamide), E-6801 (6-chloro-*N*-{3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl}imidazo[2,1-*b*][1,3]-thiazole-5-sulfonamide), and WAY-181187 (*N*-[3-(2-amino-ethyl)-1*H*-indol-5-yl]-6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonamide) have also been reported to possess procognitive activities in animal models such as novel object recognition and social recognition tests.[24,59] Although it is difficult to interpret that activation and inhibition of the receptor may evoke similar responses, the mechanism for paradoxically similar effects of agonists and antagonists on cognition could be related to the existence of alternative biological signaling pathways triggered by 5-HT$_6$ receptors.

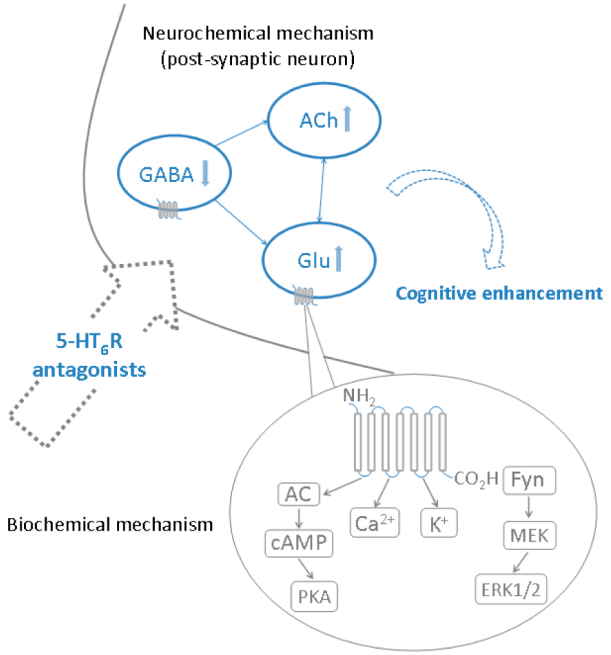

Figure 2. Neurochemical and biochemical mechanisms involved in the blockade of 5-HT$_6$ receptors that are thought to contribute to the cognitive enhancement induced by 5-HT$_6$R antagonists (adapted with permission from Figure 1 in ref 37. Copyright 2011, Elsevier).

It is well-known that the 5-HT$_6$R is a GPCR positively coupled to the stimulatory G (Gs) protein, meaning that upon agonist (first messenger) activation, adenylyl cyclase (AC) is stimulated to convert ATP to cyclic AMP (cAMP),[71] which in turn acts as second messenger in the cell by activating protein kinase A (PKA) (Figure 2). In fact, AC activity confers the classical definition as agonist/antagonist upon 5-HT$_6$ receptors and measurements of cAMP formation are the most widely reported index of activity for described 5-HT$_6$R ligands. However, it appears that the definition of the functional activity of the compounds showing affinity for 5-HT$_6$ receptors depends on the biological system used, ranging in some cases from antagonism to agonism at the same receptor. Accordingly, the coupling of 5-HT$_6$ receptors to other G proteins (Gi/o or Gq) has also been recently reported, and Ca^{2+} signaling by using a chimeric G protein has been described.[72] In addition to the G-protein-linked system activating cAMP signaling pathways, at least two other second-messengers systems have been reported for 5-HT$_6$ receptors. Their activation triggers phosphorylation of the

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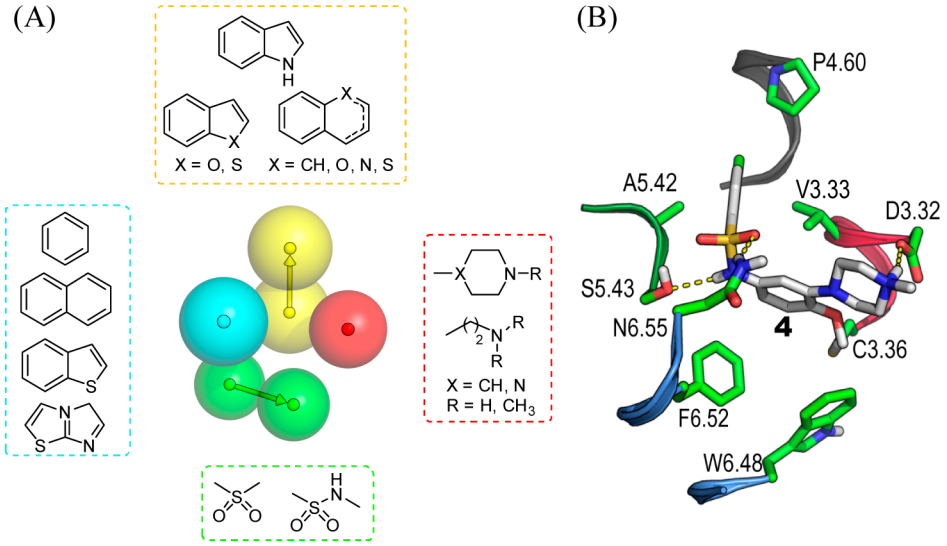

Figure 3. (A) Main structural moieties covering common pharmacophore features of 5-HT$_6$R antagonists. The pharmacophoric elements are a positive ionizable atom (PI, red), a hydrogen bond acceptor group (HBA, green), a hydrophobic site (HYD, blue), and an aromatic-ring hydrophobic site (AR, gold). The HYD and PI features are drawn as globes, whereas HBA and AR features are shown as two globes due to the directional nature of these chemical functions (see ref 92). (B) Molecular model of antagonist **4** in complex with a 5-HT$_{1B}$R-based homology model of the 5-HT$_6$R (see ref 97). In this model the positively charged group (PI) interacts with D3.32 while the sulfonamide group (HBA) hydrogen-bonds S5.43 and N6.55 in agreement with the model reported by Hirst et al. for sulfonamide analogues (see ref 46). In other models the interaction of the ligand with D3.32 is maintained, but Pullargurla et al. have proposed that arylsulfonyl-containing antagonists might bind in a domain (toward TM 7) different from agonists (see ref 95), while Dukat et al. have proposed that sulfonyl oxygens hydrogen bond S3.37 and T5.46 (see ref 96). The amino acids of the 5-HT$_6$R are shown in green, and the ligand is shown in white. The color code of the helices is TM 3 in red, TM 4 in gray, TM 5 in green, and TM 6 in blue.

extracellular regulated kinase 1/2 (ERK1/2) via Fyn, a member of the Src family of non-receptor protein-tyrosine kinases.[64,73] The third signaling pathway mediated by 5-HT$_6$ receptors is associated with K^+ channels.[74]

An important aspect in the definition of agonist/antagonist in different biological systems is the much lower (about 30 times) density of 5-HT$_6$ receptors in native tissues than in recombinant cells.[75] Since such definition depends on receptor and G protein densities, the use of cloned cells may be misleading.[25] Another consideration that may account for the apparent inconsistencies reporting similar pharmacological properties shared by 5-HT$_6$R agonists and antagonists comes from preclinical and clinical studies that have suggested that agonists and antagonists could be able to act on receptors located on distinct neuronal populations.[76] Therefore, in the case of the 5-HT$_6$R, there is a considerable amount of uncertainty regarding the functionality of many ligands, and consequently, a degree of caution needs to be exercised when attempting to define pharmacological effects as being agonist-, antagonist-, or inverse-agonist-mediated.

Overall, the potential therapeutic effects of modulating 5-HT$_6$ receptors are still unclear. However, it needs to be noted that to date there is a general agreement that 5-HT$_6$R antagonists enhance memory and learning, the strongest data coming from preclinical models (see section 4).

3. MEDICINAL CHEMISTRY OF 5-HT$_6$R ANTAGONISTS

Shortly after its cloning, 5-HT$_6$R became an attractive target for drug discovery since some classical serotonergic agents, such as 5-methoxytryptamine, and several antipsychotic and antidepressant drugs (e.g., bromocriptine, clozapine, olanzapine, loxapine, chlorpromazine, fluophenazine) showed moderate affinity (K_i < 50 nM) for this receptor.[39,77−80] The intense search carried out since then by medicinal chemists has allowed the identification of more than 1000 5-HT$_6$R ligands (see Thomson Reuters Integrity Database), most of them characterized as antagonists, and the exploration of new compounds as 5-HT$_6$R ligands continues.

In addition to the identification of new ligands, several efforts have been done in the development of chemical tools based on 5-HT$_6$R antagonists, such as selective radiolabeled ligands for positron emission tomography (PET), reviewed by Zimmer and Le Bars,[81] and fluorescent probes that enable the direct visualization of this GPCR in complex biological systems. For instance, [^{11}C]GSK215083 (3-[(3-fluorophenyl)sulfonyl]-8-(4-methylpiperazin-1-yl)quinoline) has been used as a PET tracer to measure the human whole-body distribution of this antagonist,[82] and dansyl or biotin probes based on ligand **3** has allowed the visualization of the human 5-HT$_6$R in transiently transfected COS7 cells.[83]

The first selective 5-HT$_6$R antagonists **1**,[50] **2**,[50] and **3**[51,52] were identified in the late 1990s by high-throughput screening (HTS) at Roche and GlaxoSmithKline (Figure 1). The three of them are bisaryl sulfonamides with a basic amino group. Soon afterward, Glennon et al., one of the pioneers in the synthesis of 5-HT$_6$R ligands, developed MS-245 (**5**),[84,85] the first indole molecule based on the endogenous ligand 5-HT. This antagonist was concurrently discovered by Merck Sharp & Dohme.[86] Since then, several research groups have contributed to the development of structurally different 5-HT$_6$R antagonists (as summarized in recent reviews).[33,35,87−91] Structure−activity relationship (SAR) studies as well as complementary methodologies of drug design such as pharmacophore-based[92−94] and homology models[46,95−97] have allowed the identification of four common key structural elements for 5-HT$_6$R antagonism: a positive ionizable atom (PI), an aromatic ring-hydrophobic site (AR), a hydrogen bond acceptor group (HBA), and a hydrophobic site (HYD) (Figure 3A). The PI, a nitrogen atom protonated at physiological pH, is generally represented by a piperazine or a (dimethylamino)ethyl fragment. The AR region is mainly

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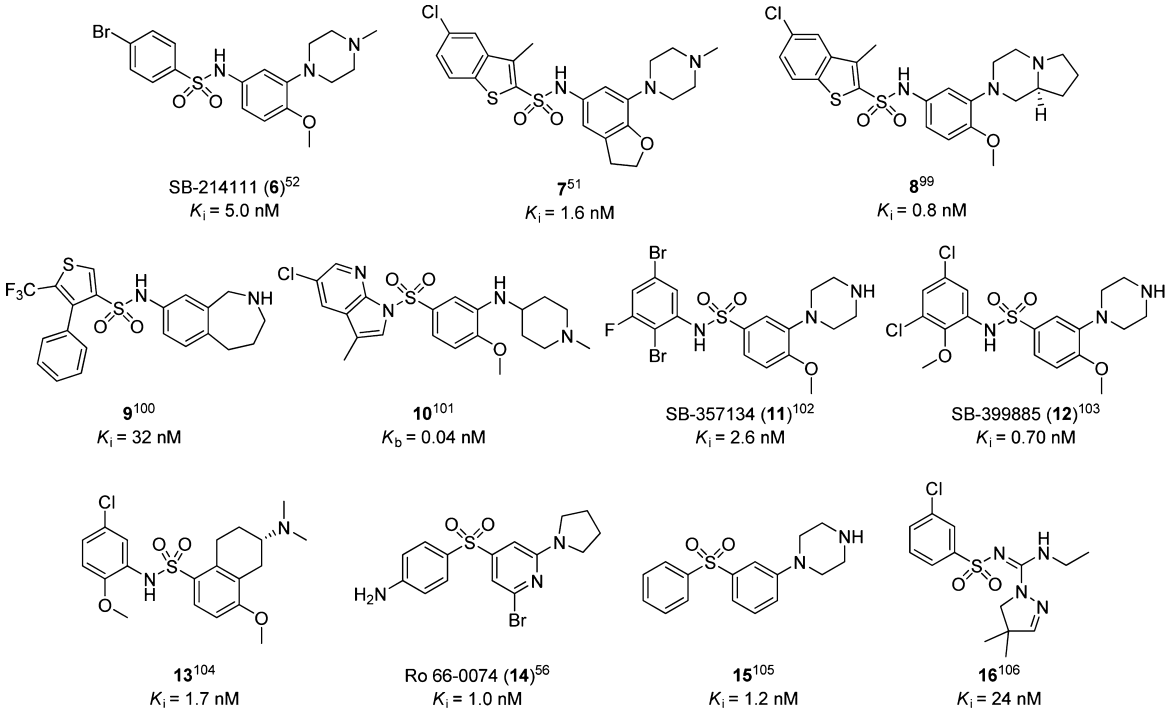

Figure 4. Representative bisaryl sulfonamides **6**–**16** characterized as 5-HT$_6$R antagonists.

occupied by indole or indole-like cores, including a number of mono- or bisaryl π-electron donor aromatic or heteroaromatic systems. The HBA is nearly always a sulfonamide or sulfone group, and the HYD is open to diverse hydrophobic aromatic rings, such as benzene, naphthalene, benzothiophene, or imidazo[2,1-*b*]thiazole. In particular, compound **4** contains the common piperazine ring as the PI pharmacophore element, a methoxyphenyl system as AR, a sulfonamide group as HBA, and a 4-iodophenyl ring as HYD. The binding mode of the pharmacophoric elements of **4** to the 5-HT$_6$R was explored by site-directed mutagenesis and molecular models of the ligand–receptor complex.[97] As shown in Figure 3B, D3.32 anchors the protonated piperazine ring, the methoxyphenyl system interacts with F6.52 and C3.36, the sulfonamide group hydrogen-bonds both S5.43 and N6.55, and the substituted benzene interacts with the hydrophobic side chains of V3.33 and A5.42. In addition to these amino acids, W3.28 and T5.46 have been proposed to interact with tryptamine and ergoline compounds.[78,98]

Taking into account the different moieties that may occupy the common pharmacophoric features, 5-HT$_6$R antagonists can be classified into four structural families: bisaryl sulfonamides, indoles, indole-like derivatives, and non-sulfonyl compounds.

Bisaryl Sulfonamides. After the discovery of antagonists **1** and **2** (Figure 1), a number of related bisaryl sulfonamides have been reported (Figure 4). Arylpiperazine SB-214111 (**6**) was identified by HTS as a 5-HT$_6$R antagonist (IC$_{50}$ = 16 nM), highly selective over 50 receptors, enzymes, and ion channels, displaying moderate brain exposure (brain/plasma ratio = 0.25) and low oral bioavailability (F = 12%).[52] This finding promoted an extensive SAR around this hit showing that lipophilic arylsulfonyl moieties, such as halogen-substituted aromatic rings [e.g., 4-iodophenyl derivative **4** (Figure 1)], were beneficial for 5-HT$_6$R affinity. Thus, the 5-chloro-3-methylbenzothiophene system was found to be an optimal aromatic system, which provided analogue **3** (Figure 1) as an antagonist with excellent potency (IC$_{50}$ = 2.0 nM), moderate half-life ($t_{1/2}$ = 4.8 h), and excellent oral bioavailability (F > 80%) in rat, although its major drawback was again a poor brain penetrability (brain/plasma ratio = 0.1).[52] Additional modifications carried out within this family of compounds involved the development of conformationally constrained derivatives with better pharmacokinetic (PK) profile. Thus, 2,3-dihydrobenzofuran **7**[51] can be considered as a tethered analogue of the 4-methoxyphenyl central core (present in compounds **3**, **4**, and **6**), and bicyclic piperazines such as **8**[99] were synthesized to block the N-dealkylation observed during metabolism studies carried out in the methylpiperazine series (e.g., **6**).[52] In this line, AstraZeneca has also contributed to this family of antagonists with tetrahydrobenzazepines such as **9**[100] and Suven Life Sciences has recently designed the constrained compound **10** to improve brain penetration due to the lack of hydrogen bond donor capability of the tertiary sulfonamide group.[101] Indeed, this compound exhibited an adequate brain penetration (brain/plasma ratio = 0.9), good PK profile in rat and dog, no cardiotoxicity (hERG liability), and activity in rat models of cognition (3 mg/kg, po) as well as in brain microdialysis studies (10 mg/kg).[101]

On the other hand, further studies around the sulfonamide linkage demonstrated that reverse sulfonamides or sulfones also retained the 5-HT$_6$R binding affinity. Antagonist SB-357134 (**11**) showed good oral bioavailability (F = 65%) and moderate brain exposure (brain/plasma ratio = 0.19),[102] whereas SB-399885 (**12**) was later characterized as a potent, selective, brain-penetrant, and orally active 5-HT$_6$R antagonist with in vivo efficacy in rat models of cognition (see section 4).[103] Other examples of reverse sulfonamides are tetrahydronaphthalene derivatives such as **13**.[104] Replacement of the sulfonamide by a sulfone group led to the pyrrolidine Ro 66-0074 (**14**), which was characterized as a full antagonist (IC$_{50}$ = 3.2 nM), selective against other 5-HT receptors, and showed good PK properties and moderate brain penetrability (brain/plasma ratio = 0.24).[56] Interestingly, sulfone **15** represents one of the smallest 5-HT$_6$R

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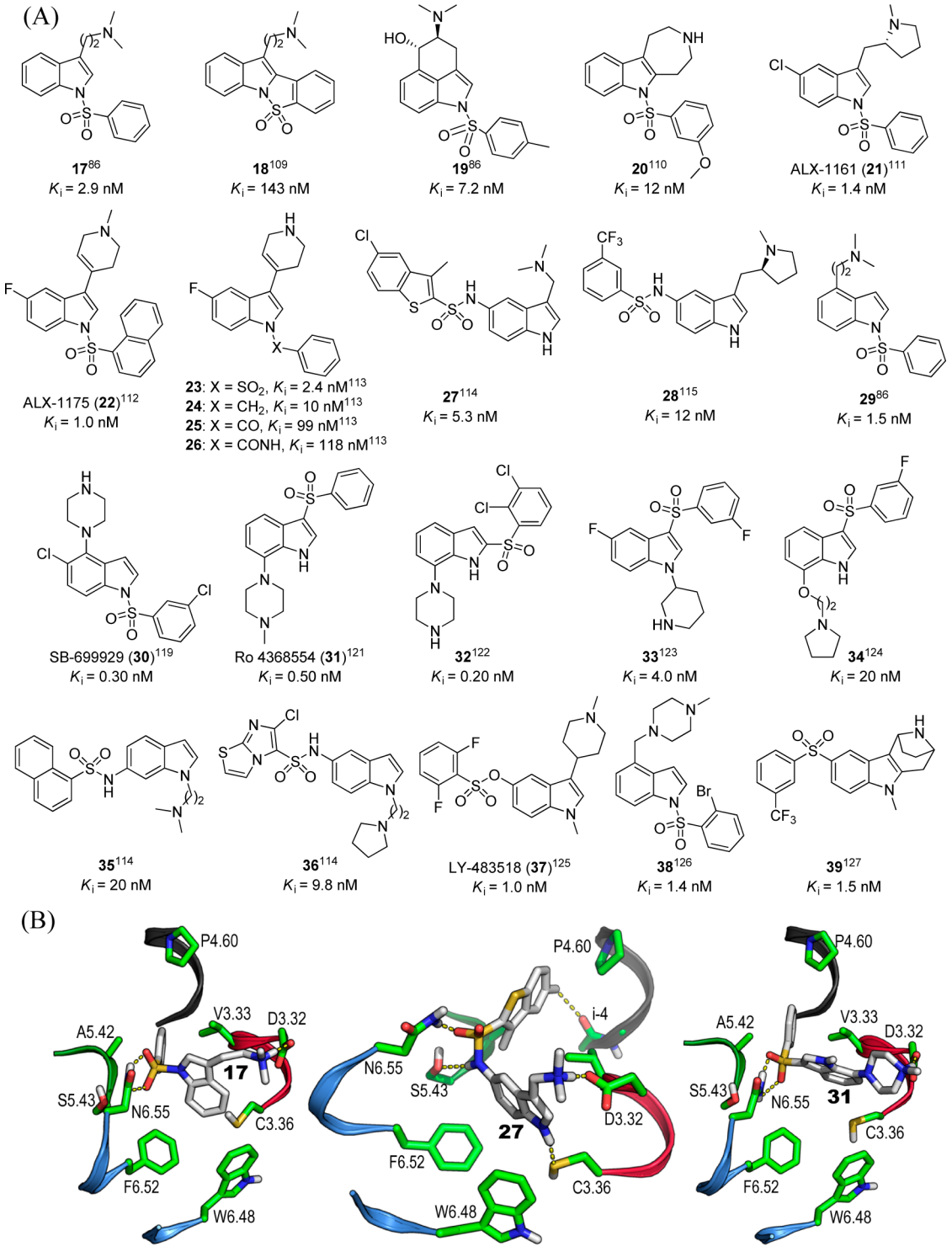

Figure 5. (A) Representative indole derivatives **17**–**39** characterized as 5-HT_6R antagonists. (B) Molecular models of compounds **17**, **27**, and **31** in complex with the 5-HT_6R. SAR studies within this family indicate that the arylsulfonyl (HBA) and the alkylamino (PI) moieties can be attached to several positions of the indole scaffold (AR). These molecular models exemplify this finding showing that the AR system must hold the HBA and PI elements in the proper orientation to interact with N6.55 and D3.32, respectively. Moreover, the indole ring forms aromatic–aromatic interactions with F6.52 and W6.48 (see models of **17** and **27**) and in some cases hydrogen-bonds C3.36 (see model of **27**). The key protonated amine group (PI) might be incorporated at different chemical scaffolds, being the only requirement to be capable of forming an ionic interaction with D3.32 (see models of **17**, **27**, and **31**). Sulfone and sulfonamide groups are permitted as HBA pharmacophoric element. The model of the complex between the receptor and compound **27** shows that the NH group of the sulfonamide forms an additional hydrogen bond with S5.43. The terminal substituted ring (HYD) expands toward TM 4 interacting with V3.33 and A5.42. Importantly, halogen substituted aromatic rings are beneficial for affinity. Compound **27** in complex with the receptor shows that the chlorine atom forms a halogen bond interaction with the free carbonyl at position i-4 from P4.60. The color code is as in Figure 3B.

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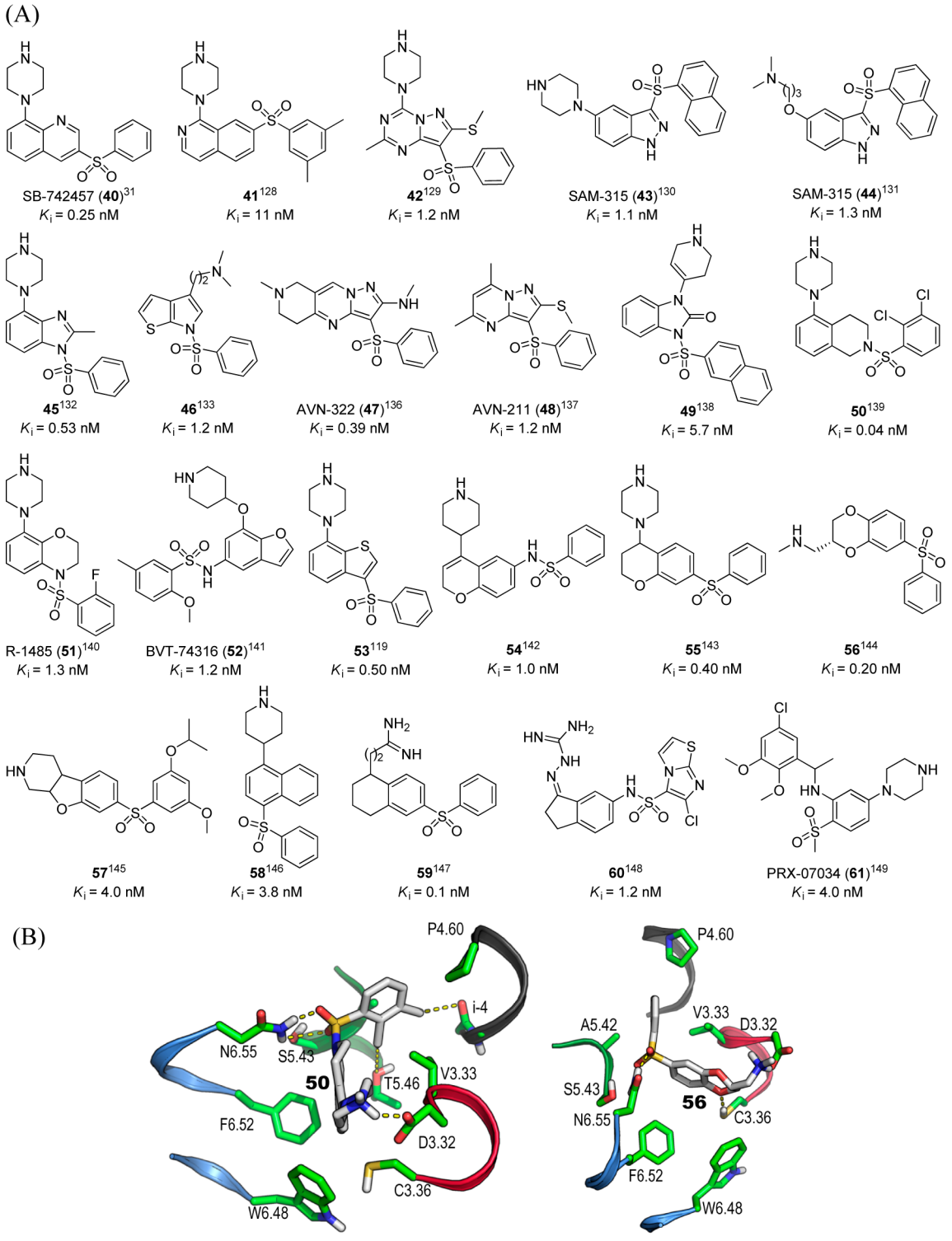

Figure 6. (A) Representative indole-like derivatives **40**–**61** characterized as 5-HT$_6$R antagonists. (B) Molecular models of compounds **50** and **56** in complex with the 5-HT$_6$R. Indole-like derivatives follow the same trend as indoles (see Figure 5B); any chemical scaffold (AR) that positions PI and HBA at the proper orientation to interact with D3.32 and N6.55, respectively, is beneficial for 5-HT$_6$R affinity. This AR system forms aromatic−aromatic interactions with W6.48 or/and F6.52 and optionally hydrogen-bonds C3.36. Moreover, compound **50** in complex with the receptor represents an example where two halogen atoms can be attached to the terminal aromatic ring (HYD). In this case both chlorines form halogen bond interactions with T5.46 and the free carbonyl at position i-4 from P4.60. The color code is as in Figure 3B.

antagonists that fulfils the four key features of the pharmacophore model.[105]

One of the most recent additions to the bisaryl sulfonamide family cames from Abbott Healthcare Products, which has identified the *N*′-(sulfonyl)pyrazoline-1-carboxamide scaffold as a promising core for 5-HT$_6$R antagonism in a HTS campaign focused on neutral compounds in order to potentially improve off-target selectivity compared to the predominant basic scaffolds previously reported.[106] The optimized compound **16** was characterized as an antagonist with high selectivity against 103

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receptors, ion channels, neurotransmitter transporters, and enzymes. The lack of hERG affinity, good PK profile, and moderate brain penetrability (brain/plasma ratio = 1.0) promoted the in vivo investigation of **16** in rat models for episodic memory, which showed that this compound ameliorated the scopolamine-induced deficits in object recognition tests (3 mg/kg, ip).[107]

Indoles. Design of 5-HT$_6$R ligands based on serotonin and 5-methoxytryptamine led to the identification of *N*-[2-(2-ethyl-5-methoxy-1*H*-indol-3-yl)ethyl]-*N*,*N*-dimethylamine (EMDT) as a selective agonist at the beginning of the 2000s.[84] In this family of indole derivatives, N-alkylation with small chains was found to be detrimental for the affinity,[84] whereas larger substituents such as benzyl were tolerated;[108] more interestingly, arylsulfonyl groups provided full antagonists with low nanomolar affinity. Among these new antagonists, the above-mentioned indole **5** (Figure 1) was the first potent and selective contribution to this family. Afterward, the huge number of SAR studies carried out around indoles converted these derivatives into one of the most studied and recurring chemical motifs present in many 5-HT$_6$R ligands (Figure 5A).

Thus, removal of the methoxy group at the 5-position of indole in compound **17** demonstrated that this substituent was not essential for binding [K_i(**5**) = 2.3 nM vs K_i(**17**) = 2.9 nM].[86] In general, attempts to make constrained derivatives by tethering the sulfonyl group to the indole core (e.g., **18**) were unsuccessful,[109] whereas the alternative restriction of the amino moiety in the indole to give derivatives **19**[86] and **20**[110] was tolerated. Moreover, pyrrolidine and tetrahydropyridine derivatives such as ALX-1161 (**21**)[111] and ALX-1175 (**22**)[112] were developed by Allelix-NPS Pharmaceuticals. These compounds are potent antagonists [IC_{50} (**21**) = 8.5 nM, IC_{50} (**22**) = 24 nM] with high selectivity, reasonable oral bioavailability in rats [F (**21**) = 17%, F (**22**) = 19%], and excellent brain exposure (brain/plasma ratio = 23 and 43, respectively). Cole et al. also reported piperidine and tetrahydropyridine derivatives such as **23** and pointed out that replacement of the sulfonyl group in derivatives **24**–**26** by methylene, carbonyl, or amide moieties was detrimental for the affinity.[113]

On the other hand, Holenz at Esteve and Cole at Wyeth independently found in 2005 that highly potent antagonists such as **27**[114] and **28**[115] could be obtained by shifting the sulfonyl group from 1- to 5-position of the indole (see Figure 5B for a model of the 5-HT$_6$R in complex with **27**). Russell and co-workers showed that migration of the dimethylaminoethyl chain from 3- to 4-position yielded as well potent antagonists such as **29**,[86] whereas Roche,[116] GlaxoSmithKline,[117] and Biovitrum[118] simultaneously discovered 4-piperazinyl-1-sulfonylindoles. Among them, SB-699929 (**30**) stands out as a subnanomolar antagonist with high selectivity (>100-fold against a range of 50 receptors), excellent oral bioavailability (F = 49%), and good brain exposure (brain/plasma ratio = 3).[119] Extensive SAR studies carried out subsequently have demonstrated that the arylsulfonyl and alkylamino moieties can be attached to nearly all positions of the indole scaffold without loss of affinity [e.g., Ro 4368554 (**31**),[120,121] **32**–**36**[114,122−124]]. Indeed, no clear trend of the optimal position neither for the sulfonyl nor for the basic amine can be drawn, although the spatial orientation between these groups is critical to obtain high-affinity ligands (see Figure 5B for models of the 5-HT$_6$R in complex with **17**, **27**, and **31**). Like in the bisaryl sulfonamide family, it is important to mention that sulfone (i.e., **31**–**34**)[121−124] or sulfonamide groups (**35**, **36**)[114] can be indistinctly found as HBA in the indole family. Moreover, sulfonic esters have been reported by Eli Lilly without loss of affinity [e.g., LY-483518 (**37**)].[125]

One of the latest contributions to the indole family came from Suven Life Sciences and AMRI Global. Suven has reported several series of 1-sulfonylindoles bearing the amino group at 3- or 4-position of the central core. Among them, derivative **38** showed excellent brain penetration (brain/plasma ratio = 20) and good PK profile and oral bioavailability (F = 29%).[126] Although this antagonist exhibits moderate potency (IC_{50} = 135 nM) at the receptor, it was active in rat models of cognition and is being evaluated for further development.[126] Henderson et al. showed that the scaffold of epiminocyclohepta[*b*]indole, a constrained derivative with the amino group anchored to 2- and 3-positions of indole, is able to interact with the 5-HT$_6$R. Enantiomer (+)-**39** is one of the most active compounds of this series with favorable in vivo PK properties (e.g., $t_{1/2}$ = 10 h), excellent oral exposure (F = 91%), and moderate brain penetrability (brain/plasma ratio = 1.3) in rat.[127]

Indole-like Derivatives. The next step in the development of new structurally diverse 5-HT$_6$R antagonists was the assessment of the role of indole as central core. Indeed, numerous SAR studies carried out in indole derivatives suggest that the central core of indole is merely acting as a template to hold the rest of the pharmacophoric elements in the appropriate orientation to effectively interact with the receptor. Therefore, other scaffolds leading to similar topographical orientations of the arylsulfonyl moiety and the basic amino group should render biomimetic analogues of indole-type ligands. Thus, several bicyclic and tricyclic systems were employed as indole biomimetics, maintaining similar substitution patterns for the other key features. Once again, sulfonamides, reverse sulfonamides, and sulfones were used as HBA and gave equally potent antagonists (Figure 6A).

Several research groups have worked in the replacement of indole by other N-heterocycles. GlaxoSmithKline reported quinoline derivatives such as SB-742457 (**40**), a potent antagonist, with high selectivity (>100-fold vs 84 receptors, enzymes, and ion channels), excellent oral bioavailability (F = 76%) in rat, moderate brain penetrability (brain/blood ratio = 0.5),[31] and in vivo efficacy in rat models of cognition (see section 4). Isoquinoline **41**,[128] pyrazolotriazine **42**,[129] indazoles SAM-315 (**43**)[130] and SAM-531 (**44**),[131] benzimidazole **45**,[132] and thienopyrrole **46**[133] are alternative examples of indole bioisosteres reported by Biovitrum, Roche, or Wyeth. In the past few years, Ivachtchenko and co-workers have identified a large number of pyrazolopyrimidines as 5-HT$_6$R antagonists [e.g., AVN-322 (**47**) and AVN-211 (**48**)].[134−137] Interestingly, both compounds exhibit excellent selectivity (>2500-fold) within a panel of more than 65 relevant therapeutic targets including GPCRs, ion channels, and neutrotransmitter transporters and are currently being evaluated in phase I clinical trials for AD (see section 5). Moreover, fused aromatic/nonaromatic systems such as dihydrobenzimidazolones (e.g., **49**),[138] tetrahydroisoquinolines (e.g., **50**),[139] and bezoxazine derivatives [e.g., R-1485 (**51**)][140] have also been reported to provide potent 5-HT$_6$R antagonists.

Regarding heterocycles bearing oxygen and sulfur, some benzofuran and benzothiophene analogues were found to be as potent as their corresponding indole counterparts. Moreover, replacement of NH by O or S should improve brain penetration because of the decrease in the number of hydrogen bond donor groups in the molecule. BVT-74316 (**52**)[141] and **53**[119] are representative examples of these non-nitrogen containing

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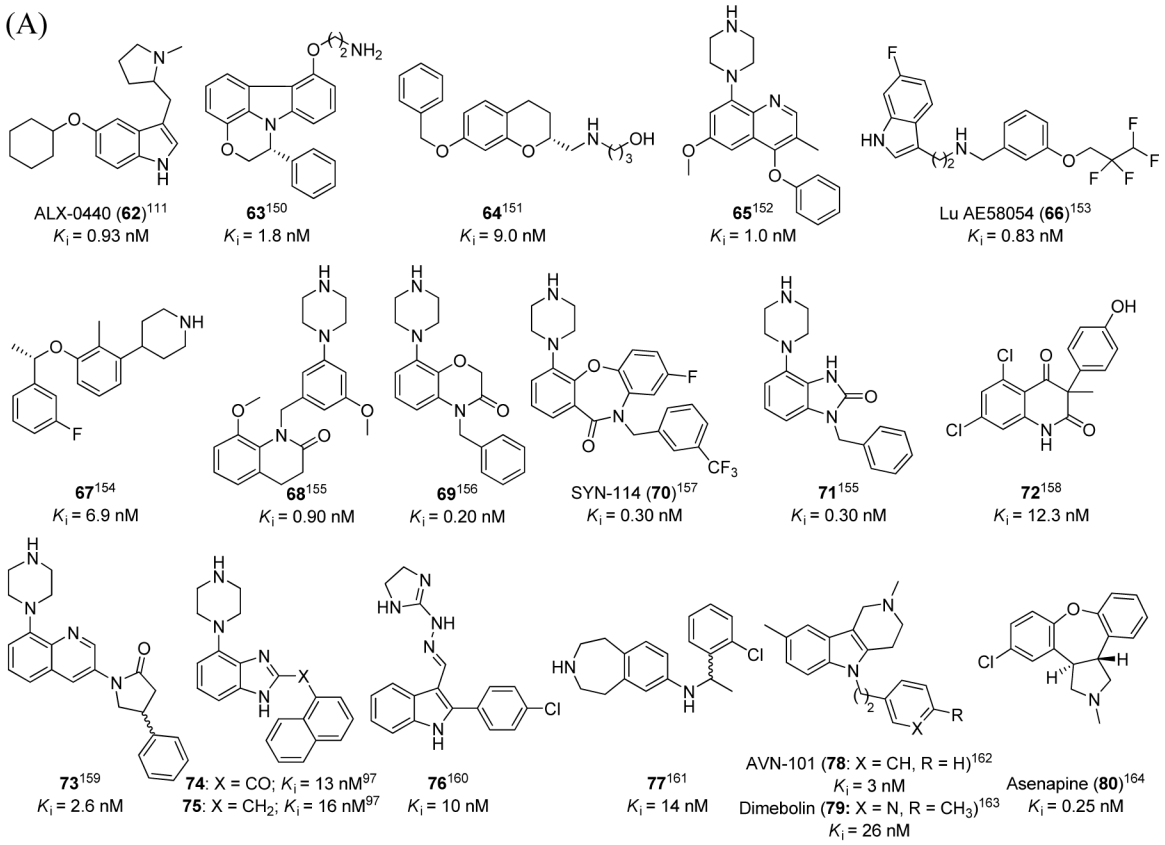

Figure 7. (A) Non-sulfonyl compounds **62**–**80** characterized as 5-HT_6R antagonists. (B) Molecular models of compounds **65**, **71**, and **75** in complex with the 5-HT_6R. The PI and AR pharmacophoric elements expand from TM 3 to TM 6 and the orientation of the molecule must allow the HBA element to interact with N6.55 and the HYD region to expand toward TM 4. Sulfonamide and sulfone groups are optimal for this purpose (see Figures 3B, 5B, and 6B), although there are other chemical moieties that can achieve similar geometrical features. For instance, in compound **65** the phenoxy moiety allows the methoxy group (HBA) to hydrogen-bond N6.55, while the phenyl ring (HYD) points toward TM 4. Similarly, the carbonyl group (HBA) of the benzimidazolone ring in compound **71** interacts with N6.55, while the methylene orientates the phenyl ring to occupy the HYD region. In the case of compound **75** the NH group of the benzimidazole ring can hydrogen-bond N6.55 (acting now as hydrogen bond acceptor), whereas the naphthalene ring (HYD) points toward TM 4. The color code is as in Figure 3B.

scaffolds. Chromenes and chromanes (e.g., **54**,[142] **55**[143]) as well as 1,4-benzodioxins such as **56**[144] have also been employed as indole mimics. Worldwide Discovery Research has recently described a series of hexahydrobenzofuropyridines as high-affinity ligands. Among them, derivative **57** was characterized as a potent and selective antagonist (IC_{50} = 67 nM) with good oral bioavailability (F = 39%) and brain penetration (brain/plasma ratio = 2.8) and displayed in vivo activity in the rat social recognition test.[145]

Interestingly, not only heterocycles but also carbocycles such as naphthalene,[146] tetraline,[147] indene and indane,[148] and even benzene[93,149] [e.g., **58**–**60** and PRX-07034 (**61**)] have successfully replaced the central core of indole, which supports the initial hypothesis that the relative position of the basic amine and the arylsulfonyl moieties plays a key role in the interaction with the receptor, whereas the central scaffold just holds these substituents in the proper orientation (see Figure 6B for models of the 5-HT_6R in complex with **50** and **56**).

Non-Sulfonyl Compounds. As already pointed out, most 5-HT_6R antagonists bear a sulfonyl group (sulfonamide or sulfone) as HBA. However, some examples of antagonists containing a carbonyl or an alkoxy moiety able to act as HBA have been

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reported (Figure 7A). Similar to the structures of sulfonyl ligands, not only indole ring but also 5,6- and 6,6-bicycles have been used as central cores, while the spatial orientation of the rest of pharmacophoric features is kept in most cases (see Figure 7B for models of 5-HT$_6$R−ligand complexes). Although compounds belonging to this family show in general lower antagonist potency, the replacement of the sulfonyl moiety by carbonyl or alkoxy groups might be considered potentially advantageous for the increment of brain penetration due to the reduction of the polar surface area.

One of the first identified antagonists without a sulfonyl group was the cyclohexyl ether ALX-0440 (**62**), reported by Slassi et al.[111] Other compounds bearing alkoxy moieties are carbazole **63**,[150] chromane **64**,[151] quinoline **65**,[152] indole Lu AE58054 (**66**),[153] and tolylpiperidine **67**.[154] Compound **66** is a selective antagonist (>50-fold over 70 targets examined) with good oral bioavailability and is currently in phase III clinical trials for AD (see section 5).[153] Compound **67** showed a good in vivo PK profile (e.g., $t_{1/2}$ = 5.9 h) and excellent oral and CNS exposure (F = 90%, brain/plasma ratio = 23). Furthermore, **67** was active (3−10 mg/kg) in the rat novel object recognition paradigm.[154]

Among carbonyl derivatives, quinolinone **68**,[155] benzoxazinone **69**,[156] dibenzoxazepinone SYN-114 (**70**) (described as 5-HT$_{2A}$ and 5-HT$_6$R dual antagonist),[157] benzimidazolone **71**,[155] quinolinedione **72**,[158] lactam **73**,[159] and benzimidazole **74**[97] were reported as antagonists. Currently, compound **70** is being evaluated in phase I clinical trials for AD (see section 5).

Other non-sulfonyl compounds described as 5-HT$_6$R antagonists are benzimidazole **75**,[97] carboximidamide **76**,[160] benzazepine **77**,[161] AVN-101 (**78**),[162] structurally related to the antihistamine agent dimebolin (**79**),[163] and antipsychotics such as asenapine (**80**),[164] although the last two compounds are examples of multimodal ligands. Among them, compound **78** is currently under phase II clinical development for AD (see section 5).

4. 5-HT$_6$R ANTAGONISTS AND COGNITIVE DISORDERS: ALZHEIMER'S DISEASE

In addition to the localization and mechanistic studies described above (see section 2), 5-HT$_6$R ligands have been also used in behavioral models to delineate the role of 5-HT$_6$ receptors in memory and learning processes. Except for some initial discrepancies (see below), a growing body of preclinical evidence has supported the use of 5-HT$_6$R antagonists for the treatment of cognitive dysfunction, as reviewed by Meneses,[36] Mitchell,[70] and Fone.[76] The results obtained in these in vivo studies showed the dependence on the age of the animals as well as on the paradigm of cognition used. Of particular importance in the study of 5-HT$_6$ receptors are the differences in pharmacology observed in mice when compared with rats and humans. The high homology in the primary structure and distribution between the human and rat 5-HT$_6$ receptors indicate that the rat is a good substitute species to predict pharmacological activity in humans.[26]

Soon after the initial evidence of 5-HT$_6$R involvement in memory was provided by using AOs, selective 5-HT$_6$R ligands **1** and **2** were disclosed, which helped increase knowledge of the potential therapeutic effects of modulating this receptor.[50] Similar to 5-HT$_6$R AOs, administration of antagonist **1** in normal adult rats induced enhanced memory retention of the previously learned spatial platform in the Morris water maze test.[49] This work revealed the influence of pharmacological 5-HT$_6$R blockade on cognitive processes relevant to the retention of information but not on learning acquisition. Characterization of 5-HT$_6$R antagonist **3** quickly followed,[165] and it was also shown to enhance retention but not acquisition in young unimpaired rats, using the same test.[166] However, two independent groups were reported to fail in replicating these findings with both **1** and **3** in the water maze paradigm of spatial memory in normal rats.[167,168] In contrast, in aged rats both antagonists were consistently capable of improving both acquisition and retention in the same model of cognition, suggesting that these drugs may have a greater influence on declining cognitive function.[54]

Although the first 5-HT$_6$R antagonists **1** and **3** have been extensively used as pharmacological tools, they were less than ideal for in vivo studies mainly because of their low brain penetration after systemic delivery. Persistent drug discovery efforts led to the identification of compounds with improved brain exposure, including **11**, **12**, **31**, and **40**. In addition to compounds **1** and **3**, the effects of several of these antagonists have also been studied in a diverse array of rodent paradigms of cognition, and positive results have been reported. Hence, as more potent, selective and druglike 5-HT$_6$R antagonists were developed, evidence accumulated suggesting that these drugs may become clinically useful in cognition enhancement therapy.

A similar behavior as that of compounds **1** and **3** in spatial learning task was observed for the new antagonists. Compound **11** improved retention in the Morris water maze but did not affect performance during the acquisition phase of the test.[166] The cognitive enhancement in aged animals was demonstrated again with antagonists **12** and **40**, which induced consistent improvements in both acquisition and retention in the water maze.[35,103] Alternative preclinical models were used to confirm the procognitive effects of 5-HT$_6$R antagonists in a number of memory and learning tasks. For example, **1**, **3**, orally active **12**, and **31** were all active in the novel object recognition test, a task based on the natural tendency of rodents to investigate a novel object instead of a familiar one.[60,103,120] Again, improvement on consolidation and storage in normal adult rats, rather than encoding or retrieval per se, was inferred from these experiments. Antagonist **3** was also shown to reverse novel object recognition memory deficit in aged rats, supporting that 5-HT$_6$R blockade confers cognitive benefit within an aged background.[54]

Altogether, it appears that 5-HT$_6$R blockade is more consistently effective in alleviating memory deficits rather than increasing memory in normally functioning animals. Since age-related cognitive deficits strongly correlate with significant decline in the cholinergic neurotransmission, especially in AD patients, these studies suggested that 5-HT$_6$R antagonists could potentially be used for the treatment of AD. In several studies 5-HT$_6$R antagonists **1**, **3**, **11**, **12**, and **31** have also been shown to improve overall performance in autoshaping and/or attentional set shifting tasks in rats, which suggests a role for 5-HT$_6$R blockade in enhancing cognitive flexibility.[120,169−171] These findings may provide some basis for the potential treatment of social cognition and attentional deficits demonstrated in AD patients.

One of the most robust findings regarding the involvement of 5-HT$_6$ receptors in memory is the ability of their antagonists [**1**, **3**, **12**, **31**, **40**, and the most recently discovered **43** and SUVN-507 (structure not disclosed)] to reverse cognitive deficit induced by the muscarinic antagonist scopolamine in Morris water maze, novel object recognition, or passive avoidance test.[31,53,54,107,120,130,171] At the same time, compound **1** was unable to prevent memory deficits produced by the dopamine D$_2$ receptor antagonist raclopride in the novel object recognition

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Table 1. 5-HT_6R Antagonists in Clinical Trials for Alzheimer's Disease

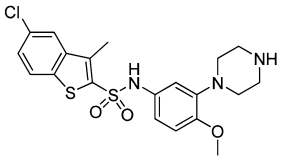
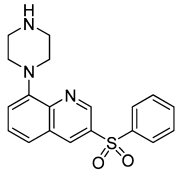
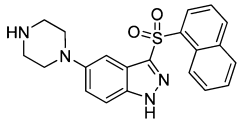
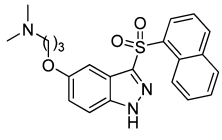
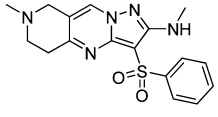
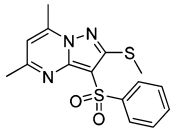
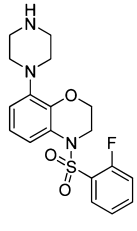
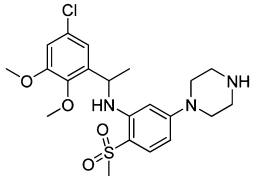
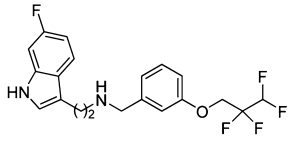
Compound	Structure	Company	Development Phase[a]	Current Status[a]
3		SmithKline Beecham	Phase I	Discontinued
40		GlaxoSmithKline	Phase II	Unknown[b]
43		Wyeth	Phase I	Discontinued
44		Pfizer	Phase II	Discontinued[c]
47		Avineuro Pharmaceuticals	Phase I	Active
48		Avineuro Pharmaceuticals	Phase I[d]	Active[c]
51		Roche	Phase I	Discontinued
61		Epix Pharmaceuticals	Phase I	Unknown[c,e]
66		Lundbeck and Otsuka Pharmaceutical	Phase III	Active[c]

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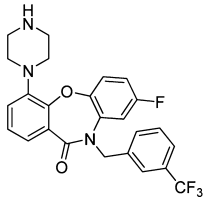
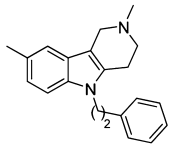
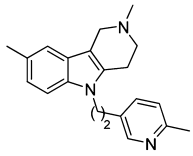
Table 1. continued

Compound	Structure	Company	Development Phase[a]	Current Status[a]
70		Biotie Therapies	Phase I	Active
78		Avineuro Pharmaceuticals	Phase II	Active[f]
79		Pfizer and Medivation	Phase III	Discontinued[g]
81	S.N.D.[h]	Wyeth	Phase I	Unknown
82	S.N.D.	Biotie Therapies	Phase I[d]	Active[c]
83	S.N.D.	AbbVie	Phase I	Active
84	S.N.D.	Suven Life Sciences	Phase I	Active[c]
85	S.N.D.	Pfizer	Phase II	Active

[a]Information on the design and purpose of the clinical trials and results data were obtained from the U.S. National Institutes of Health (www.clinicaltrials.gov) and from press releases on the Web sites of each company. [b]This compound was listed as being in phase II clinical trials for the indication of dementia in February 2013. [c]This compound also entered clinical trials for the treatment of schizophrenia. [d]This compound is planned to enter phase II in 2014. [e]This compound also entered clinical trials for the treatment of obesity. [f]This compound also entered clinical trials for the treatment of anxiety. [g]This compound was marketed as Dimebon in Russia for the treatment of skin allergy and allergic rhinitis. [h]S.N.D., structure not disclosed.

paradigm. This would be in line with the hypothesis that 5-HT$_6$R functions are mediated, at least partially, by a modulation of central cholinergic neurotransmission (see section 2). The cholinergic−serotonergic link is relevant considering that cholinergic replacement strategy is the primary therapeutic option for AD treatment.

Another interesting development in the therapeutic potential of the 5-HT$_6$R has been the discovery that coadministration of a 5-HT$_6$R antagonist with an AcChEI to age-impaired rats resulted in additive or synergistic effects. Animals dosed with compound **3** or **61** in combination with donepezil (Aricept, approved for symptomatic treatment of AD) demonstrated significantly improved performance in water maze, passive avoidance cognition, and/or novel object recognition models, compared with animals treated with either substance alone.[172,173] Similarly, **3** in combination with the AcChEI galantamine (also approved for AD treatment) was able to reverse scopolamine-induced impairment.[173] This suggests that the administration of 5-HT$_6$R antagonists together with AcChEIs may be of some utility to increase therapeutic responsiveness in AD.

As pointed out earlier, the NMDA receptor antagonist dizocilpine blocked the cognitive enhancing effect of **1** in the novel object recognition test, suggesting that 5-HT$_6$R antagonists may enhance consolidation and storage processes through increasing central glutamatergic neurotransmission.[60] This was further corroborated by the more recently developed 5-HT$_6$R antagonist **66** that was able to reverse cognitive impairment induced by the NMDA receptor antagonist phencyclidine in the same test in rats.[153]

Interestingly, the procognitive effects observed for 5-HT$_6$R antagonists in rodents have been extended to include non-human primates, though a limited number of studies have been published to date. Compound **3** has been shown to improve correct responses in aged rhesus monkeys in the delayed matching-to-sample task and in marmosets. Furthermore, the antagonist reversed the dizocilpine-induced deficits on both perceptual visual discrimination and visuospatial conditional discrimination tasks.[31] These results indicate that 5-HT$_6$R blockade can enhance cognitive function in a primate species,

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and clinical data show that this observation also extends to humans (see section 5).

Therefore, the development of potent, selective, and druglike 5-HT$_6$R antagonists has been crucial in the clarification of the role of 5-HT$_6$ receptors in learning and memory. Indeed, several of them alone have been consistently shown to significantly enhance the memory retention or formation in young and aged rats in multiple behavioral models reflecting diverse cognitive tasks. The results suggest that the 5-HT$_6$R may regulate long-term memory in normal adult rats. In addition, these antagonists have been demonstrated to reverse cognitive deficits pharmacologically induced by muscarinic or NMDA receptor antagonists in a number of cognition paradigms. Moreover, the combined data on the coadministration of 5-HT$_6$R antagonists with AcChEIs are encouraging and suggest additional opportunities for the clinical use of 5-HT$_6$R antagonists as an add-on therapy to established agents, as well as stand-alone treatments.

5. 5-HT$_6$R ANTAGONISTS IN CLINICAL TRIALS FOR ALZHEIMER'S DISEASE

Considering the encouraging results at the preclinical level, the challenge remains to confirm whether 5-HT$_6$R antagonists could be developed as effective therapeutics to treat learning and memory deficits associated with AD in humans. To date, a number of these compounds have reached clinical trials for the treatment of cognitive disorders in AD patients (Table 1). Some of them have successfully completed phase I studies exhibiting good safety and tolerability profiles, which indicates no apparent target-related liabilities for the 5-HT$_6$R approach at this stage. Furthermore, several 5-HT$_6$R antagonists are still under active development in phase II/III trials, which keeps the promise for these compounds as novel therapeutic agents for the treatment of AD.

Compounds **3** and **40** were the first 5-HT$_6$R antagonists reported to enter into phase I clinical trials. While the development of **3** was stopped probably because of its insufficient blood−brain barrier permeability,[52] the second antagonist progressed to phase II trials for the treatment of AD. Hence, GlaxoSmithKline completed four phase II clinical studies of **40**.[174] A dose-ranging trial comparing this compound with placebo was first conducted, and the reported data showed a small but dose-dependent benefit of the antagonist on both cognitive and global function, as well as acceptable tolerability.[175] In a subsequent exploratory study, compound **40** was compared to donepezil, a widely prescribed AcChEI that is standard therapy in AD, and the data indicated some improvement on global function but little enhancement of cognition.[176] Overall, these results constituted the first reports of an efficacy signal with a 5-HT$_6$R antagonist in an AD patient population. However, two following trials with **40** reported in 2011 failed to meet their coprimary end points of significant improvement according to the cognition clinical scales named Clinician's Interview-Based Impression of Change Plus Caregiver Input and AD Assessment Scale, Cognitive Subscale (ADAS-Cog).[177,178] Since then, no further development of the compound in AD has been reported, although **40** was listed as being in phase II clinical trials for the indication of dementia in February 2013.[179]

Wyeth is another company that has widely contributed to the discovery of 5-HT$_6$R antagonists. Among them, **43** (also known as WAY-255315) was selected as a clinical candidate for the treatment of cognitive impairment in AD but was ceased after three phase I studies to evaluate the safety, tolerability, PKs, and pharmacodynamics of single and multiple ascending doses.[180] Also antagonist **44** (also known as PF-05212365), initially developed by Wyeth and then by Pfizer, progressed to clinical trials for the oral treatment of AD and schizophrenia. However, phase II studies of **44** were discontinued because of ineffectiveness at three dosage levels in outpatients with mild-to-moderate AD.[181] Additionally, Wyeth has conducted phase I clinical trials of antagonist SRA-444 (**81**, structure not disclosed). Safety, tolerability, PK, and pharmacodynamic studies after administration of ascending single oral doses were completed in 2007, although the current development of this compound is unknown.[182]

Compound **79** (also known as latrepirdine) is a multimodal ligand approved in Russia (marketed as Dimebon) as a nonselective antihistamine drug that also displays good affinity for the 5-HT$_6$R. Hence, **79** demonstrated promising cognitive benefits in phase II clinical studies,[183] slowing cognitive decline and improving cognition.[184] However, its development was ended by Pfizer and Medivation in 2012 after failing to meet two primary end points (ADAS-Cog scale of cognitive ability and AD Cooperative Study—Activities of Daily Living, which measures self-care and daily functioning) in a phase III trial as add-on therapy with donepezil.[185]

The 5-HT$_6$R antagonist **61** has been developed by Epix Pharmaceuticals for the treatment of obesity, as well as for cognitive impairment associated with AD and schizophrenia. The compound showed a dose-dependent trend for improvement when evaluating cognitive function as a secondary end point in a phase Ib trial designed to assess safety, tolerability, PKs, and pharmacodynamics of oral administration.[186] Unfortunately, there is no data about a phase IIa study planned to start in 2008 to evaluate the efficacy of **61** in cognitive impairment,[187] and the current status of the compound remains unclear. Another compound whose clinical trials were ceased is **51**, a 5-HT$_6$R antagonist developed by Roche that had completed a phase I study.[188]

Biotie Therapies has also conducted several clinical trials on 5-HT$_6$R antagonists. Thus, compound SYN-120 (**82**, structure not disclosed) is under study for the treatment of AD and other cognitive disorders, including schizophrenia. Single and multiple ascending dose phase I studies have been successfully completed to show that **82** is well tolerated, and it is currently transitioning to phase II trials, which are expected to start by the end of 2014. Interestingly, a PET study disclosed in 2012 demonstrated that the compound engages the target in the brain with levels of 5-HT$_6$R occupancy expected to be efficacious. This high receptor occupancy was achieved with doses that are 10-fold lower than those that have previously been shown to be safe and well tolerated for up to 2 weeks in healthy elderly subjects. Antagonist **70**, a backup to **82**, has also satisfactorily completed phase I trials with single and multiple ascending dose studies.[189]

The 5-HT$_6$R antagonist ABT-354 (**83**, structure not disclosed) is also under active development by AbbVie as cognition enhancer add-on therapy with AcChEIs in subjects with mild-to-moderate AD. Phase I trials were completed in 2013.[190]

In 2009 Suven Life Sciences presented clinical phase I data for the 5-HT$_6$R antagonist SUVN-502 (**84**, structure not disclosed), a drug candidate for the symptomatic treatment of AD and other disorders of memory and cognition. The study showed that the compound was well tolerated at all dose levels, having a dose-proportional PK profile with good exposure levels.[191] Moreover, in 2011 **84** successfully passed long-term chronic studies and developmental toxicology studies, demonstrating a very high

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margin of safety, which is essential for FDA approval to initiate phase IIa clinical trials in patient populations. Therefore, the next stage for compound **84** will be phase IIa proof of concept trials in patients with AD.[192]

The 5-HT$_6$R antagonists **47** and **78** are currently being developed by Avineuro Pharmaceuticals for the treatment of AD. Clinical phase I results on **78** were reported in 2009, and the data indicated that it was well tolerated in a wide range of doses without adverse event. Subsequently, phase II trials in AD patients were initiated in 2010.[193] Compound **47** also showed satisfactory results in terms of safety and tolerability in phase I studies, and its advancement to clinical phase II was planned for the end of 2010.[194] Since then, no further progress has been reported for any of the compounds. **48** is another 5-HT$_6$R antagonist that has entered phase IIb studies last year for the treatment of schizophrenia, and it will also be evaluated in additional clinical trials in AD in 2014.[195]

In addition to the discontinued 5-HT$_6$R antagonists **44** and **79**, Pfizer has conducted clinical trials in AD with compound PF-05212377 (**85**, structure not disclosed, also known as SAM-760). Thus, four phase I studies were completed with the compound between 2009 and 2011. Two of them evaluated safety, tolerability, and PKs of single and multiple ascending oral doses, and another trial assessed the effect of a single dose of the compound on scopolamine-induced cognitive impairment. Finally, a forth study determined the relationship between plasma drug levels and receptor binding in brain using PET. At present, two clinical trials of **85** are active: a phase II study to assess safety and efficacy in subjects with mild-to-moderate AD with existing neuropsychiatric symptoms on a stable dose of donepezil, which is currently recruiting participants, and a phase I trial to examine the distribution of the compound in the brain of healthy volunteer subjects using PET and a radioactive tracer.[196]

Interestingly, antagonist **66** is currently under clinical development by Lundbeck and Otsuka Pharmaceutical for the treatment of AD.[197] A phase II study to evaluate the potential of the compound for the treatment of cognitive impairment in schizophrenic patients was conducted, but the clinical trials for this indication were ceased in 2010 based on lack of efficacy. Between 2009 and 2011, **66** was also assessed as an add-on treatment to donepezil in a phase II study in patients with probable AD. This trial met its primary cognition end point as determined by the ADAS-Cog scale. Nevertheless, secondary end points, including measurements of global status and activities of daily living, showed trends for a benefit but fell short of achieving statistical significance.[198] In October 2013, a global phase III program to study compound **66** in AD patients was launched. The clinical trial design consists of four studies enrolling approximately 3000 patients worldwide. Several doses of the antagonist will be used in combination with donepezil in order to explore the effect of the compound in mild-to-moderate AD as adjunctive therapy to commonly used AcChEIs.[199] Therefore, to the best of our knowledge, **66** remains as the most advanced 5-HT$_6$R antagonist in the clinical setting.

In summary, the promise of the 5-HT$_6$R as a potential drug target for cognition enhancement in AD is underscored by the transition of several 5-HT$_6$R antagonists into clinical trials. Although the first wave of enthusiasm was attenuated by some unsatisfactory results, as far as we are aware, nine compounds are still under active development, and three of them have progressed to phase II/III trials. The results of these ongoing clinical studies will hopefully unveil the therapeutic utility of 5-HT$_6$R antagonists as a new drug class for the treatment of AD.

6. CONCLUDING REMARKS AND PERSPECTIVES

Disorders that lead to a decreased ability to cogitate, assimilate, or recall new information have a significantly negative impact on a person's quality of life, especially in 21st century societies. Alzheimer's disease, in particular, represents one of the greatest human health challenges in this century because of its clinical and socioeconomic impact. Although only touched on briefly here, the processes leading to neuronal cell death in AD are highly complex, with multiple drug targets that come into play, rendering Alzheimer's research very challenging. Moreover, the path that goes from new potential treatment approaches in basic research to effective new medicines in clinic is particularly difficult in the case of AD, and the number of "failures" is disappointing. Thus, from 1998 to 2011 there were 101 attempts to develop drugs targeting AD and among them only three new medicines were approved to treat the symptoms of the disease.[3] Notwithstanding the large research effort devoted to the identification of disease-modifying agents that slow the progression of the disease, new therapies aimed at attenuating the severe cognitive impairment of the disease are also required and would be of immense benefit to relieve this major burden on both patients and their caregivers. Although widely prescribed AcChEIs (tacrine, donepezil, rivastigmine, and galantamine) and memantine have represented an advance as cognitive enhancers in the treatment of AD, these drugs are by no means panaceas and there is still a clear need to develop novel therapeutic approaches with improved efficacy and tolerability profiles, responder rates, or overall clinical benefit.

In this context, the serotonin 5-HT$_6$R has been recently placed in the limelight as an attractive drug target for cognition enhancement in Alzheimer's and other diseases where memory loss and learning complications are symptoms. Since its cloning and identification 2 decades ago, significant progress has been made in the understanding of the biology of this receptor. A plethora of in vitro and in vivo neurochemical and pharmacological studies have shown that 5-HT$_6$ receptors are present in brain regions that are associated with learning and memory and that blockade of their function increases acetylcholine- and glutamate-related neurotransmission, known to enhance cognition processes. Hence, central antagonism of the 5-HT$_6$R may provide a mechanistically distinct palliative treatment for AD cognitive deficits acting through neuronal cholinergic and glutamatergic systems. Extensive medicinal chemistry studies in both academic and industrial laboratories in the past years have led to the discovery of potent, selective, and druglike 5-HT$_6$R antagonists, which have contributed to validate the potential for this approach at the preclinical level. Indeed, pharmacological blockade of the 5-HT$_6$R with these tool molecules has been shown to produce significant behavioral effects in a range of animal models of cognition. In addition, a crucial point regarding compounds acting at 5-HT$_6$ 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 antagonist with good affinity but also of developing compounds able to trigger the necessary mechanisms for the procognitive effects. Despite early contradictory data reported by some research groups, today there is compelling evidence that 5-HT$_6$ receptors are involved in learning and memory processes and the ability of 5-HT$_6$R antagonists to improve cognitive function has been well established at the preclinical level. Furthermore, it has been recently suggested that there may be some synergistic or additive cognitive benefit in

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combining a 5-HT$_6$R antagonist with an AcChEI, strengthening the hypothesis for the use of these compounds in the treatment of cognitive disorders in AD. Therefore, 5-HT$_6$R antagonists may be viable drug candidates for the symptomatic relief of cognitive decline associated with aging and AD, either alone or in combination with other agents.

Further substantiation has been provided from emerging clinical data. Indeed, several 5-HT$_6$R antagonists have advanced to clinical development, and to date, some of them have reached phase II/III trials as drug candidates for cognitive enhancement, which holds promise for these compounds as novel therapeutic agents for the treatment of AD. Overall, the encouraging preclinical findings along with the promising (but mixed) outcome of the clinical trials contribute to an increasing body of evidence that supports the viability of the 5-HT$_6$R as a drug target for cognition enhancement in AD. Nevertheless, the challenge still remains to confirm whether the use of 5-HT$_6$R antagonists may be translated to mild-to-moderate AD patients as a novel therapeutic strategy to treat the severe impairment of memory and learning observed as a hallmark of the disease. The medical and scientific communities eagerly await the results of the ongoing and future clinical trials with the various 5-HT$_6$R antagonists currently in development that will shed some light on the validation of these molecules as a new drug class for the treatment of AD.

■ ASSOCIATED CONTENT

Supporting Information

Generation of the 5-HT$_6$R homology model in complex with different ligands. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

Biographies

Bellinda Benhamú received her Ph.D. in Chemistry in 1996 from Complutense University of Madrid, Spain. After a postdoctoral stay at the Weizmann Institute of Science, Israel, she joined the Department of Organic Chemistry at Complutense University where she is now Associate Professor and a member of the Medicinal Chemistry Laboratory led by Prof. María Luz López-Rodríguez. Her research in the area of medicinal chemistry and chemical biology has been focused on the design and development of new therapeutic agents for the treatment of CNS-related and cancer diseases. She is currently interested in the validation of new therapeutic strategies (i.e., allosteric modulators of GPCRs, LRH-1 nuclear receptor ligands) and identification of new drug targets (via chemical probes of GPCRs).

Mar Martín-Fontecha received her Ph.D. in Chemistry in 2005 from Complutense University of Madrid, Spain. Afterwards, she joined the Medicinal Chemistry Laboratory led by Prof. María Luz López-Rodríguez. In 2008, she did a postdoctoral stay at Imperial College London to work in the field of organometallic chemistry with Prof. Susan E. Gibson. She was promoted to Assistant Professor of the Department of Organic Chemistry at Complutense University in 2009, where she is currently a member of the research and academic staff. Her current research areas include the development of new therapeutic agents for the treatment of neurodegenerative and cancer diseases, as well as chemical probes for the study of GPCRs and new inhibitors of the bacterial protein FtsZ as antibacterial agents.

Henar Vázquez-Villa received her Ph.D. in Chemistry from University of Oviedo, Spain, under the guidance of Prof. José Barluenga and Prof. José Manuel González in 2005. Subsequently she did a postdoctoral stay in Prof. Erick M. Carreira's group at ETH-Zürich to continue her education in organic chemistry. In 2007 she moved to the Faculty of Chemistry at University of Alcalá, Spain, and then she joined Prof. María Luz López-Rodríguez's group at Complutense University of Madrid to work in medicinal chemistry. Her current research areas include lysophosphatidic acid receptors, allosteric modulators for type A GPCRs, chemical probes for the study of serotonin receptors, and inhibitors of the bacterial cell division protein FtsZ.

Leonardo Pardo received his Ph.D. in Physical Chemistry in 1986 from Autónoma University of Barcelona, Spain. He is now Professor of Bioinformatics at the Faculty of Medicine of this university. Mainly, his current research consists of combining structural bioinformatics, molecular dynamics, and data-mining of structure and sequence databases with experimental results to study the structure and function of GPCRs. This knowledge is applied to ligand- and structure-based drug design.

María L. López-Rodríguez obtained her Ph.D. in Chemistry from Complutense University of Madrid, Spain. After a postdoctoral stay in the Sloan Kettering Institute and Florida University with a Fulbright grant, she started her independent career as the leader of the Medicinal Chemistry Laboratory at Complutense University. In 2004 she was promoted to Full Professor of Organic Chemistry at this university, a position she currently holds. Her research is focused on medicinal chemistry and chemical biology, including the development of small molecules in challenging targets related to cancer and CNS as well as chemical platforms for the identification of new therapeutic targets. She has published 125 original research articles, and she is an inventor on 11 patents. She has supervised 20 Ph.D. students and trained numerous postdoctoral researchers.

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■ ABBREVIATIONS USED

5-HT$_6$R, 5-HT$_6$ receptor; AC, adenylyl cyclase; AcChEI, acetylcholinesterase inhibitor; ADAS-Cog, Alzheimer's Disease Assessment Scale, Cognitive Subscale; AO, antisense oligonucleotide; AR, aromatic ring; EL, extracellular loop; IL, intracellular loop; HYD, hydrophobic site; PI, positive ionizable atom; TM, transmembrane

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