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Its unique distribution, almost exclusively in the brain, combined with its therapeutic potential for CNS disorders make the 5-HT$_6$ receptor one of the most promising targets to enhance cognitive function and to combat obesity.

Medicinal chemistry strategies to 5-HT$_6$ receptor ligands as potential cognitive enhancers and antiobesity agents

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Although the 5-hydroxytryptamine$_6$ (5-HT$_6$) receptor was discovered only recently, its almost exclusive distribution in the brain makes it a promising, novel, target for central nervous system (CNS)-mediated diseases such as Alzheimer's disease (cognitive function), schizophrenia, anxiety and obesity. In the past few years a significant research interest has advanced the understanding of the functional roles and the pharmacophore requirements of this receptor. Two 5-HT$_6$ receptor antagonists have already entered Phase II clinical trials for the enhancement of cognitive function. Since the first discovery of selective ligands for the 5-HT$_6$ receptor by HTS in 1998, several medicinal-chemistry-driven approaches have delivered highly selective lead structures with well-defined functionalities, starting from either the endogenous ligand 5-HT or the chemical structures identified by HTS. The concept of 'scaffold hopping' has been employed to expand the variability of the available chemical scaffolds and to generate patentable ligands. Supported by pharmacophore models, which have been established recently, the binding and functionality (structure–activity relationships) of the lead structures have been optimized further.

The 5-hydroxytryptamine$_6$ (5-HT$_6$) receptor is one of the most recent additions to the family of mammalian 5-HT receptors. It was identified in the 1990s through molecular biological approaches [1–3] and belongs to a group of 5-HT receptors (5-HT$_4$, 5-HT$_6$ and 5-HT$_7$) that are coupled positively to adenylate cyclase [4]. More information on the distribution and functional roles of the 5-HT$_6$ receptor is given in two recent reviews [5,6]. The 5-HT$_6$ receptor has no known functional splice variants and it appears to be expressed almost exclusively in the central nervous system (CNS), so it is possible that new therapeutic agents targeted towards 5-HT$_6$ receptors might have relatively few peripheral side-effects.

A 5-HT$_6$ receptor-knockout mouse has been developed [7]. Transgenic mice that are homozygous for a disruption in the endogenous 5-HT$_6$ receptor gene have a phenotype of increased anxiety behavior that includes diminished investigation of foreign objects and elevation in

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Jörg Holenz (1968) was born in Bergisch-Gladbach, Germany, and studied chemistry at the universities of Cologne and Würzburg (both in Germany). He received his PhD in 1997, researching on the antimalarial potential of a new class of plant alkaloids of natural and semi-synthetic origin. In 1998 he joined Grünenthal, Aachen, Germany, as a medicinal chemist, becoming involved in several projects targeting novel analgesic principles. In addition, from 2000 he worked as a project manager (CMC affairs) of one of Grünenthal's clinical drug candidates. In 2003, he joined Laboratorios Dr. Esteve S.A., Barcelona, Spain, as Head of Medicinal Chemistry. His current research interests comprise mainly CNS drugs, such as analgesics, antidepressants and anxiolytics, as well as memory enhancement, schizophrenia, antiobesity and anti-inflammatory drugs. Besides his work, he enjoys playing volleyball, spending time with his friends and traveling.

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stretched attend postures. However, caution must be taken when drug-discovery efforts are performed in mice because there are differences in the CNS distribution and the pharmacology of the 5-HT_6 receptor in mice compared with rats and humans [8,9].

The high affinity of atypical antipsychotics [1] for the 5-HT_6 receptor and its localization in striatal, limbic and cortical regions of the brain [10] has prompted much interest into the potential role of the 5-HT_6 receptor as a therapeutic target for antipsychotic compounds. However, data indicate that the situation might not be straightforward. Downregulation of the 5-HT_6 receptor has been described after treatment with clozapine but not haloperidol [11], which indicates that the receptor might be involved in the therapeutic activity of atypical antipsychotics. Moreover, a polymorphism study in schizophrenic patients indicates that the response to clozapine might be predictable [12]. Nevertheless, another study [13] reports a lack of association between this polymorphism and the response to clozapine. In addition, the selective 5-HT_6 receptor antagonist SB-271046 (**35**, Table 1) is inactive in animal tests related to either positive or negative symptoms of schizophrenia [14]. Monsma [1] and Kohen [15] have shown that several tricyclic antidepressant compounds, such as amitryptiline, and atypical antidepressant compounds, such as mianserin, have high affinity for the 5-HT_6 receptor. These findings have led to the hypothesis that the 5-HT_6 receptor is involved in the pathogenesis and/or treatment of affective disorders. Rodent models of anxiety-related behavior yield conflicting results about the role of the 5-HT_6 receptor in anxiety. Treatment with 5-HT_6 receptor antagonists increases seizure threshold in a rat maximal electroconvulsive-shock test [16,17]. Although this indicates that 5-HT_6 receptors might regulate seizure threshold, the effect is not as pronounced as that of known anticonvulsant drugs.

Our understanding of the roles of 5-HT_6 receptor ligands is most advanced in two therapeutic indications in which this receptor is likely to have a major role: learning and memory deficits; and abnormal feeding behavior. The exact role of the 5-HT_6 receptor is yet to be established in other CNS indications such as anxiety; although one 5-HT_6 agonist has reached Phase I clinical trials recently, the exact role of the receptor is still to be established and is the focus of significant investigation.

5-HT_6 receptor ligands as treatments for cognitive dysfunction

5-HT_6 receptors are present in brain regions that are associated with learning and memory, and blockade of their function increases acetylcholine (ACh)- and glutamate-mediated neurotransmission, and enhances cognitive processes. Recently, King *et al.* [18] used novel-object discrimination (NOD) as a two-trial test of visual-recognition memory [19] to examine the modulatory effects of 5-HT_6 receptor antagonists on acquisition, consolidation, retrieval and/or attentional processes. When the inter-trial interval (ITI) is short, rats presented with two identical objects during the first (familiarization) trial spend longer exploring a novel object than the familiar object during the subsequent choice trial. From this it is inferred that they have a memory of the familiar object, and the main neural substrates appear to be the perirhinal and entorhinal cortices, cortical association areas and globus pallidus following short (<10 min) ITIs, with additional participation from the hippocampus occurring with intermediate ITIs. Longer ITIs disrupt memory of the familiar object and, hence, object discrimination during the choice trial. The pharmacological validity of the NOD task in rodents to predict novel compounds with potential clinical advantage has been demonstrated previously because donepezil, which is used currently for symptomatic relief in Alzheimer's disease, reverses age-related deficits in this task [20].

Administration of a 5-HT_6 receptor antagonist [either Ro 04-6790 (**60**) or SB-271046 (**35**) at 10 mg kg^{-1}, intraperitoneal (i.p.) (Table 1)] either 20 min before or immediately after the familiarization trial, but not 20 min before the choice trial, reverses the deficit in object discrimination produced by an ITI of 4 h [18]. The nootropic effects of these 5-HT_6 receptor antagonists in this task, thus, appear to involve enhanced consolidation and/or storage, but probably not retrieval, processes. An effect on consolidation is consistent with the ability of Ro 04-6790 to enhance performance in a food-motivated autoshaping task when administered post-training [21]. Although performance was improved only by 5 mg kg^{-1} and 10 mg kg^{-1} Ro 04-6790 in this study, this might result from hypophagia, which is reported with higher doses of this antagonist [22,23], compromising task performance. Pretreatment with the noncompetitive *N*-methyl-d-aspartate (NMDA) receptor antagonist MK-801 (0.05 mg kg^{-1}) prevents the effect of Ro 04-6790 on delay-induced deficits in object discrimination [18], which indicates that the enhancement of consolidation induced by the 5-HT_6 receptor antagonist involves increased glutamate-mediated neurotransmission in the CNS. Ro 43-68554 (**45**, Table 1), which has a high penetration of the blood–brain barrier (>80%), does not improve a time-related retention deficit in the rat NOD task. However, it reverses ACh-mediated and 5-HT-mediated memory deficits, which indicates that these mechanisms might be involved in the facilitation of object memory by this 5-HT_6 receptor antagonist [24]. It is possible that differences in the strain of rats (Wistar- versus Lister-hooded) and delay-interval (24 h versus 4 h) might account for the differences observed between Ro 43-68554, Ro 04-6790 and SB-271046 in a NOD task in the studies of Lieben *et al.* [24] and King *et al.* [18]. It might also be that the intrinsic efficacy of these 5-HT_6 receptor antagonists differs, so that they might be a silent antagonist, a partial or an inverse agonist.

Given the fundamental role of both the ACh and glutamate systems in cognitive processes, and their disturbance in memory dysfunction, 5-HT_6 receptors have been implicated in the modulation of normal and/or dysfunctional memory. Consistent with this, Ro 04-6790 overcomes muscarinic ACh receptor antagonist-induced deficits in object discrimination [25], autoshaping [21], Morris water maze and passive-avoidance [26–28] tests. In addition, when administered alone, Ro 04-6790 improves the performance of aged rats in operant T-maze delayed-alternation tasks [29] and enhances the performance of healthy, unimpaired, young adult rats in a food-motivated autoshaping task [21]. Acute and chronic oral administration of either SB-357134 (**36**, Table 1) or SB-399885 (**38**, Table 1) improves memory consolidation in naïve animals [30]. Either acute or repeated administration of SB-399885 at 10 mg kg^{-1} reverses memory deficits produced by either scopolamine or dizolcipine, and SB-357134 (at 3 mg kg^{-1} and 10 mg kg^{-1}) prevents amnesia and improves memory formation [30].

Interestingly, the numbers of 5-HT_6 receptors are diminished in patients with Alzheimer's disease [31].

Both 5-HT_6 receptor-directed antisense oligonucleotides (complementary to bases 1–18 of the rat 5-HT_6 cDNA initiation sequence) and Ro 04-6790 (10 mg kg^{-1} and 30 mg kg^{-1}) enhance retention of the learned platform position in the rat Morris water maze, an experimental model of spatial learning [23]. Administration of SB-271046 and SB-357134 has no effect on learning *per se* [32]. However, at 10 mg kg^{-1}, both compounds significantly improve retention of a previously learned platform position when tested seven days after training. By contrast, the acetylcholinesterase inhibitor donepezil has no effect in this task, which agrees with previous studies in which donepezil had no effect on water maze learning in unimpaired rats [33]. Acetylcholinesterase inhibitors are reported to enhance cognition in rat maze tasks, but these effects are restricted largely to procedures in which deficits have been induced pharmacologically by, for example, administration of scopolamine [34,35], and by lesion of the basal forebrain [36]. Acute administration of SB-271046 (3–20 mg kg^{-1}) also reverses a scopolamine deficit in a passive-avoidance task, and chronic treatment with either 10 or 20 mg kg^{-1} day^{-1} for 40 days improves task acquisition and recall in a spatial learning paradigm in aged rats [37]. The significant improvement of task recall indicates that SB-271046 both induces symptomatic cognition-enhancing actions and attenuates an age-related decline in neural function.

Stean *et al.* [38] have demonstrated enhanced acquisition, measured by path length, in addition to enhanced retention of a learnt platform position in the Morris water maze following chronic administration of SB-357134 [10 mg kg^{-1}, *per os* (p.o.), twice daily, seven days before training], which indicates a role for the 5-HT_6 receptor in learning and mnemonic processes involved in the spatial learning test. Therefore, potent 5-HT_6 antagonists might be useful in treating age-related memory decline and dysfunctional memory in Alzheimer's disease.

Subchronic administration of the antagonists SB-271046 and SB-399885 improves performance of an attentional set-shifting task, which indicates increased cognitive flexibility [39]. These findings indicate a potential role for 5-HT_6 receptor antagonists in treating the cognitive impairments associated with disorders such as schizophrenia.

Notwithstanding these positive studies, one study [40] is inconsistent with the hypothesis that 5-HT_6 receptor antagonists have therapeutic potential in cognitive disorders. Indeed, with Ro 04-6790 and SB-271046 Lindner and colleagues [40] failed to attenuate scopolamine-induced deficits in a test of contextual fear conditioning, and to replicate significant positive effects in an autoshaping task and in a version of the Morris water maze.

Assessing the data as a whole, we conclude that 5-HT_6 receptor antagonists are likely to have a future in learning and memory. In particular, the recent press release of Saegis [41] reports on the effectiveness of a novel, selective antagonist, SGS-518/LY-483518 (**9**, Table 1), in behavioral studies of learning and memory. Recently, this compound completed placebo-controlled, dose-ranging Phase I clinical studies in healthy volunteers, indicating safety and good tolerability, and it is currently profiled in Phase II clinical studies. GlaxoSmithKline's SB-742457 (**51**, Table 1) has also progressed to Phase II clinical studies for the treatment of dementia associated with Alzheimer's disease and schizophrenia [6,42].

5-HT_6 receptor ligands as potential treatments for obesity

It is likely that the 5-HT_6 receptor has a major role in obesity [43]. Early studies demonstrated that chronic administration of 5-HT_6 receptor antisense oligonucleotides significantly reduced food intake and body weight in rats [22]. Furthermore, 5-HT_6 receptor-knockout mice are resistant to weight gain when exposed to a high-fat diet [44]. Studies *in vivo* also demonstrate a role for selective 5-HT_6 receptor antagonists in the regulation of feeding: Ro 04-6790 administered i.p. to rats over three days (30 mg kg^{-1}) facilitates a reduction in body weight [23]. Further studies reveal a dose-related reduction in food consumption following acute administration of Ro 04-6790 (ID_{50} = 18.6 mg kg^{-1}) and SB-271046 (ID_{50} = 14.5 mg kg^{-1}) to rats accustomed to a fixed, daily feeding regimen [45]. BVT-5182 [**49** (Table 1); 3 mg kg^{-1}, subcutaneous (s.c.)] potently reduces food intake in a genetic mouse model of obesity without affecting either general motor activity or water intake. Chronic administration of BVT-5182 also reduces body weight and cumulative food intake by 9% and 11%, respectively, in mice fed a high-fat diet [46,47]. Analysis of the meal pattern indicates that the compound reduces food intake by enhancing satiety. Specifically, increases in the inter-meal interval and satiety ratio (inter-meal interval:meal size) were observed in animals that consumed fewer meals [44]. BVT-5182 also decreases serum leptin and epididymal fat in diet-induced obese mice and rats [46,47]. Similar results have been observed following treatment with SB-271046 [46]. The effect of 5-HT_6 receptor antagonists on food intake in mice is potentiated by co-treatment with a 5-HT_{2C} receptor agonist [44,48]. Recently, Perez-Garcia and Meneses [30] have reported that food-intake is suppressed in food-deprived animals 24 h after administrating two other 5-HT_6 receptor antagonists, SB-357134 and SB-399885.

We can predict these new 5-HT_6 receptor agents will have relatively few peripheral side-effects because the receptor is distributed almost exclusively within the CNS. It has been proposed [5] that 5-HT_6 receptor antagonists reduce γ-aminobutyric acid (GABA)-mediated signaling and increase the release of α-melanocyte-stimulating hormone (α-MSH), thereby suppressing food intake. In summary, antagonism of 5-HT_6 receptors appears to be a promising new strategy for the management of obesity, with the potential to ameliorate the complex-defined disease known as 'metabolic syndrome'. Currently, at least one pharmaceutical company (Biovitrum) has reported developing selective 5-HT_6 receptor antagonists to treat obesity [6].

The first 5-HT_6 receptor ligands

Several antipsychotic and antidepressant drugs have reasonable affinity for the 5-HT_6 receptor in addition to their main pharmacological targets [1,6,15,49]. Agents that bind to human 5-HT_6 receptors with K_i values <50 nM include 5-methoxytryptamine, bromocriptine, octoclothepin, and the neuroleptics clozapine, olanzapine, loxapine, chlorpromazine and fluphenazine [6,50]. The first ligands for the 5-HT_6 receptor were identified in the late 1990s by HTS of compound libraries at Roche and GlaxoSmithKline. This resulted in the antagonist tools Ro 04-6790 (**60**, Table 1)

TABLE 1

Summary of compounds

Compound number	Code name	Source	References
1	EMDT	Glennon, R.A. *et al.*	[54]
2	ALX-0440	NPS–Allellix	[107,114]
3	ALX-1161	NPS–Allellix	[107,114]
4	ALX-1175	NPS–Allellix	[107,114]
5	MS-245	Merk Sharp & Dohme	[55,58,78,136]
6	NA	Merk Sharp & Dohme	[55,58]
7	Ro 65-7199	Roche	[27,131]
8	NA	Merck KGaA and Carlsson	[108,109]
9	LY-483518 or SGS518	Eli Lilly or Saegis	[116,117]
10	NA	Esteve	[50,110]
11	NA	Esteve	[50,110]
12	WAY-181187	Wyeth	[111–113]
13	NA	Wyeth	[73]
14[a]	NA	Wyeth	[118]
15	NA	Wyeth	[119]
16	NA	Roche	[120]
17	WAY-466	Wyeth	[74,75]
18	NA	Wyeth	[121]
19	NA	Glennon, R.A. *et al.*	[122]
20	NA	Glennon, R.A. *et al.*	[67]
21	NA	Wyeth	[123]
22[a]	NA	Wyeth	[71]
23	NA	Merk Sharp & Dohme	[58]
24	NA	Wyeth	[84]
25	NA	Pharmacia	[77]
26[a]	NA	Wyeth	[83]
27	NA	Glennon, R.A. *et al.*	[78]
28	NA	Wyeth	[80]
29	NA	Wyeth	[124]
30[a]	NA	Wyeth	[79]
31	NA	Wyeth	[81]
32	NA	Glennon, R.A. *et al.*	[67]
33	NA	Biovitrum	[82]
34[a]	NA	Suven Life Sciences	[85]
35	SB-271046 (R = H) SB-258510 (R = Me)	GlaxoSmithKline	[52,87,132–135]
36	SB-357134	GlaxoSmithKline	[69]
37	SB-214111	GlaxoSmithKline	[8]
38	SB-399885	GlaxoSmithKline	[86]
39	NA	Pharmacia	[89]
40	NA	Roche	[125]
41	NA	GlaxoSmithKline	[88]
42	NA	Roche	[65]
43	Ro 65-7674	Roche	[90]
44	SB-699929	GlaxoSmithKline	[87,96]
45	Ro 43-68554	Roche	[91,92]
46	NA	GlaxoSmithKline	[96]
47	No data	Pharmacia	[126]

TABLE 1 (*Continued*)

Compound number	Code name	Source	References
48	NA	GlaxoSmithKline	[97]
49	Thought to be BVT-5182	Biovitrum	[104,115]
50	NA	Roche	[93]
51	Thought to be SB-742457	GlaxoSmithKline	[42,98,137]
52	NA	Wyeth	[101]
53	NA	Wyeth	[102]
54	NA	Wyeth	[103]
55	NA	Roche	[94]
56	NA	Roche	[66]
57	NA	Roche	[95]
58	NA	Glennon, R.A. *et al.*	[127]
59	NA	GlaxoSmithKline	[99,100]
60	Ro 04-6790	Roche	[51,131]
61	Ro 63-0563	Roche	[51]
62	NA	Esteve	[50,106]
63	NA	GlaxoSmithKline	[128]
64	Ro 66-0074	Roche	[28]
65	NA	Bristol-Myers-Squibb	[70,129]
66	NA	GlaxoSmithKline	[130]
67	[11C]GSK-215083	GlaxoSmithKline	[100]

[a] Stereochemistry not described for these compounds.

and Ro 63-0563 (**61**, Table 1) [51], and the first candidate for clinical development, the phenyl-piperazine SB-271046 [52], which entered Phase I human trials (www.integrity.prous.com) but was discontinued, probably because of insufficient penetration of the blood–brain barrier (www.iddb3.com). At about the same time, Glennon, one of the pioneers of the synthesis of 5-HT_6 receptor ligands, developed the first indole-based structures, starting from the endogenous ligand 5-HT [49,53–56]. Using a 'deconstruction–reconstruction' strategy, he identified first the 'minimum' pharmacophore requirements for efficient binding to 5-HT_6 receptors, and proceeded to consecutively introduce chemical groups into this to enhance selectivity and functionality while maintaining high affinity [57]. His work culminated in the synthesis of many indole-derived, selective, 5-HT_6 receptor-binding structures such as the agonist EMDT (**1**, Table 1) [54] and the antagonists MS-245 (**5**, Table 1) discovered independently by Glennon and Merck Sharp & Dohme [55,58], ALX-1161 (**3**, Table 1) and ALX-1175 (**4**, Table 1) discovered by the research team of Allelix/NPS Pharmaceuticals during a collaboration with Glennon in 2000 [49]. Glennon was the first to discover the importance of a sulfonamide motif in the indole-type structures for efficient binding to (and antagonism of) 5-HT_6 receptors [55]. This was introduced originally as an *N*-protective group [54] and is still the main common structural motif within 5-HT_6 receptor ligands.

Pharmacophore models: how to construct a 5-HT_6 ligand?

Since Glennon's publication on the first SAR of 5-HT-like structures in 1999 (part 1) [53] and 2003 (part 2) [57], significant contributions to the understanding of the receptor pharmacophore have been made by receptor-based and ligand-based modeling. The first receptor-based pharmacophore modeling studies were described in 2003 in the PhD thesis of a student in Glennon's group (M.R. Pullagurla, PhD thesis, Virginia Commonwealth University, 2003, which was published in 2004 [59]), and by Hirst *et al.* [8]. Pullagurla *et al.* [59] developed a pharmacophore model based on homology modeling with the bovine rhodopsin crystal structure. Automated docking studies indicate two binding sites for indole-based ligands, one attributed to agonist functionality and the other to antagonist functionality. These binding-site proposals are consistent with previous site-directed mutagenesis studies [8,60–62]. In 2004, two papers from Pae's group in South Korea were published, which established Hologram quantitative SAR (HQSAR) [63] and CoMFA/CoMSIA 3D QSAR [64] studies based on different training sets of 5-HT_6 receptor antagonists (monocyclic/bicyclic aryl-piperazines and indoles, respectively). The structural requirements for a potent 5-HT_6 receptor ligand were postulated first in 2004 by the research group of Esteve [50] and a simplified, qualitative pharmacophore-framework model was established based on medicinal-chemistry-guided analysis of reference compounds. The main components for the construction of a 5-HT_6 receptor ligand are depicted in Figure 1. They comprise two hydrophobic areas [squares (i) and (iv)], with the core area (iv) generally an indole, indole-like or a monocyclic/bicyclic aryl motif. The other area (i), which can accommodate diverse hydrophobic structural elements, is dominated by the commercial availability of sulfonyl chlorides. Favorable motifs include phenyl, naphthyl, benzothiophenyl, imidazo[2,1-*b*]thiazolyl and *p*-aminophenyl, as suggested from the modeling study of Pullagurla, Glennon *et al.* [59]. In addition, an ionizable nitrogen [proton donor, in the majority of cases a tertiary aliphatic amine function;

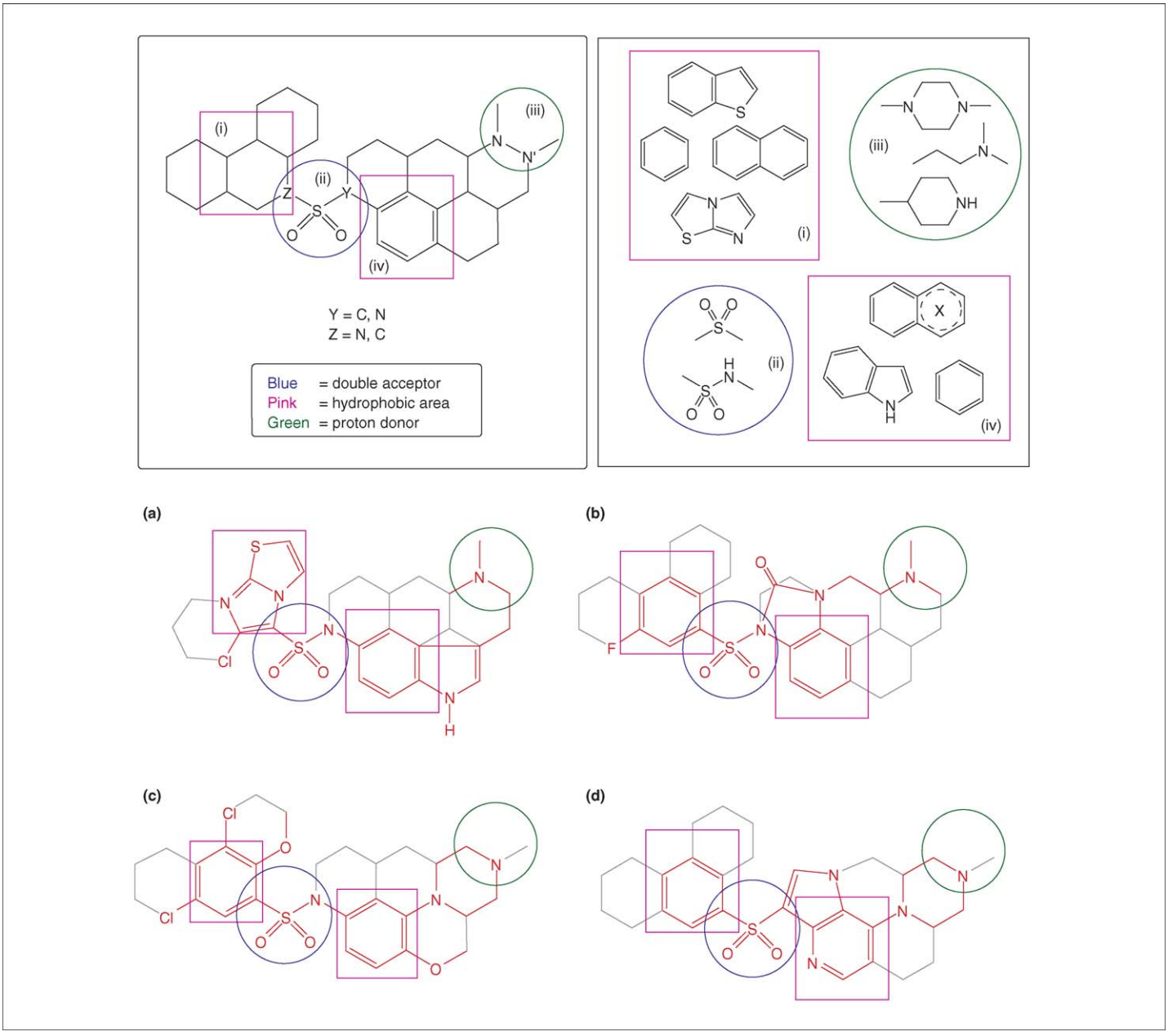


FIGURE 1

Simplified pharmacophore framework model [50] and the most common functional groups: try to construct your own 5-HT_6 receptor ligand. The model has four key requirements. These include two hydrophobic areas [squares (i) and (iv)]. The core area (iv) is generally an indole, indole-like, or a monocyclic/bicyclic aryl motif. Square (i) can accommodate diverse hydrophobic structural elements and is dominated by the commercial availability of sulfonyl chlorides. In addition, an ionizable nitrogen, in the majority of cases a tertiary aliphatic amine function, circle (iii), and, in most cases, a double-hydrogen-bond acceptor, circle (ii), are also necessary. Step 1: fill the framework with chemical life. Step 2: check for unprecedence and/or patentability. Step 3: realize the synthesis. Step 4: good luck with the binding affinity! (a) An indole example (see Figure 2). (b) An indole-like example (see Figure 3). (c) A monocyclic aryl-piperazine (see also Figure 4). (d) An example of a bicyclic aryl-piperazine (see Figure 5).

circle (iii)] and, in most cases, a double-hydrogen-bond acceptor [circle (ii)] are among the four key requirements. The hydrogen-bond acceptor function is nearly always represented by a sulfonamide or a sulfonyl motif. In some cases either lactams (**42**,**56**, Table 1) or a benzyl function (**20**,**32**, Table 1) have been reported [65–67], which indicates that the hydrogen-bond acceptor function can be omitted in some circumstances. The topographical orientation of the four key motifs within the proposed framework allows the prediction (and optimization) of novel 5-HT_6 receptor ligands. Independently, López-Rodríguez *et al.* [68] came to similar conclusions on the basis of a more elaborated 3D pharmacophore model using Catalyst software and a training set of 45 5-HT_6 receptor antagonists. By matching their results with a computational 5-HT_6 receptor model (again based on the crystal structure of bovine rhodopsin), the exact interactions of the four motifs in the pharmacophore model with amino acids in the transmembrane domain of the receptor were predicted. In addition, other studies [55,58,69–71] have used modeling tools to interpret binding results by, for example, superimposition.

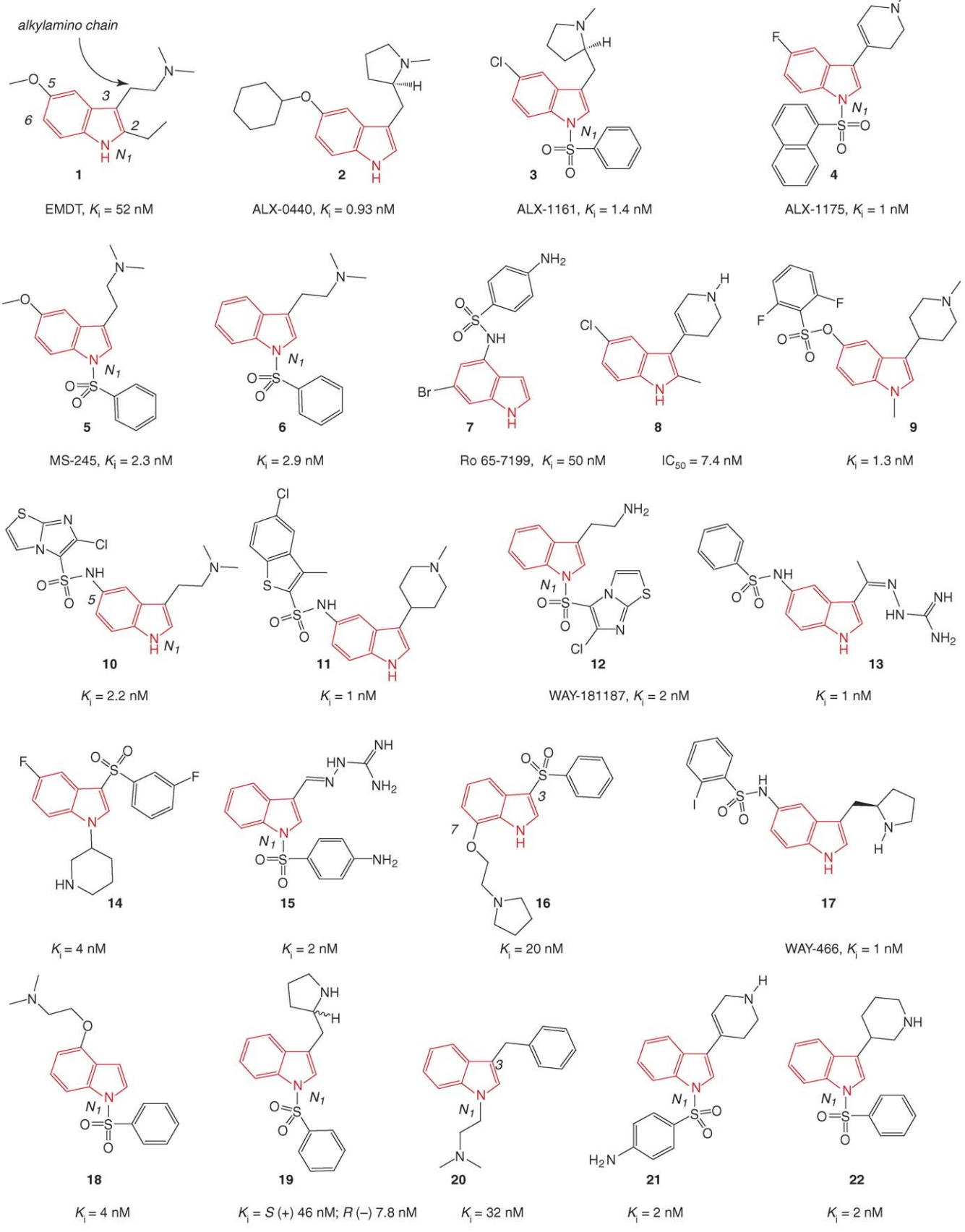


FIGURE 2

5-HT_6 receptor ligands containing indole structures. See Table 1 for more details on these compounds (K_i values as reported in the references cited in Table 1).

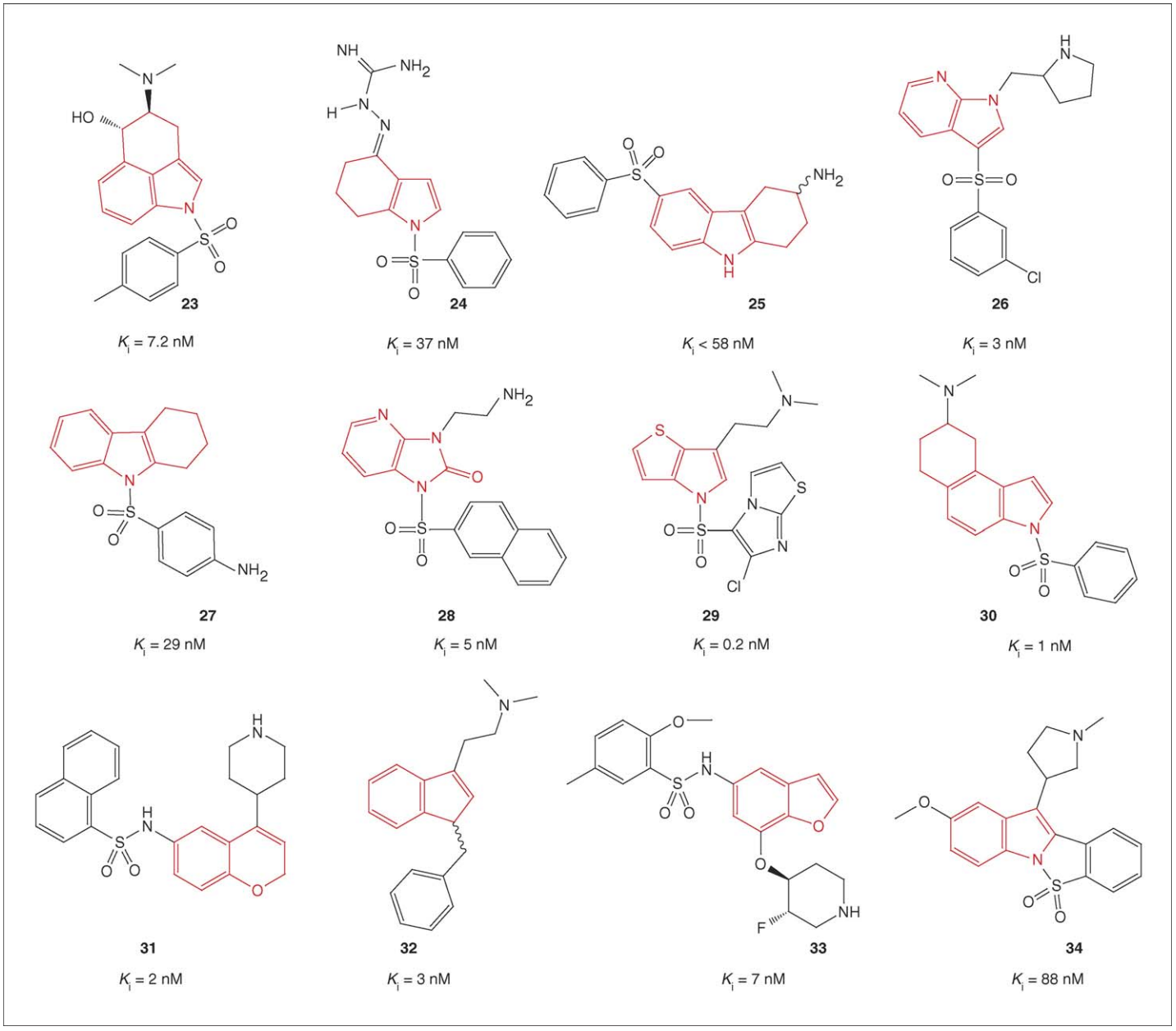


FIGURE 3

5-HT$_6$ receptor ligands containing indole-like structures. See Table 1 for more details on these compounds (K_i values as reported in the references cited in Table 1).

Clustering of 5-HT$_6$ receptor ligands

Given the tight pharmacophore requirements postulated above, nearly all reported 5-HT$_6$ receptor ligands have a strong general resemblance. Chemically, they cluster into two main groups. One group comprises the indole (Figure 2) and indole-like (Figure 3; scaffold hopping) subclasses that are derived from the endogenous ligand 5-HT. The other main group comprises the monocyclic (Figure 4), bicyclic and tricyclic aryl-piperazine (Figure 5) subclasses, which are analogs from the first HTS hits found by GlaxoSmithKline. A fifth class comprises miscellaneous core structures that have an aryl-sulfonyl motif as a common feature (Figure 6).

Indole structures

The earlier indole-type structures of 5-HT$_6$ receptor ligands resemble 5-HT, with a sulfonyl function attached to the indole N_1, such as in the antagonist MS-245 from Merck Sharp & Dohme and Glennon and the agonist from Merck KGaA and Carlsson Research (**8**) (Figure 2). SARs [57] of 5-HT-like structures show that either benzyl or -SO_2R substituents at the indole N_1 position enhance binding affinity but, in most cases, they convert function from agonism to antagonism (**3–5**, **18**, **19**, **21** and **22**; but **6** and **12** are reported to be partial agonist and agonist, respectively). Based on the simplified pharmacophore-framework model (see earlier), the research group at Esteve found that moving the sulfonamide structural motif from the N_1 position to the 5-position of the indole results in potent ligands (e.g. compounds **10** and **11**) [50]. Some of these structures are selective for the 5-HT$_6$ receptor, have favorable *in vitro* absorption, distribution, metabolism, excretion and toxicity (ADME–Tox) characteristics and are profiled currently as preclinical candidates because they are active in

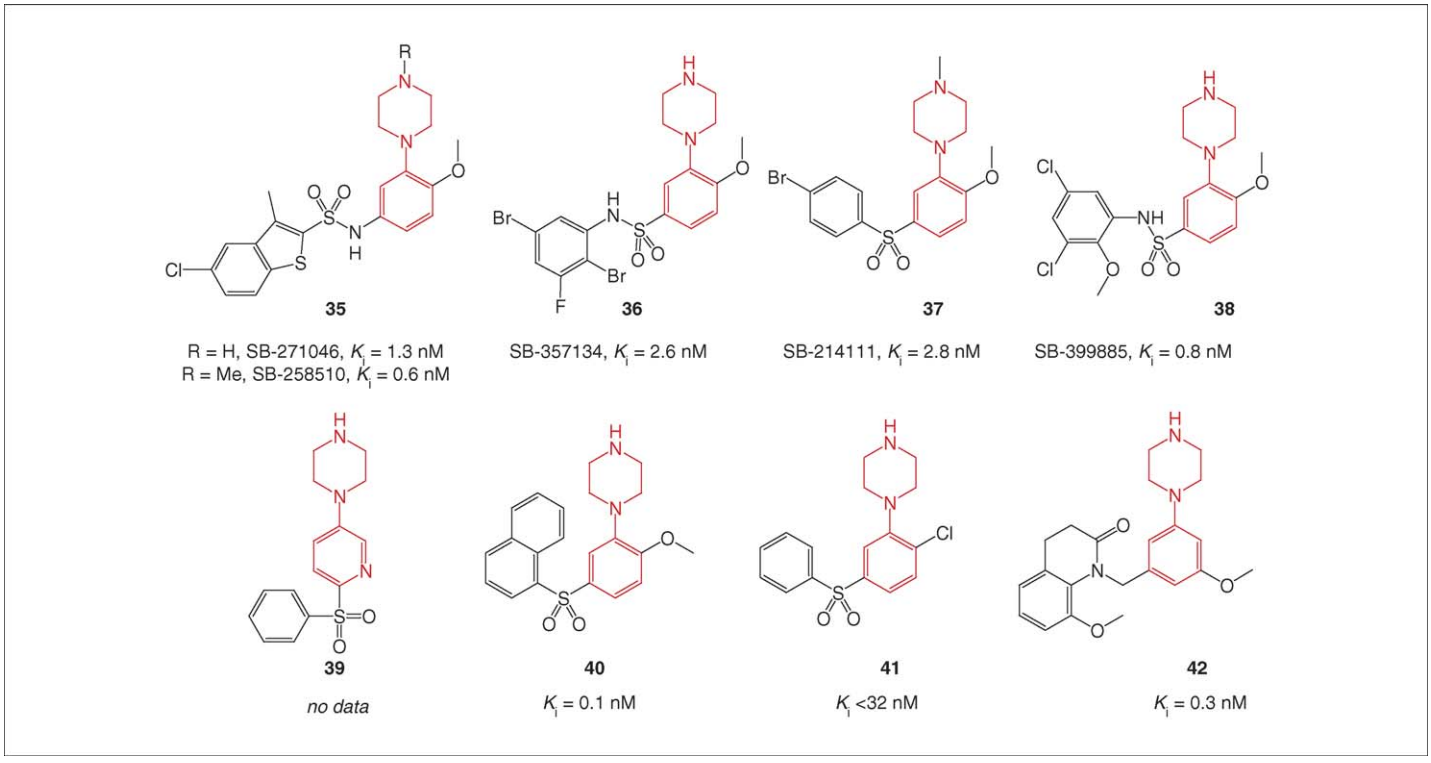


FIGURE 4

5-HT$_6$ receptor ligands containing monocyclic aryl-piperazine structures. See Table 1 for more details on these compounds (K_i values as reported in the references cited in Table 1).

animal models related to obesity and cognitive enhancement [72]. Simultaneously, and using a similar approach, Wyeth succeeded in producing useful ligands by exchanging the amine function with an amino-guanidine function (**13**) [73]. Other examples of different connections of the aryl-sulfonyl (or benzyl) motif and the alkylamino chain to the indole scaffold are provided by compounds **14**, **16–18** and **20**. Most of these retain a similar angle between the two motifs, in agreement with the simplified pharmacophore-framework model (Figure 1). Substitution at position 2 of the indole core of 5-HT-like structures with small alkyl substituents (methyl and ethyl) is tolerated in terms of potency and the retention of agonist function [e.g. EMDT (**1**), an agonist], whereas substitution with bulkier groups (such as phenyl) results in a switch to antagonism [54]. Glennon has described the synthesis of 2-phenyl-5-methoxy-*N*,*N*-dimethyl-tryptamine (PMDT, sometimes referred to as MPDT), which is considered to be the 'first non-sulfonamido' 5-HT$_6$ receptor antagonist [54]. With respect to the conformational orientation of the alkylamino chain, it was deduced that an ergoline-like conformation is preferable. This is supported by the low affinity of 1,2,3,4-tetrahydro-β-carboline for the 5-HT$_6$ receptor [53], and because the partial ergotamine structure [compound **23**, from Merck Sharp & Dohme (Figure 3)], in which the amine function is fixed in an ergoline-like conformation, has good binding affinity [58]. The optimum alkylamino chain length seems to be 2–3 carbon atoms [50]. Small alkyl substituents attached to the nitrogen of the alkylamine function (e.g. either methyl or ethyl, as in EMDT and MS-245) enhance affinity slightly, whereas larger substituents (e.g. propyl) reduce affinity compared with the corresponding -NH$_2$ compounds such as 5-HT [57]. Although many cyclic amines, such as piperidines, pyrrolidines and related groups (compounds **2–4**, **8**, **9**, **11**, **14**, **16**, **17**, **19**, **21** and **22**), lead to slightly decreased affinity compared with lower alkyl-substituted amines such as NMe$_2$ [50], they should be more stable metabolically. Interestingly, chiral 2-pyrrolidinyl amines similar to compound **17** (first introduced for 5-HT$_6$ receptor ligands by NPS Pharmaceuticals-Allelix, see compounds **2** and **3**) have different functions and binding behavior depending on the stereochemistry: in general, it seems that, *R*-enantiomers are potent agonists, with EC$_{50}$ values of $\leq$1 nM, whereas *S*-enantiomers display moderate antagonist activity [74,75]. Compound **7** (Roche) and compound **15** (Wyeth) make use of the enhancement of binding affinity by *p*-aminophenyl sulfonamide group (see section on Pharmacophore models), with the Roche compound being devoid of an aliphatic amine function. In 2003 Organon (Akzo Nobel N.V.) published on a class of indole- and indoline-type ligands with N_1-aryl-sulfonyl substitution, in which the tertiary amine function is attached to the 3-position of the core structure by a carboxamide function [76].

Indole-like structures

The principle of 'scaffold hopping' has been employed widely to both enhance the freedom to operate (with respect to patentability) within the indole-type structural class (Figure 3) and understand in more detail the conformational requirements of the four key motifs for high-affinity ligands (see earlier section on Pharmacophore models). Scaffold hopping is a well-known concept in medicinal chemistry that uses either 2D or 3D modeling tools to substitute a core scaffold that is known to produce high-affinity ligands with another scaffold that leads to similar topographical orientation of the substituents (which are pharmacophore key

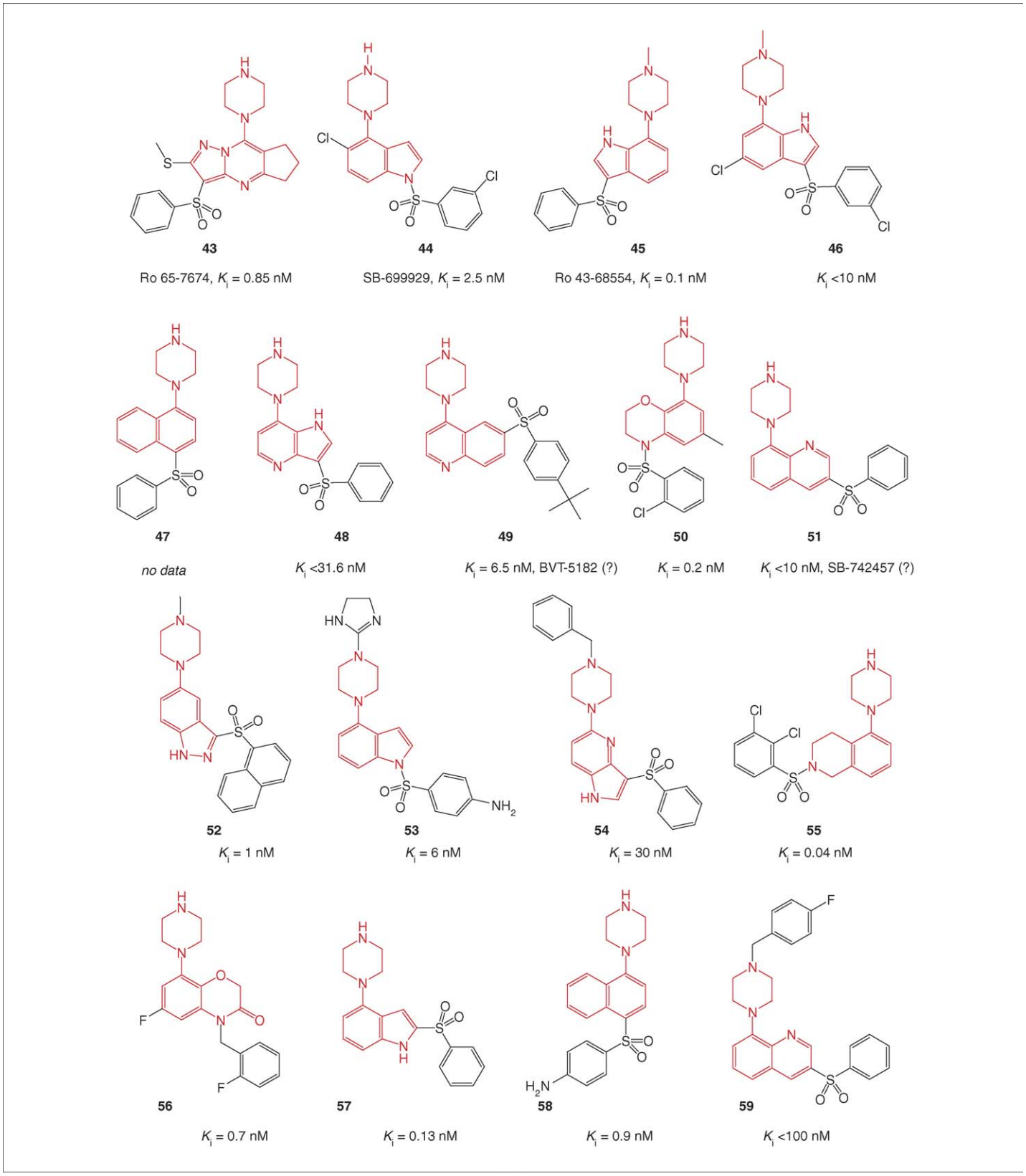


FIGURE 5

5-HT$_6$ receptor ligands containing bicyclic and tricyclic aryl-piperazine structures. See Table 1 for more details on these compounds (K_i values as reported in the references cited in Table 1).

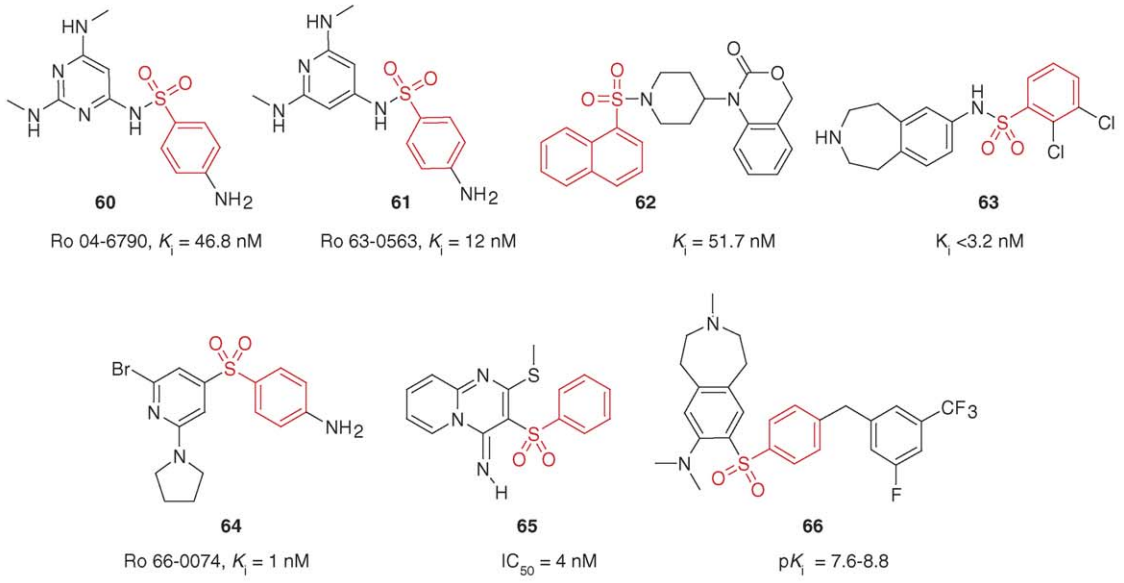


FIGURE 6

5-HT$_6$ receptor ligands containing miscellaneous, arylsulfonyl structures. See Table 1 for more details on these compounds (K_i values as reported in the references cited in Table 1).

motifs). This results in novel biomimetic compounds with potentially high binding affinities. Thus, using similar substitution patterns for the key motifs, several bicyclic and polycyclic systems have been synthesized to generate biomimetic analogs of indole-type ligands. On the one hand, some research groups have attempted to enhance affinity by adding other cycles to the indole core, thereby increasing conformational rigidity, such as in ergoline-like systems (**23**) [58], tetrahydrocarbazoles [77] [e.g. (**25**), which displays a lower binding affinity than compounds **10** or **17**, in apparent agreement with the postulate that an ergoline-like conformation of the alkylamino chain (compare with compound **23**) is preferred], compound **27** [78] – again a compound with the

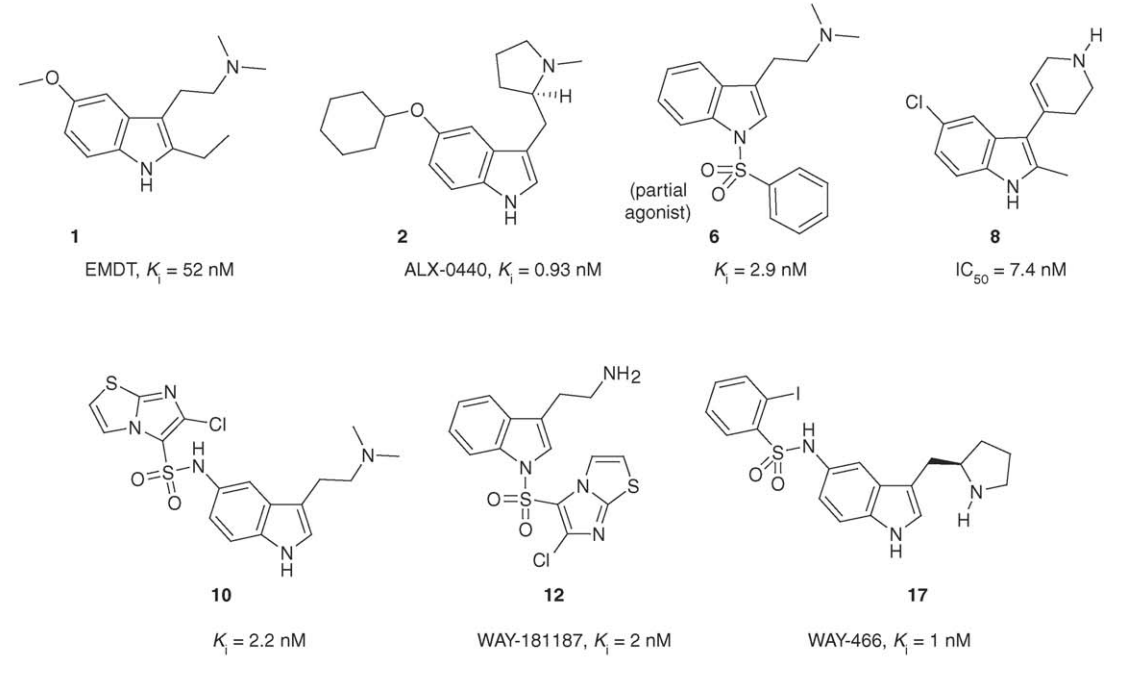


FIGURE 7

Structures of reported 5-HT$_6$ receptor agonists. See Table 1 for more details on these compounds (K_i values as reported in the references cited in Table 1).

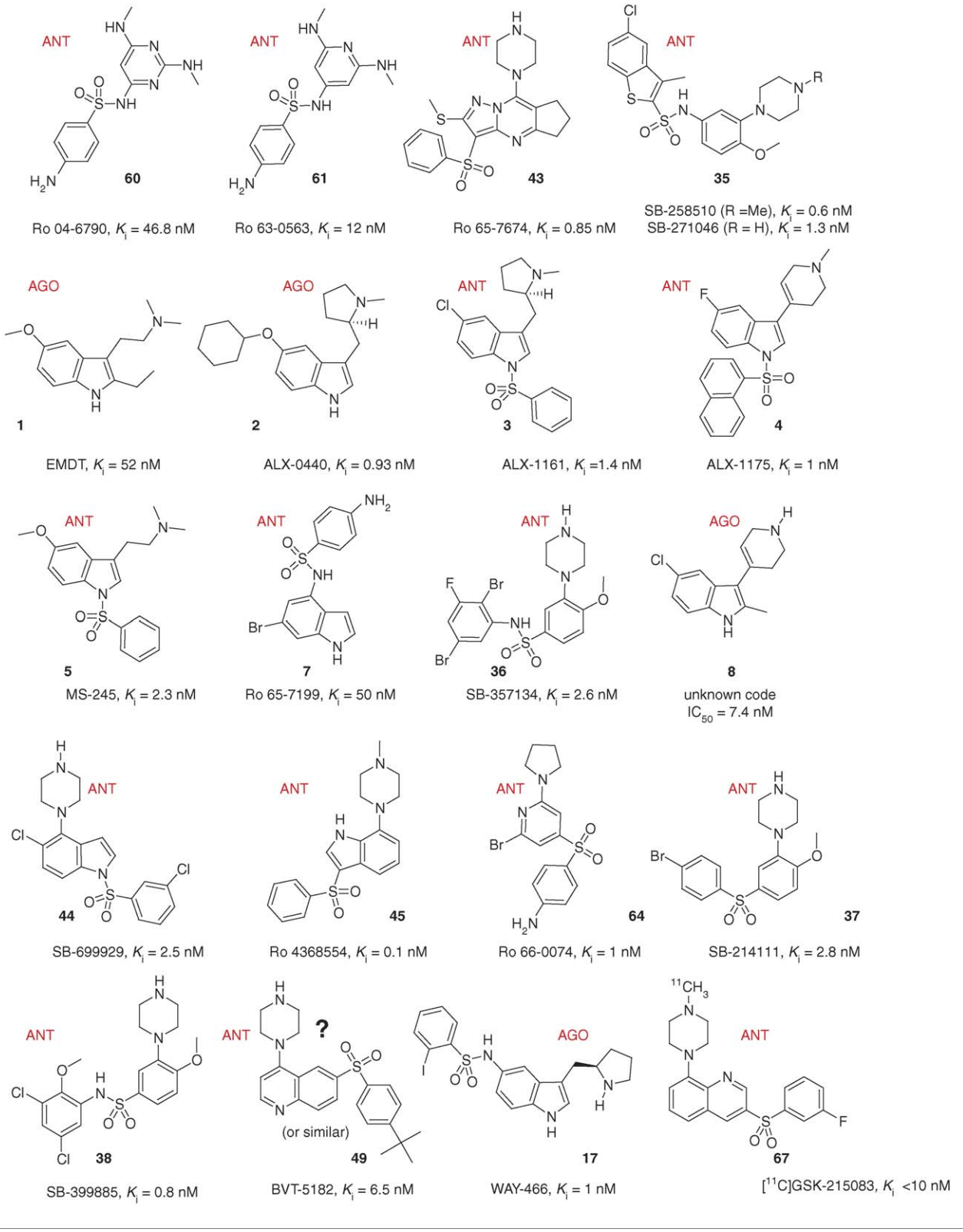
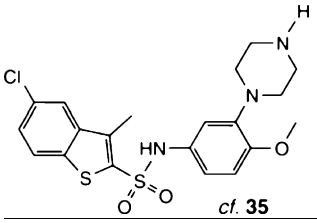
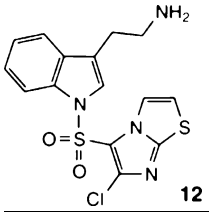
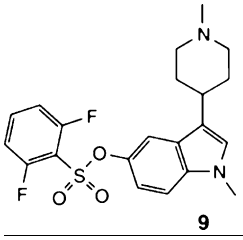
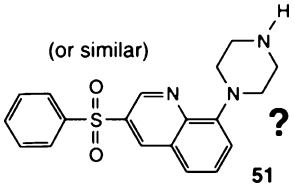


FIGURE 8

Preclinical candidates and tool compounds. See Table 1 for more details on these compounds (K_i values as reported in the references cited in Table 1). Abbreviations: AGO, agonist; ANT, antagonist.

TABLE 2

Compounds in clinical development

Structure	Code name	Source	Development phase	Functionality: therapeutic indication(s)	Refs
 *cf.* **35**	SB-271046	GlaxoSmithKline	Phase I[a]	Antagonist: Alzheimer's disease, schizophrenia	[52,87]
 **12**	WAY-181187 or SAX-187	Wyeth	Phase I[b]	Agonist: anxiety	[111–113]
 **9**	LY-483518 or SGS518	Eli Lilly or Saegis[c]	Phase IIa[b]	Antagonist: cognitive impairment associated with schizophrenia	[116,117]
 **51**	SB-742457	GlaxoSmithKline	Phase IIb[b]	Antagonist: cognitive dysfunction associated with Alzheimer's disease	[42,98,137]

[a] Development stopped, probably because of low penetration of the blood–brain barrier.
[b] Under active development, see Integrity Database, Prous Science, (www.integrity.prous.com).
[c] Saegis in-licensed SGS518 from Eli Lilly in October 2002 (www.iddb3.com).

p-aminophenyl sulfonamide motif, thus not necessarily requiring an aliphatic amine function for high binding – and tetrahydrobenzo[*e*]indoles (**30**) [79]. On the other hand, substitution of the 'pyrrole moiety' of the indole by imidazolone (**28**) [80], pyrane (**31**) [81], cyclopentadiene (**32**) [67] and furane (**33**) [82], and substitution of the 'phenyl ring' part of indole by pyridine (**26** [83], **28** [80]), its common bioisoster thiophene (**29**) and its saturated counterpart cyclohexane (**24**) [84] have been performed successfully, mainly by the research group at Wyeth. Again, lessons learnt with the indole-type ligands have been employed, such as the replacement of the tertiary amine function by an amino-guanidine function in compound **24** [84]. Recently, Suven Life Sciences [85], a new entrant into this field, have published an approach that uses the 'cyclization' of the aryl-sulfonamide moiety to generate novel ligands (e.g. compound **34**) that have slightly decreased affinity compared with compound **5**, for example.

Monocyclic aryl-piperazine structures

Historically, the research group of GlaxoSmithKline pioneered the monocyclic aryl-piperazine structural class of 5-HT_6 receptor ligands (Figure 4) that was identified by HTS. Chemically, the first optimization efforts involved mainly the sulfonamide motif, introducing a range of commercial sulfonylchlorides (e.g. compound **35** [52]), inverse sulfonamide (compounds **36** and **38** [69,86]) and sulfone (compound **37** [8]) motifs, and the free piperazine nitrogen [e.g. functionalization with a methyl group, as in SB-258510 (see **35**) and compound **37**]. One of the main focuses for optimization was to improve the penetration of the blood–brain barrier [87] of their lead compound, the Phase I candidate SB-271046 (**35**). Replacing the *o*-methoxy group in the phenyl-piperazine unit by chloro seems to reduce affinity slightly (compound **41** [88]). Later, Pharmacia and, mainly, Roche also worked on in this structural class, synthesizing ligands such as compounds **39** [89] and **40**, and the lactam-type compound **42** [65], in which the sulfonamide motif is replaced by a lactam unit.

Bicyclic and tricyclic aryl-piperazine structures

In common with the phenyl-piperazine ligands described in the previous section, bicyclic and tricyclic aryl-piperazine structures (Figure 5) with appropriately attached aryl-sulfonyl groups have promising binding affinities for the 5-HT_6 receptor. The first representatives of this class (e.g. compound **43**) were reported in 1999 by Roche [90]. Since then, many of the possible attachments of piperazine and aryl-sulfonyl motifs to bicyclic and

tricyclic (partial) aromatic systems have been realized, mainly by the research groups from Roche [66,90–95], GlaxoSmithKline [87,96–100], Wyeth [101–103] and Biovitrum [104]. These studies have resulted in high-affinity ligands such as compounds **44–55** [87,91–94,96–98,101–104] and **57–59** [95,99,100]. Interestingly, compounds **44–46** [87,91,92,96], **53** [102] and **57** [95] have a piperazine-substituted indole core scaffold and, thus, strongly resemble the indole-type ligands (Figure 2). This indicates that, like the phenyl-piperazine structures, these structures can be viewed as tryptamine (or 5-HT) mimics. Similarily, compounds **48** [97], **52** [101] and **54** [103] bear piperazine-substituted indole-like core scaffolds and can be compared with the indole-like structures (Figure 3: scaffold hopping). Again, Roche reported a piperazine-substituted benzoxazinone structure (compound **56**) [66] in which the sulfonyl motif is replaced by a lactam unit. Compound **49**, a quinoline-piperazine [104], is probably identical to the Biovitrum compound BVT-5182, which is currently being profiled preclinically for the treatment of obesity [105].

Miscellaneous aryl-sulfonyl structures

Although the compounds in Figure 6 have different core structures, they all have an aryl-sulfonyl motif. These compounds include the first triamino-pyrimidine and triamino-pyridine 5-HT_6 receptor antagonist tools from Roche (compounds **60** and **61** [51]). In addition, compound **62** from Esteve [50,106] is a potent and selective 5-HT_6 receptor ligand without either a basic amine function or the *p*-aminophenyl-sulfonyl motif.

Structures of 5-HT_6 receptor agonists

Figure 7 provides an overview of agonists and partial agonists at the 5-HT_6 receptor [50,54,55,58,74,75,107–114]. In general, all the agonists form part of the class of indole-type structures (Figure 2) and are closely related structurally to the endogenous ligand 5-HT, especially compounds **1** [54], **2** [107,114] and **8** [108,109]. Structure–functionality relationships are described in the section on indole-like structures (and in a receptor-modeling study in which Pullagurla *et al.* claim different binding sites for agonists and antagonists [59]). Most antagonists that are reported form part of the monocyclic, bicyclic and tricyclic aryl-piperazine classes (Figures 4 and 5, e.g. compounds **35–38** [8,52,69,86] and compounds **43–45** [87,90–92,96]), and the miscellaneous, aryl-sulfonyl structure-containing class of 5-HT_6 receptor ligands (Figure 6, e.g. compounds **60–62** [50,51,106]).

Preclinical candidates and tool compounds

Figure 8 summarizes pharmacological tools and preclinical candidates (www.integrity.prous.com and www.iddb3.com) and includes representative compounds from Roche [27,28,51,62,90–92], GlaxoSmithKline [8,52,69,86,87,96,100], Glennon [54], NPS-Allelix [49,107,114], Merck Sharp & Dohme [55,58], Merck KGaA and Carlsson Research [108,109], Biovitrum [104,115] and Wyeth [74,75]. The pharmacological use of compounds **35**, **36**, **38**, **45**, **49** and **60** has been discussed in detail in this review. In addition, these compounds and others in Figure 8 have been used to evaluate the involvement of 5-HT_6 receptors in illnesses such as schizophrenia, other dopamine-related disorders and depression, and to profile the neurochemical and electrophysiological effects of either blockade or activation of 5-HT_6 receptors. Furthermore, they have been used to characterize the 5-HT_6 receptor and to investigate its distribution.

BOX 1

Key resources and further reading

Chemistry:

Davies, S.L. *et al.* (2005) Drug discovery targets: 5-HT_6 receptor. *Drugs of the Future* 30, 479–495

Glennon, R.A. *et al.* (2003) Higher-end serotonin receptors: 5-HT_5, 5-HT_6, and 5-HT_7. *J. Med. Chem.* 46, 2795–2812

Slassi, A. *et al.* (2002) Recent progress in 5-HT_6 receptor antagonists for the treatment of CNS diseases. *Expert Opin. Ther. Patents.* 12, 513–527

Biology and Pharmacology:

Woolley, M.L. *et al.* (2004) 5-HT_6 receptors. *Curr. Drug Targets CNS Neurol. Disord.* 3, 59–79

Compounds in clinical development

To our best knowledge, the four compounds in Table 2 have entered clinical trials [41,42,87,98,111–113,116,117], and three are still considered to be 'under active development'. The most advanced are the Phase II antagonist candidate from GlaxoSmithKline, SB-742457 (probably compound **51**) for the therapeutic indication of cognitive dysfunction associated with Alzheimer's disease [42,98], and the Lilly compound LY-483518 (**9**) [116,117], which is licensed to Saegis Pharmaceuticals (SGS-518) for the treatment of cognitive impairment associated with schizophrenia [41]. The Wyeth agonist WAY-181187 (SAX-187, **12**) is currently in Phase I trials to target anxiety (www.integrity.prous.com) [111–113]. As described previously, SB-271046, the first 5-HT_6 receptor antagonist to enter Phase I clinical development, has been discontinued (probably because of low penetration of the blood–brain barrier [87]).

Concluding remarks

In recent years several research groups have contributed to the deeper understanding of the pharmacological roles and the pharmacophore requirements of the 5-HT_6 receptor. This has resulted in the development and characterization of several, selective, high-affinity tool compounds. In total, four 5-HT_6 receptor ligand candidates have advanced to clinical phases, two of which have the potential to ameliorate cognitive disorders associated with Alzheimer's disease and schizophrenia. Further clinical candidates based on 5-HT_6 receptor ligands should follow. In addition to the above indications, these are also likely to be useful in the treatment of obesity and anxiety (see Box 1 for additional reading).

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