



Its unique distribution, almost exclusively in the brain, combined with its therapeutic potential for CNS disorders make the 5-HT₆ receptor one of the most promising targets to enhance cognitive function and to combat obesity.

Medicinal chemistry strategies to 5-HT₆ receptor ligands as potential cognitive enhancers and antiobesity agents

Reviews • KEYNOTE REVIEW



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Although the 5-hydroxytryptamine₆ (5-HT₆) 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-HT₆ 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-HT₆ 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-hydroxytryptamine₆ (5-HT₆) 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-HT₄, 5-HT₆ and 5-HT₇) that are coupled positively to adenylate cyclase [4]. More information on the distribution and functional roles of the 5-HT₆ receptor is given in two recent reviews [5,6]. The 5-HT₆ 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-HT₆ receptors might have relatively few peripheral side-effects.

A 5-HT₆ receptor-knockout mouse has been developed [7]. Transgenic mice that are homozygous for a disruption in the endogenous 5-HT₆ 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-HT₆ receptor in mice compared with rats and humans [8,9].

The high affinity of atypical antipsychotics [1] for the 5-HT₆ 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-HT₆ receptor as a therapeutic target for antipsychotic compounds. However, data indicate that the situation might not be straightforward. Downregulation of the 5-HT₆ 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-HT₆ 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 amitriptyline, and atypical antidepressant compounds, such as mianserin, have high affinity for the 5-HT₆ receptor. These findings have led to the hypothesis that the 5-HT₆ 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-HT₆ receptor in anxiety. Treatment with 5-HT₆ receptor antagonists increases seizure threshold in a rat maximal electroconvulsive-shock test [16,17]. Although this indicates that 5-HT₆ receptors might regulate seizure threshold, the effect is not as pronounced as that of known anticonvulsant drugs.

Our understanding of the roles of 5-HT₆ 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-HT₆ receptor is yet to be established in other CNS indications such as anxiety; although one 5-HT₆ 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-HT₆ receptor ligands as treatments for cognitive dysfunction

5-HT₆ 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-HT₆ 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-HT₆ 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-HT₆ 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-HT₆ 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-HT₆ receptor antagonist [24]. It is possible that differences in the strain of rats (Wistar- versus Listerhooded) 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-HT₆ 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-HT₆ 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-HT₆ receptors are diminished in patients with Alzheimer's disease [31].

Both 5-HT₆ receptor-directed antisense oligonucleotides (complementary to bases 1–18 of the rat 5-HT₆ 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-HT₆ receptor in learning and mnemonic processes involved in the spatial learning test. Therefore, potent 5-HT₆ 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-HT₆ 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-HT₆ 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-HT₆ 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-HT₆ receptor ligands as potential treatments for obesity

It is likely that the 5-HT₆ receptor has a major role in obesity [43]. Early studies demonstrated that chronic administration of 5-HT₆ receptor antisense oligonucleotides significantly reduced food intake and body weight in rats [22]. Furthermore, 5-HT₆ 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-HT₆ 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 (ID₅₀ = 18.6 mg kg⁻¹) and SB-271046 (ID₅₀ = 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-HT₆ 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 administering two other 5-HT₆ receptor antagonists, SB-357134 and SB-399885.

We can predict these new 5-HT₆ 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-HT₆ 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-HT₆ 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-HT₆ receptor antagonists to treat obesity [6].

The first 5-HT₆ receptor ligands

Several antipsychotic and antidepressant drugs have reasonable affinity for the 5-HT₆ receptor in addition to their main pharmacological targets [1,6,15,49]. Agents that bind to human 5-HT₆ receptors with K_i values <50 nM include 5-methoxytryptamine, bromocriptine, octoclotheptin, and the neuroleptics clozapine, olanzapine, loxapine, chlorpromazine and fluphenazine [6,50]. The first ligands for the 5-HT₆ 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. <i>et al.</i>	[54]
2	ALX-0440	NPS–Allelix	[107,114]
3	ALX-1161	NPS–Allelix	[107,114]
4	ALX-1175	NPS–Allelix	[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. <i>et al.</i>	[122]
20	NA	Glennon, R.A. <i>et al.</i>	[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. <i>et al.</i>	[78]
28	NA	Wyeth	[80]
29	NA	Wyeth	[124]
30 ^a	NA	Wyeth	[79]
31	NA	Wyeth	[81]
32	NA	Glennon, R.A. <i>et al.</i>	[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. <i>et al.</i>	[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.prou.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-HT₆ 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-HT₆ 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-HT₆ 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-HT₆ receptors [55]. This was introduced originally as an *N*-protective group [54] and is still the main common structural motif within 5-HT₆ receptor ligands.

Pharmacophore models: how to construct a 5-HT₆ 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 pharmaco-

phore 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 (HQ SAR) [63] and CoMFA/CoMSIA 3D QSAR [64] studies based on different training sets of 5-HT₆ receptor antagonists (monocyclic/bicyclic aryl-piperazines and indoles, respectively). The structural requirements for a potent 5-HT₆ 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-HT₆ 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;

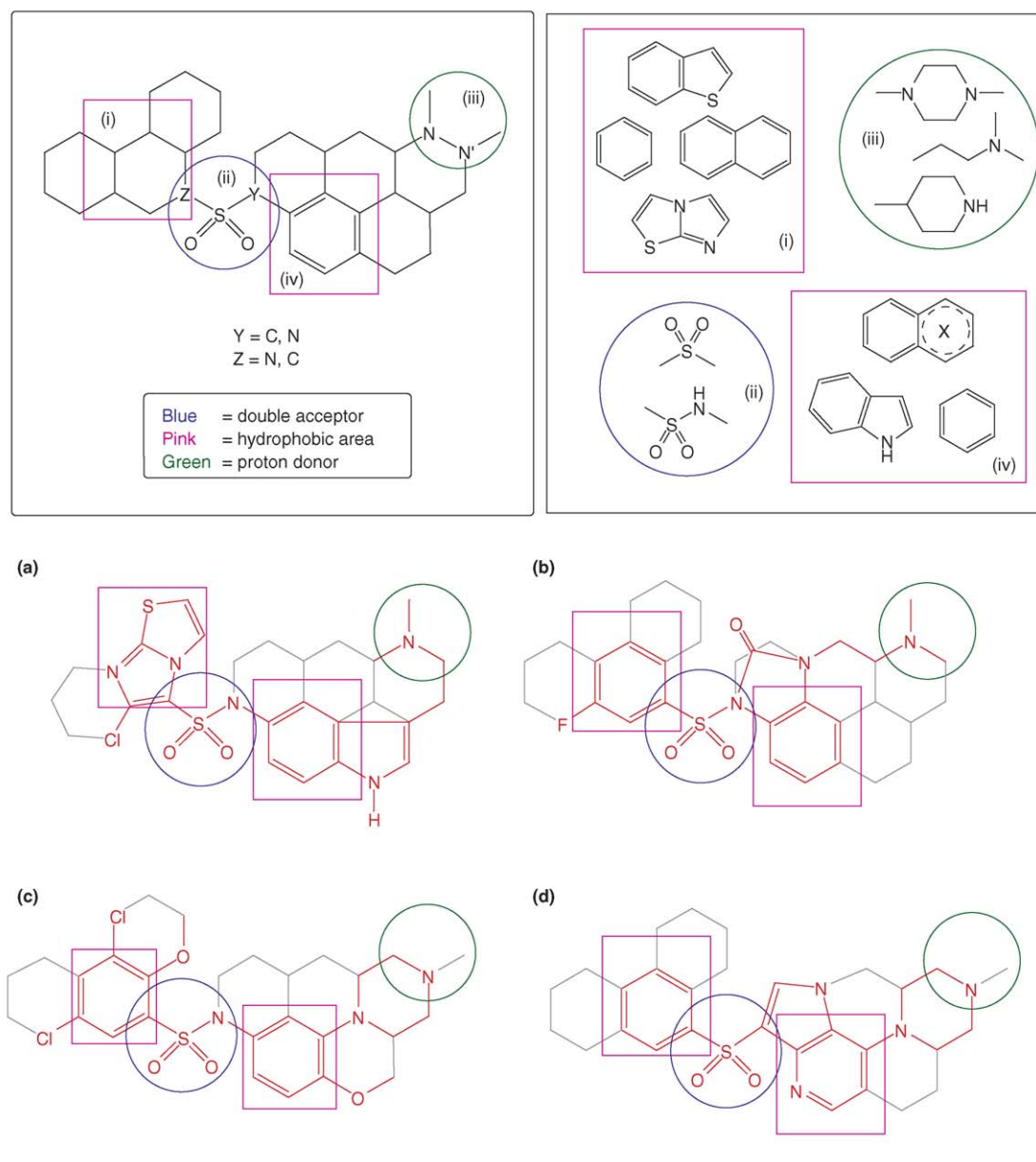


FIGURE 1

Simplified pharmacophore framework model [50] and the most common functional groups: try to construct your own 5-HT₆ 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 unprecedent 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-HT₆ 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-HT₆ receptor antagonists. By matching their results with a computational 5-HT₆ 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.

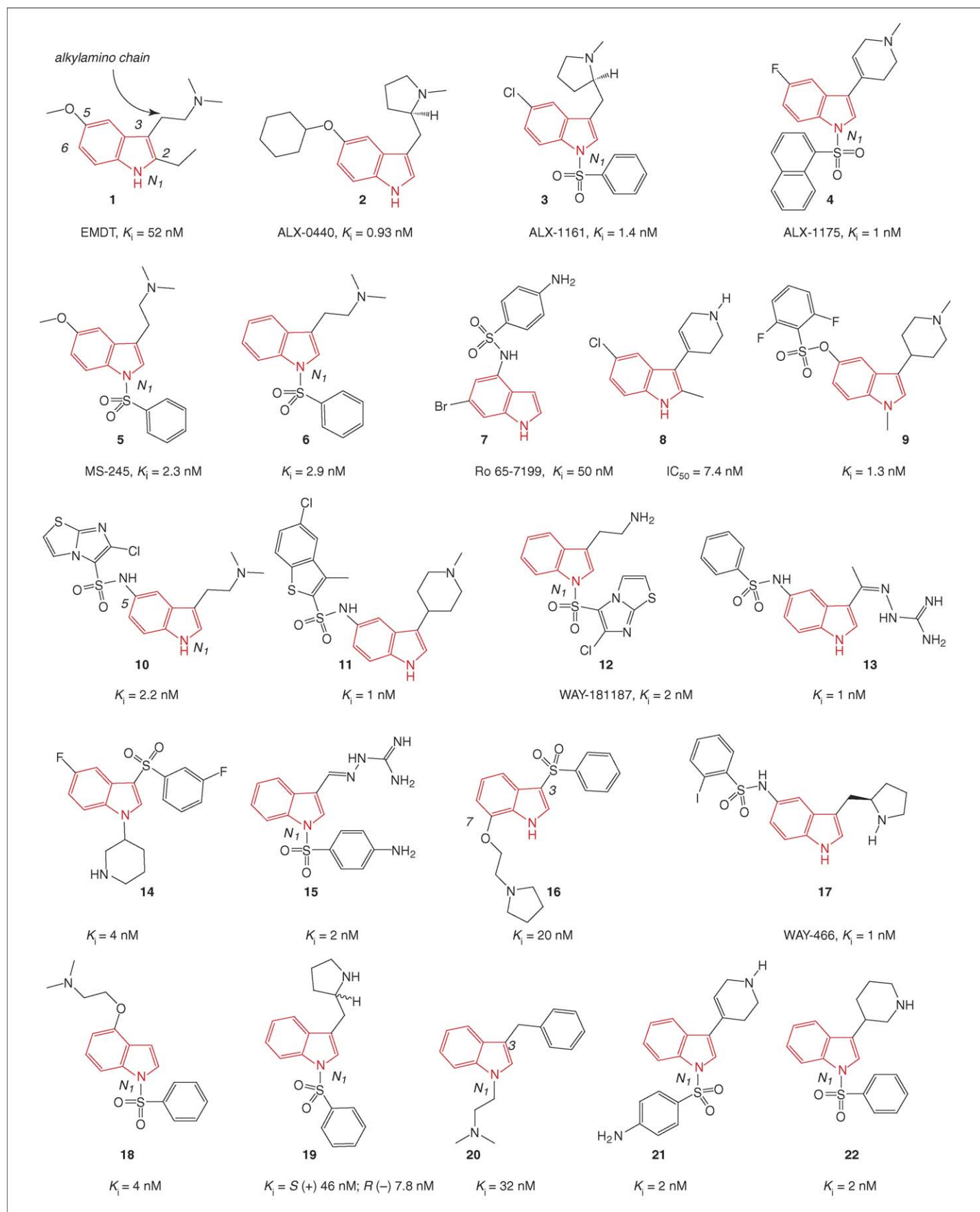
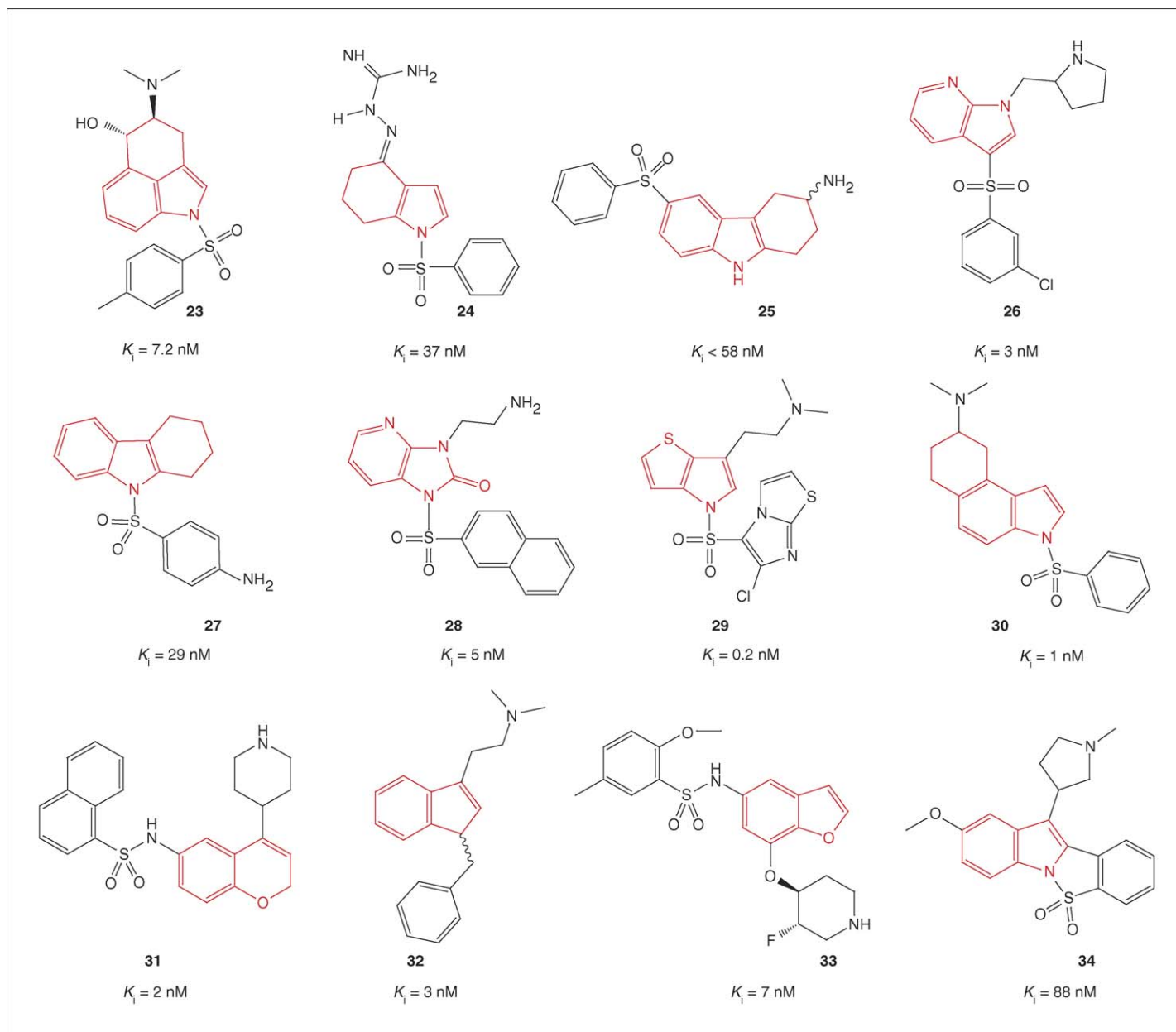


FIGURE 2

5-HT₆ 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-HT₆ 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-HT₆ receptor ligands

Given the tight pharmacophore requirements postulated above, nearly all reported 5-HT₆ 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-HT₆ 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 -SO₂R 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-HT₆ 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

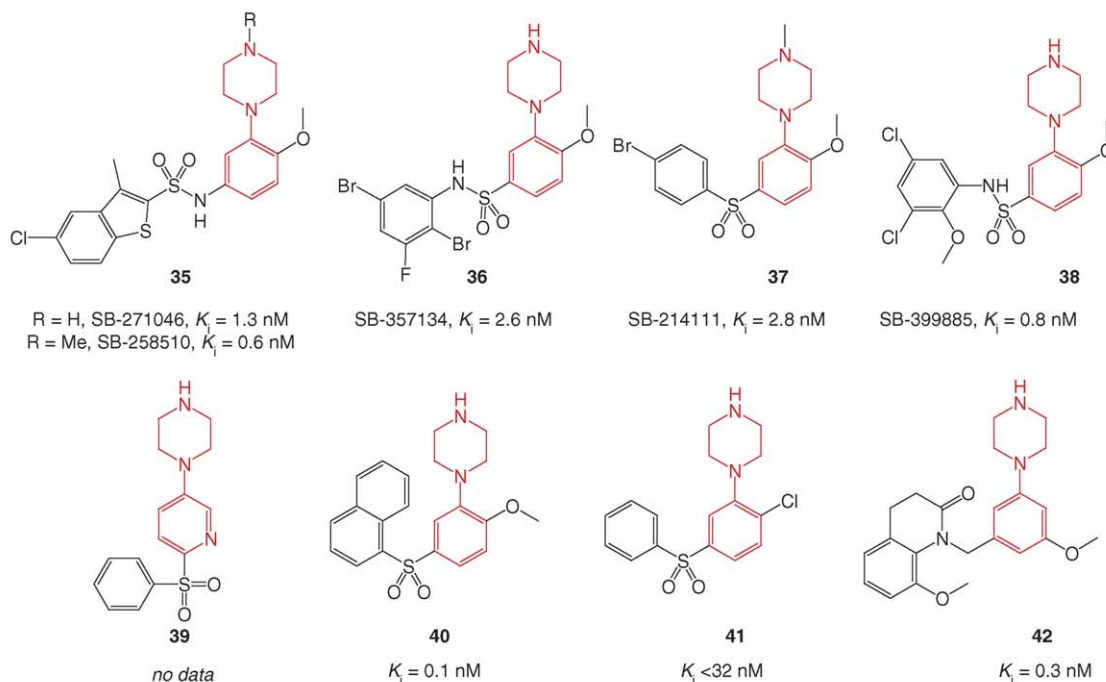


FIGURE 4

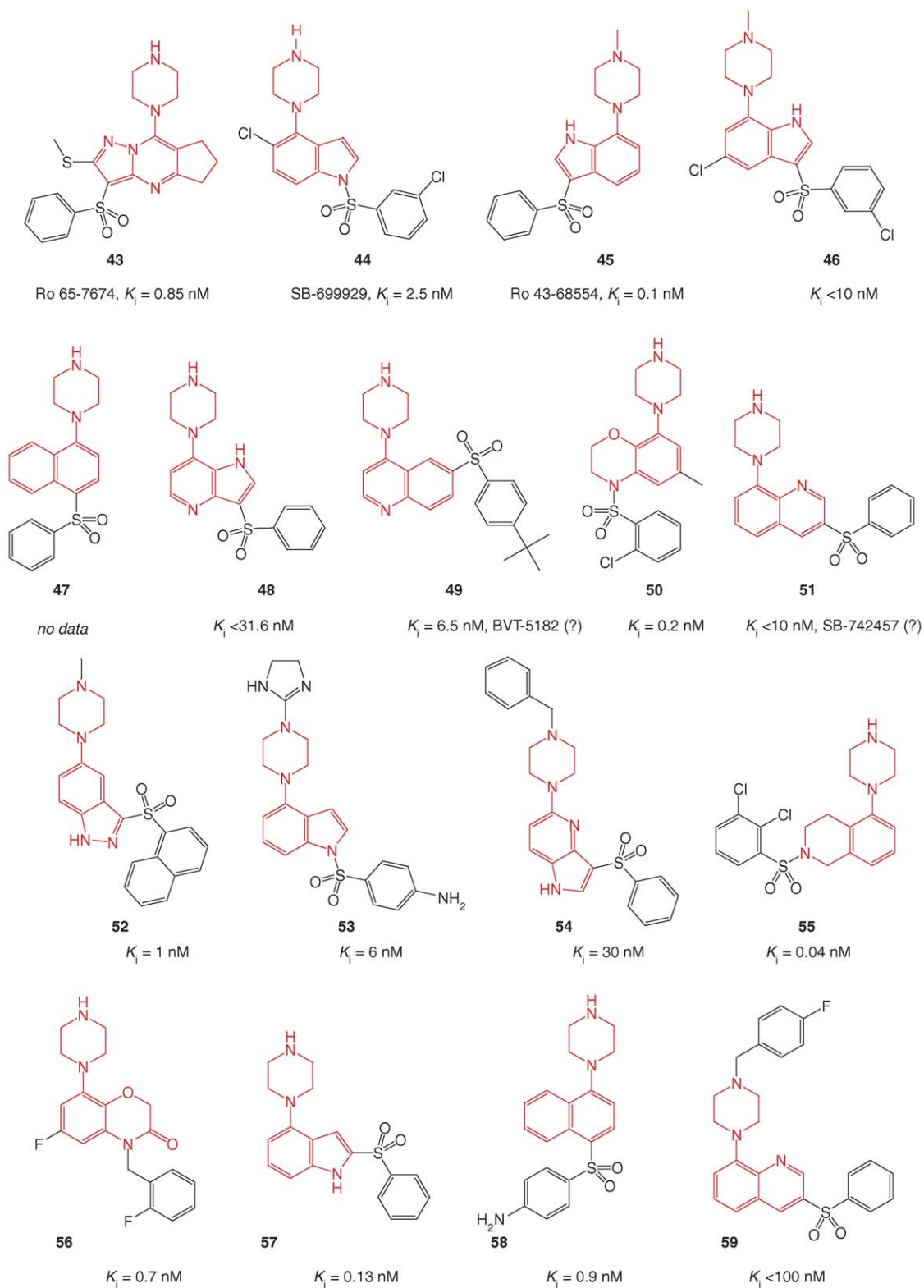
5-HT₆ receptor ligands containing monocyclic aryl-piperazine structures. See Table 1 for more details on these compounds (K_i values as reported in the references cited in Table 1).

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-HT₆ 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-HT₆ 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 -NH₂ compounds such as 5-HT [57]. Although many cyclic amines, such as piperidines,

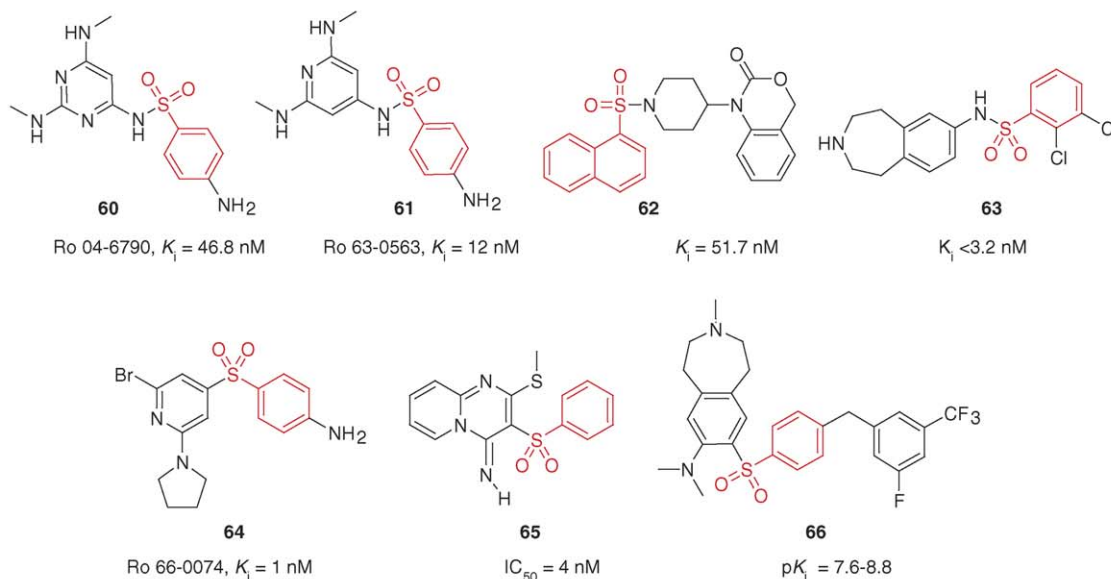
pyrrolidines and related groups (compounds **2–4**, **8**, **9**, **11**, **14**, **16**, **17**, **19**, **21** and **22**), lead to slightly decreased affinity compared with lower alkyl-substituted amines such as NMe₂ [50], they should be more stable metabolically. Interestingly, chiral 2-pyrrolidinyl amines similar to compound **17** (first introduced for 5-HT₆ 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 EC₅₀ values of ≤ 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**

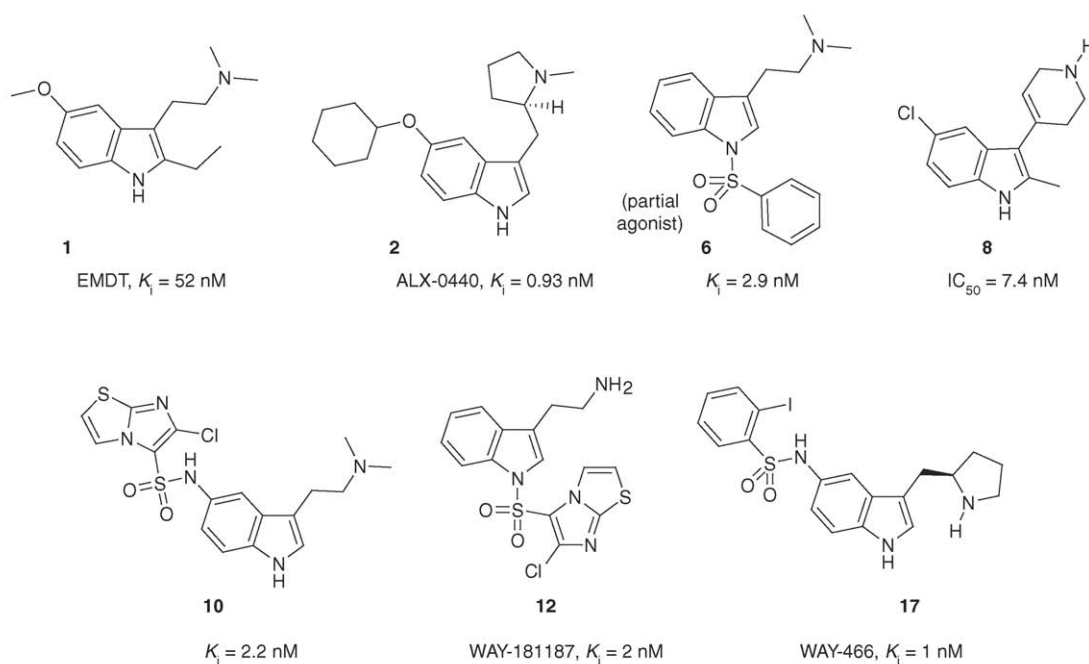
5-HT₆ receptor ligands containing bicyclic and tricyclic aryl-piperazine structures. See Table 1 for more details on these compounds (K_i values as reported in the references cited in Table 1).

**FIGURE 6**

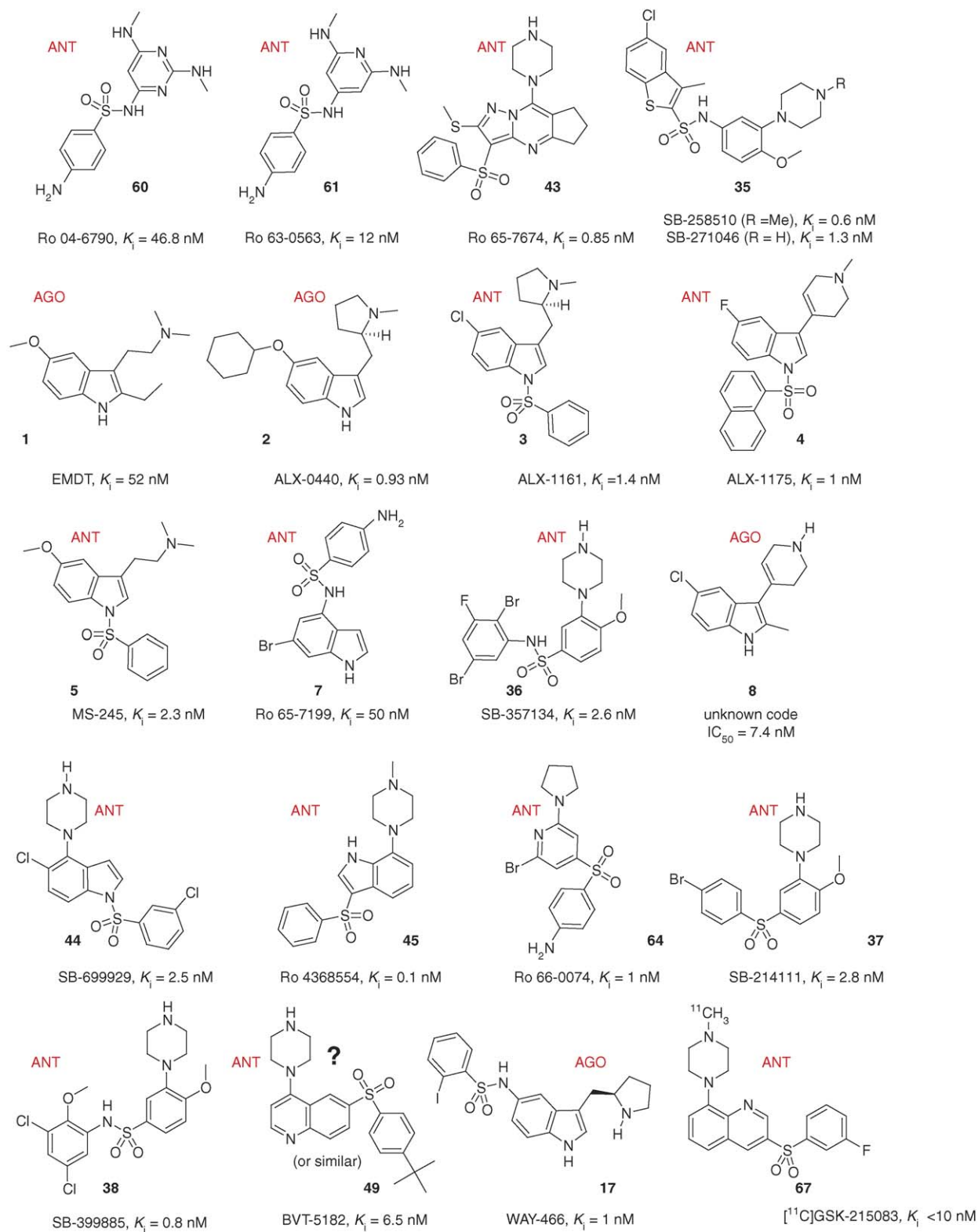
5-HT₆ receptor ligands containing miscellaneous, arylsulfonyl structures. See Table 1 for more details on these compounds (K_i values as reported in the references cited in Table 1).

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**

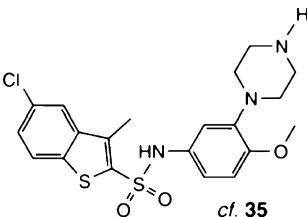
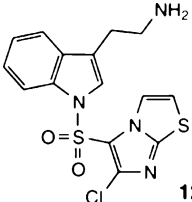
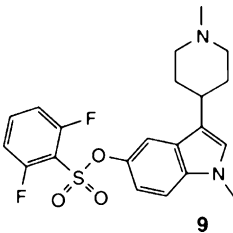
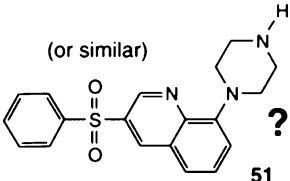
Structures of reported 5-HT₆ receptor agonists. See Table 1 for more details on these compounds (K_i values as reported in the references cited in Table 1).

**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-HT₆ 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-HT₆ 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. Similarly, 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-HT₆ receptor antagonist tools from Roche (compounds **60** and **61** [51]). In addition, compound **62** from Esteve [50,106] is a potent and selective 5-HT₆ receptor ligand without either a basic amine function or the *p*-aminophenyl-sulfonyl motif.

Structures of 5-HT₆ receptor agonists

Figure 7 provides an overview of agonists and partial agonists at the 5-HT₆ 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-HT₆ 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**,

BOX 1

Key resources and further reading

Chemistry:

Davies, S.L. *et al.* (2005) Drug discovery targets: 5-HT₆ receptor. *Drugs of the Future* 30, 479–495
 Glennon, R.A. *et al.* (2003) Higher-end serotonin receptors: 5-HT₅, 5-HT₆, and 5-HT₇. *J. Med. Chem.* 46, 2795–2812
 Slassi, A. *et al.* (2002) Recent progress in 5-HT₆ 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-HT₆ receptors. *Curr. Drug Targets CNS Neurol. Disord.* 3, 59–79

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-HT₆ 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-HT₆ receptors. Furthermore, they have been used to characterize the 5-HT₆ receptor and to investigate its distribution.

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-HT₆ 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-HT₆ receptor. This has resulted in the development and characterization of several, selective, high-affinity tool compounds. In total, four 5-HT₆ 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-HT₆ 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).

References

- 1 Monsma, F.J. *et al.* (1993) Cloning and expression of a novel serotonin receptor with high affinity for tricyclic psychotropic drugs. *Mol. Pharmacol.* 43, 320–327
- 2 Unsworth, C.D. and Molinoff, P.B. (1994) Characterization of a 5-hydroxytryptamine receptor in mouse neuroblastoma N18TG2 cells. *J. Pharmacol. Exp. Ther.* 269, 246–255

- 3 Kohen, R. *et al.* (1996) Cloning, characterisation, and chromosomal location of human 5-HT₆ serotonin receptor. *J. Neurochem.* 66, 47–56
- 4 Sebben, M. *et al.* (1994) 5-HT₆ receptors positively coupled to adenylyl cyclase in striatal neurones in culture. *Neuroreport* 5, 2553–2557
- 5 Woolley, M.L. *et al.* (2004) 5-HT₆ receptors. *Curr Drug Targets CNS Neurol Disord.* 3, 59–79
- 6 Davies, S.L. *et al.* (2005) Drug discovery targets: 5-HT₆ receptor. *Drugs of the Future* 30, 479–495
- 7 Tecott, L.H. and Brennan, T.J. (2000) Serotonin 5-HT₆ receptor knockout mouse. US patent 6,060,642.
- 8 Hirst, W.D. *et al.* (2003) Differences in the central nervous system distribution and pharmacology of the mouse 5-hydroxytryptamine-6 receptor compared with rat and human receptors investigated by radioligand binding, site-directed mutagenesis, and molecular modeling. *Mol. Pharmacol.* 64, 1295–1308
- 9 Setola, V. and Roth, B.L. (2003) Why mice are neither miniature humans nor small rats: A cautionary tale involving 5-Hydroxytryptamine-6 serotonin receptor species variants. *Mol. Pharmacol.* 64, 1277–1278
- 10 Sleight, A.J. *et al.* (1997) 5-HT₆ and 5-HT₇ receptors: molecular biology, functional correlates and possible therapeutic indications. *Drug News Perspect.* 10, 214–224
- 11 Fredericks, J.A. and Woodruff, J.H. (1999) Effects of clozapine and haloperidol on 5-HT₆ receptor mRNA levels in the rat brain. *Schizophr. Res.* 38, 7–12
- 12 Yu, Y.W. *et al.* (1999) Serotonin-6 receptor variant (C267T) and clinical response to clozapine. *Neuroreport* 10, 1231–1233
- 13 Masellis, M. *et al.* (2001) Lack of association between the T → C 267 serotonin 5-HT₆ receptor gene (HTR6) polymorphism and prediction of response to clozapine in schizophrenia. *Schizophr. Res.* 47, 49–58
- 14 Pouzet, B. *et al.* (2002) Effects of the 5-HT (6) receptor antagonist, SB-271046, in animal models for schizophrenia. *Pharmacol. Biochem. Behav.* 71, 635–643
- 15 Kohen, R. *et al.* (2001) Cloning of the mouse 5-HT₆ serotonin receptor and mutagenesis studies of the third cytoplasmic loop. *Brain Res. Mol. Brain Res.* 90, 110–117
- 16 Stean, T. *et al.* (1999) Anticonvulsant properties of the selective 5-HT₆ receptor antagonist SB-271046 in the rat maximal electroshock seizure threshold test. *Br. J. Pharmacol.* 127, 131P
- 17 Routledge, C. *et al.* (2000) Characterization of SB-271046: a potent, selective and orally active 5-HT (6) receptor antagonist. *Br. J. Pharmacol.* 130, 1606–1612
- 18 King, M.V. *et al.* (2004) 5-HT₆ receptor antagonists reverse delay-dependent deficits in novel object discrimination by enhancing consolidation – an effect sensitive to NMDA receptor antagonism. *Neuropharmacology* 47, 195–204
- 19 Ennaceur, A. and Delacour, J. (1988) A new one-trial test for neurobiological studies of memory in rats. I: behavioural data. *Behav. Brain Res.* 31, 47–59
- 20 Prickaerts, J. *et al.* (2005) Dissociable effects of acetylcholinesterase inhibitors and phosphodiesterase type 5 inhibitors on object recognition memory: acquisition versus consolidation. *Psychopharmacology (Berl.)* 177, 381–390
- 21 Meneses, A. (2001) Effects of the 5-HT₆ receptor antagonist Ro 04-6790 on learning consolidation. *Behav. Brain Res.* 118, 107–110
- 22 Bentley, J.C. *et al.* (1997) 5-HT₆ antisense oligonucleotide i.c.v. affects rat performance in the water maze and feeding. *J. Psychopharmacol.* 11, A64
- 23 Woolley, M.L. *et al.* (2001) A role for 5-HT₆ receptors in retention of spatial learning in the Morris water maze. *Neuropharmacology* 41, 210–219
- 24 Lieben, C.K. *et al.* (2005) The selective 5-HT₆ Receptor antagonist Ro 4368554 restores memory performance in cholinergic and serotonergic models of memory deficiency in the rat. *Neuropsychopharmacology* 30, 2169–2179
- 25 Woolley, M.L. *et al.* (2003) Reversal of a cholinergic-induced deficit in a rodent model of recognition memory by the selective 5-HT₆ receptor antagonist, Ro 04-6790. *Psychopharmacology (Berl.)* 170, 358–367
- 26 Sleight, A.J. *et al.* (1999) 5-HT₆ receptors: functional correlates and potential therapeutic indications. *Behav. Pharmacol.* 10, S86
- 27 Bös, M. *et al.* (2001) 5-HT₆ receptor antagonists: Lead optimisation and biological evaluation of N-aryl and N-heteroaryl 4-amino-benzene sulphonamides. *Eur. J. Med. Chem.* 36, 165–178
- 28 Riemer, C. *et al.* (2003) Influence of the 5-HT₆ receptor on acetylcholine release in the cortex: pharmacological characterization of 4-(2-bromo-6-pyrrolidin-1-ylpyridine-4-sulfonyl)phenylamine, a potent and selective 5-HT₆ receptor antagonist. *J. Med. Chem.* 46, 1273–1276
- 29 Rogers, D.C. *et al.* (1999) Cognitive enhancement effects of the selective 5-HT₆ antagonist SB-271046. *Br. J. Pharmacol.* 127, 22P
- 30 Perez-Garcia, G. and Meneses, A. (2005) Oral administration of the 5-HT₆ receptor antagonists SB-357134 and SB-399885 improves memory formation in an autoshaping learning task. *Pharmacol. Biochem. Behav.* 81, 673–682
- 31 Garcia-Alloza, M. *et al.* (2004) Differential involvement of 5-HT_{1B/1D} and 5-HT₆ receptors in cognitive and non-cognitive symptoms in Alzheimer's disease. *Neuropsychopharmacology* 29, 410–416
- 32 Rogers, D.C. and Hagan, J.J. (2001) 5-HT₆ receptor antagonists enhance retention of a water maze task in the rat. *Psychopharmacology (Berl.)* 158, 114–119
- 33 Van der Staay, J. *et al.* (1996) Effects of metrifonate, its transformation product dichlorvos, and other organophosphorus and reference cholinesterase inhibitors on Morris water escape behavior in young-adult rats. *J. Pharmacol. Exp. Ther.* 278, 697–708
- 34 Braid, D. *et al.* (1996) An inverted U-shaped curve for heptylphosphostigmine on radial maze performance in rats: comparison with other cholinesterase inhibitors. *Eur. J. Pharmacol.* 302, 13–20
- 35 Cheng, D.H. *et al.* (1996) Huperzine-A, a novel promising acetyl-cholinesterase inhibitor. *Neuroreport* 8, 97–101
- 36 Ohara, T. *et al.* (1997) SDZ ENA 713 facilitates central cholinergic function and ameliorates spatial memory impairment in rats. *Behav. Brain Res.* 83, 229–233
- 37 Foley, A.G. *et al.* (2004) The 5-HT₆ receptor antagonist SB-271046 reverses scopolamine-disrupted consolidation of a passive avoidance task and ameliorates spatial task deficits in aged rats. *Neuropsychopharmacology* 29, 93–100
- 38 Stean, T.O. *et al.* (2002) Pharmacological profile of SB-357134: A potent, selective, brain penetrant, and orally active 5-HT₆ receptor antagonist. *Pharmacol. Biochem. Behav.* 71, 645–654
- 39 Hatcher, P.D. *et al.* (2005) 5-HT₆ receptor antagonists improve performance in an attentional set shifting task in rats. *Psychopharmacology (Berl.)* 181, 253–259
- 40 Lindner, M.D. *et al.* (2003) An assessment of the effects of serotonin 6 (5-HT₆) receptor antagonists in rodent models of learning. *J. Pharmacol. Exp. Ther.* 307, 682–691
- 41 Saegis, (2005) Saegis pharmaceutical completes phase IIa clinical study of SG5518. *Saegis Press Release*, December 15.
- 42 Information on structure class and clinical status from Integrity database, Prous Science, and from Investigational Drugs Database IDdb3, Thomson Current Drugs, and from <http://www.newhealth.govt.nz/ethicscommittees/committees/agenda-and-minutes/multi-region/17may05/mec-minutes-17may2005.doc>.
- 43 Vickers, S.P. and Dourish, C.T. (2004) Serotonin receptor ligands and the treatment of obesity. *Curr. Opin. Investig. Drugs* 5, 377–388
- 44 Caldirola, P. (2003) 5-HT₆ receptor antagonism: A novel mechanism for the management of obesity. *SMI Conf. obesity and related disorders* (Feb. 17–18, London).from: www.iddb3.com.
- 45 Bentley, J.C. *et al.* (1999) Investigation of stretching behaviour induced by the selective 5-HT₆ receptor antagonist Ro 04-6790 in rats. *Br. J. Pharmacol.* 126, 1537–1542
- 46 Svartengren, J. *et al.* (2003) The serotonin 5-HT₆ receptor antagonist BVT-5182 reduces body weight of high fat diet-induced mice, *Int. J. Obes.* 27, Suppl.1. *Abst T1*, 1-094.
- 47 Svartengren, J. *et al.* (2004) The selective serotonin 5-HT₆ receptor antagonist BVT-5182 decreases food intake and body weight in both rats and mice. *34th Annu. Meet. Soc. Neurosci.* Abstract 75.8.
- 48 Jossan, S. *et al.* (2002) Formulations comprising a 5-HT agonist and 5-HT₆ antagonist useful for the treatment of obesity. WO patent 2002008178.
- 49 Slassi, A. *et al.* (2002) Recent progress in 5-HT₆ receptor antagonists for the treatment for the CNS diseases. *Expert Opin. Ther. Pat.* 12, 513–527
- 50 Holenz, J. *et al.* (2005) Medicinal chemistry driven approaches toward novel and selective serotonin 5-HT₆ receptor ligands. *J. Med. Chem.* 48, 1781–1795
- 51 Sleight, A.J. *et al.* (1998) Characterization of Ro 04-6790 and Ro 63-0563: Potent and selective antagonists at human and rat 5-HT₆ receptors. *Br. J. Pharmacol.* 124, 556–562
- 52 Bromidge, S.M. *et al.* (1999) 5-Chloro-N-(4-methoxy-3-piperazin-1-ylphenyl)-3-methyl-2-benzothiophenesulfonamide (SB-271046): A potent, selective, and orally bioavailable 5-HT₆ receptor antagonist. *J. Med. Chem.* 42, 202–205
- 53 Glennon, R.A. *et al.* (1999) 5-HT₆ serotonin receptor binding of indolealkylamines: A preliminary structure-affinity investigation. *Med. Chem. Res.* 9, 108–117
- 54 Glennon, R.A. *et al.* (2000) 2-Substituted tryptamines: agents with selectivity for 5-HT₆ serotonin receptors. *J. Med. Chem.* 43, 1011–1018
- 55 Tsai, Y. *et al.* (2000) N1-(Benzenesulfonyl)tryptamines as novel 5-HT₆ antagonists. *Bioorg. Med. Chem. Lett.* 10, 2295–2299
- 56 Lee, M. *et al.* (2000) 5-HT₆ receptor serotonin receptor binding affinities of N1-benzenesulfonyl and related tryptamines. *Med. Chem. Res.* 10, 230–242
- 57 Glennon, R.A. *et al.* (2003) Higher-end serotonin receptors: 5-HT₅, 5-HT₆, and 5-HT₇. *J. Med. Chem.* 46, 2795–2812
- 58 Russell, M.G.N. *et al.* (2001) N-Arylsulfonylindole derivatives as serotonin 5-HT₆ receptor ligands. *J. Med. Chem.* 44, 3881–3895

- 59 Pullagurta, M.R. *et al.* (2004) Possible differences in modes of agonist and antagonist binding at human 5-HT₆ receptors. *Bioorg. Med. Chem. Lett.* 14, 4569–4573
- 60 Boess, F.G. *et al.* (1997) Interaction of tryptamine and ergoline compounds with threonine 196 in the ligand binding site of the 5-hydroxytryptamine₆ receptor. *Mol. Pharmacol.* 52, 515–523
- 61 Boess, F.G. *et al.* (1998) Identification of residues in transmembrane regions III and VI that contribute to the ligand binding site of the serotonin 5-HT₆ receptor. *J. Neurochem.* 71, 2169–2177
- 62 Boess, F.G. *et al.* (1998) The 5-hydroxytryptamine₆ receptor-selective radioligand [³H]Ro 63-0563 labels 5-hydroxytryptamine receptor binding sites in rat and porcine striatum. *Mol. Pharmacol.* 54, 577–583
- 63 Doddareddy, M.R. *et al.* (2004) Hologram quantitative structure activity relationship studies on 5-HT₆ antagonists. *Bioorg. Med. Chem.* 12, 3815–3824
- 64 Doddareddy, M.R. *et al.* (2004) CoMFA and CoMSIA 3D QSAR analysis on N1-arylsulfonylindole compounds as 5-HT₆ antagonists. *Bioorg. Med. Chem.* 12, 3977–3985
- 65 Harris, R.N., III *et al.* (2004) Preparation of quinolinone and benzoxazinone derivatives as 5-HT₆ modulators. WO patent 2004080969.
- 66 Maag, H. *et al.* (2004) Preparation of substituted benzoxazinones as selective 5-HT₆ antagonists for treating central nervous system diseases and gastrointestinal tract disorders. US patent 2004092512.
- 67 Kolanos, R. *et al.* (2005) Binding of isotryptamines and indenes at h5-HT₆ serotonin receptors. *Bioorg. Med. Chem. Lett.* 15, 1987–1991
- 68 López-Rodríguez, M.L. *et al.* (2005) A three-dimensional pharmacophore model for 5-hydroxytryptamine₆ (5-HT₆) receptor antagonists. *J. Med. Chem.* 48, 4216–4219
- 69 Bromidge, S.M. *et al.* (2001) Phenyl benzenesulfonamides are novel and selective 5-HT₆ antagonists: identification of N-(2,5-dibromo-3-fluorophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulfonamide (SB-357134). *Bioorg. Med. Chem. Lett.* 11, 55–58
- 70 Wu, Y.-J. *et al.* (2003) Identification of a potent and selective 5-HT₆ antagonist: One-step synthesis of (E)-3-(benzenesulfonyl)-2-(methylsulfonyl)pyrido[1,2-a]pyrimidin-4-ylidenamine from 2-(benzenesulfonyl)-3,3-bis(methylsulfonyl)acrylonitrile. *J. Med. Chem.* 46, 4834–4837
- 71 Cole, D.C. *et al.* (2004) Conformationally constrained N1-arylsulfonyltryptamine derivatives as 5-HT₆ receptor antagonists. *Bioorg. Med. Chem. Lett.* 15, 4780–4785
- 72 Aldridge, S. (2005) Medicinal Chemistry Equals New Leads. *Gen. Engineering News* 25, 1
- 73 Cole, D.C. *et al.* (2003) Preparation of 1-(indol-3-yl)alkylidenhydrazine carboximidamides as 5-hydroxytryptamine-6 ligands. US patent 2003232843.
- 74 Cole, D.C. *et al.* (2005) Discovery of 5-arylsulfonamido-3-(pyrrolidin-2-ylmethyl)-1H-indole derivatives as potent, selective 5-HT₆ receptor agonists and antagonists. *J. Med. Chem.* 48, 353–356
- 75 Schechter, L.E. *et al.* (2004) WAY-466: In vitro and in vivo pharmacological characterization of a novel and selective 5-HT₆ receptor agonist. *Neuropsychopharmacology* 29 (Suppl. 1), S237
- 76 Spinks, D. *et al.* (2003) Preparation of 1-arylsulfonyl-3-substituted indoles and indolines for the treatment of central nervous system disorders. WO patent 2003068220.
- 77 Fu, J.-M. (2003) Preparation of arylsulfonyl-substituted tetrahydro- and hexahydrocarbazolamines as 5-HT₆ receptor ligands. WO patent 2003030901.
- 78 Chang-Fong, J. *et al.* (2004) 1,2,3,4-Tetrahydrocarbazoles as 5-HT₆ serotonin receptor ligands. *Bioorg. Med. Chem. Lett.* 14, 1961–1964
- 79 Cole, D.C. *et al.* (2005) Preparation of 3-[(hetero)arylsulfonyl]-tetrahydro-3H-benzo[e]indol-8-amines as 5-hydroxytryptamine-6 ligands. US patent 2005101596.
- 80 Cole, D.C. *et al.* (2005) Preparation of sulfonyldihydroimidazopyridinones as serotonin 5-HT₆ ligands. WO patent 2005010003.
- 81 Greenblatt, L.P. (2005) Preparation of piperidinylchromenylsulfonamides as 5-HT₆ ligands. WO patent 2005037830.
- 82 Johansson, G. *et al.* (2005) Preparation of benzofuran derivatives that can be used in prophylaxis or treatment of 5-HT₆ receptor-related disorders like obesity. WO patent 2005058858.
- 83 Bernotas, R.C. *et al.* (2004) Preparation of heterocyclylalkyl-sulfonylazaindole or -azaindazole derivatives 5-hydroxytryptamine-6 (5-HT₆) ligands. WO patent 2004009600.
- 84 Kelly, M.G. *et al.* (2003) Preparation of pyrrolylalkylidene-hydrazinecarboximidamides as 5-hydroxytryptamine-6 ligands. WO patent 2003068740.
- 85 Jasti, V. *et al.* (2005) Preparation of indeno[2,1-a]indenes and isoindol[2,1-a]indoles as modulators of 5-HT receptors. WO patent 2005066184.
- 86 Hirst, W.D. *et al.* (2003) Characterisation of SB-399885, a potent and selective 5-HT₆ receptor antagonist. *33rd Annu. Meet. Soc. Neurosci.* (Nov. 8–12, New Orleans), Abstract 576.7; from: <http://integrity.prous.com>.
- 87 Medicinal Chemistry - XVIIIth International Symposium (Part V) (2004). Copenhagen, Denmark, and Malmö, Sweden, <http://www.iddb3.com>.
- 88 MacDonald, G.J. *et al.* (2004) Preparation of novel phenyl sulfone derivatives and their use in the treatment of CNS disorders. WO patent 2004080986.
- 89 Tenbrink, R.E. *et al.* (2003) Preparation of pyridyl phenyl sulfones as 5-HT₆ receptor modulators. WO patent 2003072548.
- 90 Stadler, H. *et al.* (1999) 5-HT₆ antagonists: a novel approach for the symptomatic treatment of Alzheimer's disease. *37th IUPAC Cong.* (Aug 14–19, Berlin), Abstract MM-7.
- 91 Bonhaus, D.W. *et al.* (2002) Ro-4368554, a high affinity, selective, CNS penetrating 5-HT₆ receptor antagonist. *32nd Annu. Meet. Soc. Neurosci.* (Nov 2–7, Orlando), Abstract 884.5.
- 92 Beard, C.C. *et al.* (2002) Preparation of new indole derivatives with 5-HT₆ receptor affinity. WO patent 2002098857.
- 93 Berger, J. *et al.* (2003) Preparation of benzoxazines as 5-HT₆ modulators. WO patent 2003095434.
- 94 Putman, D. (2004) Preparation of 2,5- and 2,6-substituted tetrahydroisoquinolines as 5-HT₆ modulators, in particular selective 5-HT₆ antagonists, for treating CNS disorders. WO patent 2004078176.
- 95 Madera, A.M. *et al.* (2004) Preparation of 2,4-substituted indoles as 5-HT₆ modulators. WO patent 2004026831.
- 96 Bromidge, S.M. *et al.* (2002) Preparation of 4-piperazinoindoles for treating CNS disorders. WO patent 2002041889. Part of this work was later published in: Ahmed, M. *et al.* (2005) Bicyclic heteroaryl piperazines as selective brain penetrant 5-HT₆ receptor antagonists. *Bioorg. Med. Chem. Lett.* 15, 4867–4871.
- 97 Johnson, C.N. *et al.* (2003) Preparation of arylsulfonylquinolinyl- of azaindolylpiperazines as 5-HT₆ antagonists. WO patent 2003080608.
- 98 Ahmed, M. *et al.* (2003) Novel compounds. WO patent 2003080580.
- 99 Johnson, C.N. *et al.* (2005) Quinoline compounds and pharmaceutical compositions containing them. WO patent 2005026125.
- 100 A [¹¹C] labeled compound is described: Martarello, L. *et al.* (2005) Radiolabelling and in vivo evaluation of [¹¹C]GSK215083 as potential PET radioligand for the 5-HT₆ receptor in the porcine brain. *7th Int. Conf. Quantification Brain Function PET* (Jun 8–9, Amsterdam), Abstract BP-11; from: <http://integrity.prous.com>.
- 101 Bernotas, R.C. *et al.* (2004) Preparation of heterocyclyl-3-sulfonylindazoles as 5-hydroxytryptamine-6 ligands. US patent 2004167122.
- 102 Kelly, M.G. *et al.* (2004) Preparation of 1-alkylsulfonylheterocyclylbenzazoles and related compounds as 5-hydroxytryptamine-6 ligands. US patent 2004192749.
- 103 Bernotas, R.C. *et al.* (2004) Heterocyclyl-3-sulfonylazaindole or -azaindazole derivatives as 5-HT₆ receptor ligands, and their use for the treatment of central nervous system disorders. WO patent 2004074286.
- 104 Johansson, G. *et al.* (2004) Preparation of pyridino-fused heterocycles useful for the treatment of obesity, type II diabetes and CNS disorders. WO patent 2004000828.
- 105 Patent Alert (2003) from *Current Opinion in Investigational Drugs* 4, 911.
- 106 Torrens, A. *et al.* (2003) Compuestos sulfonamídicos derivados de benzoxazinona, su preparación y uso como medicamentos. ES patent Application 200301812.
- 107 Demchishyn LI. *et al.* (2001) ALX-1161: pharmacological properties of a potent and selective 5-HT₆ receptor antagonist. *31st Annu. Meet. Soc. Neurosci.* (Nov 10–15), Abstract 266.6; from: www.iddb3.com.
- 108 Mattsson, C. *et al.* (2002) Novel, potent and selective 2-alkyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole as 5-HT₆ receptor agonists. *XVIIIth International Symposium on Medicinal Chemistry* (Sep 1–5, Barcelona).
- 109 Mattsson, C. *et al.* (2005) 2-Alkyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indoles as novel 5-HT₆ receptor agonists. *Bioorg. Med. Chem. Lett.* 15, 4230–4234
- 110 Mercè, R. *et al.* (2003) Derivatives of sulfonamides, their preparation and use as medicaments. WO patent 2003042175.
- 111 Cole, D.C. *et al.* (2003) Indolylalkylamine derivatives as 5-hydroxytryptamine-6 ligands. WO patent 2003053433.
- 112 Wang, Y. *et al.* (2006) Indolylalkylamine metabolites as 5-hydroxytryptamine-6 ligands. WO patent 2006002125.
- 113 Cole, D.C. *et al.* (2005) Discovery of a potent, selective and orally active 5-HT₆ receptor agonist, WAY-181187. *230th ACS Natl. Meet.* (Aug 28–Sept 1, Washington DC), Abstract MEDI 17.
- 114 Slassi, A. *et al.* (2000) Preparation of 1-(arylsulfonyl)-3-(tetrahydropyridinyl)indoles as 5-HT₆ receptor inhibitors. WO patent 200063203.
- 115 Caldirola, P. (2003) Use of sulfonamide derivatives in the treatment of obesity or for the reduction of food intake. WO patent 2003039547.
- 116 Filla, S.A. *et al.* (2002) Preparation of benzenesulfonic acid indol-5-yl esters as antagonists of the 5-HT₆ receptor. WO patent 2002060871.

- 117 Piñeiro-Núñez, M.M. *et al.* (2005) Discovery and SAR studies of 2,6-difluorobenzenesulfonic acid 1-methyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, a novel and potent 5-HT₆ antagonist for the treatment of cognitive deficit. *229th ACS Natl. Meet. (Mar 13-17, San Diego), Abstract MEDI 282.*
- 118 Bernotas, R.C. *et al.* (2004) Preparation of 1-heterocyclylalkyl-3-sulfonylindoles and indazoles as 5-HT₆ ligands. WO patent 2004009548.
- 119 Cole, D.C. *et al.* (2004) Preparation of indolylalkylidenehydrazine-carboximidamide derivatives as 5-hydroxytryptamine-6 ligands. US patent 2004002527.
- 120 Zhao, S-H. (2004) Preparation of aminoalkoxyindoles as 5-HT₆-receptor ligands, in particular selective 5-HT₆ antagonists, for treating CNS disorders. WO patent 2004050085.
- 121 Zhou, P. *et al.* (2005) 4-(2-Aminoethoxy)-N-(phenylsulfonyl)indoles as novel 5-HT₆ receptor ligands. *Bioorg. Med. Chem. Lett.* 15, 1393–1396
- 122 Abate, C. *et al.* (2005) Interaction of chiral MS-245 analogs at h5-HT₆ receptors. *Bioorg. Med. Chem. Lett.* 15, 3510–3513
- 123 Cole, D.C. *et al.* (2005) N1-arylsulfonyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole derivatives are potent and selective 5-HT₆ receptor antagonists. *Bioorg. Med. Chem. Lett.* 15, 379–383
- 124 Cole, D.C. (2005) Preparation of N-sulfonylheterocyclopyrrolalkylamine compounds as 5-hydroxytryptamine-6 ligands. WO patent 2005012311.
- 125 Berger, J. *et al.* (2003) Preparation of 1-[2-alkoxy-5-(arylsulfonyl)phenyl]piperazines with 5-HT₆ receptor affinity. WO patent 2003014097.
- 126 Tenbrink, R.E. *et al.* (2003) Preparation of arylsulfones as 5-HT₆ receptor modulators. WO patent 2003072558.
- 127 Lee, M. *et al.* (2005) 1-(1-Naphthyl)piperazine as a novel template for 5-HT₆ serotonin receptor ligands. *Bioorg. Med. Chem. Lett.* 15, 1707–1711
- 128 Bromidge, S.M. *et al.* (2003) Preparation of 7-arylsulfonamido-2,3,4,5-tetrahydro-1H-benzo[d]azepines with 5-HT₆ receptor affinity for the treatment of CNS disorders. WO patent 2003068751.
- 129 Wu, Y-J. *et al.* (2004) Preparation of pyridopyrimidines as 5-HT₆ antagonists. US patent 2004019064.
- 130 Forbes, I.T. *et al.* (2005) Preparation of 7-phenylsulfonyl-tetrahydro-3-benzazepine derivatives as antipsychotic agents. WO patent 2005051398.
- 131 Leng, A. *et al.* (2003) Effect of the 5-HT₆ receptor antagonists Ro 04-6790 and Ro 65-7199 on latent inhibition and prepulse inhibition in the rat: comparison to clozapine. *Pharmacol. Biochem. Behav.* 75, 281–288
- 132 Dawson, L.A. *et al.* (2001) The 5-HT₆ receptor antagonist SB-271046 selectively enhances excitatory neurotransmission in the rat frontal cortex and hippocampus. *Neuropsychopharmacology* 25, 662–668
- 133 Dawson, L.A. *et al.* (2001) In vivo effects of the 5-HT₆ antagonist SB-271046 on striatal and frontal cortex extracellular concentrations of noradrenaline, dopamine, 5-HT, glutamate and aspartate. *Br. J. Pharmacol.* 130, 23–26
- 134 Frantz, K.J. *et al.* (2002) 5-HT₆ receptor antagonism potentiates the behavioral and neurochemical effects of amphetamine but not cocaine. *Neuropharmacology* 42, 170–180
- 135 Minabe, Y. *et al.* (2004) Effect of the acute and chronic administration of the selective 5-HT₆ receptor antagonist SB-271046 on the activity of midbrain dopamine neurons in rats: an in vivo electrophysiological study. *Synapse* 52, 20–28
- 136 Pullagurta, M. *et al.* (2004) Modulation of the stimulus effects of (+)-amphetamine by the 5-HT₆ antagonist MS-245. *Pharmacol. Biochem. Behav.* 78, 263–268
- 137 Structure is most probably identical with the one protected as polymorph in: Galdwin, A. E. WO patent 2005040124.

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